

Proceed, with Caution: SPECT Cerebral Blood Flow Studies of Children and Adolescents with Attention Deficit Hyperactivity Disorder

As reported in this issue of *The Journal of Nuclear Medicine*, Langleben et al. (1) found significant increases in motor, premotor, and anterior cingulate cortex blood flow in 22 boys with attention deficit hyperactivity disorder (ADHD) when they were scanned with ^{99m}Tc -ethylcysteinate dimer (ECD) SPECT 36 h after their last dose of methylphenidate (MPH), compared with while on their usual doses of MPH. Control subjects ($n = 7$) were also scanned twice, including a scan after a 10-mg fixed dose of MPH; however, those scans did not reveal any significant differences. This has been the only study to include both children with ADHD and healthy control children in a comparison of regional cerebral blood flow (rCBF) while subjects were receiving medication and rCBF while subjects were not receiving medication. If only for that reason, the study is worthy of additional comment. On one reading, the data are consistent with the idea that MPH has therapeutic effects in ADHD partly by decreasing rCBF in the anterior cingulate, motor, and premotor cortices. This conclusion is consistent with findings of decreased motor cortex blood flow after stimulant treatment in a rat study (2) and in a human study (3), as Langleben et al. point out.

However, the authors are correct in warning readers that their results must be interpreted with considerable caution. In part because of difficulties in

recruiting healthy children for studies that involve injecting radiopharmaceuticals, their negative results in the control group of 7 children are uninformative. Second, because the authors could not, for ethical reasons, withdraw MPH from the patients for more than 36 h, the possibility exists that the results reflect withdrawal rather than treatment effects. Having a larger control group might have helped determine whether rCBF in the anterior cingulate, motor, and premotor cortices is abnormally elevated in untreated children with ADHD when they are performing a go/no-go task.

In a prior study by the same group (5), the SPECT scans of 20 male right-handed subjects who fulfilled the ADHD criteria of the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV (4)), were free of other comorbid conditions, and had been unmedicated for at least 24 h were compared with the SPECT scans of 4 healthy boys, who were presumably a subset of the subjects in the present report (1). The control group was judged too small for valid comparisons, and those data were not included in final analyses. The patients were divided into 3 subgroups by clinically rated severity: severe, moderate, and low ($n = 7, 6$, and 7, respectively). The subjects were scanned while performing a go/no-go task. Automated image analyses yielded regions of interhemispheric asymmetry with empiric statistical significance defined dichotomously (significant—not significant). The primary finding was that the severe and moderate ADHD groups showed decreased dorsolateral prefrontal cortical (DLPFC) perfusion

on the right and increased DLPFC perfusion on the left.

Granted that no single study can provide definitive answers, this is an appropriate time to review rCBF SPECT studies in ADHD. Has progress been made since the early ^{133}Xe studies (6)? If so, what has been established, what is still in doubt, and what are the pivotal studies that remain? Most important, should such studies continue to be performed on children and adolescents given the ethical and practical constraints?

In the first of 3 articles with overlapping subjects, Lou et al. reported on a highly heterogeneous group of 13 children and adolescents (one female) in 1984 (7). Eight subjects had expressive language disorders, and 11 were clinically diagnosed with attention deficit disorder (without hyperactivity, known as ADD in the nomenclature of the time), although the criteria for diagnosis were not specified for patients or controls. The 9 controls (3 female) were mostly siblings of patients, who were, on average, 2.4 y older. Subjects inhaled 370 MBq/L of ^{133}Xe for 1 min, and three 1-min scans followed. A single 17-mm-thick axial slice was analyzed qualitatively. All 11 patients with ADD were reported to exhibit hypoperfusion of frontal white matter, and 7 had hypoperfusion of the caudate. Six ADD subjects were rescanned 30 and 60 min after receiving MPH. All 6 were reported to show qualitatively increased flow in central regions, including the basal ganglia. In a subsequent article (8), data from 4 subjects described as having “pure ADHD” diagnosed by the criteria of the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III-R (9)) were added and combined

Received Jul. 30, 2002; revision accepted Aug. 21, 2002.

For correspondence or reprints contact: F. Xavier Castellanos, MD, NYU Child Study Center, 577 First Ave., New York, NY 10016.

E-mail: castef01@med.nyu.edu

with data from a pair of brothers included in the first article. Compared with the older sibling controls (8.2 y old vs. 11.9 y old), the pure-ADHD group showed significantly less normalized perfusion of the right striatum and significantly more normalized perfusion in the occipital and left sensorimotor/primary auditory regions. Thirteen children (4 with pure ADHD and 9 with ADHD plus central nervous system dysfunction) were administered MPH and were rescanned 30 and 60 min later. MPH increased perfusion significantly in the left striatum and in the periventricular region bilaterally in this mixed group. The 1990 report included 3 additional children with DSM-III-R ADHD and 6 additional control subjects (6). The results reinforced the prior conclusions. Children with ADHD had significantly decreased normalized perfusion in striatum and posterior periventricular regions, although the results were not broken down by side.

These pioneering reports had important limitations. Most of the patients had substantial neurologic or developmental impairment as well as ADHD. Even the 9 subjects with "pure ADHD," accrued over nearly a decade, included children with histories of serious neonatal complications, including cerebral ischemia with neonatal asphyxia, placenta previa with maternal hemorrhage, precipitous birth (8), measles encephalitis, or head trauma judged to be the "probable cause of brain dysfunction" (9,10). Siblings were included among patients as well as controls without taking into account the effects of violating the assumption of statistical independence. Controls were not well matched for sex and were even more problematically matched for age, which is related to rCBF (11). Analyses were limited to a single thick axial slice per subject, with limited resolution and substantial partial-volume effects.

In another early qualitative study, SPECT imaging was performed using ^{99m}Tc -hexamethylpropyleneamine oxime (HMPAO) on 54 medication-free children and adolescents with DSM-III-R ADHD and on 18 psychi-

atric controls (12). All subjects had a resting scan and an intellectual stress scan that consisted of 20 min of math problems. A nuclear medicine physician who was unaware of subject diagnoses scored the scans, although data on intrarater or interrater reliability were not reported. The authors reported that 65% of ADHD subjects "had significant prefrontal cortex deactivation in response to an intellectual challenge as compared with only 5% of those clinical patients who did not have ADHD or ADD ($P < 0.0001$)."
The apparent absence of methodologic rigor and the brevity of the report (which was published as a letter) have made it impossible to evaluate this otherwise intriguing result.

Gustafsson et al. examined 28 children with DSM-III-R ADHD who were participating in neurobiologic studies that included MRI, electroencephalography, and SPECT performed with 10 MBq/kg of ^{99m}Tc -HMPAO (13). The SPECT rCBF results were visually interpreted by a trained technician who was unaware of the subjects' degree of impairment, and a large number of individual regions of interest (ROIs) were placed manually on the basis of the external borders of each of 10 slices (although no information on reliabilities was provided). Seven of the 28 children were judged to have a suspected or clear abnormality in rCBF on visual examination. Factor analysis was performed on the quantitative ROI data, and 3 factors were reported. The first factor represented low rCBF in temporal regions and cerebellum relative to basal ganglia; this factor correlated positively with motor impairment on a neurodevelopmental examination. Right frontal and frontolateral hypoperfusion correlated significantly with the severity of behavior problems, and the number of minor physical anomalies correlated significantly and negatively with rCBF in bilateral frontal and frontolateral regions.

Recent SPECT studies have attempted to address some of the problems posed by the early work cited above. Spalletta et al. screened 40 con-

secutive patients with ADHD to select 8 children (sex unspecified) who had never been previously treated and who did not have any other comorbid psychiatric or neurologic disorders (14). The subjects were also required to have normal MRI and EEG findings. After injection of 10 MBq/kg of ^{99m}Tc -ECD, 36 ROIs were placed manually on axial sections. Seven of the 8 subjects demonstrated left DLPFC hypoperfusion and right DLPFC hyperperfusion (i.e., the opposite of Langleben et al. (5)). These asymmetries remained statistically significant even when corrected for multiple comparisons, and right DLPFC rCBF correlated significantly and positively with a clinician's masked rating of hyperactivity. Correlations with left DLPFC rCBF were not significant. Despite the care with which subjects were chosen, the authors concluded that their results must be considered cautiously because of the absence of healthy controls and particularly because of the small sample size.

Granted that conducting neurobiologic studies on children is difficult, most concerns about statistical power relate to the potential for type II errors because of too small a sample to demonstrate a true effect. However, as Rossi noted more than a decade ago (15): "When the average statistical power of an entire research literature is low, the veracity of even statistically significant results may be questioned, because the probability of rejecting a true null hypothesis may then be only slightly smaller than the probability of rejecting the null hypothesis when the alternative is true.... Thus, a substantial proportion of published significant results may be type I errors. When power is marginal (e.g., approximately 0.50), an inconsistent pattern of results may be obtained in which some studies yield significant results while others do not."

Fortunately, a recent study has successfully addressed many of the limitations of the literature. Kim et al. enrolled 32 right-handed boys aged 7–14 y who had DSM-IV ADHD, had never been medicated, and were free of all

comorbid psychiatric conditions including learning disorders (16). Standard validated ratings and neuropsychologic measures were obtained, and the patients underwent 2 resting SPECT scans with 555 MBq of ^{99m}Tc -HMPAO before and after 8 wk of treatment with clinically appropriate doses of MPH. Clinical response to treatment was operationally defined, and 20 of 32 patients (62.5%) were classified as responders. Images were analyzed with valid and reliable techniques, most of which were fully automated. Areas that increased in perfusion from pretreatment scan to posttreatment scan were considered significant only if the change exceeded 30% for an area with a diameter greater than 1 cm. Analyses limited to the clinical responders showed that most (64%) had robust perfusion increases in the caudate nuclei and frontal lobes. Thalamus and temporal lobe perfusion also increased in many responders. Perfusion increases were far greater in the right hemisphere than in the left (28 vs. 10). Confirmatory analyses using all subjects and automated ROIs (except for subcortical ROIs, which were drawn manually with high interrater and intrarater reliabilities) also showed robust increases in perfusion after treatment in bilateral DLPFC, primarily right caudate, and right thalamus. The limitations of this study included the absence of a control group, which is less problematic in this case than in most other studies because primary analyses took place before and after treatment. The primary limitations that should be addressed in future work include the lack of appropriate activation paradigms and the lack of anatomic MRI images to provide better individual landmarks.

So, what can we conclude?

First, the excellent report by Kim et al. (16) truly replicates and extends the pioneering if problematic studies of Lou et al. (6–8). Despite the problems inherent in scanning during rest (a state that can range from extreme stress [for a hyperactive child who is attempting to remain still] to somnolence [for other subjects]), these authors provided convincing evidence that effective treatment with MPH is associated

with increases in perfusion in the prefrontal cortex and caudate nucleus. Because their initial scans preceded any treatment with medications, there is no need to worry about withdrawal or tolerance effects. At the same time, the lack of an activation paradigm makes it impossible to integrate their results with those of Langleben et al. (1,5).

Second, attempts to obtain SPECT scans of healthy pediatric controls may not be worth the effort. Even in those rare institutions in which these procedures are deemed to constitute minimal risk (which, incidentally, is a defensible judgment in my opinion), the practical reality is that it is exceedingly difficult to recruit such subjects. Thus, either subjects are recruited who may not be optimal controls, by being siblings, for example (6–8), or the groups are too small to yield statistically meaningful results (1,5).

Third, studies must be designed to yield adequate statistical power. This conclusion may seem counterintuitive. After all, is it not better to conduct exploratory studies with a few subjects than no studies at all? Given the extraordinary effort required by all participants (not least the children and parents), I would argue that underpowered and inadequately controlled studies have a greater potential to confuse than to enlighten us (8). In this regard, investigators need to be specially cautious in studying interhemispheric asymmetries, which are particularly prone to yielding low measurement reliabilities (17) and, as noted above, seem to yield diametrically opposite results (5,13).

Fourth, I echo the conclusion of Langleben et al. (1) that future studies of rCBF are best conducted using functional MRI. Techniques such as near-infrared spectroscopic imaging may also be useful alternatives for some applications (18,19). However, PET and SPECT will remain indispensable as the primary means of interrogating the neuropharmacology of the living human brain (20–22), and future studies in children and adolescents with ADHD should focus on continued exploration of central catecholamines by

quantifying dopamine transporter densities (23–25); dopamine receptors (21,26); and basal-, stimulant-, and magnetic stimulant-evoked dopamine release (27–29).

F. Xavier Castellanos, MD

*NYU Child Study Center
New York, New York*

REFERENCES

- Langleben DD, Acton PD, Elman I, et al. Effects of methylphenidate treatment discontinuation on cerebral blood flow in prepubescent boys with attention deficit hyperactivity disorder. *J Nucl Med*. 2002;43:1624–1629.
- Bell RD, Alexander GM, Schwartzman RJ. Methylphenidate decreases local glucose metabolism in the motor cortex. *Pharmacol Biochem Behav*. 1983;18:1–5.
- Devous MD Sr, Trivedi MH, Rush AJ. Regional cerebral blood flow response to oral amphetamine challenge in healthy volunteers. *J Nucl Med*. 2001;42:535–542.
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 1994.
- Langleben DD, Austin G, Krikorian G, Ridlehuber HW, Goris ML, Strauss HW. Interhemispheric asymmetry of regional cerebral blood flow in prepubescent boys with attention deficit hyperactivity disorder. *Nucl Med Commun*. 2001;22:1333–1340.
- Lou HC, Henriksen L, Bruhn P. Focal cerebral dysfunction in developmental learning disabilities. *Lancet*. 1990;335:8–11.
- Lou HC, Henriksen L, Bruhn P. Focal cerebral hypoperfusion in children with dysphasia and/or attention deficit disorder. *Arch Neurol*. 1984;41:825–829.
- Lou HC, Henriksen L, Bruhn P, Borner H, Nielsen JB. Striatal dysfunction in attention deficit and hyperkinetic disorder. *Arch Neurol*. 1989;46:48–52.
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 3rd ed. Washington, DC: American Psychiatric Association; 1987.
- Lou HC. Cerebral glucose metabolism in hyperactivity [letter]. *N Engl J Med*. 1991;324:1216–1217.
- Barthel H, Wiener M, Dannenberg C, Bettin S, Sattler B, Knapp WH. Age-specific cerebral perfusion in 4- to 15-year-old children: a high-resolution brain SPECT study using ^{99m}Tc -ECD. *Eur J Nucl Med*. 1997;24:1245–1252.
- Amen DG, Paldi JH, Thisted RA. Brain SPECT imaging [letter]. *J Am Acad Child Adolesc Psychiatry*. 1993;32:1080–1081.
- Gustafsson P, Thernlund G, Ryding E, Rosen I, Cederblad M. Associations between cerebral blood-flow measured by single photon emission computed tomography (SPECT), electro-encephalogram (EEG), behaviour symptoms, cognition and neurological soft signs in children with attention-deficit hyperactivity disorder (ADHD). *Acta Paediatr*. 2000;89:830–835.
- Spalletta G, Pasini A, Pau F, Guido G, Menghini L, Caltagirone C. Prefrontal blood flow dysregulation in drug naïve ADHD children without structural abnormalities. *J Neural Transm*. 2001;108:1203–1216.
- Rossi JS. Statistical power of psychological re-

- search: what have we gained in 20 years? *J Consult Clin Psychol.* 1990;58:646–656.
16. Kim BN, Lee JS, Cho SC, Lee DS. Methylphenidate increased regional cerebral blood flow in subjects with attention deficit/hyperactivity disorder. *Yonsei Med J.* 2001;42:19–29.
 17. Arndt S, Cohen G, Alliger RJ, Swayze VW II, Andreasen NC. Problems with ratio and proportion measures of imaged cerebral structures. *Psychiatry Res.* 1991;40:79–89.
 18. Barbour RL, Gruber HL, Pei Y, Zhong S, Schmitz CH. Optical tomographic imaging of dynamic features of dense-scattering media. *J Opt Soc Am A Opt Image Sci Vis.* 2001;18:3018–3036.
 19. Franceschini MA, Toronov V, Filiaci ME, Gratton E, Fantini S. On-line optical imaging of the human brain with 160-ms temporal resolution. *Optics Express.* 2000;6:49–57.
 20. Volkow ND, Ding YS, Fowler JS, et al. Is methylphenidate like cocaine? Studies on their pharmacokinetics and distribution in human brain. *Arch Gen Psychiatry.* 1995;52:456–463.
 21. Volkow ND, Wang GJ, Fowler JS, et al. Effects of methylphenidate on regional brain glucose metabolism in humans: relationship to dopamine D₂ receptors. *Am J Psychiatry.* 1997;154:50–55.
 22. Volkow ND, Wang GJ, Fowler JS, et al. Therapeutic doses of oral methylphenidate significantly increase extracellular dopamine in the human brain. *J Neurosci.* 2001;21:U1–U5.
 23. Dougherty DD, Bonab AA, Spencer TJ, Rauch SL, Madras BK, Fischman AJ. Dopamine transporter density is elevated in patients with attention deficit hyperactivity disorder. *Lancet.* 1999;354:2132–2133.
 24. Krause KH, Dresel SH, Krause J, Kung HF, Tatsch K. Increased striatal dopamine transporter in adult patients with attention deficit hyperactivity disorder: effects of methylphenidate as measured by single photon emission computed tomography. *Neurosci Lett.* 2000;285:107–110.
 25. van Dyck CH, Quinlan DM, Cretella LM, et al. Unaltered dopamine transporter availability in adult attention deficit hyperactivity disorder. *Am J Psychiatry.* 2002;159:309–312.
 26. Ilgin N, Senol S, Gucuyener K, Gokcorna N, Atavci S, Sener S. Is increased D₂ receptor availability associated with response to stimulant medication in ADHD. *Dev Med Child Neurol.* 2001;43:755–760.
 27. Koepp MJ, Gunn RN, Lawrence AD, et al. Evidence for striatal dopamine release during a video game. *Nature.* 1998;393:266–268.
 28. Strafella AP, Paus T, Barrett J, Dagher A. Repetitive transcranial magnetic stimulation of the human prefrontal cortex induces dopamine release in the caudate nucleus. *J Neurosci.* 2001;21:RC157.
 29. Volkow ND, Wang GJ, Fowler JS, et al. Relationship between blockade of dopamine transporters by oral methylphenidate and the increases in extracellular dopamine: therapeutic implications. *Synapse.* 2002;43:181–187.

