

Broken Brains or Flawed Studies? A Critical Review of ADHD Neuroimaging Research

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A review of over thirty neuroimaging studies on children diagnosed with Attention Deficit/Hyperactivity Disorder (ADD, ADHD) by Giedd, Blumenthal, Molloy, and Castellanos (2001) is organized around tables listing the main findings of studies using different types of neuroimaging. Like most researchers in this field, Giedd et al. conclude that the evidence supports the involvement of right frontal–striatal circuitry with cerebellar modulation in ADHD. However, Giedd et al. do not report on a confounding variable of crucial interest in this field of research — whether subjects had been previously treated with stimulants or other psychotropic drugs. In the present paper, we have redone five of the tables from the Giedd et al. review, adding information on the subjects' prior medication exposure, as reported in the individual studies included in the review. We found that most subjects diagnosed with ADD or ADHD had prior medication use, often for several months or years. This substantial confound invalidates any suggestion of ADHD-specific neuropathology. Moreover, the few recent studies using unmedicated ADHD subjects have inexplicably avoided making straightforward comparisons of these subjects with controls.

Some of the most often cited literature in support of the medication of children with stimulants such as amphetamine or methylphenidate comes from research utilizing modern neuroimaging techniques. Researchers in this field use several different imaging modalities to look for anatomical and physiological differences in the brains of children diagnosed with Attention Deficit Hyperactivity Disorder (ADHD). Images published in scientific jour-

nals and in the media supposedly show abnormalities (or differences) in the brains of children diagnosed with ADHD. For clinicians, families, and the public who are wondering whether or not the ADHD diagnosis points to an underlying disease, and whether its treatment requires drugs, the neuroimaging research and its accompanying images can be deciding factors.

Researchers have long tried to discover biological lesions in children diagnosed with ADHD. Principally using neuropsychological studies, pharmacological manipulations of brain chemistry, and attempts to find biochemical correlates of the ADHD behavior cluster, investigators have produced "a huge, diverse, and often conflicting literature," but "no biological abnormality has ever been specifically and unambiguously linked to the disorder by conventional techniques" (Baumeister and Hawkins, 2001, pp. 3–4). However, in contrast to generally negative assessments of conventional research, assessments of the neuroimaging studies have been more positive. For example, a review by Faraone and Biederman concluded that "taken together, the brain imaging studies fit well with the idea that dysfunction in the frontosubcortical pathways occurs in ADHD" (cited in Baumeister and Hawkins, p. 4).

Similarly, Giedd, Blumenthal, Molloy, and Castellanos (2001) summarized over thirty ADHD neuroimaging studies. Although Giedd et al. note that few findings have been replicated and most studies have inadequate statistical power, they conclude that, "Taken together, the results of the imaging and neuropsychological studies suggest right frontal–striatal circuitry involvement in ADHD with a modulating influence from the cerebellum" (p. 44). Most of Giedd et al.'s review consists of six tables summarizing results from studies using different modalities to compare the brains of "ADHD" children to the brains of "normal" children.¹ Computerized tomography (CT) and magnetic resonance imaging (MRI) are used to image various neuroanatomical structures. Images of glucose brain metabolism and cerebral blood flow are obtained using single photon emission computerized tomography (SPECT) and positron emission tomography (PET). In each table, Giedd et al. identify the studies that have employed that particular technique, report on variables such as numbers of patients and controls, and summarize the key findings.

Although positive findings on neuroimaging studies of psychiatric disorders, including ADHD, are usually given wide coverage in scientific publications and the mass media, the fact remains that this body of research has not provided support for a specific "biological basis" for ADHD. This is well shown by Baumeister and Hawkins (2001) who report, "inconsistencies

¹Giedd et al. (2001) presented six tables. Since one of their tables summarized studies examining stimulant response we have not included it in our review because we are primarily interested in studies investigating differences between ADHD and control subjects. Thus while the Giedd et al. review has six tables we only present five tables in our study.

among studies raise questions about the reliability of the findings” (p. 2). These researchers noted that “the complexity of many of these studies and [the] methodologic variation among them” make it “difficult to discern whether these inconsistencies are apparent or real” (p. 4). Baumeister and Hawkins therefore isolated specific reported structural and functional abnormalities and examined the congruence among studies with respect to each. “The principal conclusion is that the neuroimaging literature provides little support for a neurobiological etiology of ADHD” (p. 4). Writing, for instance, about the tendency for studies to find decreases in the size and activity of the frontal lobes, Baumeister and Hawkins summarize that

Even in this instance, however, the data are not compelling. The number of independent replications is small, and the validity of reported effects is compromised by a lack of statistical rigor. For example, several of the major functional imaging studies failed to employ standard statistical controls for multiple comparisons. This means that many of the reported findings are almost certainly spurious. Moreover, considering the likely existence of bias toward reporting and publishing positive results, the literature probably overestimates the occurrence of significant differences between subjects with ADHD and control subjects. (p. 8, references omitted)

In addition, virtually all researchers in this field acknowledge that no brain scan can currently detect anomalies in any given individual diagnosed with a primary mental disorder, nor can it help clinicians to confirm such a diagnosis. In the case of ADHD, for example, Giedd et al. (2001) conclude unequivocally that:

MRI is not currently diagnostically useful in the routine assessment or management of ADHD The brain imaging studies . . . are not currently specific enough to be used diagnostically If a child has no symptoms of ADHD but a brain scan consistent with what is found in groups of ADHD, treatment for ADHD is not indicated. Therefore, at the time of this writing, clinical history remains the gold standard of ADHD diagnosis. (p. 45)

Given this crucial limitation of the neuroimaging data, what is its utility in ADHD? Giedd et al. (2001) believe that “. . . may help to uncover the core neuropathology of the disease . . .” (p. 45). However, Giedd et al. do not provide in their tables information on a variable with undoubtedly weighty consequences on the interpretation of such research: whether or not subjects diagnosed with ADD or ADHD had a prior use of stimulant or other psychotropic medications. For investigators directly or not directly involved in neuroimaging research, information on the prior use of medication in the experimental subjects is simply too important to ignore. This is because an astronomical number of experimental and clinical studies on animals and humans find that almost every studied psychotropic drug has been consistently shown to produce subtle or gross, transient or persistent effects on the

functioning and structure of the central nervous system. The very definition of "psychotropic" (acting on the central nervous system to produce changes in thinking, feeling, and behaving) presumes such effects. The effects vary depending on several factors, typically including dose and duration of use, as well as others such as the general state of the organism.

Sufficient evidence exists to view prior use of stimulants as a confounding factor in ADHD neuroimaging research. Research with rodents has documented that dopamine depletion is one of the intermediate and long-term effects of methylamphetamine and d-amphetamine treatment, but results about methylphenidate's effects have been mixed (Breggin, 1999; Wagner, Schuster, and Seiden, 1981; Wan, Lin, Huang, Tseng, and Wong, 2000; Yuan, McCann, and Ricaurte, 1997). However, several studies have confirmed long-term pathology. In a study of young adult rats treated with methylphenidate twice daily for four days, there was evidence of "attenuated presynaptic striatal dopamine function" 14 days after the end of treatment (Sproson, Chantrey, Hollis, Marsden, and Fonel, 2001). In another experiment, methylphenidate was administered for two weeks to very young and older rats and the researchers found the density of dopamine transporters in the striatum (but not in the midbrain) to be "significantly reduced after early methylphenidate administration (by 25% at day 45), and this decline reached almost 50% at adulthood (day 70), that is, long after termination of the treatment" (Moll, Hause, Ruther, Rothenberger, and Huether, 2001, RC 121). Based on these findings Moll et al. (2001) concluded that "long-lasting changes in the development of the central dopaminergic system [are] caused by the administration of methylphenidate during early juvenile life" (p. 15).

There have been several important studies on the effects of stimulants in humans. Volkow et al. (2001) utilized PET scans to look for functional changes following exposure to methylphenidate in healthy male subjects with no known psychiatric history and no past history of drug or alcohol abuse. Each subject underwent one scan 60 minutes after orally ingesting placebo and a second scan 60 minutes after orally ingesting 60 mg of methylphenidate. Methylphenidate induced large changes in the dopamine volume in the striatum (but not in the cerebellum). Volkow et al. (2001) conclude: "These results provide direct evidence that oral methylphenidate significantly increases extracellular dopamine concentration in the human brain" (p. 3). If changes in the concentration of dopamine persist, however, they are likely to desensitize target areas to dopamine's effects, leading to a loss of dopamine receptors (downregulation). In this regard, in another study using SPECT to estimate striatal dopamine (D_2) receptor availability, non-drug treated children diagnosed with ADHD were scanned before and three months after methylphenidate treatment (Ilgin, Senol, Gucuyener, Gokcora,

and Sener, 2001). The investigators found “D₂ availability reduced significantly as a function of methylphenidate therapy in patients with ADHD in all four regions of the striatum.” More to the point, the authors conclude: “The effect of methylphenidate on D₂ receptor levels in patients with ADHD is similar to that observed in healthy adults: a downregulation phenomenon within 0 to 30%” (p. 755).

The stimulant-specific findings briefly reviewed above illustrate the general point that, when striving to establish whether cerebral pathology or dysfunction is associated with a given psychiatric diagnosis, or to some symptoms or signs making up the criteria for a given diagnosis, it is critical to be able to rule out the probable impact on the brain of prior psychotropic drug use. This is especially the case in studies involving children, as significant changes occur in the number and patterning of brain cells well into adolescence (Vitiello, 1998). The clearest way to rule out such an impact is to select patients who have had no exposure to psychotropic medications, and to compare these patients to normal controls without the diagnosis.

In the search for biological causes of behavior disorders that characterizes psychiatric research — and perhaps as reassurance for the safety of the widespread and long-term use of prescribed psychotropics — investigators have been prone to treat the variable of prior psychotropic drug use with less objectivity than its importance requires. They do so by “mentioning” this important variable but downplaying its impact, or by mentioning the variable but not discussing its impact, or by not mentioning it at all. These strategies are not used solely by authors who evaluate neuroimaging findings positively, as even Baumeister and Hawkins’ (2001) highly critical review does not raise the issue of medication status of ADHD subjects in any of the thirty-one studies reviewed.

The question thus arises: How do researchers treat the confounding variable of prior drug exposure? Further, to what extent does this variable need to be considered in studies used to support the belief that cerebral pathology underlies the ADHD diagnosis in children? To answer these questions, we retrieved all the reports cited in Giedd et al.’s (2001) review and extracted from each the relevant information. Below we present the same tables that Giedd et al. present, with additional columns indicating how many ADHD patients in each study were identified as having prior history of stimulant or other psychotropic drug use. Occasionally, we summarize or comment on some of the studies, highlighting what we judged to be noteworthy aspects or failings not raised by Giedd et al. Finally, we discuss two individual neuroimaging studies published since the Giedd et al. review, one of which made newspaper headlines to the effect that a biological basis of ADHD had been established.

Findings

Computerized Tomography

The six studies listed in Table 1 used computerized tomography (CT) to measure various regions of the cortex. Computerized tomography scanning was one of the first non-invasive brain imaging technologies developed, and the studies in Table 1 were all conducted before 1986. Only three studies included a control group. Four did not report the medication history of the patients, and in one study unclear reporting prevented making this determination.

Bergstrom and Bille (1978). The authors examined 50 children diagnosed with Minimal Brain Dysfunction (one of the immediate precursor terms of ADD/ADHD). Bergstrom and Bille reported various abnormalities in 15

Table 1
Computerized Tomography Studies of Attention Deficit/Hyperactivity Disorder,
Modified from Giedd et al. (2001)

<i>Study</i>	<i>Patients</i>	<i>Controls</i>	<i>Findings</i>	<i>Medication History and Status of Patients</i>
Bergstrom and Bille (1978)	46 (minimal brain dysfunction)	None	33% had "abnormal" ventricles	Not reported
Thompson et al. (1980)	44 (minimal brain dysfunction)	None	4.5% abnormal	Not reported
Caparulo et al. (1981)	14 (DSM-III ADD)	None	28% abnormal	Not reported
Reiss et al. (1983)	7 (DSM-III ADD)	19 (neurological patients)	VBR larger	Unclear reporting
Shaywitz et al. (1983)	35 (DSM-III ADD)	27	None	Not reported
Nasrallah et al. (1986)	24 (hyperkinetic/minimal brain dysfunction)	27	None	100% previously treated

Note: Tables 1–5 are from J.N. Geidd, J. Blumenthal, E. Molloy, and F.X. Castellanos (2001). *Brain Imaging of Attention Deficit/Hyperactivity Disorder*. In J. Wassertein, and L.E. Wolf, and FF Lefever (Eds.), *Adult Attention Deficit Disorder: Brain Mechanisms and Life Outcomes* (Vol. 931, pp. 33–49) New York: New York Academy of Sciences. Copyright © 2001 by New York Academy of Sciences., U.S.A. Adapted with permission. To the original tables, we have added an additional column (in bold) containing information on the medication history of the subjects.

cases, and provided detailed descriptions of three children, each manifesting "hypotonia, traces of persisting neonatal reflexes, abnormal associated movements and motor and visuomotor incoordination after sensorimotor stress" (pp. 380–382). Case #1 was an 8-year old boy who at birth weighed merely 1680 grams, had a one-minute APGAR score of 4, and suffered from perinatal asphyxia. On CT, he showed dilation of the left lateral ventricle and fissure of sylvius (p. 380). Case #2 was an 11-year old boy whose CT showed dilation of the third ventricle. Case #3 was a 12-year old boy who, at age seven, ". . . dribbled a lot" (p. 382). He also had "a huge arachnoid cyst in the left temporal region" (p. 382). The children in this study have obvious neurological problems — some of which are suggestive of cerebral palsy, according to Shaywitz and colleagues (1983) — that go far beyond hyperactivity and inattention in typical classroom situations.

Shaywitz, Shaywitz, Byrne, Cohen, and Rothman (1983). As Table 1 shows, under the column "Findings" Giedd et al. (2001) reported "None." This is somewhat misleading, as Shaywitz et al. (1983) actually did report finding *no difference* between the ADHD group versus controls. These authors stated unambiguously: "Our findings suggest that when quantitative techniques, contrast populations, and blind analysis of CTs are employed, CTs of children with ADD are indistinguishable from contrasts. It further suggests that if anatomic abnormalities are present in ADD, they are not discernible using present-day CT technology" (p. 1502).

Thompson, Ross, and Horwitz (1980). The brains of 44 children with minimal brain dysfunction and learning disabilities were scanned. Forty-two of these were normal and two (4.5%) exhibited obvious organic pathology. In the first, "Delta CT examination of the brain revealed a focal area of decreased density deep in the right occipital region suggesting localized gliosis and atrophy that may have been ischemic or post-inflammatory in nature" (p. 49). In the second, agenesis of the corpus callosum was observed. Thompson et al. concluded: "Most children evaluated with computed tomography can be expected to have normal scans. Little additional information will be provided from CAT scanning after neurologic and psychomotor testing" (p. 51).

Reiss et al. (1983). This study compared 20 psychiatric patients, an unknown number of which had an ADD diagnosis, to controls. Thirteen of the patients had diagnoses ranging from borderline personality disorder to schizophrenia, including separation anxiety and Tourette's syndrome. Eleven patients had had one or more psychiatric hospitalizations and ten had been treated with psychoactive medications (including one with diphenylhydantoin for three months, and another with thioridazine for five years). The authors do not report how many patients were diagnosed with ADD, nor how many of these were treated with medication.

Nasrallah et al. (1986). Again, under "Findings," Giedd et al. (2001) report "None," but this is incorrect. Nasrallah and colleagues measured four different physical characteristics: lateral ventricular size, third ventricle size, sulcal widening, and cerebellar atrophy. They found statistically significant differences for sulcal widening between patients and controls. In addition, they reported that 25% of the patients had cerebellar atrophy, versus only 3.8% of the controls. However, Nasrallah et al. do not interpret their results to support the hypothesis of ADHD-related neuropathology: ". . . since all of the hyperkinetic/minimal brain dysfunction patients had been treated with psychostimulants, cortical atrophy may be a long-term adverse effect of this treatment" (p. 245). Nasrallah et al. (1986) also took the bold step of suggesting that future studies should investigate whether stimulants result in structural brain changes. It is also important to mention that seven of the 24 patients had a history of alcohol abuse.

Magnetic Resonance Imaging

The fourteen studies listed in Table 2 all used magnetic resonance imaging (MRI). Two of the studies did not report on the issue of prior medication use by patients, and one did not report clearly. The eleven remaining studies involved a total of 259 patients and 271 controls, with 247 of the patients (95%) having had prior medication use. Only two studies actually discussed prior drug use (Castellanos et al., 1994, 1996) but neither devoted more than two sentences to the topic.

It should be mentioned that four of the articles in Table 2 (Berquin et al., 1998; Casey et al., 1997; Castellanos et al., 1994, 1996) used the same pool of experimental subjects (or a portion of). Furthermore, these subjects were originally part of yet another study, which compared methylphenidate to dextroamphetamine in children diagnosed with ADHD (Elia, Borcharding, Rapoport, and Keysor, 1991).

Mostofsky, Reiss, Lockhart, and Denckla (1998). In this study, seven of the 12 boys diagnosed with ADHD had a prior history of psychotropic drug use. No discussion appears in this article about the potential problems with such use.

Castellanos et al. (1994). According to the authors, "Fifty-three of [57 ADHD children] had been previously treated with psychostimulants, and 56 participated in a 12-week double-blind trial of methylphenidate, dextroamphetamine and placebo, as described elsewhere" (p. 608). In the discussion section of the paper the authors caution: "Because almost all (93%) of the subjects with ADHD had been exposed to stimulants, we cannot be certain that our results are not drug related. A replication study with stimulant-naïve boys with ADHD is under way" (p. 614). This probably refers to the study by Castellanos et al. (2002) discussed below in detail.

Table 2

Magnetic Resonance Imaging Studies of Attention Deficit/Hyperactivity Disorder,
Modified from Giedd et al. (2001)

<i>Study</i>	<i>Patients/ Controls</i>	<i>Findings</i>	<i>Medication History and Status of Patients</i>
Hynd et al. (1990)	10/10	Normal R>L anterior frontal width reversed in ADHD	100% previously treated
Hynd et al. (1991)	7/10	Anterior and posterior corpus callosum areas smaller in ADHD	100% previously treated
Hynd et al. (1993)	11/11	L caudate wider than R in normal subjects; reversed in ADHD	100% previously treated
Giedd et al. (1994)	18/18	Rostrum, rostral body of corpus callosum smaller in ADHD	Not reported, but patients recruited from day treatment program at NIMH
Castellanos et al. (1994)	50/48	R caudate smaller and loss of normal R> L caudate asymmetry in ADHD	100% treated for 12 weeks prior to scans (78% longer treatment)
Semrud-Clikeman et al. (1994)	15/15	Splenium significantly smaller in ADHD group (posterior corpus callosum)	100% previously treated
Baumgardner et al. (1996)	13/27	Rostral body of corpus callosum smaller in ADHD	Not reported
Aylward et al. (1996)	10/11	Globus pallidus smaller in ADHD (significant on left)	100% previously treated, all on medication at time of scanning
Castellanos et al. (1996)	57/55	Total cerebral volume, caudate, globus pallidus smaller in ADHD	93% previously treated
Filipek et al. (1997)	15/15	Caudates and R anterior superior white matter smaller in ADHD; posterior white matter volumes decreased only in stimulant non-responders	100% treated for at least six months prior to scans
Casey et al. (1997)	26/26	Performance on response inhibition tasks correlate with anatomical measures of front striatal circuitry, particularly on right	88.5% previously treated
Mataro et al. (1997)	11/19	Larger R caudate at time of experiment	No subject was receiving medication
Berquin et al. (1998)	46/47	Smaller posterior inferior cerebellar vermal volume	100% previously treated, 100% on medication during scanning
Mostofsky et al. (1998)	12/23	Smaller posterior inferior cerebellar vermal volume	58% previously treated with MPH, on medication at time of scanning

Baumgardner et al. (1996). All of the ADHD children in this study were also diagnosed with Tourette's syndrome, making them atypical of the children being diagnosed with ADHD in North America. No medication history is reported.

Single Photon Emission Tomography

The three articles cited in Table 3 (Lou, Henriksen, and Bruhn, 1984, 1990; Lou, Henriksen, Bruhn, Borner, and Neilson, 1989), utilized single photon emission tomography (SPECT) scans. In the earliest study (Lou et al. 1984), six of the 11 ADHD patients had a history of prior medication. In their follow-up, Lou et al. (1989) increased the patient sample and divided it into two groups. The first group of six children was classified as "ADHD" while the second group of 13 children was classified as "ADHD plus" because its children presented additional conditions. For instance, three of the children had IQs between 50 and 70, five had motor problems such as apraxia, and nine had various forms of dysphasia. Out of the 19 children in the two ADHD groups, 13 (68%) had a prior history of medication with methylphenidate.

Table 3
Single Photon Emission Tomography Studies Using Inhaled ¹³³Xenon,
Modified from Giedd et al. (2001)

<i>Study</i>	<i>Patients</i>	<i>Control Subjects</i>	<i>Findings</i>	<i>Medication History and Status</i>
Lou et al. (1984)	N = 13 11 w/mixed ADD; 8 "dysphasic"	N = 9, mostly siblings (3F)	Frontal hypoperfusion in all ADD; caudate hypoperfusion in 7/11 w/ADD; central perfusion increased in 6/6 after methylphenidate (MPH)	54% treated with 10 to 30 mg daily MPH, discontinued one week before scanning
Lou et al. (1989)	N = 6 "pure ADHD"; N = 13 ADHD plus other CNS dysfunction; 13 (includes 4 "pure ADHD") scanned pre- and post- MPH [total subjects: 19]	N = 9	"Pure ADHD": decreased R striatal perfusion, increased occipital and L sensorimotor and auditory regions; MPH significantly increased L striatal perfusion	68% treated in "pure ADHD" group, 69% treated in other groups
Lou et al. (1990)	N = 9 "pure ADHD" (2F); N = 8 ADHD plus dysphasia (0 F)	15 contrast subjects (6 new, 7F)	Normalized striatal and posterior periventricular perfusion decreased in ADHD and ADHD plus; occipital perfusion increased in "pure ADHD"	Not reported

These studies sought to answer two questions: (1) Is there a difference in the brains of ADHD children compared to controls? and (2) What is the effect of methylphenidate on the brains of ADHD children? The ADHD children in these studies who had been receiving methylphenidate discontinued their medication for one week prior to the study, an event which complicates answering both questions. Regarding the first question, any difference in the brains of the ADHD versus control subjects could be attributed to the medication. Regarding the second question, Lou et al. (1989) claimed they were examining the effect of methylphenidate on the brains of ADHD children. It would be more correct to say that the study examined the effect of methylphenidate on a group of children who had first been treated with methylphenidate (for an indeterminate time), then taken off the drug for a week of withdrawal, and then re-medicated. Thus, changes seen in the striatum of these patients could be attributed to either long-term medication use, withdrawal effects, the effect of retreatment, or the entire sequence of treatment, withdrawal and re-treatment.

In the third, and most recent study, Lou et al. (1990) included 24 children but only nine were placed in the "pure" ADHD group. According to the authors: "In retrospect, 11 of the children had a history of adverse, but mostly poorly described, antenatal and perinatal events such as vaginal haemorrhage, pre-clampsia, weak prenatal cardiac sounds, prolonged labor, and perinatal asphyxia. In 2 cases the probable cause of brain dysfunction was head trauma and measles encephalitis . . ." (p. 8). Despite these obvious confounds, data from these 11 children's scans were not partitioned into a different group for more specific comparisons with controls or with the other ADHD subjects. Lou et al. (1990) do not mention prior medication use in the patients although it appears that some of them also participated in the previous studies (Lou et al., 1984, 1989).

Positron Emission Tomography of Glucose Cerebral Metabolism

The three articles in Table 4 were all published by Alan Zametkin's research group. The earliest study (Zametkin et al., 1990) compared cerebral glucose metabolism between normal adults and adults with a history of hyperactivity in childhood. However, several authors (DeGrandpre, 1999; Reid, Maag, and Vasa, 1994) have noted problems with this study. In particular, control females have a higher rate of cerebral glucose metabolism than control males, a finding that accounts entirely for the difference that Zametkin found between the ADHD patients and controls.

Zametkin et al. (1993) used ten adolescents diagnosed with ADHD, seven of whom had a history of prior medication use. Ernst et al. (1994) extended the 1993 study by adding ten more ADHD subjects, eight with a history of

Table 4
 Positron Emission Tomography Studies of Glucose Cerebral Metabolism,
 Modified from Giedd et al. (2001)

Study	Patients	Control Subjects	Findings	Medication History and Status of Patients
Zametkin et al. (1990)	25 adults (7F)	50 adults (22F)	Global cerebral metabolism 8% lower in ADHD, with absolute significant decreases in 30 of 60 regions. Normalized differences all on left; superior posterior frontal, medial and anterior frontal and rolandic	None previously treated
Zametkin et al. (1993)	10 adolescents (3F)	10 adolescents (3F; 7 were siblings of ADHD probands, only 2 in this study)	No differences in global metabolism. Normalized metabolism decreased significantly in 6 regions and increased in 1	70% previously treated, 100% medication free for 3 weeks prior to scan
Ernst et al. (1994)	20 adolescents (6F); includes all subjects from study above	19 adolescents (5F)	No group differences in global metabolism; metabolism significantly lower in 6 ADHD females than controls of either sex or ADHD boys	80% previously treated, 100% medication free for 2 weeks prior to scan

Note: one unpublished study omitted

prior medication. The main finding of these studies was that in *adolescents* there was no difference in global brain metabolism between the ADHD patients and controls, unlike the findings in *adults* by Zametkin et al. (1990). Ernst et al. (1994) provide a list of reasons why a difference between the adolescent ADHD patients and controls might not have been detected; yet the authors never discuss the possibility that their results correctly show that there is *no difference between ADHD and control brains in adolescents*. Ernst et al. (1994) also looked at gender effect and did find a difference between the female ADHD patients and female controls, but not between male patients and male controls.

Functional Imaging Studies of Cerebral Blood Flow in ADHD

With the exception of Amen and Paldi (1993), all articles in Table 5 were published after 1995, when it must have been clear to any researcher in the field that the issue of prior medication use was a variable that needed to be

Table 5
 Functional Imaging Studies of Cerebral Blood Flow in ADHD,
 Modified from Giedd et al. (2001)

<i>Study</i>	<i>Method</i>	<i>Patients</i>	<i>Controls</i>	<i>Findings</i>	<i>Medication History and Status of Patients</i>
Amen and Paldi (1993)	[^{99m} Tc] SPECT at rest and during math stress test	54 (8F)	18 (8F)	Prefrontal deactivation significantly greater in ADHD (65% vs 5%)	Unclear on prior history; medication free during scan
Sieg et al. (1995)	[¹²³ I] SPECT at rest	10 (3F)	6 (1F)	L (vs R) blood flow reduced in frontal and parietal regions in ADHD	Not reported
Teicher et al. (2000)	T2 relaxation times with MRI	11 children	6	Optimal dose methylphenidate significantly increased R caudate blood flow, decreased R frontal cortical flow	See discussion and footnotes
Schweitzer et al. (2000)	[¹⁵ O]water PET, neural activation related to working memory	6 male adults	6 male adults	Task-related changes in rCBF in men without ADHD were more prominent in the frontal and temporal regions, but rCBF changes in men with ADHD were more widespread and primarily located in the occipital regions	33% previously treated with MPH but had been medication free for 2 and 10 years respectively
Bush et al. (1999)	fMRI, counting stroop	8 adults	8 adults	ADHD subjects failed to activate the anterior cingulate cognitive division (ACCd) during the counting stroop. ACCd activity higher in control group. ADHD subject did activate a frontostriatal-insular network, indicating ACCd hypoactivity was not caused by globally poor neuronal responsiveness.	100% previously treated with various ADHD medications. 48 hour washout prior to scans
Rubia et al. (1999)	fMRI	7 males	9 males	ADHD adolescents showed lower power of response in the right medial prefrontal cortex during a stop task and a motor timing task, and in the R inferior pre-frontal cortex and L caudate during the stop task.	Not reported
Vaidya et al. (1998)	fMRI, two go/no-go tasks with and without drug	10 male children	6 male children	ADHD impaired inhibitory control on two tasks. Off-drug frontal-striatal activation during response inhibition differed between ADHD and healthy children.	Patients had a 1 to 3 year history of medication

examined. Nonetheless, four of the seven articles do not mention whether the patients had prior medication use.

Amen and Paldi (1993). Giedd et al. (2001) refer to a one page abstract by Amen and Paldi (1993). This study was later expanded upon in a more detailed report (Amen and Carmichael, 1997), which is what we discuss here. The primary purpose of this study was to determine if there were similarities between reported PET and QEEG (quantified computerized EEG) findings in children diagnosed with ADHD. Because of dangers involved in exposing individuals to radioactive substances, the control subjects were patients from a psychiatric outpatient clinic who were diagnosed with a psychiatric condition but not with ADHD. Amen and Carmichael (1997) state that both ADHD and control patients were "medication free," but no other details are provided.

Amen, who is prominent in the ADHD marketing enterprise, has received significant media attention based on his theory that there are six types of ADHD, each of which has distinctive behavioral symptoms with distinct neuroanatomical pathologies that can be visualized with SPECT scans (Amen, 2001). To our knowledge, Amen has not published a study showing that by using a brain scan, he can tell the difference between the brain of an ADHD child and that of a normal child, or that he can use neuroimaging to diagnose any of his proposed six subdivisions of ADHD. Also problematic is that Amen uses SPECT scans as a regular tool to diagnose ADHD. Within psychiatry, neuroimaging is typically used for research, not diagnosis, because this technology involves low doses of radiation. Thus its use in children without life-threatening conditions is controversial, as Amen and Carmichael acknowledge (p. 84). Amen is one of only a handful of practitioners who use neuroimaging as an aid in the diagnosis of ADHD.

Teicher et al. (2000).² This study used functional MRI relaxometry (fMRI) to assess blood volume in the striatum. It reportedly found differences in the putamen of 11 ADHD children compared to six healthy control children. Teicher et al. (2000) concluded: "On average, T2-RT was 3.1% higher in ADHD children than control subjects in the left putamen . . . and 1.6% in the right putamen" (p. 471). However like many of the neuroimaging studies this conclusion is tempered by the issue of prior medication exposure. Some explanation of the experimental design of the Teicher et al. study is necessary.

The 11 children with ADHD were randomized to one of four groups: placebo, or methylphenidate at 0.5, 0.8, or 1.5 mg/kg in divided doses. The

²Giedd et al. cite a 1996 paper by Teicher that is not concerned with brain imaging. We are not exactly sure which paper they meant to refer to but Teicher's most significant paper is the one that we discuss here.

children received the appropriate dose for a week after which they were tested for drug efficacy using objective measures of attention/activity and fMRI within 1–3 hours of their afternoon dose. The children then moved into the next group for a week, received the appropriate dose and were again scanned and tested. All children were cycled through all four groups but they started out in *different* groups. The researchers then compared the fMRI results of the unmedicated healthy control subjects and the ADHD subjects following their week of placebo treatment and it is this difference that is reported as significant. For instance in a scatterplot (Figure 1, p. 472) the T2 relaxation times of the 11 ADHD children on placebo are compared to controls and Teicher et al. (2000) report that “The increased T2 relaxation times in the ADHD sample indicate diminished regional blood volume” (p. 472). However, one problem with this scatterplot (and the experiment) is that the scans of the ADHD children performed during the week of the placebo treatment are not comparable. The *prescan* interval for each child might have been preceded by one, two, or three weeks of treatment with methylphenidate. A child randomized to placebo and then scanned is not comparable to a child administered three weeks of the drug followed by placebo and then scanned. Teicher and colleagues grouped children who *never* received drug treatment with children experiencing withdrawal from drug treatment.³ Since exact treatment protocol is not supplied for each child, precise interpretation of the results is impossible.

Studies Published Since the Giedd et al. Review

Two studies published since the Giedd et al. 2001 review are noteworthy for what they could have accomplished — but did not. Both studies had the chance to compare non-medicated patients to appropriate controls yet merely addressed “secondary” issues. Our analysis of these studies focuses on sifting through the “secondary” issues and asking: What about the essential comparison between non-medicated patients and controls?

Kim, Lee, Cho, and Lee (2001). These investigators used SPECT to examine rCBF in 32 previously unmedicated ADHD children before and after eight weeks of treatment with methylphenidate. Changes were detected in the prefrontal cortex and the caudate nucleus. We have two concerns with this study. First, the drug-induced changes in the striatum and frontal lobes

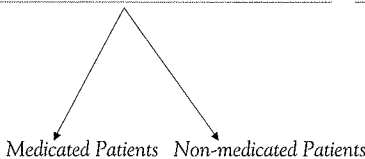
³It is difficult, if not impossible, to determine the exact design of this study — it is only by communicating directly with Teicher that we obtained information on the study design. He supplied only limited information so while we have done our best to fairly present his study we are still unsure of the exact protocol. We also wonder how the reviewers of this paper were able to judge its merit given the limited explanation of the methodology.

are reported to occur in the same cerebral circuit that Giedd et al. (2001) pointed to as the neuropathological locus of ADHD. But whereas Giedd et al. attributed such findings to an endogenous organic pathology, Kim et al. attributed their findings to methylphenidate exposure. Second, the researchers did not include a control group of “normal” children to compare to the medication-free ADHD children. Kim et al. appear to be one of the first research groups to report on ADHD children not previously medicated, yet they have not run the essential comparison between non-medicated children and controls

It would have been more fruitful to have divided the procedure into two parts: the first part simply comparing the scans of ADHD children to controls, and the second part examining the effect of medication on the scans of ADHD children, as in the study by Lou et al. (1990). Researchers may be perplexed that the scans of the children diagnosed with ADHD were not compared to controls. Kim et al. state that it would have been unethical to examine the effect of methylphenidate on a control group — and they are correct. However, their study would have been more significant if, *prior to the drug administration*, they had compared the scans of the ADHD children to a control group.

Castellanos et al. (2002). This study, carried out between 1991 and 2001, reported that the brains of ADHD children are smaller compared to those of controls. The study is significant because of the size of the sample (291 parti-

	Entire Patient Group		Controls		p value for patients vs. controls
	Female N=63	Male N=89	Female N=56	Male N=83	
Age, mean (SD), y	9.4 (2.6)	10.5 (3.1)	10.0 (2.6)	10.9 (3.5)	.13
Height, mean (SD), cm	134.9(15.0)	141.7(18.0)	140.2(16.0)	147.3(20.3)	.01
Weight, mean(SD), kg	33.0(12.2)	36.9(14.4)	35.8(12.5)	42.0(16.5)	.02



	Medicated Patients	Non-medicated Patients
Age*	10.9 (2.7)	8.3 (2.6)
Height	Not provided	Not provided
Weight	Not provided	Not provided

Figure 1: Participants' physical characteristics in the Castellanos et al. (2002) study.

*p value for medicated versus non-medicated .001

cipants) and because one third of the patients never received medication. Three groups were constituted: 49 unmedicated patients, 103 medicated patients, and 139 controls. Thus the authors had the opportunity to make numerous comparisons: unmedicated versus medicated, unmedicated versus controls, medicated versus controls, and ADHD versus controls. The most important — and we would say legitimate — comparison was between unmedicated patients and controls. However, compared to the controls, *the unmedicated patients were two years younger, shorter and lighter.*⁴

Castellanos et al. state that height and weight did not correlate with brain size in their study. Yet in that study these variables were significantly correlated with the diagnosis of ADHD. Thus, although finding three biological differences between the ADHD children and controls, the researchers only focused on brain size. Height and weight have never been shown to be part and parcel of ADHD, but the results from this study suggest otherwise. Conversely, if height and weight are only spuriously correlated with ADHD, then the appropriateness of the control group is called into question.⁵

Consider the following data as shown in Figure 1: the entire ADHD patient group (medicated plus unmedicated) is significantly shorter and lighter than the control group; for the most important comparison in the paper the subgroup of *unmedicated* patients is drawn from this already smaller and lighter group of patients; we are not told the height and weight of this subgroup of unmedicated patients but we are told that they are almost two years younger than the entire patient group; and for this reason the unmedicated patients are probably also significantly shorter and lighter than the control group. We say “probably” because for the most important comparison in the article the subjects’ specific physical characteristics are not provided. The issue of height and weight is especially relevant here because most research on brain size has found brain size to be correlated with body weight. Gould has pointed out that in studies that have incorrectly associated brain size to other factors, the most common mistake has been in sample selection and that “modern students of brain size have still not agreed on a proper measure to eliminate the powerful effect of body size” (1996, p. 138). We suggest

⁴Regarding the age discrepancy, the authors reported that they conducted a secondary analysis restricted to an age-matched subset of 24 unmedicated ADHD children and 54 controls and, “All measures essentially remained unchanged” (p. 1745). However, given a more appropriate control group these types of secondary analyses would not have been required.

⁵Since the first studies of brain size in the nineteenth century, scientists have correlated brain size with various other factors such as intelligence, race, predisposition to violence, and even nationality. For instance, in 1861 Gratiolet reported that German brains were on average 100 grams larger than French brains (Broca, 1861, pp. 441–442). With the exception of height, weight, and sex most of these correlations have not stood the test of time.

that this effect was not eliminated in the Castellanos et al. (2002) study. Thus, besides a diagnosis of ADHD, the unmedicated children could have had smaller brains due to the fact that they were shorter, lighter, and younger. In fact, given all these other variables it would be noteworthy *if they did not have smaller brains*.⁶

To conduct a study to determine if there is something unique about the brains of ADHD children, one need not involve medicated children at all. The only apparent reason Castellanos et al. (2002) used medicated children was to answer questions about drug effects on the brain. To do so they compared unmedicated to medicated children: and they found no significant differences and concluded that the medications have no effect on brain size. However, this hardly seems the type of study to adequately address this issue, since the authors provided no information whatsoever about medication use (such as doses, durations, or even types of drugs used) except this one sentence: "At the time of the first scan, 103 patients (68%) were being treated with psychostimulants" (pp. 1742–1743). We note also that, compared to medicated children, unmedicated children were not as severely affected by ADHD according to teachers and doctors.

What at first seems like a straightforward comparison of two groups of children reveals itself as a tangle of unnecessary complications, including secondary statistical analyses of subgroups, discussions about differences in amounts of white matter in 8-year olds versus 10-year olds, or concerns about height and weight as confounding variables. By itself, a simple comparison between unmedicated ADHD children and controls would certainly have stood out as an important experiment. Peripheral questions could have been addressed as extensions of the primary question without complicating the experiment. But in this study peripheral questions did hopelessly confuse the essential comparison.

Our criticism of the experimental design of the Castellanos et al. (2002) study might seem excessive, but in light of the problems we have pointed out regarding selection of control groups, and considering that the study's patients and controls came from highly select populations, the concern seems justified. Yet, we would like to point out that the more straightforward comparison was — and still remains — well within the authors' grasp. The authors could still compare the scans of the non-medicated children to the scans of a control group matched for, among other things, height, weight, and age. This simpler comparison would be more direct and meaningful, and would not take ten years to complete.

⁶It would also be surprising if they did not have smaller skulls. If there is an association between skull size and ADHD then future studies would save time and money by using a tape measure.

In the past, researchers in this field have been unable to find unmedicated patients for their studies. Finally, here is one of the first research groups to overcome this obstacle, but immediately the question arises: Why is the control group two years older, taller, and heavier than the group of unmedicated patients? It seems odd that, given ten years and the resources of the NIMH, these experienced researchers could not find a more appropriate control group. Ironically, previous studies were contaminated by a medication confound; in this study the reverse is true: the control group is not comparable with the treatment group.

Nevertheless, the findings of Castellanos et al. (2002) will be more valuable if they are replicated with a more comparable set of controls — and will be of great interest to more than just ADHD researchers — for two reasons. If the Castellanos et al. study is replicated it will be the first to correlate subtle differences in brain size with a behavioral trait, in this case activity level; and also the first to find that brain size is *not* correlated with height and weight.

Discussion

Of the thirty-three relevant studies summarized in Tables 1 to 5, twenty-nine included a control group of normal subjects, but only nineteen reported on the ADHD patients' prior use of medication. These nineteen studies involved a total of 356 patients and 365 controls, and all but one study found differences between ADHD and non-ADHD children. However, in each group of studies using an imaging modality, an average of 77% of the ADHD children had prior exposure to medication. Because of this confound, any suggestions about differences between the brains of "ADHD" children and the brains of "normal" children must await future studies.

To their credit, the two neuroimaging studies published since the Giedd et al. (2001) review used non-medicated children. Yet they avoided a simple and straightforward comparison between non-medicated children and appropriate controls. The Kim et al. (2001) study did not compare unmedicated children to controls, instead they started with unmedicated children, administered medications to them, and then performed scans. The most perplexing study was reported by Castellanos et al. (2002) who used unmedicated ADHD children who were younger, lighter, and shorter than the control group. Peripheral questions sidetracked each of these research groups from the more important comparison: that of unmedicated ADHD children to controls.

We are also concerned about how results are sometimes reported both in the Giedd et al. (2001) review and in the ADHD neuroimaging literature in general. For instance, in their review Giedd et al. categorize the findings of

Shaywitz et al. (1983) as “None” yet what Shaywitz et al. reported was that they found no significant differences between ADHD patients and controls. Readers of the Giedd et al. review who are trying to determine if neuroimaging researchers have found an anatomical basis for ADHD should be told if a study found no difference between ADHD patients and controls.⁷ As another example, in adolescent males Ernst et al. (1994) found no difference in global cerebral glucose metabolism between ADHD and controls, but the researchers did find a difference in adolescent females. While the title of their paper — “Reduced Brain Metabolism in Hyperactive Girls” — certainly conveys their findings, it would have been just as correct to have titled it “Normal Brain Metabolism in Hyperactive Boys.” Apparently studies finding a difference between ADHD children and controls are more significant than studies that find no difference. Studies finding a difference between ADHD children and controls are probably more likely to get published.

It is interesting to note how neuroimaging findings are used in the related field of research concerning the effects of illegal psychotropics. For example, in humans with persistent exposure to methylenedioxymethamphetamine (MDMA, commonly known as Ecstasy), brain imaging research is often cited as evidence that MDMA causes a deficit in serotonin rich areas of the brain (Reneman et al., 2001). In the case of MDMA, drug users are compared to controls and observed differences are attributed to drug use; but in the case of methylphenidate, drug users are compared to controls and differences are attributed to an underlying organic pathology?

The ADHD neuroimaging research also exemplifies how the media fail to take even a moderately critical view of medical research. Following the publication of the Castellanos et al. (2002) article reporting smaller brain size in ADHD children, *The New York Times* discussed the study. In the beginning of the newspaper article, Castellanos is quoted: “I’ve always been extremely cautious about overinterpreting results.” One page later Castellanos is reported as saying that the findings raised the possibility that medication might enhance the normal maturation of the brain in children with attention disorders (Goode, 2002). On the one hand, Castellanos says that he does not like to overinterpret results; on the other hand, he suggests the remarkable “possibility” that Ritalin might lead to enhanced brain maturation. Granted, Castellanos only raised the “possibility” — but two months later *The Detroit Free Press* ran an article with the headline: “Ritalin is Safe and It Works:

⁷Without entering into an elaborate discussion about the null hypothesis versus the research hypothesis (and the inability to prove the null hypothesis) suffice it to say that if you take two groups of people and compare a given trait and find no difference between the two groups it is quite possible that indeed there is no difference. Under “findings” it would have been more accurate for Giedd et al. (2001) to say “No Difference” rather than “None” because this does relate to the research hypothesis of ADHD neuroimaging researchers.

Research Disperses Fears that Drug Hurts Kids, and *Finds That It Actually Helps Brains Grow*" (Kurth, 2002, italics added). The scenario, where Ritalin is portrayed as something akin to a vitamin, exemplifies misguided medical advice by the media. Yet, in this case it is difficult to fault only the media.

Prior Medication as a Confounding Variable

Slightly over half the papers in Giedd et al.'s (2001) review actually mention medication status of subjects; the rest do not inform readers about prior use. But most problematic is that not a single paper devotes more than a sentence (or two) to the topic. Prior medication use by ADHD subjects is virtually a "non-issue." Only one of the thirty-three studies even suggests that we actually study the effect of chronic stimulant treatment on the brain (Nasrallah et al., 1986).

There is, of course, no such thing as a perfect experiment: if one looks long enough, flaws will be detected. Competing hypothesis can always be found. However, when investigating subtle neuroanatomical or metabolic changes in the brain, it is hard to imagine a more problematic variable than prior history of psychotropic drug use. In this light then, what are we to make of the fact that some researchers fail to even *mention* this variable?⁸ Consider the variable of right or left handedness. In some studies researchers made a point of only using right handed children (Rubia et al., 1999) or of matching controls and patients for handedness (Giedd et al., 1994). But the same researchers did not mention medication history. Are researchers more concerned about handedness than they are about prior medication use?

At best, Giedd et al.'s (2001) concern with prior medication use is equivocal, illustrating how such concern is handled in the literature. On the one hand, in their 1994 study that purports to "support theories of abnormal frontal lobe development and function in ADHD" (p. 655), Giedd et al. (1994) do not mention medication history of the patients even though this information must have been available because the patients were recruited from an NIMH program. On the other hand, in their 2001 review Giedd et al. qualify Rubia et al.'s (1999) findings by stating, ". . . we must note that all the patients had been medicated with methylphenidate until 36 hours prior

⁸For all studies with no information on medication history, we attempted to contact lead authors to obtain this information. Most did not respond. One author replied: "I am sorry, but I would have to go through all the files, and it is too time-consuming." We do not know if this information was not reported because authors were unaware that prior drug use is a major confounding variable or, conversely, if authors were aware of it but realized that it lessened the validity of their findings to establish a biological basis for ADHD. Either possibility is a cause for serious concern.

to their scans” and by noting that findings in control subjects scanned after an ingestion of MPH may “reflect medication withdrawal effects . . .” (p. 39).⁹ Also, in their final summary, Giedd et al. identify one limitation of this research as: “. . . none of the studies published to date has accounted for possible source of confounding such as prior medication exposure” (2001, p. 45). But clearly, if that is the case, the issue requires extensively more discussion and integration than four lines in a 13-page review article. Indeed, given the explicit warning from one of the earliest studies (Nasrallah et al., 1986), why not remind readers of the confound and immediately conduct studies without the confounding factor? Perhaps the answer is found in Giedd et al.’s (2001) own explanation of the value of neuroimaging in ADHD: “Imaging studies may help educate families and the public that ADHD is a biological entity” (p. 45).

For those researchers who feel that our concerns about prior psychotropic drug use are excessive it is important to remember how prior psychotropic use confounded the first experiments that tested the dopamine hypothesis of schizophrenia. Early reports that schizophrenic patients had more dopamine receptors than controls were eventually tempered by the realization that the patients in these studies had taken neuroleptics for years. Subsequent attempts to replicate the findings in medication-free patients have met with inconsistent results (Valenstein, 1998).

Conclusion

Imaging research is often used to justify the medication of children diagnosed with ADHD (Barkley et al., 2002). For instance, in the most recent ADHD imaging study, Castellanos et al. (2002) state that based on their findings of smaller brain size in ADHD children, “Future studies should focus on younger patients being enrolled into controlled treatment studies while in preschool” (p. 1747). However, we question the logic behind the idea that smaller brains justify drug treatment for younger children. If one follows this logic, what is one to make of the height and weight issues? Do height and weight differences also justify “treating” preschoolers?

A significant and oft overlooked issue about brain imaging research concerns the distinction between normal biological variation and “disease.” All measurable traits such as height, weight, activity level, or brain size, fall onto a bell-shaped curve. Where along the curve one draws the line between normal and abnormal becomes arbitrary. As DSM-IV-TR (American Psychia-

⁹Giedd et al. (2001) report that all of the ADHD patients in the Rubia et al. (1999) study were previously medicated, yet Rubia et al. state that “The patients *were either unmedicated or medication free* for one week before scanning” (1999, p. 892).

tric Association, 2000) states with regard to ADHD, "Estimates of prevalence rates has been revised upward, reflecting increased prevalence due to the inclusion of the Predominantly Hyperactive-Impulsive and Predominantly Inattentive types in DSM-IV" (p. 830). Do 3% of school-aged children have ADHD? Or is it 7%? Or is ADHD approaching 15% as some authors have recently suggested (Paule et al., 2000)? In a review article titled "Is ADHD a Valid Disorder?," Carey points out that there is a correlation between brain function and temperament even in children who fall under the rubric of "normal" (2002, pp. 3-7). If 15% of the population exhibits a particular trait, one might consider it an example of normal biological variation. Still, if researchers are inclined to consider 15% of the population as brain-diseased, then they will need to look elsewhere than the body of ADHD neuroimaging research for confirmatory evidence.

A comment in an earlier review of ADHD imaging research by two prominent researchers seems particularly instructive (Ernst and Zametkin, 1995). In addressing the fact that in the Nasrallah et al. (1986) study seven of the 24 patients had a history of alcohol abuse, Ernst and Zametkin pointed out: "Unfortunately, the inclusion of individuals with a history of alcohol abuse, representing 30% of the sample, confused the interpretation of the results, because the findings mirrored those reported in CT studies of alcoholic adults" (p. 1646). If interpreting results from a single study becomes confusing because 30% of the sample had a prior history of alcohol abuse, then, undoubtedly, results from a field of research where over three quarters of the patients were persistently exposed to a centrally active drug would be similarly compromised.

The necessary and definitive test to confirm the suggestion that ADHD children have a neuroanatomic pathology consists of using a brain scan to detect a difference between a "typical" ADHD child as found in the classroom, and a "normal" child. As we pointed out at the beginning of this paper, there is virtual unanimity that this cannot be accomplished at present. Experiments with highly selective patient and control groups are, at best, only preliminary studies, and we have shown — in complement to the critical analysis by Baumeister and Hawkins (2001) — that the findings of these studies must be called into question. In response to persistent pressure from critics such as Baughman (1998) and Breggin (1991), it seems that neuroimaging researchers now acknowledge the importance of medication history. The publication of the Castellanos et al. (2002) article, using non-medicated children, essentially trivializes any further studies that use medicated children. Yet, after twenty-five years, and thirty-five studies, there is not a single straightforward experiment comparing typical unmedicated children with an ADHD diagnosis to typical controls. We are perplexed.

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