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## An Update on ADHD Neuroimaging Research

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Since the publication of a critical review on ADHD neuroimaging in a past issue of this journal (Leo and Cohen, 2003), several relevant studies have appeared, including one study that had a subgroup of unmedicated ADHD children (Sowell, Thompson, Welcome, Henkenius, Toga, and Peterson, 2003). In this update to our earlier review we comment on this last study's failure to report on the crucial comparison between unmedicated and medicated ADHD subjects. The issue of prior medication exposure in ADHD subjects constitutes a serious confound in this body of research, and still continues to be dismissed and willfully obscured by researchers in this field.

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In a previous issue of this journal, we reviewed the attention-deficit/hyperactivity disorder (ADHD) neuroimaging research (Leo and Cohen, 2003). We pointed out the difficulty in drawing meaningful conclusions from this body of research because of a significant confounding variable: prior or current medication use by the ADHD patients. As we documented, in the large majority of ADHD neuroimaging studies, researchers have compared brain scans from normal control subjects to brain scans from medicated ADHD subjects. This makes it difficult to know if between-group differences reported by researchers might result from an idiopathic organic brain defect — as implied or stated in most studies — or from brain changes resulting

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from prior drug use by the subjects diagnosed with ADHD. Critics over the past decade pointed out that prior medication use constitutes an important potential confounding variable that limits the validity of these studies, but most researchers have continued to use medicated patients in their studies, sometimes without acknowledgement of the issue.

Despite the dismissal of the issue of prior medication use in published reports, the issue must have been quite sensitive in the minds of researchers nonetheless. Indeed, immediately upon the publication of a large study ( $n=291$ ) by Castellanos, Lee, Sharp, Jeffries, Greenstein and Clasen (2002), that included a subset of ADHD patients who had never taken medication, the sponsor of that study, the National Institute of Mental Health (NIMH), released a press briefing declaring: "Brain Shrinkage in ADHD Not Caused by Medications" (NIMH, 2002). This announcement rested on results of a subgroup comparison between 103 medicated and 49 unmedicated ADHD subjects, which found that, just like their medicated peers, unmedicated youths also demonstrated statistically significant smaller brain volumes than normal control subjects. There was no mention in this study about the specifics of the medication history of the medicated children. In our earlier review (Leo and Cohen, 2003) we discussed several problems with the Castellanos et al. study. The following is a brief summary of that discussion:

1. On average the unmedicated ADHD subjects were two years younger than the medicated ADHD subjects.
2. The unmedicated ADHD subjects were stated to be shorter and lighter than the normal controls but precise figures on height and weight were not provided.
3. No details were given about previous treatment histories of the medicated ADHD subjects, such as duration, dose, or even what drug or drugs were prescribed.

Since our review appeared, several ADHD neuroimaging studies have been published. Unfortunately, by failing to exercise appropriate control over the variable of prior medication, these studies perpetuate the confusion and uncertainty that, we argued, characterizes findings in this body of research. For example, Mostofsky, Cooper, Kates, Denckla, and Kaufmann (2002) had 12 ADHD subjects in their study, ten of whom had a prior history of medication. MacMaster, Carrey, Sparkes, and Kusumakar (2003) entitled their study "Proton Spectroscopy in Medication-Free Pediatric Attention-Deficit/Hyperactivity Disorder," yet eight of their 9 ADHD subjects had a prior history of medication: three stopped taking their medication 48 hours before the scan, and five stopped taking it one to 3 weeks before the scan. Taking medicated ADHD subjects off their medication before the imaging and then classifying them as "medication-free" is unsound. We cannot emphasize enough that a study wishing to reach conclusions about the neuropathology of

ADHD needs to recruit a control group of medication-naïve subjects, especially given the well-documented neuropathological effects of psychotropic medication (Leo and Cohen, 2003).

In our view, the most significant recent report was of a relatively large study involving 27 ADHD and 46 normal control subjects, conducted by the Laboratory of Neuroimaging at the University of California, Los Angeles (LONI). Sowell, Thompson, Welcome, Henkenius, Toga, and Peterson (2003) reported that the ADHD children had smaller frontal lobes compared to normal controls subjects, but overall the ADHD subjects had more cortical grey matter. In our view, this study's significance derives not necessarily from this result, but — as with several previous ADHD neuroimaging studies — from important comparisons that researchers could have made, *but did not*.

As in the Castellanos et al. (2002) study, some of the ADHD subjects in the Sowell et al. (2003) study were apparently medication-naïve. We say “apparently” because specific descriptions were not provided: “15 of the 27 patients were taking stimulant medication at the time of imaging” (p. 1705). It is unclear how to categorize the remaining 12 patients. Did they have a history of medication and then stop taking it for 48 hours, or some other arbitrary time period, before imaging? It surprises us that a study published in *Lancet* could be so vague about one of the most important variables in the study. Conclusions based on a comparison of normal control subjects to medication-naïve ADHD subjects would be very different than conclusions based on a comparison of control subjects to ADHD subjects with varying durations of medication exposure and with some patients undergoing abrupt withdrawal.

The issue becomes considerably more muddled and confusing due to a brief discussion of the potential role of stimulant medication on their findings at the end of Sowell et al.'s (2003) paper. The authors first appropriately acknowledged that, since 55% of their ADHD children were taking stimulants, “the effects of stimulant drugs could have confounded our findings of abnormal brain morphology in children with [ADHD]” (p. 1705). The simplest way to properly evaluate this confounding effect would have been to compare the 15 medicated ADHD children with the 12 unmedicated ADHD children. However, Sowell et al. consciously chose to not make that comparison: “We did not directly compare brain morphology across groups of patients on and off drugs because the sample size was considerably compromised when taking lifetime history of stimulant drugs into account” (p. 1705). The authors further explain that this comparison, between unmedicated and medicated ADHD children, is not needed because a prior study by Castellanos et al. (2002) suggested that medications do not affect brain size [a contention which ignores the problems we identified in our lengthy review].

Sowell et al.'s methodological choice, and its justification, is both unconvincing and puzzling. First, although one can obviously sympathize with their

judgment that “taking lifetime history of stimulant drugs into account” compromised their sample size, this judgment ignores that for thirty years ADHD neuroimaging researchers have deemed it perfectly acceptable to compare ADHD subjects and normal controls *regardless of medication history* (Leo and Cohen, 2003). Indeed, virtually all the studies Sowell et al. cite to contextualize their study and interpret their results exemplify this practice. Thus, it is difficult to see why Sowell et al. would feel that they should not compare medicated and unmedicated ADHD subjects. Clearly, just as they acknowledged limitations to their *main* study results, Sowell et al. could obviously have reported the results of the more specific comparison with an acknowledgement of appropriate limitations. Second, Sowell et al. cite Castellanos et al. to support the methodological choice of not comparing medicated and unmedicated ADHD subjects. But, Castellanos et al. made that very comparison regardless of medication history! Third, and most important, Sowell et al.’s data appear directly relevant to either support or refute the conclusions that Castellanos et al. (2002) drew from their comparison. Put another way, the results of Castellanos et al.’s comparison of brain volumes of medicated and unmedicated ADHD children were deemed worthy of a major press release by the NIMH concerning stimulant drugs’ effects on developing brains, yet the same comparison in the Sowell et al. study is considered insignificant and not even reportable.<sup>1</sup> For the above reasons, we suspect that the comparison of medicated with unmedicated ADHD subjects in Sowell et al.’s study might have produced results that would have diluted the findings that Sowell et al. chose to emphasize instead.

Following the publication of the Sowell et al. (2003) study, the media paid significant attention to it. In one interview, the study’s last author stated: “The next phase of the work will be to see whether the magnitude of the abnormalities in these individuals might influence the course of the condition, *their response to medication*, and which medications different children respond to” (cited in Edelson, 2003, italics added). We assume that this next phase of investigation will involve a comparison of medicated with unmedicated children — but how this will differ from their previous study, or from most ADHD neuroimaging studies, remains completely unclear.

### Discussion

In our earlier review (Leo and Cohen, 2003) we discussed our concern about the careless or distorted way that imaging results were often reported in the sci-

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<sup>1</sup>Following the publication of the Sowell et al. study, we corresponded with the lead author who graciously answered our queries but expressed no interest in comparing brain volume data of medicated and unmedicated ADHD children. A month before submitting the current article for publication, we communicated with all authors of the Sowell et al. study, asking them to share the data to allow us to make the stated comparison, but received no reply.

entific literature, professional publications and the media. In several discussions with imaging researchers since our review appeared, we have heard repeatedly that the media is the culprit when it comes to “reading too much” into a study. However, examples of oversimplification abound within the professional and scientific literature. For instance, in a recent article about the Castellanos et al. study on the Internet site Medscape, excerpted from the 2004 *Child and Adolescent Psychiatry Meeting*, the author declares: “On an anatomic level, total cerebral volume is approximately 3% smaller in youth with ADHD” (Gutman, 2004). It is hard to conceive of a more fitting example of a complex study being presented in an overly simplistic manner. Gutman discusses no problems or limitations of the Castellanos study; she simply asserts to a huge audience of clinicians that it is a fact that ADHD children have smaller brains. The website includes a test that clinicians can take after reading the article if they wish to earn continuing medical education credits, and one of the questions reads: “When looking at ADHD and cerebral volume in children, researchers have found . . .” — and the “correct” answer is given as: “Total cerebral volume is approximately 3% smaller in youth with ADHD.” It is deeply troubling to us that a professional society can propagate such a statement based on a single study with major limitations.

Ruling out the effects of psychotropic medication is merely one of the tasks confronting researchers conducting neuroimaging research with ADHD patients. Even if the field accomplishes this task, several other important tasks remain. One of these will involve trying to make sense of findings of brain abnormalities or differences among some individuals diagnosed with ADHD. And in this task, a few observations will deserve serious consideration, though they are very rarely discussed in the ADHD neuroimaging literature. One exception is an article by Rubia (2002), from which we find it useful to quote at some length, despite our disagreement with the author’s characterization of ADHD as a “disorder”:

Neurodevelopmental psychiatric disorders, as opposed to neurodegenerative disorders, are known to be dynamic and are very likely to be even more dynamic than currently assumed . . . Only about a third of children with ADHD still meet criteria for ADHD in adulthood . . . A highly dynamic interplay between nature and nurture is likely and the causalities between them may be bi-directional rather than unidirectional. Until today, it has been erroneously assumed that biological correlates of abnormal behavior are necessarily the cause of brain “basis” of abnormal behavior. Recent reports from neuroscience point towards a much more plastic concept of the brain-behavior relationship with bi-directional causalities . . . Use-dependent functional and structural reorganization in sensory cortices, for example, has been observed in skilled subjects, pianists and musicians. Post-traumatic stress disorder in war veterans and victims of child abuse causes smaller hippocampi and abnormal amygdala activation. Amputation studies show that function is necessary for structure to develop. These examples show that behavior, experience, and function can alter and determine brain structure. This has fundamental implications especially for psychiatric research, given that psychiatric disorders are characterized and defined by deviation from normal functioning. (Rubia, 2002, p. 49)

In sum, brain differences (or "abnormalities") may be related to the state rather than the trait of the syndrome or behavior in question, and this fundamental issue will require immense creativity and rigor to tackle. By comparison, the issue of prior medication is extremely uncomplicated: to rule out effects of medication exposure on brain volume, one simply needs to compare a group of ordinary medicated ADHD patients with a control group of ordinary, age- and weight-matched unmedicated ADHD patients. A single study of this type with no more than 60 subjects could practically settle the question. Unfortunately, given how the ADHD neuroimaging field has so far treated this simple issue, it is doubtful to expect that researchers in this field will make progress on the more significant scientific challenge ahead.

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