A Commentary on the Proposal to Observe the Effects
Of a Single Dose of Amphetamine in Children

by:
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Introduction

The experiment under discussion, designed to compare the effect of a single dose of amphetamine in children diagnosed with ADHD to normal controls, is flawed for several reasons. Before discussing the specifics, it is important to provide some background and history of ADHD neuroimaging research. After almost thirty years and over forty studies ADHD neuroimaging researchers have still not found a biological basis for ADHD.

Background and History of ADHD Neuroimaging Research

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 journals 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.

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 among studies raise questions about the reliability of the findings” (p. 2) or, “The principal conclusion is that the neuroimaging literature provides little support for a neurobiological etiology of ADHD” (p. 4).

Another review (Leo and Cohen, 2003) of the ADHD imaging research pointed out the difficulty on drawing meaningful conclusions because of a significant confounding variable: prior or current medication use by the ADHD patients. As we documented, in the overwhelming majority of ADHD neuroimaging studies, researchers have compared 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 from prior drug use by the subjects diagnosed with ADHD. There have been two recent studies both funded by NIMH which exemplify the problems with the ADHD neuroimaging field.

Castellanos et al. (2002). This study was heralded because it was one of the first ADHD neuroimaging studies to have a group of unmedicated children diagnosed with ADHD. For many years ADHD researchers have defended the practice of using medicated ADHD children because of the difficulty in finding unmedicated children diagnosed with ADHD. Thus, finally given the availability of a group of unmedicated ADHD children, and all the resources of NIMH, it is perplexing that the controls in this study were two years older than the non-medicated patients.
Sowell et al. (2003). In this study the researchers had three groups: 1) controls, 2) medicated ADHD children, and 3) unmedicated ADHD children. But they did not report on the comparison between medicated and unmedicated ADHD children because they believed that the medication histories of the ADHD children were not comparable and would confound the comparison— the same comparison which was the basis of the Castellanos study, and subsequent press release by NIMH declaring that stimulants do not harm the brain (NIMH, 2002). Neither NIMH nor Castellanos et al. felt that the medication histories confounded the comparison between medicated and unmedicated children. Because we (See Cohen and Leo, In Print) were interested in the unreported comparison between unmedicated and medicated ADHD children in the Sowell et al. study, we requested data on this information from the authors, but they have not responded to our requests. The unwillingness of these authors to release their data seems at odds with NIH’s “Guidelines to Investigators”:

There are many reasons to share data from NIH-supported studies. Sharing data reinforces open scientific inquiry, encourages diversity of analysis and opinion, promotes new research, makes possible the testing of new or alternative hypotheses and methods of analysis, supports studies on data collection methods and measurement, facilitates the education of new researchers, enables the exploration of topics not envisioned by the initial investigators, and permits the creation of new data when data from multiple sources are combined (http://grant.nih.gov/grants/guide/notice-files/NOT-OD-02-035.html).

Exactly who is supposed to enforce these guidelines is unclear. Based on these guidelines there seems to be no reason for having to resort to filing a Freedom of Information Act Request, but we did, and it was denied (For a more in-depth discussion of the Sowell et al. study see Cohen and Leo, In Press).

The Current Experiment

As just one example of how the ADHD neuroimaging researchers have ignored the potential confounding variable of prior drug use one need not look further than the experiment we are discussing today. While this experiment plans to compare children diagnosed with ADHD to normal controls these authors plan to use children who have already been exposed to medication (See age 9, Section III G of the protocol). How will these researchers know if any difference they find between the ADHD children and controls is due to an organic brain deficit, or to prior drug use? To supposedly get around this issue the researchers plan to withhold medication from the ADHD children for some unspecified time prior to administering the single dose of amphetamine and the subsequent brain scan. Yet, this only complicates the issue even further because in addition to the confounding variable of prior drug use they have now introduced another confounding variable: The withdrawal effect.
Consider this: The proposed researchers plan to obtain “base-line” scans of the ADHD children prior to administering the single dose of amphetamine. But this “base-line” scan will be in children with a history of medication use undergoing withdrawal. Can this truly be called a “base line” scan? It seems more appropriate to call it the scan of child with a history of medication use, or the scan of a child undergoing withdrawal, or even worse – the scan of child with a history of both long term drug use and withdrawal effects. If there is a difference between the “base-line” scans of the ADHD children and controls how will the researchers know what caused the difference: drugs, the withdrawal effect, or an organic pathology. Even more problematic, following the “base-line” scan, to then give this child a single dose of amphetamine complicates the matter even further. In short, any conclusions drawn from this experiment will be severely compromised by the faulty experimental design.

Imagine a group of researchers observing the effect of a single dose of methamphetamine in addicts compared to normal controls. Most likely the researchers would attribute any deficits in the addicts to the long-term effect of methamphetamine— and not an organic pathology. It is unclear how this experiment with methamphetamine would differ from the proposed experiment under discussion.

On the other hand, if these researchers do manage to find a group of fourteen medication-naïve children diagnosed with ADHD, then their initial experiment should be to simply compare brain scans from the ADHD children to the brain scans of the fourteen age-matched controls. It would be a first. There would no need to give them a dose of any medication at all. Compared to all the complications that go along with using medicated children, a simple comparison between unmedicated ADHD children and age-matched controls would be easier, cheaper, simpler, much more straightforward, and most importantly it would provide much more valuable information about the nature of children diagnosed with ADHD. Critics of the ADHD imaging research continue to wonder why NIMH does not do this simple experiment. Of course there is the alternate possibility. Namely, that the experiment has been done, but because no “deficits” were found in the ADHD children that the results are considered “negative” and not worthy of publishing.

The Ethical Dilemma

While the research protocol for this experiment, and ADHD research in general, is couched with terms like “disorder,” “treatment,” and “medication” this experiment is essentially nothing more than administering a drug to minors and observing the effects. Certainly, the scientists proposing this experiment believe that a single dose of amphetamine will not harm the developing human brain. And, indeed, it is impossible to cite a study showing that a single dose has harmful long-term effects to the developing human brain. But the advisory committee’s decision to allow this study should go beyond the ability, or inability, to cite a study documenting the harmful effects of a single dose of amphetamine on the human brain. If this is the basis for your decision, what if a group of researchers proposed a study to look at the effects of a single dose of methamphetamine, or cocaine, or alcohol, or even nicotine on the developing brain? Would the committee’s decision be swayed by a scientist looking at the effects of cocaine
on children who said there are no studies showing that a small amount of cocaine is detrimental to long-term neuronal development? There are no citable studies documenting long-term harm to human neuronal development following a single dose of amphetamine, but likewise, there are no citable studies documenting harmful long-term effects from a single dose of cocaine. My guess is that the committee would not sanction an experiment that involved giving a single dose of cocaine to children — especially a study in which parents get paid for volunteering their own children.

Conclusions

I fully realize that most of you reading this proposal believe that ADHD is a disease that needs to be medicated. As the authors of the proposal state, “ADHD is the most common behavioral disorder of childhood, affecting an estimated 5-10% of the general population.” Unfortunately this mode of thinking is responsible for large numbers of children in this country being medicated so that they can attend school. Whatever arguments we could make about the folly of this thinking they will most likely fall on deaf ears. Thus, the main purpose for writing this brief is for the sake of history. At some point the medical community will realize the folly of medicating 5-10% of children in this country. At least it will be in the public record that there were some people standing up for the rights of children.

References


