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The Fallacy of the Impaired Brain in Attention Deficit/Hyperactivity Disorder (ADHD) Continues: A Critical Review of Recent Neuroimaging Studies

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This paper reviews seven recent studies that employed magnetic resonance imaging (MRI) to calculate volumetric brain differences between groups of children diagnosed with attention-deficit/hyperactivity disorder (ADHD) and a control group. These seven studies were selected because they included a group of participants diagnosed with ADHD who had not been treated with psychiatric medication, a group of children diagnosed with ADHD undergoing pharmacological treatment, and a control group of participants. Methodological flaws and incoherencies that invalidate the conclusions of these studies are described. Criticisms are presented in four groups: (a) sample sizes; (b) percentage of boys and girls per group; (c) weight and body mass of participants; and (d) the neuroanatomical incoherence of the findings.

Keywords: ADHD, methodological faults, neurological inconsistencies

The desire to find structural differences in areas of the brain in children diagnosed with ADHD has been the focus of several studies in recent decades (Aylward et al., 1996; Castellanos et al., 1996, 2002; Durston et al., 2004; Overmeyer et al., 2001). However, numerous reviews have highlighted serious methodological flaws that invalidate these neuroimaging studies (Baughman and Hovey, 2007; Baumeister and Hawkins, 2001; Galves and Walker, 2012; García de Vinuesa, González, and Pérez Alvarez, 2014; Gonon, Bezard, and Boraud, 2011; Hyman, 2003; Leo and Cohen, 2003; Lindstrøm, 2012; Weyandt, Swentosky, and Gudmundsdottir, 2013). The mistakes analyzed by these reviews are: (a) the formation of groups employing children of various ages, who have

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different body and brain mass; (b) the lack of a control group composed of healthy participants (or non-diagnosed nor medically treated participants); (c) the inclusion of children who had been treated with psychostimulant drugs in the ADHD group, which prevented identification of the actual variable responsible for the supposed structural differences observed through brain scans; and (d) inaccuracy and incoherence in the interpretation of the neuroimages obtained by magnetic resonance imaging (MRI) and positron emission tomography (PET).

Moreover, some neurologists and researchers discourage the use of neuroimages for diagnostic purposes in the case of ADHD and other psychiatric disorders, and recommend such techniques only when a contrasted neurological disorder is found (Eklund, Nichols, and Knutsson, 2016; Hedman, van Haren, Schnack, Kahn, and Hulshoff, 2012; Illes et al., 2006; Verdú, 2016). According to Wilkinson and Graves (2015), MRI serves to locate the following neurological problems: (a) an anatomical birth defect; (b) subarachnoid bleeding; (c) an aneurysm; (d) a brain abscess or infection; (e) tumors; (f) hormonal disorders such as acromegaly or galactorrhea; (g) multiple sclerosis; and (h) a stroke. However, MRI is being used to estimate brain volume differences across groups of individuals.

The main confounding variable when MRI techniques are employed to find these between-groups differences is the presence of medicated children in ADHD groups. The first comparative study in which ADHD researchers included a specific group of non-medicated children diagnosed with ADHD was Castellanos et al. (2002). Although these researchers included a treatment-naïve group, the ages of the children that participated in this group varied considerably with respect to the control group. Consequently, there was also a wide range in their body mass (they were two years younger, shorter, and lighter than the children in the control group) [Leo and Cohen, 2003]. The sample sizes of the three groups were clearly unbalanced. The non-medicated ADHD group was formed by 49 children, the medicated ADHD group was composed of 103 children, and the control group had 139 children.

The inclusion of a non-medicated group is the minimum requirement for a comparative study to test an hypothesis. Thus, in this work I have included studies that compared a group of participants diagnosed with ADHD who were treated pharmacologically, a group of participants diagnosed with ADHD who were not treated pharmacologically, and a control group. Groups in which all or a large proportion of participants have been medicated (which is the prevalent situation in ADHD neuroimaging research) can be considered contaminated by the effect that the psychostimulants and other psychiatric drugs have on the brains of the participants. In fact, numerous experimental studies have demonstrated that a treatment consisting of amphetamine and methamphetamine — equivalent to

the treatment prescribed to people diagnosed with ADHD (i.e., methylphenidate) — produces long-term effects and damage (either in humans or in non-human analogues) to the same brain regions that neurobiologists posit as responsible for ADHD. The prolonged presence of dopamine and noradrenaline in the synaptic space is caused by methylphenidate, dextroamphetamines, or mixed amphetamine salts blocking the reuptake of these neurotransmitters, and provokes a decrease in dendritic complexity, peak spine density, and dendritic length and projection distance. Some brain areas affected by this process of adaptation to these pharmacological substances are: (a) damage in the dopaminergic nerve endings in the striatum (Cole, Konradi, Douglass, and Hyman, 1995; Moll, Hause, Rüther, Rothenberger, and Huether, 2001; Ricaurte et al., 2005); (b) decreased neural activity in the insula, putamen, and anterior cingulate cortex (Konrad, Neufang, Fink, and Herpertz–Dahlmann, 2007); (c) gray matter deficits in the cingulate, limbic, and paralimbic cortices (Thompson et al., 2004); (d) atrophic prefrontal cortical pyramidal neurons (Selemon, Begovic, Goldman–Rakic, and Castner, 2007); and (e) damage to the basal ganglia (Chang, Alicata, Ernst, and Volkow, 2007).

Although this leads to an obvious conclusion about the role of pharmacological treatments in the possible modification of neural substrates, mainstream neurobiological research neglects this point, and attributes the results of comparative studies to the biological conditions of children diagnosed with ADHD. In response, Curatolo, D'Agati, and Moavero (2010) did conclude that neuroanatomical findings reported on ADHD-focused MRI studies are genetically determined. However, they also acknowledged that "the mechanism of action is not completely understood, and genome-wide association studies have failed to report any associations" (p. 300). Curatolo et al. further asserted that an alleged abnormal gene expression mechanism related to the production of dopamine receptors (D2, D4, and D5) or dopamine transporters (DAT1) can be explained by the neurological adaptation process described above. Additionally, Joseph (2009) has debunked much of the groundwork of ADHD genetic research, demonstrating the lack of control over the influence of environmental and educational variables upon family, twin, and adoption studies.

Since Castellanos et al. (2002), other studies have tried to find volumetric differences in brain areas of ADHD-diagnosed children. Some of these studies have incorporated additional methodological improvements in their designs. One of these methodological improvements has been the inclusion of a group of participants diagnosed with ADHD but non-treated pharmacologically. However, I consider it necessary to continue the critical analysis of these recent neuroimaging studies, since their comparative conclusions are not as clear and well-grounded conceptually and methodologically as they propose. Thus, my interest was to continue along the lines of the work of Leo and Cohen (2003). The search of these

studies was conducted by entering the terms "ADHD" and "magnetic resonance imaging" along with the temporal interval "2004/01/01 to present (2017/06/01)" in the PubMed® database.[1] This gave a total of 1,343 results, from which I selected studies focusing only on anatomical differences between ADHD-diagnosed children and a control group, and also met the criterion of including a non-treated group of children diagnosed with ADHD. Thus, with the exception of any possible erroneous omission, I will review a total of seven MRI studies which incorporate this specified methodological control (see Table 1).

Several studies were rejected because many, if not all, of the participants included in the ADHD group were undergoing treatment and were not clearly separated when they were compared (e.g., Batty et al., 2015; Bledsoe, Semrud–Clikeman, and Pliszka, 2011, 2013; Carmona et al., 2005; Castellanos et al., 2003; Gehricke et al., 2017; Mackie et al., 2007; Plessen et al., 2006; Semrud–Clikeman, Fine, Bledsoe, and Zhu, 2014; Seymour et al., 2017; Shaw et al., 2007; Xia et al., 2012; Zhan, Liu, Wu, Gao, and Li, 2017). Some studies were also rejected because they did not specify the pharmacological treatment history of the participants (Kumar, Arya, and Agarwal, 2017; Liu, Chen, Li, Li, and Wang, 2017). For example, Kumar et al. (2017) stated that their ADHD participants were non-medicated at recruitment, but they did not include these participants' previous history of medication, although they had included this information with their control participants.[2]

Other studies were rejected either because they focused on activation or connectivity patterns but not on anatomical structures and volumes[3] (e.g., Li et al., 2012; Mills et al., 2012) or because ADHD participants were diagnosed with additional extreme behavioral disorders such as "psychopathic traits" and were not assigned to treated and non-treated groups (Wellington, Semrud–Clikeman, Gregory, Murphy, and Lancaster, 2006). The main characteristics of these studies are described in Table 1.

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[1] United States National Library of Medicine.

[2] Kumar et al. (2017, p. 404) stated: "18 non-medicated ADHD male children/adolescents(…) were selected from the child and adolescent outpatient unit of Department of Psychiatry, King George Medical University"; however, the authors stated: "Typically developing (TD)(…) were right-handed and non-medicated (no history of medicine)." It is a light but fundamental nuance. In addition, they did not include an ADHD-Treated group for making a more complete comparison.

[3] I have refused "connectivity" or "activation" studies because a distinct neurological activity pattern cannot be considered an abnormality per se, but rather a proof of the idiosyncratic nature of individual history and behavior. Even some range of anatomical differences can be considered as normal products of the learning and experiential histories — see the case of London taxi drivers studied by Maguire et al. (2000). Only specific types of atrophy or hypertrophy can lead to biological dysfunctions; however, I have focused exclusively on anatomical differences because it is the strong argument maintained by the ADHD neurobiological view.

Table 1
Main Characteristics of the Studies Reviewed

Study	Number of Participants per Group*	Age Means and Standard Deviations	Cerebral Areas Studied
1. Semrud–Clikeman et al. (2006)	ADHD–T: 16	12.75 2.10	Caudate nucleus and anterior cingulate cortex
	ADHD–NT: 14	12.50 1.90	
	Control: 21	13.20 1.90	
2. Bledsoe et al. (2009)	ADHD–T: 18	11.47 1.50	Cerebellar vermis and anterior and posterior cerebellum
	ADHD–NT: 14	12.01 2.13	
	Control: 15	11.10 3.32	
3. Schnoebelen et al (2010)**	ADHD–T: 12	13.02 2.20	Corpus callosum and splenium
	ADHD–NT: 13	12.60 1.60	
	Control: 15	13.60 2.00	
4. Ivanov et al. (2010)	ADHD–T: 31	12.60*** 3.10	Thalamus
	ADHD–NT: 15		
	Control: 59	11.10 2.80	
5. Sobel et al. (2010)	ADHD–T: 31	12.90 3.30	Caudate, basal ganglia, globus pallidus, and putamen
	ADHD–NT: 16	12.40 2.90	
	Control: 57	11.70 3.10	
6. Semrud–Clikeman, Pliszka et al. (2014)	ADHD–T: 16	13.20 2.10	Frontal and pre-frontal cortex, caudate nucleus, and anterior cingulate cortex
	ADHD–NT: 13	14.50 1.50	
	Control: 15	14.50 3.30	
7. Ivanov et al. (2014)****	ADHD–T: 31	12.60*** 3.10	Cerebellum
	ADHD–NT: 15		
	Control: 59	11.60 2.80	

* ADHD–T: ADHD–Treated group. ADHD–NT: ADHD–Non-Treated group.
** Age in this study has been transformed into years; the study provided age in months.
*** Not provided age per ADHD group.
**** Although this study states its participants are the same as in the Ivanov et al. (2010), the age means for the control group do not coincide across studies.

Findings of the Studies Reviewed

Study 1 (Semrud–Clikeman, Pliszka, Lancaster, and Liotti, 2006) reported a smaller volume of the caudate for both of the ADHD groups (Treated and Non-Treated) than for the control group. It also noted a smaller volume of the right anterior cingulate cortex (ACC) in the Non-Treated group of ADHD children in comparison to the two other groups, although no statistical differences were found between the Treated and Non-Treated groups regarding the ACC as a whole. The authors hypothesized that "normalization" effects of medication on the caudate would be observed between both ADHD groups, yet in fact "no significant differences in asymmetry between the groups" was found (p. 1025). An additional result was that no relationship was found between ACC volume and the parent ratings on response inhibition, or between ACC and attention scores on the Behavior Assessment Scale for Children.

In study 2 (Bledsoe, Semrud–Clikeman, and Pliszka, 2009), the Non-Treated group had smaller posterior-inferior vermis (a part of the cerebellum) than the Treated and control groups. This time the authors concluded that a pharmacological normalization effect was produced in the chronically treated children, but only on this particular area of the cerebellum. Other vermal structures, total vermis area, or intracranial area did not differ statistically between the groups. The children included in the ADHD–Treated group had been treated with stimulant medication, unspecified in the study, for at least one year (range from 2.3 to 5 years). As I have described above, the chronic intake of such medication produces changes, specifically atrophy, in a wide range of cerebral areas.

In study 3 (Schnoebelen, Semrud–Clikeman, and Pliszka, 2010), contrary to the authors' initial hypothesis, no significant differences were found for corpus callosum, and only the splenium (its thickest part) was smaller in the ADHD–Non-Treated group. This time the authors could not invoke a "normalizing" effect of the medication, and they opted for explaining this finding by stating that "the current investigation did not suggest that chronic stimulant treatment results in significant, potentially negative neuroanatomical changes" (p. 263). However, why did the medication not produce any changes this time, since the neurobiological view of these authors, along with others, is that pharmacological treatment compensates and normalizes abnormal anatomical differences between ADHD-diagnosed and normal children?

In study 4 (Ivanov et al., 2010), the authors reported significantly smaller surface volumes in the pulvinar in both the ADHD groups (Treated and Non-Treated) compared with the control group, as well as larger thalamic surface volumes in ADHD–Treated compared with ADHD–Non-Treated participants. However, for the ADHD–Treated group the authors reported smaller regional volumes in the right lateral and medial posterior thalamic surfaces which were associated with a longer duration of treatment (p. 401). It seems contradictory

that, on the one hand, some ADHD–Treated children showed larger general thalamic volumes, but, on the other hand, different children in the same group who had a longer history of pharmacological treatment showed smaller volumes. The atrophic effects of medication are obvious in this case; however, the authors did not explain this contradiction. The only reasonable explanation is a methodological artifact.

Study 5 (Sobel et al., 2010) found significant differences only in the putamen, which was smaller for ADHD children (without distinguishing Treated or Non-Treated) than for control children. In addition, an enlargement of all basal ganglia surfaces was found in ADHD–Treated youths compared to Non-Treated–ADHD-diagnosed children. The caudate and globus pallidus did not differ between ADHD groups. Although the authors could attribute the first result to the biological difference between ADHD-diagnosed and control children, how could they explain the absence of difference between both ADHD groups? The authors mentioned "seeming morphological normalizing effects of stimulant medications" on basal ganglia or on regions connected to them (p. 986). If this is so, it is hard to explain why areas directly related to basal ganglia, or sub-areas that are part of them, did not show differences between Treated and Non-Treated ADHD-diagnosed children.

Study 6 (Semrud–Clikeman, Pliszka, Bledsoe, and Lancaster, 2014) found larger frontal, prefrontal, and caudate volumes for both ADHD groups compared to the control group, as well as smaller right anterior cingulate cortex for the ADHD–Non-Treated group. The discussion of this study is astonishingly contradictory. The authors concluded that:

> The caudate was smaller bilaterally in the controls relative to children with ADHD, and there was no effect of stimulant treatment history on this variable. These findings may indicate that the caudate is a structure that is "hard-wired"; that is, medication may not change its volume. This volume is consistent with previous literature indicating that boys with ADHD have smaller caudate volumes throughout development compared with typically developing peers. (p. 517)

Semrud–Clikeman, Pliszka et al. considered that the caudate is "hard wired" (i.e., not modifiable by medication) because both ADHD groups present larger mean volumes than that of the control group, but this fact is not sufficient for extracting such a conclusion. Only a pre/post treatment analysis of anatomical differences at an individual level permits this conclusion. Furthermore, the first sentence of the paragraph ("The caudate was smaller bilaterally in the controls relative to children with ADHD") is not consistent with the third, which entirely states the contrary ("boys with ADHD have smaller caudate volumes throughout development compared with typically developing peers"). Thus, the results reported by this study in relation to the caudate contradict the results of other studies. The conclusions of Semrud–Clikeman et al. with respect to pre-frontal

volumes are also contradictory. They found greater grey and white matter volumes in ADHD–Treated and ADHD–Non-Treated compared to control children, and they claimed this was coherent with the results reported by Castellanos et al. (2002). However, Castellanos et al. stated the contrary: "unmedicated children with ADHD also exhibited strikingly smaller total white matter volume compared with controls and with medicated children with ADHD" (p. 1740). These contradictions obviously weaken the coherency of Semrud–Clikeman et al.'s arguments.

Finally, study 7 (Ivanov, Murrough, Bansal, Hao, and Peterson, 2014) reported findings obtained from the same sample of subjects employed by Ivanov et al. (2010). However, Ivanov et al. (2014) did not state why they chose not to report these findings in their earlier study (Ivanov et al., 2010).[4] In the 2014 study, the authors found smaller regional volumes in the left anterior surface of the cerebellum for ADHD children compared with control participants. The ADHD–Treated group showed an increased left anterior cerebellar volume compared with non-medicated ADHD participants. However, the authors acknowledged that "these findings did not survive false discovery rate (FDR) corrections" (p. 722); that is, the rate of type I errors when conducting multiple comparisons. Thus, Ivanov et al. could be reporting a "false positive." Furthermore, overall cerebellar volume did not differ between ADHD and control groups. As the authors observed differences in areas other than those reported in earlier studies, they concluded that "treatment did not `normalize´ morphological abnormalities linked to ADHD but rather increased regional volumes in neighboring structures, suggesting that the enlargement may have in turn attenuated ADHD symptoms via a compensatory morphological abnormality" (p. 724). The logic of this ad hoc explanation is intriguing. Ivanov et al. supposedly detected anatomical differences between ADHD-diagnosed and control children, but since the specific areas they found in the group of ADHD–Treated children did not coincide with those of other studies, these authors concluded that the pharmacological effect of medication had been produced on adjacent areas instead of on the ADHD-relevant areas themselves. However, Ivanov et al. did not explain why this occurred.

In summary, several incoherencies appear when these seven studies are examined in detail. In all seven studies the authors are trying to demonstrate two things at the same time: (a) that psychiatric medication for ADHD does not have negative effects — that is, atrophic effects, as reported by the studies I have cited in the first pages of this paper; and (b) that psychiatric medication for ADHD "normalizes" and thus enlarges abnormal areas. The second hypothesis is based on the assumption that the atrophic results found in traditional ADHD studies are due to underlying intrinsic neurobiological conditions and are not a consequence of ADHD treatment. Some contradictions appear in the attempts

[4] Ivanov et al. (2014, p. 719) state: "This sample has been described elsewhere (Ivanov et al., 2010)."

to demonstrate both hypotheses. For instance, no systematic differences were found between ADHD–Treated and ADHD–Non-Treated, ADHD–Treated and control, or ADHD–Non-Treated and control. Following the authors' logic, ADHD–Non-Treated should have always shown smaller cerebral areas than controls and ADHD–Treated, with the ADHD–Treated displaying areas equal to those of the controls. The results are far from this. In the next section, I consider the methodological flaws in these seven studies (see Table 2). In the last section I will review the conceptual and neuroanatomical incoherencies that I have found in these seven studies. These incoherencies are so pronounced that the validity of those studies must be called into question.

Critical Review of Methodological Variables

Insufficient Sample Size

Steen, Hamer, and Lieberman (2007) examined the requirements (e.g., statistical power) that samples must have to be considered appropriate in cross-sectional neuroimaging research. They concluded that such studies must have a minimum of 73 participants per group. Furthermore, some areas such as the caudate nucleus require a larger sample size of at least 128 participants per group. Only longitudinal designs permit a lesser number of participants. Whether this group size is met or not, individual differences do not allow for the conclusion that the volumetric indices found are consistent in a given group of subjects. As we can see in Table 2, the size of the groups in the seven studies is far below those specified by Steen et al.'s guidelines. The seven studies I have reviewed are cross-sectional, and although four of them included a follow-up, none reported the temporal interval elapsed until the follow-up was carried out. To put these figures in context, studies 1 and 6 would have needed more than one hundred children per group.

The fact that the studies reviewed did not meet this fundamental criterion for research on group comparisons nor presented individualized data impedes establishing any type of conclusion. Remember that the statistical grouping of participants was inappropriate since MRI is indicated as an individual diagnostic tool (Wilkinson and Graves, 2015, p. 91). Moreover, the image representation employed by some of these studies (4, 5, and 7) is confusing. The researchers provided some colored images of brain areas, but these images were neither real nor individual, being mere generic representations in which the authors symbolized *p* values in different colors.

An additional problem concerns the statistic calculations employed, given the construction of sample sizes. In six of the seven studies reviewed, the ADHD–Non-Treated condition had fewer children than the other two conditions. The percentage of difference in the number of participants between the groups was above 10% in nearly all of the cases. In the only study in which the Non-Treated

Table 2
Main Methodological Faults Involved in the Studies Reviewed

Study	Number of Participants Needed in Each Group to Form Statistically Appropriate Groups*	Percentage of Difference in the Number of Participants between the Groups	Percentage of Boys and Girls per Group	Mean Bodily Volume of the Participants per Group	Mean Brain Volume of the Participants per Group (Cubic Centimeters)
1. Semrud–Clikeman et al. (2006)	ADHD–T: 57/112 ADHD–NT: 59/114 Control: 52/107	ADHD–T/ADHD–NT: 12% ADHD–T/Control: 23% ADHD–NT/Control: 33%	ADHD–T ADHD–NT: 71%/29% Control	Not specified	Not specified
2. Bledsoe et al. (2009)	ADHD–T: 55 ADHD–NT: 59 Control: 58	ADHD–T/ADHD–NT: 22% ADHD–T/Control: 16% ADHD–NT/Control: 6%	ADHD–T ADHD–NT: 79%/31% Control	Not specified	ADHD–T: 127.9 ADHD–NT: 125.6 Control: 125.1
3. Schnoebelen et al. (2010)	ADHD–T: 61 ADHD–NT: 60 Control: 58	ADHD–T/ADHD–NT: 7% ADHD–T/Control: 20% ADHD–NT/Control: 13%	ADHD–T: 84%/16% ADHD–NT: 54%/46% Control: 74%/26%	Not specified	ADHD–T: 137.9 ADHD–NT: 134.9 Control: 133.2
4. Ivanov et al. (2010)	ADHD–T: 42 ADHD–NT: 58 Control: 14	ADHD–T/ADHD–NT: 51% ADHD–T/Control: 47% ADHD–NT/Control: 74%	ADHD: 82%/18%** Control: 55%/45%	Not specified	Not specified
5. Sobel et al. (2010)	ADHD–T: 42 ADHD–NT: 57 Control: 16	ADHD–T/ADHD–NT: 48% ADHD–T/Control: 45% ADHD–NT/Control: 68%	ADHD–T: 69%/31% ADHD–NT: 87%/13% Control: 66%/34%	Not specified	Not specified
6. Semrud–Clikeman, Pliszka et al. (2014)	ADHD–T: 57/112 ADHD–NT: 60/115 Control: 58/113	ADHD–T/ADHD–NT: 18% ADHD–T/Control: 6% ADHD–NT/Control: 13%	ADHD–T: ADHD–NT: 66%/34% Control	Not specified	Not specified
7. Ivanov et al. (2014)	ADHD–T: 42 ADHD–NT: 58 Control: 14	ADHD–T/ADHD–NT: 51% ADHD–T/Control: 47% ADHD–NT/Control: 74%	ADHD: 82%/18%** Control: 55%/45%	Not specified	Not specified

* I take the criteria established by Steen et al. (2007). The first number refers to general minimum size (n = 73) for cross-sectional neuroimaging studies, and the second number refers to specific minimum size for comparing caudate nucleus (n = 128).
** The study does not differentiate between ADHD–T and ADHD–NT.

group was not the smallest, the proportion of boys and girls was clearly unbalanced (see below). Five studies employed an ANOVA (Bledsoe et al., 2009; Ivanov et al., 2010, 2014; Semrud–Clikeman et al., 2006; Sobel et al., 2010), and the other two employed, respectively, a MANCOVA (Schnoebelen et al., 2010) and a MANOVA (Semrud–Clikeman, Pliszka et al., 2014). Again, the samples in the seven studies did not reach the appropriate criteria required to optimally apply these analyses because unbalanced data diminishes the robustness and power of the tests (see Gelman, 2017; Montgomery, 2001; Wilkinson, 1999). In addition, Moore and McCabe (2003, p. 556) argued that an ANOVA cannot be applied as an hypothesis test to determine whether two different samples have the same variance; instead, they recommend an ANOVA when two estimates of the variance for the same sample are compared.

Number of Boys and Girls per Group

Several studies have found sex differences in normal brain volume maturation. For example, De Bellis et al. (2001) described significant age- and sex-related differences in the volume of white and gray matter, as well as in the volume of the corpus callosum, even when intracranial and total cerebral volume did not change significantly. They specifically found that males had a greater age-related decrease of gray matter as well as an increase of white matter and corpus callosum when compared to females. Additionally, Sowell, Trauner, Gamst, and Jernigan (2002) found that females had greater relative volumes in the meso-temporal cortex, caudate, thalamus, and basomesial diencephalic structures than males. Durston et al. (2001) replicated this finding with regard to the caudate, and also noted that the average volumes of the amygdala and brain were larger in boys. Paus (2010) found that boys also have a larger putamen and pallidum than do girls, and Reiss, Abrams, Singer, Ross, and Denckla (1996) found that after five years of age total cerebral volume was 10% larger in boys as compared to girls. This difference remained constant up to 17 years of age. No evidence of growth in total cerebral volume between the ages of five and 17 years was found. Additionally, the authors described both a loss of cortical (pre-frontal) gray matter and a gain in white matter with age. This is probably due to the process of myelination produced in the first two decades of life, which illustrates the dynamism of the brain during childhood and adolescence. Although some of these studies about sex differences also employ MRI in cross-sectional samples, and therefore are subject to the same criticisms I have made in regard to the application of such techniques to calculate brain volume differences across groups, such studies should be taken into account by neuroimaging research to at least consider the importance of sex when bodily volumes (brain volumes in this case) are estimated at group level. In any case, what is evident beyond the studies mentioned is that boys and girls differ in their body mass; consequently, this variable must be balanced across groups.

What do we find when we explore the formation of the comparative groups in the ADHD studies reviewed? Semrud–Clikeman et al. (2006) and Semrud–Clikeman, Pliszka et al. (2014) stated that there were no significant differences between the groups in terms of sex, ethnicity, age, IQ, or WIAT achievement scores in reading or mathematics. However, in the demographic data table only details on means and standard deviations of age, IQ, WIAT results, general cognitive ability, and Conners's scale scores are found. There is no distribution by sex, as would have been advisable, since the sample was composed of 15 girls and 36 boys in the first study, and 15 girls and 29 boys in the second. In the Bledsoe et al. (2009) study, the researchers simply failed to specify the distribution of children by sex and the significance of this variable (the sample included 15 girls vs. 32 boys).

In Schnoebelen et al. (2010), the number of boys and girls assigned to the ADHD–Non-Treated group was disproportionate, in comparison to the other two groups (see Table 2). However, either no significance tests were conducted, or if the authors did so they did not report them. Sobel et al. (2010, p. 985) asserted that both ADHD–Treated and Non-Treated groups were similar in sex and age; however, the ADHD–Treated condition had 69% boys compared to 66% (38 boys) in the control group, whereas the ADHD–Non-Treated group had 87% boys. Obviously, the groups were disparate on this variable. The authors reported an enlargement of the basal ganglia surface in the ADHD–Treated group compared to the ADHD–Non-Treated group; i.e., for the group with a larger number of girls, which is an expected result according to normal sex differences (Kipke, 1999; Sowell et al., 2002).

Ivanov et al. (2010, 2014) employed the same samples, and both studies only mentioned that the control group (59 youths) was composed of 33 boys (and therefore 26 girls) while the ADHD total group (46 participants) was composed of 38 boys (and therefore 12 girls). Within this ADHD group there were 31 treated youths and 15 non-treated youths, but no additional information was provided about the distribution of sex in these two sub-groups.

One of the basic principles of research is to provide the most specific description as possible of the conditions and participants, so that the study can be replicated. The lack of information in some of the reviewed studies obviously makes replication impossible. The studies that did provide specific information had an unequal number of boys and girls per group.

Age, Body Mass, and Volume

Another fundamental issue pertains to the body mass of the participants. A positive correlation between some anthropometric indices (height, weight, age, and body mass index) and brain volume has been found for both sexes (Bayat, Ghanbari, Sohouli, Amiri, and Sari–Aslani, 2012). Therefore, there are differences in brain volumes not only depending on the sex and age of the subjects, but also depending on the height and weight of subjects of the same age. None of the seven

ADHD studies presents data concerning these variables, and the fact that the variables were not controlled invalidates these studies. Likewise, as mentioned above, the age range of the participants was from seven to 18 years old. Only Bledsoe et al. (2009) omitted the age range, instead providing the mean age (i.e., 11.34 years ± 2.42). Although the mean age seems well distributed in the seven studies, the control group had the oldest participants (or the highest mean) in three of the seven studies (Schnoebelen et al., 2010; Semrud–Clikeman et al., 2006; Semrud–Clikeman, Pliszka et al., 2014). In Bledsoe et al. (2009), the group with the highest mean was the ADHD–Non-Treated one. In Semrud–Clikeman et al. (2006), the control group showed the largest volumes in all the areas measured except for one: the ADHD–Treated group had the second oldest participants with regard to mean age. In Bledsoe et al. (2009), the ADHD–Non-Treated group (the group with the highest mean age) showed the largest volume of the total vermis, and the ADHD–Treated group (the second oldest group in terms of mean age) showed the largest intracranial volume and posterior superior vermis lobules. In Schnoebelen et al. (2010), the control group (the group with the highest mean age) showed the largest volume in the only area for which statistically significant differences were found; i.e., the splenium. This was found despite the fact that this group did not show the largest brain volume. The ADHD–Treated group (the second highest mean age) and the ADHD–Non-treated group (the third highest mean age) had, respectively, smaller splenium volumes.

In contrast, in Semrud–Clikeman, Pliszka et al. (2014), the control group (highest mean age according to the measures reported) showed the largest volumes for the caudate. The ADHD–Non-Treated group (second highest mean age) showed the largest volume for right-side pre-frontal white matter, and the ADHD–Treated group showed the largest volume for the right prefrontal gray matter and right-side anterior cingulate cortex. Even so, Semrud–Clikeman, Pliszka et al. (2014) stated that "the age range for the current study was children aged 11.17 to 16.3 years with the majority of children aged 12.75 to 15 years, whereas for the first study the range was from 9.0 to 12.6 with the majority of children aged 9 to 10.6 years" (p. 518). Semrud–Clikeman et al. thus acknowledged that the age of the participants was not well balanced between the groups.

Clinical Neuroanatomy and Inconsistent Findings

ADHD has been defined by mainstream psychiatry as a mental disorder characterized by three groups of symptoms: a) lack of sustained attention when individuals are required to complete complex tasks, which generally results in a task being abandoned before its completion or completed with many errors; b) impulsive behaviors, such as responses that an individual emits without considering how they must be performed or the consequences they have; and c) hyperactive behaviors, such as behaviors that are goal-directed, continuous, and

successive in contexts requiring delay in achieving some targets or the inhibition of disruptive actions (DSM-5; APA, 2013, pp. 59–60). These three groups of criteria include chains of responses, given sorts of social situations in which they appear, and some types of demands made by others. Consequently, these behaviors are not simple muscular movements. Although ADHD consists of complex behaviors that happen according to a social setting, mainstream psychiatry has traditionally defined it as a mental disorder with biological causes.

Classically (see Castellanos et al., 2002), neurobiological research on ADHD has stipulated that the main brain effects on ADHD-diagnosed children were: a) smaller total white matter volume; b) smaller total cerebral volume; c) smaller cerebellar volume; and d) smaller caudate nucleus. Other authors (see Curatolo et al., 2010) have added additional areas for study: a) pre-frontal cortex; b) dorsal anterior cingulate cortex; c) putamen; d) corpus callosum; and e) basal ganglia. Involving all of these areas is similar to saying that 80% of the brain is impaired in ADHD subjects, a figure which seems somewhat exaggerated. Furthermore, as mentioned above, the majority of these areas are affected by psychiatric drugs prescribed to ADHD-diagnosed children.

However, the results on brain areas are not as firm as researchers claim (see Table 3). I will focus specifically on the seven ADHD studies I have reviewed above, and I will examine the neurological functions of the areas mentioned in the seven studies from a clinical perspective (i.e., when a pathology is involved in an area) to decide whether the role of those areas is consistent with the ADHD clinical behavioral implications.

Semrud–Clikeman et al. (2006) found smaller volumes for the caudate nucleus in the ADHD groups compared to those of the control group, whereas Semrud–Clikeman, Pliszka et al. (2014) found larger volumes for the caudate nucleus in the ADHD groups compared to those of the control group. Both results are clearly contradictory; besides, there were no significant differences between the two ADHD groups. According to Snell (1992), the caudate nucleus, as a part of the basal ganglia, controls muscular movements through fibers which project into the cerebral cortex. The most common clinical syndromes observed when there are alterations or pathologies in the caudate are Huntington's chorea and Parkinson's disease. In addition, the tail of the caudate seems to be involved in visual processing, and a lesion in this part affects visual discrimination (Seger, 2013). Investigators researching ADHD seem to confound "muscular control" with "behavioral control" and "attention" with "visual capability." As I have stated at the beginning of this section, the clinical criteria that define ADHD are complex behaviors that are produced in social situations and in relation to demands made by other persons. Conversely, the functions impaired by neurological pathologies in the basal ganglia consist of the alteration of basic muscular movements and of motor coordination. In the specific clinical pathologies of the caudate nucleus the voluntary control of muscles is altered, while behaviors under the label of ADHD

Table 3
Anatomical and Clinical Incoherencies of the Findings Reported

Brain Areas Studied	**Neurological Functions***	**Common Clinical Neuropathologies Associated with Anatomical and Functional Abnormalities***	**Types of Abnormalities Affecting Normal Neurological Functions***	**Findings Reported as Alleged Abnormalities and Contradictory Findings****	
Basal ganglia	Control of voluntary movements	Parkinson-like involuntary movements Dystonia	Calcification Atrophy Sclerosis Infectious neurodegeneration Pharmacological neurodegeneration (metoclopramide, antihystaminics, neuroleptics, antiepyleptics, SSRI, methylphenidate)	Surface in ADHD–T > ADHD–NT and Control [5]	ADHD–T < Control (d)
Putamen	Control of fine voluntary movements	Parkinson's disease Wilson's syndrome	Perinatal hypoxic isquemic stroke (neuronal death or apoptosis)	No differences between ADHD–T and ADHD–NT [5]	ADHD–T and ADHD–NT < Control [5]
Caudate	Control of muscular movements Visual information processing	Huntington chorea Parkinson's disease Visual discrimination impairment	Lack of dopamine release due to degenerative neuronal atrophy Hypertrophy by tumors that compress the internal arm of the internal capsule Damage	Bilateral caudate volume in ADHD–T and ADHD–NT < Control [1]	Bilateral caudate volume in ADHD–T and ADHD–NT > Control [6] No differences between ADHD–T, ADHD–NT and Control [5] Left in ADHD–T < Control; no difference in right caudate (a) Right in ADHD–T < Control; left asymmetric in ADHD (b) Bilateral in ADHD–T < Control (c, d) Right in ADHD–NT > Control (e)
Globus pallidus	Control of voluntary and involuntary muscular movements	Parkinson's disease Wilson's syndrome	Perinatal hypoxic isquemic stroke (neuronal death or apoptosis) Damage	No differences between ADHD–T and ADHD–NT [5]	ADHD–T < Control (c)

Table 3 (Continued)

Brain Areas Studied	Neurological Functions*	Common Clinical Neuropathologies Associated with Anatomical and Functional Abnormalities*	Types of Abnormalities Affecting Normal Neurological Functions*	Findings Reported as Alleged Abnormalities and Contradictory Findings**	
Anterior cingulate cortex (ACC)	Musculoskeletal activity Autonomic activation Endocrinal activation Painful stimulation transmission Reinforcing stimulation transmission	Fear reactions abolishment Exaggerated aggressive responding Lack of identification of voices and facial expressions	Damage	Right ACC in ADHD–T < ADHD–NT and Control; left ACC no differences [1]	Right ACC in ADHD–NT < ADHD–T and Control [6]
Cerebello	Muscular tone Movement coordination	Hypotonicity Postural alterations Tremor, ataxias Dysdiadochokinesia Dysarthria by ataxia of larynx muscles	Aplasia Atrophy Cerebellar hypoplasia Hemorrhage (stroke)	No differences between ADHD–T, ADHD–NT, and Control [2]	Left anterior and right posterior in ADHD–T and ADHD–NT < Control [7]. Whole left surface in ADHD–T > ADHD–NT [7]
Vermis	Control of medial body structures	Lack of coordination of head and trunk muscles	Aplasia Atrophy Agenesia	Posterior inferior V. in ADHD–NT < ADHD–T and Control [2]	Posterior inferior V. in ADHD–T < control (f, g) Superior in more severe ADHD< ADHD less severe (but not significant) [7]
Corpus callosum (CC)	Interconnection of symmetric areas of the cortex	Two-brains syndrome Joubert syndrome (ocular–motor apraxias, hypotonicity...) Gillespie syndrome Dandy–Walker syndrome Instability syndrome	Damage Dysgenesia Hypoplasia	No differences between ADHD–T, ADHD–NT, and Control [3]	Anterior and posterior CC in ADHD–T < Control (h) Rostral body of CC in ADHD–T < Control (i, j)

Table 3 (Continued)

Brain Areas Studied	Neurological Functions*	Common Clinical Neuropathologies Associated with Anatomical and Functional Abnormalities*	Types of Abnormalities Affecting Normal Neurological Functions*	Findings Reported as Alleged Abnormalities and Contradictory Findings**	
Splenium	Interconnection of parietal-temporal fibers projected from visual areas	Dysarthrias, ataxias Disconnection syndrome Apraxias Hallucinations	Damage	ADHD–NT < Control [3]	ADHD–T < Control (k)
Thalamus	Connection between visual and pre-motor areas; sensorial information transmission Movement coordination Arousal, sleep regulation, etc.	Wilson's syndrome Progressive encephalic paralysis Spastic tetraparesia Cognitive deterioration Ataxia Dysarthria	Perinatal hypoxic isquemic stroke (neuronal death or apoptosis) Tumor (hypertrophy)	Total volume in ADHD–T > ADHD–NT [4] Anterior, posterior, ventral-lateral right hemi-thalamus, and posterior surface of left hemi-thalamus in ADHD–T and ADHD–NT < Control [4]	Total volume in ADHD–T < Control [l] Only left thalamus in ADHD–T < Control (m)
Vermis	Integration of multiple somatic–sensorial afferences, pre-motor ocular control, motor speech control, complex social discriminations, initiative actions, judgments, and values, etc.	Emotional recognition impairment Perceptual judgment impairment Impairment in decision-taking tasks Others	Damage Focal cortical dysplasias Tumor on supratentorial area	Frontal and pre-frontal in ADHD–T and ADHD–NT > Control [6]	ADHD–T < Control (d) ADHD–T < Control (n) ADHD–NT < Control (o)

* Main bibliographic sources: Snell (1992); Verdú (2016).

** The numbers inside brackets refer to the studies included in Table 1. The letters in parentheses refer to the following studies, whose participants will be considered as ADHD–Treated (ADHD–T), because all or a major part were on pharmacological treatment, except study e, in which no subject was receiving medication:

(a) Hynd et al. (1993)
(b) Castellanos et al. (1994)
(c) Castellanos et al. (1996)
(d) Filipek et al. (1997)
(e) Mataro, Garcia–Sanchez, Junque, Estevez–Gonzalez, and Pujol (1997)
(f) Berquin et al. (1998)
(g) Mostofsky, Reiss, Lockhart, and Denckla (1998)
(h) Hynd et al. (1991)
(i) Giedd et al. (1994)
(j) Baumgardner et al. (1996)
(k) Semrud–Clikeman et al. (1994)
(l) Batty et al. (2015)
(m) Xia et al. (2012)
(n) Edmond et al. (2009)
(o) Castellanos et al. (2002)

are "voluntarily" hyperactive. Tremors and uncoordinated jerky movements are not in the same category as inconvenient behaviors, such as standing up in situations in which sitting down is requested, running around at inappropriate times, and talking excessively or blurting out an answer before a question has been completed (these are some hyperactive criteria included in DSM-5 for ADHD; APA, 2013, p. 60).

Curatolo et al. (2010) and Edmond, Joyal, and Poissant (2009) summarized the ADHD literature as reporting reductions in the volume of the basal ganglia (see also Filipek et al., 1997). Sobel et al. (2010) found larger basal ganglia surfaces in ADHD-treated participants compared with non-treated participants, and they concluded that stimulants normalized morphological features of this region in children with ADHD (p. 977). However, other researchers have reached contradictory conclusions (see Ivanov et al., 2014, p. 724). That is, this treatment did not normalize the ADHD morphological abnormalities, but rather increased adjacent regional volumes. Marsden and Obeso (1994) posit that the basal ganglia play a role in controlling voluntary movements through their influence on motor regions of the cortex via the thalamus. This is because basal ganglia are a set of nucleuses that controls the firing of neurons of the reticulata and of the medial pallidal areas, permitting movements generated by cortical motor areas. Damage to these nucleuses produces involuntary movements such as those observed in Parkinson's disease. As I have argued above, these "involuntary" movements cannot be classified as "hyperactive" behaviors.

Ivanov et al. (2014) reported an additional finding regarding the putamen. Although some research describes a correlation of "ADHD traits" in children with median lesions in the putamen (see Max et al., 2002), traditional neurological research has systematically related lesions of the putamen with dystonia (Burton, Farrell, Li, and Calne, 1984; Fross et al., 1987), a neurological disorder in which muscle contractions produce twisting movements and abnormal postures.

In contrast, regarding the anterior cingulate cortex, Semrud–Clikeman et al. (2006) found that the ADHD–Non-Treated group showed smaller volume only for the right side of the structure. This group did not differ from the other two groups for the left side of the anterior cingulate cortex. The anterior cingulate cortex plays a relevant role in the control of biological functions such as musculoskeletal activity, autonomic and endocrinal activation, processing of painful information, emotions, and stimulation reinforcement (Devinsky, Morrell, and Vogt, 1995). According to Semrud–Clikeman et al. (2006), the implication of this region in ADHD is justified as part of an "abnormal fronto–striatal circuitry" that would produce a "response inhibition," particularly for the performance of a "behavioral response" (p. 1026). Sobel et al. (2010) extended this "fronto–striatal circuitry" to a cortico–striato–thalamo–cortical one. These authors unfairly deduce that an abnormality in this area can be inferred from a volumetric difference between groups of subjects.

However, a musculoskeletal response inhibition that could produce a neuropathological condition in this area is not akin to the inattention observed when individuals make careless mistakes in schoolwork, have difficulty sustaining attention on tasks like reading, experience difficulty in organizing tasks, or are reluctant to engage in tasks that require sustained mental effort (these are some of the inattentiveness criteria included in DSM-5 for ADHD; APA, 2013, p. 59). Some classic experiments report the elimination of fearful reactions and exaggerated aggressiveness when the cingulate cortex is damaged (Koridze and Oniani, 1972). More recent studies have found that a combined lesion of the orbitofrontal and cingulate cortices produces a serious impairment of the identification of both voices and emotional face expressions (Hornak et al., 2003). However, neither of these extremes is considered in the ADHD clinical criteria.

In addition, Semrud–Clikeman, Pliszka et al. (2014) found that the prefrontal volume was larger in the ADHD groups than in the control group. However, as I have just described, research suggests smaller rather than larger prefrontal volumes in ADHD individuals (Castellanos et al., 2002; Curatolo et al., 2010; Edmond et al., 2009; Hynd et al., 1993). Thus, this result is clearly incongruent with previous research, and has no coherent explanation within the current ADHD neurobiological understanding. In addition, the neurological implications of these brain areas are quite complex, and involve the integration of multiple cortical and subcortical afferents. The frontal cortex is involved in multiple functions such as pre-motor ocular control, motor speech control, and somatesthetic integration of stimuli. The prefrontal cortex integrates manifold information and regulates facets of complex social discriminations and behaviors linked to personality, initiative, judgments, and values (Snell, 1992). Therefore, prefrontal and frontal lesions do not produce uniform behavioral patterns, and depending on the specific sub-area affected, the extent of the damage, and the connection of these sub-areas with other areas, the effects are somewhat different on emotional recognition, perceptual judgment, and decision-making tasks (Driscoll, 2009; Manes et al., 2002).

Another brain region implicated in ADHD is the cerebellum. Bledsoe et al. (2009) found statistically significant differences in the posterior inferior vermis of the cerebellum after scanning the entire cranium on distinct planes (according to their procedural explanations). No other area of the vermis, of the cerebellum, or any intracranial region showed statistically significant differences (p. 622). This contrasts with, and contradicts, the results found by Ivanov et al. (2014), who found statistically significant differences in the left anterior and right posterior cerebellum. It is rather disconcerting that none of the typical areas involved in ADHD presented statistically significant differences in this study. Furthermore, when cerebellar anatomic pathologies are taken into account, typical cerebellar dysfunctions found are: hypo-tonicity, postural and walking alterations, tremors, ataxias, lack of motor coordination, dysdiadochokinesia (i.e., inability to alternate

movements), increases in the latency of the patellar reflex, nystagmus, and dysarthria by ataxia of the larynx muscles (Snell, 1992). This clearly shows that the cerebellum plays a leading role in the maintenance of muscular tone and movement coordination. Snell (1992) also details some specific consequences of vermis impairment. Due to the fact that the vermis influences the control of medial body structures, damage in the vermis results in a lack of coordination of the head and trunk muscles, but does not affect the extremities. Consequently, it is hard to imagine how one could link a true cerebellar pathology (or damage to the vermis) to the behavioral criteria included in the diagnosis of ADHD.

Ivanov et al. (2010) found greater surface volumes of the thalamus in ADHD–Treated youths than in ADHD–Non-Treated youths, but discovered lesser surface volumes of the pulvinar (the posterior regions of the thalamus) in both ADHD groups compared with the control group. The different nuclei of the pulvinar play a leading role in connecting visual and pre-motor cortical areas, and a lesion to them induces an alteration of saccadic eye movements, therefore altering the temporal order of perceptual judgments (Arend, Rafal, and Ward, 2008).

Schnoebelen et al. (2010) reviewed studies that focused on differences in the corpus callosum. Other authors have also cited this area in ADHD research (Castellanos et al., 1994; Hynd, et al., 1991). However, Schnoebelen et al. (2010) did not find differences in the total volume of the corpus callosum or in the total cerebral volume; this is also inconsistent with previous ADHD neuroimaging studies. They only reported differences in the splenium between the control group and the ADHD–Non-Treated group, but not between the control and the ADHD–Treated groups, or between both ADHD groups. The neuroanatomy and anatomic pathology of the corpus callosum consist of a series of fibers that interconnect symmetric areas of the cortex. The corpus callosum is fundamental in learning to discriminate between different sensorial modalities, as well as in transferring stimulation related to discriminative operant behavior from one hemisphere to the other (Snell, 1992). In fact, the destruction of this region results in the subject acting as if he had two separate brains. For example, a subject may not be able to describe an object laid on his left hand due to his inability to transmit the tactile information to the linguistic areas of the brain. Specifically, the splenium is the posterior and thinnest part of the corpus callosum, and its function is to connect parietal and temporal fibers that emanate from visual areas of the cortex (Knyazeva, 2013).

In summary, there is a low level of consistency in findings reported by different MRI-based ADHD studies at a neurological level. The same brain region may not consistently show statistically significant differences across studies. If we keep in mind the clinical manifestations of actual neuropathologies that can affect the brain areas reviewed, the studies that claim that an abnormal brain is at fault in ADHD-diagnosed subjects can be considered out of place. Sobel et al. (2010) made this type of claim. Bledsoe et al. (2009, p. 622) also suggested that

chronic medication treatment is related to the *normalization* of brain structures associated with symptoms of ADHD, and this pre-supposes "abnormal brain structures." However, when we examine specific structural brain abnormalities, we do not find clinical manifestations like those claimed to play a part in ADHD by researchers using MRI. Moreover, recent MRI research has not found differences among ADHD, control, and healthy siblings of individuals with ADHD in the process of cortical gyrification[5] (Forde et al., 2017), which is a new contradiction.

Finally, abnormal levels of dopamine in the brain are also a common and abstract explanation provided by the neurobiologist view of ADHD. But the only pathological causes identified until now for those abnormal levels are some metabolic diseases that involve deficits of three enzymes and one chemical precursor. When enzyme deficits produce abnormal levels of dopamine, the following neurological effects are produced: (a) a deficit of aromatic L-amino acid decarboxylase provokes deglutition impairment, hypotonia, dystonia, and oculogyric crisis; (b) a deficit of dopamine β-hydroxilase provokes hypothermia, hypotension, and convulsions; and (c) a deficit of tyrosine-hydroxilase provokes hypotonia, tremors, bradykinesia, myoclonia, oculogyric crisis, and palpebral ptosis. Abnormal levels of dopamine that are caused by a deficit in the metabolism of biopterins — a chemical precursor of dopamine — by GTPCH-I (guanidine–triphosphate–cyclo–hydroxilase) provoke dystonia, hypertonia, tremors, axial hypotonia, psychomotor delay, and autonomic dysfunctions (see Verdú, 2016). Therefore, deficits of dopamine caused by well-known metabolic diseases do not reflect ADHD-like symptoms.

Conclusions: Methodological Artifacts and Conflicting Personal Interests

Sample sizes of the studies reviewed in this paper are insufficient for achieving reliable and representative measures of brain volumes. A considerable deviation in the number of participants per group, a questionable use of inferential statistics, and a clear imbalance in the distribution of boys and girls per groups are areas of concern. Other problems include a subtle but consistent age bias that is reflected in the results of three of the seven studies reviewed, a total absence of information about the body mass indices of the participants in all studies, an astonishing list of incoherencies regarding structural "abnormalities" found across studies, and a total absence of correspondence between ADHD neurobiological proposals and experimentally documented neuro-pathological alterations. These are the methodological artifacts that, in my view, invalidate this "latest generation" of MRI

[5] "Gyrification" is the process by which the brain undergoes changes in surface morphology to create sulcal and gyral regions, which involves the functional organization of the cortex (see Ronan and Fletcher, 2015, p. 2475).

studies of ADHD. These studies did incorporate a necessary methodological control: separating ADHD participants into two groups (treated and non-treated). This was absent in all the studies reviewed by Leo and Cohen (2003). This control alone, however, was not enough. Other methodological faults limited the validity of these studies. An additional issue concerns the supposed normalization that chronic administration of stimulant medication produces in brain volume (Bledsoe et al., 2009, p. 622; Semrud–Clikeman et al. 2006, p. 1023; Sobel et al. 2010, p. 977), despite the avoidance of the fact that chronic stimulant treatment produces significant and potentially negative neuroanatomical changes (Ivanov et al., 2014, p. 724; Schnoebelen et al., 2010, p. 263; Semrud–Clikeman, Pliszka et al., 2014, p. 517). What are these researchers trying to say? Apparently, they are saying that chronic medication in ADHD improves (in their consideration) abnormal brain areas, and, simultaneously, that the same medication does not change (in their consideration) normal brain areas. Where differences are found, a "normalizer" effect is produced; where differences are not found, the drug "chooses" not to produce changes. Needless to say, the pharmacodynamic nature of psychostimulants prescribed for ADHD (i.e., methylphenidate, dextroamphetamines, and mixed amphetamine salts), as well as that of non-stimulants like atomoxetine and guanfacine, is not a "selective intelligent entity." The pharmacodynamic process affects all receptors of some specific neurotransmitters (usually dopamine and norepinephrine), regardless of the brain region where these receptors appear (Curatolo et al., 2010).

Finally, I would like to highlight an additional troublesome issue in this type of research. Just as previous authors have addressed the controversial interrelation that exists between pharmaceutical industries and psychiatric research support (Breggin, 2008; Gotzsche, 2013; Whitaker, 2011), there are also conflicts of interest in the studies reviewed. Steven Pliszka declared a conflict of interest for the Bledsoe et al. (2009, p. 621) study, inasmuch as he was a consultant for Shire and Ortho McNeil Pharmaceutical, and he received a grant from Ortho McNeil for that research. Likewise, both Margaret Semrud–Clikeman and Steven Pliszka, as involved researchers, declared a conflict of interest for the Schnoebelen et al. (2010, p. 263) study. They received a grant from Ortho McNeil Janssen and Shire Honorarium Pharmaceuticals, and worked as expert witnesses for Eli Lilly. Iliyan Ivanov, James Murrough, and Bradley Peterson declared in Ivanov et al. (2014) that they had no conflicts of interest; however, in the acknowledgements section they mentioned the contributions that Lundbeck, Janssen Research & Development, Avanir Pharmaceuticals, Eli Lilly, and Pfizer made to their research (p. 724).

The clinical use of psychiatric drugs can have effects beyond those on the central nervous system (Breggin, 2008). Several studies have reported effects on the cardiovascular system (Fischer and Barner, 1977; Henderson and Fischer, 1994), the endocrine system, and growth and biological maturation (Kohn, Tsang, and

Clark, 2012; Poulton, 2005). These side effects create a serious health concern for the children who are prescribed these medications, and therefore such drug use must be clearly justified. According to the analysis of these recent MRI studies, this justification does not exist, and clinicians must be aware of this situation when choosing between a behavioral and a pharmacological intervention. Furthermore, clinicians must reflect whether the diagnosis of ADHD refers to a well-established biological disorder, or to a descriptive label for a group of normal behaviors that some contexts require to be modulated and controlled.

References

APA. (2013). *Diagnostic and statistical manual of mental disorders* (fifth edition). Washington, DC: Author.

Arend, I., Rafal, R., and Ward, R. (2008). Spatial and temporal deficits are regionally dissociable in patients with pulvinar lesions. *Brain*, *131*, 2140–2152. doi: 10.1093/brain/ awn135.

Aylward, E.H., Reiss, A.L., Reader, M.J., Singer, H.S., Brown, J.E., and Denckla, M.B. (1996). Basal ganglia volumes in children with attention-deficit hyperactivity disorder. *Journal of Child Neurology*, *11*, 112–115. doi.org/10.1177/088307389601100210.

Batty, M.J., Palaniyappan, L., Scerif, G., Groom, M.J., Liddle, E.B., Liddle, P.F., and Hollis, C. (2015). Morphological abnormalities in prefrontal surface area and thalamic volume in attention deficit/ hyperactivity disorder**.** *Psychiatry Research*, *233*, 225–232. doi: 10.1016/ j.pscychresns.2015.07.004.

Baughman, F., and Hovey, C. (2007). *The ADHD fraud*: *How psychiatry makes "patients" of normal children*. Victoria, British Columbia: Trafford.

Baumeister, A.A., and Hawkins, M.F. (2001). Incoherence of neuroimaging studies of attention deficit/hyperactivity disorder. *Clinical Neuropharmacology*, *24*, 2–10. doi.org/ 10.1097/00002826-200101000-00002.

Baumgardner, T.L., Singer, H.S., Denckla, M.B., Rubin, M.A., Abrams, M.T., Colli, M.J., and Reiss, A.L. (1996). Corpus callosum morphology in children with Tourette syndrome and attention deficit hyperactivity disorder. *Neurology*, *47*, 477–482. doi.org/10.1212/ WNL.47.2.477.

Bayat, P.D., Ghanbari, A., Sohouli, P., Amiri, S., and Sari–Aslani, P. (2012). Correlation of skull size and brain volume, with age, weight, height and body mass index of Arak Medical Sciences students. *International Journal of Morphology*, *30*, 157–161. doi.org/ 10.4067/S0717-95022012000100028.

Berquin, P.C., Giedd, J.N., Jacobsen, L.K., Hamburger, S.D., Krain, A.L., Rapoport, J.L., and Castellanos, F.X. (1998). Cerebellum in attention-deficit hyperactivity disorder: A morphometric MRI study. *Neurology*, *50*, 1087–1093. doi.org/10.1212/WNL.50.4.1087.

Bledsoe, J., Semrud–Clikeman, M., and Pliszka, S. (2009). A magnetic resonance imaging study of the cerebellar vermis in chronically treated and treatment-naïve children with attention-deficit/hyperactivity disorder combined type. *Biological Psychiatry*, *65*, 620–624. doi: 10.1016/j. biopsych.2008.11.030.

Bledsoe, J.C., Semrud–Clikeman, M., and Pliszka, S. (2011). Neuroanatomical and neuropsychological correlates of the cerebellum in children with attention-deficit/hyperactivity disorder–combined type. *Journal of American Academy of Child and Adolescence Psychiatry*, *50*, 593–601. doi.org/10.1016/j.jaac.2011.02.014.

Bledsoe, J.C., Semrud–Clikeman, M., and Pliszka, S. (2013). Anterior cingulate cortex and symptom severity in attention-deficit/hyperactivity disorder. *Journal of Abnormal Psychology*, *122*, 558–565. doi: 10.1037/a0032390.

Breggin, P. (2008). *Brain-disabling treatments in psychiatry: Drugs, electroshock, and the psychopharmaceutical complex*. New York: Springer.

Burton, K., Farrell, K., Li, D., and Calne, D.B. (1984). Lesions of the putamen and dystonia: CT and magnetic resonance imaging. *Neurology*, *34*, 962–965. doi.org/10.1212/WNL. 34.7.962.

Carmona, S., Vilarroya, O., Bielsa, A., Trèmols, V., Soliva, J.C., Rovira, M., Tomàs, J., Raheb, C., Gispert, J.D., Batlle, S., and Bulbena, A. (2005). Global and regional gray matter reductions in ADHD: A voxel-based morphometric study. *Neuroscience Letters*, *389*, 88–93. doi.org/10.1016/j. neulet.2005.07.020.

Castellanos, F.X., Giedd, J.N., Eckburg, P., Marsh, W.L., Vaituzis, A.C., Kaysen, D., Hamburger, S.D., and Rapoport, J.L. (1994). Quantitative morphology of the caudate nucleus in attention deficit hyperactivity disorder. *American Journal of Psychiatry*, *151*, 1791–1796.

Castellanos, F.X., Giedd, J.N., Marsh, W.L., Hamburger, S.D., Vaituzis, A.C., Dickstein, D.P., Sarfatti, S.E., Vauss, Y.C., Snell, J.W., Lange, N., Kaysen, D., Krain, A.L., Ritchie, G.F., Rajapakse, J.C., and Rapoport, J.L. (1996). Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. *Archives of General Psychiatry*, *53*, 607–616. doi.org/10.1001/archpsyc.1996.01830070053009.

Castellanos, F.X., Lee, P.P., Sharp, W., Jeffries, N.O., Greenstein, D.K., Clasen, L.S., Blumenthal, J.D., James, R.S., Ebens, C.L., Walter, J.M., Zijdenbos, A., Evans, A.C., Giedd, J.N., and Rapoport, J.L. (2002). Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. *Journal of the American Medical Association*, *288*, 1740–1748. doi.org/10.1001/jama.288.14.1740.

Castellanos, F.X., Sharp, W.S., Gottesman, R.F., Greenstein, D.K., Giedd, J.N., and Rapoport, J.L. (2003). Anatomic brain abnormalities in monozygotic twins discordant for attention deficit hyperactivity disorder. *American Journal of Psychiatry*, *160*, 1693–1696. doi:10.1176/appi.ajp.160.9.1693.

Chang, L., Alicata, D., Ernst, T., and Volkow, N. (2007). Structural and metabolic brain changes in the striatum associated with methamphetamine abuse. *Addiction*, *102* [Suppl. 1], 16–32. doi.org/10.1111/j.1360-0443.2006.01782.x.

Cole, R.L., Konradi, C., Douglass, J., and Hyman, S.E. (1995). Neuronal adaptation to amphetamine and dopamine: Molecular mechanisms of prodynorphin gene regulation in rat striatum. *Neuron*, *14*, 813–823. doi.org/10.1016/0896-6273(95)90225-2.

Curatolo, P., D'Agati, E., and Moavero, R. (2010). The neurobiological basis ofADHD. *Italian Journal of Pediatrics*, *36*, 299–304. http://doi.org/10.1186/1824-7288-36-79.

De Bellis, M.D., Keshavan, M.S., Beers, S.R., Hall, J., Frustaci, K., Masalehdan, A., Noll, J., and Boring, A.M. (2001). Sex differences in brain maturation during childhood and adolescence. *Cerebral Cortex*, *11*, 552–557. doi.org/10.1093/cercor/11.6.552.

Devinsky, O., Morrell, M.J., and Vogt, B.A. (1995). Contributions of anterior cingulate cortex to behaviour. *Brain*, *118*, 279–306. doi.org/10.1093/brain/118.1.279.

Driscoll, D.M. (2009). *The effects of prefrontal cortex damage on the regulation of emotion* (unpublished doctoral dissertation). Iowa City: University of Iowa.

Durston, S., Hulshoff, H.E., Casey, B.J., Giedd, J.N., Buitelaar, J.K., and van Engeland, H. (2001). Anatomical MRI of the developing human brain: What have we learned? *Journal of the American Academy of Child and Adolescent Psychiatry*, *40*, 1012–1020. doi.org/10.1097/00004583-200109000-00009.

Durston, S., Hulshoff, H.E, Schnack, H.G., Buitelaar, J.K., Steenhuis, M.P. Minderaa, R.B., Kahn, R.S., and van Engeland, H. (2004). Magnetic resonance imaging of boys with attention-deficit/hyperactivity disorder and their unaffected siblings. *Journal of the American Academy of Child and Adolescent Psychiatry*, *43*, 332–340. doi.org/ 10.1097/00004583-200403000-00016.

Edmond, V., Joyal, C., and Poissant, H. (2009). Structural and functional neuroanatomy of attention-deficit hyperactivity disorder (ADHD). *Encephale*, *35*, 107–114. doi: 10.1016/ j.encep.2008.01.005.

Eklund, A., Nichols, T.E., and Knutsson, H. (2016). Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates. *PNAS*, *113*, 7900–7905.doi:10.1073/pnas.1602413113.

Filipek, P.A., Semrud–Clikeman, M., Steingard, R.J., Renshaw, P.F., Kennedy, D.N., and Biederman, J. (1997). Volumetric MRI analysis comparing subjects having attention-deficit hyperactivity disorder with normal controls. *Neurology*, *48*, 589–601. doi.org/ 10.1212/WNL.48.3.589.

Fischer, V.W., and Barner, H. (1977). Cardiomyopathic findings associated with methylphenidate. *Journal of the American Medical Association*, *238*, 1497. doi: 10.1001/ jama.1977.03280150067014.

Forde, N.J., Ronan, L., Zwiers, M.P., Alexander–Bloch, A.F., Faraone, S.V., Oosterlaan, J., Heslenfeld, D.J., Hartman, C.A., Buitelaar, J.K., and Hoekstra, P.J. (2017). No association between cortical gyrification or intrinsic curvature and attention-deficit/hyperactivity disorder in adolescents and young adults. *Frontiers in Neuroscience*, *11*, 218. Retrieved from https://www.frontiersin.org/articles/10.3389/fnins.2017.00218/full.

Fross, R.D., Martin, W.R., Li, D., Stoessl, A.J., Adam, M.J., Ruth, T.J., Pate, B.D., Burton, K., and Calne, D.B. (1987). Lesions of the putamen: Their relevance to dystonia. *Neurology*, *37*, 1125. doi.org/10.1212/WNL.37.7.1125.

Galves, A., and Walker, D. (2012). Debunking the science behind attention-deficit/hyperactivity disorder as a "brain disorder." *Ethical Human Psychology and Psychiatry*, *14*, 27–40. doi.org/10.1891/1559-4343.14.1.27.

García de Vinuesa, F., González, H., and Pérez Alvarez, M. (2014). *Volviendo a la normalidad: La invención del TDAH y del trastorno bipolar infantil* [*Returning to normality: The invention of ADHD and child bipolar disorder*]. Madrid: Alianza.

Gehricke, J.G., Kruggel, F., Thampipop, T., Alejo, S.D., Tatos, E., Fallon, J., and Muffuler, L.T. (2017). The brain anatomy of attention-deficit/hyperactivity disorder in young adults — a magnetic resonance imaging study. *PLOS One*, *12*, 1–21. e0175433. doi:10.1371/journal.pone.0175433.

Gelman, A. (2017). Variance, analysis of. In *The new Palgrave dictionary of economics online*. Retrieved from http://www.dictionaryofeconomics.com/article?id=pde2008_A000098.

Giedd, J.N., Castellanos, F.X., Casey, B.J., Kozuch, P., King, A.C., Hamburger, S.D., and Rapoport, J.L. (1994). Quantitative morphology of the corpus callosum in attention deficit hyperactivity disorder. *American Journal of Psychiatry*, *151*, 665–669. doi: 10.1176/ajp.151.5.665.

Gonon, F., Bezard, E., and Boraud, T. (2011). Misrepresentation of neuroscience data might give rise to misleading conclusions in the media: The case of attention deficit hyperactivity disorder. *PLOS One*, *156*, 989–991. doi.org/10.1371/journal.pone.0014618.

Gotzsche, P. (2013). *Deadly medicines and organised crime: How big pharma has corrupted healthcare.* London: Radcliffe.

Hedman, A.M., van Haren, N.E., Schnack, H.G., Kahn, R.S., and Hulshoff, H.E. (2012). Human brain changes across the life span: A review of 56 longitudinal magnetic resonance imaging studies. *Human Brain Mapping*, *33*, 1987–2002. doi: 10.1002/hbm. 21334.

Henderson, T.A., and Fischer, V.W. (1994). Effects of methylphenidate (Ritalin) on mammalian myocardial ultrastructure. *American Journal of Cardiovascular Pathology*, *5*, 68–78.

Hornak, J., Bramham, J., Rolls, E.T., Morris, R. Doherty, J., Bullock, P.R., and Polkey, C.E. (2003). Changes in emotion after circumscribed surgical lesions of the orbitofrontal and cingulate cortices. *Brain*, *126*, 1691–1712. doi.org/10.1093/brain/awg168.

Hyman, S.E. (2003). Methylphenidate-induced plasticity: What should we be looking for? *Biological Psychiatry*, *54*, 1310–1311. doi.org/10.1016/j.biopsych.2003.10.003.

Hynd, G.W., Hern, K.L., Novey, E.S., Eliopulos, D., Marshall, R., Gonzalez, J.J., and Voeller, K.K. (1993). Attention deficit-hyperactivity disorder and asymmetry of the caudate nucleus. *Journal of Child Neurology*, *8*, 339–347. doi.org/10.1177/088307389300800409.

Hynd, G.W., Semrud–Clikeman, M., Lorys, A.R., Novey, E.S., Eliopulos, D., and Lyytinen, H. (1991). Corpus callosum morphology in attention deficit-hyperactivity disorder: Morphometric analysis of MRI. *Journal of Learning Disabilities*, *24*, 141–146. doi.org/10.1177/002221949102400302.

Illes, J., Kirschen, M.P., Edwards, E., Stanford, L.R., Bandettini, P., Cho, M., Ford, P., Glover, G., Kulynych, J., Macklin, R., Michael, D., and Wolf, M. (2006). Incidental findings in brain imaging research: What should happen when a researcher sees a potential health problem in a brain scan from a research subject? *Science*, *311*, 783–784. doi: 10.1126/ science.1124665.

Ivanov, I., Bansal, R., Hao, X., Zhu, H., Kellendonk, C., Miller, L., Sanchez, J., Miller, A., Mallar, M., Klahr, K., Durkin, K., Greenhill, L., and Peterson, B. S. (2010). Morphological abnormalities of the thalamus in youths with attention deficit hyperactivity disorder. *American Journal of Psychiatry*, *167*, 397–408. doi.org/10.1176/ appi.ajp.2009.09030398.

Ivanov, I., Murrough, J. W., Bansal, R., Hao, X., and Peterson, B. S. (2014). Cerebellar morphology and the effects of stimulant medications in youths with attention deficit-hyperactivity disorder. *Neuropsychopharmacology*, *39*, 718–726. doi.org/10.1038/npp.2013.257.

Joseph, J. (2009). ADHD and genetics: A consensus reconsidered. In S. Timimi and J. Leo (Eds.), *Rethinking ADHD: From brain to culture* (pp. 58–91). London: Palgrave Macmillan.

Kipke, M. (1999). *Adolescent development and the biology of puberty: Summary of a workshop on new research.* Washington, DC: National Academy Press.

Knyazeva, M. (2013). Splenium of corpus callosum: Patterns of interhemispheric interaction in children and adults. *Neural Plasticity*, vol. 2013, 12 pgs., article ID 639430. Retrieved fromhttps://www.hindawi.com/journals/np/2013/639430/.

Kohn, M.R., Tsang, T., and Clark, S.D. (2012). Efficacy and safety of atomoxetine in the treatment of children and adolescents with attention deficit hyperactivity disorder. *Clinical Medicine and Insights in Pediatrics*, *5*, 95–162. doi: 10.4137/CMPed.S7868.

Konrad, K., Neufang, S., Fink, G.R., and Herpertz–Dahlmann, B. (2007). Long-term effects of methylphenidate on neural networks associated with executive attention in children with ADHD: Results from a longitudinal functional MRI study. *Journal of the American Academy of Child and Adolescent Psychiatry*, *46*, 1633–1641. doi.org/10.1097/chi.0b013e318157cb3b.

Koridze, M.G., and Oniani, T.M. (1972). Effects of cingulate cortex lesions on emotional behavior and delayed responses in cats. *Acta Neurobiologica*, *32*, 9–18.

Kumar, U., Arya, A., and Agarwal, V. (2017). Neural alterations in ADHD children as indicated by voxel-based cortical thickness and morphometry analysis. *Brain and Development*, *39*, 403–410. doi.org/10.1016/j.braindev.2016.12.002.

Leo, J., and Cohen, D. (2003). Broken brains or flawed studies? A critical review of ADHD neuroimaging research. *Journal of Mind and Behavior*, *24*, 29–56.

Li, X., Sroubek, A., Kelly, M.S., Lesser, I., Sussman, E., He, Y., Branch, C., and Foxe, J.J. (2012). Atypical pulvinar-cortical pathways during sustained attention performance in children with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *51*, 1197–1207.e4. doi: 10.1016/j.jaac.2012.08.013.

Lindstrøm, J. (2012). Why attention-deficit/hyperactivity disorder is not a true medical syndrome. *Ethical Human Psychology and Psychiatry*, *14*, 61–73. doi.org/ 10.1891/1559-4343.14.1.61.

Liu, T., Chen, Y., Li, C., Li, Y., and Wang, J. (2017). Altered brain structural networks in attention deficit/hyperactivity disorder children revealed by cortical thickness. *Oncotarget*, *8*, 44785–44799. doi: 10.18632/oncotarget.14734.

Mackie, S., Shaw, P., Lenroot, R., Pierson, R., Greenstein, D.K., Nugent, T.F., Sharp, W.S., Giedd, J.N., and Rapoport, J.L. (2007). Cerebellar development and clinical outcome in attention deficit hyperactivity disorder. *American Journal of Psychiatry*, *164*, 647–655. doi: 10.1176/ajp.2007.164.4.647.

Maguire, E.A., Gadian, D.G., Johnsrude, I.S., Good, C.D., Ashburner, J., Frackowiak, R.S., and Frith, C.D. (2000). Navigation-related structural change in the hippocampi of taxi drivers. *PNAS*, *97*, 4398–4403. doi: 10.1073/pnas.070039597.

Manes, F., Sahakian, B., Clark, L., Rogers, R., Antoun, N., Aitken, M., and Robbins, T. (2002). Decision-making processes following damage to the prefrontal cortex. *Brain*, *125*, 624–639. doi.org/10.1093/brain/awf049.

Marsden, C.D., and Obeso, J.A. (1994). The functions of the basal ganglia and the paradox of stereotaxic surgery in Parkinson's disease. *Brain*, *117*, 877–897. doi.org/10.1093/brain/117. 4.877.

Mataro, M., Garcia–Sanchez, C., Junque, C., Estevez–Gonzalez, A., and Pujol, J. (1997). Magnetic resonance imaging measurement of the caudate nucleus in adolescents with attention-deficit hyperactivity disorder and its relationship with neuropsychological and behavioral measures. *Archives of Neurology*, *54*, 963–968. doi.org/10.1001/archneur.1997.00550200027006,1997.

Max, J.E., Fox, P.T., Lancaster, J.L., Kochunov, P., Mathews, K., Manes, F.F., Robertson, B.A., Arndt, S., Robin, D.A., and Lansing, A.E. (2002). Putamen lesions and the development of attention-deficit/hyperactivity symptomatology. *Journal of the American Academy of Child and Adolescent Psychiatry*, *41*, 563–571. doi.org/10.1097/00004583-200205000-00014.

Mills, K.L., Bathula, D., Costa, T., Iyer, S.P., Fenesy, M.C., Musser, E.D., Stevens, C.A., Thurlow, B.L., Carpenter, S.D., Nagel, B.J., Nigg, J.T., and Fair, D. (2012). Altered cortico–striatal–thalamic connectivity in relation to spatial working memory capacity in children with ADHD. *Frontiers in Psychiatry*, *3*, 17 pgs. Retrieved from https://www.frontiersin.org/articles/10.3389/fpsyt.2012.00002/full.

Moll, G.H., Hause, S., Rüther, E. Rothenberger, A., and Huether, G. (2001). Early methylphenidate administration to young rats causes a persistent reduction in the density of striatal dopamine transporters. *Journal of Child and Adolescent Psychopharmacology*, *11*, 15–24. doi.org/10.1089/104454601750143366.

Montgomery, D. (2001). *Design and analysis of experiments*. New York: Wiley.

Moore, D.S., and McCabe, G.P. (2003). *Introduction to the practice of statistics*. New York: W.H. Freeman & Co.

Mostofsky, S.H., Reiss, A.L., Lockhart, P., and Denckla, M.B. (1998). Evaluation of cerebellar size in attention-deficit hyperactivity disorder. *Journal of Child Neurology*, *13*, 434–439.doi.org/10.1177/088307389801300904.

Overmeyer, S., Bullmore, E.T., Suckling, J., Simmons, A., Williams, S.C.R., Santosh, P.J., and Taylor, E. (2001). Distributed grey and white matter deficits in hyperkinetic disorder: MRI evidence for anatomical abnormality in an attentional network. *Psychological Medicine*, *31*, 1425–1435. doi:10.1017/S0033291701004706.

Paus, T. (2010). Sex differences in the human brain: A developmental perspective. In I. Savic (Ed.), *Sex differences in the human brain, their underpinnings and implications*. *Progress in Brain Research*, vol. 186, pp. 13–28. Amsterdam: Elsevier. doi.org/10.1016/B978-0-444-53630-3.00002-6.

Plessen, K.J., Bansal, R., Zhu, H., Whiteman, R., Amat, J., Quackenbush, G.A., Martin, L., Durkin, K., Blair, C., Royal, J., Hugdahl, K., and Peterson, B.S. (2006). Hippocampus and amygdala morphology in attention-deficit/hyperactivity disorder. *Archives of General Psychiatry*, *63*, 795–807. doi: 10.1001/archpsyc.63.7.795.

Poulton, A. (2005). Growth on stimulant medication; clarifying the confusion: A review. *Archives of Disease in Childhood*, *90*, 801–806. dx.doi.org/10.1136/adc.2004.056952

Reiss, A.L., Abrams, M.T., Singer, H.S., Ross, J.L., and Denckla, M.B. (1996). Brain development, gender and IQ in children: A volumetric imaging study. *Brain*, *119*, 1763–1774.

Ricaurte, G.A., Mechan, A.O., Yuan, J., Hatzidimitriou, G., Xie, T., Mayne, A.H., and McCann, U.D. (2005). Amphetamine treatment similar to that used in the treatment of adult attention-deficit/hyperactivity disorder damages dopaminergic nerve endings in the striatum of adult nonhuman primates. *Journal of Pharmacological Experimental Therapy*, *315*, 91–98. doi.org/10.1124/jpet.105.087916.

Ronan, L., and Fletcher, P.C. (2015). From genes to folds: A review of cortical gyrification theory. *Brain Structure & Function*, *220*, 2475–2483. doi.org/10.1007/s00429-014-0961-z.

Schnoebelen, S., Semrud–Clikeman, M., and Pliszka, S.R. (2010). Corpus callosum anatomy in chronically treated and stimulant naïve ADHD. *Journal of Attention Disorders*, *14*, 256–266.

Seger, C.A. (2013). The visual corticostriatal loop through the tail of the caudate: Circuitry and function. *Frontiers in Systems Neuroscience*, *7*, 104. Retrieved from https://www.frontiersin.org/articles/10.3389/fnsys.2013.00104/full.

Selemon, L.D., Begovic, A., Goldman–Rakic, P.S., and Castner, S.A. (2007). Amphetamine sensitization alters dendritic morphology in prefrontal cortical pyramidal neurons in the non-human primate. *Neuropsychopharmacology*, *32*, 919–931. dx.doi.org/10.1038/sj.npp.1301179.

Semrud–Clikeman, M., Filipek, P.A., Biederman, J., Steingard, R., Kennedy, D., Renshaw, P., and Bekken, K. (1994). Attention-deficit hyperactivity disorder: Magnetic resonance imaging morphometric analysis of the corpus callosum. *Journal of the American Academy of Child and Adolescent Psychiatry*, *33*, 875–881.doi: 10.1097/00004583-199407000-00014.

Semrud–Clikeman, M., Fine, J., Bledsoe, J., and Zhu, D. (2014). Regional volumetric differences based on structural MRI in children with two subtypes of ADHD and controls. *Journal of Attention Disorders*, *21*, 1040–1049. doi: 10.1177/1087054714559642.

Semrud–Clikeman, M., Pliszka, S.R., Bledsoe, J., and Lancaster, J. (2014). Volumetric MRI differences in treatment naïve and chronically treated adolescents with ADHD–combined type. *Journal of Attention Disorders*, *18*, 511–520. doi: 10.1177/1087054712443158).

Semrud–Clikeman, M., Pliszka, S.R., Lancaster, J., and Liotti, M. (2006). Volumetric MRI differences in treatment-naïve vs chronically treated children with ADHD. *Neurology*, *67*, 1023–1027.

Seymour, K.E., Tang, X., Crocetti, D., Mostofsky, S.H., Miller, M., and Rosch, K.S. (2017). Anomalous subcortical morphology in boys, but not girls, with ADHD compared to typically developing controls and correlates with emotion dysregulation. *Psychiatry Research, 261,* 20–28. doi: 10.1016/j.pscychresns.2017.01.002.

Shaw, P., Eckstrand, K., Sharp, W., Blumenthal, J., Lerch, J.P., Greenstein, D., Clasen, L., Evans, A., Giedd, J., and Rapoport, J.L. (2007). Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *PNAS*, *104*, 19649–19654. doi: 10.1073/pnas.0707741104.

Snell, R. (1992). *Clinical neuroanatomy*. Baltimore: Lippincott Williams & Wilkins.

Sobel, L., Bansal, R., Maia, T., Sanchez, J., Mazzone, L., Durkin, K., Liu, J., Hao, X., Ivanov,I., Miller, A., Greenhill, L.L., and Peterson, B. (2010). Basal ganglia surface morphology and the effects of stimulant medications in youth with attention-deficit/hyperactivity disorder. *American Journal of Psychiatry*, *167*, 977–986.doi.org/10.1176/appi.ajp.2010.09091259.

Sowell, E.R., Trauner, D.A., Gamst, A., and Jernigan, T.L. (2002). Development of cortical and subcortical brain structures in childhood and adolescence: A structural MRI study. *Developmental Medicine & Child Neurology*, *44*, 4–16. doi.org/10.1111/j.1469-8749.2002.tb00253.x.

Steen, R.G., Hamer, R.M., and Lieberman, J.A. (2007). Measuring brain volume by MR imaging: Impact of measurement precision and natural variation on sample size requirements. *American Journal of Neuroradiology*, *28*, 1119–1125. doi.org/10.3174/ ajnr.A0537.

Thompson, P.M., Hayashi, K.M., Simon, S.L., Geaga, J.A., Hong, M.S., Sui, Y.,Lee, J.Y., Toga, A.W., Ling, W., and London, E.D. (2004). Structural abnormalities in the brains of human subjects who use methamphetamine. *Journal of Neuroscience*, *24*, 6028–6036. doi.org/10.1523/JNEUROSCI.0713-04.2004.

Verdú, A. (2016). *Manual de neurología infantil* [*Handbook of child neurology*]. Madrid: Panamericana.

Wellington, T., Semrud–Clikeman, M., Gregory, A., Murphy, J.M., and Lancaster, J.L. (2006). Magnetic resonance imaging volumetric analysis of the putamen in children with ADHD: Combined type versus control. *Journal of Attention Disorders*, *10*, 171–180. doi.org/10.1177/1087054705284242.

Weyandt, L., Swentosky, A., and Gudmundsdottir, B.G. (2013). Neuroimaging and ADHD: fMRI, PET, DTI findings, and methodological limitations. *Developmental Neuropsychology*, *38*, 211–225. doi: 10.1080/87565641.2013.783833.

Whitaker, R. (2011). *Anatomy of an epidemic: Magic bullets, psychiatric drugs, and the astonishing rise of mental illness in America*. New York: Broadway Paperbacks.

Wilkinson, I.D., and Graves, M.J. (2015). Magnetic resonance imaging. In A. Adam, A.K. Dixon, J.H. Gillard, and C.M. Schaefer–Prokop (Eds.), *Grainger and Allison diagnostic radiology* (pp. 90–114). New York: Elsevier.

Wilkinson, L. (1999). Statistical methods in psychology journals: Guidelines and explanations. *American Psychologist*, 5, 594–604. dx.doi.org/10.1037/0003-066X.54.8.594.

Xia, S., Li, X., Kimball, A.E., Kelly, M.S., Lesser, J., and Branch, C. (2012). Thalamic shape and connectivity abnormalities in children with attention-deficit/hyperactivity disorder. *Psychiatric Research*, *204*, 161–167. doi:10.1016/j.pscychresns.2012.04.011.

Zhan, C., Liu, Y., Wu, K., Gao, Y., and Li, X. (2017). Structural and functional abnormalities in children with ADHD: A focus on subgenual anterior cingulate cortex. *Brain Connectivity*, *7*, 106–114.doi.org/10.1089/ brain.2016.0444.