Recent publications by Gonon et al. [2011] have reiterated critical statements concerning the genetics and the neurobiology of Attention-Deficit/Hyperactivity Disorder (ADHD) put forward in the past by other authors [e.g., Joseph, 2000]. It is possible that these critiques have been fostered, at least in part, by mixed research findings in the field. Such discrepant results are accounted for by several factors, including the phenotypic heterogeneity of ADHD and specific methodological biases inevitable even in the most methodological sound empirical studies. However, meta-analytic techniques and other quantitative systematic approaches have allowed pooling of results of studies and, importantly, taking into account their heterogeneity. Although constructive critical appraisals are welcome and essential in science, we think that some critical statements on the genetics and neurobiology of ADHD are clearly in contrast with the pooled evidence of available empirical studies. Therefore, such statements may lead to possible misunderstandings of empirical findings and may be confusing for the readers.

In this editorial, we discuss two of these possible misunderstandings in the light of available empirical findings, pointing out the strengths, but also the limitations, of current meta-analyses and empirical evidence on the genetics and neurobiology of ADHD.

The first misunderstanding pertains to the etiology of ADHD and is represented by the anachronistic dichotomy between genetic and environmental risk factors.

Some authors in the past have argued against the involvement of genetic etiological factors [Joseph, 2000; Timimi et al., 2004], pointing out that ADHD may be accounted for entirely by environmental factors.

Indeed, the influence of genes in the etiology of ADHD has been consistently proven by several lines of evidence. The first body of evidence comes from behavioral genetics studies. In particular, pooled data from twin studies show that the concordance of ADHD is significantly higher in monozygotic (MZ) than in dizygotic (DZ) twins [Hudziak and Faraone, 2010]. Using structural equation modeling, a weighted meta-analysis of twin studies found that 70% of the variance of ADHD phenotype was due to additive and non-additive genetic factors [Burt, 2009]. A more recent quantitative systematic approach that took into account possible biases of previous twin studies (such as lack of power to detect sibling interaction and the correction used for contrast effects), concluded that genetic factors explained 60% of the variance of ADHD [Wood et al., 2010]. It has been pointed out that, if the "equal environment assumption" (EEA) does not hold true (i.e., the environments of MZ and DZ twin are not the same), twin studies, as well as their meta-analysis, cannot prove the involvement of genes in the etiology of a disorder [Joseph, 2000]. However, two studies reporting measures of ADHD have actually shown that biases introduced by possible violation of the EEA do not significantly impact the results [Thapar et al., 1995; Cronk et al., 2002]. To our knowledge, there are no published studies showing that violation of the EEA significantly impacts the results of twin studies in ADHD. Therefore, twin studies provide a first line of evidence supporting the involvement of the genes in the etiology of ADHD.

A second line of evidence comes from molecular genetics studies. The most recent meta-analysis of candidate association studies reported significant associations for SLC6A3, DRD4, DRD5, 5HTT, HTR1B, and SNAP25 [Gizer et al., 2009]. As in previous meta-analyses, the odds ratio for each gene, although statistically
significant, was very small (the highest mean OR, reported for DRD4, was 1.33, with CI 95%: 1.15–1.54). This does not diminish in any way the implication of genetics in ADHD. On the contrary, it is in line with the multifactorial polygenic model in which a plethora of genes each confer a small but significant risk to the disorder [Hudziak and Faraone, 2010]. Although it goes far beyond the available space to present in depth evidence accrued from different levels of neuroscientific enquiry, we note that, interestingly, alterations of some of the genes identified candidate genes studies (such as SLC6A3 and DRD4) have been associated also with neuropsychological deficits [Bellgrove et al., 2005a,b] as well as with anatomical and functional brain abnormalities [Durston et al., 2010]. This shows how a multilevel approach has the potential to bring substantial convergence in findings.

By definition, candidate studies are based on a priori hypotheses. Accordingly, these studies in ADHD have focused on only a very limited amount of genes possibly involved in the etiology of this disorder. Moreover, most of available candidate studies have explored only common variants (i.e., genetic variants occurring in approximately 5% or more of the population), while rare variants (that, according to some authors, may account for much of the heritability of psychiatric disorders) have been quite overlooked [Hudziak and Faraone, 2010]. Therefore, it is not surprising at all that the total variance explained so far by candidate genes is small (about 5%) [Hudziak and Faraone, 2010].

Genome-wide association studies (GWASs) (an unbiased approach to identify single nucleotide polymorphisms (SNPs) significantly associated with a given disorder), have been carried out to identify other possible abnormal genes beyond those assessed in candidate association studies [Franke et al., 2009]. To date, top association findings from available GWASs have suggested several genes possibly involved in ADHD that deserve to be explored in the future, although available GWASs as well as their recent pooled meta-analysis of 2,064 trios, 896 cases, and 2,455 controls are still underpowered to detect the small (but significant) effect sizes of the single genes [Neale et al., 2010]. Based on the positive results from GWAS for other psychiatric disorders (such as bipolar disorder), it has been calculated that sample sizes between 10,000 and 20,000 subjects would be necessary to accurately detect novel genes involved in ADHD etiology by means of GWAS studies [Neale et al., 2008]. Interestingly, a recent systematic study based on bioinformatics pathway analyses has shown that 45 out of 85 proteins encoded by the top-ranked genes of available GWASs are involved in neurite outgrowth [Poelmans et al., 2011]. This provides neurobiological plausibility to the preliminary findings of GWASs, suggesting that larger GWASs have the potential to provide novel insights into the molecular bases of ADHD and, therefore, need to be further implemented and encouraged. We think that a negative and biased view of the role of genetics in ADHD will not facilitate the promotion, by funding agencies, of such necessary but expensive studies.

A major point that we would like to stress is that the aforementioned findings from genetic studies do not imply that genes are the only and exclusive factor in the etiology of ADHD. It is well know that heritability does not imply genetic determination, as clearly illustrated by the often quoted example of the secular rise in height in many human populations, likely due to improved nutrition and medical care, despite the high heritability of height (80%) [Visscher et al., 2008].

One of the crucial steps in genetics research of ADHD has been the acknowledgement of the interaction between genes and environment. That environmental factors do play a significant role in the etiology of ADHD is unquestionable. One of the best evidence supporting this point comes from the aforementioned twin studies, showing that the risk of ADHD in the MZ twins is much <100%.

More than 10 years ago, Faraone and Biederman, in a rebuttal to a critique to ADHD genetic studies, clearly stated: “Most scientists who study the genetics of psychiatric disorders embrace the idea that these disorders are influenced by both genes and environmental factors” [Faraone and Biederman, 2000]. Indeed, an increasing amount of empirical data has shown significant gene–environment interactions in ADHD. At present time, the heterogeneity of environmental measures used so far has hampered a formal meta-analysis of this evidence. However, the appraisal of studies in this field according to a quantitative box-score perspective has shown that G × E interactions in ADHD have been reported and some of them have been replicated across studies [Nigg et al., 2010]. Therefore, the opposition between “genetic” and “environmental factor” is an anachronistic dichotomy.

Despite this evidence, in a recent article, a group of researchers reintroduced the dichotomy “genes versus environment” [Gonon et al., 2011]. Although these authors provided thoughtful and reasonable considerations about media misrepresentation of scientific findings in ADHD, their article misrepresents key scientific findings. It states: “There are three partially overlapping positions in the public debate about ADHD. The first one posits that ADHD is primarily caused by biological factors… The first position is not consistent with data demonstrating that environmental factors play a role in ADHD (low economic status, severe child mistreatment, maternal smoking during pregnancy, premature birth, teenage pregnancy, and other environmental adversities).” We need to point out here that “primarily” does not mean “exclusively” and models where genetic factors have a significant role do not exclude at all the interaction with environmental factors. We also note that the authors seem to confound “genetic” with “biological” since some of the “environmental” factors that they quote (such as maternal smoking and premature birth) are, indeed, biological.

The same author questioned the role of genetics in another recent article titled “Le trouble déficitaire de l’attention avec hyperactivité. La génétique est-elle impliquée?” (“Attention-deficit/hyperactivity disorder. Is genetics involved?”) [Gonon and Cohen, 2011]. Indeed, the text of this article itself provides the answer to this question when the authors remind that heritability studies cannot differentiate between the pure role of genes and that of genes–environment interactions. So, in both of these cases, genes would still be involved, either alone or in combination with environmental factors. As a consequence, the answer to the question in the title is: “Yes.” In our opinion, in 2011, with available evidence, the question should not be “Are genetic (or environmental) factors involved?” because clearly both of them are. Rather, the question should be phrased as follows: “How do genes and environment interact in a developmental perspective?” Answering this question would offer precious insights into the etiopathophysiology and psychopathology of
ADHD much more than reiterating an anachronistic and false dichotomy.

The second misunderstanding that we address is the belief that genetic research may favor the use of pharmacotherapy against other forms of treatment. This distorted idea is an example of what has been termed “therapeutic nihilism” [Meehl, 1973]. More than a decade ago, Joseph stated that “the results of genetic studies have often been used . . . to support the use of psychotropic drugs to treat problems caused by social and psychological factors.” More recently, Gonon et al. [2011] emphasized that the neurobiological theory of ADHD “favors medical interventions over prevention and psychosocial interventions.” Actually, both Joseph and Gonon confounded the causes of a disorder with its treatment. Some examples usually reported to illustrate this misunderstanding include the following: (1) a traumatic injury (an environmental factor) can lead to epilepsy, and nobody questions the medical treatment of epilepsy in this case; (2) smoking (an environmental risk factor) contributes to cancer, which, once developed, still needs to be treated with a medical approach; (3) phenylketonuria is caused by a known mutation, yet a modified diet (an environmental manipulation) effectively treats the disorder. These types of examples are endless. We do not think that research in the neurobiology of ADHD favors the use of pharmacological treatments and we are not aware of any empirical study, systematic quantitative reviews or meta-analysis supporting this statement. On the contrary, gaining insight into the neurobiological correlates of ADHD may help us understand how non-pharmacological treatments work, as well as in which patients (and why) they do not work. Interestingly, there is an increasing literature on the brain correlates of non-pharmacological treatments for ADHD. For example, the reader may refer to the articles on the effects of neurofeedback, summarized in a recent meta-analysis [Arns et al., 2009], or to research exploring the brain effects of attention training [Hoekzema et al., 2011].

We hope that the thoughts expressed in this editorial may be of help for the reader interested in gaining insights in to the state-of-the-art of genetic and neurobiological research of ADHD. We are not against the practice of reporting critiques of such research, but we think that such critiques should be based on scientific rigor. An example of lack of rigor is offered by the aforementioned article by Gonon et al. [2011]. In the abstract, the authors stated that “Data misrepresentations are frequent in the scientific literature dealing with ADHD.” According to these authors “discrepancies” (i.e., “inconsistencies between results and claimed conclusions in the article”) and “fact omission” (i.e., “putting in the summary a fixed conclusion while raw data, which strongly limits the relevance of this conclusion, are only given in the section”) contribute to these misrepresentations. However, in the results section, they stated: “We have read about 360 articles and we have found only two studies showing obvious discrepancies between results and claimed conclusions” and, in the discussion: “Our study is mainly qualitative and does not provide quantitative information about the extent of data misrepresentation in the ADHD literature as a whole.” So, we wonder how they can state that misrepresentations are frequent in the scientific literature. Ironically, their article is an example of misrepresentation of scientific data.

In scientific debates, critical statements per se, are sometimes useful, but rarely sufficient. They should be accompanied by empirical data. We are aware of only one-way of doing science: falsify theories with data. The articles by Gonon et al. fall far short of that standard.

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REFERENCES


