**Statistical evidence that inattention drives hyperactivity/impulsivity in Attention Deficit-Hyperactivity Disorder. Causal inference from observational data**

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**Abstract**

**Background:** Numerous factor analytic studies consistently support a distinction between two symptom domains of attention-deficit/hyperactivity disorder (ADHD), inattention and hyperactivity/impulsivity. Both dimensions show high internal consistency and moderate to strong correlations with each other. However, it is not clear what drives this strong correlation. The aim of this paper is to address this issue.

**Method:** We applied a sophisticated approach for causal discovery on three independent data sets of scores of the two ADHD dimensions in NeuroIMAGE (total N=685), ADHD-200 (N=245), and IMpACT (N=164), assessed by different raters and instruments, and further used information on gender or a genetic risk haplotype.

**Results:** In all data sets we found strong statistical evidence for the same pattern: the clear dependence between hyperactivity/impulsivity symptom level and an established genetic factor (either gender or risk haplotype) vanishes when one conditions upon inattention symptom level. Under reasonable assumptions, e.g., that phenotypes do not cause genotypes, any causal model that is consistent with this pattern must contain a causal path from inattention to hyperactivity/impulsivity.

**Conclusions:** The robust dependency cancellation observed in three different data sets strongly suggests that inattention is a driving factor for hyperactivity/impulsivity. This causal hypothesis can be further validated in intervention studies. Our model suggests that interventions that affect inattention will also have an effect on the level of hyperactivity/impulsivity. On the other hand, interventions that affect hyperactivity/impulsivity would not change the level of inattention. This causal model may explain earlier findings on heritable factors causing ADHD reported in the study of twins with learning difficulties.

Keywords: ADHD; inattention; hyperactivity; causal discovery;

1. **Introduction**

*Problem description*

Attention-deficit/hyperactivity disorder (ADHD) is a common and highly heritable neurodevelopmental disorder that affects about 5-6% of children worldwide (1, 2). ADHD persists into adulthood in about 30-50% of the childhood cases, depending on definition of remission (3), and prevalence of ADHD in adults is estimated between 2.5-4.9% (4). In pediatric populations, ADHD is about 2-3 times more common in boys than girls (5), but gender balance is rather equal in adult populations (6). The genetics of ADHD is complex and several candidate genes have been associated with ADHD in meta-analyses, among which the dopamine transporter gene *SLC6A3/DAT1(7)*. Genetic variation of the *DAT1* gene may affect the functioning of the dopamine transporter caused by individual variation in regulating levels of dopamine (8). The *DAT1* gene has a differential risk haplotype (formed by a variable number of tandem repeat (VNTR) polymorphisms in the 3’ UTR and in intron 8) associated with childhood ADHD (10R/6R) and adult ADHD (9R/6R) (9, 10). Furthermore, both *DAT1* knockout and knockdown transgenic mice demonstrate face validity with documented increases in hyperactivity and impulsivity (11).

As evident from its name, ADHD is characterized by inappropriate and pervasive levels of inattention and/or hyperactivity and impulsivity. Exploratory and confirmatory factor analyses of ADHD symptoms assessed by parents, and teachers, as well as self-report ratings in adolescents and adults consistently support a distinction between two symptom dimensions: inattention and hyperactivity/impulsivity (see (12) for a review). Inattention and hyperactivity/impulsivity both show high internal consistency and are moderately to strongly correlated (correlation coefficient between .63 and .75), indicating that they constitute separable but substantially correlated dimensions (12). Inattention is more strongly related to internalizing problems of anxiety and depression and to academic underachievement. In contrast, hyperactivity/impulsivity is linked to peer rejection and externalizing behavioral problems such as oppositional defiant and antisocial behavior (12).

The cause of the strong correlation between the two symptom dimensions of ADHD inattention and hyperactivity/impulsivity is yet unclear. Are these two dimensions two sides of the same coin, i.e., the consequence of a (possibly unknown) common cause, or could it be that one dimension drives the other? This question is relevant to the current literature: some studies assume a bi-factor model to explain the correlation (13), others propose a driving effect of inattention on hyperactivity based on the analysis of twin studies (14).

*Causal discovery from observational data*

The standard approach to establish causal relationships is through experimental manipulation or intervention. For example, in order to establish a causal effect of inattention upon hyperactivity/impulsivity, one would need to apply an intervention that only acts upon inattention and then measure its effect on hyperactivity/impulsivity. When analyzing the results of these experiments the Bransford Hill criteria for causation should be taken into account (15). Although in theory such an intervention, e.g., through a well-designed therapy or some novel highly specific medication, could be attainable, we are not aware of any such attempts or studies in the current literature.

That being the case, the emerging field of causal discovery from observational data may provide a powerful alternative (16, 17). In apparent contradiction with the good old adagio “correlation does not imply causation”, theoretical and experimental studies have shown that, under certain reasonable assumptions, it *is* possible to learn cause-effect relationships from purely observational data. The key insight is that, where a single number such as a mere correlation indeed cannot reveal anything about causal direction, other, more subtle characteristics may contain important directional information. Just considering pairs of variables, these can be found in higher-order moments (18). In higher-dimensional systems, the seminal work of Turing award winner Judea Pearl and others revealed the close connection between causal relationships and conditional independencies. Since then, causal discovery algorithms have successfully been applied in various domains, and slowly find their way into the biomedical sciences (19-22). To the best of our knowledge, the current paper is the first to describe an application of causal discovery for the analysis of observational neuro-psychological data.

Intuitively, two variables *‘Z’* and *‘Y’* are conditionally independent given *‘X’* if, once the value of variable *‘X’* is known, the value of *‘Z’* does not add any additional information about *‘Y’*. For example, in the context of children with ADHD, we can call gender and hyperactivity/impulsivity conditionally independent given inattention, if knowing whether a subject is a boy or a girl does not help to better estimate the hyperactivity/impulsivity symptom score, once we already know the child’s inattention symptom score. In this paper we investigate whether such conditional independencies can be derived from observational data.

Most causal discovery algorithms start by assuming that real-world events are governed by specific, yet unknown causal mechanisms. Given a particular causal model, one can in principle read off the conditional dependencies and independencies one should then find in observational data. Reasoning backwards, given particular observed conditional dependencies and independencies in observational data, one may be able to infer causal relations that any causal model should have to be consistent with the observed statistical patterns.

It is exactly this kind of inverse reasoning that underlies so-called constraint-based algorithms for causal discovery such as PC/Fast Causal Inference (23) and Bayesian Constraint-based Causal Discovery (24). Specialized variants, such as Cooper’s local causal discovery algorithm (LCD) (25) and the Trigger algorithm (20), handle the case of three variables and are particularly relevant for our purposes. The statistical pattern in LCD takes a triplet of mutually dependent variables with the additional prior knowledge that one of the variables (‘*Z*’) cannot be caused by the other two (*‘X’* and *‘Y’*). As we will show in more detail in the supplementary material, any causal model that now implies a conditional independence between the variables *‘Y’* and *‘Z’* conditioned upon *‘X’* *must* have a causal link from *‘X’* to *‘Y’*. So, reasoning backward, if we observe such a conditional independence in our observational data, we can interpret this as evidence for a causal link from *‘X’* to *‘Y’*. This causal pattern was first derived by Cooper in (25), and later independently rediscovered in the context of genome biology in (20). It has been applied in various papers in the biomedical research literature, such as (26, 27).

*Goal*

The goal of this paper is to analyze whether such statistical patterns can be observed in studies of ADHD populations, and if so, what causal relationships these patterns then suggest. We will use symptom scores for inattention and hyperactivity/impulsivity as substitutes for the actual level of inattentiveness and hyperactivity/impulsivity. These then play the role of the variables ‘*X*’ and ‘*Y*’ above. For the variable ‘*Z*’ we will consider genetic variables such as gender and the *DAT1* risk haplotype. These three variables clearly satisfy the premises of LCD: they are all mutually dependent (as shown in various other studies and easily checked for the data sets analyzed in this paper) and it seems completely reasonable to assume that manipulations of inattentiveness and hyperactivity/impulsivity do not affect gender, nor the *DAT1* risk haplotype. LCD is closely related to other, arguably more standard approaches, such as mediation analysis and instrumental variable analysis (see supplementary material for details).

1. **Materials and Methods**

*Materials*

To infer causal relationships between ADHD symptoms we used three data sets, describing children, adolescents, and adults with ADHD. For each data set we only consider three variables: inattention symptom scores, hyperactivity/impulsivity symptom scores, and a genetic variable (either gender or a risk haplotype). The rationale for choosing these data sets is availability, as explained in more detail in the discussion.

The first data set was collected for the NeuroIMAGE project (28) (see [www.neuroimage.nl](http://www.neuroimage.nl)) and considers adolescents. We will refer to this data set as the NeuroIMAGE data set. This data set includes N=903 participants (413 adolescents with ADHD, 228 unaffected siblings of ADHD probands, and 262 healthy control subjects) with a mean age of 16.7 years (min=5.7 years, max=28.6 years). The presence of ADHD symptoms was assessed by a semi-structured diagnostic interview Schedule for Affective Disorders and Schizophrenia for School-Age Children - Present and Lifetime Version (K-SADS-PL (29)) and Conners' ADHD questionnaires from multiple informants (30). An algorithm was applied to create a combined symptom count from the interview and questionnaires (symptom range 0-18). Participants were diagnosed with ADHD if they met the full DSM-IV criteria for the disorder. For the current analyses, the sum of the symptom counts on the two symptom dimensions inattention (0-9) and hyperactivity/impulsivity (0-9) was used. In addition, we used the information on gender. In order not to complicate our analysis with ways to account for the dependencies between probands and their unaffected siblings, we ignore the siblings, leaving N=685 subjects in total.

The second data set was collected by Peking University and is publicly available as part of the ADHD-200 Sample (31), <http://fcon_1000.projects.nitrc.org/indi/adhd200/>) and considers children. We will refer to this data set as the ADHD-200 data set. This data set includes N=245 participants (102 children with ADHD, 143 control subjects) with a mean age of 11.7 years (min=8.1 years, max=17.3 years). The data set contains information about subjects’ ADHD symptom scores, disease status, gender, and IQ. Symptom scores were measured using the ADHD Rating Scale (ADHD-RS) IV (32), for which scores can range from 0 to 27 for each symptom domain. Also for this data set we will restrict our analysis again to the two symptom scores and gender. We did not use the other data sets that are part of the ADHD-200 Sample, because in those data sets the ADHD symptom scores were provided corrected for the effect of gender, which makes them inappropriate for the type of causal analysis we aim for in this paper.

The third data set was collected for the IMpACT project (33) and considers adults. We will refer to this data set as the IMpACT data set. This data set contains N=164 participants (87 adults with ADHD, 77 control subjects) with a mean age of 36.6 years (Min=18.0 years, Max=63.0 years). Subjects were assessed using the Diagnostic Interview for Adult ADHD (DIVA) ([www.divacenter.eu](http://www.divacenter.eu)). This interview focuses on the 18 DSM-IV symptoms of ADHD and uses concrete and realistic examples to thoroughly investigate whether the symptom is present now or was in childhood. In addition, a quantitative measure of clinical symptoms was obtained using the ADHD-DSM-IV Self Rating scale (6), which has a range of scores from 0 to 9 for each symptom domain and was used for the current analysis. Patients were included in the study if they met the DSM-IV-TR criteria for ADHD in childhood as well as adulthood. As gender was not associated with ADHD in the adult data, we used an alternative genetic variable: the presence/absence of the *DAT1* 9/6 risk haplotype, a genetic polymorphism associated with ADHD in adulthood (33).

*Data analysis*

The inference of causal relationships from observational data crucially depends on the detectable absence and presence of conditional dependencies between variables (16). For random variables that follow a multivariate Gaussian distribution, conditional independence corresponds to zero partial correlation. The partial correlation between X and Y given controlling variable Z is defined as the correlation between the residuals  and  resulting from the linear regression of X with Z and of Y with Z, respectively. In other words, partial correlation measures the degree of association between two random variables, with the effect of the controlling random variable removed. By measuring partial correlation it is possible to measure conditional independencies in the data.

Our symptom scores are not normally distributed and both gender and presence/absence of risk haplotype are binary variables. Therefore, Pearson partial correlation is not guaranteed to represent conditional dependencies and independencies correctly for our data (34). We therefore replaced Pearson by Spearman rank partial correlation. Technically, a standard test for zero partial correlation with Spearman correlation instead of Pearson is valid for variables that obey a so-called non-paranormal distribution (35): a multivariate Gaussian distribution on latent variables, each of which is related to the observed variables through a monotonic transformation.

An alternative method to infer conditional independencies/dependencies from non-normally distributed data is to discretize the data and use the so-called Mantel‐Haenszel test (36). The basic idea of this test is to turn observed counts into expected counts under the assumption that there is a conditional independence and then check whether there is a significant difference between the expected and observed counts. For all three data sets we discretized the symptom scores into a binary variable using a median split, which had its threshold at 4.5. The observed counts were visualized in a cross table with a mosaic plot. A mosaic plot is an area-proportional hierarchical visualization of (typically observed) counts, composed of tiles (corresponding to the cells) created by recursive vertical and horizontal splits of a rectangle. The area of each tile is proportional to the corresponding cell entry given the dimensions of previous splits (37). Mosaic plots are excellent tools for visualizing conditional independencies: if two variables are conditionally independent given a third, this will show in the mosaic plot through straight lines as long as the conditioning variable is not represented at the lowest level of the hierarchy.

1. **Results**

We obtained strong and consistent results for all three data sets. We provide a detailed description of the results for the ADHD adolescence data, including figures, in the main text. Figures for the other two data sets can be found in the Supplementary material. The comparison of the results for the three data sets is presented in Table 1.

Figure 2 displays the NeuroIMAGE data set. It can be clearly seen that all three variables were highly correlated (see Table 2). Spearman’s partial correlation between gender and hyperactivity/impulsivity symptom scores conditioned upon inattention symptom scores was zero (Spearman R=-0.0008, p=0.9826). However, the Spearman partial correlation between gender and inattention symptom scores conditioned upon hyperactivity/impulsivity symptom was significantly different from zero (Spearman R=0.1235, p=0.0013). Spearman’s rank partial correlation coefficients are visualized in Figure 3.

The Mantel‐Haenszel test for discretized data provided similar results. As shown in the mosaic plots in Figure 4, there was a significant difference (= 11.37, p<0.001) between the observed and expected scores of inattention for the different genders, conditioned upon hyperactivity/impulsivity symptom level (Figure 4a). No significant difference (= 0.15, p=0.70) was seen between the observed and expected scores of hyperactivity/impulsivity for different gender, conditioned upon inattention symptoms (Figure 4b).

1. **Discussion**

The aim of this paper was to apply a novel approach for causal discovery to improve our understanding of the strong correlation between the two symptom dimensions of ADHD. In three different and independent data sets, employing different instruments and raters to measure ADHD symptoms, and using different genetic variables we found robust statistical evidence for a conditional independence of hyperactivity/impulsivity symptom level from a genetic variable, conditioned upon inattention symptom level. Without conditioning, the genetic variable (gender/risk haplotype) and hyperactivity/impulsivity were clearly dependent. Causal inference offers an explanation for this dependency cancellation: inattention causes hyperactivity/impulsivity.

*Interpretation*

The causal statement explaining the association between hyperactivity/impulsivity and inattention asks for a careful interpretation. Obviously, inattention as well as hyperactivity/impulsivity could be caused by many factors, directly or indirectly through yet other factors. What the causal model implies is that there is a causal path from inattention to hyperactivity/impulsivity, but not the other way around. Furthermore, there appears to be no (unobserved) factor with a causal path to both inattention and hyperactivity/impulsivity, since in that case the genetic variable and hyperactivity/impulsivity should be dependent, conditioned upon inattention that contradicts with the obtained conditional independence.

Note also that in this causal interpretation, we treat the outcome of the interviews/questionnaires as surrogates of what constitutes “inattention” and “hyperactivity/impulsivity”. In fact, “inattention” and “hyperactivity/impulsivity” themselves are perhaps best viewed as hidden concepts, which can be represented as latent variables that by themselves are linked to (causing) the respective symptoms. That we find this causal link between inattention symptoms and hyperactivity/impulsivity implies that there appears to be a latent concept (which we may call “inattention”) that is quite accurately captured by the interview/questionnaire items related to inattention and which “causes” another latent concept (which we may call “hyperactivity/impulsivity”) that is quite accurately represented by items for hyperactivity/impulsivity in the interviews/questionnaires, see Figure 5. Furthermore, when we say that one variable “causes” another, we mean that if we manage to intervene on the first variable, this will change (the probability distribution of) the second variable. A similar subtle interpretation is implicit in many practical applications of causal discovery.

*Related literature on ADHD*

It is important to put our result into a historical context of literature on ADHD. Early work on what we now know as ADHD in the 1940’s emphasized characteristics as hyperactivity and impulsivity as part of the so-called Minimal Brain Damage syndrome (38). Later on, research failed to establish a firm link between hyperactivity and brain damage. Most children suffering brain damage did not develop hyperactivity, and fewer than 5% of hyperactive children appeared to suffer from brain damage (39). During the late 60's and early 70's, the focus shifted to problems in attention regulation. Virginia Douglas and her colleagues at McGill University in Canada were among the first to demonstrate the marked attention deficits seen in these children. Douglas argued that the major deficit was the inability to “stop, look, and listen” (40). After intense debate on what the primary features of the disorder were, the American Psychiatric Association published the DSM-III I 1980, and coined the disorder “Attention Deficit Disorder, with or without hyperactivity”. The fact that hyperactivity is usually observed on earlier stage in children does not necessarily mean that these children do not have inattention. It can be an indication that inattention is harder to diagnose in small children rather than hyperactivity. Moreover, hyperactivity is more apparent in small children compared to inattention, as children in general have a more limited attention span than adults. The results of this research reflected the consensus that attention deficit, not hyperactivity, was the key to the disorder. Our findings in the current analysis indeed substantiate this consensus further.

The proposed model has many characteristics in common with the bi-factor model that is currently often discussed in the literature (13). The bi-factor model allows symptoms to be associated with the general factors that are common for both symptoms, and specific factors for each symptom in particular. The model proposed in this paper suggests that there are general factors that influence inattention and consequently hyperactivity, and specific factors that influence only hyperactivity. Thus, the proposed model as well as the bi-factor model suggests a presence of general and specific factors. The difference between the models in terms of causal modeling, is that bi-factor model explains a correlation between symptoms by a common cause (general factor), while the proposed model explains it by an effect from inattention to hyperactivity/impulsivity. The bi-factor model explains the correlation between symptoms, but cannot explain the conditional independencies observed in this study. Unfortunately, we cannot directly compare our study with the study in (13), which suggest that bi-factor model is a superior model to existing factor models of ADHD, since it requires symptom scores per each question, while in this study only aggregated scores per symptom were available. As a future work, we would like to repeat the analysis made in (13) and compare bi-factor model with the model proposed in this paper.

Our causal model may support findings by Willcutt and coworkers (14) in a study of ADHD heritability in adolescent twin pairs. They showed that inattention is heritable for all levels of hyperactivity/impulsivity, whereas hyperactivity/impulsivity is heritable only when the level of inattention symptoms is high. This made the authors suggest that the etiology of hyperactivity/impulsivity is different in subjects who show a high level of inattention from that in subjects with low inattention. Such a hypothesis is perfectly in line with our causal model: there are heritable factors that cause inattention, and affect hyperactivity/impulsivity downstream of that, whereas those factors that lead to high hyperactivity/impulsivity do not necessarily lead to higher inattention. As for the subject of clinical management of patients, the existence of a causal path from inattention to hyperactivity/impulsivity suggests that interventions (for example medication treatment) that decrease inattention are also likely to have a beneficial effect on the level of hyperactivity/impulsivity. On the other hand, interventions that affect hyperactivity/impulsivity cannot be expected to also have a positive effect on the level of inattention symptoms. This would further be consistent with reports that methylphenidate treatment of ADHD primarily targets attentional mechanisms by blocking the dopamine transporter in the striatum and the resulting increase in synaptic dopamine (41).

Our causal model is in line with the observed pattern that hyperactivity/impulsivity symptoms remit more likely than inattention symptoms (42). As explained before, there can be two types of factors: the one that influence inattention and indirectly hyperactivity/impulsivity, and the one that influence only hyperactivity/impulsivity. With time, factors that influence inattention and indirectly hyperactivity/impulsivity may remit not as fast as factors that influence only hyperactivity/impulsivity. As a result, inattention symptoms will remit insignificantly, providing also some insignificant remission to hyperactivity/impulsivity, while hyperactivity/impulsivity will remit more significantly, since it will accumulate the effect of two factors: inattention and other factors that influence only hyperactivity/impulsivity. In order to study this phenomenon in more details, longitudinal data are required.

*Assumptions*

As any statistical analysis, causal inference relies on several assumptions. Some of these assumptions are more fundamental, such as the assumption that we can use statistical tests to uncover the probabilistic (in)dependence relationships among the measured variables, and the assumption that reality can be properly modeled by acyclic Bayesian networks. These assumptions are discussed in detail in (25). Note that we explicitly do not (have to) assume so-called causal sufficiency and hence do allow for the presence of latent confounders. Our analysis is based on the assumption that the observed conditional independencies, found in three independent data sets representing three different age groups and considering two different control variables, cannot be explained from selection bias.

The selection of the appropriate data sets for the analysis was based on previous finding in our research and availability of the data. An earlier paper (43) describes a causal analysis of data from the IMpACT study on a larger number of variables. Here we noticed, among other things, the causal link between inattention and hyperactivity/impulsivity. The analysis in this paper reveals that this causal link can also be found by restricting the analysis on the IMpACT data set to just three variables. To confirm this finding we considered the NeuroIMAGE and the ADHD-200 data sets. We did not have any other data sets available for the analysis that would satisfy the requirements mentioned in the introduction.

In this paper the ADHD case-control sample was used instead of a random sample which raises the question whether a biased sampling plan will impact the empirical associations. To answer that question we checked how the results of the conditional independence tests change if we decrease the number of ADHD cases in the sample, keeping the number of controls the same. The tests showed that if the number of ADHD cases is very small (less than 10), the correlation between the gender and symptoms becomes insignificant, due to low variation in symptoms and small sample size. Consequently, a conditional independence test between inattention and gender, conditioned on hyperactivity also becomes insignificant. When we increase the number of ADHD cases the variation in symptoms in the sample increases as well as the sample size, making the correlation between gender and symptoms more pronounced. Consequently, the dependency between inattention and gender, conditioned on hyperactivity becomes significant. However, the dependency between hyperactivity and gender, conditioned on inattention does not depend on the number of ADHD cases and is always insignificant. Thus, we suggest that considering a random sample instead of an ADHD case-control sample we would obtain the same sets of conditional independencies provided the sample size is large enough. We also repeated our analysis on the siblings from the NeuroImage data set, where we found evidence for the same pattern (not reported here, because statistically less significant than the other, larger data sets). Based on these results we conclude that we can extrapolate the results obtained from an ADHD case-control sample to a random sample.

*Conclusion*

In this paper we discuss the robust dependency cancellation observed in three different data sets. Perhaps even more than in standard statistical analyses, it is difficult to quantify one’s confidence in a statement such as “inattention causes hyperactivity/impulsivity”, if only because it strongly depends on the typical assumptions underlying causal inference. Nevertheless, the explanation provided by causal inference for the robust cancellation of dependencies in three different studies is simple and follows Ockham’s principle of parsimony. We further argued how such a causal model can be put in the historical context of the disease and may explain other findings such as those in (14). Last but not least, our causal model yields testable hypotheses, which may be validated in future intervention studies.

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**Figures**

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Figure 2. The NeuroIMAGE data set: Hyperactivity/impulsivity is plotted versus inattention symptoms for male and female. The bars indicate the histogram of the distribution. For visualization purposes random noise has been added to the discrete symptom scores.

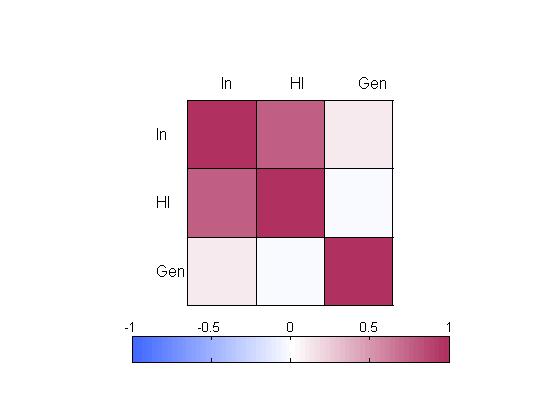


Figure 3. Spearman’s partial correlation coefficients for the NeuroIMAGE data set representing inattention symptoms (In), hyperactivity/impulsivity (HI) symptoms, and gender (Gen).

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Figure 4. Mosaic plots of the observed counts for the NeuroIMAGE data set under the assumptions that a) hyperactivity/impulsivity symptom level and gender are conditionally independent given inattention symptom level; b) inattention symptom level and gender are conditionally independent given hyperactivity/impulsivity symptom level. The color of the cell represents the value of Pearson residuals.

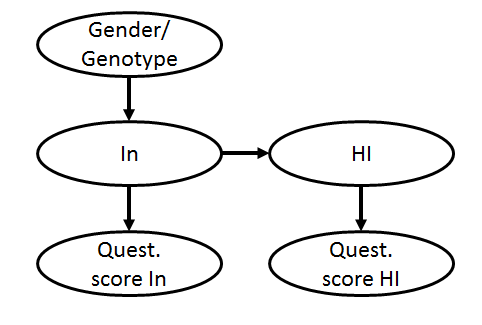


Figure 5. Causal relationships implied by our data for inattention (In), hyperactivity-impulsivity (HI), genetic variables (Gender or genotype) and behavioral estimates based on interview/questionnaire symptom scores.

Table 1 results of Partial correlation test and Mantel‐Haenszel test for three data sets.

|  |  |  |  |
| --- | --- | --- | --- |
| Type of test | | Gender/DAT1 and hyperactivity/impulsivity symptom scores conditioned upon inattention | Gender/DAT1 and inattention symptom scores conditioned upon hyperactivity/impulsivity |
| NeuroIMAGE | |  |  |
|  | Partial correlation test | R=-0.0008, p=0.9826 | R=0.1235, p=0.0013 |
|  | Mantel‐Haenszel test | = 11.37, p<0.001 | = 0.15, p=0.70 |
| ADHD-200 | |  |  |
|  | Partial correlation test | R=0.05, p=0.42 | R =0.18, p = 0.006 |
|  | Mantel‐Haenszel test | =10.98, p=0.001 | =0.47, p=0.49 |
| IMpACT | |  |  |
|  | Partial correlation test | R=-0.01, p=0.91 | R=0.19, p=0.02 |
|  | Mantel‐Haenszel test | =11.21, p=0.001 | =0.005, p=0.95 |

Table 2 Pearson correlation between variables for three data sets

|  |  |  |  |
| --- | --- | --- | --- |
|  | Gender/DAT1 and Inattention | Gender/DAT1 and Hyperactivity/Impulsivity | Inattention and Hyperactivity/Impulsivity |
| NeuroIMAGE | R=0.187, p<0.001 | R=0.141 p<0.001 | R=0.759, p<0.001 |
| ADHD-200 | R=0.288 , p<0.001 | R=0.215, p=.001 | R=0.679, p<0 .001 |
| IMpACT | R= 0.307, p=0.001 | R=0.224 p=0.004 | R=0.764 p<0.001 |

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**Supplementary material**

*Derivation of the LCD pattern*

To explain the type of reasoning and underlying assumptions in more detail, we will spell out the LCD pattern (25)for the three variables that we are interested in: inattentiveness (‘In’), hyperactivity/impulsivity (‘HI’), and a genetic factor (‘Gen’), which can be either gender or a risk haplotype such as *DAT1*. We follow essentially the same reasoning as in (22). An alternative proof can be found in (20).

Figure 1 displays eight models, represented as so-called CPAGs (44). We only consider models that have at least two edges, since with less than two edges at least one of the variables will be independent of the other two, clearly violating the fact that all three variables are mutually dependent. Each CPAG, short for ‘complete partial ancestral graph’, by itself represents a whole class of possible causal models, not only over the observed variables but also over unknown latent variables. In these graphs, “*X*→*Y*” means that there must be a causal path from *X* to *Y* in the underlying causal model, “*X*↔*Y*” that there must be a latent common cause affecting both *X* and *Y*. Circle marks are wild cards, that is, “*X*∘→*Y*” means either “*X*→*Y*” or “*X*↔*Y*”, and “*X*∘→∘*Y*” any of “*X*→*Y*”, “*X*←*Y*”, and “*X*↔*Y*” (note that here, in technical terms, we do allow for the possibility of latent variables, i.e., do not assume so-called causal sufficiency, but do assume that there is no selection bias and there cannot be any cycles; we will get back to these assumptions in the discussion). When there is an edge between ‘Gen’ and, for example, ‘In’, it always comes with an arrowhead at ‘In’ and typically a circle mark at ‘Gen’. This implements our assumption that ‘In’ cannot cause ‘Gen’, without excluding the possibility that there is a latent common cause affecting the two.

Reasoning forward, each CPAG now implies a set of (conditional) dependencies and independencies. They can be derived using a general procedure called m-separation (45), here with just three variables arguably also through common sense. The implied (conditional) dependencies for each possible combination of variables are shown in the columns on the right, next to each of the CPAGs. Here, for example, “In ⊥ HI | Gen” means that ‘In’ is independent of ‘HI’ when conditioned upon ‘Gen’. Graph (a) is boring, in the sense that it implies only (conditional) dependencies. Graphs (b1) through (d2) are potentially more interesting: they all at least suggest one (conditional) independence.

Now, if we observe a particular pattern of dependencies and independencies in the data, we can reason backward to tell which graph(s) can explain these. If indeed all variables are mutually dependent, graphs (b3), (c2), and (d2) drop out because they imply marginal independence between ‘In’ and ‘HI’. If all variables are mutually dependent, but we still have a conditional independence, graph (a) drops out, and only one of (b1), (b2), (c1), or (d1) applies, depending on which conditional independence holds true. If we find that ‘In’ and ‘HI’ are conditionally independent given ‘Gen’, we can conclude that ‘Gen’ must cause either ‘In’ or ‘HI’, but cannot tell which one. However, when one of the other two conditional independencies holds true, we have either (c1) or (d1), and in both cases we can infer a causal statement. Specifically, if according to the data ‘HI’ is independent of ‘Gen’ conditioned upon ‘In’, LCD concludes that there must be a causal path from ‘In’ to ‘HI’ in any underlying causal model that can explain this particular pattern of (conditional) dependencies and independencies.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| CPAG | In ⊥ HI | Gen ⊥ HI | Gen ⊥ In | In ⊥ HI | Gen | Gen ⊥ HI | In | Gen ⊥ In | HI |
| (a)  Gen  HI  In | No | No | No | No | No | No |
| (b1)  HI  In  Gen | No | No | No | *Yes* | No | No |
| (b2)  HI  In  Gen | No | No | No | *Yes* | No | No |
| (b3)  HI  In  Gen | Yes | No | No | No | No | No |
| (c1)  In  HI  Gen | No | No | No | No | *Yes* | No |
| (c2)  In  HI  Gen | Yes | No | No | No | *Yes* | No |
| (d1)  In  HI  Gen | No | No | No | No | No | *Yes* |
| (d2)  In  HI  Gen | Yes | No | No | No | No | *Yes* |

*Related models and methodologies*

*Mediation analysis*

Mediation analysis starts from the assumption that the independent variable *‘Z’* (genetic factor) causes the dependent variable *‘Y’* (impulsivity/hyperactivity) and then aims to answer the question whether the effect of *‘Z’* on *‘Y’* can be (fully) explained by the mediator *‘X’* (inattention). The important difference with the analysis underlying LCD is that LCD does not start from the assumption that there is a causal relationship, but instead aims to derive one. Nevertheless, following the analysis above, it can be seen that we can only derive a causal statement if the data reveals a conditional independence, which amounts to one variable mediating the correlation between the other two.

*Instrumental variable approaches*

In so-called instrumental variable approaches [add citations], the genetic factor *‘Z’* is called an instrument. It can be used to estimate the causal effect of the variable *‘X’* on the variable *‘Y’* in the presence of latent confounders. A valid instrument has to satisfy various criteria, among others that its effect on the variable *‘Y’* is fully mediated by the variable *‘X’* (in more complex settings possibly controlled for other variables). The main difference with LCD is that instrumental variable analysis starts from the assumption that there is a causal effect from *‘X’* to *‘Y’* and then tries to make use of the instrument *‘Z’* to estimate or bound its strength, whereas LCD uses the instrument *‘Z’* to try and infer the existence and direction of a cause-effect relationship between *‘X’* and *‘Y’*, without attempting to estimate the causal strength of this relationship.