Role of Conduct Problems in the Relation between Attention-Deficit Hyperactivity Disorder, Substance Use, and Gaming

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Word count abstract: 221
Body, including tables, figures: 5962
Number of references: 79
Number of figures: 2
Number of tables: 3

Short title: Role of Conduct Problems in ADHD and Addiction
Keywords: Attention Deficit Hyperactivity Disorder; Disruptive, Impulse Control, and Conduct Disorders; Nicotine Dependence; Alcohol Dependence; Gaming Dependence; Causal Discovery

1   **Abstract:**

2   Known comorbidities for Attention-Deficit Hyperactivity Disorder (ADHD) include conduct problems,

3   substance use disorder and gaming. Comorbidity with conduct problems may increase the risk for

4   substance use disorder and gaming in individuals with ADHD. The aim of the study was to build a causal

5   model of the relationships between ADHD and comorbid conduct problems, and alcohol, nicotine, and

6   other substance use, and gaming habits, while accounting for age and sex. We used a state-of-the-art

7   causal discovery algorithm to analyze a case-only sample of 362 ADHD-diagnosed individuals in the ages

8   12-24 years. We found that conduct problem severity mediates between ADHD severity and nicotine use,

9   but not with more severe alcohol or substance use. More severe ADHD-inattentive symptoms lead to

10   more severe gaming habits. Furthermore, our model suggests that ADHD severity has no influence on

11   severity of alcohol or other drug use. Our findings suggest that ADHD severity is a risk factor for nicotine

12   use, and that this effect is fully mediated by conduct problem severity. Finally, ADHD-inattentive severity

13   was a risk factor for gaming, suggesting that gaming dependence has a different causal pathway than

14   substance dependence and should be treated differently. By identifying these intervention points, our

15   model can aid both researchers and clinicians.

16

Introduction

Attention-deficit hyperactivity disorder (ADHD) is an etiologically complex neuropsychiatric disorder with an estimated worldwide prevalence of 5% in childhood (Polanczyk et al., 2007). ADHD is characterized by impairing symptoms of inattention and/or hyperactivity-impulsivity (American Psychiatric Association, 2013). It often co-occurs with other disorders, such as anxiety, autism spectrum disorders, and conduct disorder (Christiansen et al., 2008; Dick et al., 2005; Greydanus et al., 2009; Jensen et al., 1997; Thapar et al., 2001). Compared to the general population, individuals with ADHD have poorer functional outcomes in many areas, including academic achievement, job performance, relationship difficulties, and car accidents (Usami, 2016). Moreover, individuals with ADHD show an increased risk for developing alcohol, nicotine, and gaming dependence (Charach et al., 2011; Fuemmeler et al., 2007; Kollins et al., 2005; Kuss and Griffiths, 2012; Riggs et al., 1999; Wilens, 2004; Zulauf et al., 2014). In addiction treatment settings, individuals with ADHD are overrepresented with an estimated prevalence of 23 percent (Van Emmerik-van Oortmerssen et al., 2012). ADHD has been shown to hasten the onset of substance use disorder (SUD) (Dunne et al., 2014; Wilens et al., 1997), increase the risk of SUD two to six fold compared to the general population (Gordon et al., 2004; Groenman et al., 2013), and is associated with more functional impairment as a consequence of SUD (Kousha et al., 2012).

ADHD also has been associated with a higher risk for internet addiction (Yen et al., 2009, 2007), and specifically the inattentive domain with more hours spent playing computer games (Chan and Rabinowitz, 2006). Additionally, in two clinical populations of adult internet addiction, individuals with ADHD were overrepresented at an estimated 13-14 percent (Kuss and Lopez-Fernandez, 2016). In the general population, internet use and gaming addiction has been correlated with negative outcomes such as obesity and aggression (Weiss et al., 2011).

The mechanisms underlying the comorbidity of ADHD with addictions are not well understood. The increased risk could be explained by (a) ADHD (symptoms) directly causing addictions (e.g. through

1 impulsive or novelty seeking behaviour (Donfrancesco et al., 2015)), by (b) ADHD and addiction sharing

2 another comorbidity (i.e. such as conduct disorder; between 30-50% of ADHD cases co-occur with

3 conduct disorder (Biederman et al., 1991)) which in turn causes addictions, or (c) the existence of a

4 shared underlying factor causing both. For example, evidence has been found for both environmental and

5 genetic factors (Groenman et al., 2016; Retz et al., 2007). Some studies suggest that comorbid conduct

6 disorder fully explains the increased risk of substance use disorders found in ADHD (Biederman et al.,

7 1997), while others showed ADHD to be a risk factor for substance and nicotine use, independent from

8 conduct disorder (Groenman et al., 2017) or see ADHD + conduct disorder as a separate entity entirely

9 (Christiansen et al., 2008). As these studies are difficult to directly compare as the investigated

10 substances and instruments differ, the nature of the relation between ADHD, conduct disorder and

11 addictions remains unclear.

12 To mitigate or even prevent the increased substance use risk in individuals with ADHD, a first step is to

13 identify the factors that contribute to that risk and visualize the chain of causes and effects between those

14 factors by constructing a causal model. Such a causal model would allow us to (i) answer questions such

15 as "should we expect a treatment that reduces ADHD severity also reduces the risk of substance use?",

16 (ii) construct a blueprint of the (potential) causal factors involved in both ADHD and substance use risk (to

17 be used as predictors) and (iii) generate hypotheses for putative biological mechanisms involved in the

18 risk of these disorders. In this paper we aimed to construct a likely causal model explanation of ADHD

19 severity, conduct problems (CP), and substance use and gaming habits within a clinical sample of

20 individuals with ADHD by performing an exploratory analysis investigating the cause and effect relation

21 between these factors using a causal discovery algorithm.

22 Causal discovery algorithms are computational methods used to extract causal models underlying data.

23 These methods build a network of causes and effects where possible, using statistical tests. They are

24 becoming increasingly popular to analyze biomedical data sets for understanding epidemiology and

25 etiology. The method used in this paper has previously been used successfully in an ADHD sample,

26 showing among other results that inattention and not hyperactivity/impulsivity may be driving ADHD

27 (Sokolova et al., 2017, 2016, 2015). Causal discovery algorithms aim to fill a gap in the commonly used

1   regression analyses: causal discovery attempts to disentangle the underlying causal structure of the data,

2   whereas regression tests the directionless strength of a relation whilst assuming that relation is indeed

3   true. By finding the underlying directed structure of the data, causal discovery provides additional

4   information not obtainable with regression analysis, such as identifying the direction of an effect, or

5   distinguishing between a confounder and true predictor(s).

6

1

Experimental Procedures

3

Study design

The subjects in this case-only study were n=362 individuals (81% male; age=16±2.4) diagnosed with

ADHD who had been recruited by the Belgian, Dutch, and German sites of the 2003-2006 International

Multicenter ADHD Genetics (IMAGE) study (Asherson, 2004; Brookes et al., 2006). In IMAGE, families

having at least one child aged 5 to 17 years with ADHD-Combined type and one sibling (regardless of

ADHD status) were recruited from outpatients clinics (Brookes et al., 2006). Ethical approval was

obtained from the National Institute of Health registered ethical review boards from each center.

Phenotypical exclusion criteria included autism spectrum disorders, epilepsy, IQ < 70, and brain disorders

(Müller et al., 2011). All phenotypic measures had been collected in the IMAGE project using standard

procedures as described elsewhere (Müller et al., 2011).

On average 4.4 years (SD=0.71) after the original assessments, participating families were requested to

complete additional interviews and questionnaires about substance and behavioral addiction (Groenman

et al., 2013; von Rhein et al., 2015). From an initial sample of 419 participants we included 362 with

complete data, and excluded 57 participants with partially missing data from incomplete questionnaires.

Welch's unequal variance t-test was performed to test for possible selective attrition. Affected siblings

were included if they were not otherwise excluded. We only use ADHD and CP measures from the

original assessment because comparably taken measures are not available from the follow-up.

ADHD & conduct problem measures

ADHD symptoms and CP in probands and affected siblings were rated at baseline with the Parental

Account of Childhood Symptoms (PACS) (Chen and Taylor, 2006), the Strengths and Difficulties

Questionnaire (SDQ) (Goodman, 1997), and the Long Version of Conners Parent (CPRS-R:L) and

Teacher Rating Scale Revised (CTRS-R:L) (Conners, 1997) about a stimulant medication-free period

(either by stopping medication use for one week, or alternatively by basing the ratings on medication-free

periods no longer than two years ago) . Out of the 362 included participants, 256 participants have at

1   some point used stimulants, whereas 28 have never used stimulants. For the remaining 78 participants,

2   medication use data is unavailable. Each of the 18 DSM-IV ADHD symptoms was operationally defined

3   using a standardized algorithm combining the parent and teacher assessment, the exact description of

4   which can be found elsewhere (Asherson, 2004; Rommelse et al., 2007). Participants were screened for

5   the presence of comorbid autism spectrum disorder using the Social Communication Questionnaire and

6   the SDQ, and all screened positive were excluded.

7   Common comorbidities of ADHD including anxiety, depression, sleep disorder, and anti-social personality

8   disorder were previously shown not to differ in individuals with ADHD with or without SUD in a non-

9   overlapping sample from IMAGE (Miranda et al., 2016). In our sample, anxiety was measured using the

10   Multidimensional Anxiety Scale for Children but did not correlate with ADHD severity (.2<p<.4) and was

11   thus not included in the model. Similarly, depression and social withdrawal were measured using two

12   Youth Self-Report subscales (Social Withdrawal, Anxious/Depressed) in a subgroup (n=58) of the

13   participants, but also did not correlate with ADHD severity (.4<p<.9) and were thus not included.

14   Neurocognitive measures including IQ were previously shown not to predict SUD or nicotine dependence

15   in our sample and therefore also not included in the model (Groenman et al., 2015).

16   The conduct problem dimension was defined by the conduct items from the CPRS-R:L and CTRS-R:L

17   oppositional subscales and the SDQ conduct scale following an algorithm described previously

18   (Christiansen et al., 2008); this algorithm has been developed to provide a reflection of conduct disorder.

19   Stimulant medication use could not be included directly in the study because it violates the non-cyclic

20   assumption of the causal discovery method (see Statistical analysis for details). While ADHD and CP

21   were assessed during a medication-free period, it could be that stimulant use affects nicotine, alcohol,

22   other substance use, or gaming outcomes. To address these concerns, an additional analysis was

23   performed using only the 256 stimulant-treated participants.

24   *Dependence measures*

25   Participants over 12 years old completed questionnaires about severity of alcohol, nicotine, and other

26   drug habits (all other substances, e.g. cannabis, cocaine and MDMA, hereafter referred to as "other

1   drugs"), and gaming habit severity. Continuous scores for all measures were used in the analysis to

2   increase discriminatory power, so no diagnostic cutoff criteria were used.

3   Alcohol dependence was measured using the Alcohol Use Disorders Identification Test (Saunders et al.,

4   1993), with scores ranging from 0-40. Nicotine dependence was measured using the Fagerström Test for

5   Nicotine Dependence (Heatherton et al., 1991), with scores ranging between 0-10. Other drug

6   dependence was measured using the Drug Abuse Screening Test-20 (Gavin et al., 1989), with scores

7   ranging from 0-20. Because there was no universally accepted standard to measure pathological gaming,

8   a 24-item gaming questionnaire was constructed containing translated items from an existing

9   questionnaire (Lemmens et al., 2009), supplemented with questions about frequency of gaming, and time

10   and money spent on gaming, with scores ranging from 0-92. A Cronbach's alpha value of .84 was

11   calculated using the GNU PSPP statistical software package (GNU Project, version 0.10.2), indicating

12   good internal reliability of the gaming questionnaire.

13   *Statistical analysis*

14   Causal Discovery

15   We performed our analysis using Bayesian Constraint-based Causal Discovery (BCCD) (Claassen and

16   Heskes, 2012), a causal discovery algorithm. The causal discovery approach can add to the existing body

17   of knowledge in several ways. Firstly, because it is a largely hypothesis-free approach (see "assumption"

18   below), this method can verify known relations. Secondly, the method indicates whether or not any result

19   we find is sufficiently supported by our data. If there is insufficient evidence for a particular effect, for

20   example due to too few participants, the method will show this. Thirdly, the method provides additional

21   information over regression-based approaches for causal interpretation of data. For one, to perform a

22   regression analysis, a regression model has to be assumed. Furthermore, regression-based mediation

23   tests are directionless: i.e. they can only show correlation between variables. With causal discovery we

24   do not have to assume a model, but instead generate a quantified causal model that best explains the

25   observed structure in the data.

26   In Figure 1, the analysis steps of BCCD are shown. BCCD accepts both discrete and continuous (non-

1)normal data (Sokolova et al., 2014) as step one. Step two is a preprocessing step in which the input is

2 mapped through a Gaussian transform into a correlation matrix (Claassen and Heskes, 2012). In the third

3 step, an efficient search is performed to obtain Bayesian reliability scores based on the BGe metric

4 (Cooper and Herskovits, 1992; Heckerman et al., 1995) for detectable (in)dependence relations in the

5 data, each of which places a constraint on the output model. This results in a list of weighted

6 independence constraints. In step four, the logical causal inference engine (LoCi) uses these local

7 independence constraints together with background knowledge (such as biological constraints) and

8 creates a coherent output causal model in step five. LoCi uses straightforward logical inference similar to

9 e.g. the well-known PC algorithm by Spirtes and Glymore (Spirtes et al., 2000a) for structure learning.

10 BCCD assumes that no cyclic dependencies are present. For a complete overview on constraint-based

11 causal discovery methods and the principles behind it, we refer the reader to Pearl (2000), Spirtes et al.

12 (2000b), or Spirtes and Zhang (2016). For a more detailed description of the BCCD algorithm, see

13 Claassen and Heskes (2012).

14 This combination of Bayesian estimates and logical inference outperforms more conventional methods in

15 terms of accuracy, and also allows us to provide reliability estimates for all relations in the model. The

16 output model provides an intuitive graphical depiction of the causal structure. The graph can also be

17 interpreted in terms of a structural equation model (SEM) (Halpern and Pearl, 2001), with the parents of a

18 variable in our graph corresponding to the causal input on the right-hand-side of the structural equation

19 defining that variable in a typical SEM model.

20 Reliability estimates are calculated for the existence of an interaction (connection) between each variable

21 in the model, and (if possible) for the direction of causal influence. To improve the readability of the

22 graphs, these numbers were combined in the visualizations only by taking the minimum of the relevant

23 numbers to provide a conservative joint reliability estimate for the link and causal directionality as a

24 whole.

25 Regression analysis

26 Additionally, we performed two multiple linear regression analyses with The Mathworks MATLAB®

1 software package version R2016B to determine the strength of the effects of the model variables on

2 nicotine use with (a) the full model and (b) the model BCCD suggests.

3 Assumptions of BCCD and the effects of age

4 Two explicit assumptions based on background knowledge were incorporated in our model. First, we

5 assumed that the alcohol, nicotine, drug, and gaming variables (that generally occur at a later age)

6 cannot cause the ADHD or CP symptoms, because symptoms were measured before the age of 7. This

7 timeline is reflected in our sample by the baseline measurement of ADHD and CP severity, with a later

8 follow-up to collect substance and gaming dependency information. Second, we assumed that no variable

9 in the model had an effect on either sex or age.

10 In the age group of 12-24, we should expect a significant age effect when looking at substance use, as

11 we have found. Part of this effect can be explained by the fact that some substances, e.g. nicotine and

12 alcohol, are not yet legally available at lower ages. This means that the age effects we have found are

13 partially due to contextual effects. To mitigate the influence of these effects, we performed three analyses

14 with BCCD: one with all participants (n=362), one with only participants aged 16 and over (n=197) and

15 one with participants 18 and over (n=100).

16

Results

Sample characteristics

Table 1 shows the descriptive information of the participants included in the study. In total, 362 individuals with ADHD were included of which 81% male, with a mean age of 16±2.4, a mean ADHD-HI symptom count of 7.8±1.6, a mean ADHD-In symptom count of 8.0±1.1, and a mean CP score of 83±36. Of the 57 excluded participants, 48 have missing nicotine use data, 31 have missing alcohol use data, 5 have missing substance use data, and 6 have missing gaming habit data. These numbers do not sum to 57 because participants can have missing data in more than one category. Attrition analysis showed no significant group differences in age, sex, ADHD, or CP between the original sample and the participants that had complete data for all measurements.

In Supplementary Figure S1 shows the distribution plots for the substance and gaming variables. The BCCD method is able to robustly handle this non-normal data (Sokolova et al., 2014). Supplementary Figure S2 shows the correlation between model variables. A moderately strong (.4-.6) Pearson correlation exists between age, alcohol use, and other drug use, as well as between other drug use and nicotine and alcohol.

Causal discovery

Figure 2 shows the causal graph for our analysis. The four different connection types are shown in the legend. For an in-depth explanation of the connections, see Section S1 in the Supplementary Information. Table 2 contains the exact measures used to generate the visual model in Figure 2.

The ADHD-HI and ADHD-In symptom counts shows a causal dependence with a joint reliability estimate of 52%. As can be seen in Table 2A, the reliability estimate of ADHD-In and ADHD-HI being directly connected is 87%. The tail ending at ADHD-In shows that it is likely that ADHD-In severity influenced ADHD-HI, however this conclusion only has a reliability estimate of 52% (Table 2B), resulting in a low joint reliability estimate for the causal connection. Both inattentive (ADHD-In) and hyperactive (ADHD-HI) symptom count show a link to CP, for which no directionality could be established with sufficient certainty,

1   as indicated by the circle endings. The link between ADHD-HI and CP has a joint reliability estimate of

2   >99%, whereas the link between ADHD-In and CP shows a joint reliability of 62%. As each link is

3   corrected for all other variables in the model, this shows that ADHD-In and ADHD-HI were independently

4   connected to CP.

5   Importantly, ADHD-In and ADHD-HI are not directly connected to the substance use variables. Instead

6   the connection from ADHD-In and ADHD-HI to nicotine use is mediated by CP, which shows a directional

7   link to nicotine with a joint reliability estimate of 85%. This CP mediated link between ADHD severity and

8   nicotine use does not link to alcohol or drug use. ADHD-In shows a directional link to gaming habit with a

9   joint reliability estimate of 86% and the substance use cluster of alcohol, nicotine, and drug use appears

10   separate from gaming habit.

11   Alcohol, nicotine, and drug use severity form a cluster with reliability estimates of >85% (Table 2A). The

12   joint reliability estimates shown (53%, 77%, and 77%) are lower because the direction of causality is less

13   certain. Alcohol use is not influenced by either nicotine use (78% reliable, Table 2B) or drug use (53%

14   reliable, Table 2B). Both alcohol and drug use influence nicotine use (77% reliable, see Table 2C). Direct

15   effects of age on alcohol and drug use are found, and through these, age indirectly influences nicotine

16   use.

17   Age shows directional links to alcohol and drug use, as well as a negative directional link to ADHD-HI

18   symptom count. Sex links to gaming habit, ADHD-In, and CP severity. The influence of sex on ADHD-HI

19   appears indirect (through CP and ADHD-In).

20   In Supplementary Figure S3 the same causal discovery has been performed for the age groups of 16 and

21   over (n=197) and 18 and over (n=100). In the 16-and-over age group, we still see age affecting other drug

22   use. In the 18-and-over age group, age is a completely independent factor. The link from CP to nicotine

23   use is present in both analyses with joint reliability estimates of 95% and 65% respectively, however we

24   are unable to exclude a possible common cause underlying both CP and nicotine use in the smaller

25   groups.

1   In Supplementary Figure S4 the same causal discovery has been performed for the subgroup that has

2   ever received simulant treatment (n=256). This analysis shows that the link between CP and nicotine use

3   is also found in the smaller treatment-only group, although its reliability estimate drops from 85% to 63%.

4   The links between ADHD-In and ADHD-HI as well as CP drop below the 50% threshold.

5   *Regression analysis*

6   In Supplementary Table S1, the regression result of all model variables on nicotine use is shown. Nicotine

7   use is selected as the outcome variable here because we found a causative link from ADHD through CP

8   to nicotine use in the causal model. Four variables have a significant ($p < .05$) connection: alcohol use,

9   other drug use, gaming, and CP. The effects of age (p=.57) and sex (p=.37) are not significant, which in

10   the case of age is mostly due to the correlation of age with alcohol use, other drug use, and to a lesser

11   extent gaming (see Figure S2 for details). Also non-significant are the effects of ADHD-HI (p=.44) and

12   ADHD-In (p=.81). The adjusted R^2 of the model is 0.26, with $p < 1e-20$. This can be interpreted to mean

13   that the model variables explain about 26% of the variance observed in nicotine use, and that the model

14   is significantly better at explaining this variance compared to a constant model.

15   In Supplementary Table S2, the regression analysis of alcohol use, other drug use, and CP on nicotine

16   use is shown. These are the variables selected by BCCD, i.e. the variables that have an arrow pointing

17   towards nicotine use in Figure 2. All three selected variables have a significant effect on nicotine use, and

18   the model itself has an adjusted R^2 of 0.26 with $p < 1e-23$. This means that the three variables implicated

19   by the causal model explain as much variance as the full regression model, and do so with a higher

20   significance.

Discussion

In this study, we have constructed a causal model to examine the relationship between ADHD, CP, alcohol, nicotine, other drug use, and gaming in an ADHD case-only sample. With this map of the causal relations, we can aid both researchers and clinicians to further study and reduce the risk for nicotine and gaming dependence in individuals with ADHD. We found that the risk for nicotine use for individuals with more severe ADHD symptoms is fully mediated by CP symptom severity This might imply that treatment for CP can be effective in reducing nicotine dependence risk in individuals with ADHD, making it an interesting target for future intervention studies. Furthermore, we found that ADHD-In severity has a direct influence on the gaming dependence severity, which suggests that ADHD-In may be an effective intervention point for treatment of gaming dependence in individuals with ADHD.

We found a mediation effect of conduct disorders in the link between ADHD and nicotine, as suggested by Biederman et al. (1997). This could be because nicotine is thought to be effective in reducing symptoms for a number of neuropsychiatric conditions including ADHD and conduct disorder (Levin et al., 1996; Sacco et al., 2004; Wilens et al., 1999). This provides a possible explanation for the ADHD and CP severity connection to nicotine use in particular: it may be that individuals knowingly or unknowingly use it as self-medication. Additionally, our findings showed that within our sample of individuals with ADHD, more severe alcohol and other drug use is indicative of more severe nicotine use, whereas the reverse is not true. Nicotine is typically seen as a gateway to other drugs (Biederman et al., 2006), which seems to contrast with our finding that alcohol and other drug use influence nicotine use. However, our causal model does not imply such a time line, so our finding does not conflict with nicotine use possibly predating other substance use.

ADHD and CP severity in individuals with ADHD did not show a connection to alcohol or other drug use in our model. In case-control studies, ADHD and CP have however been shown to be risk factors for both alcohol and other drug use (Biederman et al., 1997; Charach et al., 2011; Disney et al., 1999; Szobot et al., 2007). Additionally, in an overlapping sample Groenman et al. found an increased risk for individuals with ADHD compared with healthy controls for alcohol and/or other drug use disorder and for nicotine

1   dependence (Groenman et al., 2013). In contrast, the current study examined the impact of ADHD

2   *severity* in a case-only sample: a highly specific subset of the population. This distinction is important

3   because while an ADHD diagnosis may increase the risk for addiction, it is unclear whether more severe

4   ADHD within a case-only population further increases this risk. In particular, we have shown that within a

5   clinical ADHD sample the ADHD symptom count and CP severity do not influence the severity of alcohol

6   or other drug use. Consistent with these findings, intervention studies suggest that reducing ADHD

7   symptom count does not necessarily and significantly lower alcohol or other drug use. Wilens et al.

8   (2008a) showed that atomoxetine treatment intervention reduced ADHD symptoms, but had an

9   "inconsistent" effect on drinking disorders. Riggs et al. (2004) found pemoline treatment intervention in

10   substance-abusing ADHD cases to result in a decrease of ADHD symptoms but not to decrease alcohol

11   or other drug dependence. In line with this, Crowley et al. (1998) reported, in a two-year follow-up study,

12   that treatment for combined conduct disorder and substance use dependence lowered ADHD and CP

13   severity, but did not reduce substance use dependence. The non-effectiveness of treatment may be

14   partially explained by habit forming, as intervention on the original causes for long-lasting addictions may

15   be less effective (Lüscher and Malenka, 2011). However, higher dose treatment intervention studies have

16   shown a reduction of ADHD symptoms as well as reduced amphetamine use (Konstenius et al., 2014)

17   and reduced cocaine use (Levin et al., 2015). The effect of higher dose treatment on substance use

18   suggests that while it is possible to improve both ADHD and substance dependence using the same

19   treatment, the effects on substance dependence are not achieved through reduction in ADHD symptoms

20   (because otherwise any reduction in ADHD symptoms should result in a reduction of other drug use).

21   Instead, it may be possible that a higher dose treatment is affecting a system *underlying both* ADHD and

22   substance dependence. However, as the nature of the association between ADHD, CP, and substance

23   dependence remains unclear, further study is needed to investigate underlying causes.

24   Our results strongly hint that ADHD-In severity plays an important role in gaming habit severity, even after

25   correcting for sex. Gaming habit, a behavioral addiction, has different direct risk factors in our model from

26   substance use. A categorical distinction between substance and behavioral dependence has been

27   discussed previously [e.g. (Alavi et al., 2012; Potenza, 2006)] and is becoming more recognized (Robbins

28   and Clark, 2015). Our model supports such a distinction, because gaming habit has a different causal

1   path from the substance use phenotypes. More research is needed into whether the neurobiological

2   mechanisms involved in substance and behavioral dependence also differ from each other.

3   We also looked at the effects of ADHD and CP on nicotine use with a more conventional regression

4   method. This allows us to explore similarities and differences between the BCCD analysis and observe

5   any additional merits of the BCCD analysis. The regression analyses are shown in Supplementary Table

6   3. Using only the 3 variables that BCCD suggests have a direct influence on nicotine use, we see that the

7   second regression model that explains as much of the variance as the model with all 8 variables, and

8   does so with a 1000-fold lower p-value (see Results). While it may be possible to improve upon the initial

9   model fit of the regression by simply dropping all non-significant variables from the model, this does not

10   provide any indication of direct or indirect effects, which are of vital importance in disease etiology. In this

11   case for example, the regression results in Table 3 suggests that gaming has a significant effect on

12   nicotine use (or the other way around, since regressions are directionless), whereas our causal discovery

13   shows there to be no direct relation. This should not be taken to mean that causal discovery is "better"

14   than regression analysis, for the two methods serve different purposes. Regression analysis estimates

15   the strength of the influence of model variables on an outcome variable (i.e. effect size) assuming the

16   model is correct and complete, whereas causal discovery can help to select the right model to test.

17   Almost half of our participants were not legally allowed to purchase nicotine or alcohol. To test whether

18   this influences our finding, we have repeated our causal model approach for the age groups of 16-and-

19   over and 18-and-over in Figure S3. Due to the lower sample size, the types of causal conclusions are

20   less strong, and the reliability estimates of these conclusions are reduced. But even with the reduction in

21   sample size, the figures confirm our conclusion of CP mediating the effect of ADHD.

22   The same method was used to verify whether the effects of stimulant treatment influenced our findings in

23   figure S4. While the link between CP and nicotine use remained present, the links between ADHD-In and

24   ADHD-HI as well as CP dropped below our threshold of 50%. This means that in the stimulant treated

25   group, we did not observe a mediation effect of CP in the relation between ADHD-In and nicotine use.

26   This may be caused by the lower sample size, as well as by any selection bias we have introduced by

1   looking only at stimulant-treated participants.

2   Large sections of our model are consistent with literature, showing that ADHD occurs more often in boys

3   than in girls (Arnett et al., 2015; Faraone et al., 1995), that the risk of substance use in adolescents

4   increases with increasing age (Young et al., 2002), and that ADHD hyperactivity severity declines with

5   increasing age at a higher rate than inattentive severity (Biederman et al., 2000). ADHD severity has

6   been shown to be a risk factor for nicotine use (Fuemmeler et al., 2007; Kollins et al., 2005; Riggs et al.,

7   1999), although one study did not find a link between ADHD severity and nicotine use in individuals with

8   ADHD (Wilens et al., 2008b). Previous research also showed boys to be more susceptible to gaming

9   habit (Ko et al., 2005). The current study also finds evidence to suggest that ADHD-In influences ADHD-

10   HI severity, and not nice versa. This result was previously found using the same method in two ADHD

11   samples different from the one investigated here (Sokolova et al., 2016). These consistent findings attest

12   to the reliability of both our data set and the causal discovery method.

13   Our study should be viewed in the context of some strengths and limitations. While we have tried to

14   account for the effects of stimulant treatment, it remains difficult to fully examine its effects in our model.

15   We provide reliability estimates in our causal model, but BCCD does not provide estimates of the *effect*

16   *size* of the causal influence. Furthermore, due to inherent low variance in substance use, flooring effects

17   might bias this analysis. Lastly, our causal discovery is data-driven. We did not investigate the underlying

18   biological mechanisms; instead, our work was aimed at identifying which parts of the pathway are most

19   worth investigating.

20   The strengths of our study are the high standards of ascertainment used in diagnosis, our focus on a

21   critical adolescent age group, and the novel BCCD method allowing us to give reliability estimates for our

22   conclusions. This combination of factors allows us to look at the effects of ADHD and CP severity in a

23   different way than what is commonly done using regression analyses. This enables us to leverage more

24   information from medical data and help provide a valuable tool to understand disease etiology.

25   In conclusion, we have constructed a causal model of relationship between ADHD, CP, substance use,

26   and gaming. CP was found to fully mediate the risk of ADHD for nicotine use, while gaming dependence

1   was found to be directly influenced by ADHD-In. Our identification of causal components in the ADHD-

2   addiction pathway, our work could aid future research into the overlap between ADHD and addiction, and

3   help clinicians to develop more effective treatments.

4

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TABLE 1: Sample characteristics of the full group versus the included subsection of the participants, including statistical test for group difference. ADHD-In: PACS symptom count for the ADHD-Inattentive subscale; ADHD-HI: PACS symptom count for the ADHD-Hyperactive-Impulsive subtype; CP: conduct problems severity; sd: standard deviation.

	Participants		Included		P (Welch's t)
N	419		362		
%Male	79.47		80.66		0.68
	mean	sd	mean	sd	
Age	15.93	2.46	15.93	2.46	0.82
ADHD-HI	7.72	1.68	7.72	1.68	0.80
ADHD-In	8.02	1.17	8.02	1.17	0.81
CP	82.15	36.64	82.15	36.64	1

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3   **TABLE 2**:

4   **(A)** Reliability estimates of the existence of a link between variables in percentages. E.g. the reliability

5   estimate of a direct connection between gaming dependence and ADHD-In symptom count is 86%. The

6   ranges and distributions of the substance and gaming dependency variables can be found in

7   Supplementary Figure S1.

8   **(B)** Reliability estimates of the tail endings in Figure 2 at the row variable to the column variable. E.g. the

9   tail ending at CP from its connection to Nicotine has a reliability estimate of 86%. This can be interpreted

10   as "We can be 86% sure that nicotine use does not influence CP either directly or through a common

11   cause". Only values of 50% and higher are shown.

12   **(C)** Reliability estimates of the arrow endings in Figure 2 at the row variable to the column variable. E.g.

13   the arrow ending at Nicotine coming from Other Drug Use has a reliability estimate of 77%. This can be

14   interpreted as "We can be 77% sure that nicotine use does not directly influence drug use". Only values

15   of 50% and higher are shown. Common causes are not excluded. Values indicated with an asterisk

16   result from assumptions incorporated in the model. ADHD-In: PACS symptom count for the ADHD-

17   Inattentive subscale; ADHD-HI: PACS symptom count for the ADHD-Hyperactive-Impulsive subtype; CP:

18   conduct problems severity.

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		Age	Sex	Nicotine	Alcohol	Drug	Gaming	ADHD-HI	ADHD-In	CP
2A	Age	-	0	16	>99	61	31	54	6	9
	Sex		-	6	10	9	>99	15	97	63
	Nicotine			-	85	>99	30	5	5	85
	Alcohol				-	>99	10	6	7	15
	Drug					-	11	6	11	12
	Gaming						-	10	86	20
	ADHD-HI							-	87	>99
	ADHD-In								-	62
	CP									-
2B	Age	-								
	Sex		-							
	Nicotine			-						
	Alcohol			78	-	53				
	Drug			84		-				
	Gaming						-			
	ADHD-HI							-		
	ADHD-In							52	-	
	CP			86						-
2C	Age	-								
	Sex		-							
	Nicotine			-	77	77				
	Alcohol	100*			-					
	Drug	100*				-				
	Gaming		100*				-	100*	100*	
	ADHD-HI	100*						-		
	ADHD-In		100*						-	
	CP		100*							-

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1 **Table 3**:

2 **(A)** Linear regression model of the effects of all model variables on nicotine use (n=362). The estimates

3 show how strongly variables affect nicotine use, assuming that they in fact do affect nicotine use. With our

4 causal model, we show this assumption can be flawed. Significant coefficients (p < .05) are indicated in

5 underlined boldface.

6 **(B)** Linear regression model of the effects of only the BCCD-identified variables on nicotine use (n=362).

7 LowCI: Low 95% confidence interval. HighCI: High 95% confidence interval. SE: Standard error of the

8 coefficients. tStat: T-statistic of the coefficient being zero, higher is more significant. pValue: p-value of

9 the F-statistic of the coefficient being zero, lower is more significant. Adj-R-squared: adjusted coefficient

10 of determination, higher means more variance explained. ADHD-In: PACS symptom count for the ADHD-

11 Inattentive subscale; ADHD-HI: PACS symptom count for the ADHD-Hyperactive-Impulsive subtype; CP:

12 conduct problems severity.

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	Variable	Estimate	LowCI	HighCI	SE	tStat	pValue
3A	(Intercept)	-0.1292	-1.7912	1.5328	0.8451	-0.1529	8.7855E-01
	Age	0.0210	-0.0509	0.0930	0.0366	0.5746	5.6594E-01
	Sex	0.1851	-0.2218	0.5921	0.2069	0.8947	3.7158E-01
	Alcohol	0.0422	0.0055	0.0789	0.0187	2.2623	**2.4287E-02**
	Other Drug	0.2164	0.1546	0.2782	0.0314	6.8866	**2.6270E-11**
	Gaming	-0.0140	-0.0264	-0.0016	0.0063	-2.2167	**2.7281E-02**
	ADHD-HI	-0.0388	-0.1384	0.0608	0.0507	-0.7662	4.4406E-01
	ADHD-In	-0.0165	-0.1545	0.1215	0.0702	-0.2353	8.1412E-01
	CP	0.0069	0.0024	0.0114	0.0023	3.0440	**2.5097E-03**
	Adj-R-squared		2.65E-01				
	P-value		1.18E-21				
3B	Variable	Estimate	LowCI	HighCI	SE	tStat	pValue
	(Intercept)	-0.1874	-0.5675	0.1928	0.1933	-0.9693	3.3305E-01
	Alcohol	0.0465	0.0121	0.0809	0.0175	2.6562	8.2561E-03
	Other Drug	0.2261	0.1652	0.2870	0.0310	7.3017	1.8553E-12
	CP	0.0059	0.0017	0.0101	0.0021	2.7378	6.4938E-03
	Adj-R-squared		2.60E-01				
	P-value		6.20E-24				

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3   **Figure 1:** Schematic representation of the steps in the BCCD algorithm. LoCi: logical causal inference

4   engine.

5

6   <<File: Fig_1.pdf>>

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2 **Figure 2:** Graph of the causal model. ADHD and CP variables in rectangles, substance and gaming

3 dependency variables in diamonds, and age, sex in hexagons. Numbers show joint reliability estimates in

4 percentages for the causal relation, with negative numbers showing an inhibitory relation. A ⟶ B

5 indicates that A influences B and that B does not influence A; A o⟶ B indicates that A influences

6 B, or that there is an unobserved common cause affecting both A and B; A ⟶o B shows that either

7 A influences B, or that there is some selection bias in the sample; lastly A o⟶o B can mean any of

8 the above. ADHD-In: PACS symptom count for the ADHD-Inattentive subscale; ADHD-HI: PACS

9 symptom count for the ADHD-Hyperactive-Impulsive subtype; CP: conduct problems severity.

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11 <<File: Fig_2.pdf>>

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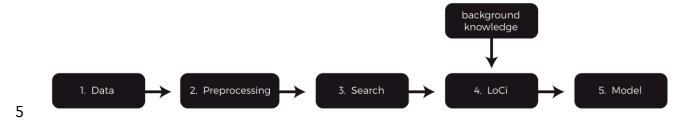46   https://doi.org/10.1111/j.1360-0443.1993.tb02093.x

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3 **Figure 1:** Schematic representation of the steps in the BCCD algorithm. LoCi: logical causal inference engine.

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2 **Figure 2:** Graph of the causal model. ADHD and CP variables in rectangles, substance and gaming dependency

3 variables in diamonds, and age, sex in hexagons. Numbers show joint reliability estimates for the causal relation,

4 with negative numbers showing an inhibitory relation. A ⟶ B indicates that A influences B and that B does

5 not influence A; A o⟶ B indicates that A influences B, or that there is an unobserved common cause

6 affecting both A and B; A ⟶o B shows that either A influences B, or that there is some selection bias in the

7 sample; lastly A o⟶o B can mean any of the above. ADHD-In: PACS symptom count for the ADHD-

8 Inattentive subscale; ADHD-HI: PACS symptom count for the ADHD-Hyperactive-Impulsive subtype; CP: conduct

9 problems severity.

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