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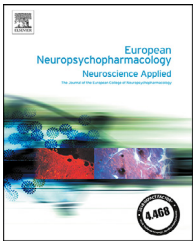

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Role of conduct problems in the relation between Attention-Deficit Hyperactivity disorder, substance use, and gaming

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Abstract
Known comorbidities for Attention-Deficit Hyperactivity Disorder (ADHD) include conduct problems, substance use disorder and gaming. Comorbidity with conduct problems may increase the risk for substance use disorder and gaming in individuals with ADHD. The aim of the study was to build a causal model of the relationships between ADHD and comorbid conduct problems, and alcohol, nicotine, and other substance use, and gaming habits, while accounting for age and sex. We used a state-of-the-art causal discovery algorithm to analyze a case-only sample of 362 ADHD-diagnosed individuals in the ages 12–24 years. We found that conduct problem severity mediates between ADHD severity and nicotine use, but not with more severe alcohol or substance use. More severe ADHD-inattentive symptoms lead to more severe gaming habits. Furthermore, our model suggests that ADHD severity has no influence on severity of alcohol or other drug use. Our findings suggest that ADHD severity is a risk factor for nicotine use, and that this effect is fully mediated by conduct problem severity. Finally, ADHD-inattentive severity was a risk factor for gaming, suggesting that gaming dependence has a different causal pathway than substance dependence and should be treated differently. By identifying these intervention points, our model can aid both researchers and clinicians.

1. 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 impulsive or novelty seeking behaviour (Donfrancesco et al., 2015)), by (b) ADHD and addiction sharing another comorbidity (i.e. such as conduct disorder; between 30–50% of ADHD cases co-occur with conduct disorder (Biederman et al., 1991)) which in turn causes addictions, or (c) the existence of a shared underlying factor causing both. For example, evidence has been found for both environmental and genetic factors (Groenman et al., 2016; Retz et al., 2007). Some studies suggest that comorbid conduct disorder fully explains the increased risk of substance use disorders found in ADHD (Biederman et al., 1997), while others showed ADHD to be a risk factor for substance and nicotine use, independent from conduct disorder (Groenman et al., 2017) or see ADHD + conduct disorder as a separate entity entirely (Christiansen et al., 2008). As these studies are difficult to directly compare as the investigated substances and instruments differ, the nature of the relation between ADHD, conduct disorder and addictions remains unclear.

To mitigate or even prevent the increased substance use risk in individuals with ADHD, a first step is to identify the factors that contribute to that risk and visualize the chain of causes and effects between those factors by constructing a causal model. Such a causal model would allow us to (i) answer questions such as “should we expect a treatment that reduces ADHD severity also reduces the risk of substance use?”, (ii) construct a blueprint of the (potential) causal factors involved in both ADHD and substance use risk (to be used as predictors) and (iii) generate hypotheses for putative biological mechanisms involved in the risk of these disorders. In this paper we aimed to construct a likely causal model explanation of ADHD severity, conduct problems (CP), and substance use and gaming habits within a clinical sample of individuals with ADHD by performing an exploratory analysis investigating the cause and effect relation between these factors using a causal discovery algorithm.

Causal discovery algorithms are computational methods used to extract causal models underlying data. These methods build a network of causes and effects where possible, using statistical tests. They are becoming increasingly

popular to analyze biomedical data sets for understanding epidemiology and etiology. The method used in this paper has previously been used successfully in an ADHD sample, showing among other results that inattention and not hyperactivity/impulsivity may be driving ADHD (Sokolova et al., 2017, 2016, 2015). Causal discovery algorithms aim to fill a gap in the commonly used regression analyses: causal discovery attempts to disentangle the underlying causal structure of the data, whereas regression tests the directionless strength of a relation whilst assuming that relation is indeed true. By finding the underlying directed structure of the data, causal discovery provides additional information not obtainable with regression analysis, such as identifying the direction of an effect, or distinguishing between a confounder and true predictor(s).

2. Experimental procedures

2.1. Study design

The subjects in this case-only study were $n = 362$ individuals (81% male; age $= 16 \pm 2.4$) 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.

2.2. 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. The decision whether medication could be discontinued was always taken by the individual with ADHD and their family, together with the responsible clinician; the latter was to ensure that proper health care would not be compromised by the research project. This procedure was approved by the local ethics committee. Out of the 362 included participants, 256 participants have at some point used stimulants, whereas 28 have never used stimulants. For the remaining 78 participants, medication use data is unavailable. Each of the 18 DSM-IV ADHD symptoms was operationally defined using a standardized algorithm combining the parent and teacher assessment, the exact description of which can be found elsewhere (Asherson, 2004; Rommelse et al., 2007). Participants were screened for the presence of comorbid autism spectrum disorder using the Social Communication Questionnaire and the SDQ, and all screened positive were excluded.

Common comorbidities of ADHD including anxiety, depression, sleep disorder, and anti-social personality disorder were previously shown not to differ in individuals with ADHD with or without SUD in a non-overlapping sample from IMAGE (Miranda et al., 2016). In our sample, anxiety was measured using the Multidimensional Anxiety Scale for Children but did not correlate with ADHD severity ($0.2 < p < .4$) and was thus not included in the model. Similarly, depression and social withdrawal were measured using two Youth Self-Report subscales (Social Withdrawal, Anxious/Depressed) in a subgroup ($n = 58$) of the participants, but also did not correlate with ADHD severity ($0.4 < p < .9$) and were thus not included. Neurocognitive measures including IQ were previously shown not to predict SUD or nicotine dependence in our sample and therefore also not included in the model (Groenman et al., 2015).

The conduct problem dimension was defined by the conduct items from the CPRS-R:L and CTRS-R:L oppositional subscales and the SDQ conduct scale following an algorithm described previously (Christiansen et al., 2008); this algorithm has been developed to provide a reflection of conduct disorder. Stimulant medication use could not be included directly in the study because it violates the non-cyclic assumption of the causal discovery method (see Statistical analysis for details). While ADHD and CP were assessed during a medication-free period, it could be that stimulant use affects nicotine, alcohol, other substance use, or gaming outcomes. To address these concerns, an additional analysis was performed using only the 256 stimulant-treated participants.

2.3. Dependence measures

Participants over 12 years old completed questionnaires about severity of alcohol, nicotine, and other drug habits (all other substances, e.g. cannabis, cocaine and MDMA, hereafter referred to as "other drugs"), and gaming habit severity. Continuous scores for all measures were used in the analysis to increase discriminatory power, so no diagnostic cutoff criteria were used.

Alcohol dependence was measured using the Alcohol Use Disorders Identification Test (Saunders et al., 1993), with scores ranging from 0–40. Nicotine dependence was measured using the Fagerström Test for Nicotine Dependence

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

(Heatherton et al., 1991), with scores ranging between 0-10. Other drug dependence was measured using the Drug Abuse Screening Test-20 (Gavin et al., 1989), with scores ranging from 0-20. Because there was no universally accepted standard to measure pathological gaming, a 24-item gaming questionnaire was constructed containing translated items from an existing questionnaire (Lemmens et al., 2009), supplemented with questions about frequency of gaming, and time and money spent on gaming, with scores ranging from 0-92. A Cronbach's alpha value of 0.84 was calculated using the GNU PSPP statistical software package (GNU Project, version 0.10.2), indicating good internal reliability of the gaming questionnaire.

2.4. Statistical analysis

2.4.1. Causal discovery

We performed our analysis using Bayesian Constraint-based Causal Discovery (BCCD) (Claassen and Heskes, 2012), a causal discovery algorithm. The causal discovery approach can add to the existing body of knowledge in several ways. Firstly, because it is a largely hypothesis-free approach (see "assumption" below), this method can verify known relations. Secondly, the method indicates whether or not any result we find is sufficiently supported by our data. If there is insufficient evidence for a particular effect, for example due to too few participants, the method will show this. Thirdly, the method provides additional information over regression-based approaches for causal interpretation of data. For one, to perform a regression analysis, a regression model has to be assumed. Furthermore, regression-based mediation tests are directionless: i.e. they can only show correlation between variables. With causal discovery we do not have to assume a model, but instead generate a quantified causal model that best explains the observed structure in the data.

In Fig. 1, the analysis steps of BCCD are shown. BCCD accepts both discrete and continuous (non-)normal data (Sokolova et al., 2014) as step one. Step two is a preprocessing step in which the input is mapped through a Gaussian transform into a correlation matrix (Claassen and Heskes, 2012). In the third step, an efficient search is performed to obtain Bayesian reliability scores based on the BGe metric (Cooper and Herskovits, 1992; Heckerman et al., 1995) for detectable (in)dependence relations in the data, each of which places a constraint on the output model. This results in a list of weighted independence constraints. In step four, the logical causal inference engine (LoCi) uses these local independence constraints together with background knowledge (such as biological constraints) and creates a coherent output causal model in step five. LoCi uses straightforward logical inference similar to e.g. the well-known PC algorithm by Spirtes and Glymore (Spirtes et al., 2000a) for structure learning. BCCD assumes that no cyclic dependencies are present. For a complete overview on constraint-based causal discovery methods and the principles behind it, we refer the reader to Pearl (2000), Spirtes et al., (2000b), or Spirtes and Zhang (2016). For a more detailed description of the BCCD algorithm, see Claassen and Heskes (2012).

This combination of Bayesian estimates and logical inference outperforms more conventional methods in terms of accuracy, and also allows us to provide reliability estimates for all relations in the model. The output model provides an intuitive graphical depiction of the causal structure. The graph can also be interpreted in terms of a structural equation model (SEM) (Halpern and Pearl, 2001), with the parents of a variable in our graph corresponding to the causal input on the right-hand-side of the structural equation defining that variable in a typical SEM model.

Reliability estimates are calculated for the existence of an interaction (connection) between each variable in the model, and (if possible) for the direction of causal influence. To improve the readability of the graphs, these numbers were combined in the visualizations only by taking the minimum of the relevant numbers to provide a conservative joint reliability estimate for the link and causal directionality as a whole.

2.4.2. Regression analysis

Additionally, we performed two multiple linear regression analyses with The Mathworks MATLAB® software package version R2016B to determine the strength of the effects of the model variables on nicotine use with (a) the full model and (b) the model BCCD suggests.

2.4.3. Assumptions of BCCD and the effects of age

Two explicit assumptions based on background knowledge were incorporated in our model. First, we assumed that the alcohol, nicotine, drug, and gaming variables (that generally occur at a later age) cannot cause the ADHD or CP symptoms, because symptoms were measured before the age of 7. This timeline is reflected in our sample by the baseline measurement of ADHD and CP severity, with a later follow-up to collect substance and gaming dependency information. Second, we assumed that no variable in the model had an effect on either sex or age.

In the age group of 12-24, we should expect a significant age effect when looking at substance use, as we have found. Part of this effect can be explained by the fact that some

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

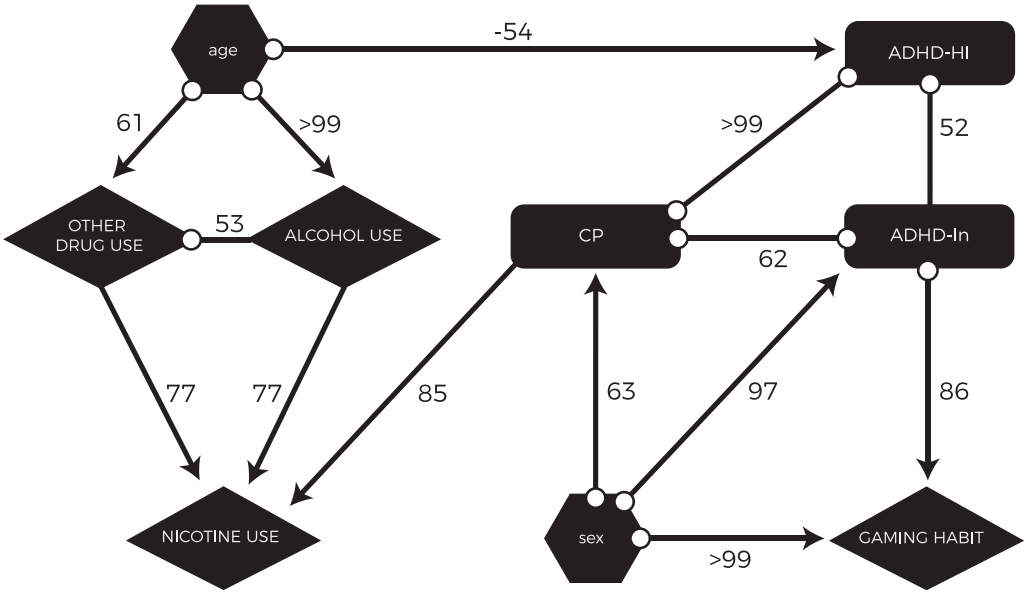

Fig. 2 Graph of the causal model. ADHD and CP variables in rectangles, substance and gaming dependency variables in diamonds, and age, sex in hexagons. Numbers show joint reliability estimates in percentages for the causal relation, with negative numbers showing an inhibitory relation. A $\longrightarrow$ B indicates that A influences B and that B does not influence A; A $\circ\!\!\longrightarrow$ B indicates that A influences B, or that there is an unobserved common cause affecting both A and B; A $\circ\!\!-\!\!\circ$ B shows that either A influences B, or that there is some selection bias in the sample; lastly A $\circ\!\!-\!\!\circ$ B can mean any of the above. 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.

substances, e.g. nicotine and alcohol, are not yet legally available at lower ages. This means that the age effects we have found are partially due to contextual effects. To mitigate the influence of these effects, we performed three analyses with BCCD: one with all participants ($n = 362$), one with only participants aged 16 and over ($n = 197$) and one with participants 18 and over ($n = 100$).

3. Results

3.1. 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 Fig. 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 Fig. S2 shows the correlation between model variables. A moderately strong (0.4-0.6) Pearson correlation exists between age, alcohol use, and other drug use, as well as between other drug use and nicotine and alcohol.

Table 2 **(A)** Reliability estimates of the existence of a link between variables in percentages. E.g. the reliability estimate of a direct connection between gaming dependence and ADHD-In symptom count is 86%. The ranges and distributions of the substance and gaming dependency variables can be found in Supplementary Fig. S1.
(B) Reliability estimates of the tail endings in Fig. 2 at the row variable to the column variable. E.g. the tail ending at CP from its connection to Nicotine has a reliability estimate of 86%. This can be interpreted as "We can be 86% sure that nicotine use does not influence CP either directly or through a common cause". Only values of 50% and higher are shown.
(C) Reliability estimates of the arrow endings in Fig. 2 at the row variable to the column variable. E.g. the arrow ending at Nicotine coming from Other Drug Use has a reliability estimate of 77%. This can be interpreted as "We can be 77% sure that nicotine use does not directly influence drug use". Only values of 50% and higher are shown. Common causes are not excluded. Values indicated with an asterisk result from assumptions incorporated in the model. 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.

		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*							-

3.2. Causal discovery

Fig. 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 Fig. 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, as indicated by the circle endings. The link between ADHD-HI and CP has a joint reliability estimate of > 99%, whereas the link between ADHD-In and CP shows a joint reliability of 62%. As each link is corrected for all other variables in the model, this shows that ADHD-In and ADHD-HI were independently connected to CP.

Importantly, ADHD-In and ADHD-HI are not directly connected to the substance use variables. Instead the connection from ADHD-In and ADHD-HI to nicotine use is mediated by CP, which shows a directional link to nicotine with a joint reliability estimate of 85%. This CP mediated link between ADHD severity and nicotine use does not link to alcohol or drug use. ADHD-In shows a directional link to gaming habit with a joint reliability estimate of 86% and the substance use cluster of alcohol, nicotine, and drug use appears separate from gaming habit.

Alcohol, nicotine, and drug use severity form a cluster with reliability estimates of > 85% (Table 2A). The joint reliability estimates shown (53%, 77%, and 77%) are lower because the direction of causality is less certain. Alcohol use is not influenced by either nicotine use (78% reliable,

Table 2B) or drug use (53% reliable, Table 2B). Both alcohol and drug use influence nicotine use (77% reliable, see Table 2C). Direct effects of age on alcohol and drug use are found, and through these, age indirectly influences nicotine use.

Age shows directional links to alcohol and drug use, as well as a negative directional link to ADHD-HI symptom count. Sex links to gaming habit, ADHD-In, and CP severity. The influence of sex on ADHD-HI appears indirect (through CP and ADHD-In).

In Supplementary Fig. S3 the same causal discovery has been performed for the age groups of 16 and over ($n = 197$) and 18 and over ($n = 100$). In the 16-and-over age group, we still see age affecting other drug use. In the 18-and-over age group, age is a completely independent factor. The link from CP to nicotine use is present in both analyses with joint reliability estimates of 95% and 65% respectively, however we are unable to exclude a possible common cause underlying both CP and nicotine use in the smaller groups.

In Supplementary Fig. S4 the same causal discovery has been performed for the subgroup that has ever received simulant treatment ($n = 256$). This analysis shows that the link between CP and nicotine use is also found in the smaller treatment-only group, although its reliability estimate drops from 85% to 63%. The links between ADHD-In and ADHD-HI as well as CP drop below the 50% threshold.

3.3. Regression analysis

In Supplementary Table S1, the regression result of all model variables on nicotine use is shown. Nicotine use is selected as the outcome variable here because we found a causative link from ADHD through CP to nicotine use in the causal model. Four variables have a significant ($p < .05$) connection: alcohol use, other drug use, gaming, and CP. The effects of age ($p = .57$) and sex ($p = .37$) are not significant, which in the case of age is mostly due to the correlation of age with alcohol use, other drug use, and to a lesser extent gaming (see Fig. S2 for details). Also non-significant are the effects of ADHD-HI ($p = .44$) and ADHD-In ($p = .81$). The adjusted R^2 of the model is 0.26, with $p < 1e\text{-}20$. This can be interpreted to mean that the model variables explain about 26% of the variance observed in nicotine use, and that the model is significantly better at explaining this variance compared to a constant model.

In Supplementary Table S2, the regression analysis of alcohol use, other drug use, and CP on nicotine use is shown. These are the variables selected by BCCD, i.e. the variables that have an arrow pointing towards nicotine use in Fig. 2. All three selected variables have a significant effect on nicotine use, and the model itself has an adjusted R^2 of 0.26 with $p < 1e\text{-}23$. This means that the three variables implicated by the causal model explain as much variance as the full regression model, and do so with a higher significance.

4. 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 dependence (Groenman et al., 2013). In contrast, the current study examined the impact of ADHD *severity* in a case-only sample: a highly specific subset of the population. This distinction is important because while an ADHD diagnosis may increase the risk for addiction, it is unclear whether more severe ADHD within a case-only population further increases this risk. In particular, we have shown that within a clinical ADHD sample the ADHD symptom count and CP severity do not influence the severity of alcohol or other drug use. Consistent with these findings, intervention studies suggest that reducing ADHD symptom count does not necessarily and significantly lower alcohol or other drug use. Wilens et al., (2008a) showed that atomoxetine treatment intervention reduced ADHD symptoms, but had an "inconsistent" effect on drinking disorders. Riggs et al., (2004) found pemoline treatment intervention in substance-abusing ADHD cases to result in a decrease of ADHD symptoms but not to decrease alcohol or other drug dependence. In line with this, Crowley et al., (1998) reported, in a two-year follow-up study, that treatment for combined conduct disorder and substance use dependence lowered ADHD and CP severity, but did not

reduce substance use dependence. The non-effectiveness of treatment may be partially explained by habit forming, as intervention on the original causes for long-lasting addictions may be less effective (Lüscher and Malenka, 2011). However, higher dose treatment intervention studies have shown a reduction of ADHD symptoms as well as reduced amphetamine use (Konstenius et al., 2014) and reduced cocaine use (Levin et al., 2015). The effect of higher dose treatment on substance use suggests that while it is possible to improve both ADHD and substance dependence using the same treatment, the effects on substance dependence are not achieved through reduction in ADHD symptoms (because otherwise any reduction in ADHD symptoms should result in a reduction of other drug use). Instead, it may be possible that a higher dose treatment is affecting a system *underlying both* ADHD and substance dependence. However, as the nature of the association between ADHD, CP, and substance dependence remains unclear, further study is needed to investigate underlying causes.

Our results strongly hint that ADHD-In severity plays an important role in gaming habit severity, even after correcting for sex. Gaming habit, a behavioral addiction, has different direct risk factors in our model from substance use. A categorical distinction between substance and behavioral dependence has been discussed previously [e.g. (Alavi et al., 2012; Potenza, 2006)] and is becoming more recognized (Robbins and Clark, 2015). Our model supports such a distinction, because gaming habit has a different causal path from the substance use phenotypes. More research is needed into whether the neurobiological mechanisms involved in substance and behavioral dependence also differ from each other.

We also looked at the effects of ADHD and CP on nicotine use with a more conventional regression method. This allows us to explore similarities and differences between the BCCD analysis and observe any additional merits of the BCCD analysis. The regression analyses are shown in Supplementary Table 3. Using only the 3 variables that BCCD suggests have a direct influence on nicotine use, we see that the second regression model that explains as much of the variance as the model with all 8 variables, and does so with a 1000-fold lower p-value (see Results). While it may be possible to improve upon the initial model fit of the regression by simply dropping all non-significant variables from the model, this does not provide any indication of direct or indirect effects, which are of vital importance in disease etiology. In this case for example, the regression results in Table 3 suggests that gaming has a significant effect on nicotine use (or the other way around, since regressions are directionless), whereas our causal discovery shows there to be no direct relation. This should not be taken to mean that causal discovery is "better" than regression analysis, for the two methods serve different purposes. Regression analysis estimates the strength of the influence of model variables on an outcome variable (i.e. effect size) assuming the model is correct and complete, whereas causal discovery can help to select the right model to test.

Almost half of our participants were not legally allowed to purchase nicotine or alcohol. To test whether this influences our finding, we have repeated our causal model approach for the age groups of 16-and-over and 18-and-over in Fig. S3. Due to the lower sample size, the types of causal conclusions are less strong, and the reliability estimates of these conclusions are reduced. But even with the reduction in sample size, the figures confirm our conclusion of CP mediating the effect of ADHD.

The same method was used to verify whether the effects of stimulant treatment influenced our findings in Fig. S4. While the link between CP and nicotine use remained present, the links between ADHD-In and ADHD-HI as well as CP dropped below our threshold of 50%. This means that in the stimulant treated group, we did not observe a mediation effect of CP in the relation between ADHD-In and nicotine use. This may be caused by the lower sample size, as well as by any selection bias we have introduced by looking only at stimulant-treated participants.

Large sections of our model are consistent with literature, showing that ADHD occurs more often in boys than in girls (Arnett et al., 2015; Faraone et al., 1995), that the risk of substance use in adolescents increases with increasing age (Young et al., 2002), and that ADHD hyperactivity severity declines with increasing age at a higher rate than inattentive severity (Biederman et al., 2000). ADHD severity has been shown to be a risk factor for nicotine use (Fuemmeler et al., 2007; Kollins et al., 2005; Riggs et al., 1999), although one study did not find a link between ADHD severity and nicotine use in individuals with ADHD (Wilens et al., 2008b). Previous research also showed boys to be more susceptible to gaming habit (Ko et al., 2005). The current study also finds evidence to suggest that ADHD-In influences ADHD-HI severity, and not nice versa. This result was previously found using the same method in two ADHD samples different from the one investigated here (Sokolova et al., 2016). These consistent findings attest to the reliability of both our data set and the causal discovery method.

Our study should be viewed in the context of some strengths and limitations. While we have tried to account for the effects of stimulant treatment, it remains difficult to fully examine its effects in our model. Secondly, because our ADHD ratings can be based on medication-free periods in the past (up to two years ago), there may be a bias in the parental reporting of ADHD symptoms. We provide reliability estimates in our causal model, but BCCD does not provide estimates of the *effect size* of the causal influence. Furthermore, due to inherent low variance in substance use, flooring effects might bias this analysis. Lastly, our causal discovery is data-driven. We did not investigate the underlying biological mechanisms; instead, our work was aimed at identifying which parts of the pathway are most worth investigating.

The strengths of our study are the high standards of ascertainment used in diagnosis, our focus on a critical adolescent age group, and the novel BCCD method allowing us to give reliability estimates for our conclusions. This combination of factors allows us to look at the effects of ADHD and CP severity in a different way than what is commonly done using regression analyses. This enables us to leverage more information from medical data and help provide a valuable tool to understand disease etiology.

In conclusion, we have constructed a causal model of relationship between ADHD, CP, substance use, and gaming. CP was found to fully mediate the risk of ADHD for nicotine use, while gaming dependence was found to be directly influenced by ADHD-In. Our identification of causal

Table 3 **(A)** Linear regression model of the effects of all model variables on nicotine use ($n = 362$). The estimates show how strongly variables affect nicotine use, assuming that they in fact do affect nicotine use. With our causal model, we show this assumption can be flawed. Significant coefficients ($p < .05$) are indicated in underlined boldface.
(B) Linear regression model of the effects of only the BCCD-identified variables on nicotine use ($n = 362$).
LowCI: Low 95% confidence interval. HighCI: High 95% confidence interval. SE: Standard error of the coefficients. tStat: T-statistic of the coefficient being zero, higher is more significant. pValue: p-value of the F-statistic of the coefficient being zero, lower is more significant. Adj-R-squared: adjusted coefficient of determination, higher means more variance explained. 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.

	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							
	(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				

components in the ADHD-addiction pathway, our work could aid future research into the overlap between ADHD and addiction, and help clinicians to develop more effective treatments.

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Contributors

Authors Buitelaar and Arias Vasquez designed the study. Authors Groenman, Oosterlaan, Rommelse, Roeyers, and Oades were involved in data acquisition. Author Schoenmacker performed the literature searches, analyses, and with authors Groenman and Arias Vasquez wrote the first draft of the manuscript. Authors Heskes and Claassen were instrumental in the correct application and interpretation of the BCCD method, and together with author Sokolova provided software for the study. Authors Faraone, Franke, and Buitelaar provided clinical interpretations of results. All authors contributed to and have approved the final manuscript. Corresponding author Schoenmacker confirms full access to the data in the study and final responsibility for the decision to submit for publication.

Conflict of interest

Authors report no conflict of interests.

Supplementary materials

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