**Causal discovery in an adult ADHD data set suggests indirect link between *DAT1* genetic variants and striatal brain activation during reward processing**

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**Running head title**

Causal discovery in an adult ADHD data

**Abstract**

Attention-deficit/hyperactivity disorder (ADHD) is a common and highly heritable disorder affecting both children and adults. One of the candidate genes for ADHD is *DAT1*, encoding the dopamine transporter. In an attempt to clarify its mode of action, we assessed brain activity during the reward anticipation phase of the Monetary Incentive Delay (MID) task in a functional MRI paradigm in 87 adult participants with ADHD and 77 controls (average age 36.5 years). The MID task activates the ventral striatum, where *DAT1* is most highly expressed. A previous analysis based on standard statistical techniques did not show any significant dependencies between a variant in the *DAT1* gene and brain activation (Hoogman et al., 2013).

Here, we used an alternative method for analyzing the data, i.e. causal modeling. The Bayesian Constraint-based Causal Discovery (BCCD) algorithm (Claassen and Heskes 2012) is able to find direct and indirect dependencies between variables, determines the strength of the dependencies, and provides a graphical visualization to interpret the results. Through BCCD one gets an opportunity to consider several variables together and to infer causal relations between them.

Application of the BCCD algorithm confirmed that there is no evidence of a direct link between *DAT1* genetic variability and brain activation, but suggested an indirect link mediated through inattention symptoms and diagnostic status.

Our finding of an indirect link of *DAT1* with striatal activity during reward anticipation might explain existing discrepancies in the current literature. Further experiments should confirm this hypothesis.

**Key-words:** ADHD, reward anticipation, Causal discovery, dopamine transporter

# Introduction

Attention- deficit/hyperactivity disorder (ADHD) is an impairing and highly heritable disorder affecting both children and adults. It is characterized by two types of symptoms, hyperactivity/impulsivity and inattention, which can occur separately or combined. ADHD is one of the most common psychiatric disorders in childhood, affecting 5-6% of children (Polanczyk et al., 2007). Symptoms persist into adulthood in up to 60% of the childhood cases (Faraone et al., 2006), and the average prevalence of ADHD in the adult population is between 2.5-4.9% (Franke et al., 2012; Simon et al., 2009). Studies show that individuals with ADHD have altered cognitive functioning in several domains, among which is reward processing. For example, people with ADHD tend to choose small immediate rewards instead of larger delayed rewards more frequently than healthy controls (Luman et al., 2005). Also on the neural level, there is evidence for altered reward processing. A key area in the brain involved in reward processing is the striatum, and many studies using magnetic resonance imaging (MRI) have shown hypoactivation in this part of the brain in individuals with ADHD. A recent meta-analysis showed a significant, moderate effect size (Cohen's *d* = 0.48–0.58) of ventral–striatal (VS) hyporesponsiveness in individuals with ADHD (Plichta and Scheres 2014).

The neurotransmitter system thought to be most strongly involved in reward processing in the brain is dopamine. Several dopamine-related genes have been associated with ADHD, among which the gene encoding the dopamine transporter, *DAT1* (official name *SLC6A3*) (Franke et al., 2010; Gizer et al., 2009). Genetic variation of the *DAT1* gene may lead to interindividual variation in the availability of dopamine transporters and, as a result, in the level of dopamine available for signaling (Faraone et al., 2014; Shumay et al., 2011). The 10-6 haplotype of two *DAT1* variable number of tandem repeat (VNTR) polymorphisms, one located in the 3’ untranslated region (UTR) and the other in intron 8, has been shown to increase risk for ADHD in childhood (Asherson et al., 2007; Brookes et al., 2006). A different haplotype of the same two VNTRs, the 9-6 haplotype, was found associated with ADHD in adults (Franke et al., 2008; Franke et al., 2010).

Several studies have been performed in an attempt to clarify whether - and if so, how - *DAT1* affects reward processing. The results of those studies have been inconsistent. Three studies in healthy adults found lower reward-related striatal activation during reward anticipation to be associated with homozygosity for the 10-repeat allele of the 3‘UTR VNTR compared to carriership of the 9-repeat allele (Aarts et al., 2010; Dreher et al., 2009; Forbes et al., 2009), two other studies did not ﬁnd an effect of *DAT1* genotype (Hahn et al., 2011; Nikolova et al., 2011). In children with ADHD, one study found lower striatal activation to be associated with the homozygous 10-repeat compared to 9-repeat carriership (Durston et al., 2008), whereas another study found the opposite (Bedard et al., 2010).

To help resolve inconsistencies between previous studies, Hoogman et al. (2013) assessed brain activity in a sample of adults with ADHD and healthy comparison subjects during a Monetary Incentive Delay (MID) task. This task is known to activate the ventral striatum (Hermans et al., 2010; Knutson et al., 2001), where *DAT1* is most highly expressed. Analyzing 87 patients and 77 controls, the standard statistical methods (F-test, t-test, $χ^{2}$ test) used in this analysis (a) showed higher prevalence of the 9-6 *DAT1* haplotype in patients compared to the healthy control group ($χ^{2}$=10.04, p=0.002), (Hoogman et al., 2013), and (b) confirmed previous findings that individuals with ADHD have lower task-related striatal activation compared to healthy subjects (t(162) =−2.32, p=0.02). The study, however, did not reveal a significant effect of the *DAT1* haplotype on striatal activation during reward anticipation (F(3,158) =0.24, p=0.63).

In the current study we used an alternative method to analyze the data reported in Hoogman et al. (2013), involving causal modeling. Bayesian Constraint-based Causal Discovery (BCCD) algorithm (Claassen and Heskes 2012) applied in this study learns a causal model from the observed data. This method focuses on the exploratory analysis of the data, suggesting probable causal dependencies and providing novel hypotheses for further testing. The causal modeling approach has several advantages over standard analysis techniques. First, it provides an opportunity to learn the causes and effects from data. Second, it detects whether the dependency between variables is direct or mediated through other variables. Third, it can visualize the results in the form of a graph that makes the interpretation of the results easier.

# Materials and Methods

## Participants

The study included 164 participants, 87 patients and 77 control subjects from the Dutch chapter of the International Multicentre persistent ADHD CollaboraTion (IMpACT) (Franke et al., 2010). Patients and controls represented two age-, gender-, and IQ-comparable groups. All subjects participated in cognitive testing and neuroimaging. Twenty-seven of the patients who underwent the tests were medication-naive. The rest used medication and had to withdraw it from 24 hours before the experiments. Patients were also asked to refrain from smoking and drinking coffee before and during testing. Diagnostic work-up of the patients and controls has been described elsewhere (Hoogman et al., 2013). Shortly, patients were included if they met DSM-IV-TR criteria for ADHD in childhood as well as adulthood. Participants were assessed using the Diagnostic Interview for Adult ADHD (DIVA) (Kooij 2010) to confirm clinical diagnosis. In addition, a quantitative measure of clinical symptoms was obtained using the ADHD-DSM-IV Self Rating scale (Kooij et al., 2005). Additional measures included IQ (using 2 subtests of the Wechsler Adult Intelligence Scale-III), smoking behavior (self-report), and medication status (self-report).

Exclusion criteria for participants were psychosis, addiction in the last 6 months, current major depression (assessed with SCID-I), full-scale IQ estimate less than 70 (Wechsler Adult Intelligence Scale-III), neurological disorders, sensorimotor handicaps, non-Caucasian ethnicity, and medication use other than psychostimulants or atomoxetine. Additional exclusion criteria for comparison subjects were a current or past neurological or psychiatric disorder according to SCID-I.

## Experiment description

In order to evaluate striatal activation in response to the reward stimulus, Hoogman and coworkers (2013) performed a set of experiments involving the MID task (Knutson et al., 2001). While performing the task, participants had to press a button as soon as possible, when seeing a target on the screen. If doing so in time, a reward could be earned. Prior to the target screen a reward cue screen was shown, which indicated if the reward could be obtained or not. After each response, the outcome was displayed. The participants could gain 1 Euro in the reward condition and no money during the non-reward condition, if they responded between 270 and 500 ms after target onset. Whole brain imaging was performed with a 1.5 Tesla MR scanner (Magnetom Avanto, Siemens Medical Systems, Erlangen, Germany) and a standard 8 channel head coil.

## Data description

To apply causal discovery using the BCCD algorithm, we selected the following seven variables measured during the study that may influence striatal activation:

* Disease status (binary: patient/control), describing whether a participant was a patient or a control.
* Smoking behavior (binary: smoking/non-smoking), describing whether a participant was a smoker or not. This variable was chosen, since smoking influences the dopamine transmission in the brain and can therefore influence the results of the fMRI experiments (Brody 2006).
* Medication status (binary: naive/not naive), describing whether a patient had ever used medication to treat his/her ADHD.
* Hyperactivity/impulsivity symptom score (discrete variable from 0 to 9), describing the self-reported current presence of the DSM-IV hyperactivity/impulsivity symptoms.
* Attention-deficit symptoms score (discrete variable from 0 to 9), describing the self-reported current presence of the DSM-IV inattention symptoms.
* Presence of the *DAT1* haplotype (binary: present /absent), describing whether a participant carried at least one copy of the 9-6 *DAT1* haplotype or not.
* Ventral-striatal brain activation during the MID task in the functional (f)MRI experiment (continuous variable, detailed explanation below), describing the level of activation of the ventral striatum during reward anticipation.

## Brain data preprocessing

Data analysis of the fMRI images showed that in the contrast of brain activations during rewarded and non-rewarded trials, some subjects showed no increased brain activation in rewarded trials, whereas some had more than five brain regions activated.

In order to correct for baseline activation we added an extra step to the normal processing pipeline of the fMRI data as described in Hoogman et al. (2013). For this, we picked a reference region, in which we did not expect any influence of reward/non-reward cue. In our case, we chose white matter. Then we applied the standard procedure to find brain activation in the ventral-striatal region of interest (ROI) and the white matter ROI. The first step was to extract information about neural signals from the data obtained during the fMRI experiments, which also contains random noise and nuisance components. For this, a General Linear Model (GLM) was derived for the voxels that corresponded to the ROIs (Lindquist 2008). In a second step, the neural signal was divided into two groups based on the reward and non-reward cues, in order to find the difference in neural signal between the groups. Then the signal in the ROIs was averaged for each subject, and the difference between groups was computed. Before doing the latter, we compared the brain activation between the striatal ROI and the reference ROI, using a Student’s t-test. The reference region thus became a modified baseline for the neural signal. The result of the Student’s t-test was used as a new estimate for the brain activation of interest. The idea of the described technique is similar in spirit to a widely used method for baseline correction of resting state MRI images using white matter (Grol et al., 2007; Majdandzic et al., 2007; Verhagen 2012).

Using the new brain activation measure we estimated the difference in striatal activation between patients and controls. The new striatal activation measure with baseline correction better captured the dependencies between patients and controls ($t(162) = -2.69, p=0.008$) than the standard measure ($t(162)=-2.32, p=0.02$), probably because using a reference region for baseline adjustment reduced the noise in the data and improved the accuracy of estimating striatal activation.

## Causal Modeling

One way to represent causal models is through structural equation modeling (SEM). This is a widely used statistical technique for testing and estimating causal relationships in the field of medical research (Beran and Violato 2010). Commonly used practice in medical research is to define the structure of a SEM manually (Neale and Schmitt 2005). An alternative approach is to learn the structure of the SEM automatically, using causal discovery algorithms (Pearl 2000).

There are two main approaches to learn the structure of a SEM automatically: score-based and constraint-based (Daly et al., 2011). An advantage of the score-based approach is that it provides a measure of reliability of inferred causal relations. This makes the interpretation of the results easier and prevents incorrect categorical decisions (Heckerman et al., 1999). A major drawback of the approach is that it relies on the causal sufficiency assumption which means that the algorithm cannot detect common confounders of the observed variables. An advantage of the constraint-based approach is that it does not have to rely on the causal sufficiency assumption, and, as a result, can detect common causes of the observed variables (Spirtes et al., 2000). A disadvantage of this approach is that its output is not always reliable. A standard approach makes use of independence tests, making the results for borderline independencies/dependencies incorrect sometimes (Spirtes 2010). The outcome of learning a network can be sensitive to such errors.

The method that we used to learn the structure of the SEM was developed by Claassen and Heskes (2012) and is called Bayesian Constraint-based Causal Discovery (BCCD). This method aims to combine the strength of constraint-based and score-based approaches. This method is able to detect common causes of the observed variables similar to constraint-based approaches and provides a reliability measure of the inferred relationship like the score-based approach. This reliability measure gives a conservative estimate of the probability of a causal relation. A recently extended version of BCCD can handle data that contains a mixture of discrete and continuous variables and does not require discretization that can lead to loss of information (Sokolova et al., 2014). BCCD works with directed acyclic graphs that can contain latent variables. These graphs are called maximal ancestral graphs (MAG). All MAGs that represent the same set of conditional independencies form an equivalence class. The equivalence class for MAGs is called a partial ancestral graph (PAG). Edge directions in a PAG are marked with “ − ” and “ >” if the direction is the same for all graphs belonging to the PAG and with “○” otherwise. The BCCD algorithm produces PAGs as an output.

# Results

Demographics of the study sample previously used in Hoogman et al. (2013) are shown in Table 1. Patients and controls represented age-, gender-, and IQ-comparable groups (p>0.22). We applied the BCCD algorithm to this data set. As prior information we incorporated the assumption that *DAT1* genotype cannot be influenced by any other factor in the model, since chronologically a gene is the first factor present in the lifespan, and that diagnosis is present downstream of symptoms, i.e., that symptoms cannot be caused by diagnosis.

Running the BCCD algorithm provided three tables (Tables 2, 3 and 4). Table 2 presents the reliability of the causal statement: “A causes B”, both for direct and indirect causal effects.If there is an edge between *A* and *B*, it has a tail from *A* to *B* and *A* causes *B* in the PAG*.* For example, variable “Patient/Control” caused variable “Medication” with reliability 89%. Table 3 represents the reliability of the causal statement: “A does not cause B”, both for direct and indirect causal effects. If there is an edge between *A* and *B,* it has anarrow head from *B* to *A*.For example, the variable “Smoking” does not cause variable “Patient/Control” with reliability 66%. The prior knowledge used in the model, i.e. that *DAT1* haplotype is not caused by other variables and that diagnosis is present downstream of symptoms, is represented in Table 3 in cells with a reliability of 100%.

**Table 1.** Demographics of the study sample. Adapted from Hoogman et al. (2012).

Table 4 provides the reliability of the statement that a direct causal link exists between two variables. The difference between Tables 2 and 3 compared to Table 4 is that Tables 2 and 3 give an estimate for the direction of the causal effect, whereas Table 4 provides estimates for the presence of the path between two variables. Moreover, Tables 2 and 3 show the reliability of the direction of both direct and indirect causal paths, whereas Table 4 gives a reliability estimate for a direct causal path between two variables only.

By combining Tables 2, 3 and 4 we constructed a causal network representing causal relationships between variables, which is presented in Figure 1. For visualization purposes, this network only includes the edges with a reliability of a direct causal link higher than 50%. The resulting network structure matched some of our expectations: symptoms caused diagnosis, and the presence of an ADHD diagnosis influenced smoking behavior, prescription of medical treatment, and level of striatal activation during the MID task. Moreover, the graph showed a direct link between the *DAT1* haplotype and inattention symptoms, but not between the *DAT1* haplotype and hyperactivity/impulsivity symptoms. These findings are in line with the results obtained by Hoogman and coworkers (2013).

**Table 2.** The reliability estimate of the logical statement “*A* causes *B”*, where A is represented in rows and B in columns.The estimate is provided for logical statements with reliability of 50% or higher.

**Table 3**. The reliability of the logical statement “*A* does not cause *B”,* where A is represented in rows and B in columns. The estimate is provided for logical statements with reliability of 50% or higher.

**Table 4.** Reliability of direct links between two variables.

**Figure 1.** Output causal model representing causal relationships between variables in the MID task experiment, where edge directions are marked with ‘-’ and ‘ >’ for identifiable edge directions and with ‘○’ for non- identifiable edge directions. Reliability estimates for the presence of an edge are depicted as percentage.

As apparent from the network in Figure 1, the causal path from the *DAT1* risk haplotype to brain activation is indirect, and mediated through other variables. This causal path was not detected in the study of Hoogman and colleagues (2013). Another causal path that had not been detected by the former study is the direct path between inattention and hyperactivity/impulsivity. Assuming that there is no common cause between the *DAT1* haplotype and inattention symptoms, we measured the strength of the causal effect using Cohen’s d and odds ratio tests, depending on the variables of interest (Cohen 1988; Nakagawa and Cuthill 2007). The causal effect of the *DAT1* risk haplotype on the inattention symptoms has a large effect size (Cohen’s d 0.8, CI= [0.41, 1.20]). The link from inattention symptoms to patient/control status has a large odds ratio of 5.5 (CI= [2.87, 10.43]), while the link from patient/control status to striatal brain activation has a medium effect size (Cohen’s d 0.4, CI= [0.11, 0.73]). As a results, the direct effect of the *DAT1* risk haplotype on brain activation was small and non-significant (Cohen’s d 0.14, CI= [-0.24, 0.52]). If we leave out the variable patient/control, then the individual link between the inattention and hyperactivity and brain activation does not pass the threshold. We interpret the variable patient/control as a summary variable that combines the influence of hyperactivity and inattention and possibly other endophenotypic variables on the other variables in the model such as smoking, striatal activation and medication.

The causal path from diagnostic status to striatal activation appears to contradict models assuming that altered brain functioning is a cause of ADHD instead of it being a consequence, like the endophenotypic model proposed by Franke and colleagues (2009). If we enforce such an assumption, i.e., if we add the constraint that there cannot be a causal path from diagnosis to striatal activation, the causal path from the *DAT1* haplotype to striatal activation disappears. Instead, in order to account for the observed correlation between diagnosis and striatal activation, our analysis yields either a causal link from striatal activation to diagnostic status, or a common cause (e.g., a comorbid disorder) that is associated with both ADHD and striatal activation. To estimate the probability of the two alternative networks with and without endophenotypic assumption, we calculated the Bayesian Information Criterion (Schwarz 1978) and estimated the posterior odd ratios. The model with the endophenotypic assumption scored a factor of two worse (posterior odd ratio= 2.2) than the model without this assumption described in the results. However, it should be mentioned that this latter does not provide particularly strong evidence against the endophenotypic assumption.

# Discussion

In the current study we proposed an alternative method of data analysis for functional MRI, and behavioral and genetic data. The standard methods for such data analysis involve statistical tests that tell whether the difference in means between two populations is statistically significant. These methods are easy to use, but are restricted in the types of questions they can answer. They are focused only on the presence of the dependency between observed variables (the ones that are directly measured) and fail to determine the direction of this dependency. Moreover, if the dependency between two observed variables is mediated through a third observed variable, the standard methods would not detect it, but only indicate that all three variables are correlated.

The method proposed in this paper has several advantages over the standard statistical techniques. It allows deeper insights into the data by building a complete model, instead of considering only pairwise dependencies, and by distinguishing between direct and indirect causal effects. Here, we applied the BCCD approach to an existing data set of adult patients with ADHD and healthy controls, which had earlier been analyzed and published using standard methods of analysis (Hoogman et al., 2013).

In line with the earlier analysis results, our approach detected a direct link between the presence of ADHD and the level of brain activation during the MID test and a link between inattention and *DAT1*; neither the earlier nor the new method provided evidence for a direct link between *DAT1* variation and brain activation during reward anticipation. The network built using the BCCD algorithm revealed additional causal paths that had not been detected by the earlier analysis. BCCD suggested that an indirect path exists between the *DAT1* risk haplotype and striatal activation that is mediated through other variables, such as inattention. That might be explained by the idea that the processing of the reward or non-reward cues requires attention skills. The effect of the *DAT1* risk haplotype on brain activation was small and did not reach formal statistical significance, thus being hard to detect using standard bivariate statistical techniques.

The existence of an *indirect* causal path from the *DAT1* haplotype to striatal activation might explain existing discrepancies between findings in the literature. Studies performed earlier (Aarts et al., 2010; Dreher et al., 2009; Forbes et al., 2009) found an effect of the *DAT1* haplotype on reward-related striatal activation, whereas others (Hahn et al., 2011; Nikolova et al., 2011) did not find this effect. The inferred indirect path shows that striatal activation depends on both inattention and hyperactivity, whereas the *DAT1* haplotype appears to have a direct influence only on inattention. As a result, the effect of hyperactivity/impulsivity symptoms may blur the effect of *DAT1* through inattention symptoms on striatal activation, which hence may appear statistically significant in one cohort, but not in another.

Our analysis further suggests that there is no direct causal link from *DAT1* to hyperactivity/impulsivity: the observed correlation between the *DAT1* haplotype and hyperactivity/impulsivity can be fully explained by the effect of *DAT1* on inattention and an effect of inattention on hyperactivity/impulsivity. The latter is of interest in itself as well, as it might suggest that hyperactivity/impulsivity occurs downstream of inattention. This finding deserves further study, as it could have implications for ADHD treatment – focusing on treating inattention would then also reduce hyperactivity/impulsivity symptoms.

The model provided by our data challenges current ideas of brain imaging measures as endophenotypes for ADHD. Our data favored a model with an indirect causal path from the *DAT1* haplotype to striatal activation mediated by symptoms and diagnosis, although, based on this first analysis, we do not claim to have strong evidence against the endophenotypic assumption. It is likely that developmental brain alterations contribute to disease risk, and may be further enhanced or modified by disease symptoms potentially reversing the direction of the causal links. Recent findings by Cortese and colleagues (2013) , for example, have suggested that brain alterations (in this case white matter alterations) cannot be linked to disease outcome in ADHD. Similarly, a recent treatment study suggests that improvements at the cognitive level upon drug treatment of ADHD do not correlate strongly with clinical improvement (Coghill et al., 2013). The general sparseness of papers describing convincing correlations of neural or cognitive findings with behavioral/clinical data suggests that such links are not readily detectable. Additional research is clearly necessary to investigate the link between brain imaging phenotypes and disease.

The strength of this study is the application of a novel causal discovery method for data analysis. This method considers all variables together, infers both direct and indirect dependencies between variables, provides a reliability measure for each edge in the network and is able to detect latent common causes. The limitation of our causal discovery method is that it is an exploratory analysis – it provides new hypotheses that need to be tested using other methods and needs an independent replication. To verify this hypothesis experiments or additional data is required.

In conclusion, application of the BCCD algorithm confirmed that there is no statistical evidence for a direct link between *DAT1* and ventral striatum activation during the MID task, but suggests that there is an indirect link mediated through inattention symptoms and diagnostic status. This finding might explain the inconsistency of results described in literature.

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**Conflict of interests**

Barbara Franke, Martine Hoogman, Elena Sokolova, Tom Claassen, Tom Heskes, Alejandro Arias Vasquez and Perry Groot report no biomedical financial interests or potential conflicts of interest. Jan K. Buitelaar has been in the past 3 years a consultant to / member of advisory board of / and/or speaker for Janssen Cilag BV, Eli Lilly, and Servier. He is not an employee of any of these companies, and not a stock shareholder of any of these companies. He has no other financial or material support, including expert testimony, patents, royalties.

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