# Causal discovery for dopamine transporter haplotype and reward- related brain activation for adult ADHD

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## 1. Study description

Attention deficit-hyperactivity disorder (ADHD) is a frequent 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, endophenotypic testing of brain activity during a Monetary Incentive Delay task was performed, known to activate the ventral striatum, where DAT1 is most highly expressed.

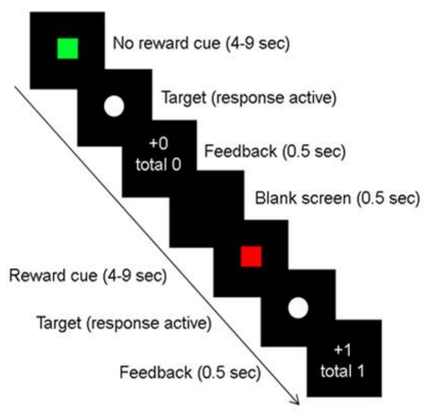


**Figure 1:** *Monetary Incentive Delay task experiments performed to indicate the influence of the DAT1 gene on reward-related brain activation.*

## 2. Testing results using standard method

Testing was performed in a sample of 87 patients and 77 controls, collected as part of the IMpACT study. As described in [2], standard statistical techniques, did not reveal any significant dependencies between the DAT1 gene and brain activation.

## 3. Alternative method

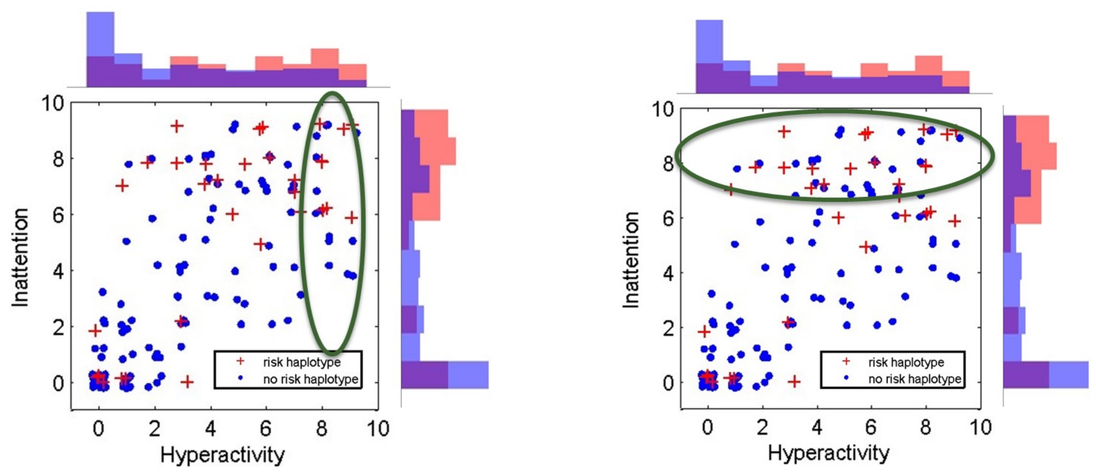


**Figure 2:** *Example of conditional independence. Hyperactivity, Inattention and Risk haplotype are pairwise correlated. Inattention depends on Risk haplotype, conditioned on Hyperactivity (right panel), but Hyperactivity is independent of Risk haplotype, conditioned on Inattention (left panel).*

We propose an alternative method for analyzing the data, involving causal modeling. The Bayesian Constraint-based Causal Discovery (BCCD) algorithm [1] is able to find direct and indirect dependencies between variables, determines the robustness of the dependencies, and provides a graphical visualization to interpret the results.

Two variables $A$ and $B$ are conditionally independent given $C$, means that if we know $C$, learning $B$ would not change our belief in $A$. For example, Hyperactivity symptoms are independent from Risk haplotype, given Inattention symptoms, see Figure 2.
Given such conditional independecies, the causal discovery approach considers all variables together and builds a probabilistic maximal ancestral graph (MAG). MAGs can have three types of arrows: directed $X \longrightarrow Y$, bi-directed $X \longleftrightarrow Y$ (hidden common cause) and undirected arcs $X - Y$ (selection bias). Different MAGs can correspond to the same set of conditional independencies. Partial ancestral graphs (PAG) represents all consistent MAGs. Edges invariant in all MAGs belonging to the same PAG are marked with' $-$ ' and ' $>$', and non invariant edges are marked with '$\circ$'

## 4. Results using BCCD

Application of the BCCD algorithm on the data set from [2] yields causal graph in Figure 3. Graph strongly suggests that there is no direct link between the DAT1 gene and brain activation, but that there is an indirect link mediated through other variables. When we further include background knowledge, for example, information that no other variables in the model cause the DAT1 gene, we obtain strong evidence that link between the DAT1 gene and brain activation is causal.

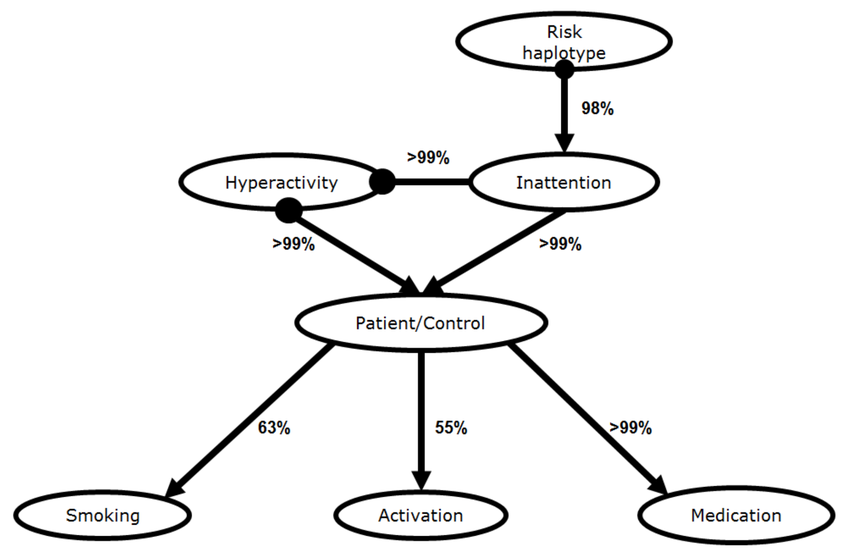


**Figure 3:** *Causal graph representing causal relationships between variables related to Monetary Incentive Delay task experiments. Technically graph represents a so-called PAG, where edge directions are marked with' $-$ ' and ' $>$' for invariant edge directions and with '$\circ$' for non- invariant.*

## 5. Conclusions

Based on this study, we conclude that the dependency between the DAT1 gene and brain activation is mediated through other variables in the model, which might explain existing discrepancies between findings in the current literature.

## References

[1] Claassen T., Heskes T., 2012. A Bayesian Approach to Constraint Based Causal Inference. *In Proceedings of the 28th Conference on Uncertainty in Artificial Intelligence.*

[2] Hoogman M., Onnink M., Cools R., Aarts E., Kan C., Vasquez A.A., Buitelaar J., Franke B., 2012. The dopamine transporter haplotype and reward-related striatal responses in adult ADHD. *European Neuropsychopharmacology, 23.*

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