

On the challenges of predicting treatment response in psychosis

CPC 2020

Philipp Homan^{1,2}

¹University Hospital of Psychiatry Zurich

²Feinstein Institute for Medical Research, NY, USA

philipp.homan@bli.uzh.ch

homanlab.github.io

[@philiphoman](https://twitter.com/philiphoman)

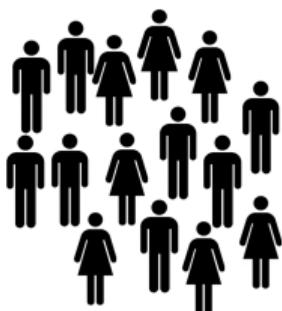
What is this talk about?

- ① differential diagnosis of alternative disease mechanisms
- ② stratification / subgroup detection into mechanistically distinct subgroups
- ③ prediction of clinical trajectories and treatment response

From Klaas' talk on Monday

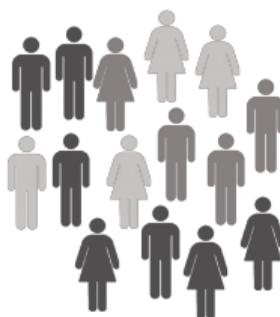
Towards meaningful subgroups

First episode psychosis patients



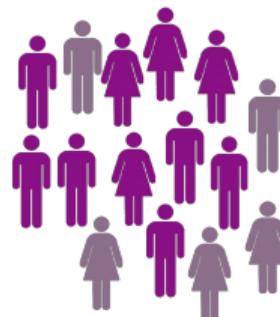
■ Unlabeled

Symptom subgroups



- Paranoid
- Disorganized
- Catatonic

Biological subgroups



- Treatment responder
- Treatment resistant

What are (some of) the challenges?

1. The scope challenge
2. The operationalization challenge
3. The inference-vs.-prediction challenge

The scope challenge

In other words: How much precision medicine is actually needed?

The scope challenge

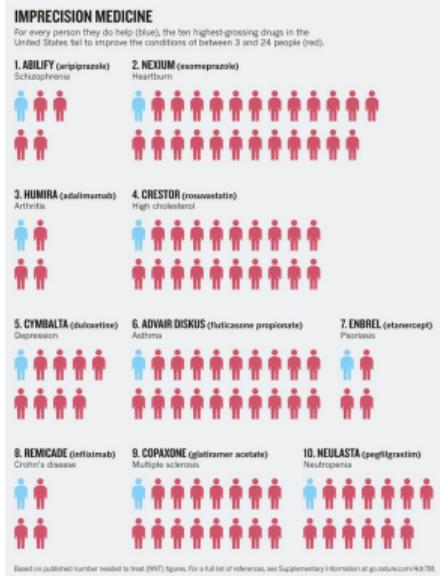
ILLUSTRATION BY DAVID PARKINS



Statistical pitfalls of personalized medicine

Senn 2018, Nature

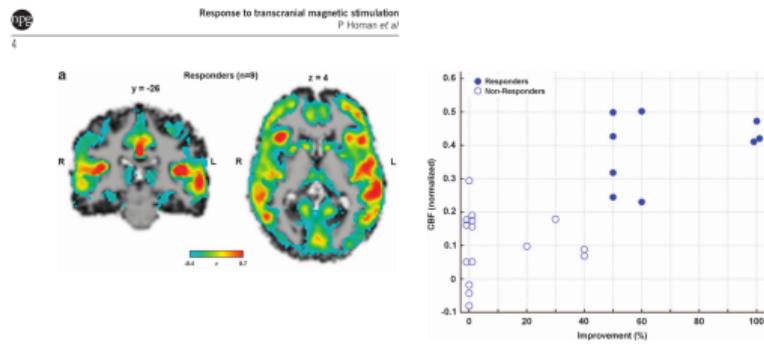
Imprecision medicine



“Every day, millions of people are taking medications that will not help them.”

Imprecision medicine

“53% of patients responded to the treatment”



Homan et al. 2012

Such statements

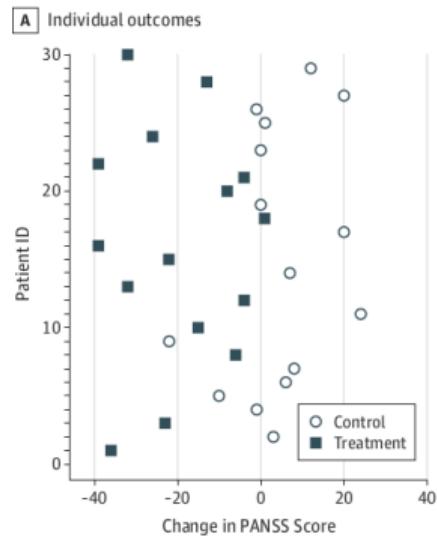
- Are relatively common
- Are surprisingly difficult to prove

Such statements

- Are relatively common
- **Are surprisingly difficult to prove**

A simulated clinical trial

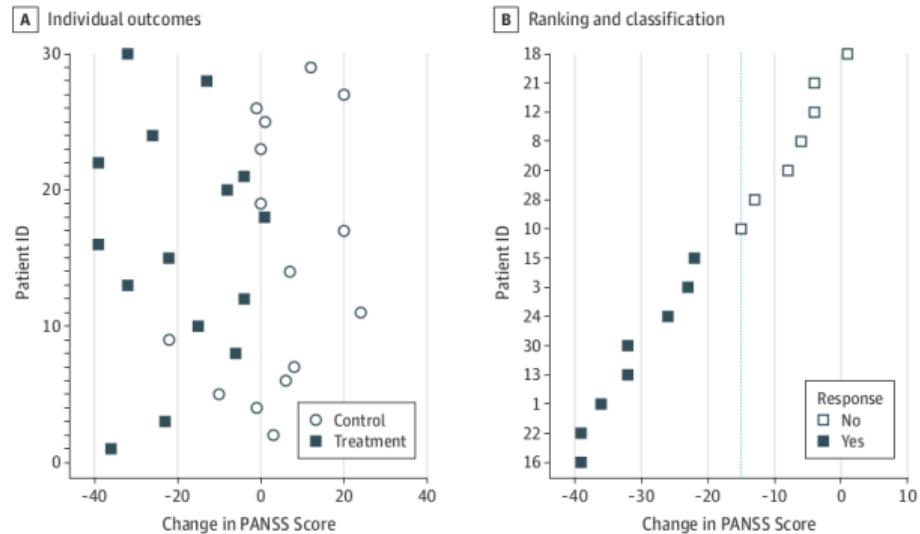
Figure 1. Observed Response Suggests Heterogeneity in Treatment Response



Winkelbeiner et al. 2019, JAMA Psych

A simulated clinical trial

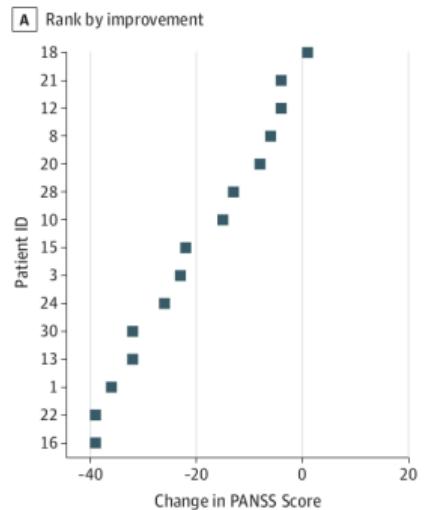
Figure 1. Observed Response Suggests Heterogeneity in Treatment Response



Winkelbeiner et al. 2019

A simulated clinical trial

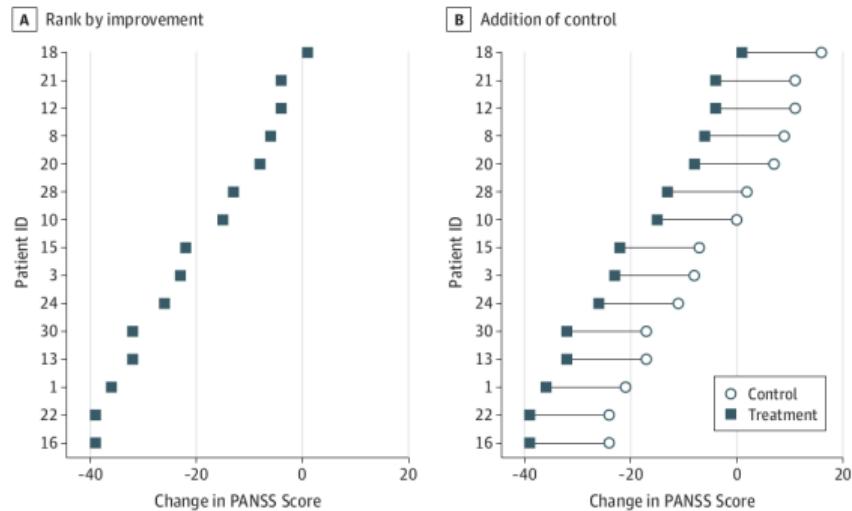
Figure 2. Consequences of Between-Patient Variation



Winkelbeiner et al. 2019

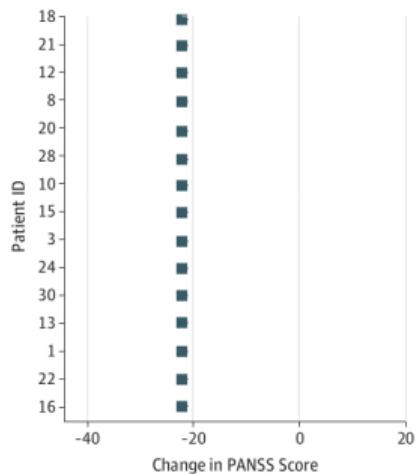
A simulated clinical trial

Figure 2. Consequences of Between-Patient Variation



A simulated clinical trial

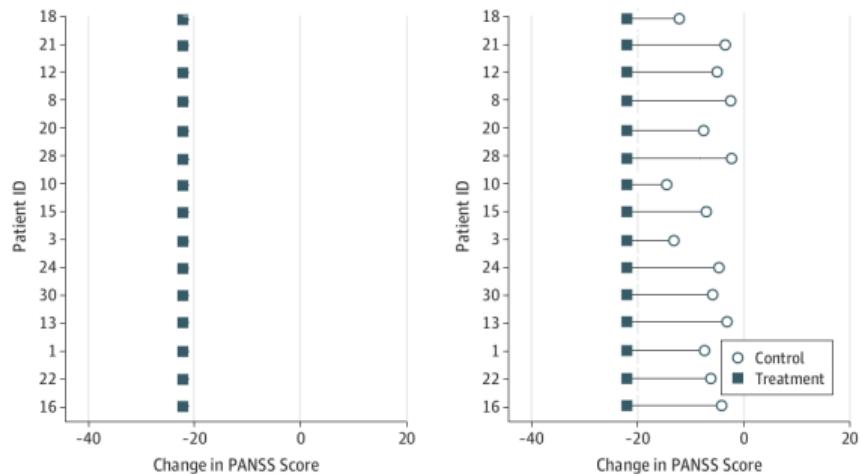
Figure 2. Consequences of Between-Patient Variation



Modified from Winkelbeiner et al. 2019

A simulated clinical trial

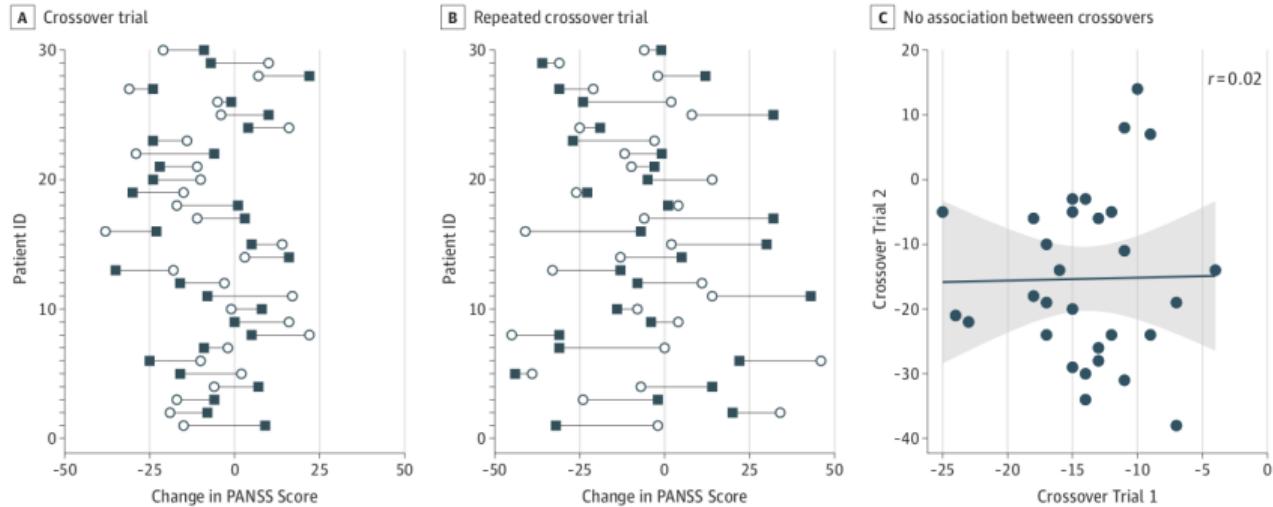
Figure 2. Consequences of Between-Patient Variation



Modified from Winkelbeiner et al. 2019

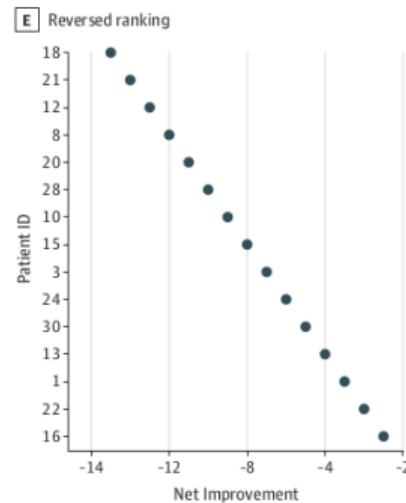
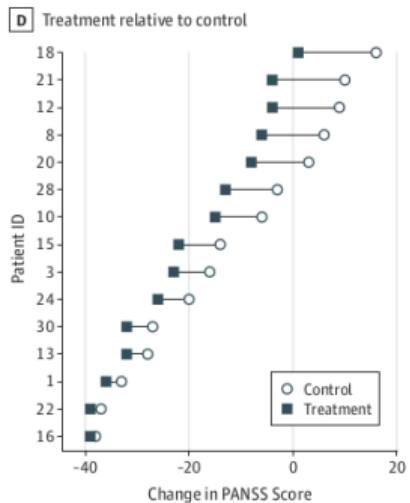
A simulated clinical trial

Figure 4. Estimating Treatment-by-Patient Interaction With Repeated Crossover Trials



Winkelbeiner et al. 2019

A simulated clinical trial



Winkelbeiner et al. 2019

N-of-1 trials in schizophrenia

BJPsych

The British Journal of Psychiatry (2018)
213, 398–403. doi: 10.1192/bjp.2018.71

Review article

Application of *n*-of-1 treatment trials in schizophrenia: systematic review

Katie F. M. Marwick, Anna J. Stevenson, Caitlin Davies and Stephen M. Lawrie

Background

Single patient or '*n*-of-1' trials are a pragmatic method to achieve optimal, evidence-based treatments for individual patients. Such trials could be particularly valuable in chronic, heterogeneous, difficult to treat illnesses such as schizophrenia.

Conclusions

In conclusion, *n*-of-1 trials are currently underutilised in schizophrenia. Existing trials suggest the method is well tolerated and potentially effective in achieving optimal treatments for patients, but more standardised methods of design, execution and analysis are required in future trials.

N=6 studies

Interim conclusion: we need repeatable variation

Otherwise 53% response could mean:

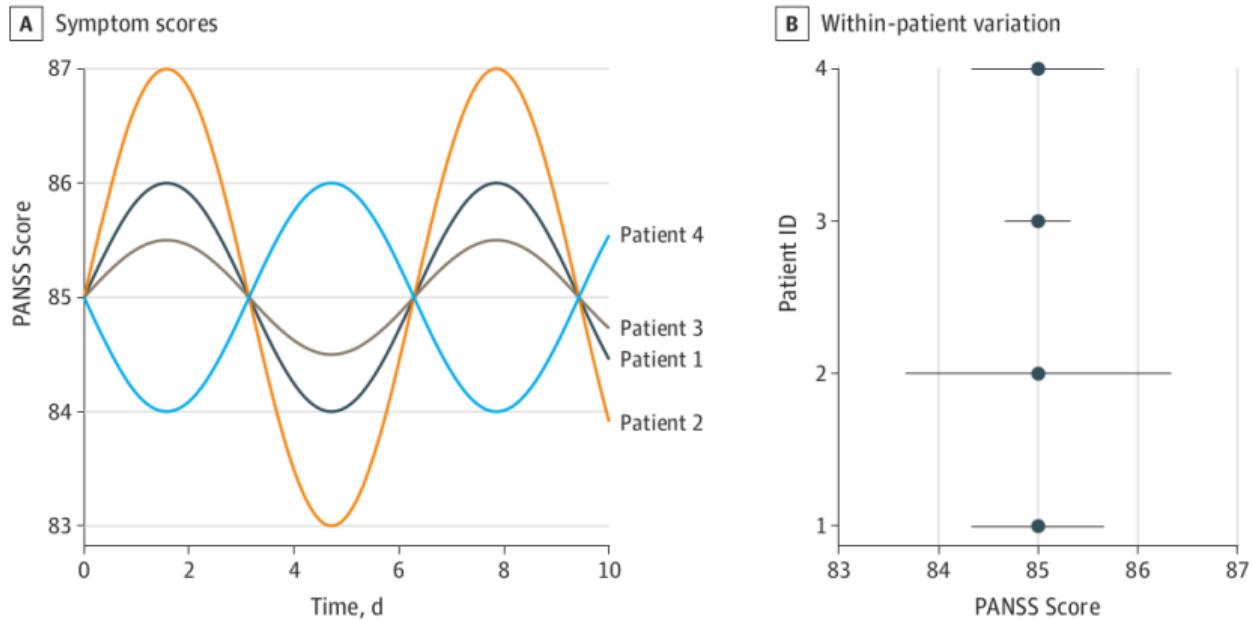
- 53% of the patients respond 100% of the time
- 100% of the patients respond 53% of the time

The operationalization challenge

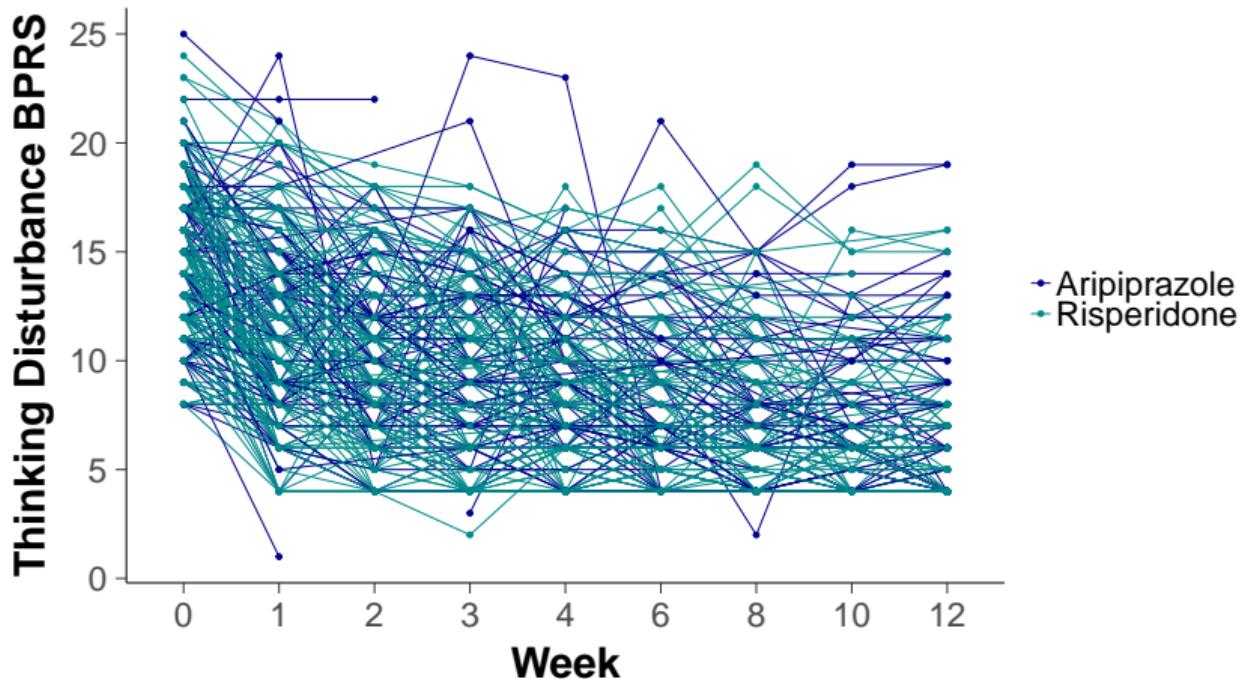
In other words: how do we define treatment response?

Another source of variability

Figure 3. Random Within-Patient Fluctuations



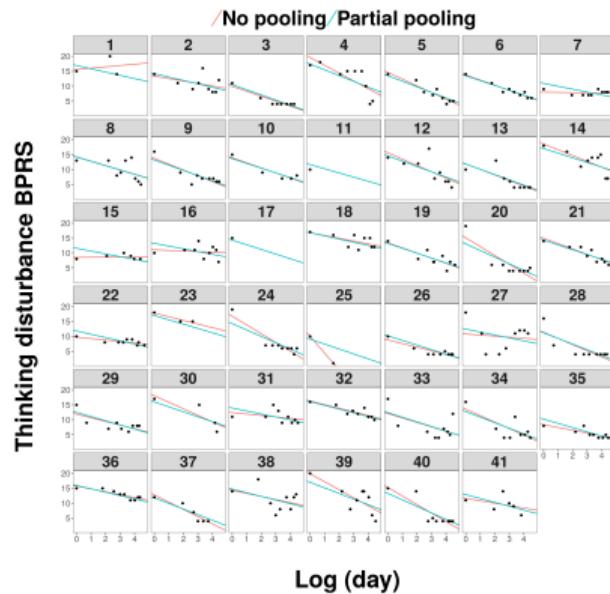
The operationalization challenge



Robinson et al. 2015; Homan et al. 2019

The operationalization challenge

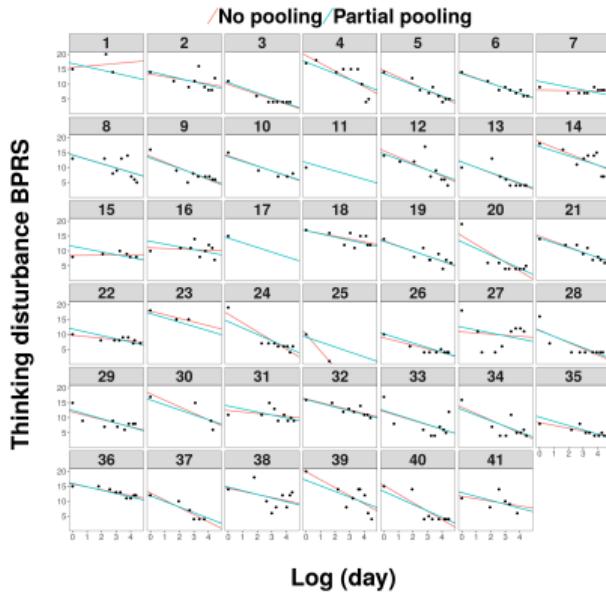
A



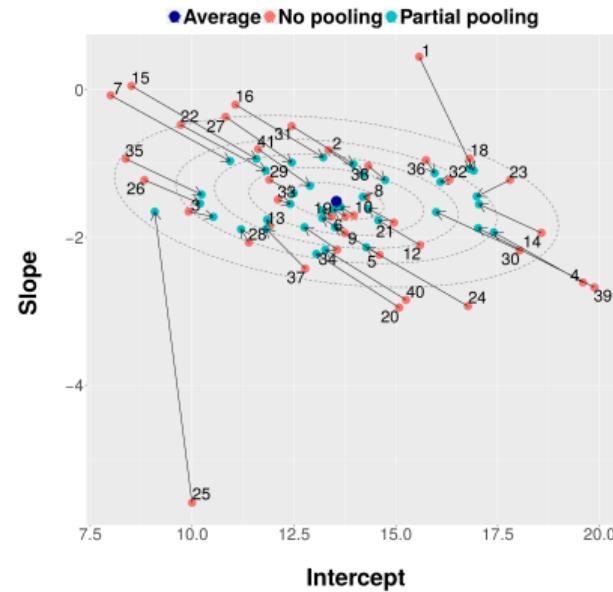
Homan et al. 2019

The operationalization challenge

A

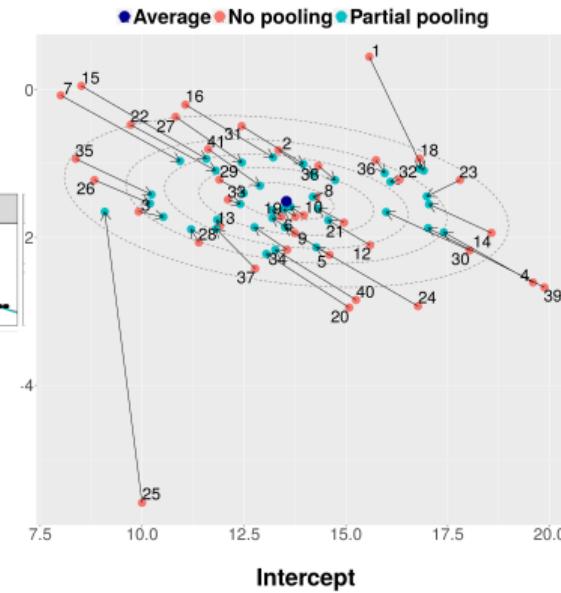
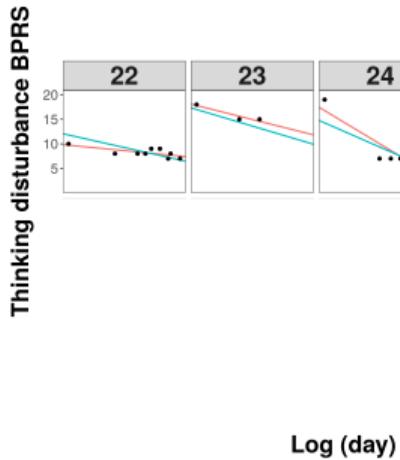


B



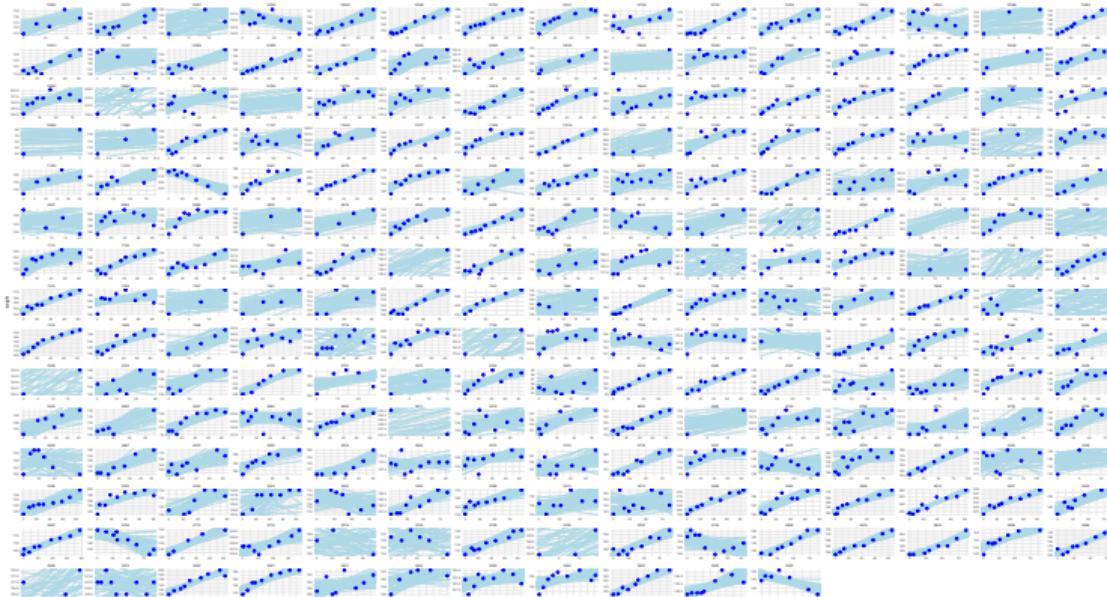
The operationalization challenge

A



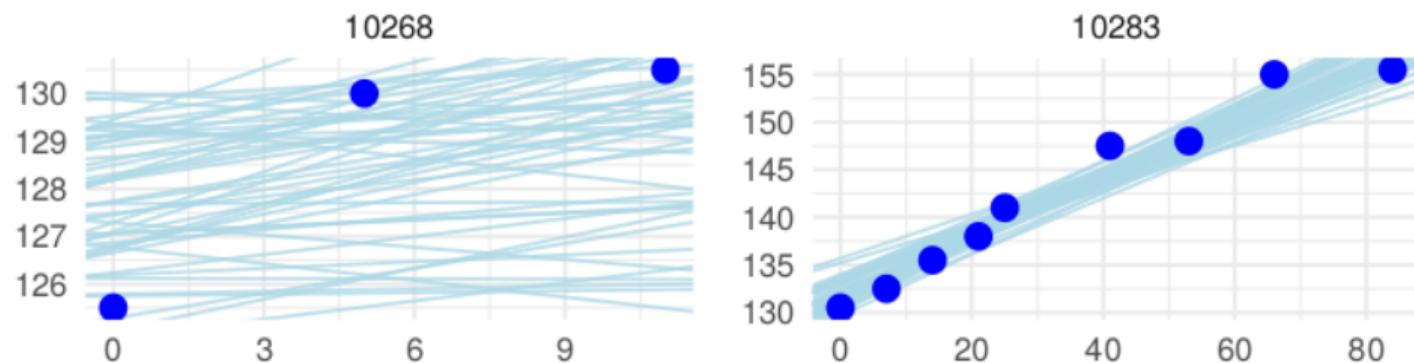
Homan et al. 2019

Posterior draws of slopes



Homan et al., in prep.

Posterior draws of slopes

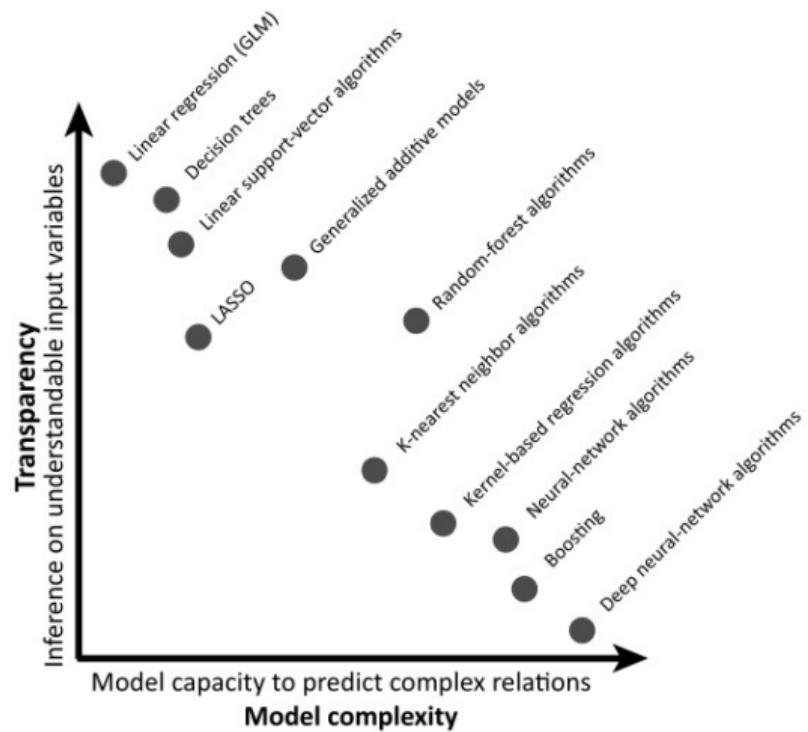


Homan et al., in prep.

The inference vs. prediction challenge

In other words: (How well) do we have to understand our circuit of interest to use it for prediction?

Transparency-complexity trade-off



Trends in Neurosciences

Bzdok & Ioannidis 2019, TICS

Linear regression

- Exploration
 - E.g., initial description of correlative relations in brain data
- Inference
 - E.g., isolating the specific contributions of experimentally varied input factors on outcome
- Prediction
 - E.g., verifying how linear relationships in the model hold up for new individuals

Linear regression

- Exploration
 - E.g., initial description of correlative relations in brain data
- Inference
 - E.g., isolating the specific contributions of experimentally varied input factors on outcome
- Prediction
 - E.g., verifying how linear relationships in the model hold up for new individuals

Not mutually exclusive!

Inference vs. prediction

Inference	Prediction
Knowledge-guided	Pattern-guided
Explainable narrative	Opaque black box
Formally justified	Empirically justified
Data efficient	Data hungry

Modified from Bzdok & Ioannidis 2019

Where does this leave us?

- Do we have a candidate circuit for treatment response to antipsychotics?
- Is there reason to believe that there is enough variation to explain?

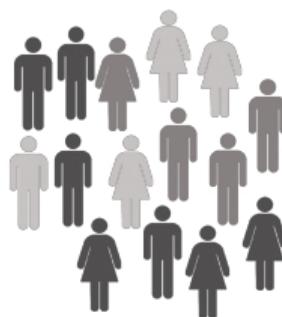
Meaningful subgroups

First episode psychosis patients



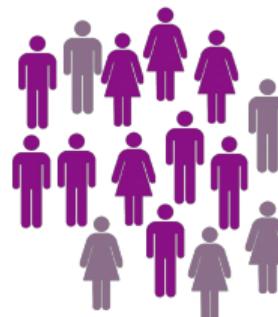
■ Unlabeled

Symptom subgroups



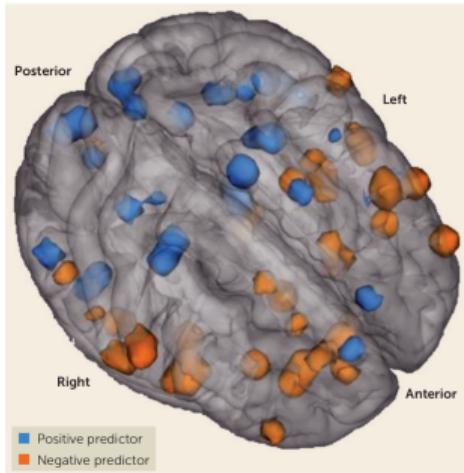
- Paranoid
- Disorganized
- Catatonic

Biological subgroups

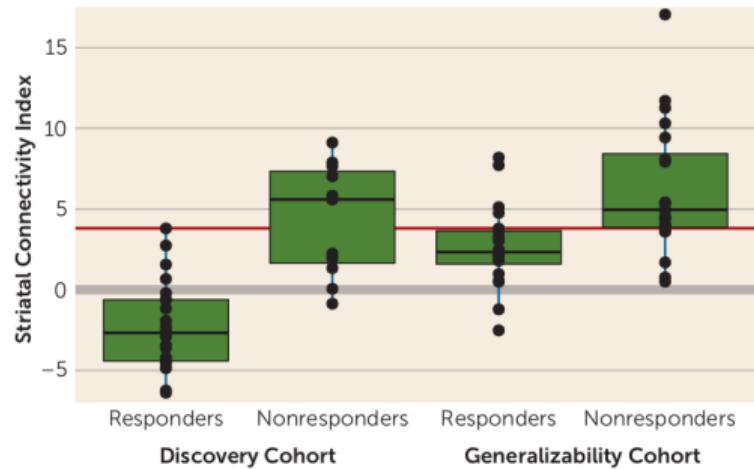


- Treatment responder
- Treatment resistant

Striatal connectivity

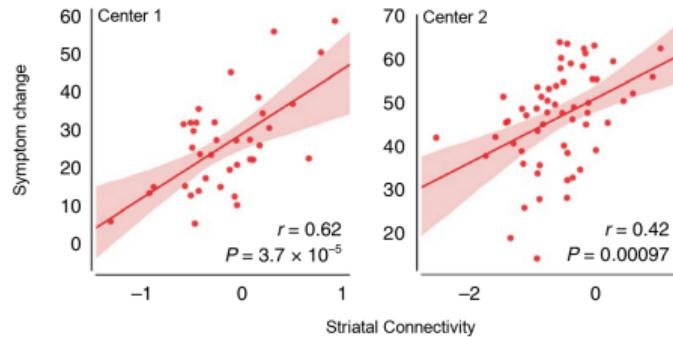


Sarpal et al. 2016, AJP

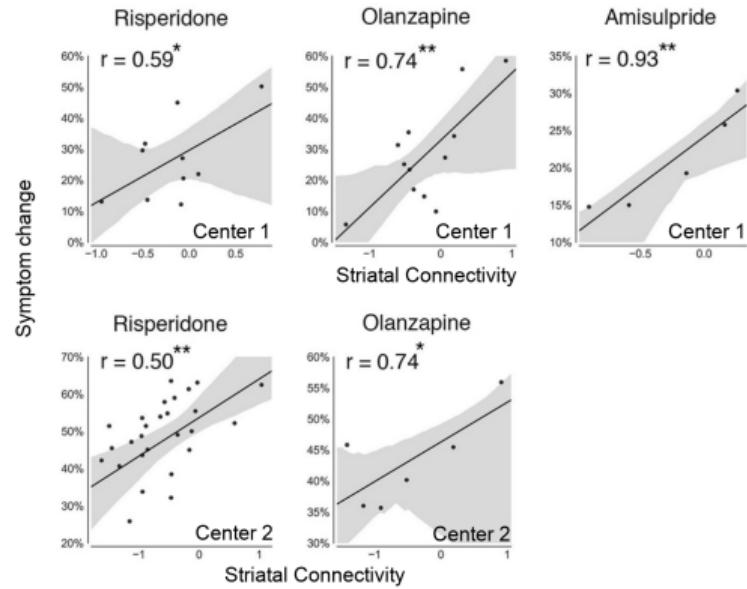


Sarpal et al. 2016, AJP

Striatal connectivity



Li et al. 2020, Nat Med



Li et al. 2020, Nat Med

Summary

- The scope challenge: make sure that there is good enough evidence for HTE
- The operationalization challenge: avoid dichotomization and make use of the full data, ideally with repeated measurements
- The inf-pred challenge: Consider pragmatic approaches for a circuit read-out

Thank you!



Fonds für wissenschaftliche Zwecke im
Interesse der Heilung von psychischen
Krankheiten



Novartis Foundation
for Medical-Biological Research



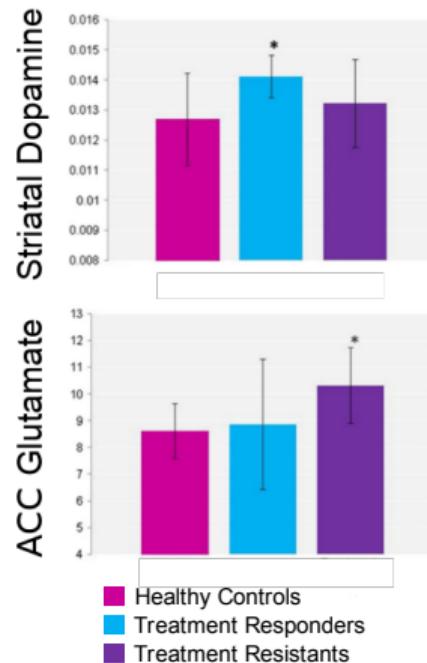
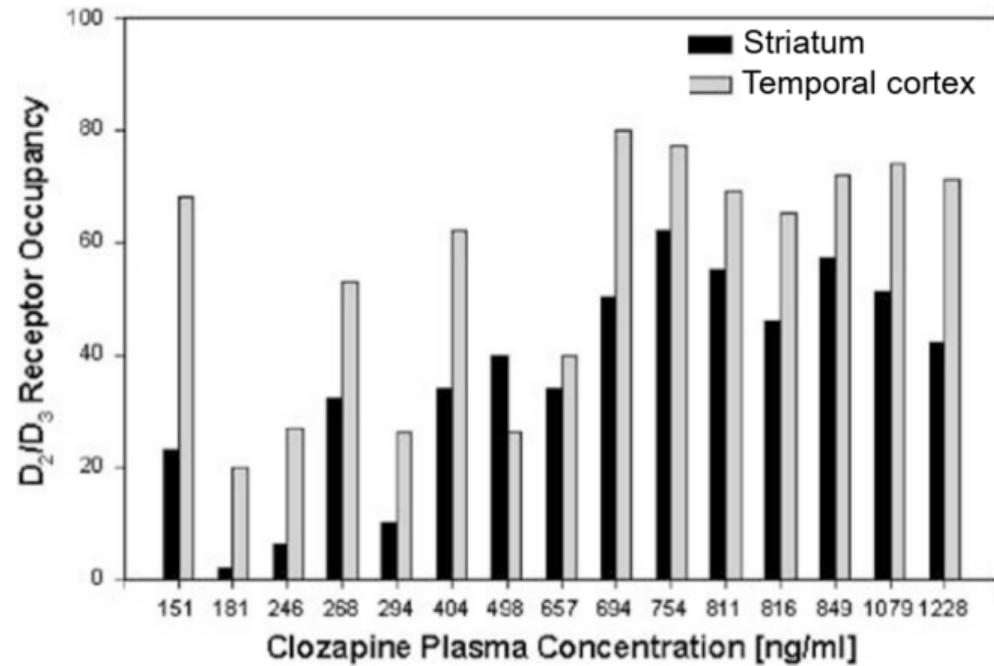
idp|lab

homanlab.github.io

The implementation challenge

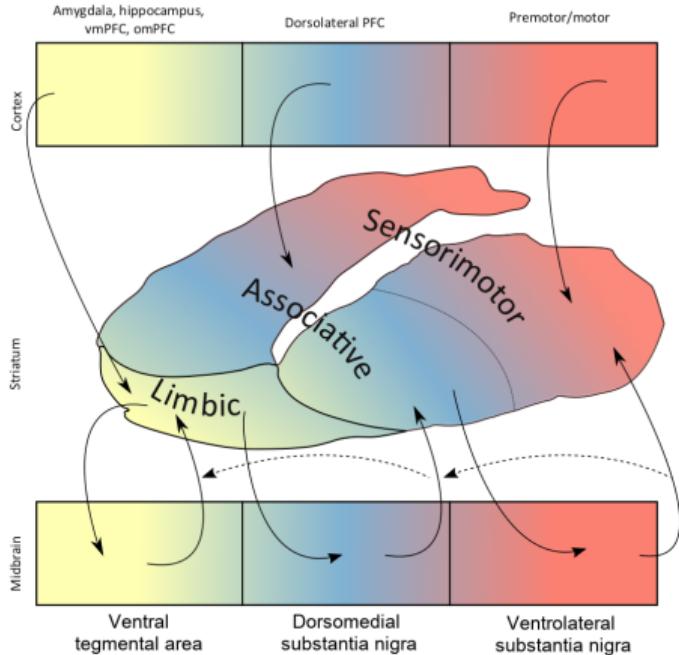
In other words: How do I apply my candidate model for prediction?

A candidate subgroup

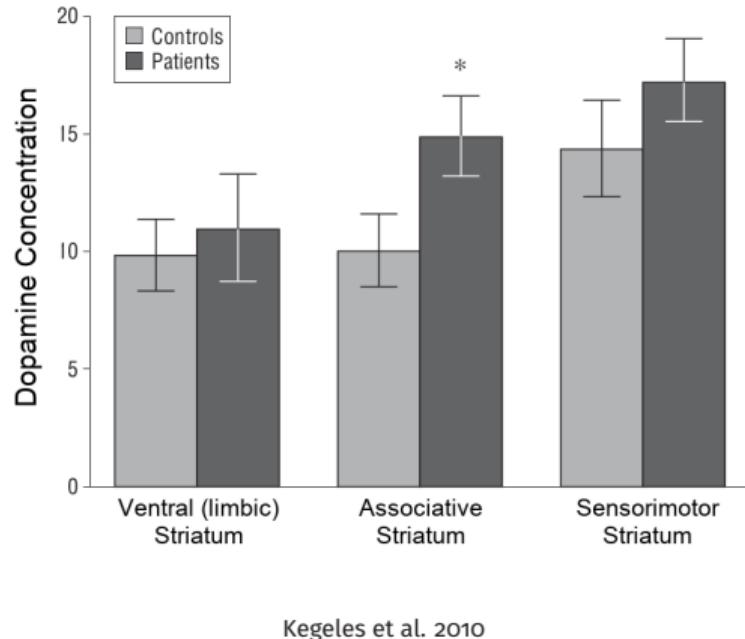


Grunder et al. 2006, Demjaha et al. 2012, 2014

The role of the striatum



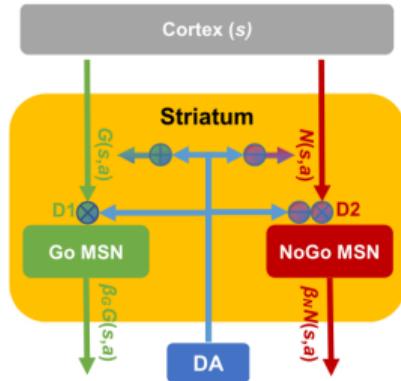
McCutcheon et al. 2019



Kegeles et al. 2010

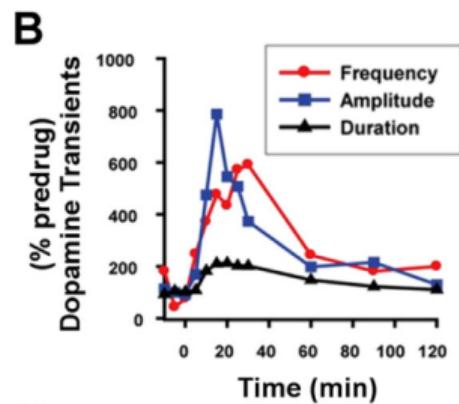
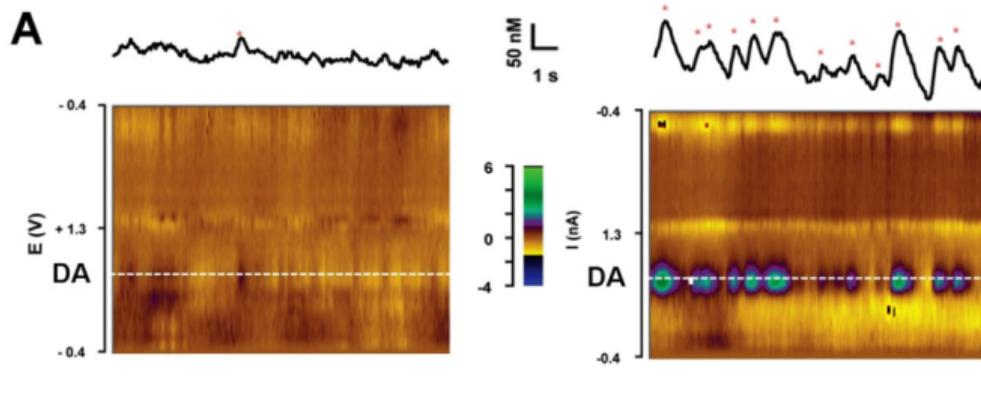
Computational model

A. Effects of dopamine on the striatum



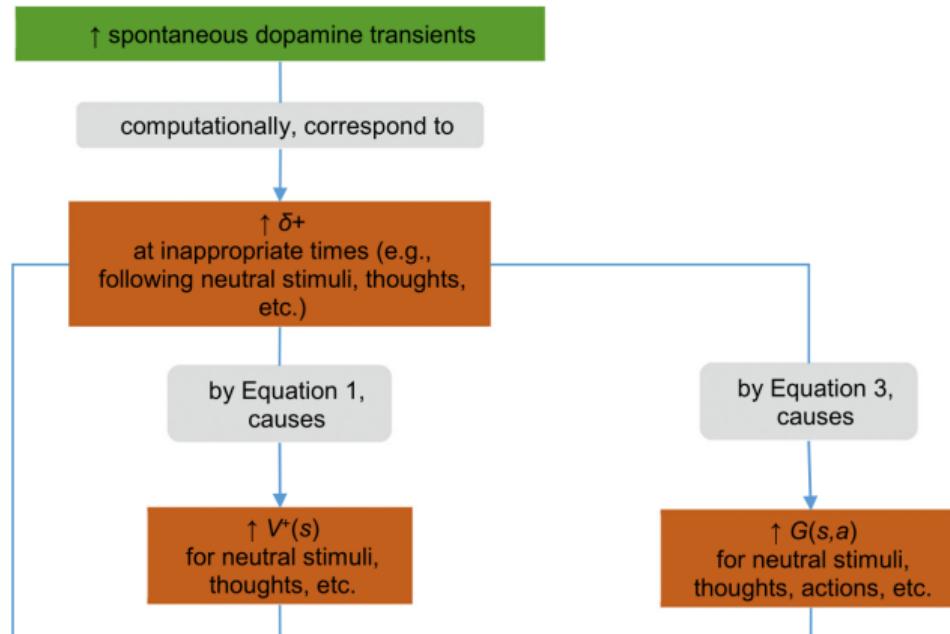
Maia & Frank 2017, BP

Dopamine transients

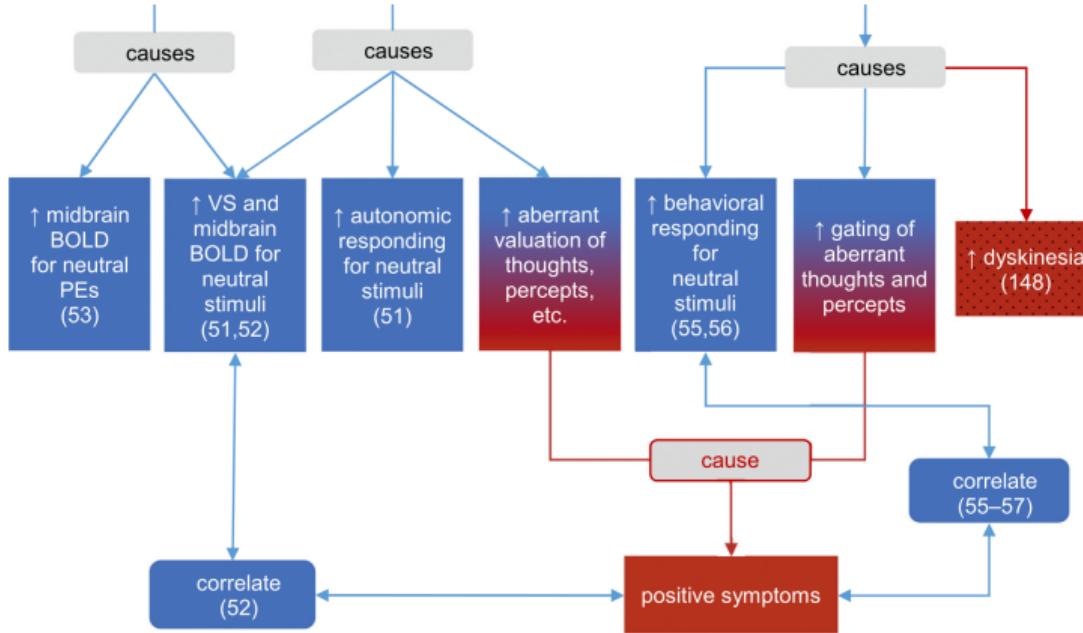


Daberkow et al. 2013, JoN

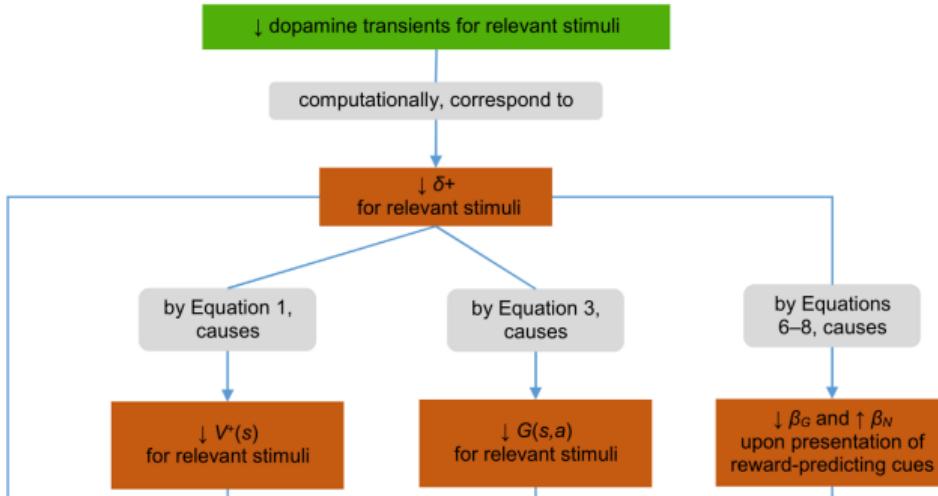
Increased & reduced dopamine transients



Increased & reduced dopamine transients

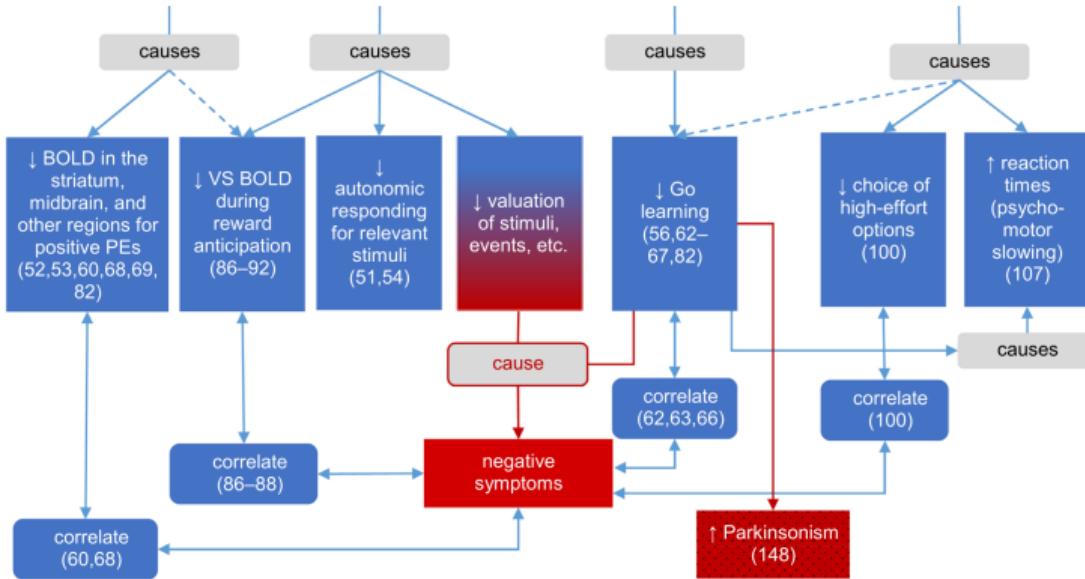


Increased & reduced dopamine transients



Maia & Frank 2017, BP

Increased & reduced dopamine transients



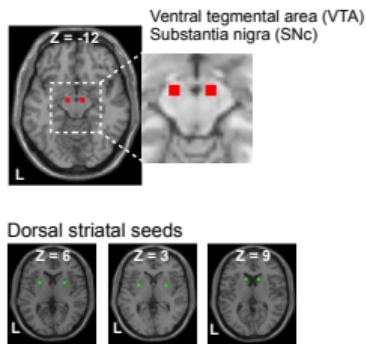
Maia & Frank 2017, BP

Pragmatic solution

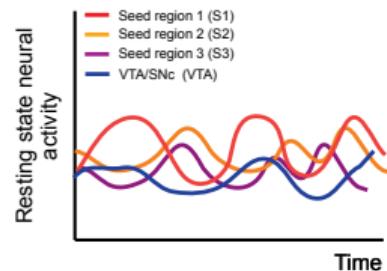
- Readout of functional connectivity at rest between midbrain and striatum -> corresponding to spontaneous dopamine transients
- Hypothesis: more nigrostriatal dysconnectivity in robust responders to standard D2-blocking antipsychotics

Nigrostriatal connectivity

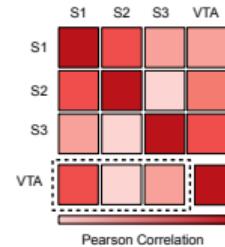
a
Nigrostriatal connections



b
Extracted neural activity



c
Connectivity matrix



d
Striatal connectivity index

