

Schizophrenia and psychosis: how can computational psychiatry help?

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***National Institute for
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**The Academy of
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- **Psychosis spectrum disorders: symptoms and diagnosis**
- Drug treatments: D₂R antagonists and Clozapine; other potential targets
- Neurobiology: the case of glutamate (variation over subgroups/time?)

What can Computational Psychiatry do for treatment, diagnosis, and mechanistic research?

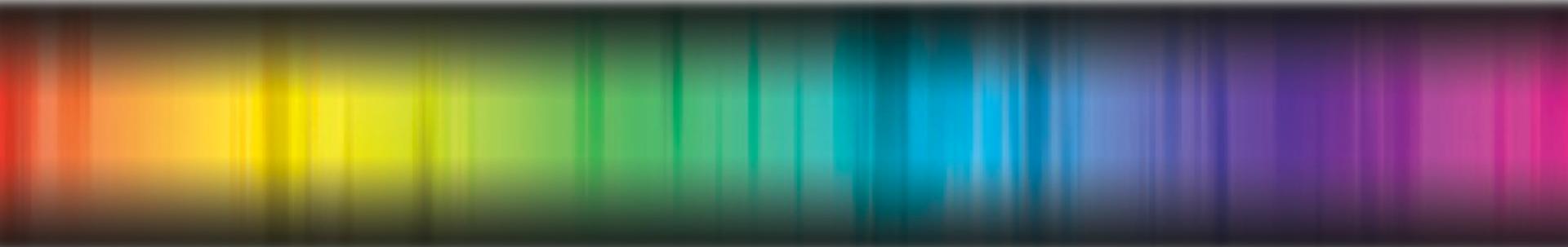
- Most machine learning approaches to (categorical) diagnosis to date have major flaws
- ML should try to delineate the major axes of variation in behaviour / brain / both – preferably using model-based feature selection

Psychotic disorders exist along a spectrum

Schizophrenia

Schizoaffective disorder

Bipolar disorder

A horizontal bar at the bottom of the slide with a rainbow gradient, transitioning from red on the left to purple on the right.

Delusions
Hallucinations
(often >unusual)

No mania or
depression

Delusions
Hallucinations
(can be unusual)

Mania or
depression

Mania or
Depression

Sometimes:
delusions
hallucinations
(often congruent
with mood)

Symptoms & diagnosis



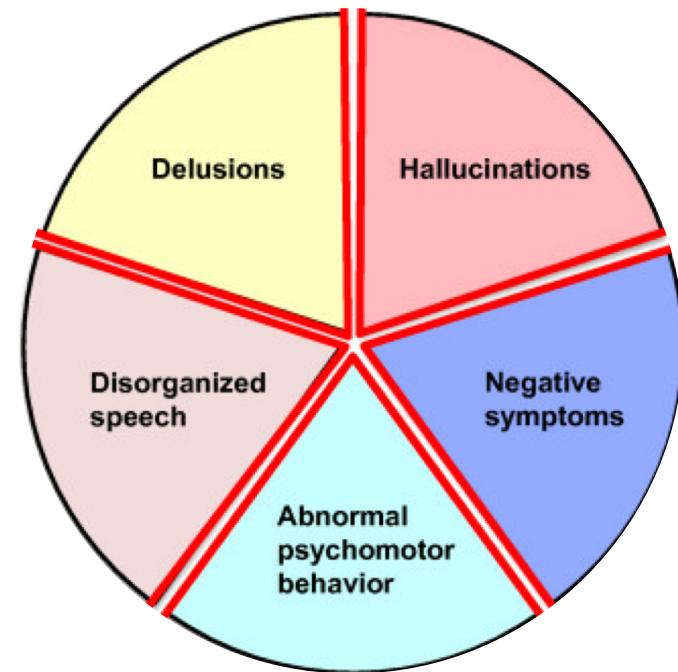
To be diagnosed with schizophrenia:

DSM V:

- ≥ 2 symptoms
- Social/occupational dysfunction
- For >6 months (at some level)

ICD-10:

- ≥ 2 symptoms
(≥ 1 if bizarre delusions/
passivity
or 3rd person AVH's/
thought interference)
- For >1 month



NB Neither include cognitive impairment!

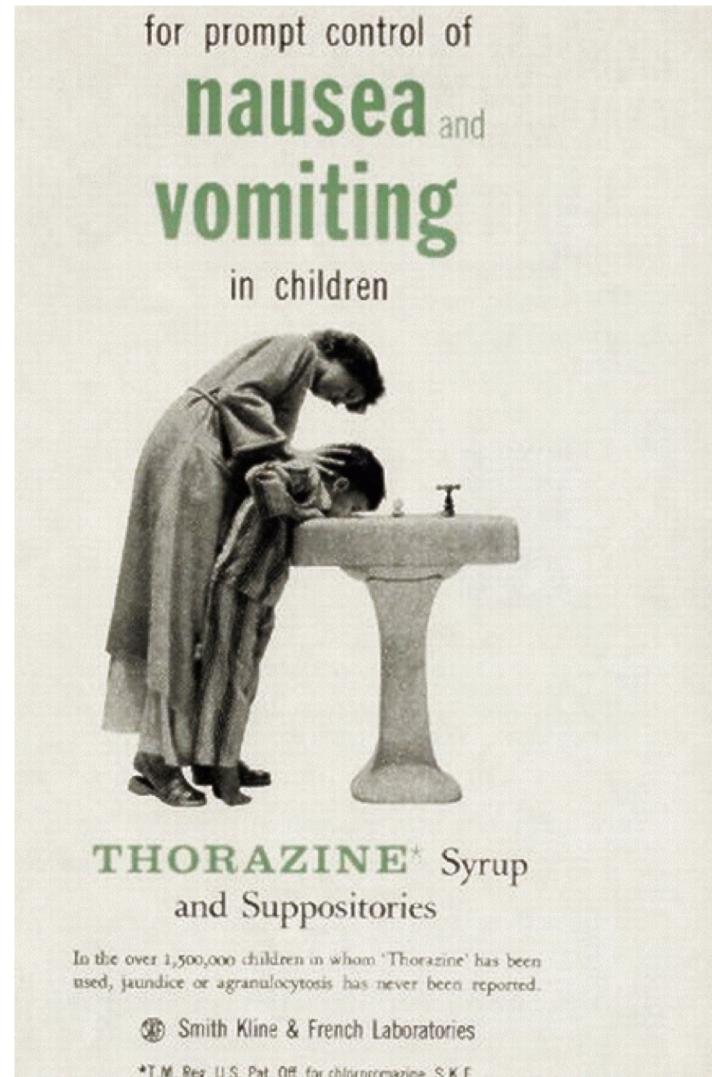
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Antipsychotics were discovered by accident in the 1950's –
they were originally used as antiemetics...

for prompt control of
nausea and
vomiting
in children



THORAZINE* Syrup
and Suppositories

In the over 1,500,000 children in whom 'Thorazine' has been used, jaundice or agranulocytosis has never been reported.

 Smith Kline & French Laboratories

*T.M. Reg. U.S. Pat. Off. for chlorpromazine, S.K.F.

...they also had useful sedative properties...

"Doctor,
what can
you do
for Pop?"



Deeply involved in the problem of the hostile, agitated senile are all members of the family . . . and you, their physician.

In discussing the use of 'Thorazine', Pollack¹ observes: "Older persons with such disorders can be treated at home by the general practitioner with much benefit and with great relief to the family."

With 'Thorazine', senile patients become calm, agreeable and sociable. They begin to eat and sleep better, often gain weight and improve physically.

for prompt control of the agitated, belligerent senile . . .

THORAZINE*

Ampuls for immediate effect—carry them in your bag

Also available: Tablets, Syrup and Suppositories

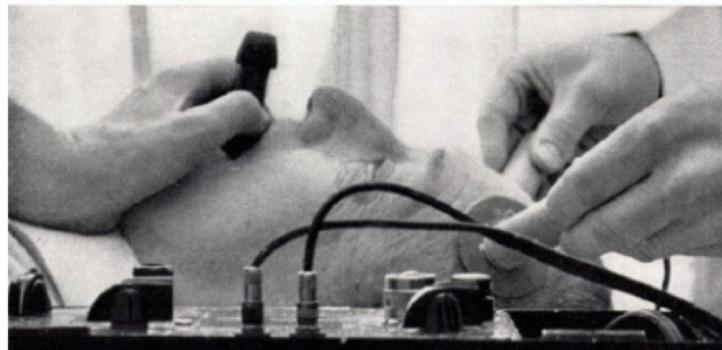
Smith, Kline & French Laboratories, Philadelphia

1. Pollack, E.: Geriatrics 21:283 (June) 1966.

*T.M. Reg. U.S. Pat. Off. for chlorpromazine, S.K.F.

...but it was soon found that they had an antipsychotic effect
independent of any sedative quality

THORAZINE*



reduces need for
electroshock therapy

For example, at Rochester State Hospital, New York, "most of the electric shock in the hospital was suddenly abolished and 'Thorazine' was substituted . . . The number of patients receiving electric shock has fallen from a former level of 300 to only 9."

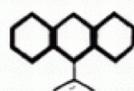
Pollack, B.: *M. Times* 83:439 (May) 1955.

'Thorazine' Hydrochloride is available in 10 mg., 25 mg., 50 mg. and 100 mg. tablets; 25 mg. (1 cc.) and 50 mg. (2 cc.) ampuls; and syrup (10 mg./5 cc.).

Additional information on 'Thorazine' is available on request.

Smith, Kline & French Laboratories, Philadelphia 1

Now available to mental hospitals: 'Thorazine' 200 mg. tablets — for economy and convenience in treating patients on the higher dosage regimens.



*T.M. Reg. U.S. Pat. Off. for S.K.F.'s brand of chlorpromazine.



THORAZINE*
helps to keep more patients out of mental hospitals

With 'Thorazine' "more patients will be released after shorter periods of hospitalization and fewer patients will require re-hospitalization. More patients can be treated in the community, at clinics or in the psychiatrist's office without being hospitalized at all."¹

'Thorazine' is available as the hydrochloride in ampuls, tablets and syrup; and as the base in suppositories.

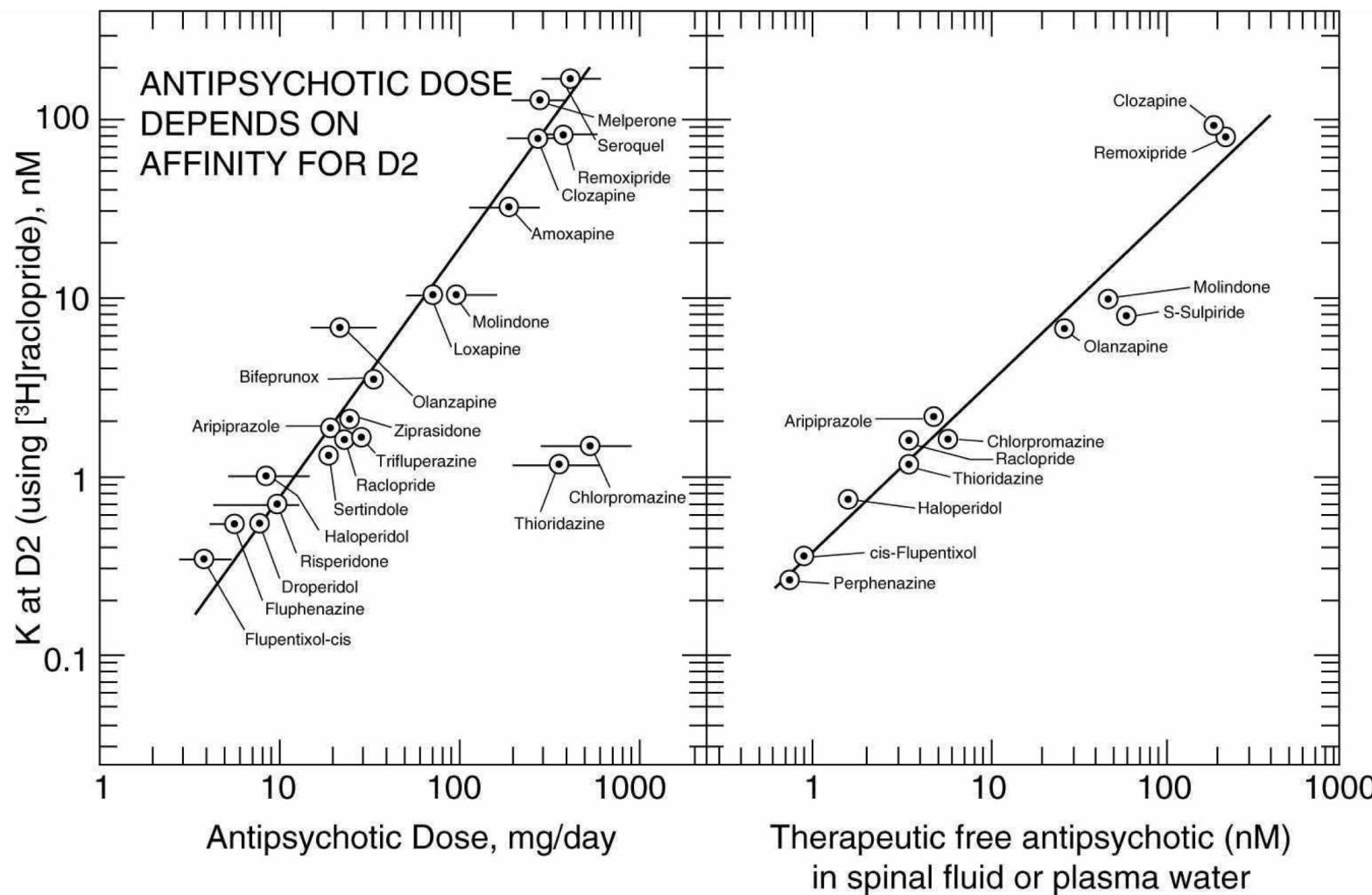
For information write: Smith, Kline & French Laboratories, 1530 Spring Garden Street, Phila. 1

¹ Hoffman, J.L.: in *Chlorpromazine and Mental Health*, Philadelphia, Lea & Febiger, 1955.

*T.M. Reg. U.S. Pat. Off. for chlorpromazine, S.K.F.

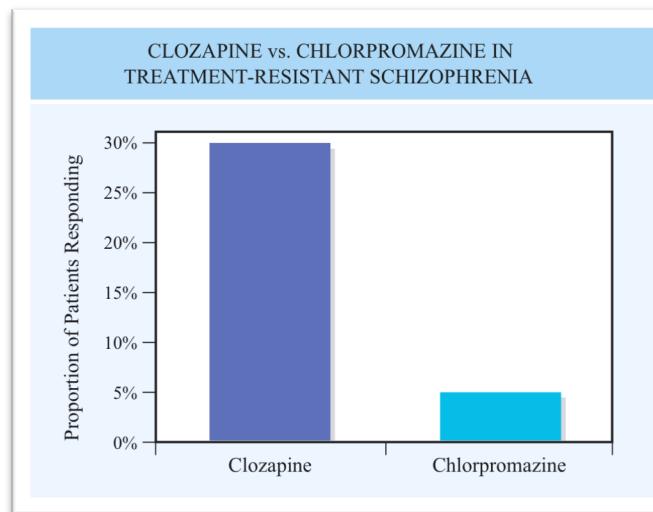
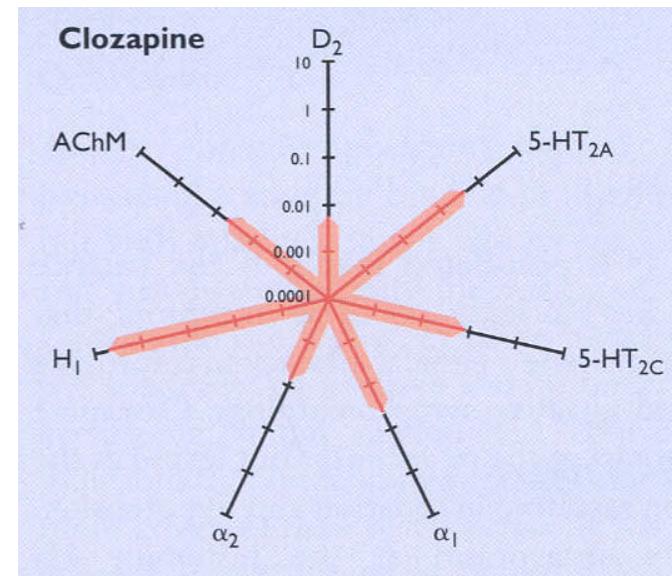
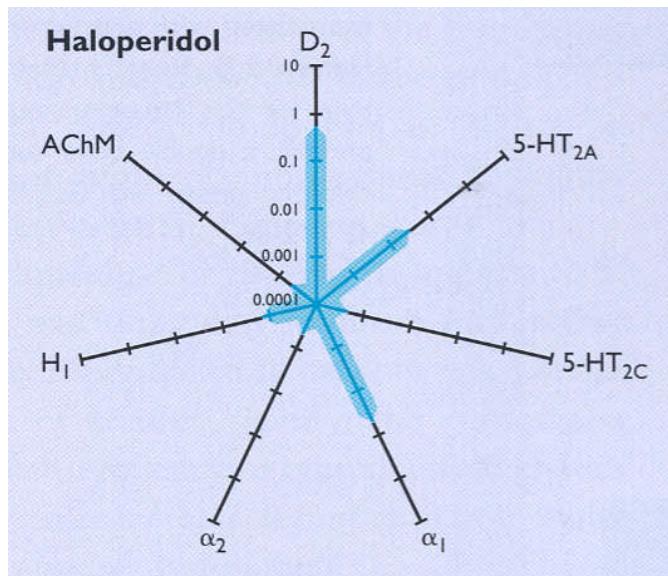
Drug treatments

Their antipsychotic effect depends ?exclusively on their D₂R antagonism



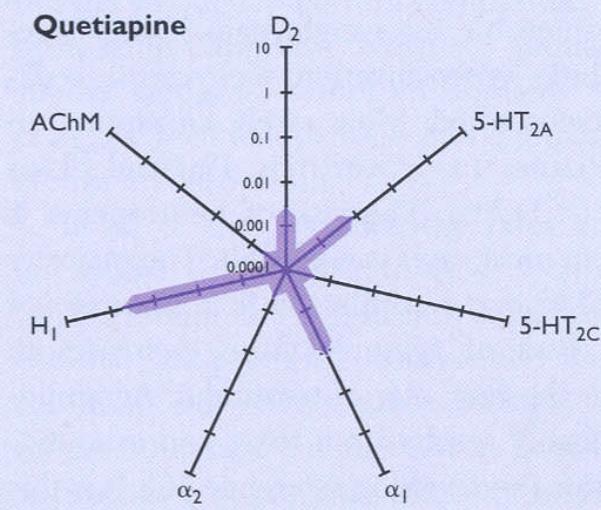
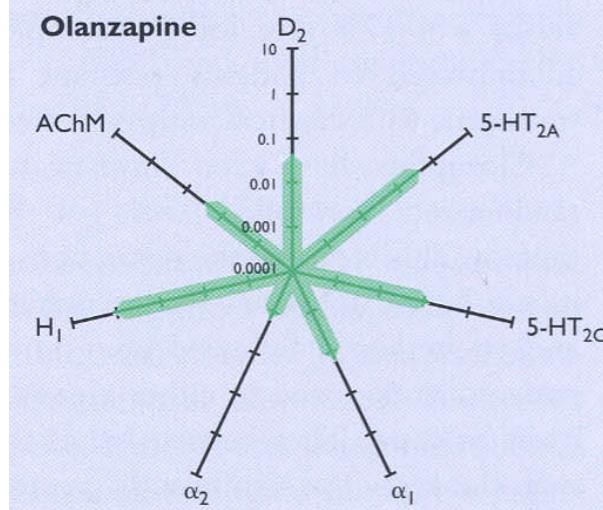
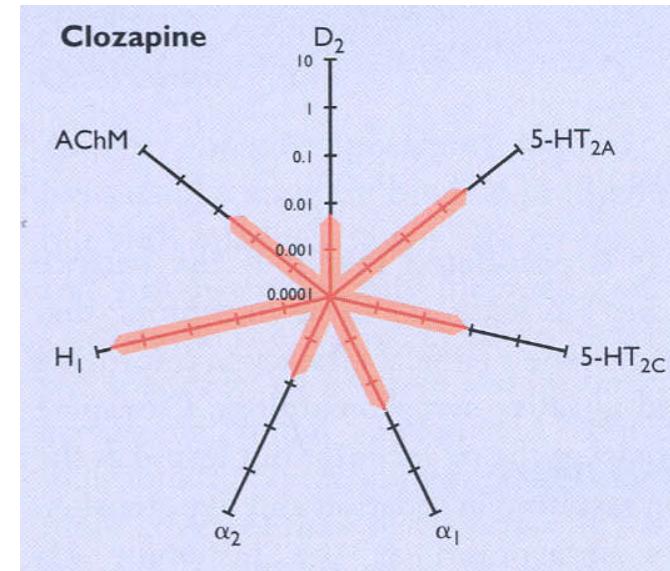
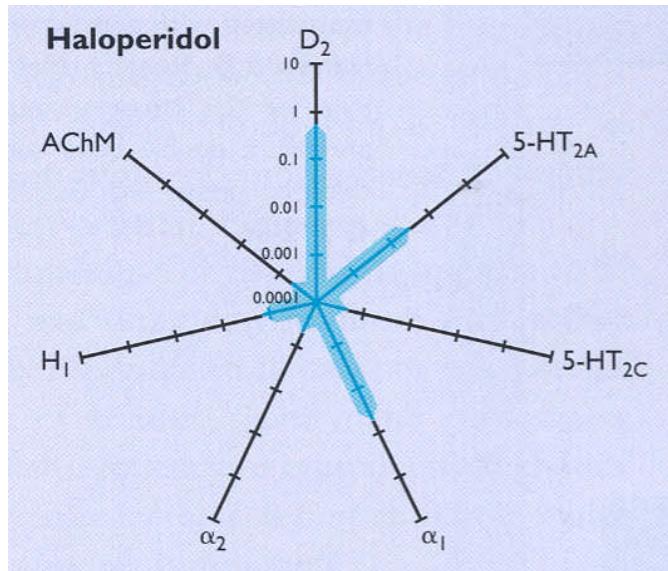
Drug treatments

One antipsychotic – Clozapine – is by far the best...



Drug treatments

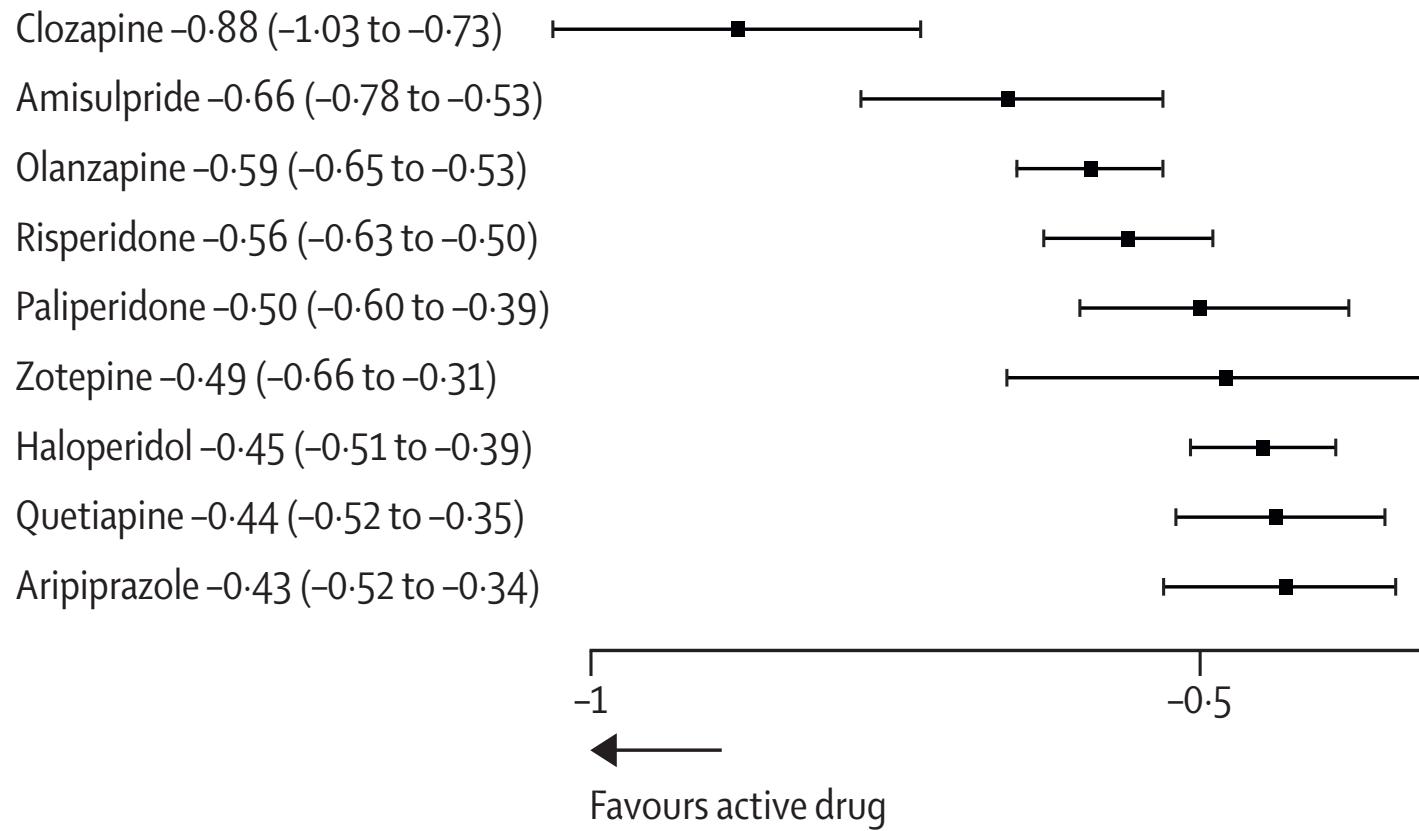
...so Pharma tried to replicate its unique receptor profile in the 1980s...



...but the resulting ‘second generation’ antipsychotics are not better
– we are stuck with anti-D₂R mechanisms (that we know of)

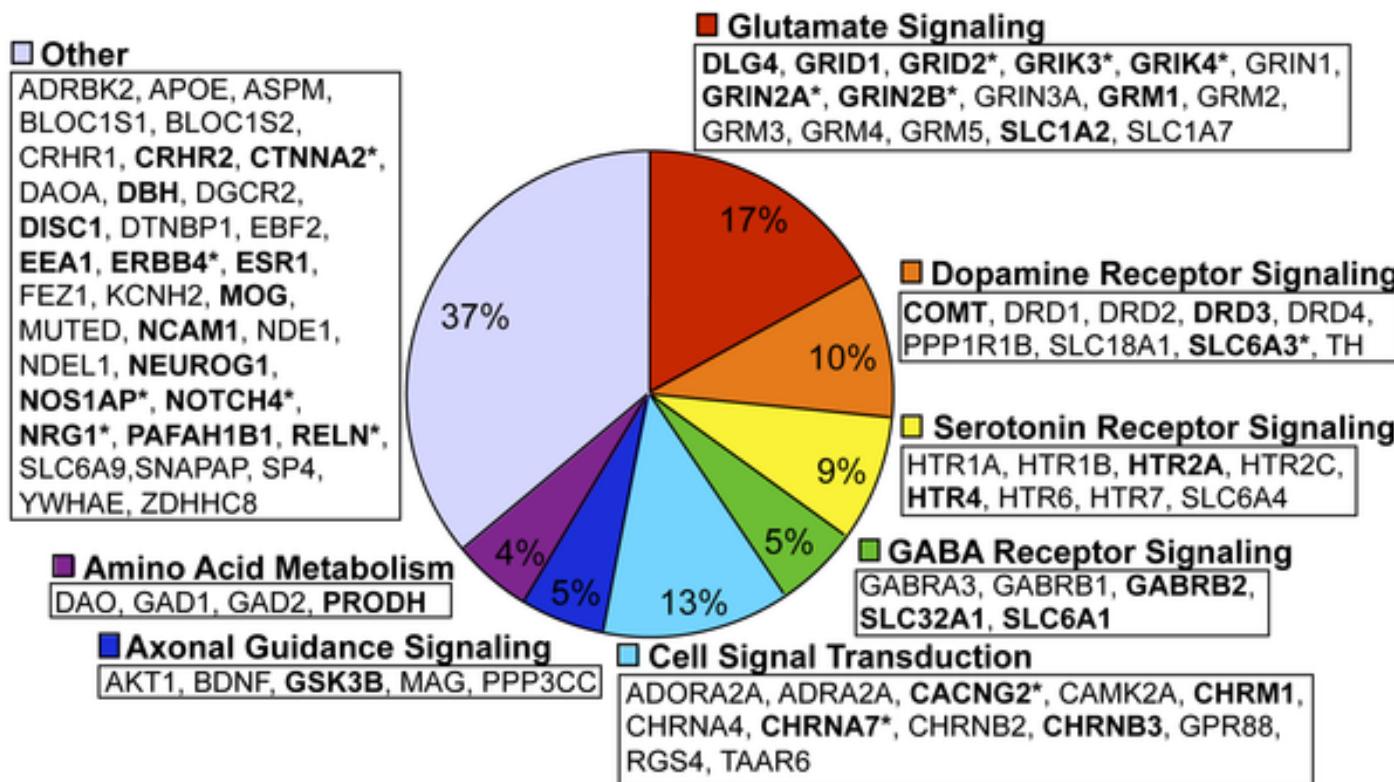
Overall change in symptoms

SMD (95% CrI)



Drug treatments

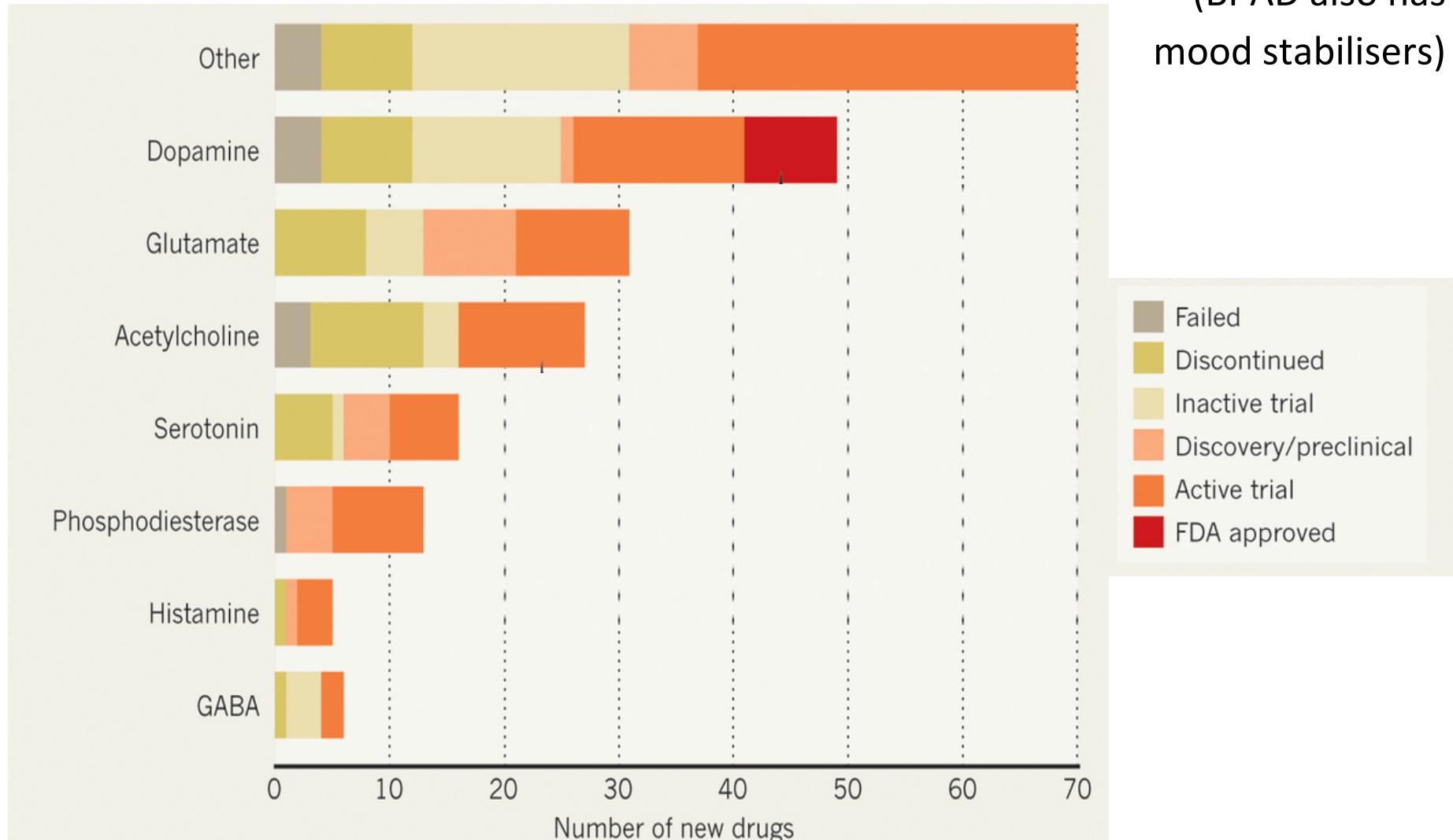
Genetic (GWAS) studies heavily implicate neuromodulators, esp NMDA-Rs,
i.e. druggable targets



Drug treatments

But all drugs based on non-D₂R mechanisms have failed clinical trials in Scz

(BPAD also has mood stabilisers)



- Psychosis spectrum disorders: symptoms and diagnosis
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- **Neurobiology: the case of glutamate (variation over subgroups/time?)**

What can Computational Psychiatry do for treatment, diagnosis, and mechanistic research?

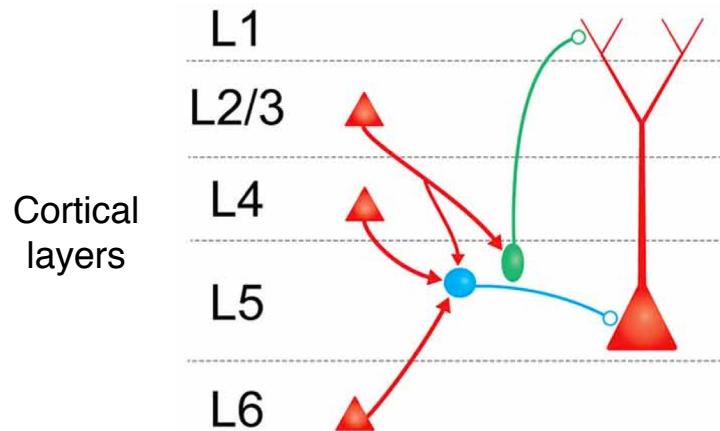
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Two major pathologies in psychosis:

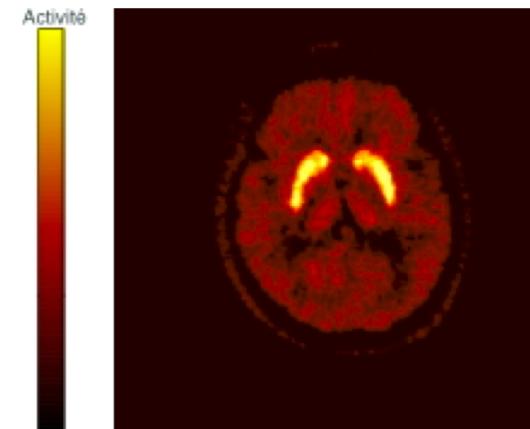
↑Excitation/Inhibition in cortex

Loss of NMDA-R function on

- PV interneurons?
- SST interneurons?
- Pyramidal cells – with inhibitory compensation?

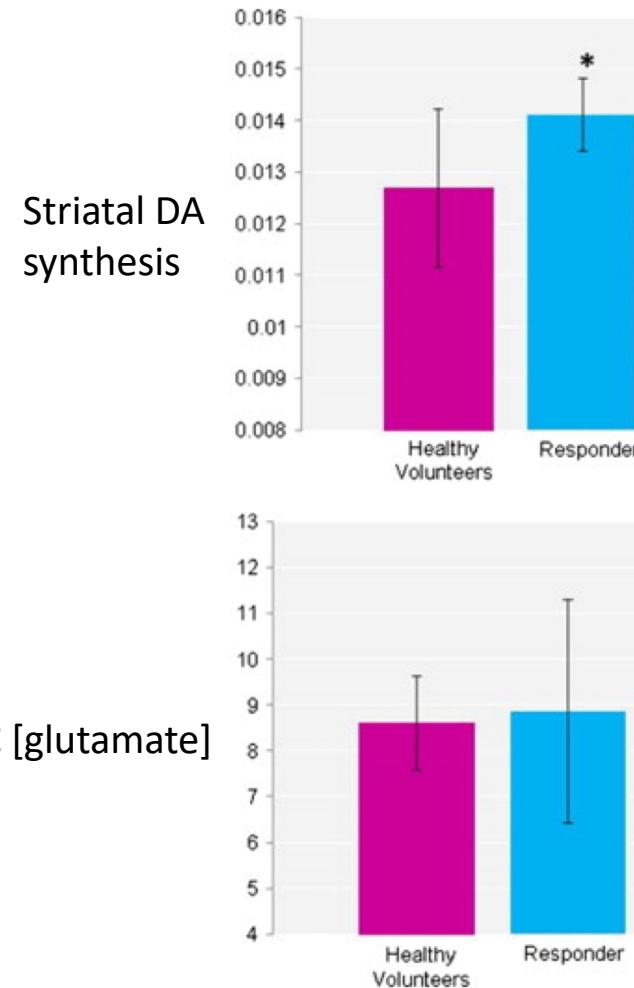
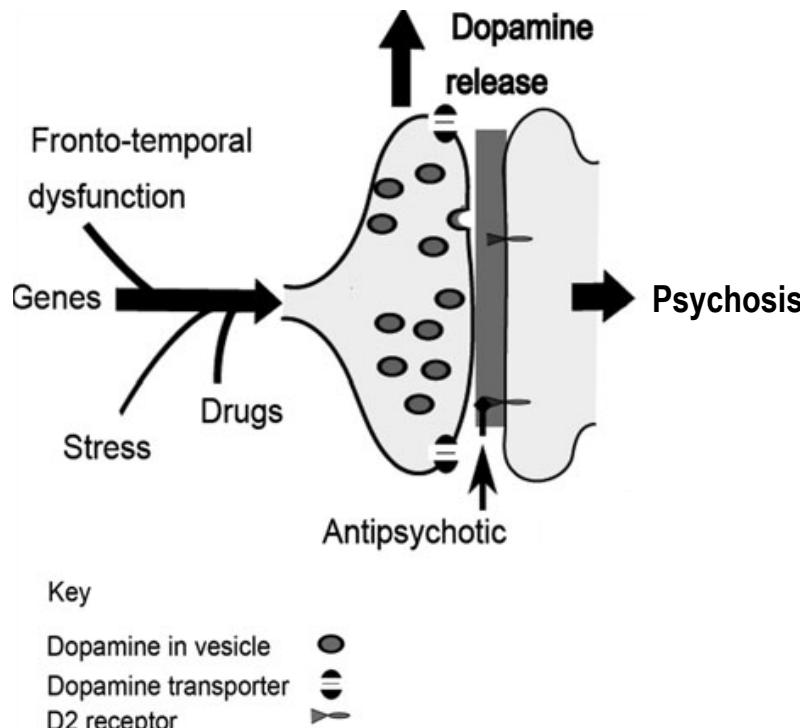


↑Striatal dopamine synthesis & release

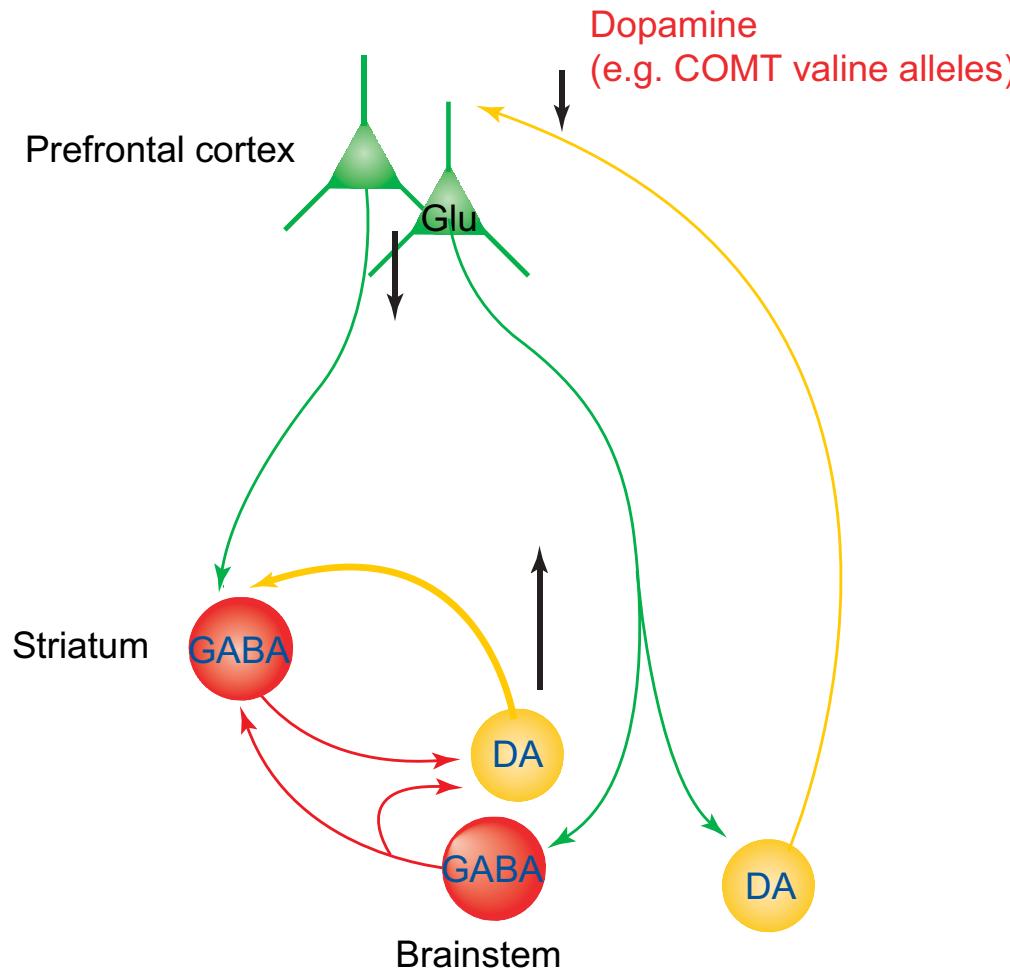


Are there distinct Scz groups with dopamine/NMDA pathology?

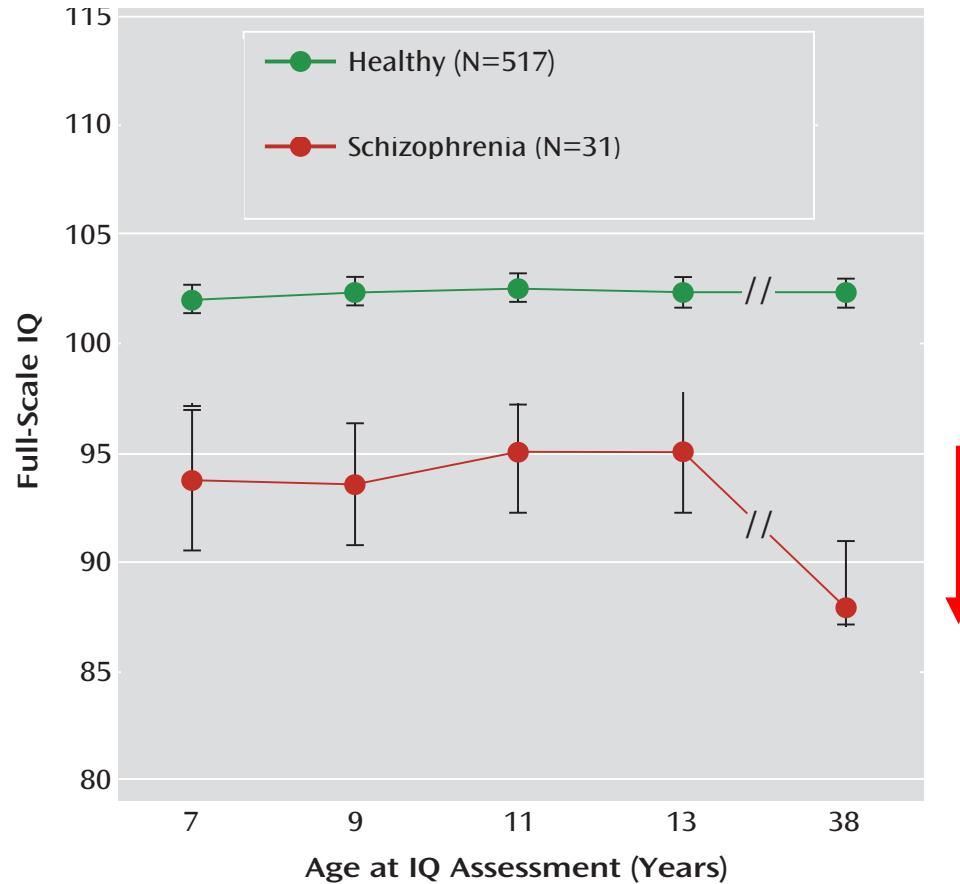
NB we cannot distinguish responders/non-responders using symptoms!



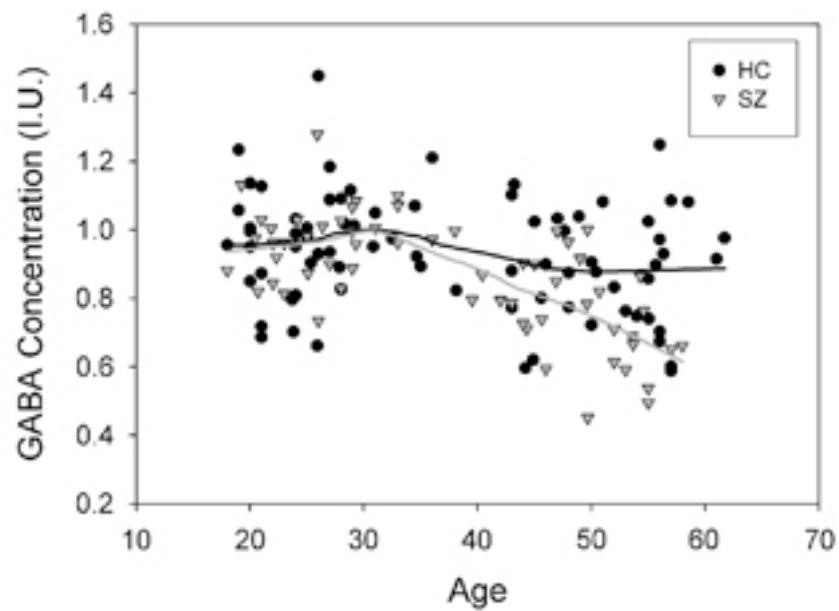
Perhaps the striatal DA and PFC (NMDA-R/GABA interneuron) pathologies aren't separate groups, but interact – at least in some?



There is also evidence of longitudinal variation in Scz:
~all Scz have ↓IQ from birth, but a subset have a further IQ drop at illness onset



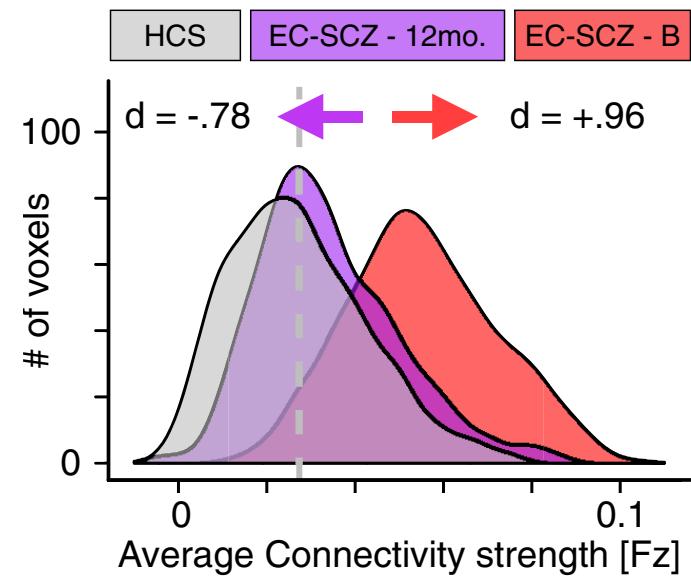
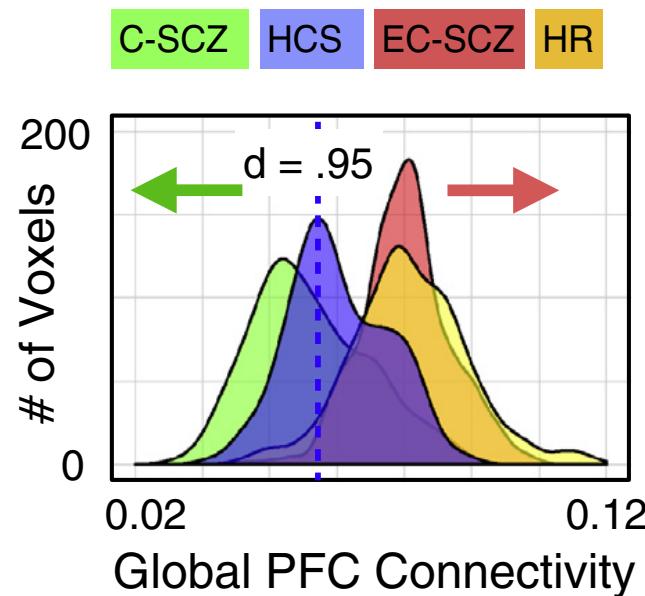
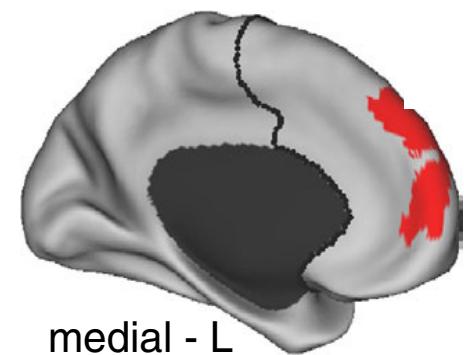
Spectroscopy => ACC [glut] and [GABA] change over illness course:
perhaps *time* determines some disease subgroups



Connectivity within mPFC seems to change over the course of Scz:

High risk/early Scz = hyper; chronic Scz = hypo

...and early Scz hyperconnectivity is reduced by medication



Two major pathologies in psychosis:

↑Excitation/Inhibition in cortex

Predrome



State of the Network

- **Deficit:** Glutamate Synaptic Dysfunction
- **Consequence:** Glutamate signaling deficit
- **Allostatic Adaptation:** GABA deficit and programmed synaptic proliferation
- **Consequence:**
 - E/I Imbalance (Disinhibition)
 - Tuning Deficit, Oscillation Abnormalities
 - Hyperconnectivity
- **Allostatic Adaptation:** Synaptic downscaling and programmed synaptic elimination
- **Consequence:**
 - Atrophy compounds synaptic deficit
 - Tuning deficits persist
 - Network functions decline

Prodrome



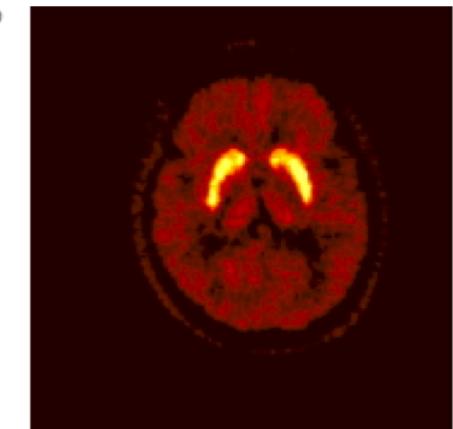
Syndrome



Chronic Illness



↑Striatal dopamine synthesis & release



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Can Computational Psychiatry inform current/future
i) treatment, ii) diagnosis or iii) mechanistic research?

Currently treatment choice is so sparse, CP prob can't much improve decisions

Many attempts have been made to apply machine learning classification algorithms to imaging data to aid diagnosis...

ML and diagnosis



Attempts to use machine learning to categorise patients using brain imaging have substantial flaws:

i) Clinicians want to distinguish *between diagnoses*, not 1 diagnosis vs controls

Modality	Disorder	Number of subjects	Overall accuracy	Reference
fMRI	Schizophrenia	HC = 45, SZ = 45 Total = 90	80%	Caprihan et al. (2008)
fMRI	Schizophrenia	HC = 24, SZ = 34 Total = 58	75%	Caan et al. (2006)
fMRI	Schizophrenia	HC = 35, SZ = 50 Total = 85	96%	Ardelt et al. (2011)
fMRI (sensorimotor, ADD, WMT tasks)	Schizophrenia	HC = 15, SZ = 13 Total = 28	96%	Honorio et al. (2012)
fMRI (ADD/Sternberg/ sensorimotor/tasks)	Schizophrenia	HC = 91, SZ = 57 Total = 138	80-90%	Demirci et al. (2008a)
fMRI (AA-CPT task)	Schizophrenia (first-episode)	HC = 10, SZ = 51 Total = 102	62%	Gur et al. (2012)
fMRI (Monetary Incentive Delay task)	Schizophrenia	HC = 44, SZ = 44 Total = 88	93%	Koch et al. (2015)
fMRI (sensorimotor task) and SNP	Schizophrenia	HC = 116, SZ = 92 Total = 208	77%	Cao et al. (2013)
fMRI (verbal fluency task)	Schizophrenia/bipolar	HC = 40, SZ = 32, BP = 40 Total = 104	92%	Costafreda et al. (2011b)
fMRI (visual task)	Schizophrenia	HC = 15, SZ = 19 Total = 34	59-72%	Vago et al. (2008)
fMRI (WMT task)	Schizophrenia with and without OCD	HC = 20, SZ = 32 (with OCD) = 16, SZ (without OCD) = 17, Total = 53	75-91%	Bleich-Cohen et al. (2014)
fMRI (AOD task)	Schizophrenia	HC = 21, SZ = 31 Total = 52	85%	Castro et al. (2014)
fMRI (AOD task)	Schizophrenia	HC = 54, SZ = 52 Total = 106	95%	Castro et al. (2011)
fMRI (AOD task)	Schizophrenia/bipolar	HC = 26, SZ = 21, BP = 14 Total = 61	83-95%	Calhoun et al. (2008)
fMRI (AOD task)	Schizophrenia/bipolar	HC = 25, SZ = 21, BP = 14 Total = 60	82-90% (AUC)	Arribas et al. (2010)
rsfMRI	Schizophrenia	HC = 25, SZ = 24, Sibling HC = 22 Total = 71	62%	Yu et al. (2013b)
rsfMRI	Schizophrenia/MDD	HC = 38, SZ = 32, MDD = 19, Total = 89	80.9%	Yu et al. (2013a)
rsfMRI	Schizophrenia	HC = 18, SZ = 18 Total = 36	75%	Venkatasan et al. (2012)
rsfMRI	Schizophrenia	HC = 22, SZ = 22 Total = 44	93%	Tang et al. (2012)
rsfMRI	Schizophrenia	HC = 32, SZ = 32 Total = 64	83%	Sue et al. (2013)
rsfMRI	Schizophrenia	HC = 20, SZ = 32 Total = 52	86%	Shen et al. (2010)
rsfMRI	Schizophrenia	HC = 50, SZ = 50 Total = 100	86%	Kim et al. (2015)
rsfMRI	Schizophrenia	HC = 196, SZ = 71 Total = 207	75-84%	Kaufmann et al. (2015)
rsfMRI	Schizophrenia	HC = 20, SZ = 19, Total = 48	80.0%	Cheng et al. (2015b)
rsfMRI	Schizophrenia	HC = 10, SZ = 8 Total = 18	100%	Fekete et al. (2013)
rsfMRI	Schizophrenia	HC = 32, SZ = 31 Total = 62	85-87%	Shen et al. (2011)
rsfMRI	Schizophrenia	HC = 74, SZ = 72 Total = 144	80-91%	Chiyzyk et al. (2015)

Modality	Disorder	Number of subjects	Overall accuracy	Reference
rsfMRI	Schizophrenia	HC = 29, SZ = 29 Total = 58	75%	Bassett et al. (2012)
rsfMRI	Schizophrenia	HC = 28, SZ = 28 Total = 56	96%	Arbabshirani et al. (2013)
rsfMRI	Schizophrenia	HC = 90, SZ = 90, Total = 180	73.9%	Anticevic et al. (2014)
rsfMRI	Schizophrenia	HC = 74, SZ = 72 Total = 146	65%	Anderson and Cohen (2013)
sMRI	Schizophrenia	HC = 79, SZ = 69 Total = 148	71%	Zhang and Davatzikos (2013)
sMRI	Schizophrenia (first episode)	HC = 62, SZ = 62 Total = 124	73%	Zanetti et al. (2013)
sMRI	Schizophrenia (first-episode)	HC = 40, SZ = 52 Total = 92	80%	Takayangi et al. (2011)
sMRI	Schizophrenia and psychosis	HC = 36, SZ = 36 Total = 72	86%	Sun et al. (2009)
sMRI	Schizophrenia/bipolar	HC1 = 66, HC2 = 43, SZ1 = 66, SZ2 = 46, BP1 = 66, BP2 = 47 Total1 = 198, Total2 = 136	67-90%	Schnack et al. (2014)
sMRI	Schizophrenia	HC = 24, SZ = 27, Total = 51	65.0-72.7%	Radulescu et al. (2014)
sMRI	Schizophrenia	HC = 42, SSD = 36, Non-SSD = 45, Total = 123	81.0-99.0%	Pina-Camacho et al. (2015)
sMRI	Schizophrenia/bipolar	HC = 10, SZ = 10, BP = 10	96%	Pardo et al. (2006)
sMRI	Schizophrenia	HC = 105, HC2 = 23, SZ1 = 38, SZ2 = 23, Total = 189	70-76%	Ota et al. (2012)
sMRI	Schizophrenia	HC1 = 111, HC2 = 122, SZ1 = 128, SZ2 = 155 Total1 = 239, Total2 = 239	71%	Nieuwenhuis et al. (2012)
sMRI	Schizophrenia	HC = 47, SZ = 57	78-86%	Nakamura et al. (2004)
sMRI	Schizophrenia/mood disorder	Total = 104, SZ = 158	76%	Koutsouleris et al. (2015)
sMRI	Schizophrenia	HC = 46, SZ = 46 Total = 92	80-90%	Kawasaki et al. (2007)
sMRI	Schizophrenia (first-episode)	HC = 39, SZ = 39 Total = 78	72%	Kasperek et al. (2011)
sMRI	Recent onset Schizophrenia	HC = 47, SZ = 28 Total = 75	72%	Karageorgiou et al. (2011)
sMRI	Schizophrenia	HC = 49, SZ = 49, Total = 98	81.6%	Janussova et al. (2015)
sMRI	Schizophrenia	HC = 20, SZ = 19, Total = 39	66.6-77%	Iwabuchi et al. (2013)
sMRI	Schizophrenia (identifying subtypes)	HC = 29, SZ = 23 Total = 52	78%	Ingallalikar et al. (2012)
sMRI	Schizophrenia (childhood onset)	HC = 99, SZ = 98 Total = 197	74%	Greenstein et al. (2012)
sMRI	Schizophrenia (cognitive deficit and cognitive spared)	HC = 163, SZ = 208, SZA = 41, Total = 412	56-72%	Gould et al. (2014)

Modality	Disorder	Number of subjects	Overall accuracy	Reference
sMRI	Schizophrenia	HC1 = 38, HC2 = 41, SZ1 = 23, SZ2 = 46	91%	Fan et al. (2007)
sMRI	Schizophrenia	Total1 = 61, Total2 = 87	92%	Fan et al. (2008)
sMRI	Schizophrenia	Total = 51	81%	Davarzinos et al. (2005)
sMRI	Schizophrenia	Total = 148	79%	Csernansky et al. (2004)
sMRI	Schizophrenia	Total = 117	66-75%	Carroll et al. (2012)
sMRI	Schizophrenia	Total = 180	94.0%	Bansal et al. (2012)
sMRI and dMRI	Schizophrenia/MDD	MDD = 25, SZ = 25 Total = 50	72-88%	Ota et al. (2013)
fMRI (AOD task) and rsfMRI	Schizophrenia	HC = 28, SZ = 28 Total = 56	93-98%	Du et al. (2012)
fMRI (AOD task) and rsfMRI	Schizophrenia	HC = 28, SZ = 27 Total = 53	72%	Cetin et al. (2015)
fMRI (AOD task) and SNP	Schizophrenia	HC = 20, SZ = 20 Total = 40	87%	Yang et al. (2010)
sMRI, rsfMRI and dMRI	Schizophrenia	HC = 28, SZ = 35 Total = 63	79%	Sui et al. (2013b)

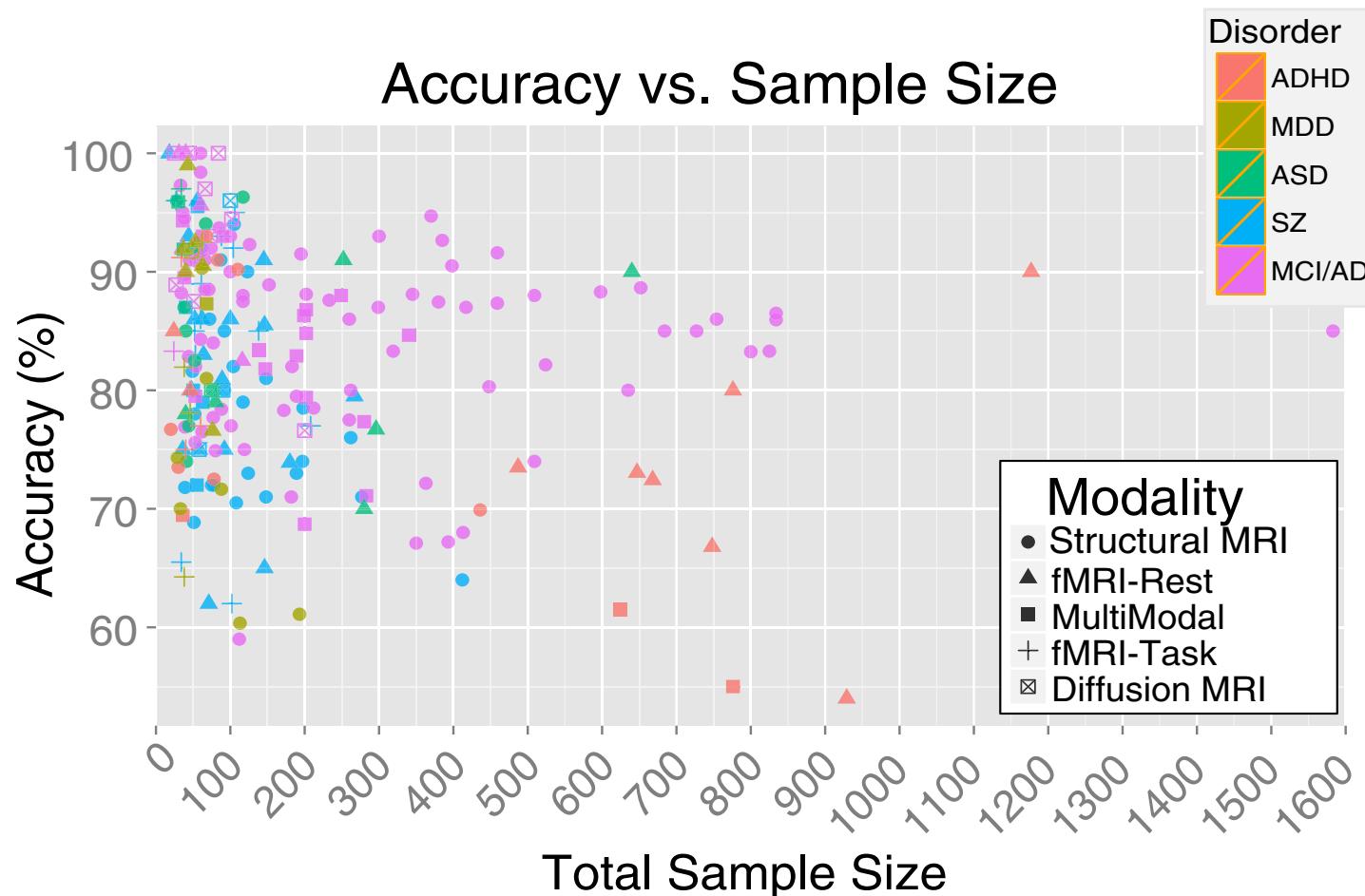
Comparing 2x n=150 samples of BPAD, Scz & Controls:

Scz v BPAD: 66%
 BPAD v Cont: 62%
 Scz vs Cont: 76%

Attempts to use machine learning to categorise patients

using brain imaging have substantial flaws:

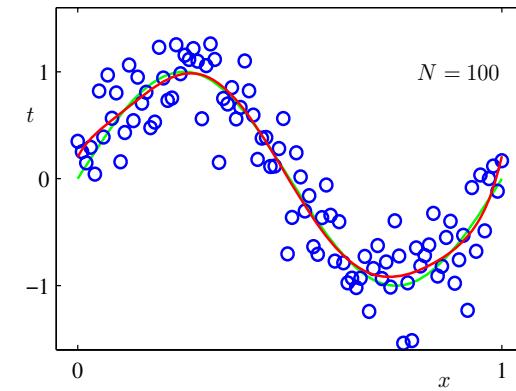
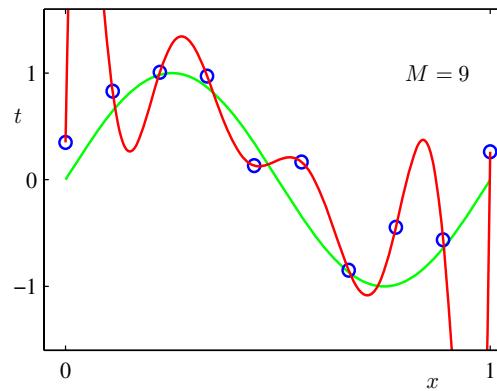
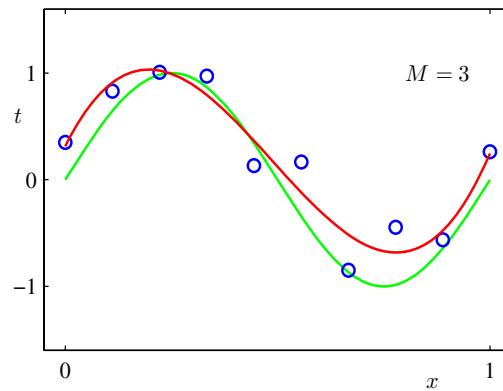
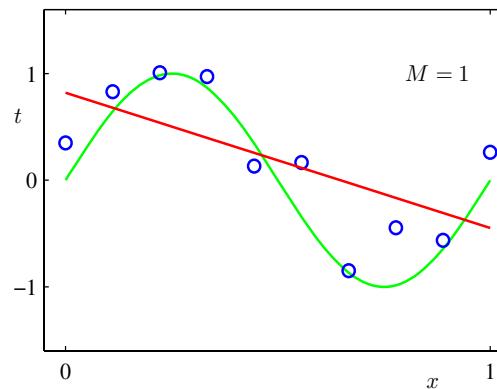
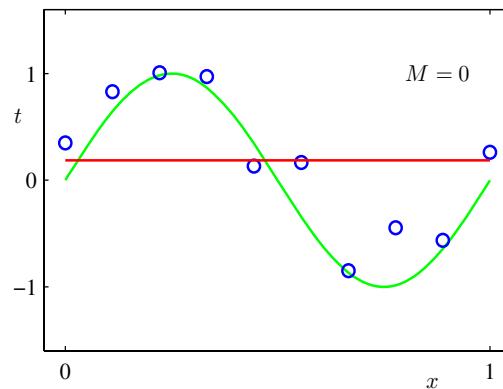
ii) Sample sizes have been far too low, making overfitting v likely



Attempts to use machine learning to categorise patients

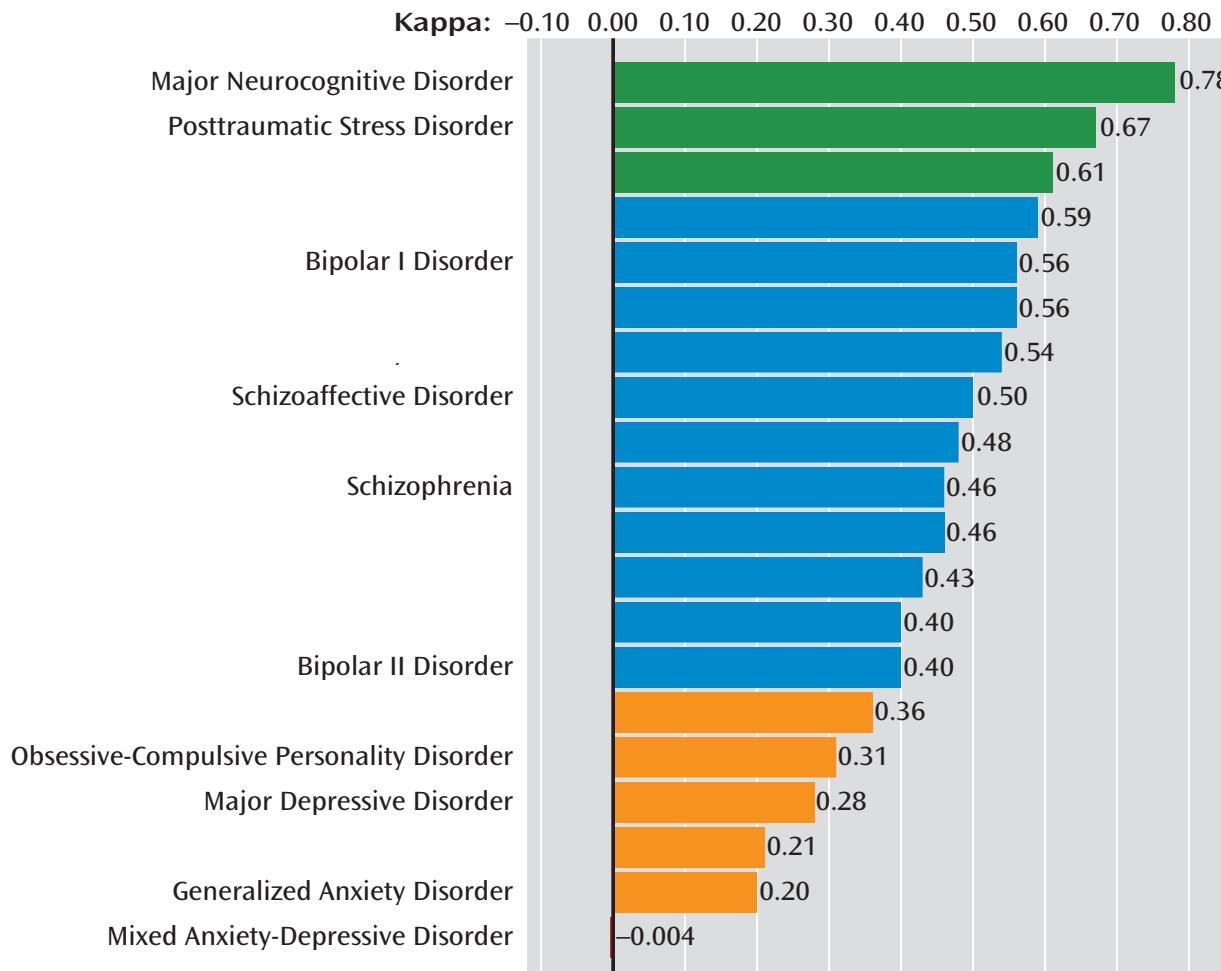
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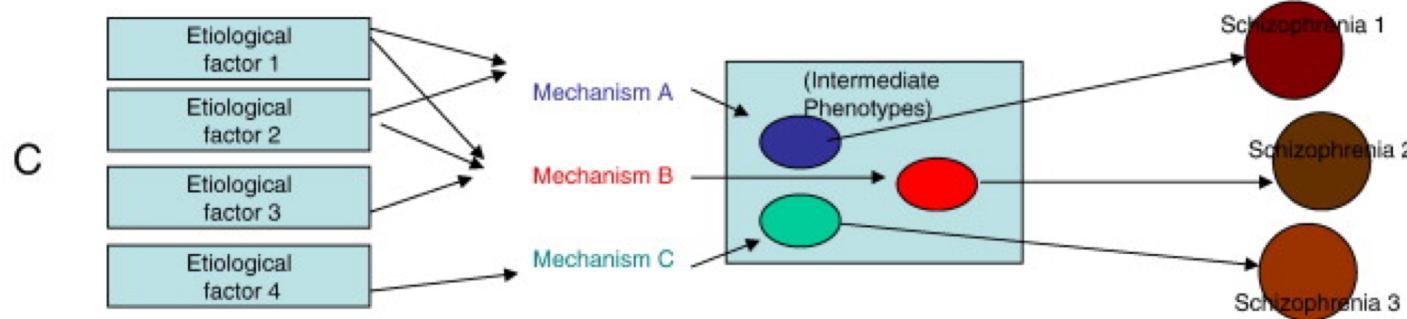
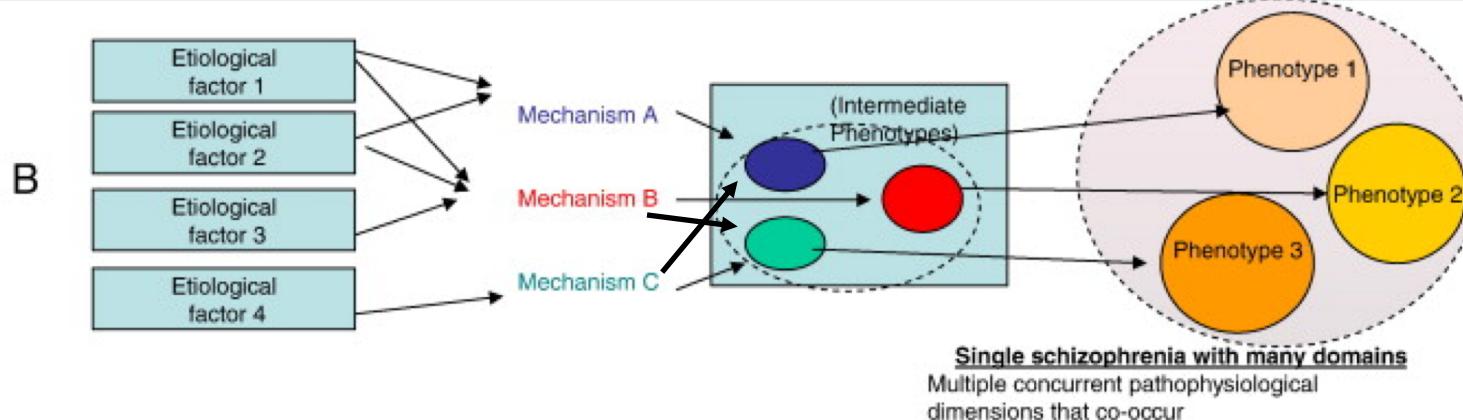
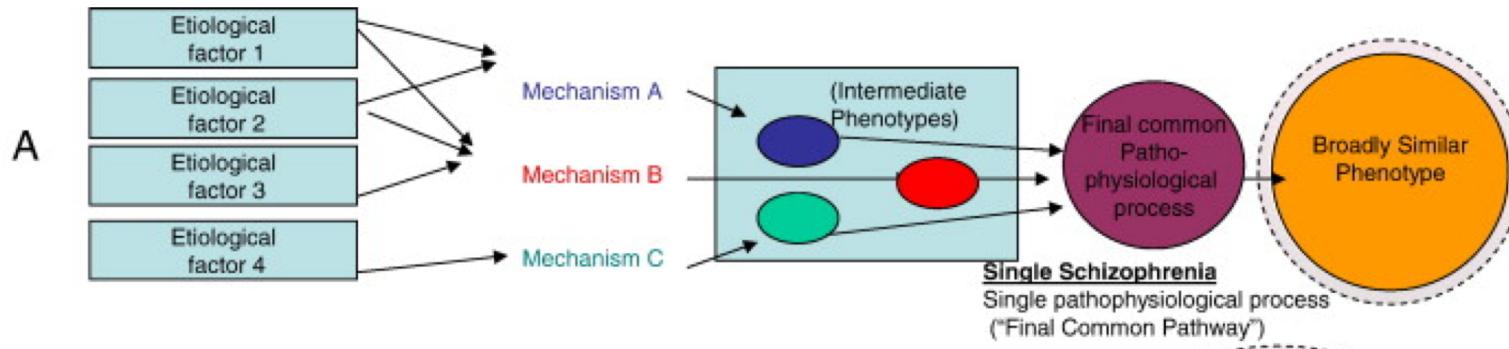
Attempts to use machine learning to categorise patients
using brain imaging have substantial flaws:

iii) Diagnoses have limited inter-rater reliability (κ) so high accuracy **isn't possible**



Computational psychiatry: beyond diagnosis

We need to replace – not assist – our current diagnoses... but how?



Can Computational Psychiatry inform current/future

- i) treatment, ii) diagnosis or iii) mechanistic research?

To delineate phenotypes we need BIG samples and computational methods
(and sensible hypotheses):

- i) Unsupervised data reduction -> classification
- ii) Feature-selective data reduction -> classification
- iii) MODEL-BASED data reduction -> classification

Computational psychiatry: beyond diagnosis

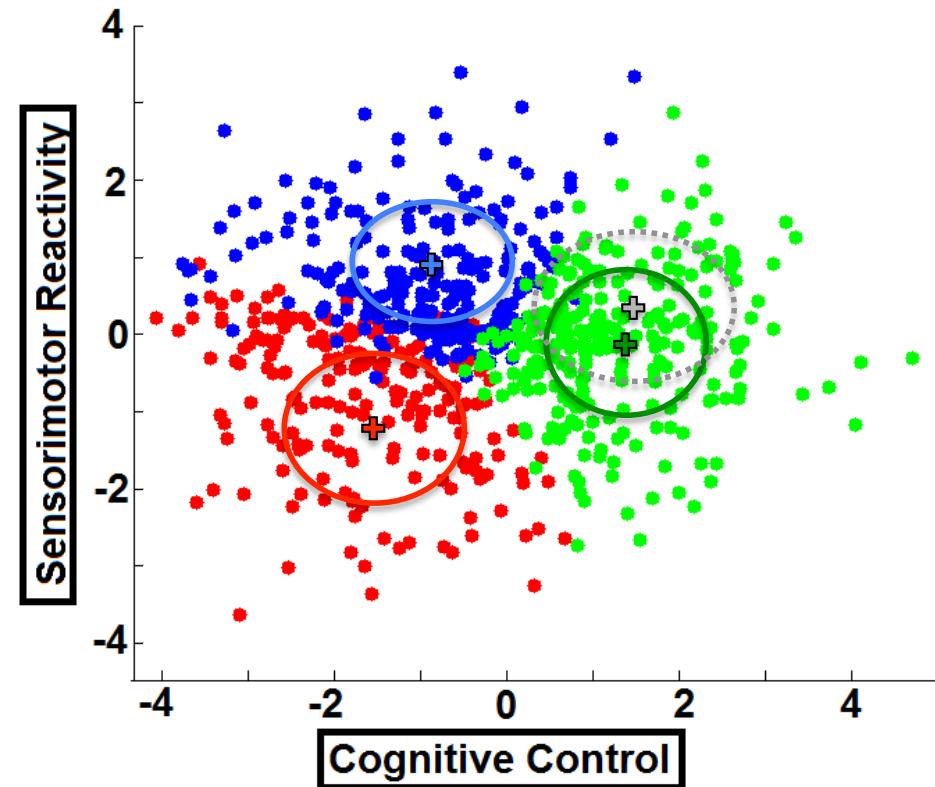
To find new phenotypes we need BIG samples and computational methods:

i) Unsupervised data reduction -> classification

Three phenotypes were generated from 700 Scz/SczAf/Bipolar pts, 900 relatives and 300 controls:

- EEG paradigms
- Cognitive tasks
- Saccadic & stop-signal tasks

They replicated in relatives & showed distinct sMRI patterns



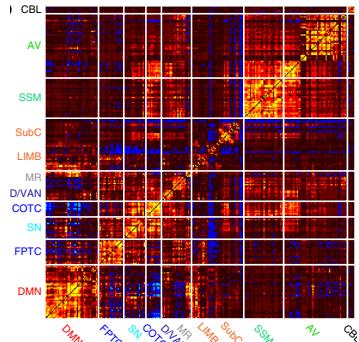
But...

- **No functional connectivity used**
- **Axes are mechanistically unclear**

Computational psychiatry: beyond diagnosis

To find new phenotypes we need BIG samples and computational methods:

ii) Feature-selective data reduction -> classification

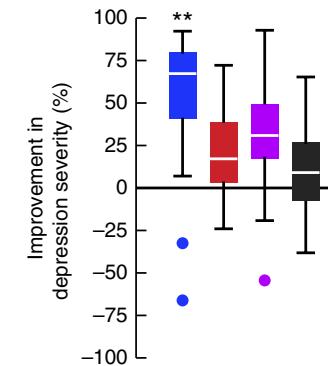
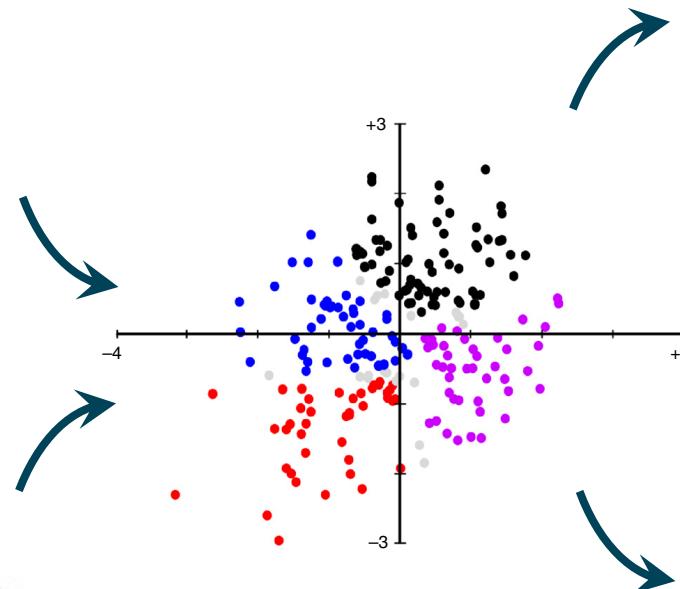


rsfMRI connectivity

n = 700 (training)
n = 500 (test)



Symptom scores



1 'cluster'
predicted
treatment response
to DBS

		Cluster ID at Time 2			
		1	2	3	4
Cluster ID at Time 1	1	7.1%	64.3%	7.1%	21.4%
	2	14.3%	42.9%	14.3%	28.6%
	3	12.5%	25.0%	37.5%	25.0%
	4	0%	0%	18.8%	81.3%

		Cluster ID on 2nd Scan			
		1	2	3	4
Cluster ID on 1st Scan	1	87.5%	0%	0%	12.5%
	2	7.7%	92.3%	0%	0%
	3	0%	0%	93.3%	6.7%
	4	14.3%	0%	0%	85.7%

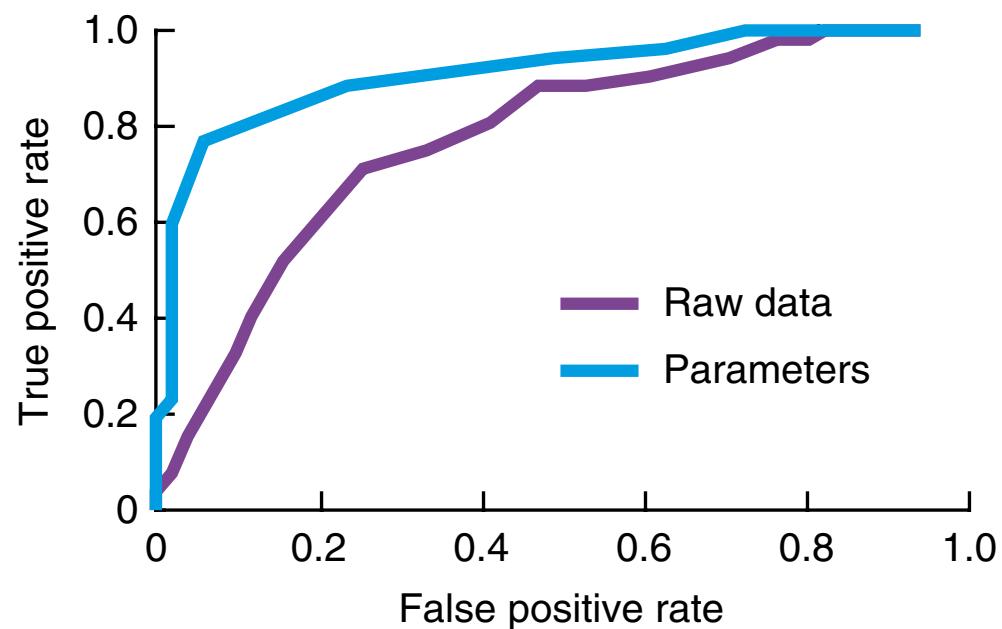
fMRI +
symptom
'clusters' are
reliable

To find new phenotypes we need BIG samples and computational methods:

iii) MODEL-BASED data reduction -> classification

Generative models of data reduce dimensionality in a hypothesis-driven way

- RL task data simulated:
2 groups differed
in learning rate
- Parameters estimated
by RL model
- 2 classifiers trained on
raw data or **parameters**
in training and test sets
(both n=100)



To find new phenotypes we need BIG samples and computational methods:

iii) MODEL-BASED data reduction -> classification

Negative symptoms have been modelled using reinforcement learning:

- Intact learning to avoid losses but impaired learning from rewards
- Use of simpler (actor-critic) models rather >complex (Q learning) ones
- Impaired (cortical?) representation of state values
- Impaired cost-benefit trade-off computation

To find new phenotypes we need BIG samples and computational methods:

iii) MODEL-BASED data reduction -> classification

Cognitive symptoms have been modelled using biophysical/>abstract models:

- NB working memory impairment can cause apparent RL deficits – the WM contribution is only seen if WM is included in the model
- Belief updating tasks (e.g. the beads task) => greater ‘noise’ in decision-making and >belief instability

To find new phenotypes we need BIG samples and computational methods:

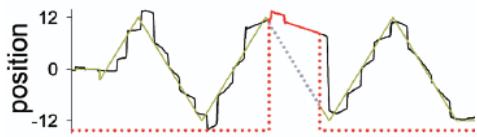
iii) MODEL-BASED data reduction -> classification

Positive symptoms & traits modelled using hierarchical Bayesian (& RL) models:

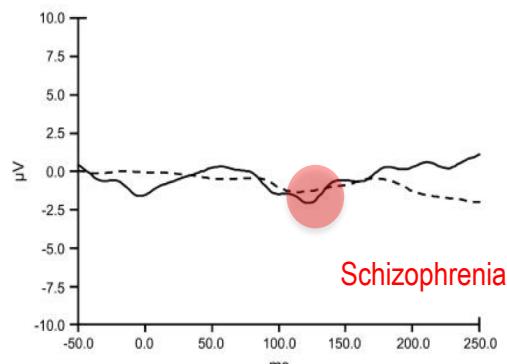
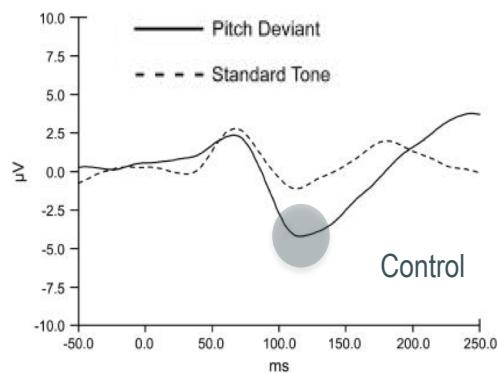
- Many traits in Scz can be modelled as a loss of precision of prior beliefs relative to sensory evidence (likelihood)

Computational psychiatry: beyond diagnosis

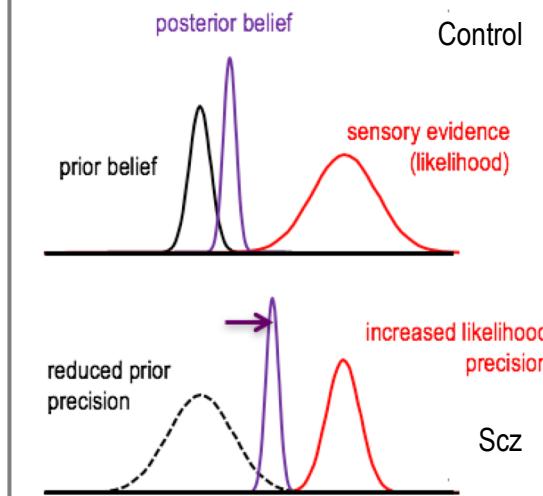
Action: impaired prediction in smooth pursuit



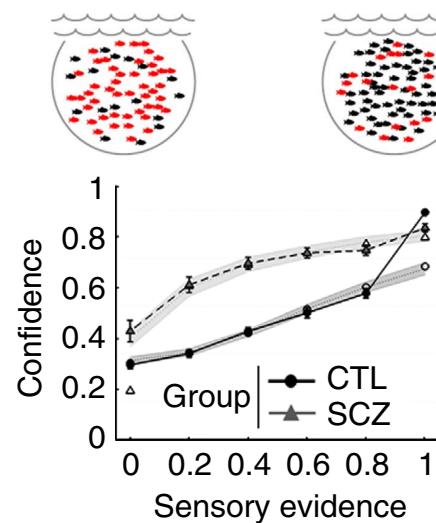
Electrophysiology: loss of mismatch negativity



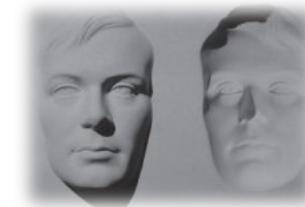
Prior precision in schizophrenia



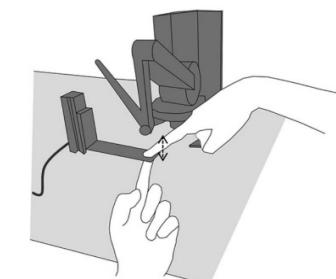
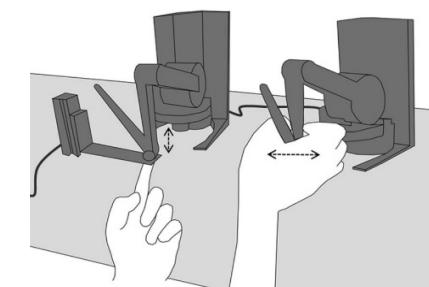
Belief updating: overweighting of sensory evidence



Perception: resistance to visual illusions



Perception: loss of sensory attenuation

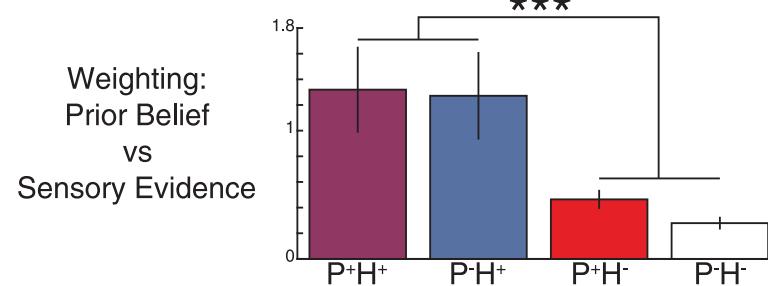
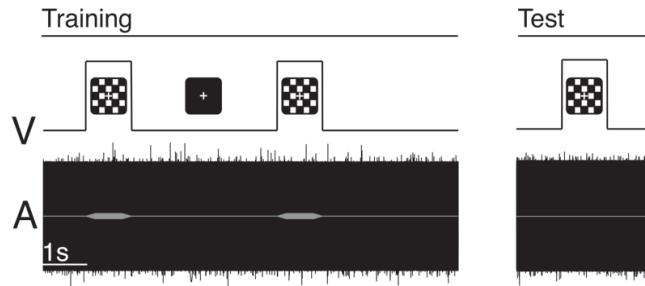


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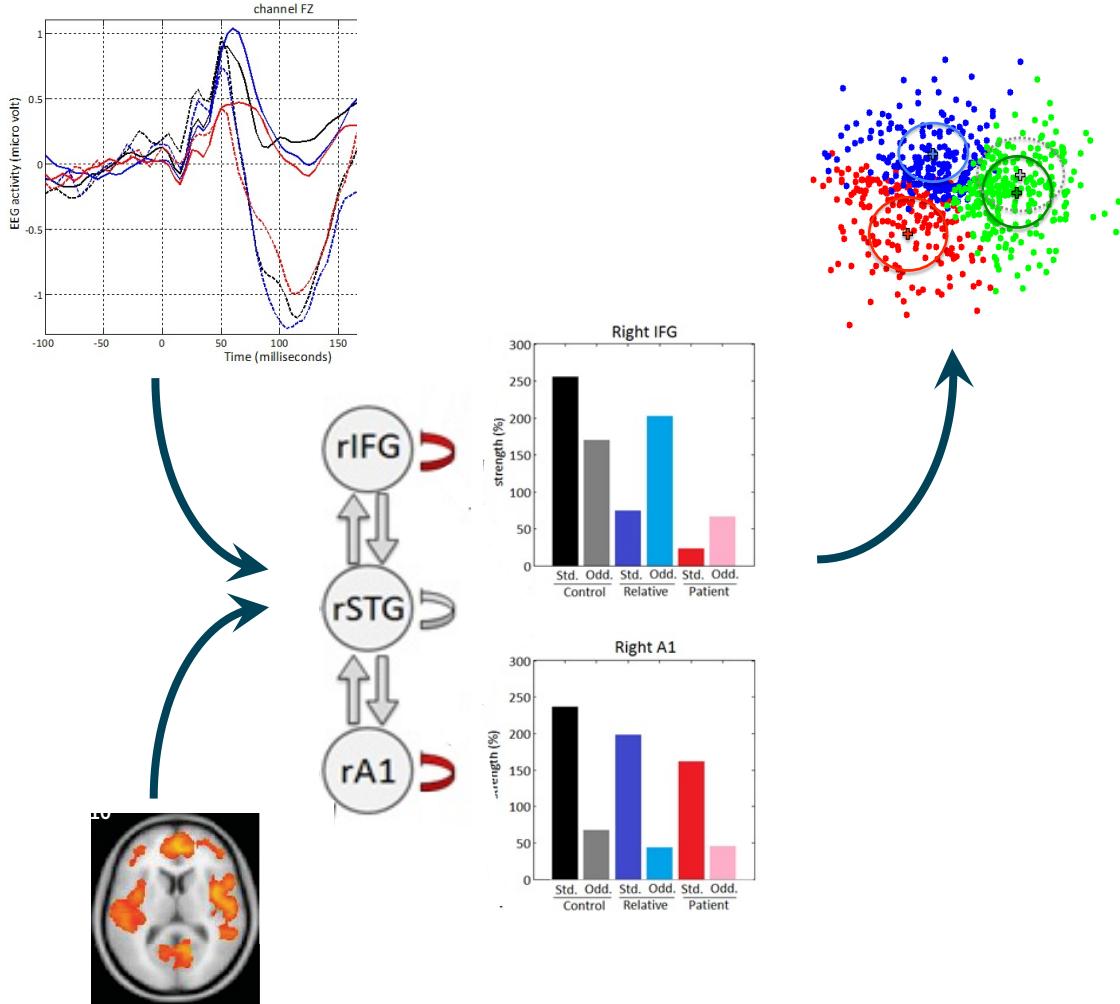
- Many traits in Scz can be modelled as a loss of precision of prior beliefs relative to sensory evidence (likelihood)
- Conversely, delusions & hallucinations are likely prior beliefs with too much precision (but some visual priors also seem to share this property)



Computational psychiatry: beyond diagnosis

To find new phenotypes we need BIG samples and computational methods:

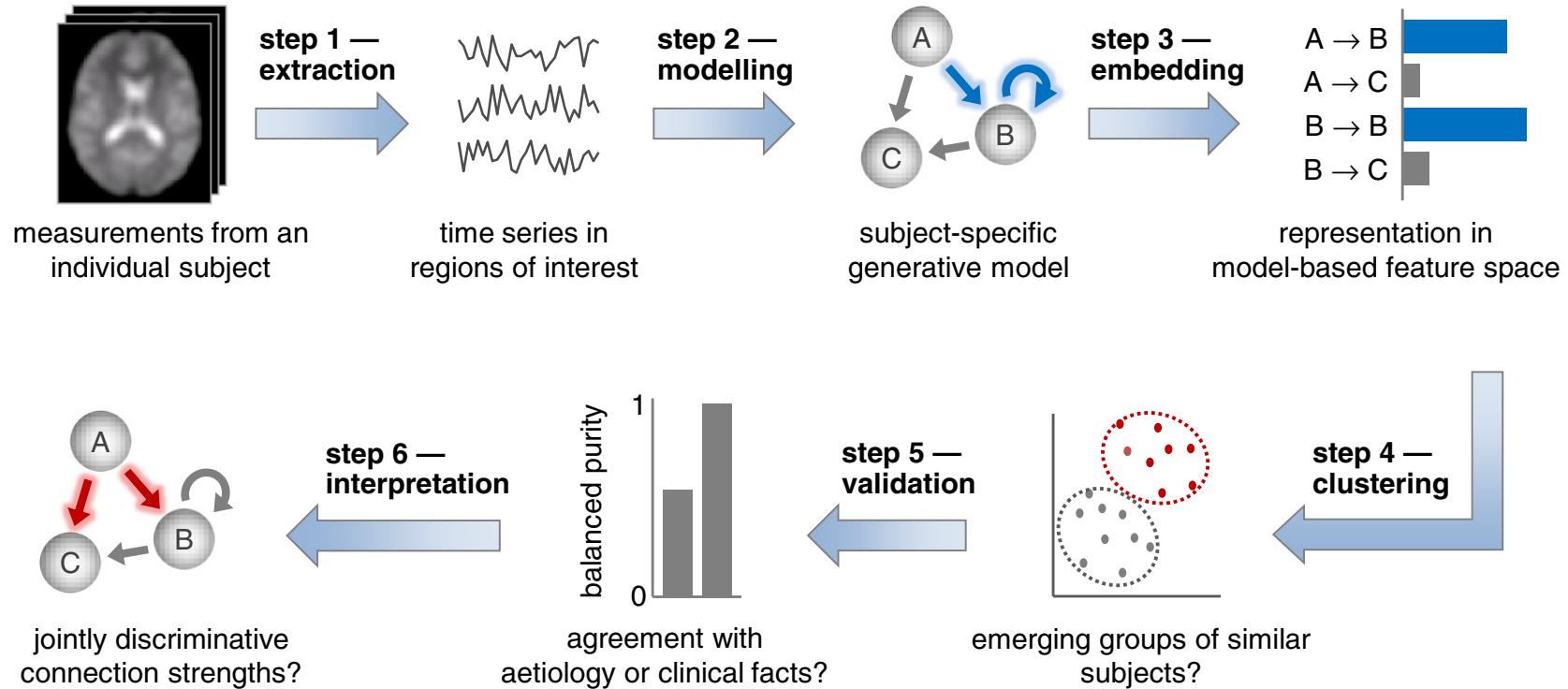
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Computational psychiatry: beyond diagnosis

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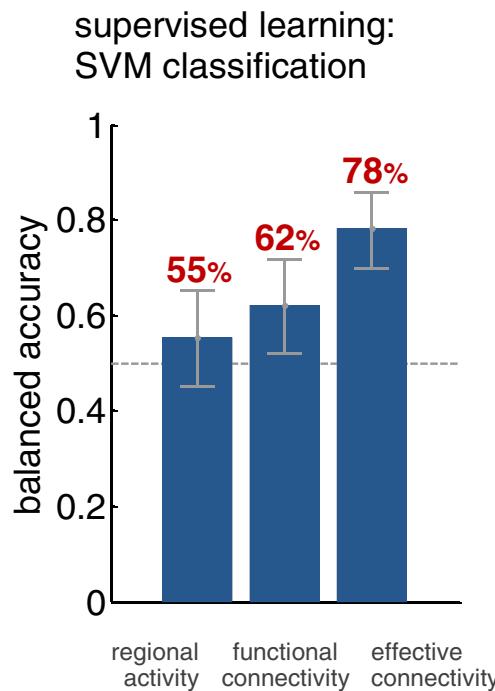
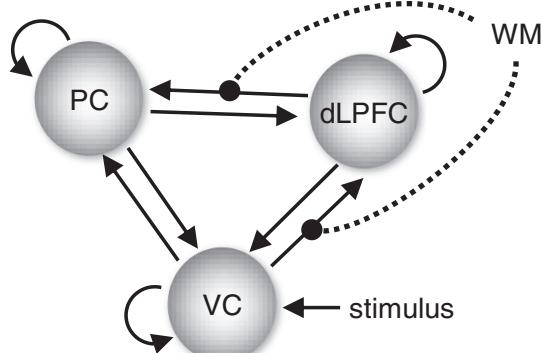


Computational psychiatry: beyond diagnosis

To find new phenotypes we need BIG samples and computational methods:

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NB effective (model-based) connectivity discriminates Scz & controls better than ROI activations or functional (correlational) connectivity

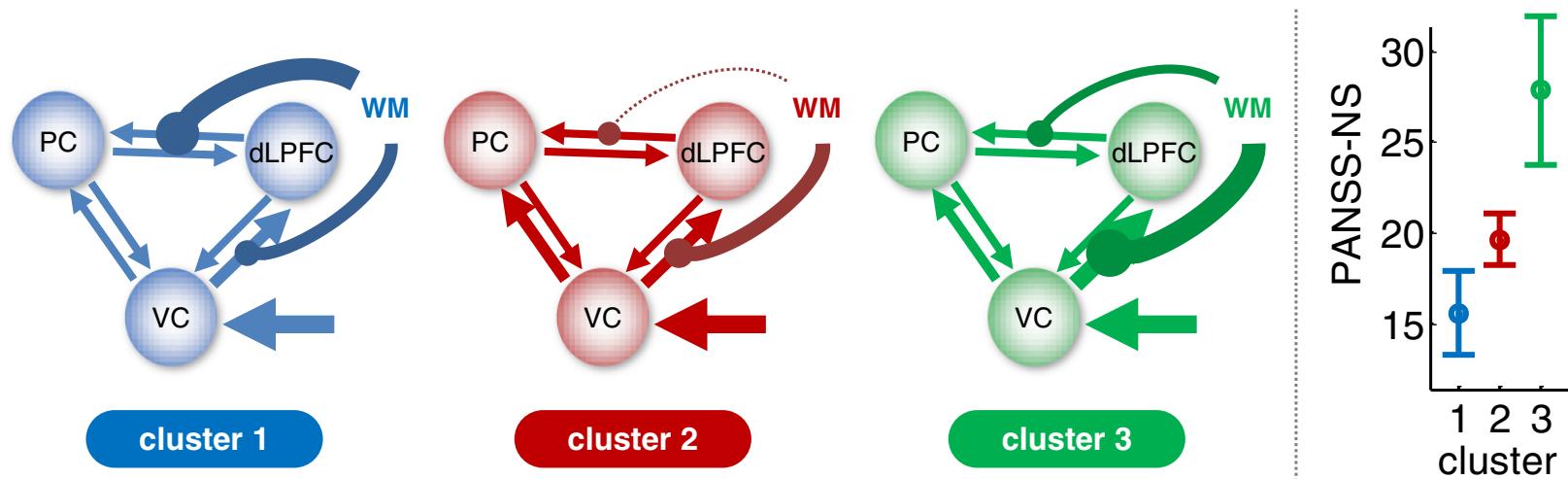


Computational psychiatry: beyond diagnosis

To find new phenotypes we need BIG samples and computational methods:

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New phenotypes/neurobiological axes of variation make drug trials & mechanistic research much more likely to be successful

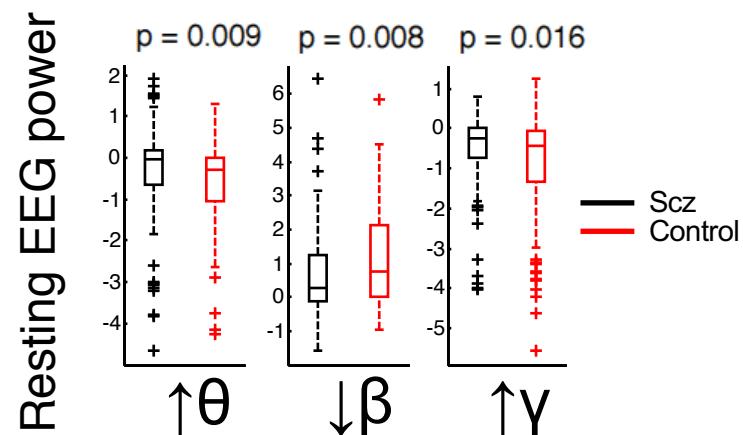
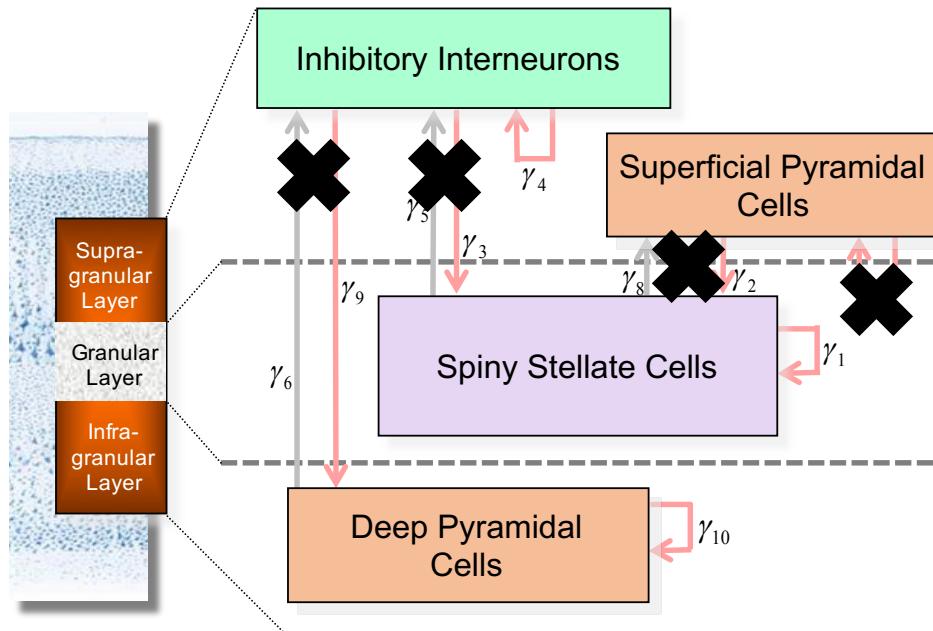


Computational psychiatry: beyond diagnosis

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Cortical microcircuit used for modelling EEG

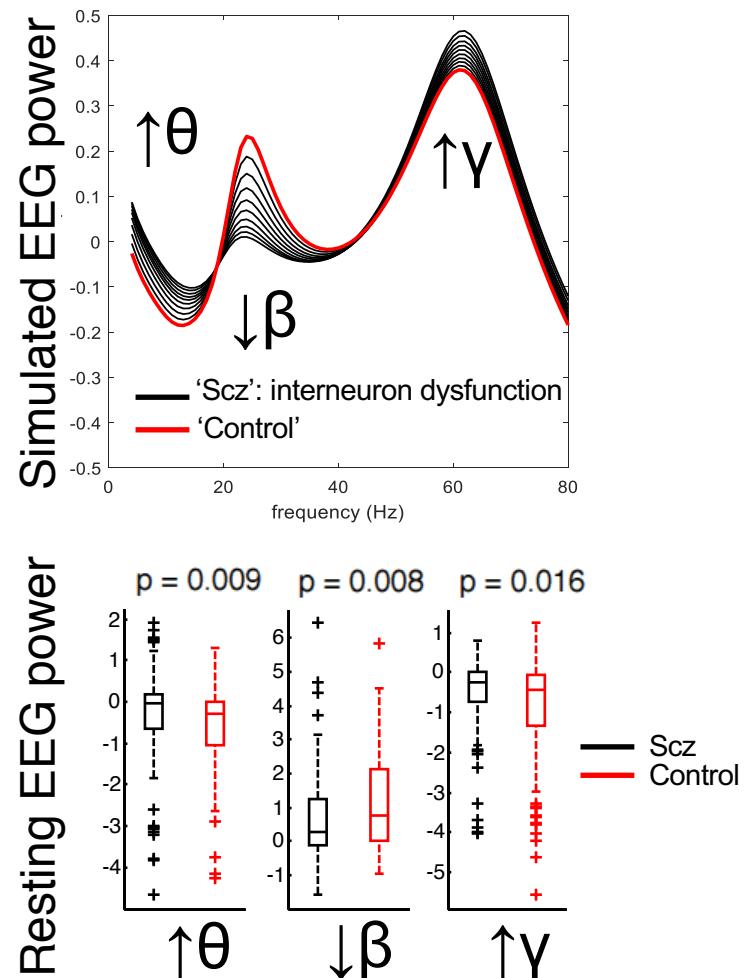
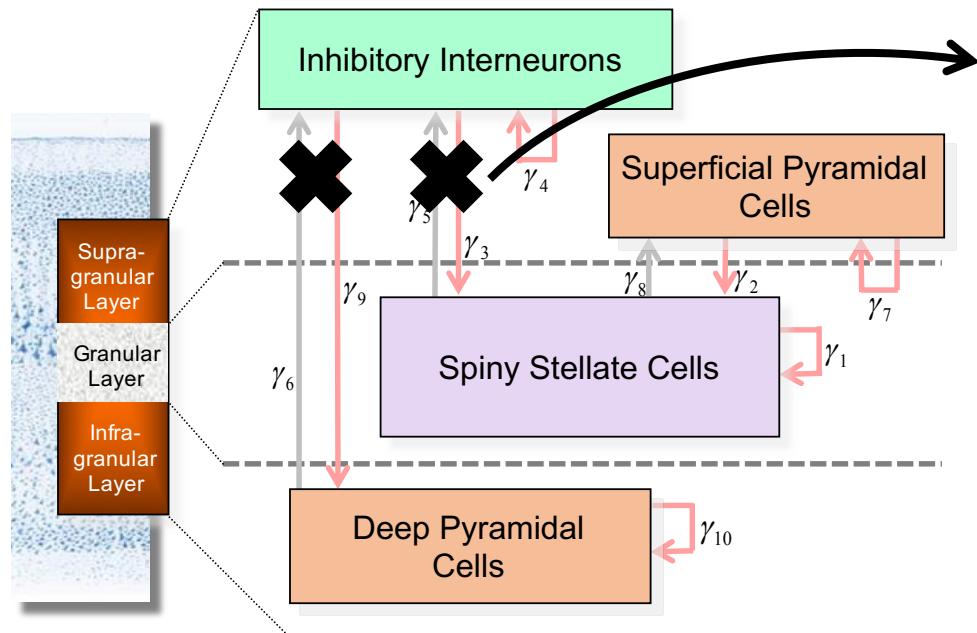


Computational psychiatry: beyond diagnosis

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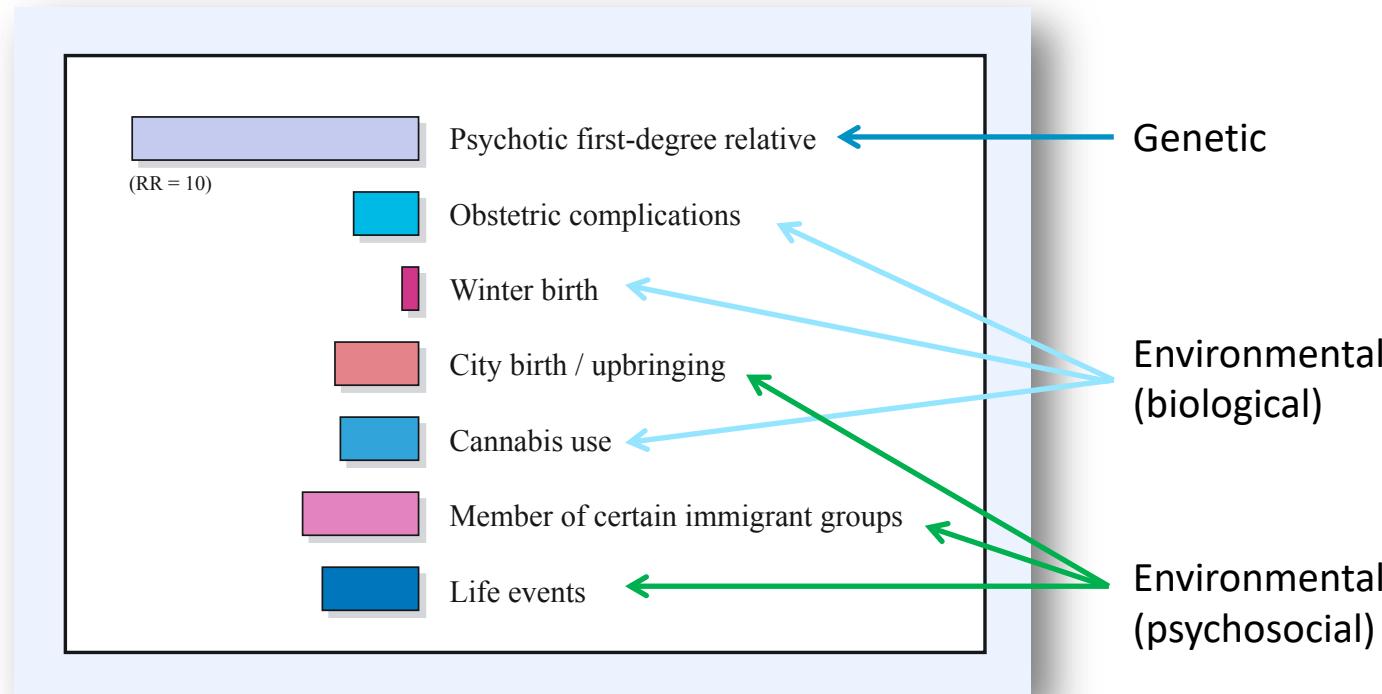
There are numerous problems still to be solved

- 1) Need to model social/environmental effects (RDoC neglects them)

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Schizophrenia risk factors and effect sizes



There are numerous problems still to be solved

- 1) Need to model social/environmental effects (RDoC neglects them)
- 2) Finding group parameter differences is easy.
Finding parameters that make predictions about individuals is MUCH harder
- 3) Parameter test-retest reliability is a key issue – this is hardly ever checked
- 4) Often behaviour/parameter changes in one disorder appear in other disorders
- 5) Parameter differences may be very small – psychiatric disorders may be e.g.s of slightly different initial conditions -> -> -> -> big effects.
Need longitudinal data!
- 6) The brain has evolved to minimise the possibility of cognitive biomarkers

- Psychosis spectrum disorders: symptoms and diagnosis
- Drug treatments: D₂R antagonists and Clozapine; other potential targets
- Neurobiology: the case of glutamate (variation over subgroups/time?)

What can Computational Psychiatry do for treatment, diagnosis, and mechanistic research?

- Most machine learning approaches to (categorical) diagnosis to date have major flaws
- ML should try to delineate the major axes of variation in behaviour / brain / both – preferably using model-based feature selection