



Schizophrenia

Stefan Kaiser

A case - I

- ▶ Paul, 22 year old student
- ▶ Withdrawn for about a year, less energy, rarely at lectures
- ▶ Starting a few months ago he thinks he is being persecuted by a secret cult. First in public places, but now thinks that cameras have been installed in his flat.
- ▶ Hears voices that tell him he will die.
- ▶ His roommates accompany him to psychiatric emergencies.

Schizophrenia – the core symptoms

Positive symptoms

Delusions
Hallucinations

Negative symptoms

Flat affect
Poverty of speech
Apathy
Social withdrawal
Anhedonia

Cognitive symptoms

Generalized:
e.g.
Attention
Memory
Planning



positive symptoms



negative
symptoms



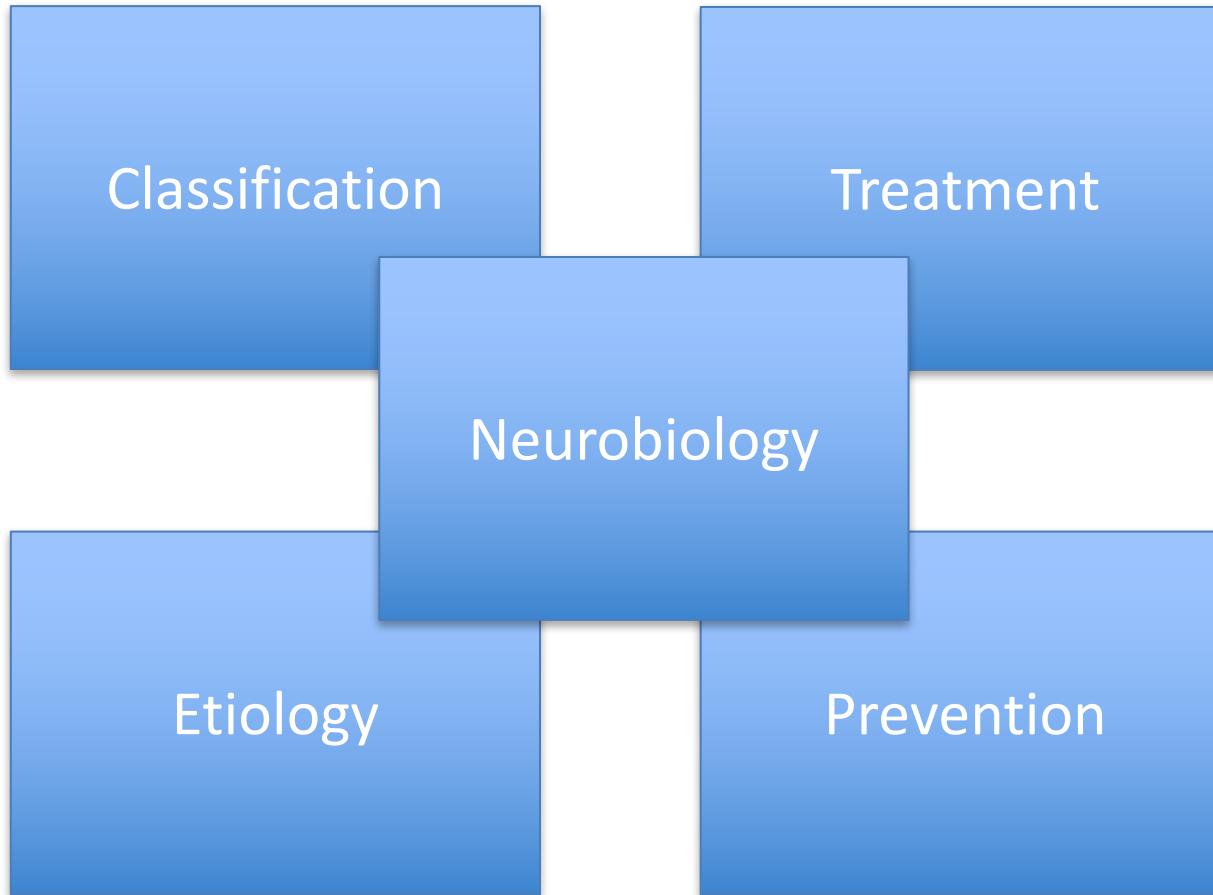
cognitive
symptoms

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Schizophrenia – some basic facts

- ▶ Lifetime prevalence 0.7-1%
- ▶ Onset most often in adolescence or early adulthood
- ▶ High risk of chronic or relapsing course
- ▶ Often associated with (long-term) impairment in everyday life (less than 1/3 work)
- ▶ Patients with schizophrenia die 15 years earlier (suicide, cardiovascular disease) than persons without schizophrenia

Questions



Questions

Classification

Schizophrenia – the core symptoms

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Hallucinations

Negative symptoms

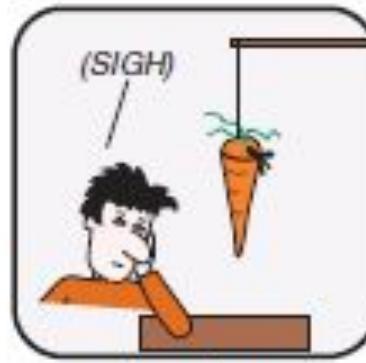
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Affective symptoms

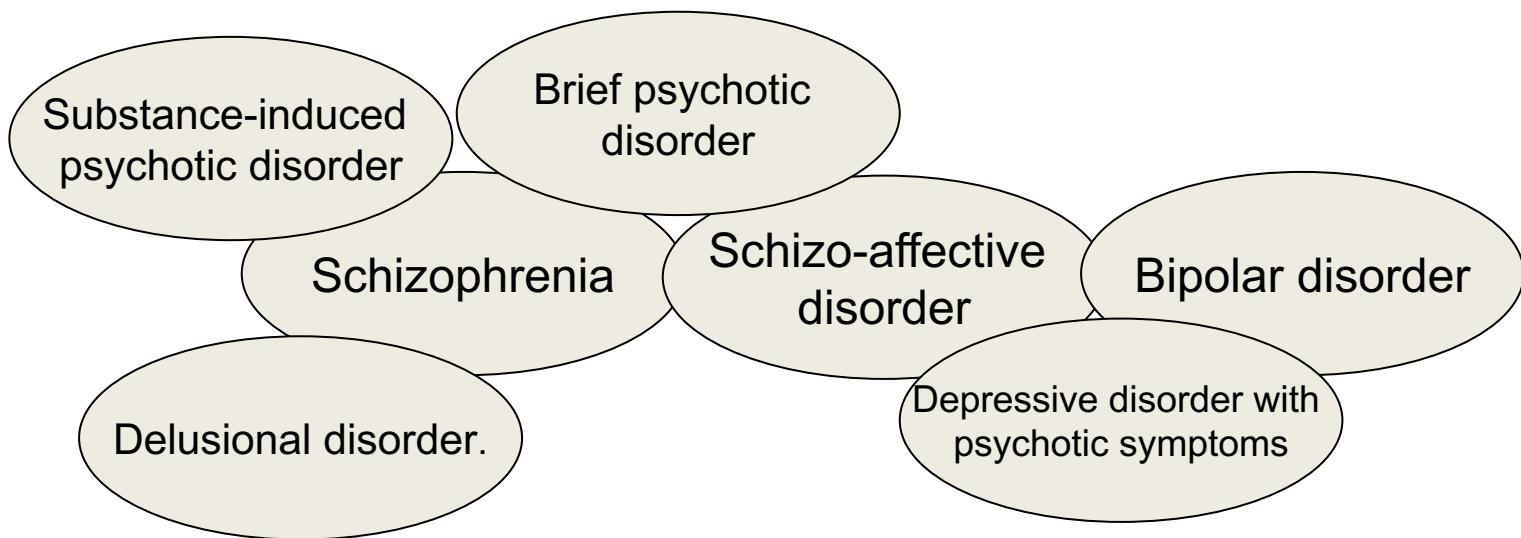
Catatonia

Disorganization

DSM 5 criteria

- A. Two of the following symptoms for 1 month
 - 1. Delusions
 - 2. Hallucinations
 - 3. Disorganized speech
 - 4. Grossly disorganized or catatonic behavior
 - 5. Negative symptoms
- B. Social / occupational dysfunction
- C. Duration of 6 months
- D. Schizoaffective and mood disorder exclusion
- E. Substance / general medical condition exclusion

Overlap with other disorders



Problems with classification

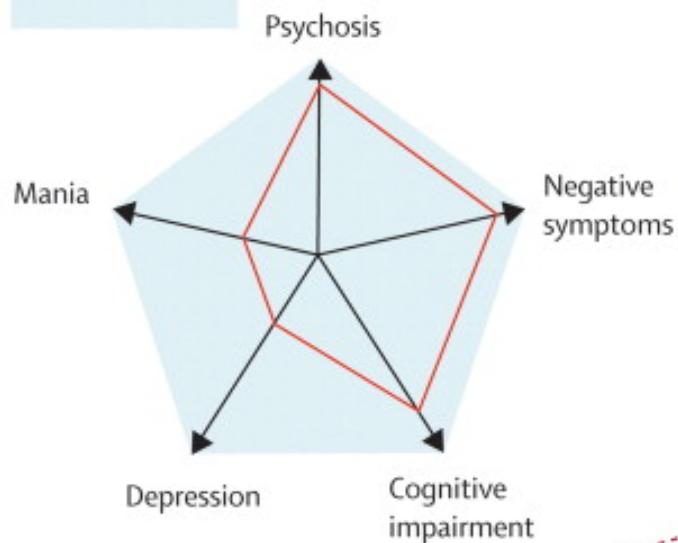
- ▶ Overlap between disorders
- ▶ Comorbidity
- ▶ No foundation in pathophysiology and etiology

Categories vs dimensions – a core question

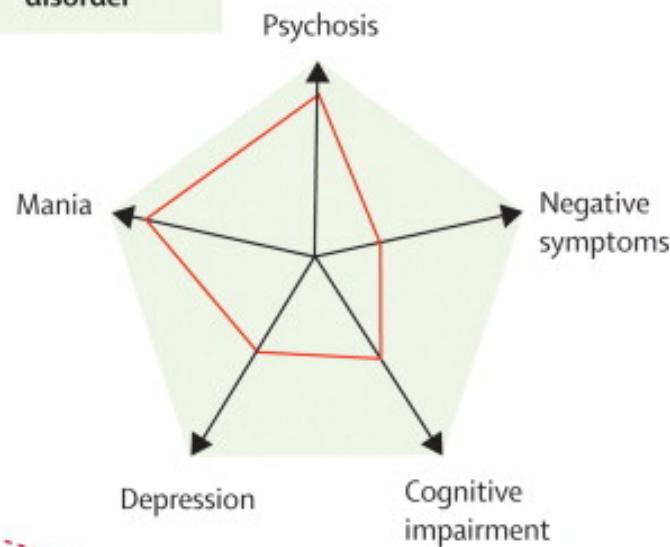
- ▶ “Funding for diagnostic research is very limited – mental health research thus continues to examine the distribution, determinants and treatments for constructs that do not exist.” (van Os, 2009)
- ▶ Diagnostic system determines research on pathophysiology, etiology and treatment

A dimensional approach

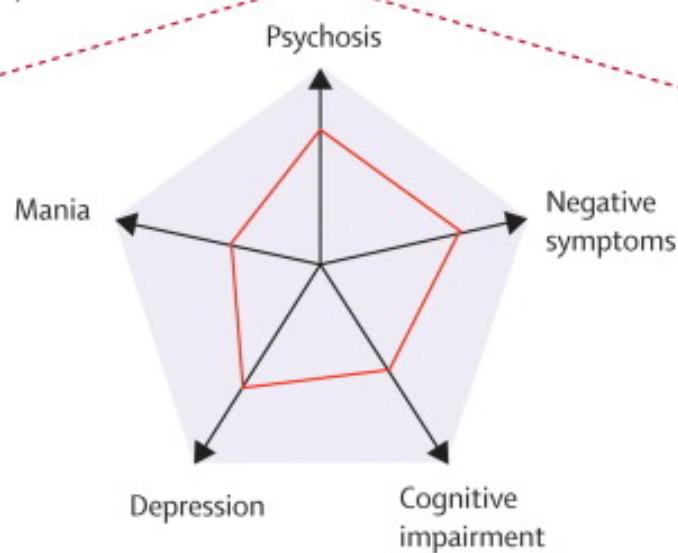
Schizophrenia



Bipolar disorder



Schizoaffective disorder



(van Os & Kapur,
2009, Lancet)

... but dimensional symptoms cluster!

Positive symptoms

Delusions
Hallucinations

Negative symptoms

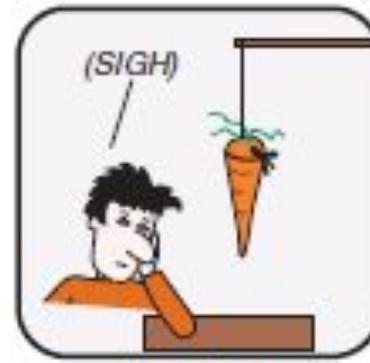
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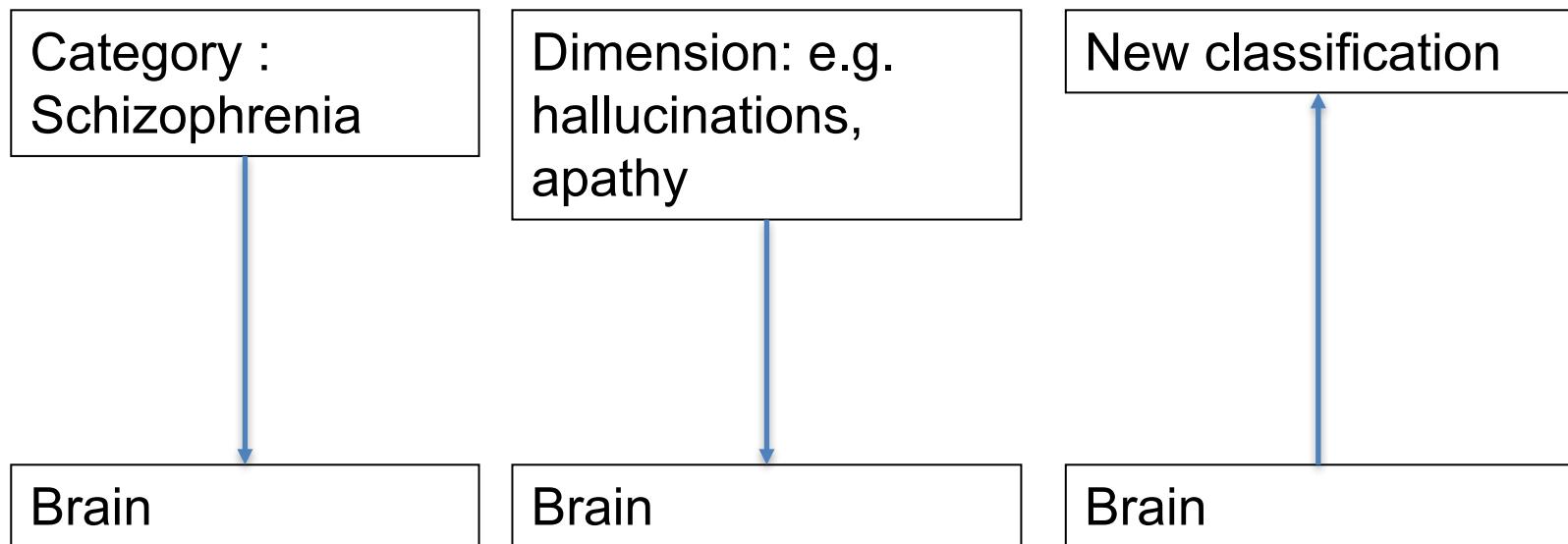


negative
symptoms

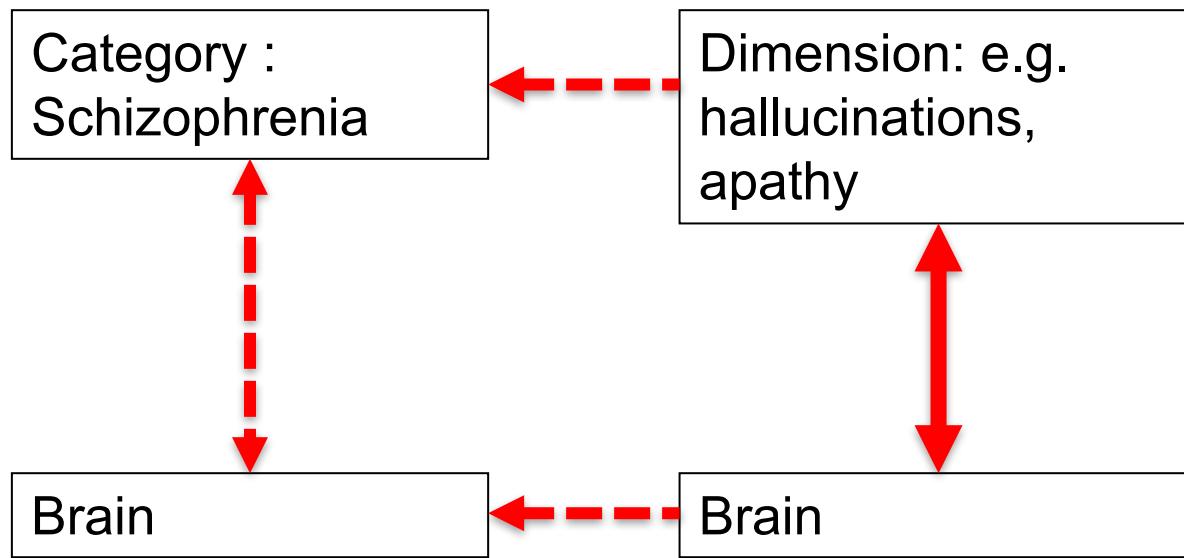


cognitive
symptoms

Neurobiology and classification of schizophrenia



Symptoms first, categories later?



Questions

Classification

Treatment

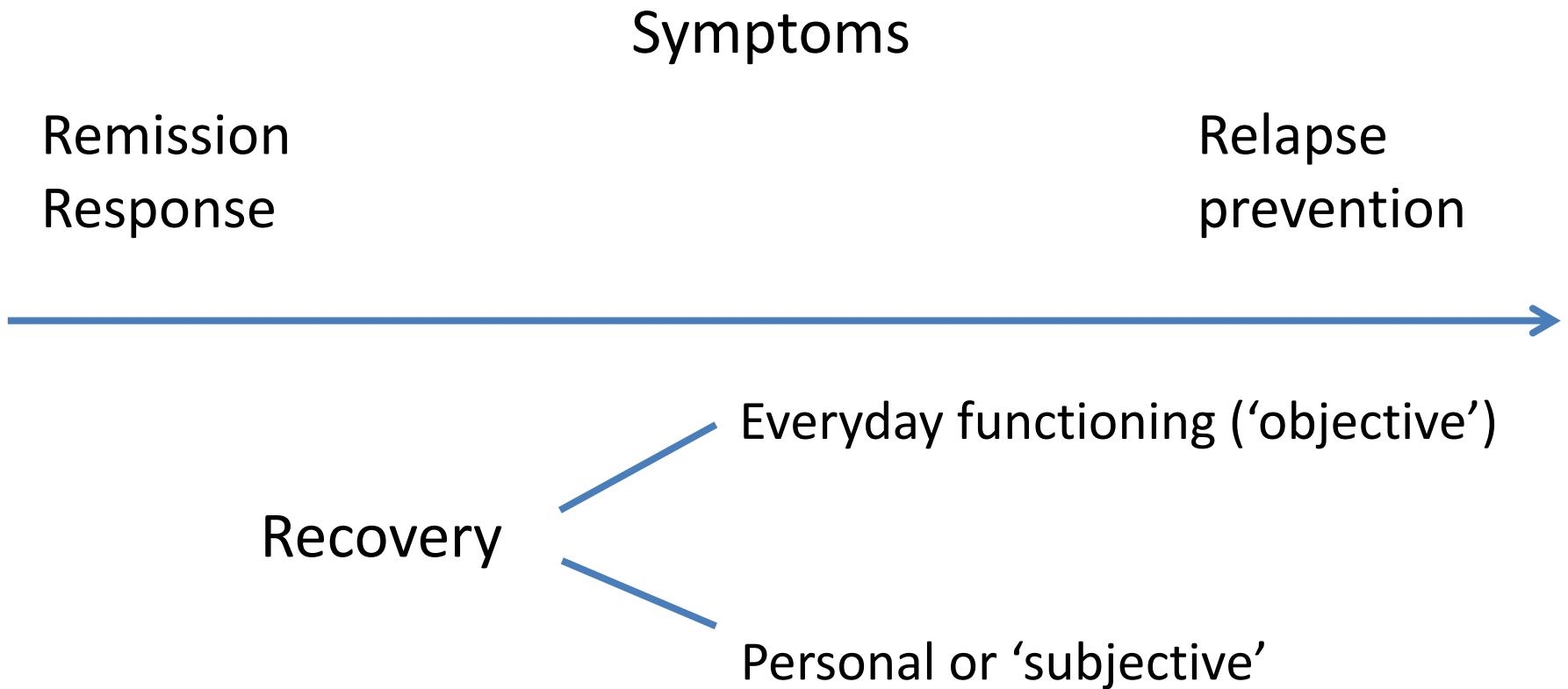
A case - I

- ▶ Paul, 22 year old student
- ▶ Withdrawn for about a year, less drive, rarely at lectures
- ▶ Starting a few months ago he thinks he is being persecuted by a secret cult. First in public places, but now cameras have been installed in his flat.
- ▶ Hears voices that tell him that he will die.
- ▶ His roommates accompany him to psychiatry emergencies.
- ▶ Very anxious and agitated, but cooperative.

A case - II

- ▶ Paul receives an initial anxiolytic treatment.
- ▶ Diagnosis of first-episode schizophrenia is confirmed
- ▶ Paul's initial treatment goals:
 - to be left in peace
 - to understand what is happening
 - to get my life back
- ▶ Treatment plan?

Treatment objectives



Treatment modalities

Treatment objectives

Pharmacological

Psychotherapeutic

Social

Examples for « psychotherapeutic » approaches

Acute

Long-term



Psychoeducation and illness management

Family interventions

Cognitive behavior therapy

Questions

Classification

Treatment

Neurobiology

Schizophrenia – symptom treatment

Positive symptoms

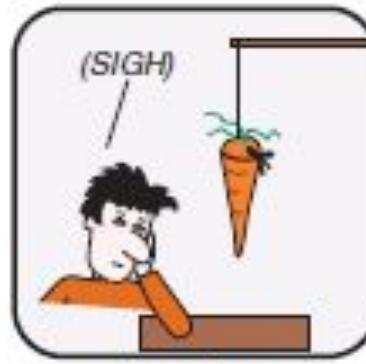
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Antipsychotics are Dopamine D2 receptor blockers

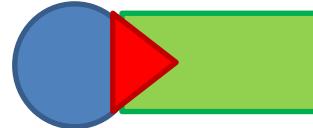


positive symptoms

Dopamine



D2 receptor



D2 antagonist

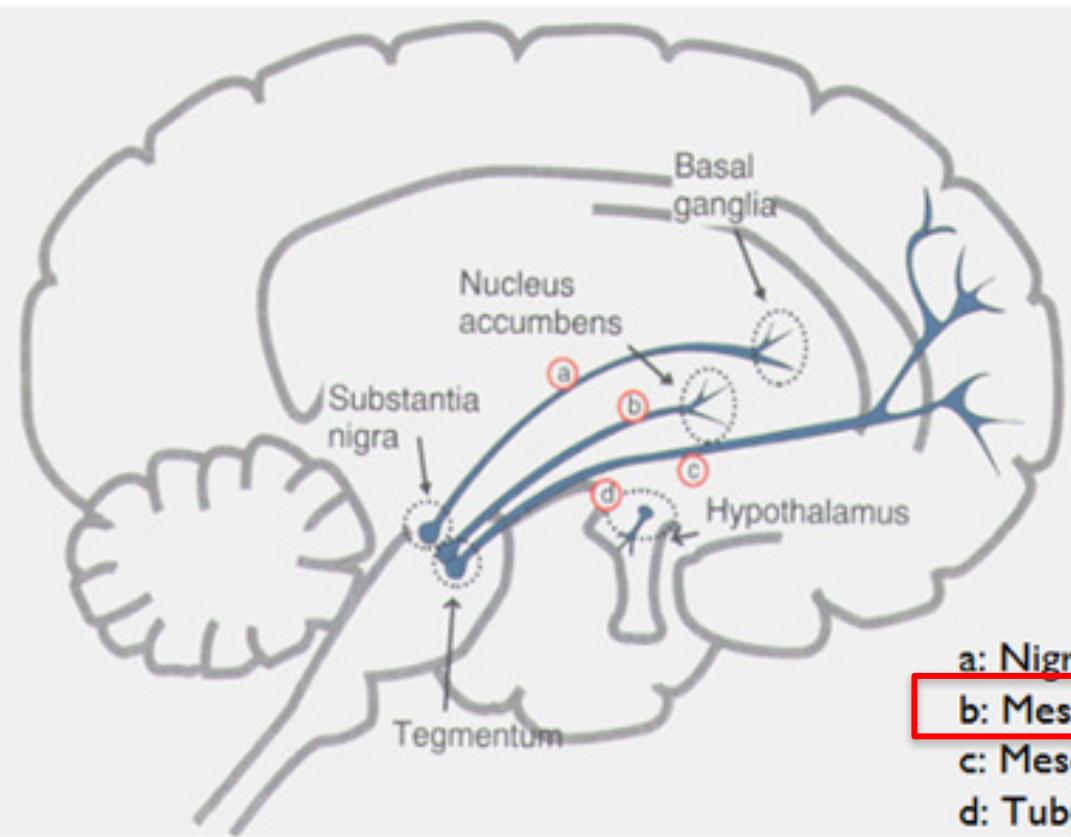


reduced
positive symptoms

(Stahl, 2013, Essential
Psychopharmacology)

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Dopamine pathways



a: Nigro-striatal pathway

b: Meso-limbic pathway

c: Meso-cortical pathway

d: Tubulo-infundibular pathway

Motor

Salience/reward

Cognition

Sexual

Salience signals in the meso-limbic pathway

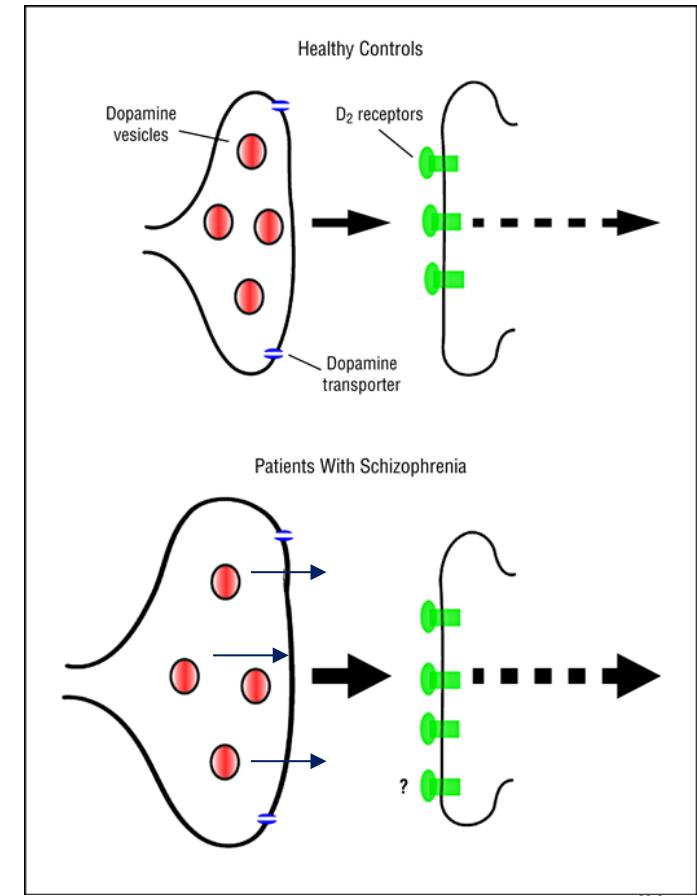
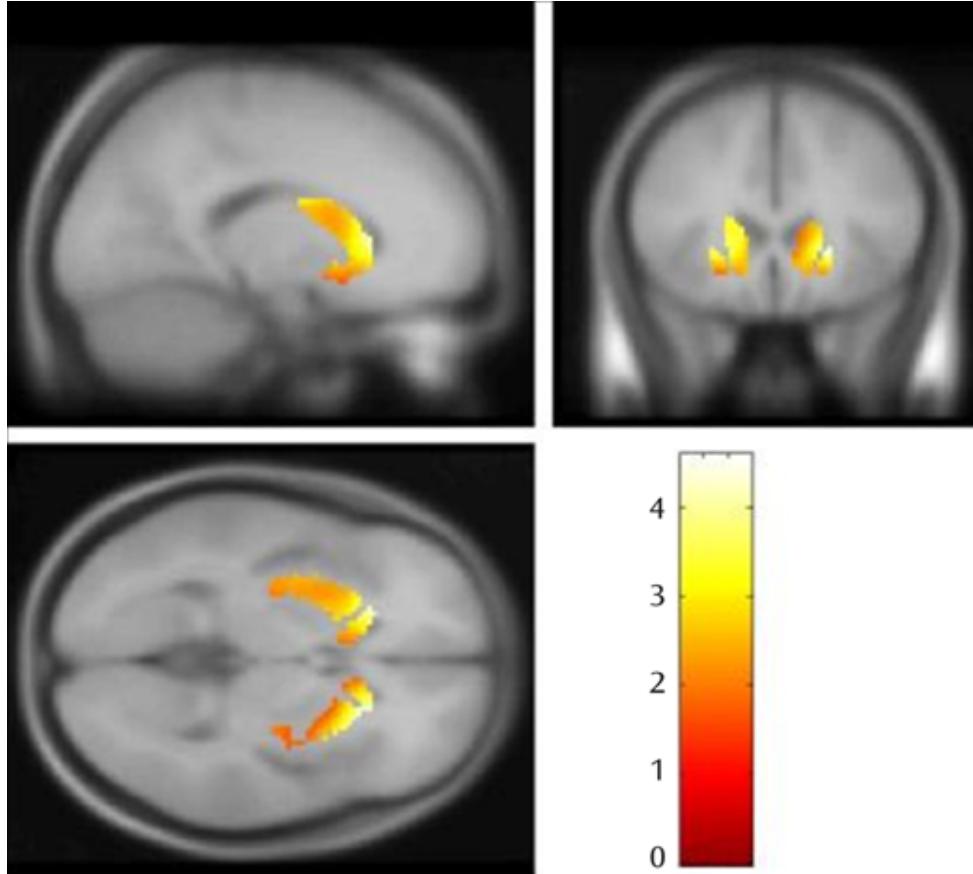


TRENDS in Neurosciences

(Winton-Brown et al., 2014, TINS)

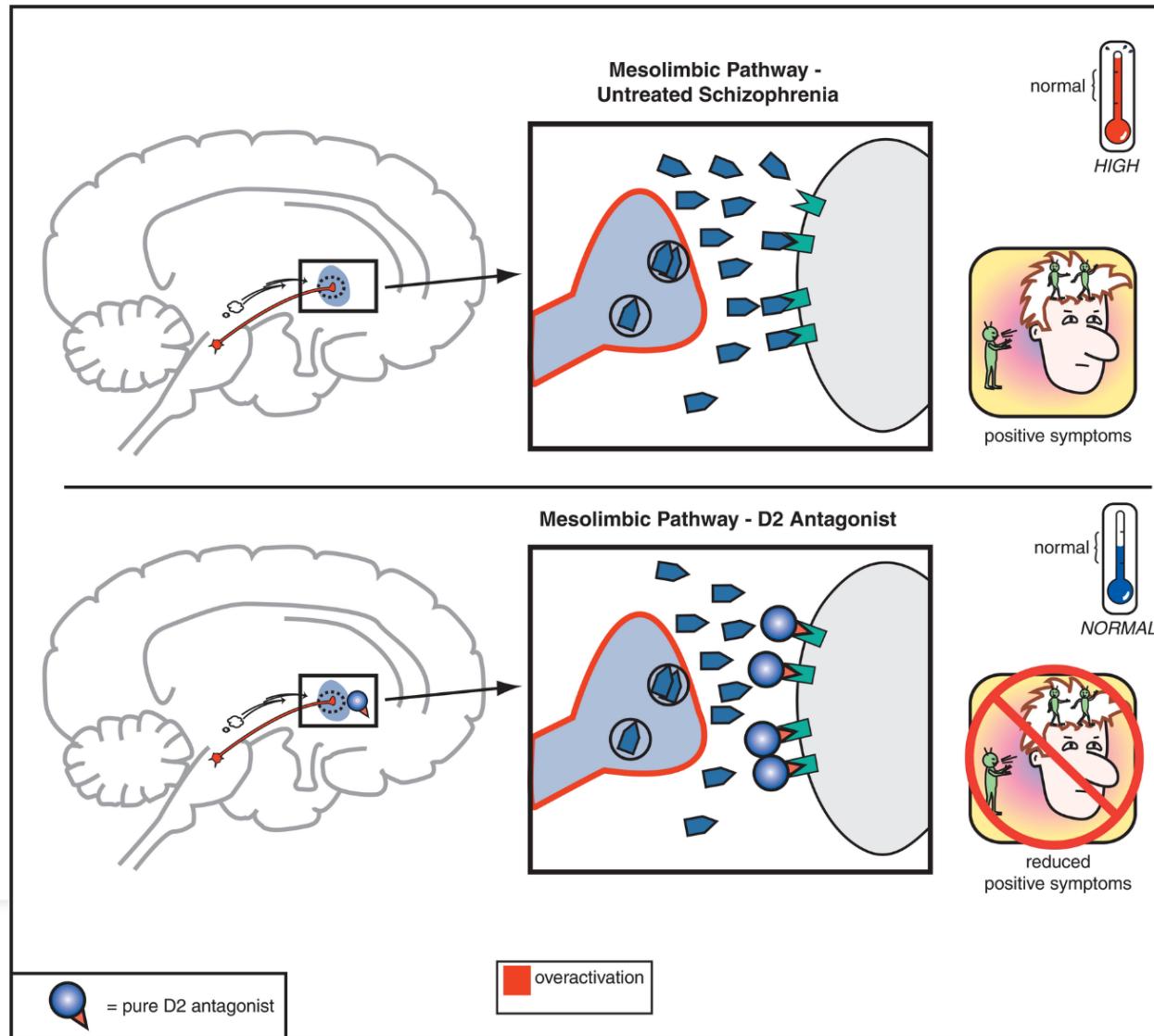
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Increased dopamine release in the striatum



(Howes et al., 2012, 2013, Arch Gen Psychiatry)

Dopamine D2 receptor blockers reduce positive symptoms



(Stahl, 2013, Essential Psychopharmacology)

Does antipsychotic treatment work?

- ▶ Antipsychotics are quite effective for treating positive symptoms in most patients with schizophrenia
- ▶ >50% respond to first treatment, 90% respond when using the full treatment algorithm

But:

- ▶ Prediction of individual response / remission is not possible
- ▶ Up to 10% are fully resistant to antipsychotic treatment

A case - III

- ▶ Paul's treatment:
- ▶ Treatment with risperidone 2mg/d is started
- ▶ Psychoeducation, work with family is started
- ▶ After 4 weeks positive symptoms have completely resolved
- ▶ But: Paul has gained 5 kg and has noted some difficulties in sexual functioning

Antipsychotic side effects

- Sexual dysfunction
- Reduced subjective well-being



Best choice



Worst choice

<u>SEDATION</u>	<u>WEIGHT GAIN</u>	<u>EPS</u>
Aripiprazole	Aripiprazole	Clozapine
Iloperidone	Lurasidone	Iloperidone
Lurasidone	Ziprasidone	Quetiapine
Paliperidone	Asenapine	Aripiprazole
Risperidone	Iloperidone	Asenapine
Ziprasidone	Paliperidone	Lurasidone
Asenapine	Risperidone	Olanzapine
Olanzapine	Quetiapine	Ziprasidone
Clozapine	Clozapine	Paliperidone
Quetiapine	Olanzapine	Risperidone

EPS =
extrapyramidal
(motor) side-effects

Positive symptoms – many open questions

- ▶ Which antipsychotic will have the best efficacy and the least side effects for the individual patient?
- ▶ Which is the most effective combination of pharmacological and psychosocial treatment approaches?
- ▶ Do the same principles for the treatment of positive symptoms apply across disorders? (-> classification)

Questions

Classification

Treatment

Neurobiology

Negative symptoms

Positive symptoms

Delusions
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positive symptoms

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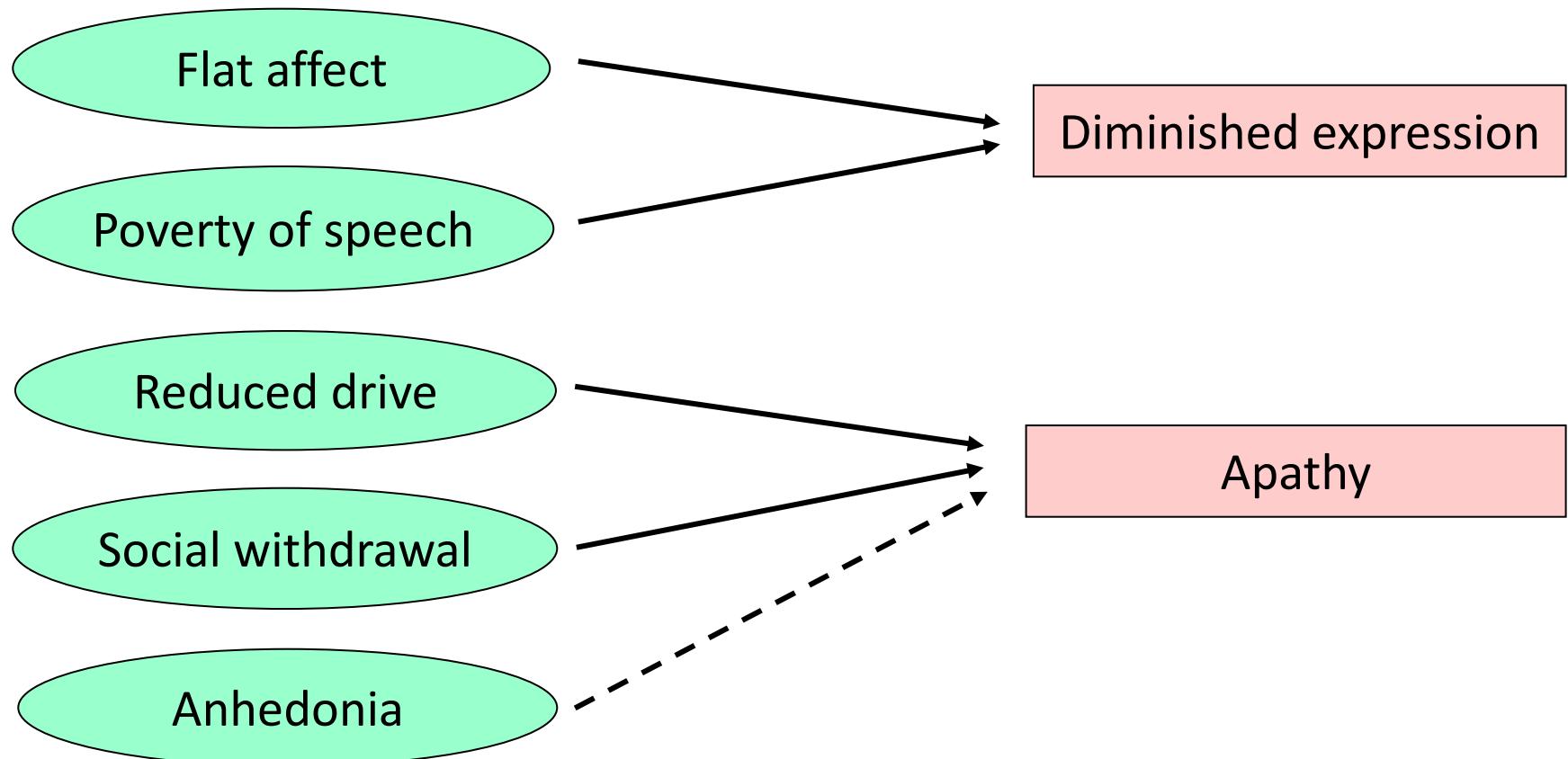


cognitive
symptoms

A case - IV

- ▶ Paul: 6 months after the start of treatment
- ▶ Outpatient treatment, 20 mg/d Aripiprazol
- ▶ No positive symptoms, no side effects
- ▶ Paul wants to return to study, but has difficulties motivating himself
- ▶ Also less motivation to meet friends and family
- ▶ Some troubles in concentration
- ▶ Treatment plan?

Negative symptoms – two dimensions



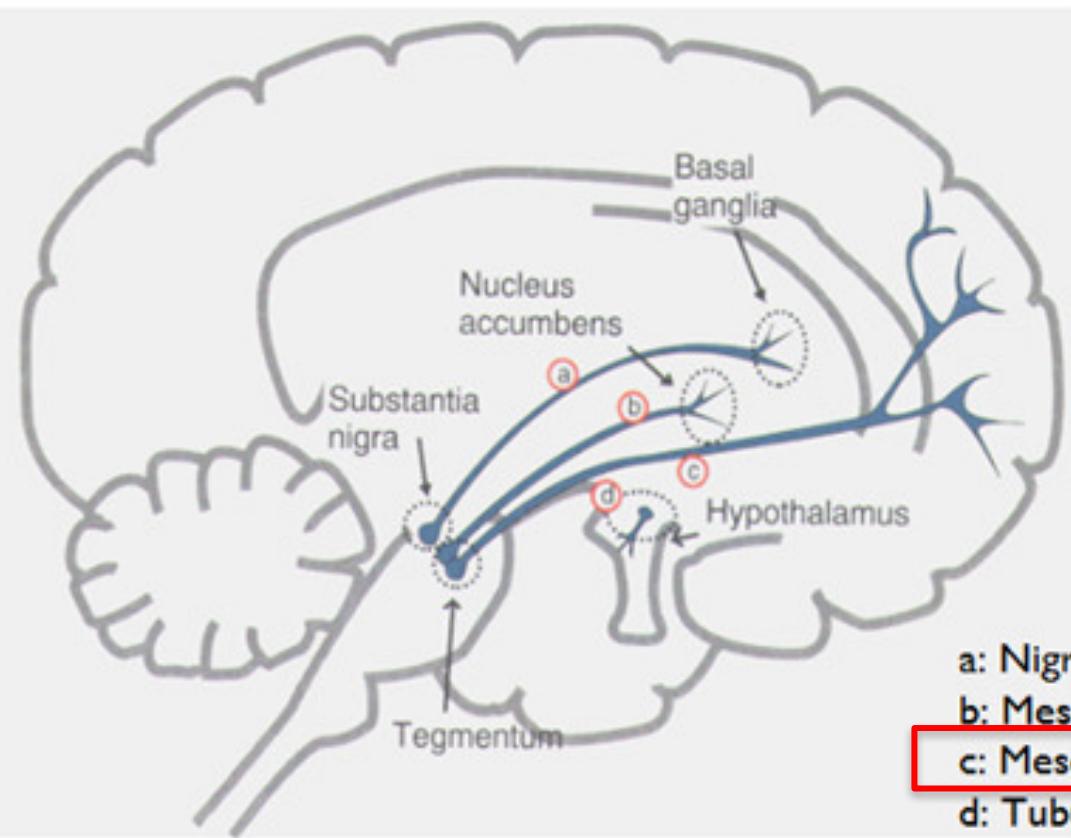
Treatment of negative symptoms

- ▶ Negative symptoms are highly predictive of functional outcome (e.g. work)

But:

- ▶ Antipsychotics are not effective in treating persistent negative symptoms
- ▶ Antidepressants help in cases of comorbid depression
- ▶ Certain psychosocial approaches (cognitive behavior therapy, social skills training) are promising but with limited effect size

Dopamine pathways



a: Nigro-striatal pathway

b: Meso-limbic pathway

c: Meso-cortical pathway

d: Tubulo-infundibular pathway

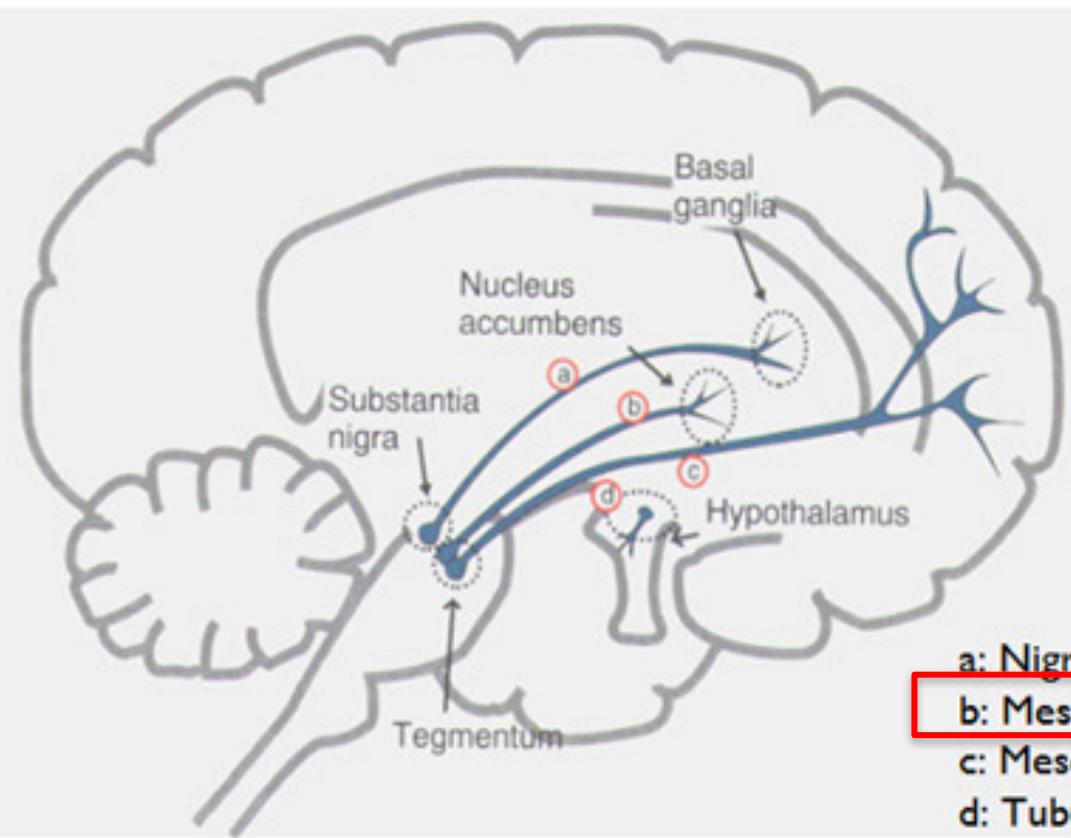
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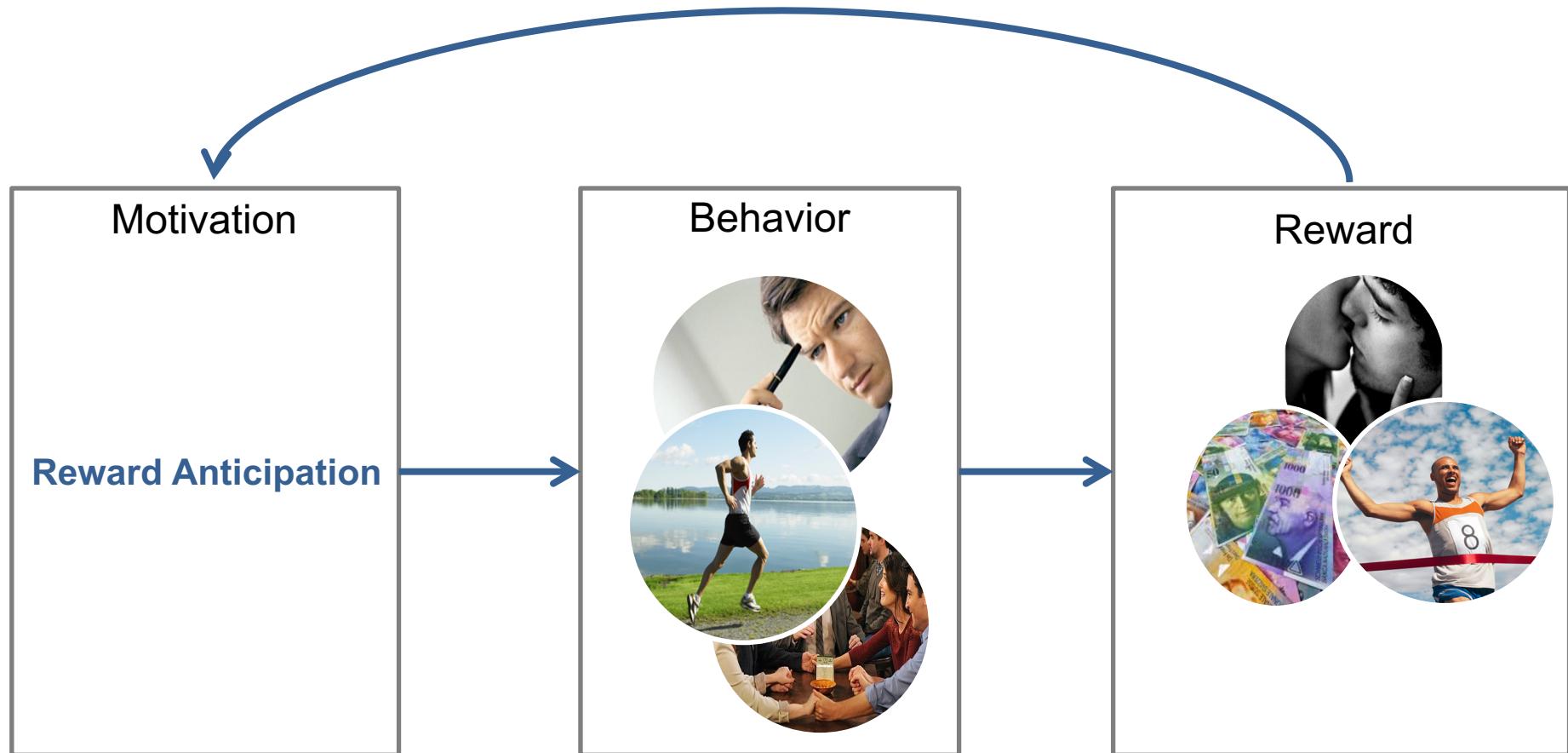
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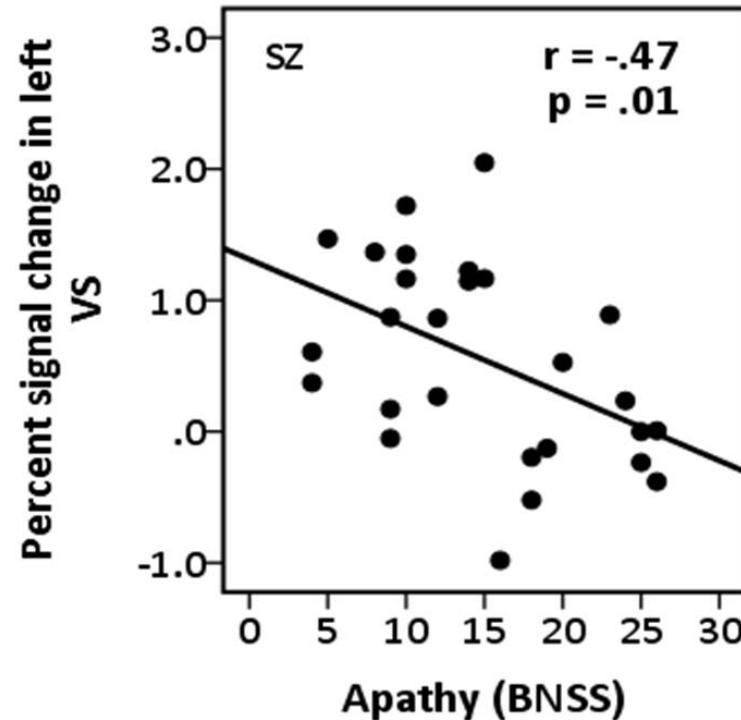
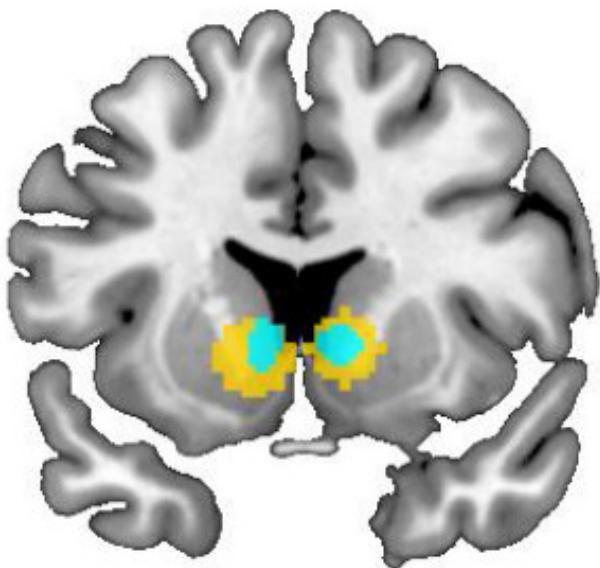
Reward anticipation



Apathy is associated with reduced ventral striatal activation during reward anticipation

Schizophrenia

C



(Kirschner et al., 2016, J Psych Neurosci)

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So what's the problem with dopamine in the striatum?

- ▶ Positive symptoms are associated increased dopamine release in the striatum
- ▶ Dopamine blockers treat positive symptoms
- ▶ Negative symptoms are associated with decreased striatal signal during reward anticipation
- ▶ Apathy can be observed in dopamine depleted states
- ▶ Both symptoms occur in the same patients

A computational approach

Review

Biological
Psychiatry

An Integrative Perspective on the Role of Dopamine in Schizophrenia

Tiago V. Maia and Michael J. Frank

<http://dx.doi.org/10.1016/j.biopsych.2016.05.021>

- ▶ Increased spontaneous phasic dopamine
 - > aberrant salience -> positive symptoms
- ▶ Reduced adaptive phasic dopamine
 - > impaired reward anticipation / learning
 - > negative symptoms

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A case - V

- ▶ Treatment of Paul's negative symptoms
- ▶ Change in antipsychotic treatment unlikely to have an effect
- ▶ “Trial” with antidepressant?
- ▶ Cognitive behavior therapy targeting increase in activities and dysfunctional thoughts
- ▶ Evaluate cognitive dysfunction, consider cognitive training
- ▶ Collaboration with counselling service at university to adapt Paul's study plan

Which treatment?

Positive symptoms

Delusions
Hallucinations



positive symptoms

Negative symptoms

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negative
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cognitive
symptoms

Questions

- ▶ What are the treatment targets for negative and cognitive symptoms?
- ▶ How to integrate pharmacologic, psychotherapeutic and social treatments?

Questions

