



Computational Psychiatry Course 2018

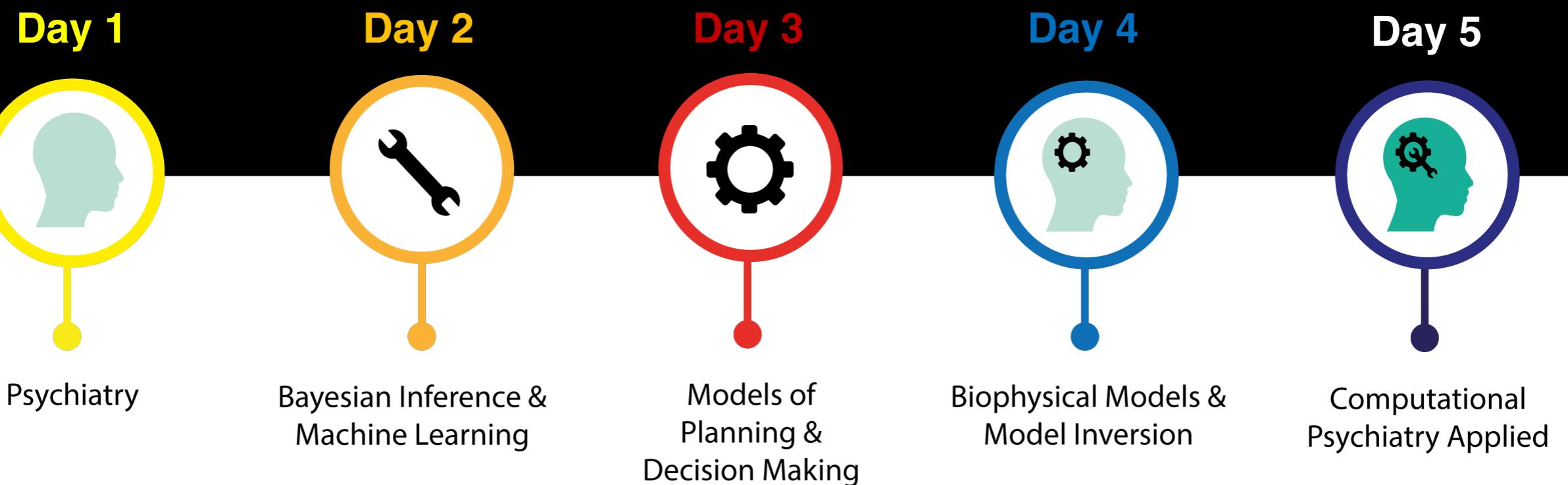
Affective disorders

Dominik R Bach

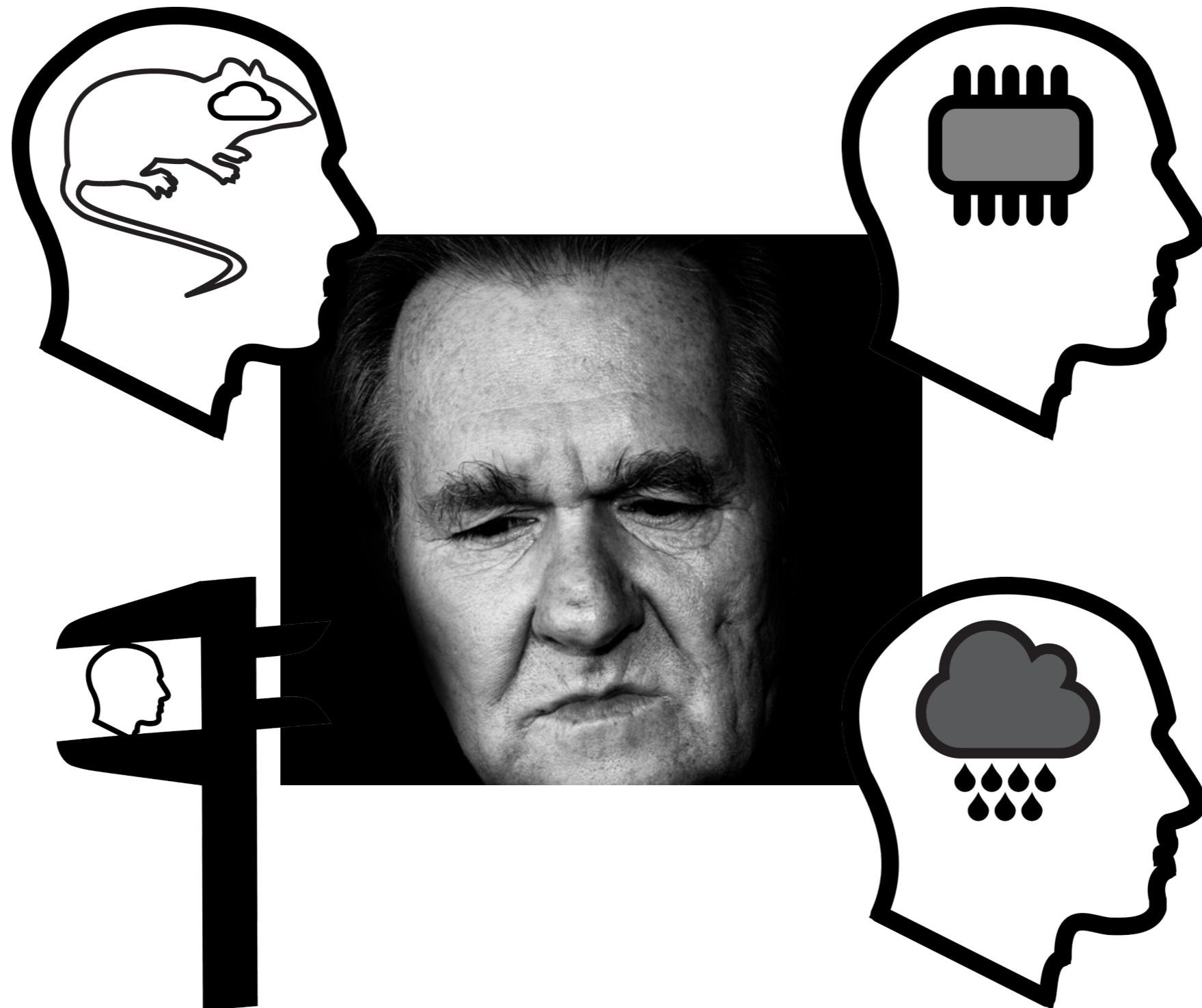
*Clinical Psychiatry Research; Department of Psychiatry, Psychotherapy and Psychosomatics; Neuroscience Centre Zurich, University of Zurich
Wellcome Trust Centre for Neuroimaging & Max Planck UCL Centre for Computational Psychiatry and Ageing, University College London*

10.09.2018

www.bachlab.org
dominik.bach@uzh.ch
[@bachlab_uzh](https://twitter.com/bachlab_uzh)

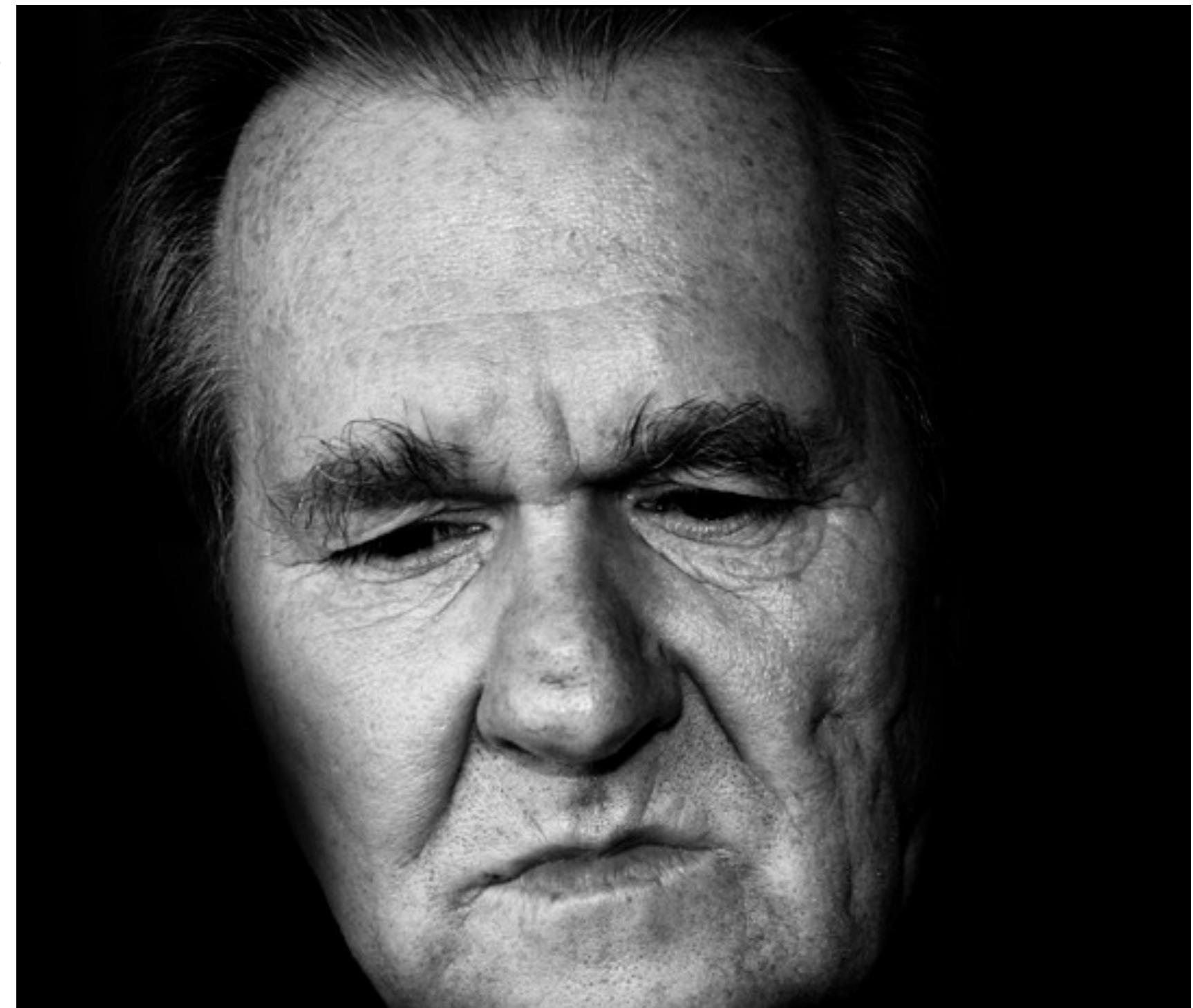








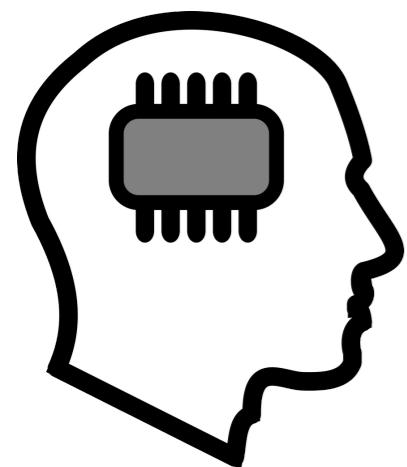
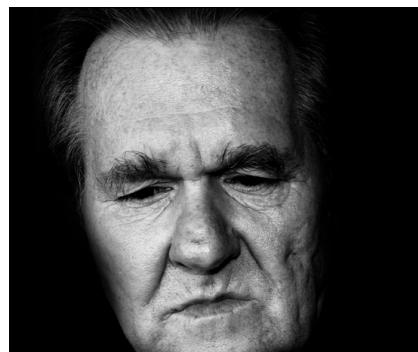
Universität
Zürich^{UZH}





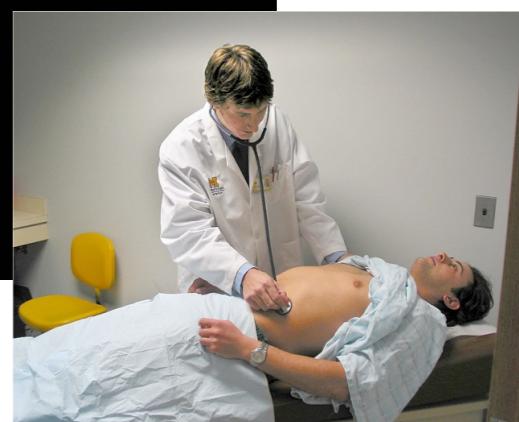
Universität
Zürich^{UZH}

Clinician's wish list



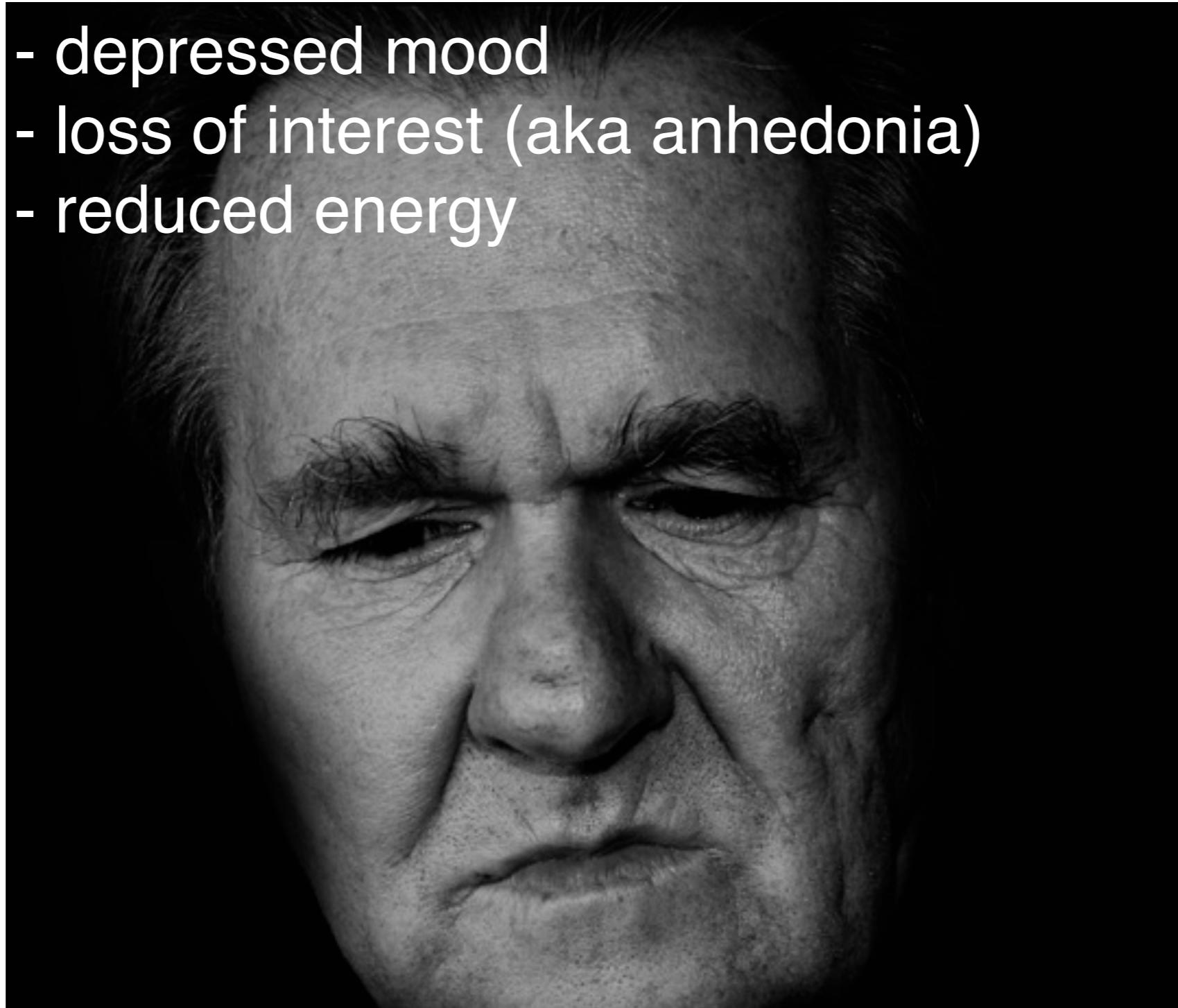
Primary symptoms

- fatigue
- disturbed sleep
- reduced appetite
- diffuse headache
- cardiovascular symptoms
- nausea
- muscle stiffness
- neuralgic pain
- loss of libido
- cognitive impairment



Depressive syndrome

- depressed mood
- loss of interest (aka anhedonia)
- reduced energy



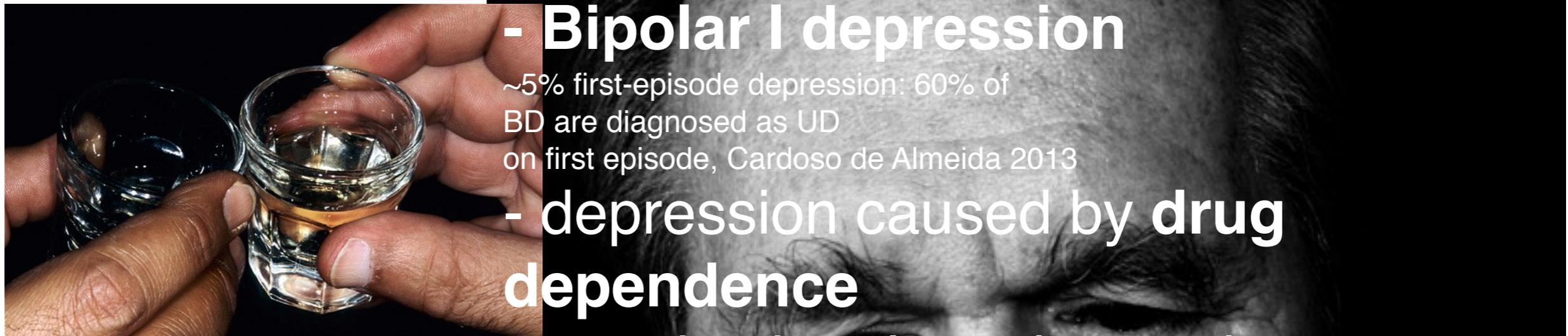


- **Bipolar I depression**

~5% first-episode depression: 60% of BD are diagnosed as UD on first episode, Cardoso de Almeida 2013

- **depression caused by drug dependence**

- amotivational syndrome due to **cannabis use** (even recreational)
- **schizophrenic prodromi, schizotypia, schizophrenia simplex**
- mood swing in **borderline personality disorder**





Universität
Zürich^{UZH}

Why does it matter?





Why does it matter?

How likely will treatment 1, 2, 3, ... work, given the sign/symptom profile?



Why does it matter?

How likely will treatment 1, 2, 3, ... work, given the sign/symptom profile?
 $p(\text{treatment_success} \mid \text{symptoms})$



Why does it matter?

How likely will treatment 1, 2, 3, ... work, given the sign/symptom profile?
 $p(\text{treatment_success} \mid \text{symptoms})$



Why does it matter?

How likely will treatment 1, 2, 3, ... work, given the sign/symptom profile?

$$p(\text{treatment_success} \mid \text{symptoms})$$

Based on individual detailed sign/symptom profiles ("personalized medicine"):



Why does it matter?

How likely will treatment 1, 2, 3, ... work, given the sign/symptom profile?

$$p(\text{treatment_success} \mid \text{symptoms})$$

Based on individual detailed sign/symptom profiles ("personalized medicine"):

very rare, even in very large data sets -> great uncertainty about empirical estimates



Why does it matter?

How likely will treatment 1, 2, 3, ... work, given the sign/symptom profile?

$$p(\text{treatment_success} \mid \text{symptoms})$$

Based on individual detailed sign/symptom profiles ("personalized medicine"):

very rare, even in very large data sets -> great uncertainty about empirical estimates



Why does it matter?

How likely will treatment 1, 2, 3, ... work, given the sign/symptom profile?

$$p(\text{treatment_success} \mid \text{symptoms})$$

Based on individual detailed sign/symptom profiles ("personalized medicine"):

very rare, even in very large data sets -> great uncertainty about empirical estimates

Diagnosis: summary description of sign/symptom/biomarker profiles on a scientifically/practically useful level of granularity



How likely will treatment 1, 2, 3, ... work, given the sign/symptom profile?

$$p(\text{treatment_success} \mid \text{symptoms})$$

Based on individual detailed sign/symptom profiles ("personalized medicine"):

very rare, even in very large data sets -> great uncertainty about empirical estimates

Diagnosis: summary description of sign/symptom/biomarker profiles on a scientifically/practically useful level of granularity

Biomarkers: apparatus-based tests with specific prognostic value



How likely will treatment 1, 2, 3, ... work, given the sign/symptom profile?

$$p(\text{treatment_success} \mid \text{symptoms})$$

Based on individual detailed sign/symptom profiles ("personalized medicine"):

very rare, even in very large data sets -> great uncertainty about empirical estimates

Diagnosis: summary description of sign/symptom/biomarker profiles on a scientifically/practically useful level of granularity

Biomarkers: apparatus-based tests with specific prognostic value



How likely will treatment 1, 2, 3, ... work, given the sign/symptom profile?

$$p(\text{treatment_success} \mid \text{symptoms})$$

Based on individual detailed sign/symptom profiles ("personalized medicine"):

very rare, even in very large data sets -> great uncertainty about empirical estimates

Diagnosis: summary description of sign/symptom/biomarker profiles on a scientifically/practically useful level of granularity

Biomarkers: apparatus-based tests with specific prognostic value

Clinical medicine: continuously revises diagnostic categories and biomarker cutoffs such that they are practically useful



How likely will treatment 1, 2, 3, ... work, given the sign/symptom profile?

$$p(\text{treatment_success} \mid \text{symptoms})$$

Based on individual detailed sign/symptom profiles ("personalized medicine"):

very rare, even in very large data sets -> great uncertainty about empirical estimates

Diagnosis: summary description of sign/symptom/biomarker profiles on a scientifically/practically useful level of granularity

Biomarkers: apparatus-based tests with specific prognostic value

Clinical medicine: continuously revises diagnostic categories and biomarker cutoffs such that they are practically useful



How likely will treatment 1, 2, 3, ... work, given the sign/symptom profile?

$$p(\text{treatment_success} \mid \text{symptoms})$$

Based on individual detailed sign/symptom profiles ("personalized medicine"):

very rare, even in very large data sets -> great uncertainty about empirical estimates

Diagnosis: summary description of sign/symptom/biomarker profiles on a scientifically/practically useful level of granularity

Biomarkers: apparatus-based tests with specific prognostic value

Clinical medicine: continuously revises diagnostic categories and biomarker cutoffs such that they are practically useful



How likely will treatment 1, 2, 3, ... work, given the sign/symptom profile?

$$p(\text{treatment_success} \mid \text{symptoms})$$

Based on individual detailed sign/symptom profiles ("personalized medicine"):

very rare, even in very large data sets -> great uncertainty about empirical estimates

Diagnosis: summary description of sign/symptom/biomarker profiles on a scientifically/practically useful level of granularity

Biomarkers: apparatus-based tests with specific prognostic value

Clinical medicine: continuously revises diagnostic categories and biomarker cutoffs such that they are practically useful

Differential diagnosis: systematically investigate signs/symptoms/biomarkers for all diagnostic categories that would fit the patients' initial presentation



Universität
Zürich^{UZH}

Why does it matter?





Why does it matter?

How likely will treatment 1, 2, 3, ... work, given the sign/symptom profile?



Why does it matter?

How likely will treatment 1, 2, 3, ... work, given the sign/symptom profile?
 $p(\text{treatment_success} \mid \text{symptoms})$



Why does it matter?

How likely will treatment 1, 2, 3, ... work, given the sign/symptom profile?
 $p(\text{treatment_success} \mid \text{symptoms})$



Why does it matter?

How likely will treatment 1, 2, 3, ... work, given the sign/symptom profile?

$$p(\text{treatment_success} \mid \text{symptoms})$$

Based on individual detailed sign/symptom profiles ("personalized medicine"):



Why does it matter?

How likely will treatment 1, 2, 3, ... work, given the sign/symptom profile?

$$p(\text{treatment_success} \mid \text{symptoms})$$

Based on individual detailed sign/symptom profiles ("personalized medicine"):

very rare, even in very large data sets -> great uncertainty about empirical estimates



Why does it matter?

How likely will treatment 1, 2, 3, ... work, given the sign/symptom profile?

$$p(\text{treatment_success} \mid \text{symptoms})$$

Based on individual detailed sign/symptom profiles ("personalized medicine"):

very rare, even in very large data sets -> great uncertainty about empirical estimates



Why does it matter?

How likely will treatment 1, 2, 3, ... work, given the sign/symptom profile?

$$p(\text{treatment_success} \mid \text{symptoms})$$

Based on individual detailed sign/symptom profiles ("personalized medicine"):

very rare, even in very large data sets -> great uncertainty about empirical estimates

Diagnosis: summary description of sign/symptom/biomarker profiles on a scientifically/practically useful level of granularity



How likely will treatment 1, 2, 3, ... work, given the sign/symptom profile?

$$p(\text{treatment_success} \mid \text{symptoms})$$

Based on individual detailed sign/symptom profiles ("personalized medicine"):

very rare, even in very large data sets -> great uncertainty about empirical estimates

Diagnosis: summary description of sign/symptom/biomarker profiles on a scientifically/practically useful level of granularity

Biomarkers: apparatus-based tests with specific prognostic value



How likely will treatment 1, 2, 3, ... work, given the sign/symptom profile?

$$p(\text{treatment_success} \mid \text{symptoms})$$

Based on individual detailed sign/symptom profiles ("personalized medicine"):

very rare, even in very large data sets -> great uncertainty about empirical estimates

Diagnosis: summary description of sign/symptom/biomarker profiles on a scientifically/practically useful level of granularity

Biomarkers: apparatus-based tests with specific prognostic value



How likely will treatment 1, 2, 3, ... work, given the sign/symptom profile?

$$p(\text{treatment_success} \mid \text{symptoms})$$

Based on individual detailed sign/symptom profiles ("personalized medicine"):

very rare, even in very large data sets -> great uncertainty about empirical estimates

Diagnosis: summary description of sign/symptom/biomarker profiles on a scientifically/practically useful level of granularity

Biomarkers: apparatus-based tests with specific prognostic value

Clinical medicine: continuously revises diagnostic categories and biomarker cutoffs such that they are practically useful



How likely will treatment 1, 2, 3, ... work, given the sign/symptom profile?

$$p(\text{treatment_success} \mid \text{symptoms})$$

Based on individual detailed sign/symptom profiles ("personalized medicine"):

very rare, even in very large data sets -> great uncertainty about empirical estimates

Diagnosis: summary description of sign/symptom/biomarker profiles on a scientifically/practically useful level of granularity

Biomarkers: apparatus-based tests with specific prognostic value

Clinical medicine: continuously revises diagnostic categories and biomarker cutoffs such that they are practically useful



How likely will treatment 1, 2, 3, ... work, given the sign/symptom profile?

$$p(\text{treatment_success} \mid \text{symptoms})$$

Based on individual detailed sign/symptom profiles ("personalized medicine"):

very rare, even in very large data sets -> great uncertainty about empirical estimates

Diagnosis: summary description of sign/symptom/biomarker profiles on a scientifically/practically useful level of granularity

Biomarkers: apparatus-based tests with specific prognostic value

Clinical medicine: continuously revises diagnostic categories and biomarker cutoffs such that they are practically useful

Blood Pressure Categories

BLOOD PRESSURE CATEGORY	SYSTOLIC mm Hg (upper number)		DIASTOLIC mm Hg (lower number)
NORMAL	LESS THAN 120	and	LESS THAN 80
ELEVATED	120 – 129	and	LESS THAN 80
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 1	130 – 139	or	80 – 89
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 2	140 OR HIGHER	or	90 OR HIGHER
HYPERTENSIVE CRISIS (consult your doctor immediately)	HIGHER THAN 180	and/or	HIGHER THAN 120

Blood Pressure Categories

BLOOD PRESSURE CATEGORY	SYS. (upper number)	DIASTOLIC mm Hg (lower number)
NORMAL	LOW THAN 120	and LESS THAN 80
ELEVATED	120 - 129	and LESS THAN 80
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 1	130 - 139 or 80 - 89	or 130 - 139
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 2	140 OR HIGHER	90 OR HIGHER
HYPERTENSIVE CRISIS (consult your doctor immediately)	HIGHER THAN 180	and/or HIGHER THAN 120

Diagnosis: summary description of sign/symptom/biomarker profiles on a scientifically/practically useful level of granularity

Biomarkers: apparatus-based tests with specific prognostic value

Clinical medicine: continuously revises diagnostic categories and biomarker cutoffs such that they are practically useful

Blood Pressure Categories

BLOOD PRESSURE CATEGORY	SYSTOLIC mm Hg (upper number)		DIASTOLIC mm Hg (lower number)
NORMAL	LESS THAN 120	and	LESS THAN 80
ELEVATED	120 – 129	and	LESS THAN 80
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 1	130 – 139	or	80 – 89
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 2	140 OR HIGHER	or	90 OR HIGHER
HYPERTENSIVE CRISIS (consult your doctor immediately)	HIGHER THAN 180	and/or	HIGHER THAN 120

Blood Pressure Categories

BLOOD PRESSURE CATEGORY	Systolic Blood Pressure (Upper number)	Diastolic Blood Pressure (Lower number)	
NORMAL	LESS THAN 120	and	LESS THAN 80
ELEVATED	120 – 129	and	LESS THAN 80
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 1	130 – 139	or	80 – 89
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 2	140 HIGHER	or	90 OR HIGHER
HYPERTENSIVE CRISIS (consult your doctor immediately)	HIGHER THAN 180	and/or	HIGHER THAN 120

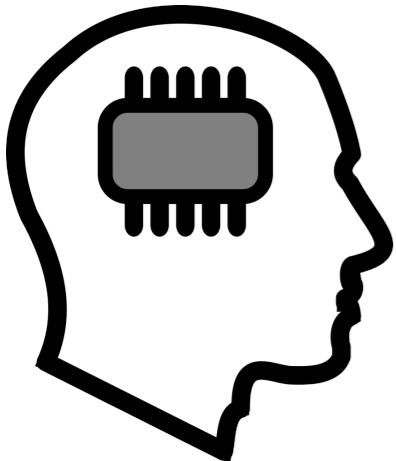
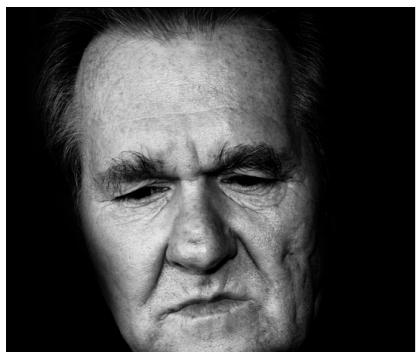
Diagnosis: summary description of sign/symptom/biomarker profiles on a scientifically/practically useful level of granularity

Biomarkers: apparatus-based tests with specific prognostic value

Clinical medicine: continuously revises diagnostic categories and biomarker cutoffs such that they are practically useful

Differential diagnosis: systematically investigate signs/symptoms/biomarkers for all diagnostic categories that would fit the patients' initial presentation

- establishing the evidence takes time (up to weeks)
- prior knowledge: age, gender, symptom dynamics, profile of additional symptoms
- MDs are fantastic model inversion machines for sparse data but individually they don't see that many patients
- to beat a trained and interested MD, you need BIG data (100s of data points per patient, or 10'000s of patients)



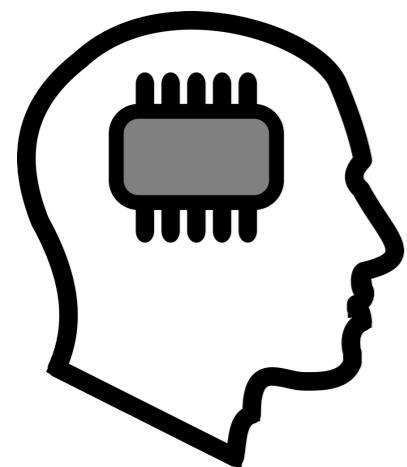
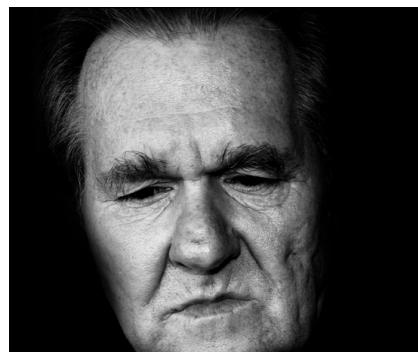
- Tests for differential diagnosis





Universität
Zürich^{UZH}

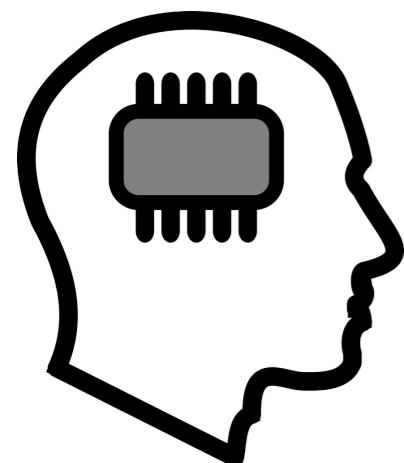
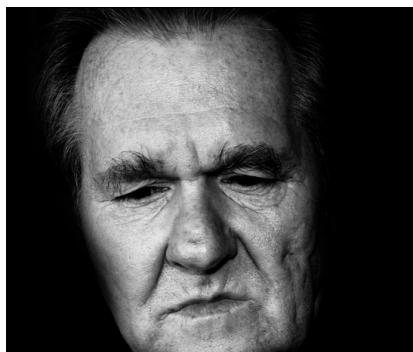
Current state



Current state



- Diagnostic tests using machine-learning so far only distinguish MDD from healthy controls (eg. based on EEG: Mumtaz et al. 2018)
- Potential clinical relevance: prospective differential diagnosis



Major symptoms

- depressed mood
- loss of interest
- reduced energy

Minor symptoms

- reduced concentration/attention
- reduced self-esteem
- ideas of guilt
- pessimism
- suicidal thoughts
- disturbed sleep
- diminished appetite

Other symptoms

- anxiety
- motor restlessness or motor slowing
- morning low
- decreased libido
- psychotic symptoms (hallucinations, delusions)



Major symptoms

- depressed mood
- loss of interest
- reduced energy

Major symptoms must be present most of the day, every day, > 2 weeks

Mild episode:

2 major + 3 minor over

Minor symptoms

- reduced concentration/attention
- reduced self-esteem
- ideas of guilt
- pessimism
- suicidal thoughts
- disturbed sleep
- diminished appetite

Moderate episode:

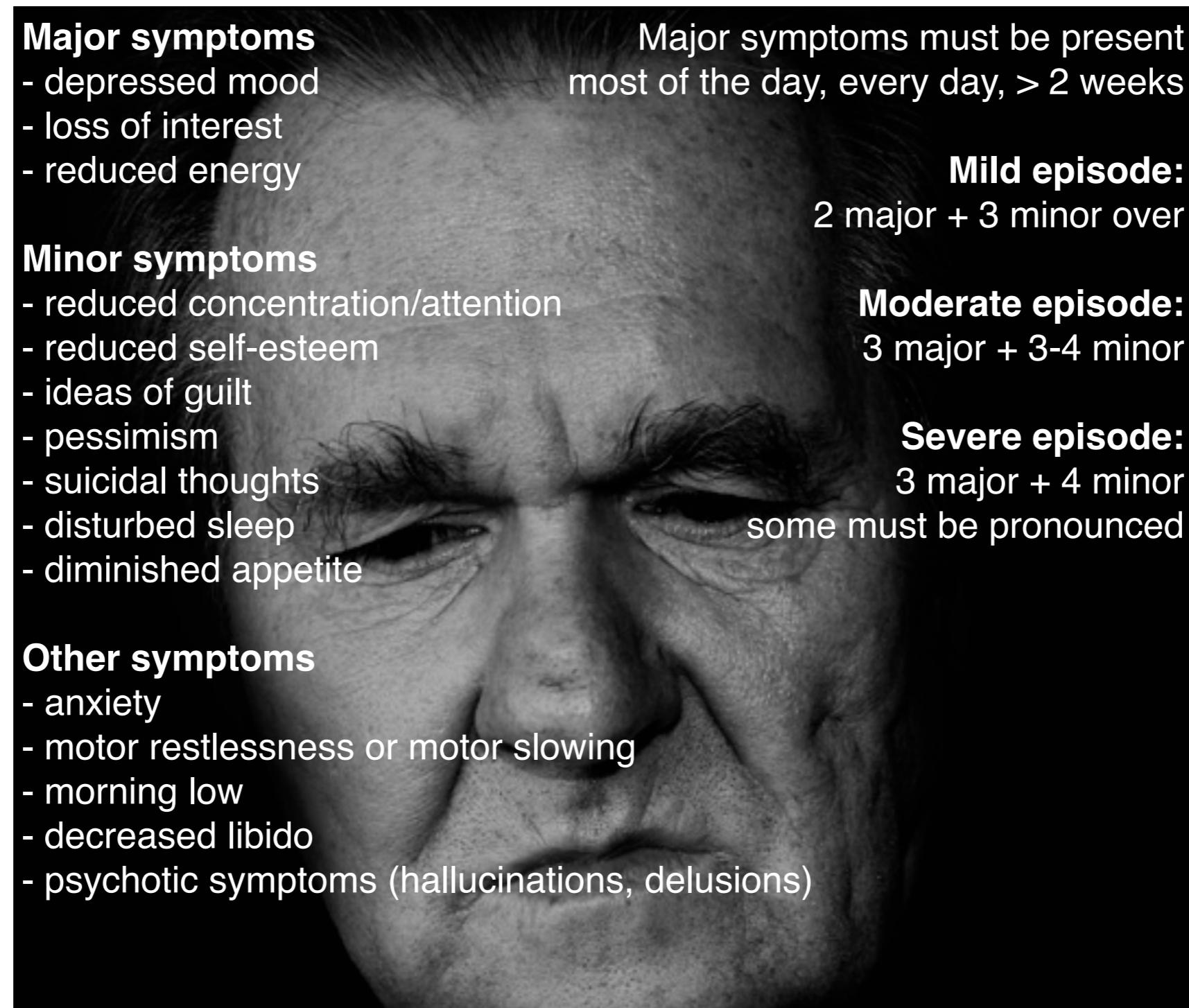
3 major + 3-4 minor

Severe episode:

3 major + 4 minor
some must be pronounced

Other symptoms

- anxiety
- motor restlessness or motor slowing
- morning low
- decreased libido
- psychotic symptoms (hallucinations, delusions)

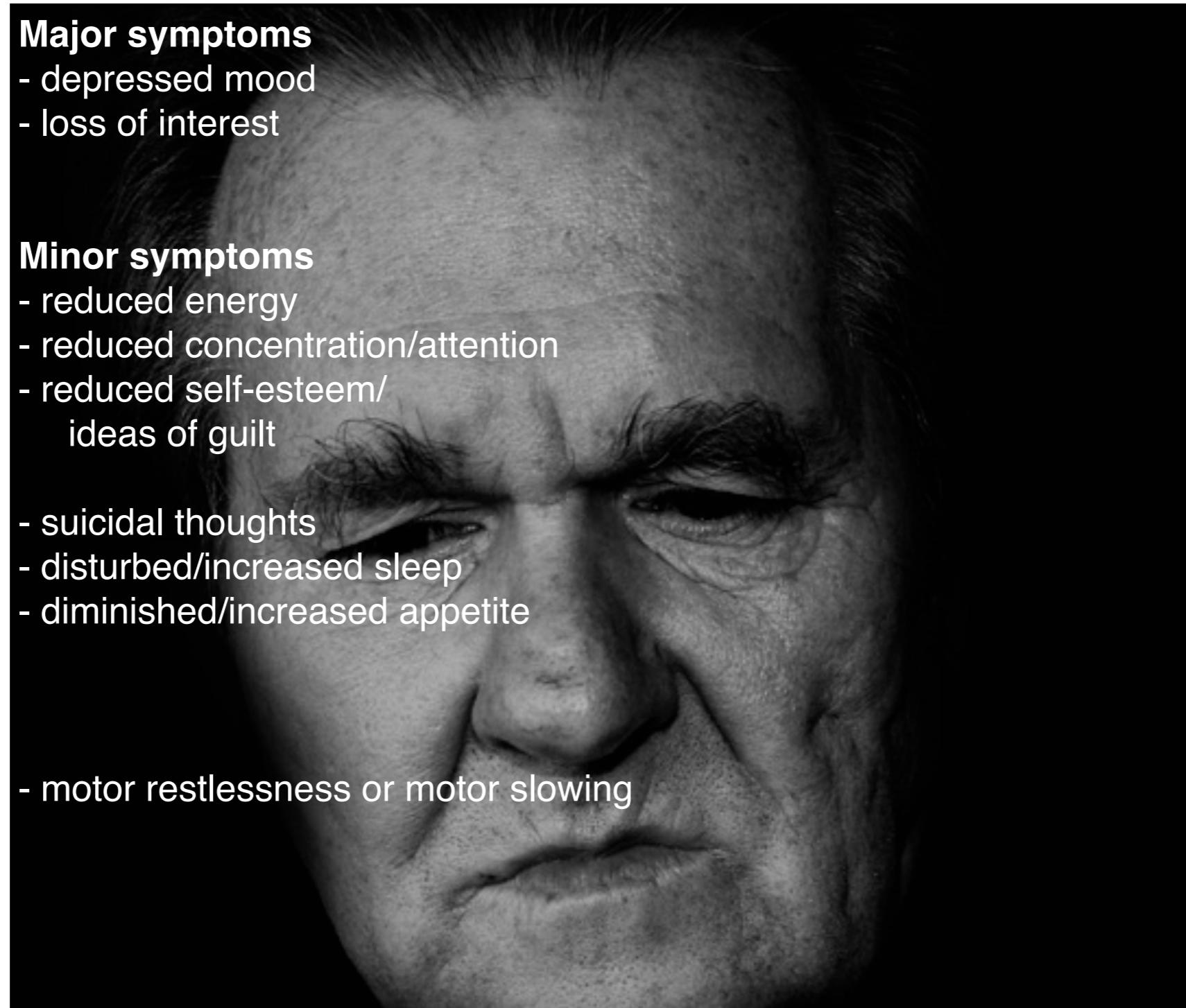


Major symptoms

- depressed mood
- loss of interest

Minor symptoms

- reduced energy
- reduced concentration/attention
- reduced self-esteem/
ideas of guilt
- suicidal thoughts
- disturbed/increased sleep
- diminished/increased appetite
- motor restlessness or motor slowing



Major symptoms

- depressed mood
- loss of interest

All symptoms must be present
most of the day, every day, > 2 weeks
1 major + overall 5

Minor symptoms

- reduced energy
- reduced concentration/attention
- reduced self-esteem/
ideas of guilt
- suicidal thoughts
- disturbed/increased sleep
- diminished/increased appetite
- motor restlessness or motor slowing

Severity rated clinically

Psychotic symptoms
(hallucinations, delusions)

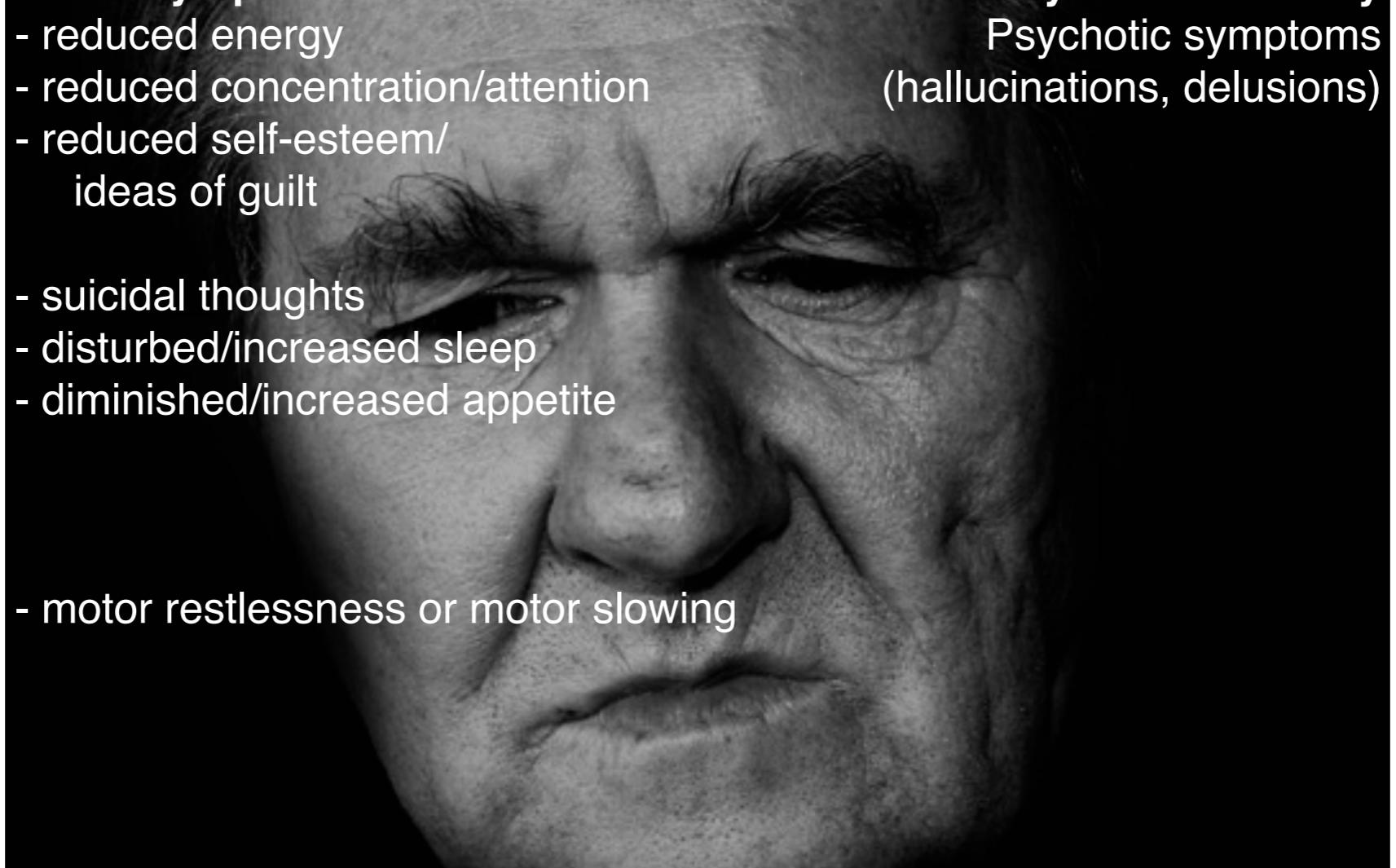


Table 2

Meta-analytic estimates for primary outcomes and for subgroup analyses.

Reliability by disorder		Schizoaffective disorder (SAD)					Schizophrenia (SCH)					Bipolar disorder (BPD)					Unipolar depression (DEP)				
		n	k	SE	I ²	p	n	k	SE	I ²	p	n	k	SE	I ²	p	n	k	SE	I ²	p
All studies		25	0.57	0.08	98	/	23	0.80	0.02	70	/	17	0.82	0.02	38	/	23	0.75	0.03	82	/
Diagnostic interview	Consistent use	16	0.56	0.12	97	0.830	14	0.79	0.05	78	0.643	12	0.83	0.04	30	0.454	15	0.78	0.04	76	0.121
	Inconsistent use	9	0.58	0.04	63		9	0.81	0.02	47		5	0.80	0.03	50		8	0.70	0.04	82	
Diagnostic manual	DSM-III-R, -IV, -5	11	0.59	0.09	85	0.902	10	0.79	0.06	74	0.998	9	0.81	0.05	47	0.511	9	0.77	0.06	84	0.047
	ICD-10	9	0.55	0.05	81		9	0.79	0.03	73		7	0.79	0.03	61		7	0.67	0.04	85	
Kind of kappa	RDC	6	0.60	0.13	88		5	0.79	0.05	23		3	0.88	0.07	0		6	0.82	0.05	49	
	Cohen's kappa	9	0.51	0.08	73	0.729	7	0.77	0.06	45	0.482	6	0.84	0.05	0	0.705	8	0.72	0.07	82	0.170
	Fleiss' kappa	5	0.57	0.02	3		5	0.83	0.02	66		4	0.79	0.03	64		4	0.67	0.04	89	
	Calculated kappa	4	0.51	0.30	98		4	0.74	0.13	92		2	0.82	0.14	72		4	0.81	0.06	68	

Table 2

Meta-analytic estimates for primary outcomes and for subgroup analyses.

Reliability by disorder		Schizoaffective disorder (SAD)					Schizophrenia (SCH)					Bipolar disorder (BPD)					Unipolar depression (DEP)				
		n	k	SE	I ²	p	n	k	SE	I ²	p	n	k	SE	I ²	p	n	k	SE	I ²	p
All studies		25	0.57	0.08	98	/	23	0.80	0.02	70	/	17	0.82	0.02	38	/	23	0.75	0.03	82	/
Diagnostic interview	Consistent use	16	0.56	0.12	97	0.830	14	0.79	0.05	78	0.643	12	0.83	0.04	30	0.454	15	0.78	0.04	76	0.121
	Inconsistent use	9	0.58	0.04	63		9	0.81	0.02	47		5	0.80	0.03	50		8	0.70	0.04	82	
Diagnostic manual	DSM-III-R, -IV, -5	11	0.59	0.09	85	0.902	10	0.79	0.06	74	0.998	9	0.81	0.05	47	0.511	9	0.77	0.06	84	0.047
	ICD-10	9	0.55	0.05	81		9	0.79	0.03	73		7	0.79	0.03	61		7	0.67	0.04	85	
	RDC	6	0.60	0.13	88		5	0.79	0.05	23		3	0.88	0.07	0		6	0.82	0.05	49	
Kind of kappa	Cohen's kappa	9	0.51	0.08	73	0.729	7	0.77	0.06	45	0.482	6	0.84	0.05	0	0.705	8	0.72	0.07	82	0.170
	Fleiss' kappa	5	0.57	0.02	3		5	0.83	0.02	66		4	0.79	0.03	64		4	0.67	0.04	89	
	Calculated kappa	4	0.51	0.30	98		4	0.74	0.13	92		2	0.82	0.14	72		4	0.81	0.06	68	



Schizoaffective disorder:

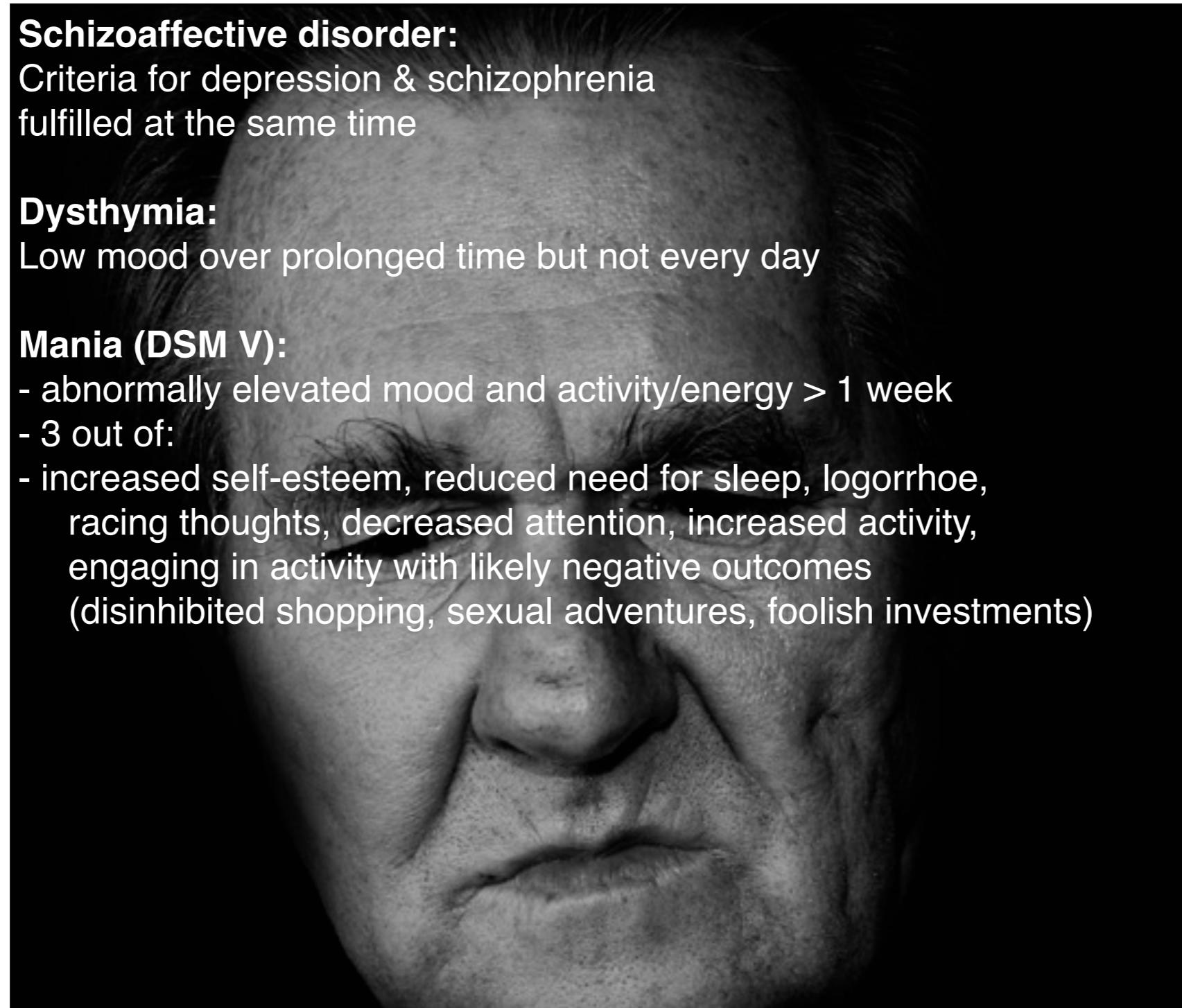
Criteria for depression & schizophrenia
fulfilled at the same time

Dysthymia:

Low mood over prolonged time but not every day

Mania (DSM V):

- abnormally elevated mood and activity/energy > 1 week
- 3 out of:
 - increased self-esteem, reduced need for sleep, logorrhoe, racing thoughts, decreased attention, increased activity, engaging in activity with likely negative outcomes (disinhibited shopping, sexual adventures, foolish investments)



12-month prevalence	Men	Women	Seniors in institutions
<i>Major unipolar episode</i>	CH, D: 5% WHO: 4%	CH, D: 10% WHO: 9%	15-25%
<i>Bipolar disorder</i>	BP I: 0.5-1% BP II: 0.5-1%		
Age	50% have onset before 30 yrs Risk decreases with age, but course worsens		
Heritability	35 %		
Culture	Prevalence differs between countries but no dependence on population income or Western/non-Western culture		

>= 1 comorbid psychiatric diagnosis	60% of UD	
3 comorbid psychiatric diagnoses	25% of UD	
Anxiety and panic disorders	50% life time comorbidity	
Dependence disorder	33% life time comorbidity	
Increased risk for non-psychiatric diagnosis	1.8 fold 12 months after remission	cardiovascular, cerebrovascular, stroke, dementia



Childhood adversity	2x increased risk
Early parental loss	in one study: 3x increased risk 10x increased risk when before 9 years (but also increases schizophrenia risk)
Contryside	City > 500 000 vs. town/settlement < 20 000 2x increased risk
Partnership	No partner vs. partner 2x increased risk
First order relative with depression	1.5x increased risk
Anxiety disorder	2x increased risk



< 50% symptom reduction	no/minimal effect
> 50% symptom reduction	response/part remission
100% symptom reduction or symptoms below cut-off	remission
New episode within 6 months	relapse
New episode after more than 6 months	recurrence

NICE	DGPPN
Mild to moderate depression, initial	Low intensity psychosocial intervention
Mild to moderate depression, persistent	Drug AND/OR psychotherapy
Moderate to severe depression	Drug AND psychotherapy
Very severe depression or risk to life	Drug AND psychotherapy, in-patient care

Cognitive/behavioural therapy (CBT), Psychodynamic psychotherapy, Psychoanalysis, Systemic psychotherapy, Interpersonal Psychotherapy (IPT), Person-centred psychotherapy
severe depression: CBT, IPT



Group 1: SSRI
(similar: Trazodon)

Group 2: SNRI
(Venlafaxin, Duloxetin)

**Group 3: Tricyclic
antidepressants**

**Group 4: alpha2-
antagonists (Mirtazapin,
Mianserin)**

Group 5: Lithium

Group 6: Antipsychotics
**(Aripiprazol, Risperidon,
Quetiapin, Olanzapin)**

**Group 7: MAO-Inhibitors,
Bupropion, Agomelatin
and others**



Group 1: SSRI
(similar: Trazodon)

Group 2: SNRI
(Venlafaxin, Duloxetin)

**Group 3: Tricyclic
antidepressants**

**Group 4: alpha2-
antagonists (Mirtazapin,
Mianserin)**

Group 5: Lithium

Group 6: Antipsychotics
(Aripiprazol, Risperidon,
Quetiapin, Olanzapin)

**Group 7: MAO-Inhibitors,
Bupropion, Agomelatin
and others**

Treatment resistance

(30-50% of patients)

Group 1: SSRI
(similar: Trazodon)

Group 2: SNRI
(Venlafaxin, Duloxetin)

**Group 3: Tricyclic
antidepressants**

**Group 4: alpha2-
antagonists (Mirtazapin,
Mianserin)**

Group 1-3 + 4 Mirtazapin

Group 1-4 + 5 Lithium

Group 1-4 + 6 Atypical
antipsychotics

[Group 1-4 + T3 (?)]

Group 5: Lithium

Group 6: Antipsychotics
**(Aripiprazol, Risperidon,
Quetiapin, Olanzapin)**

**Group 7: MAO-Inhibitors,
Bupropion, Agomelatin
and others**

Electroconvulsive therapy (ECT): 60-90% remission rate in treatment-resistant depression

Experimental treatments: TMS, ketamine, anti-inflammatory drugs, DBS, ...

Treatment resistance

(30-50% of patients)

Group
(similar)

Group
(Venlafaxine)

Group
antidepressants

Sample size?

CONSENSUS (N=250), SOLVD
(N=2500 patients), SAVE (N=2500
patients) HOPE (N=10'000 patients)

Direct comparison?

ALLHAT (N=42'000, 4 drugs)

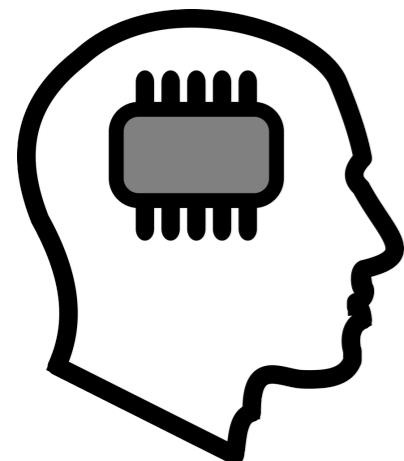
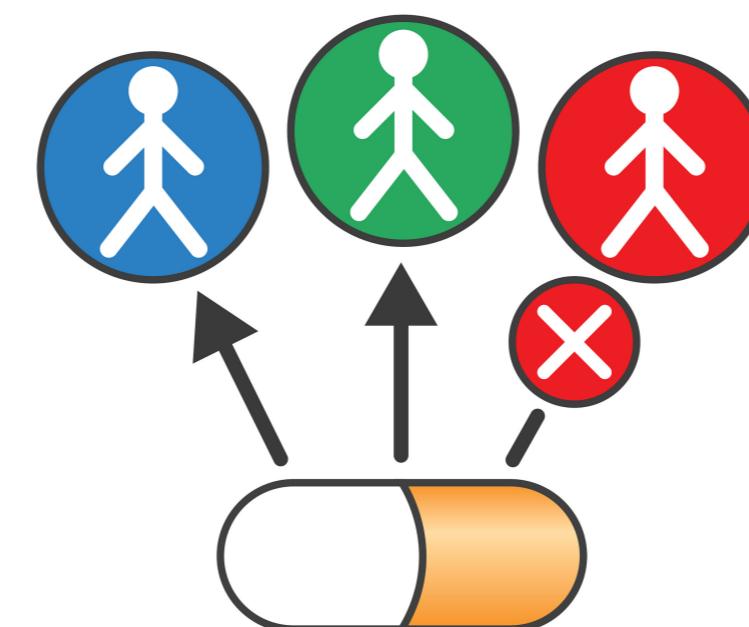
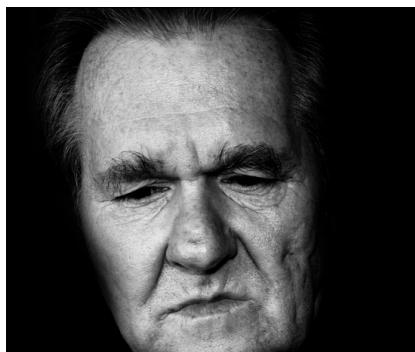
"Personalized treatment"?

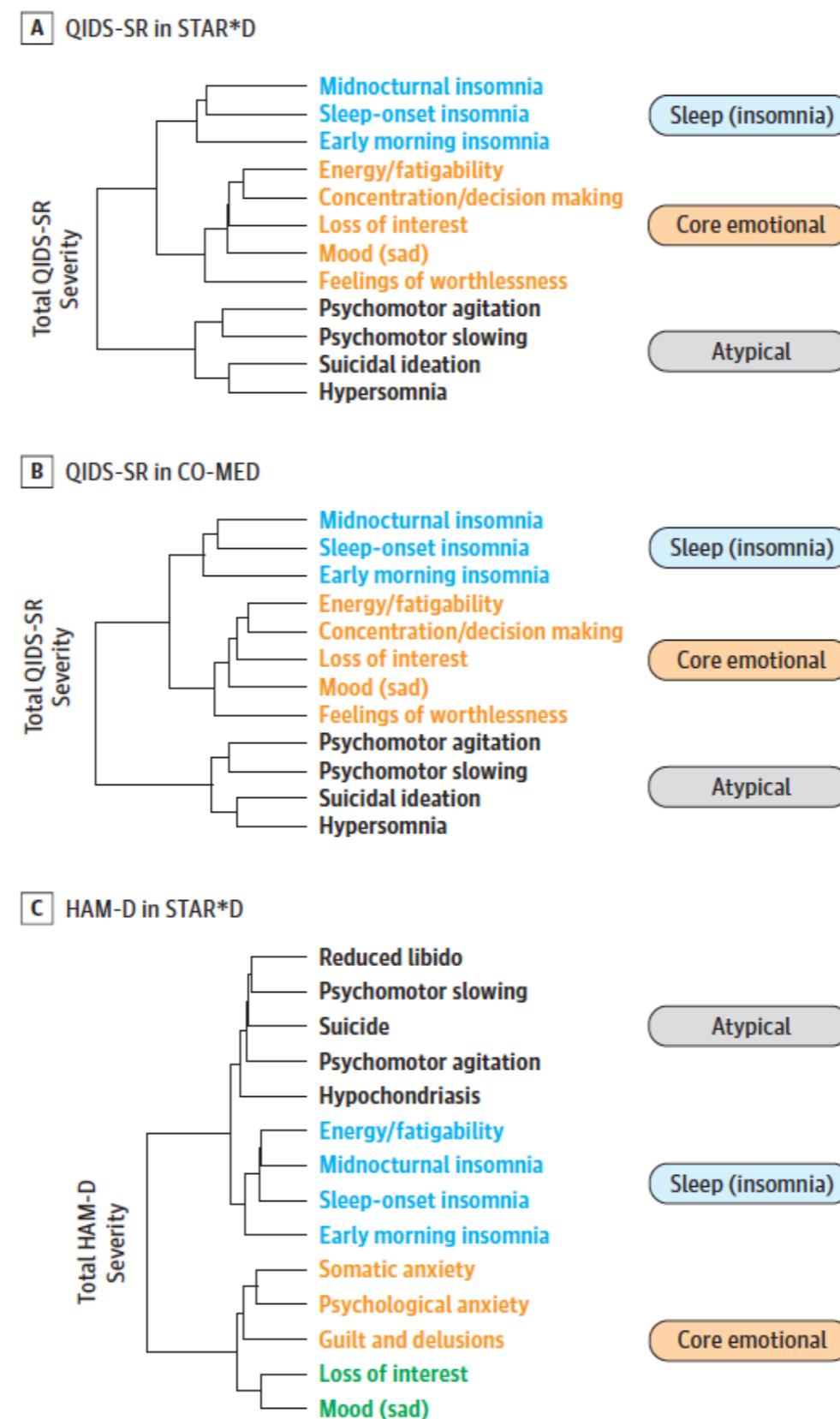
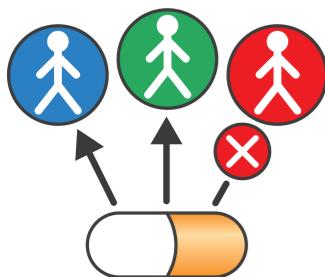
Electroconvulsive therapy (ECT): 60-90% remission rate in treatment-resistant depression

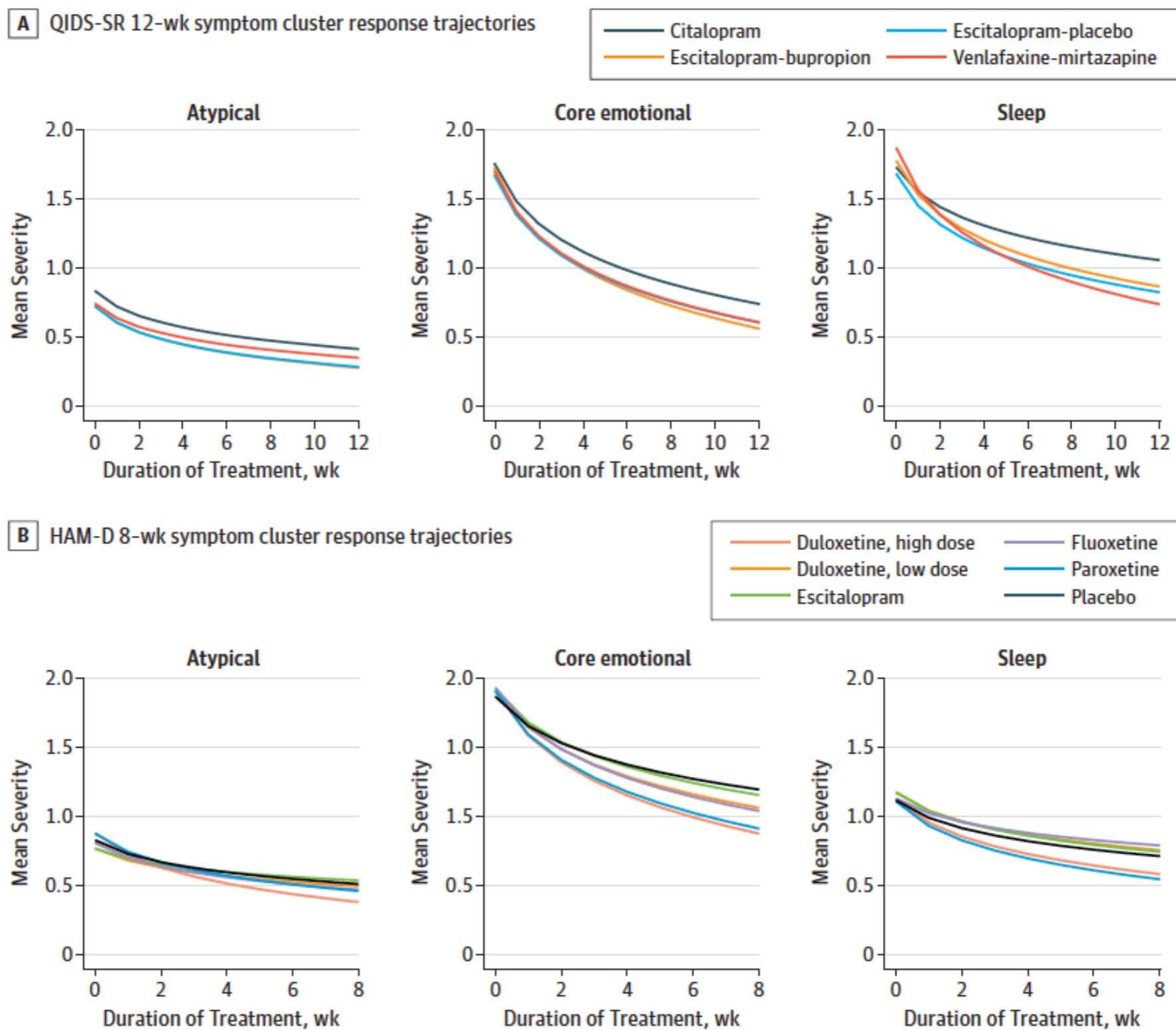
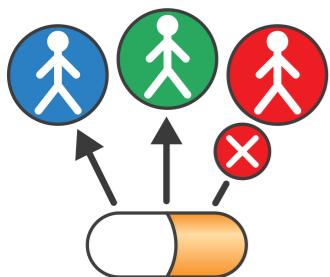
Experimental treatments: TMS, ketamine, anti-inflammatory drugs, DBS, ...



- Tests for differential diagnosis
- Predict individual treatment response

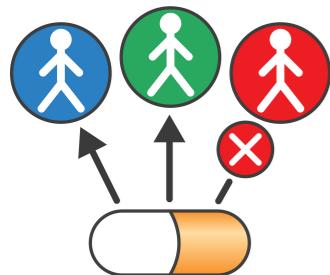




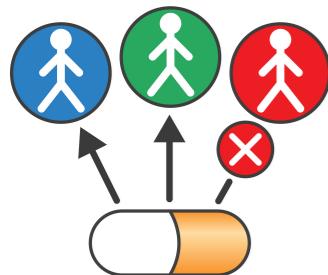




Current state

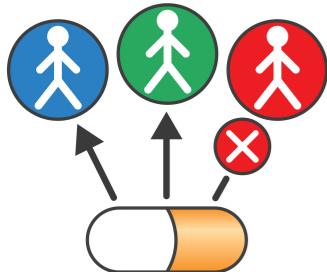


Current state



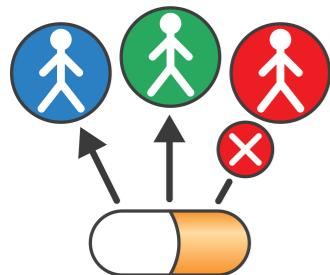
- **Unsupervised identification of subtypes:** some subtypes respond to (any) treatment better than others

Current state



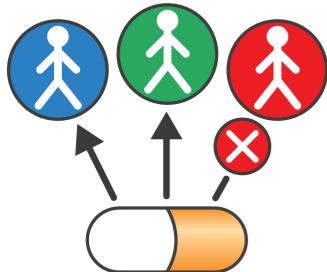
- **Unsupervised identification of subtypes:** some subtypes respond to (any) treatment better than others
- **Supervised prediction of outcome**

Current state



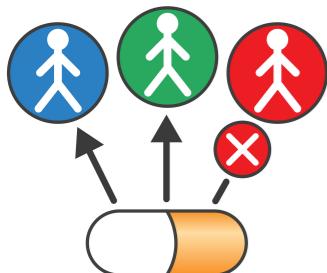
- **Unsupervised identification of subtypes:** some subtypes respond to (any) treatment better than others
- **Supervised prediction of outcome**

Current state



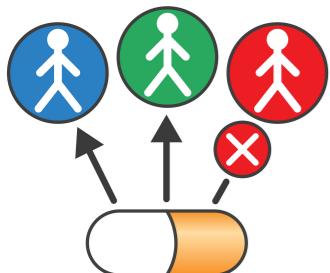
- **Unsupervised identification of subtypes:** some subtypes respond to (any) treatment better than others
- **Supervised prediction of outcome**
- Symptom clusters predict drug response: Chekroud et al. (2017)

Current state



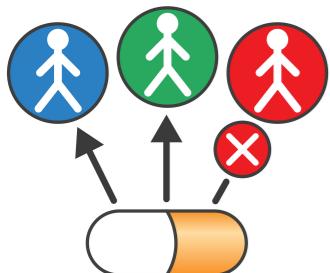
- **Unsupervised identification of subtypes:** some subtypes respond to (any) treatment better than others
- **Supervised prediction of outcome**
- Symptom clusters predict drug response: Chekroud et al. (2017)
- fMRI functional connectivity subtypes predicts rTMS response: Drysdale et al. (2017)

Current state



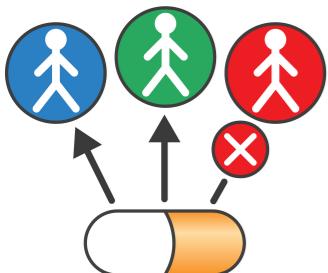
- **Unsupervised identification of subtypes:** some subtypes respond to (any) treatment better than others
- **Supervised prediction of outcome**
- Symptom clusters predict drug response: Chekroud et al. (2017)
- fMRI functional connectivity subtypes predicts rTMS response: Drysdale et al. (2017)
- Trained symptom scores predict outcome: Chekroud et al. (2016), Kessler et al. (2016)

Current state



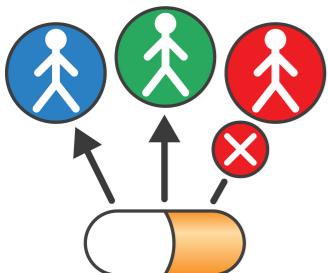
- **Unsupervised identification of subtypes:** some subtypes respond to (any) treatment better than others
- **Supervised prediction of outcome**
- Symptom clusters predict drug response: Chekroud et al. (2017)
- fMRI functional connectivity subtypes predicts rTMS response: Drysdale et al. (2017)
- Trained symptom scores predict outcome: Chekroud et al. (2016), Kessler et al. (2016)

Current state

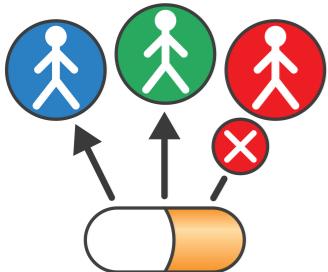


- **Unsupervised identification of subtypes:** some subtypes respond to (any) treatment better than others
- **Supervised prediction of outcome**
- Symptom clusters predict drug response: Chekroud et al. (2017)
- fMRI functional connectivity subtypes predicts rTMS response: Drysdale et al. (2017)
- Trained symptom scores predict outcome: Chekroud et al. (2016), Kessler et al. (2016)
- Potential clinical relevance:

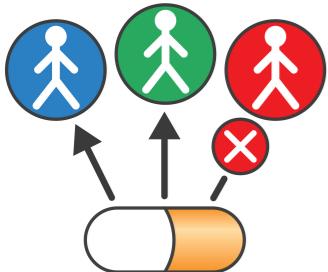
Current state



- **Unsupervised identification of subtypes:** some subtypes respond to (any) treatment better than others
- **Supervised prediction of outcome**
- Symptom clusters predict drug response: Chekroud et al. (2017)
- fMRI functional connectivity subtypes predicts rTMS response: Drysdale et al. (2017)
- Trained symptom scores predict outcome: Chekroud et al. (2016), Kessler et al. (2016)
- Potential clinical relevance:
 - (a) demonstrate that low-outcome subtypes or risk-scorers don't respond to treatment better than to placebo



- **Unsupervised identification of subtypes:** some subtypes respond to (any) treatment better than others
- **Supervised prediction of outcome**
- Symptom clusters predict drug response: Chekroud et al. (2017)
- fMRI functional connectivity subtypes predicts rTMS response: Drysdale et al. (2017)
- Trained symptom scores predict outcome: Chekroud et al. (2016), Kessler et al. (2016)
- Potential clinical relevance:
 - (a) demonstrate that low-outcome subtypes or risk-scorers don't respond to treatment better than to placebo
 - (b) cost-benefit analysis for treatments with high risk/potentially irreversible side effects (electroconvulsive therapy, some drugs)



- **Unsupervised identification of subtypes:** some subtypes respond to (any) treatment better than others
- **Supervised prediction of outcome**
- Symptom clusters predict drug response: Chekroud et al. (2017)
- fMRI functional connectivity subtypes predicts rTMS response: Drysdale et al. (2017)
- Trained symptom scores predict outcome: Chekroud et al. (2016), Kessler et al. (2016)
- Potential clinical relevance:
 - (a) demonstrate that low-outcome subtypes or risk-scorers don't respond to treatment better than to placebo
 - (b) cost-benefit analysis for treatments with high risk/potentially irreversible side effects (electroconvulsive therapy, some drugs)

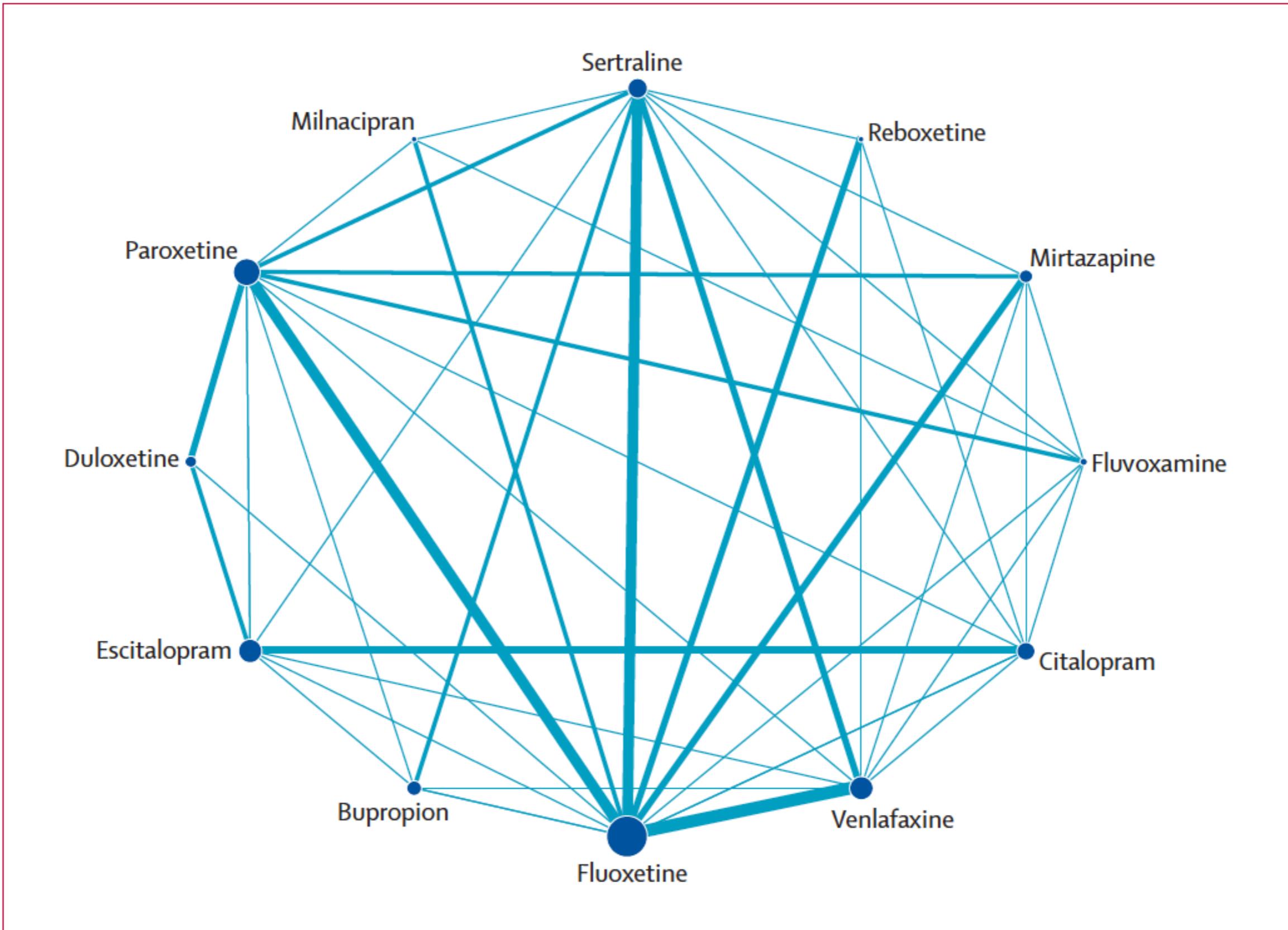
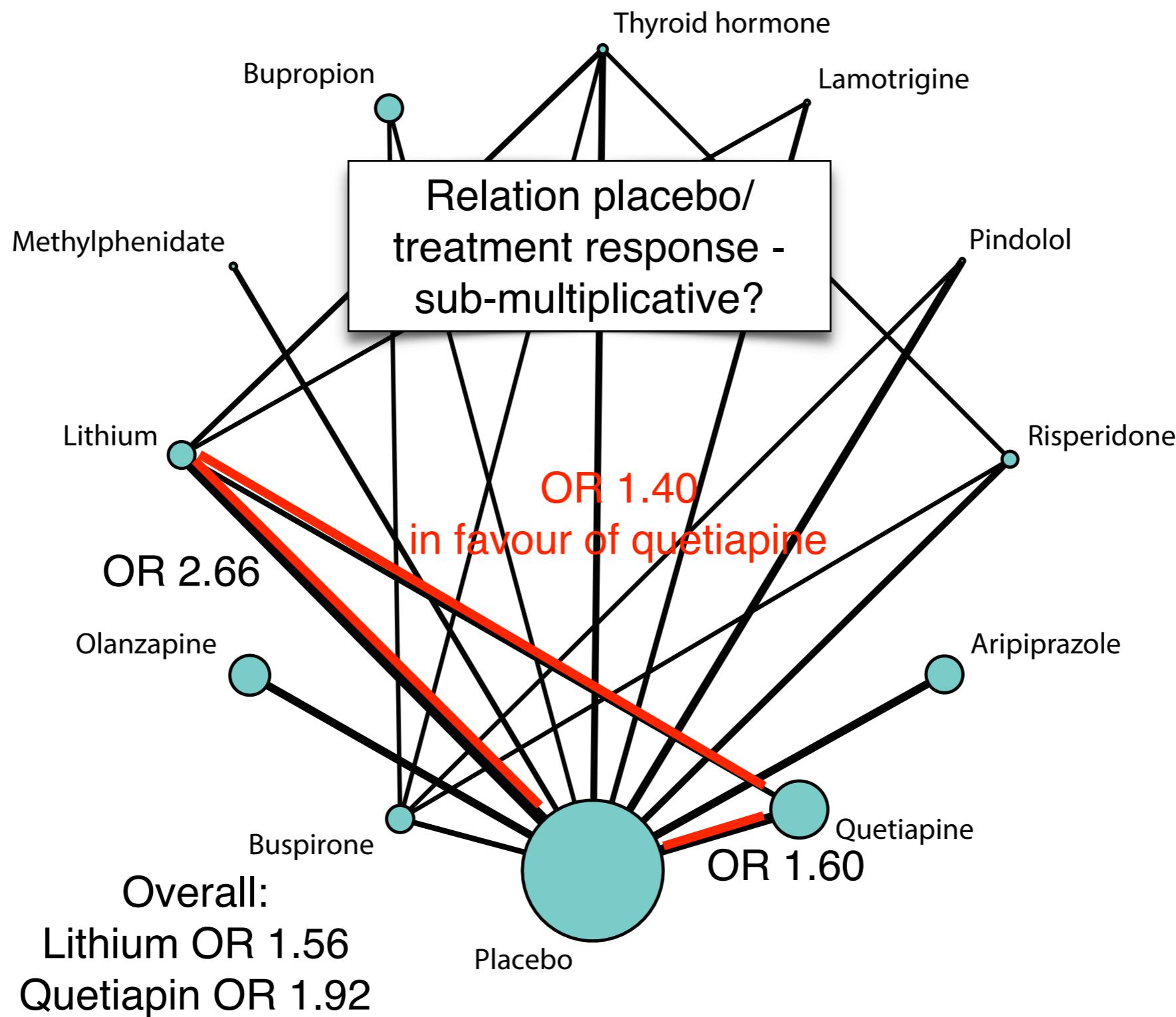


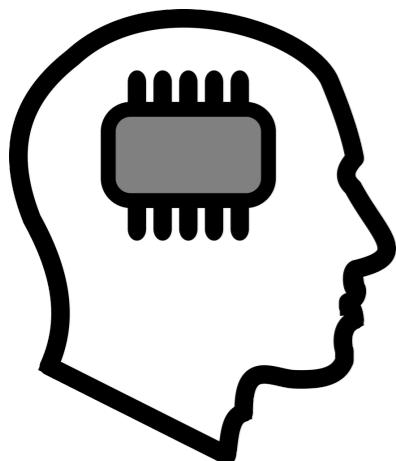
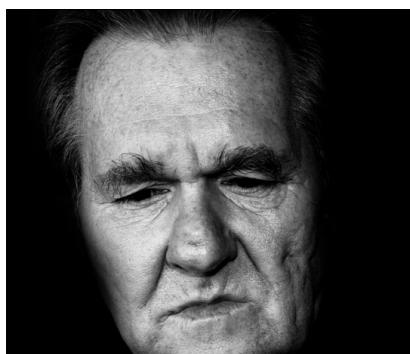
Figure 2: Network of eligible comparisons for the multiple-treatment meta-analysis for efficacy (response rate)
The width of the lines is proportional to the number of trials comparing each pair of treatments, and the size of each node is proportional to the number of randomised participants (sample size). The network of eligible comparisons for acceptability (dropout rate) analysis is similar.

Treatment resistance

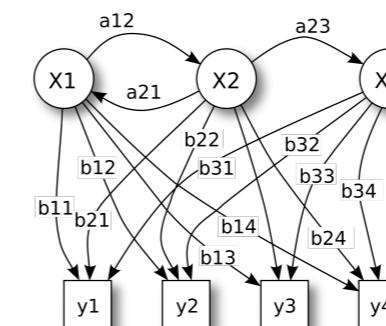
Figure 2. Network Plot of Eligible Comparisons for Primary Efficacy^a

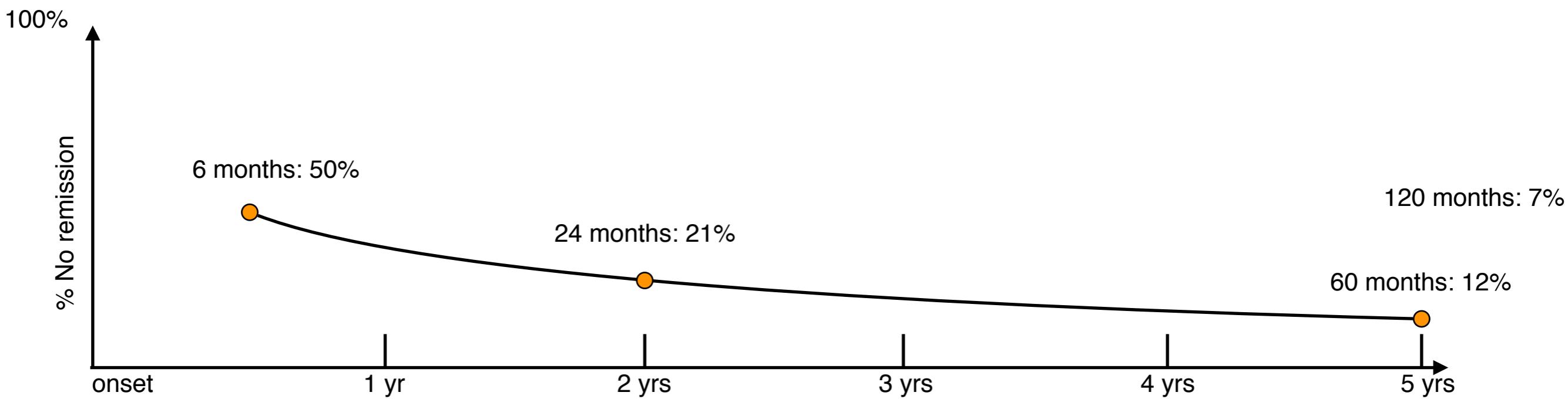


DGPPN guidelines, Carpenter et al. (2002), Bauer et al. (2002), Zhou et al. (2015)

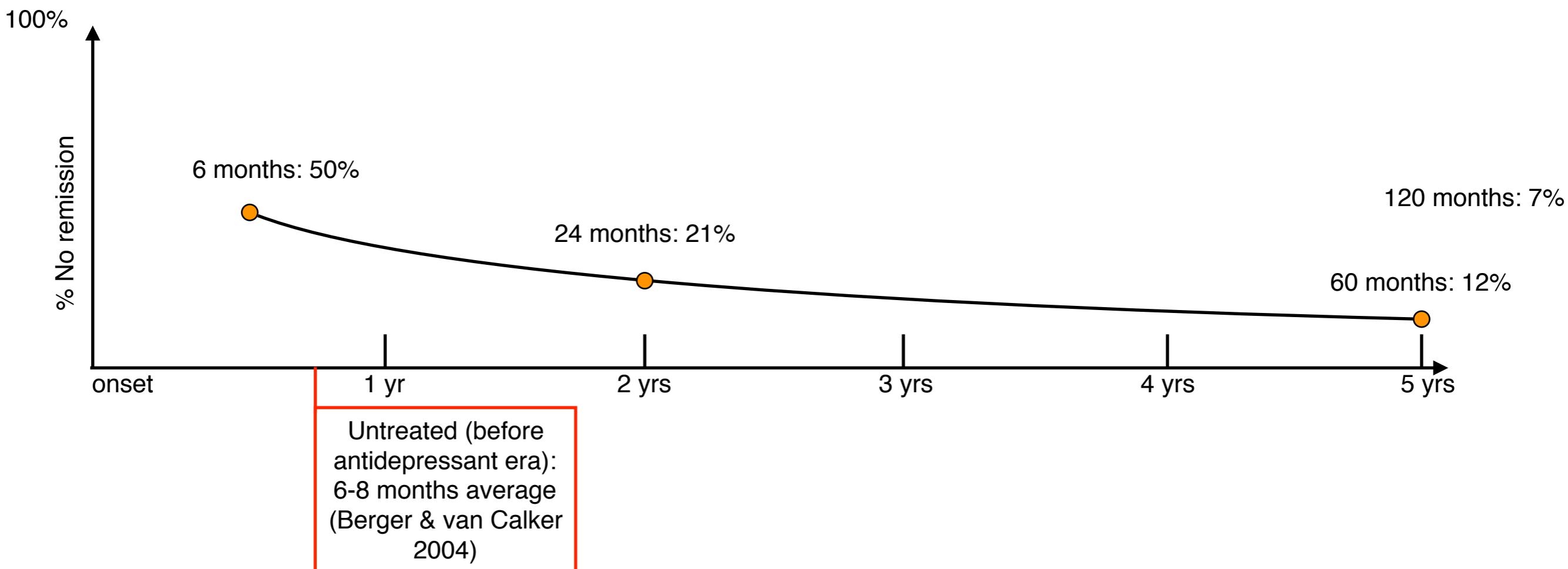


- Tests for differential diagnosis
- Predict individual treatment response
- Improve placebo response models

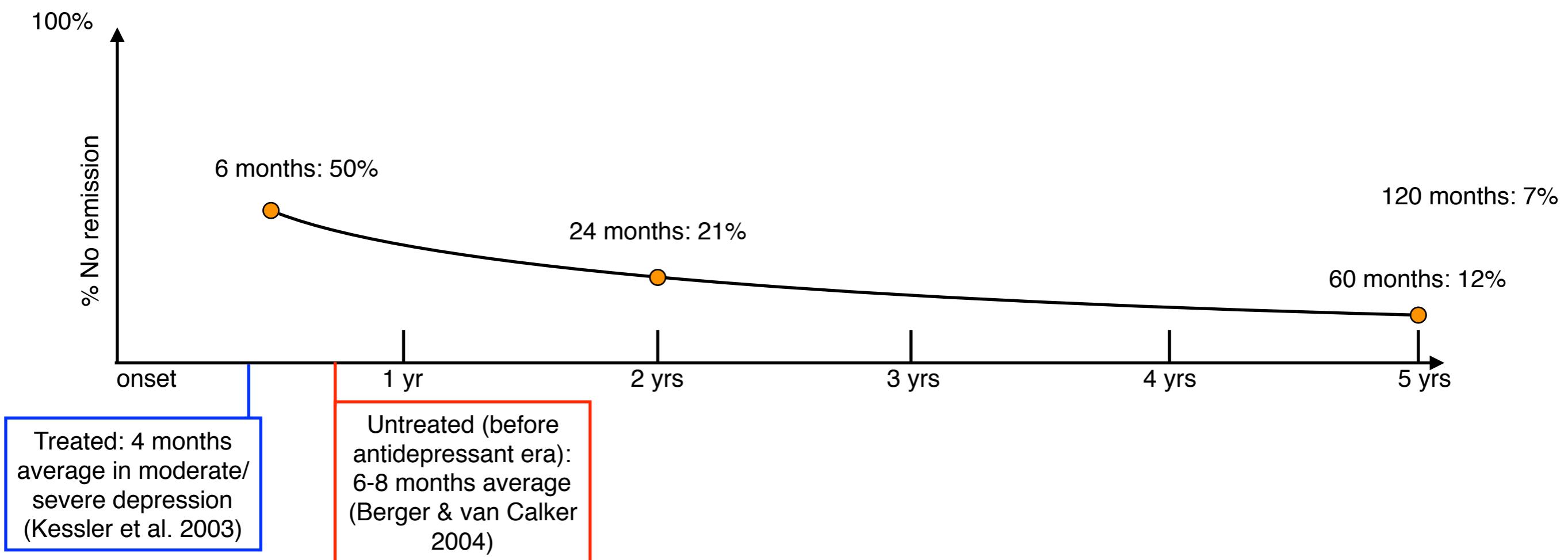




Keller et al., (1984, 1992, 1999)



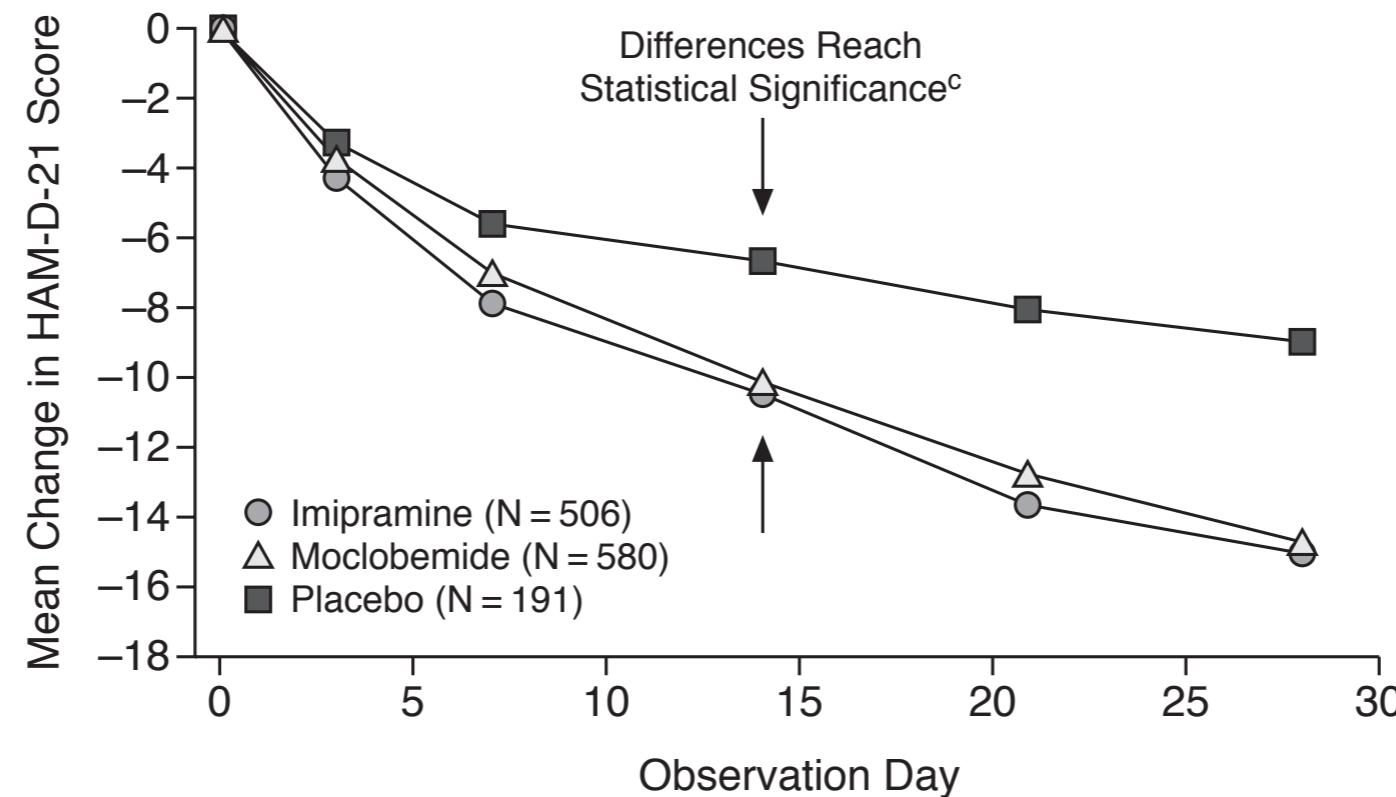
Keller et al., (1984, 1992, 1999)



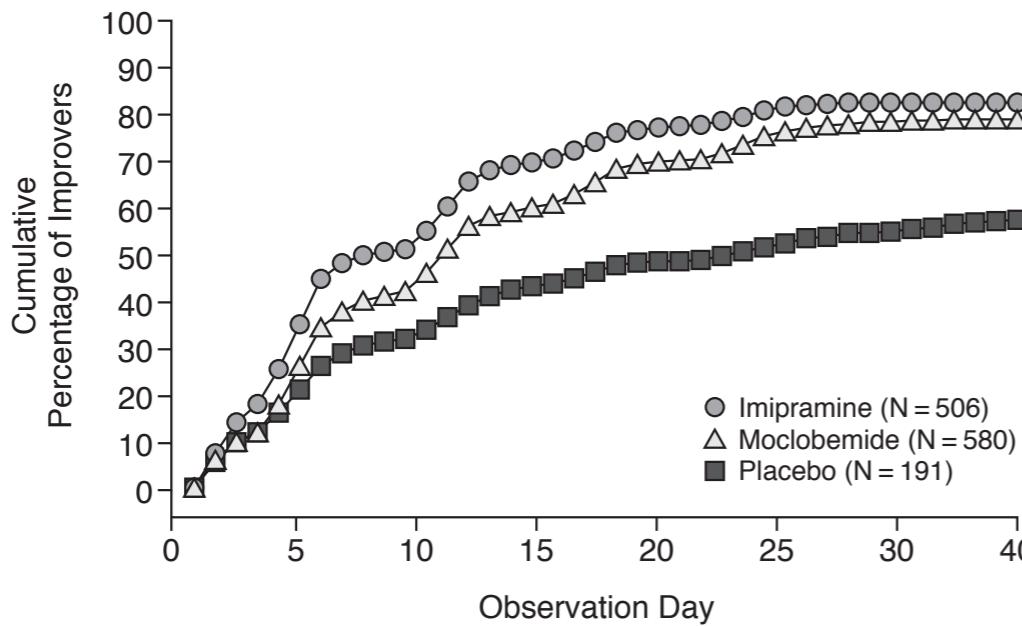
Keller et al., (1984, 1992, 1999)

Unspecific response profile

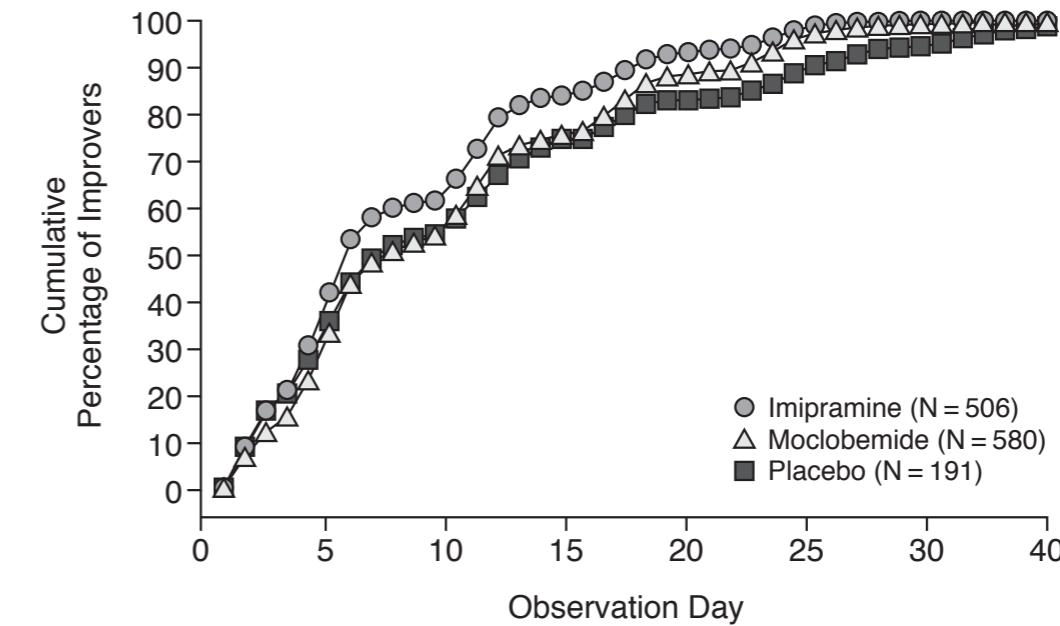
B.



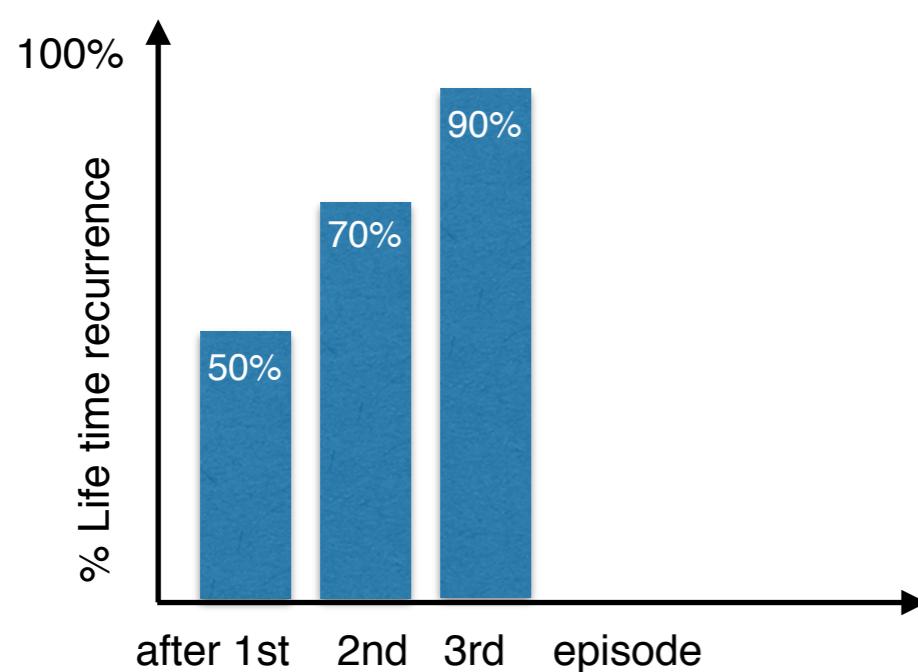
A.



B.

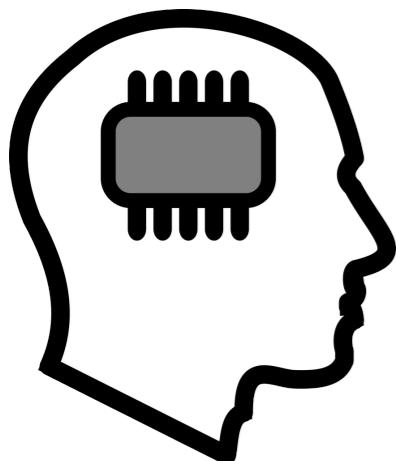
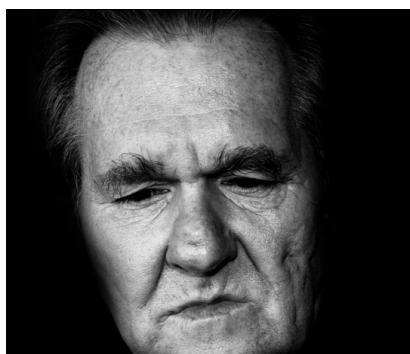


Recurrence & mortality

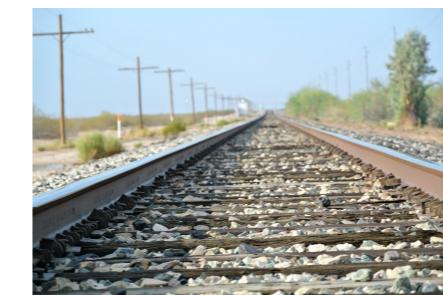


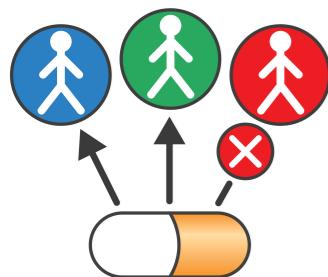
	Life time mortality from suicide
Any in-treatment due to suicidality	8 %
Any in-treatment for depression w/o suicidality	4 %
Meta-analysis	5 year mortality from suicide
Li treatment	0.17%
No Li treatment	1.48%

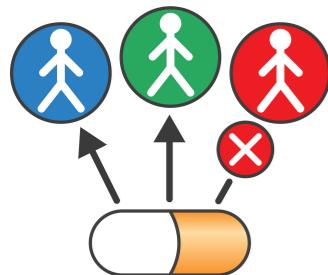
Harris & Barraclough (1997), Guzzetta et al. (2007), DGPPN guidelines



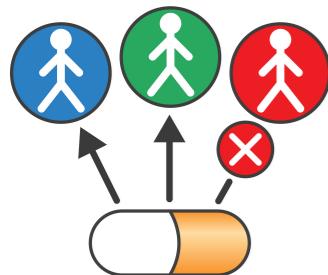
- Tests for differential diagnosis
- Predict individual treatment response
- Improve placebo response models
- Predict spontaneous remission, recurrence, suicide





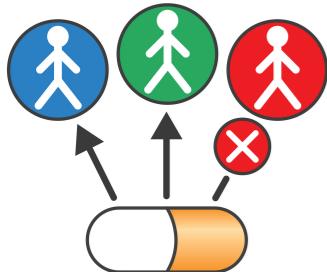


- Supervised prediction of suicidal ideation vs controls



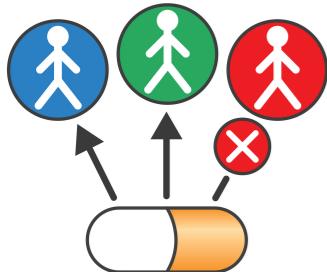
- Supervised prediction of suicidal ideation vs controls

Current state

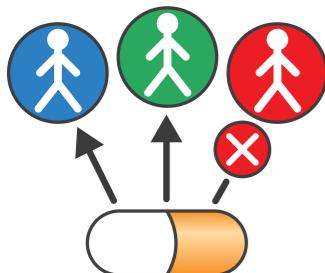


- **Supervised prediction of suicidal ideation vs controls**
- fMRI responses to death-related concepts distinguish
 - suicidal ideators ($N = 17$) from controls ($N = 17$)
 - suicide attempters from non-attempters (retrospectively)
 - Just et al. (2017)

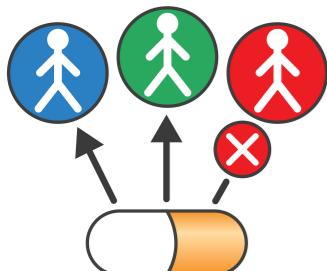
Current state



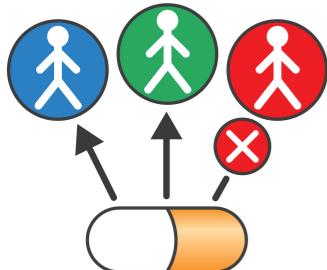
- **Supervised prediction of suicidal ideation vs controls**
- fMRI responses to death-related concepts distinguish
 - suicidal ideators ($N = 17$) from controls ($N = 17$)
 - suicide attempters from non-attempters (retrospectively)
 - Just et al. (2017)



- **Supervised prediction of suicidal ideation vs controls**
- fMRI responses to death-related concepts distinguish
 - suicidal ideators ($N = 17$) from controls ($N = 17$)
 - suicide attempters from non-attempters (retrospectively)
 - Just et al. (2017)
- Potential clinical relevance:



- **Supervised prediction of suicidal ideation vs controls**
- fMRI responses to death-related concepts distinguish
 - suicidal ideators ($N = 17$) from controls ($N = 17$)
 - suicide attempters from non-attempters (retrospectively)
 - Just et al. (2017)
- Potential clinical relevance:
- Prospectively predict later suicide attempts could allow differential treatment e.g. with Lithium



- **Supervised prediction of suicidal ideation vs controls**
- fMRI responses to death-related concepts distinguish
 - suicidal ideators ($N = 17$) from controls ($N = 17$)
 - suicide attempters from non-attempters (retrospectively)
 - Just et al. (2017)
- Potential clinical relevance:
- Prospectively predict later suicide attempts could allow differential treatment e.g. with Lithium

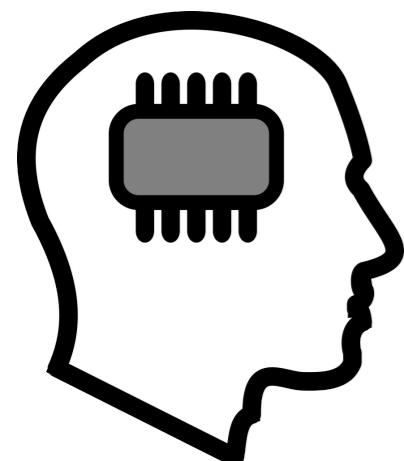
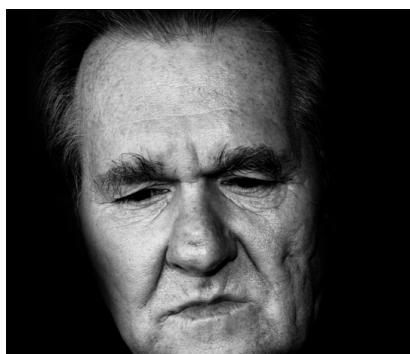


- associated with illness duration but not symptom severity
- does not remit within 8-week treatment (RCT escitalopram, sertraline, venlafaxin)
 - is not associated with symptom remission

(Shlyanski et al. 2016 Lancet Psychiatry: iSPOT-D study, 1008 outpatients)

- work productivity in first 6 treatment weeks predicts depression outcome after 3 and 7 months even when controlling for symptom remission at week 6

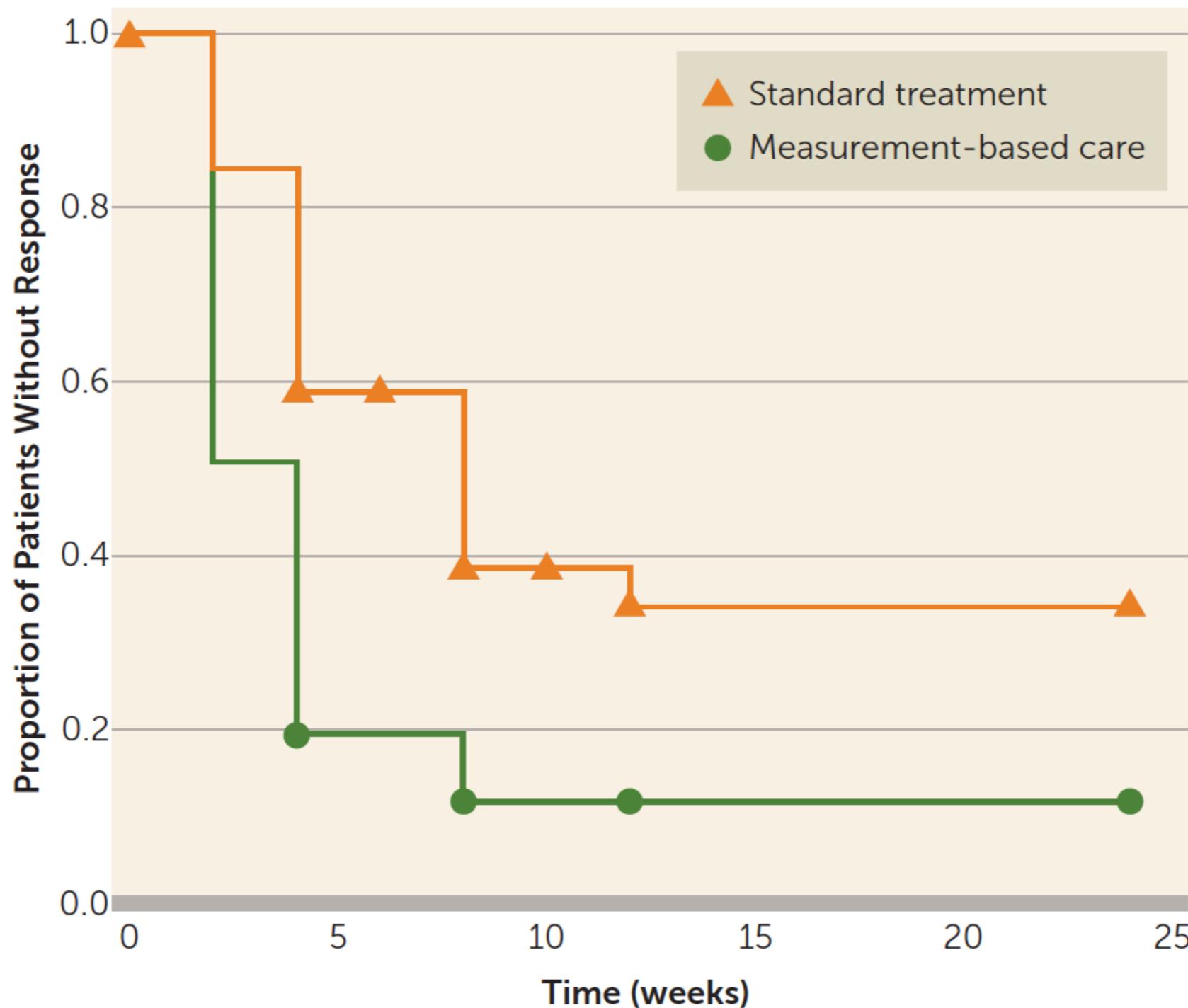
(Jha et al. 2016 Am J Psychiatry)



- Tests for differential diagnosis
- Predict individual treatment response
- Improve placebo response models
- Predict spontaneous remission, recurrence, suicide
- Models to understand cognitive impairment in absence of depressive syndrome
(computation-level: resource allocation; implementation-level)

Algorithm-based care

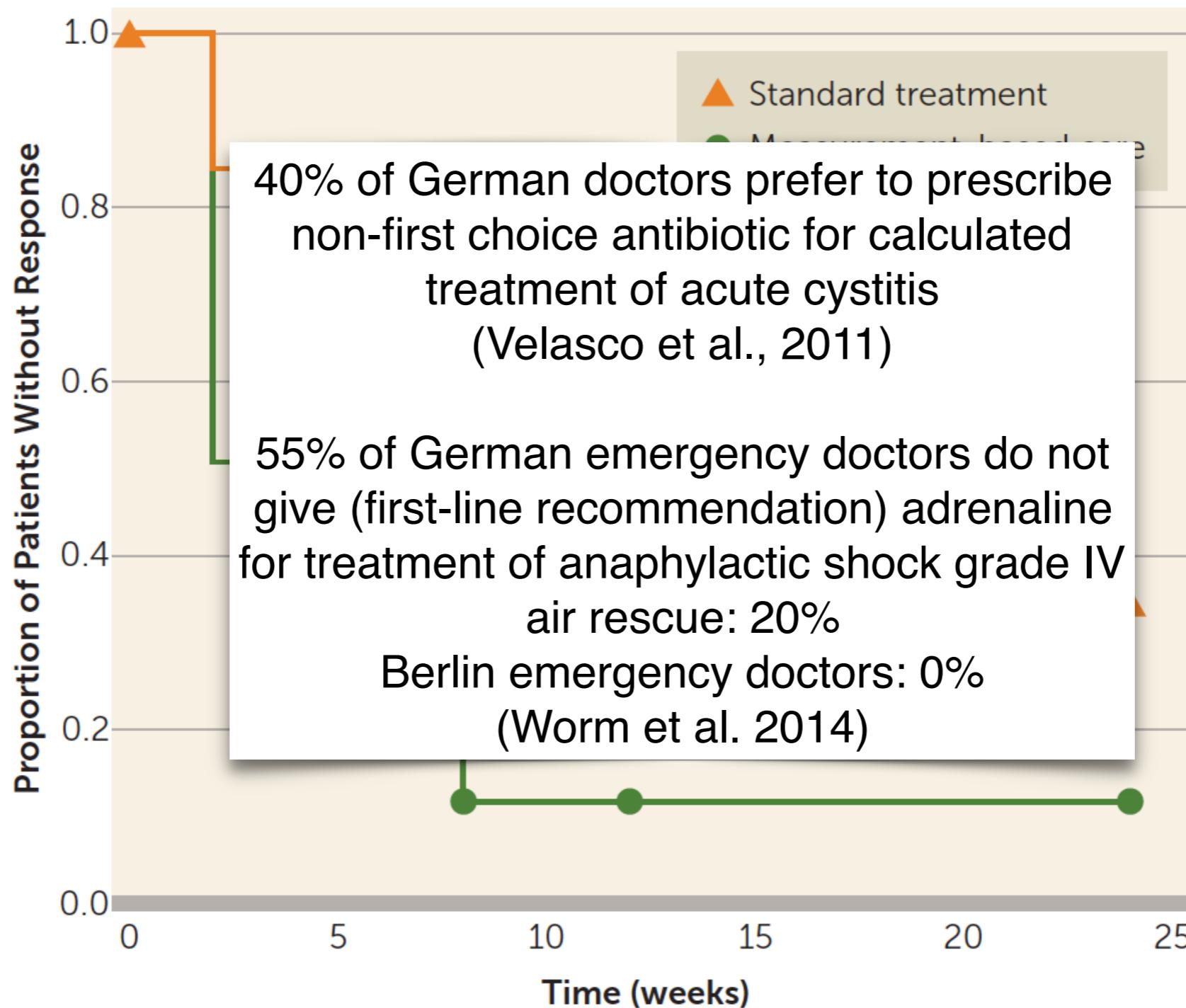
A. Estimated Mean Time to Response



Texas algorithm project, German algorithm project, STAR*D

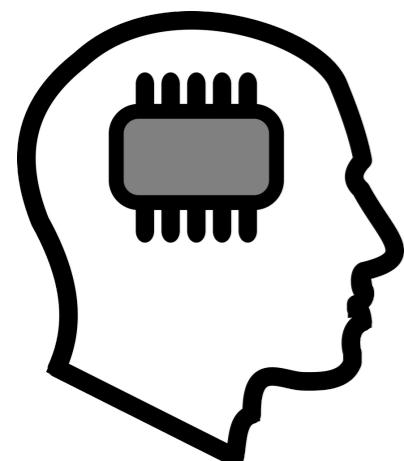
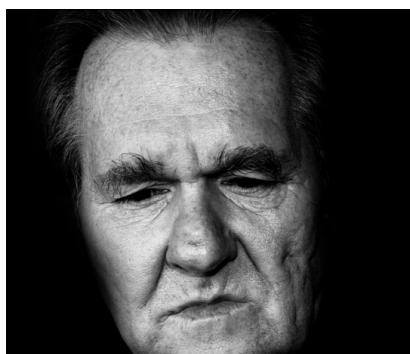
Algorithm-based care

A. Estimated Mean Time to Response



Texas algorithm project, German algorithm project, STAR*D

Clinician's wish list



- Tests for differential diagnosis
- Predict individual treatment response
- Improve placebo response models
- Predict spontaneous remission, recurrence, suicide
- Models to understand cognitive impairment in absence of depressive syndrome
(computation-level: resource allocation; implementation-level)
- **Encourage clinicians to use your results.**