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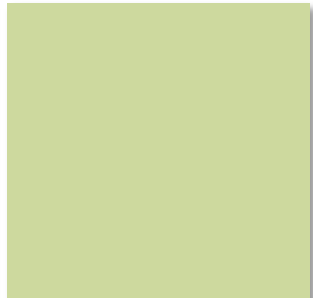
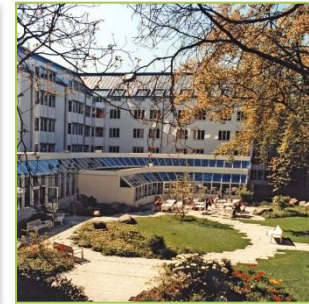


Das Recovery-Konzept bei affektiven und nicht-affektiven Psychosen - seine Bedeutung für Patienten, Angehörige, Behandelnde und zukünftige Forschung

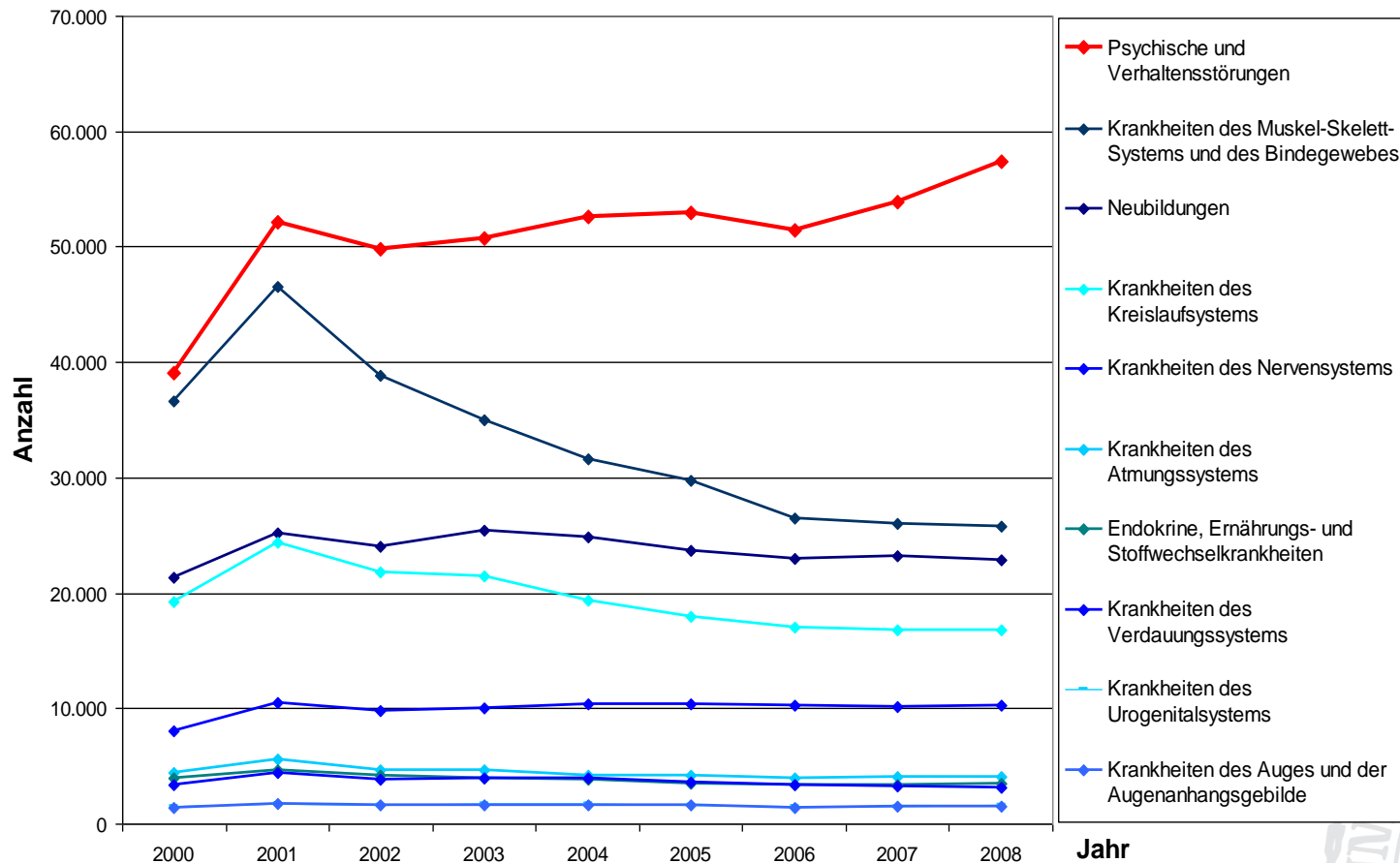


Prof. Dr. Peter Falkai

**DGBS Tagung
Haar, 09.09.2017**



PSYCHIATRIC DISEASES ARE WIDESPREAD DISEASES



Gesundheitsberichterstattung des Bundes

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<http://www.klinikum.uni-muenchen.de/Klinik-und-Poliklinik-fuer-Psychiatrie-und-Psychotherapie/de/index.html>

AFFECTIVE AND NON-AFFECTIVE PSYCHOSES: A COMMON CAUSE FOR ENDURING DISABILITY

Rank	Disease	Rank	Disease
1	Low back pain	11	Schizophrenia
2	Major depression	12	Falls
3	Iron-deficiency anaemia	13	Osteoarthritis
4	Neck pain	14	Refraction and accommodation disorders
5	Other hearing loss	15	Asthma
6	Migraine	16	Dysthymia
7	Diabetes	17	Bipolar disorder
8	COPD	18	Medication overuse headache
9	Anxiety disorders	19	Other mental and substance abuse disorders
10	Other musculoskeletal disorders	20	Dermatitis

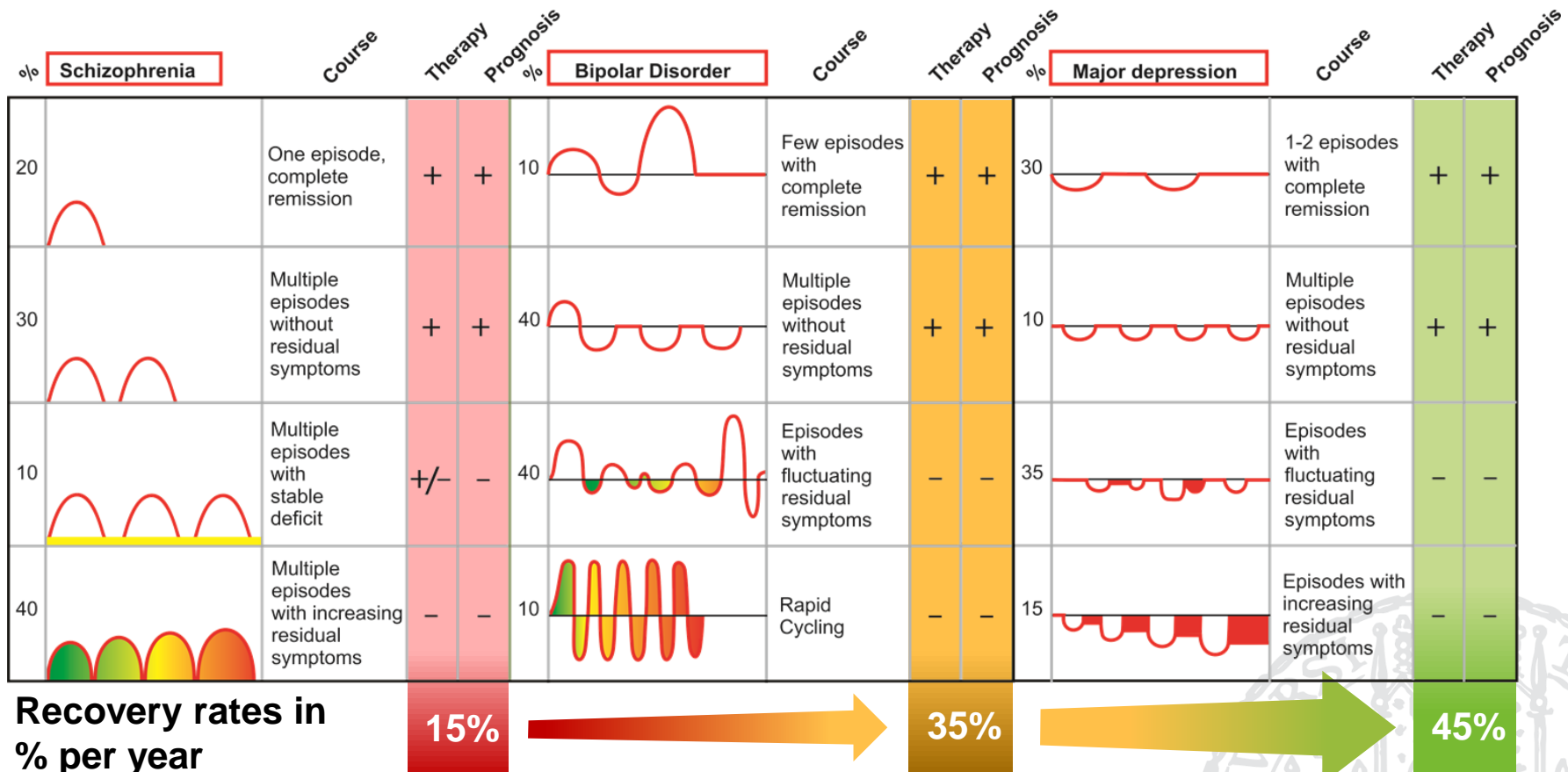
... AND A MAJOR BURDEN FOR SOCIETY

Rank	Disease	Rank	Disease
1	Low back pain	11	Schizophrenia
2	Major depression	12	Falls
3	Iron-deficiency anaemia	13	Osteoarthritis
4	Neck pain	14	Accommodation disorders
5	Other hearing loss	15	Alzheimer
6	Migraine	16	Dysthymia
7	Diabetes	17	Bipolar disorder
8	COPD	18	Medication overuse headache
9	Anxiety disorders	19	Other mental and substance abuse disorders
10	Other mental disorders		

Total of **207,000,000,000 € / year**
across 30 European countries¹

Cardiovascular diseases:
Total of **169,000,000,000 € / year**
across the EU countries²

RECOVERY IS IMPAIRED ACROSS AFFECTIVE AND NON-AFFECTIVE PSYCHOSES



**Even in the so-called episodic disorders
>50% of patients show impaired recovery**

OUTCOME DOMAINS IN AFFECTIVE AND NON-AFFECTIVE PSYCHOSES, ESPECIALLY IN SCHIZOPHRENIA

Clinical domain

- Positive symptoms
- Negative symptoms
- Cognition
- Ancillary symptoms (depression, anxiety, ...)
- Side effects

Rehabilitative domain

- Social functioning (social skills, relationships, ...)
- Instrumental functioning (coping, resources, ...)
- Occupational functioning (education, work, ...)

Humanitarian domain

- Living/housing
- Patient satisfaction
- Subjective well-being
- Quality of life

Public welfare domain

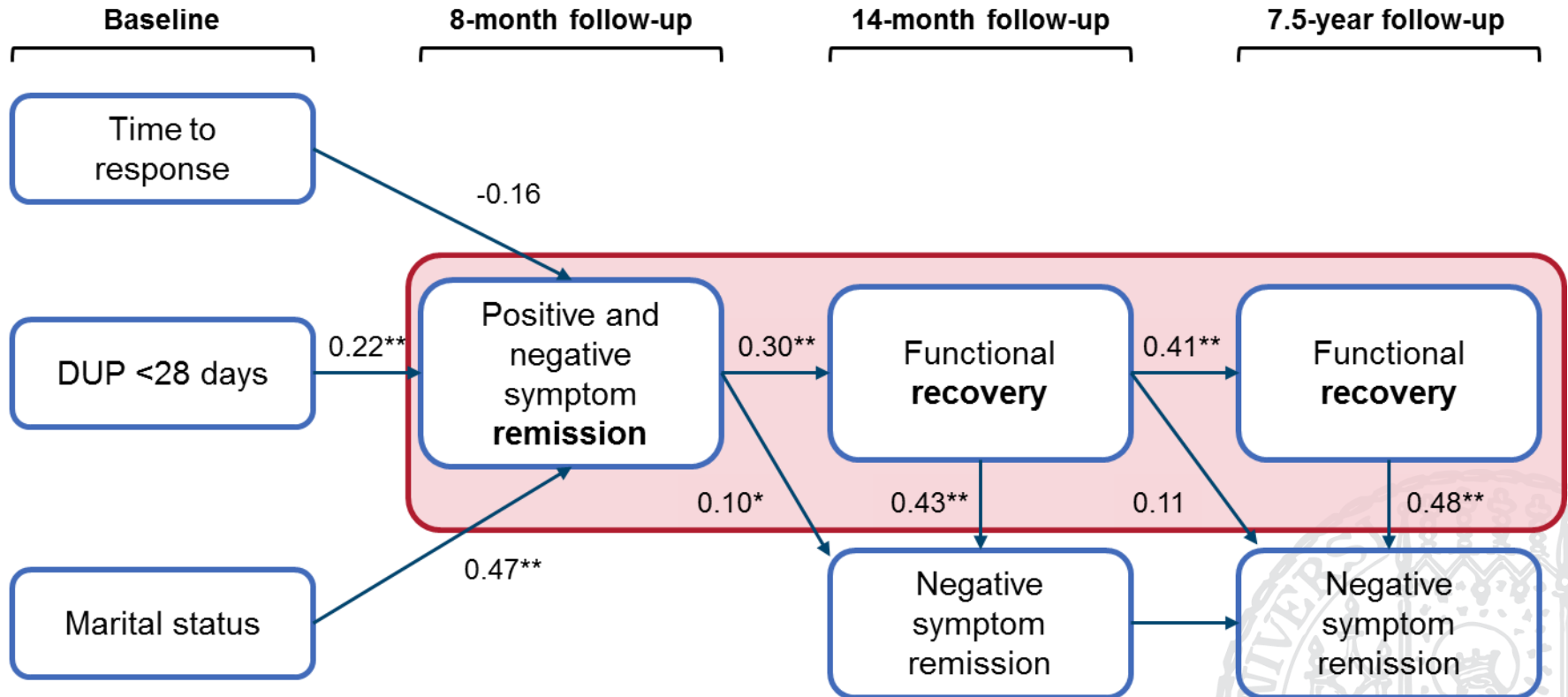
- Public safety and well-being of the individuals, family, and society

Cost domain

- Cost-benefit analysis
- Cost-effectiveness

RELATIONSHIP OF FACTORS ASSOCIATED WITH RECOVERY (n = 209 FEP)

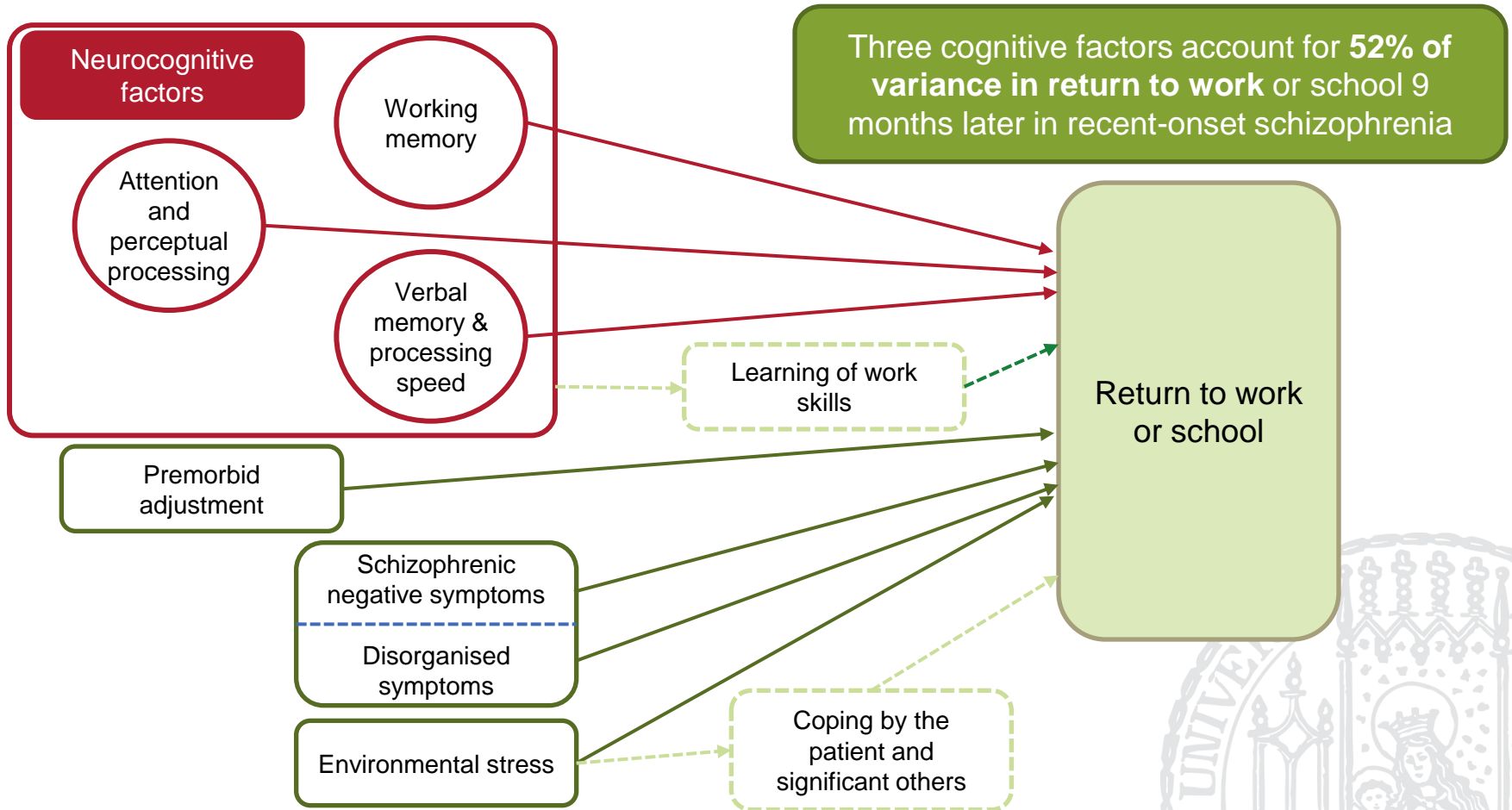
High impact of (negative) symptom remission and early functional recovery ...



*p<0.05, **p<0.01; functional recovery model; performance of the model: $\chi^2=18.98$; degrees of freedom=19; p=0.45; DUP=duration of untreated psychosis; FEP=first-episode psychosis

RELATIONSHIP OF FACTORS ASSOCIATED WITH RECOVERY (n = 47 FEP)

High impact of **cognitive functions** ...



FEP=first-episode psychosis

REMISSION IN SCHIZOPHRENIA: CONSENSUS CRITERIA ACCORDING TO ANDREASEN ET AL. 2005

Proposed items for remission criteria with cross-scale correspondence and relationship to historical constructs of psychopathology dimensions and DSM-IV criteria for schizophrenia^a

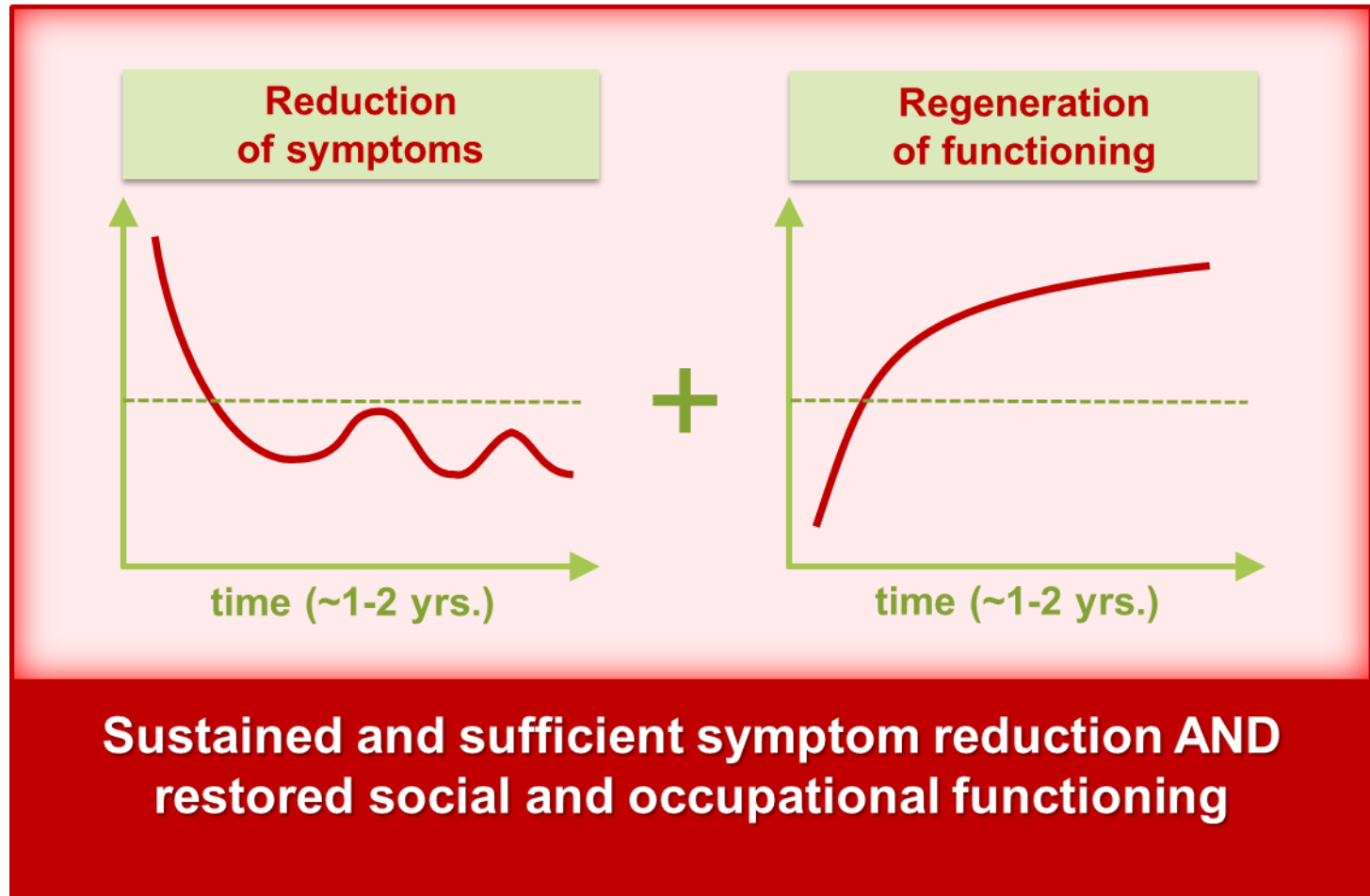
Dimensions of psychopathology	DSM-IV criterion	Proposed remission criteria items					
		SAPS and SANS items		PANSS		BPRS	
		Criterion	Global rating item number	Criterion	Item number	Criterion ^b	Item number
Psychoticism (reality distortion)	Delusions	Delusions (SAPS)	20	Delusions	P1	Grandiosity	8
				Unusual thought content	G9	Suspiciousness	11
	Hallucinations	Hallucinations (SAPS)	7	Hallucinatory behaviour	P3	Unusual thought content	15
Disorganisation	Disorganised speech	Positive formal thought disorder (SAPS)	34	Hallucinatory behaviour	P3	Hallucinatory behaviour	12
	Grossly disorganised or catatonic behaviour	Bizarre behaviour (SAPS)	25	Conceptual disorganisation	P2	Conceptual disorganisation	4
Negative symptoms (psychomotor poverty)	Negative symptoms	Affective flattening (SANS)	7	Mannerisms/posturing	G5	Mannerisms/posturing	7
		Avolition-apathy (SANS)	17	Blunted affect	N1	Blunted affect	16
		Anhedonia-asociality (SANS)	22	Social withdrawal	N4	No clearly related symptom	
		Alogia (SANS)	13	Lack of spontaneity	N6	No clearly related symptom	

^aFor symptomatic remission, **maintenance over a 6-month period** of simultaneous ratings of mild or less on all items is required; rating scale items are listed by item number; ^buse of BPRS criteria may be complemented by use of the SANS criteria for evaluating overall remission; BPRS=Brief Psychiatric Rating Scale; PANSS=Positive and Negative Syndrome Scale; SAPS=Scale for Assessment of Positive Symptoms; SANS=Scale for Assessment of Negative Symptoms

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DISABILITY AND COSTS ARE DRIVEN BY IMPAIRED RECOVERY! WHAT DOES ‚RECOVERY‘ MEAN?

RECOVERY



RECOVERY AS A PSYCHOLOGICAL CONSTRUCT (1)

Correlation of Total Recovery Scale Score with Psychosocial Variables (N=35)

	<i>Recovery Scale Score</i>
Rosenberg Self-Esteem Scale	.55***
Empowerment Scale: Self-orientation	-.71***
Empowerment Scale: Community-orientation	-.17
SSQ Satisfaction with Support Network	.14
SSQ Size of Support Network	.48***
Global Assessment of Functioning	.04
BPRS Total Score	-.44**
Quality of Life	.62***
NARA Total Needs	-.23
NARA Total Resources	.22
WAIS-R Vocabulary	.21
Education	.18
Age	.34*
Gender	.13
Race	.21
Marital Status	.10

RECOVERY AS A PSYCHOLOGICAL CONSTRUCT (2)

Results of Regression Analysis with the Recovery Scale Score as the Dependent Variable and Independent Variables of Rosenberg Self-Esteem, Self-Orientation from the Empowerment Scale, and Quality of Life

<i>Step</i>	<i>Independent Variable</i>	<i>F to Enter</i>	<i>Multiple R</i>
1	Rosenberg Self-Esteem	6.19	0.45
2	Empowerment Scale: Self-Orientation	12.70	0.70
3	Age	6.60	0.78
		F-to-Enter less than 3.00	
5	Size of Support Network	0.81	
6	Quality of Life	0.47	
7	Total BPRS Symptoms	0.02	

Achieving Remission and Recovery in Bipolar Disorder

Francesc Colom, PsyD, MSc, PhD

J Clin Psychiatry 2010;71(11):e32

10.4088/JCP.9075tx2c

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THE ILLNESS MANAGEMENT AND RECOVERY PROGRAMME: RATIONALE, DEVELOPMENT AND PRELIMINARY FINDINGS (1)

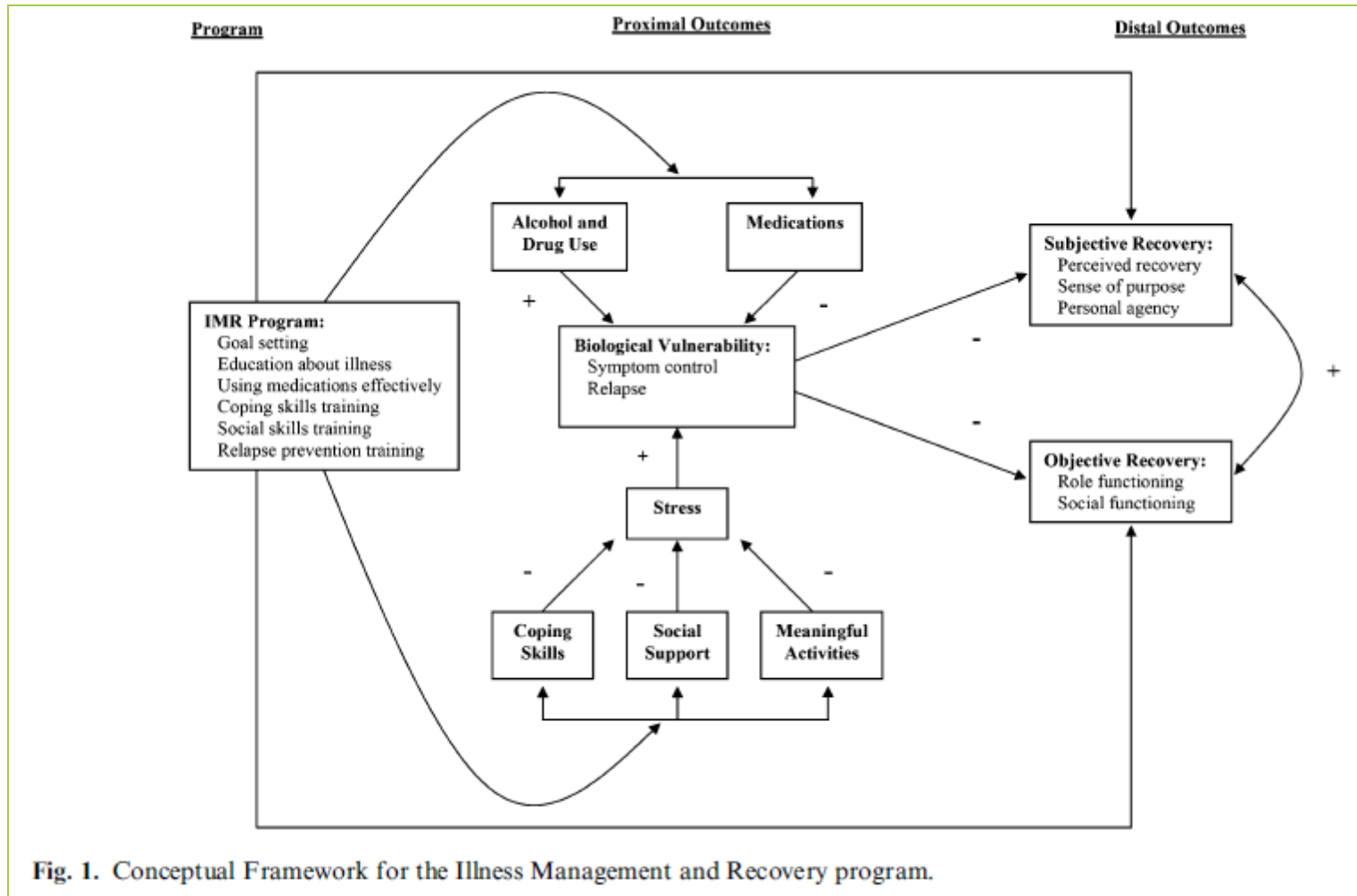
Table 1. Overview of Topics for Illness Management and Recovery (IMR) Modules

Module	Topic	Goals	Number of Sessions
1	Recovery strategies	<ul style="list-style-type: none"> • Engage clients in group • Increase awareness of recovery • Set personal recovery goals • Develop plans for achieving goals 	4
2	Practical facts about schizophrenia	<ul style="list-style-type: none"> • Identify symptoms associated with schizophrenia • Dispel myths about schizophrenia • Address stigma • Help clients become aware of people with schizophrenia who lead productive lives 	4
3	Stress-vulnerability model and treatment strategies	<ul style="list-style-type: none"> • Explain that stress and biological vulnerability cause symptoms of schizophrenia • Discuss strategies for reducing stress and biological vulnerability • Inform clients about treatment options 	3
4	Building social support	<ul style="list-style-type: none"> • Discuss how building social support can facilitate recovery • Teach strategies for increasing support, such as finding places to meet people, conversation skills, and getting closer to people 	7

THE ILLNESS MANAGEMENT AND RECOVERY PROGRAMME: RATIONALE, DEVELOPMENT AND PRELIMINARY FINDINGS (1 CONT.)

5	Using medications effectively	<ul style="list-style-type: none"> • Teach clients about benefits and side effects of medications • Increase skills for discussing medication issues with physician • Help clients weigh pros and cons of taking medications • Teach behavioral tailoring to facilitate medication adherence 	4
6	Reducing relapses	<ul style="list-style-type: none"> • Teach clients that relapses are predictable and preventable • Develop an individual relapse prevention plan 	4
7	Coping with stress	<ul style="list-style-type: none"> • Inform clients they can reduce stress and improve their ability to cope with it effectively • Identify and practice strategies to prevent and to cope with stress 	5
8	Coping with problems and persistent symptoms	<ul style="list-style-type: none"> • Teach problem-solving model • Help clients identify common problems and symptoms that cause distress • Practice coping strategies for persistent symptoms 	6
9	Getting your needs met in the mental health system	<ul style="list-style-type: none"> • Review different mental health services • Identify insurance benefits clients are entitled to • Help clients identify strategies to advocate for self in mental health system 	3

THE ILLNESS MANAGEMENT AND RECOVERY PROGRAMME: RATIONALE, DEVELOPMENT AND PRELIMINARY FINDINGS (2)



THE ILLNESS MANAGEMENT AND RECOVERY PROGRAMME: RATIONALE, DEVELOPMENT AND PRELIMINARY FINDINGS (3)

Table 2. Demographics Total Australian/US Sample ($N = 24$)

	Mean (count)	SD (%)
Age	39.12	11.20
Education ($N = 20$)	14.70	3.11
Gender		
Male	15	63
Female	9	37
Ethnicity		
Caucasian	16	89
Black	2	11
Marital situation		
Never married	20	83
Married	3	13
Divorced	1	4
Primary diagnosis		
Schizophrenia	10	42
Schizoaffective disorder	11	46
Bipolar disorder	2	8
Delusional disorder	1	4
Treatment		
Individual IMR	10	42
Group IMR	14	58



THE ILLNESS MANAGEMENT AND RECOVERY PROGRAMME: RATIONALE, DEVELOPMENT AND PRELIMINARY FINDINGS (4)

Table 3. IMR Pilot Study Assessment Measures

	Baseline (<i>N</i> = 24)		Posttreatment (<i>N</i> = 24)		Follow-up (<i>N</i> = 17)		F (<i>df</i>)	P	<i>d</i>	
	M	SD	M	SD	M	SD				
Illness management										
BSI GSI ^a	1.03	0.17	0.92	0.15	0.77	0.14	4.37 (2, 22)	.03	.50	
Coping—total symptoms ^b	6.05	1.07	4.62	0.95	5.87	1.18	2.28 (2, 14)	.14	.38	
Coping effective ^c	3.05	0.28	3.55	0.27	3.25	0.21	3.79 (2, 22)	.04	.84	
Client IMR—shortened/sum ^{c,d}	36.97	2.29	45.82	2.18	42.08	2.62	10.82 (2, 16)	.00	.83	
Knowledge of illness ^{d,e}	91.52	1.38	95.32	0.86	94.66	1.34	6.63 (2, 23)	.01	.63	
Social support	45.82	1.96	47.65	1.64	46.90	1.88	0.44 (2, 20)	.65	.18	
Recovery										
Recovery mean ^{d,e}	3.81	0.10	3.98	0.10	4.04	0.11	4.76 (2, 41)	.01	.64	
RAS—hope ^{d,e}	32.75	1.14	34.27	1.14	34.96	1.19	3.66 (2, 40)	.04	.55	
RAS—willingness ask help	12.11	0.32	12.91	0.32	12.73	0.36	2.71 (2, 40)	.08	.30	
RAS—goal oriented ^{d,e}	18.75	0.84	20.17	0.84	20.94	0.91	3.28 (2, 39)	.05	.48	
RAS—rely on others	16.90	0.41	16.53	0.41	17.03	0.44	1.24 (2, 41)	.30	.02	
RAS—not dominated symptom ^{d,e}	9.95	0.54	11.24	0.54	11.48	0.60	3.48 (2, 41)	.04	.60	
GAF ^{d,e}	53.71	2.43	61.45	3.05	59.99	3.43	10.91 (2, 18)	.00	.80	

Note: IMR, Illness Management and Recovery;
Functioning.

^aBaseline > follow-up (*P* < .05).

^b*N* = 16.

^c*N* = 15.

^dBaseline < posttest (*P* < .05).

^eBaseline < follow-up (*P* < .05).

THE ILLNESS MANAGEMENT AND RECOVERY PROGRAMME: RATIONALE, DEVELOPMENT AND PRELIMINARY FINDINGS (5)

Table 4. Participant Feedback From Illness Management and Recovery Satisfaction Survey (*N* = 22)

	Not Helpful/Respectful/ Useful <i>N</i> (%)	Helpful/Respectful/ Useful <i>N</i> (%)	Very Helpful/Respectful/ Useful <i>N</i> (%)
Covers sufficient material	1 (4)	21 (96)	0
Materials are understandable ^a	1 (5)	10 (48)	10 (48)
Useful	0	13 (59)	9 (41)
Respectful	0	9 (41)	13 (59)
Helps better manage symptoms	0	15 (68)	7 (32)
Helps recovery	0	14 (64)	8 (36)

^a*N* = 21.

COGNITIVE REMEDIATION INDUCES PLASTIC CHANGES IN SCHIZOPHRENIA (1)

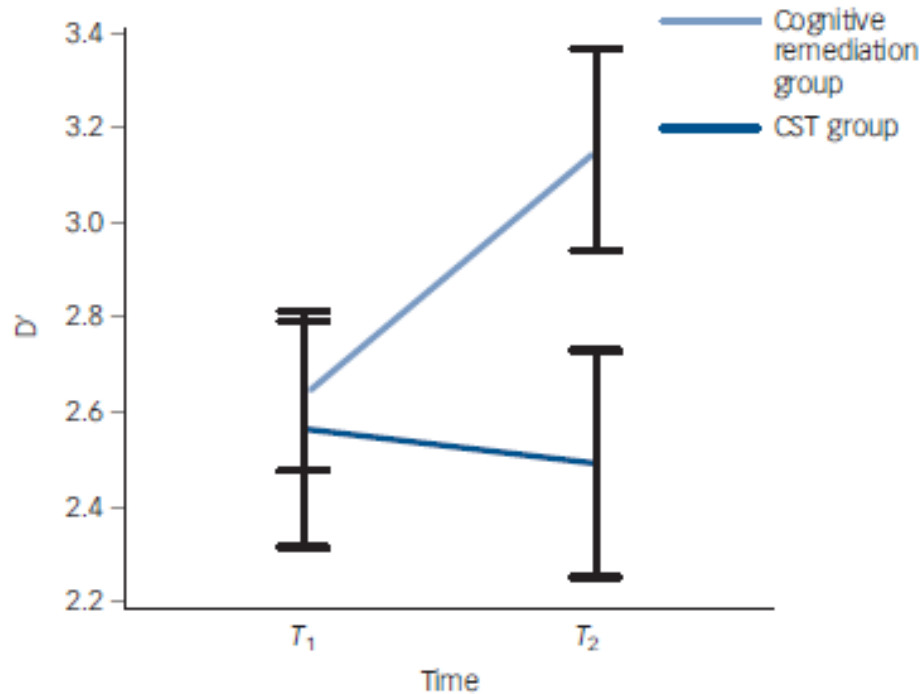


Fig. 1 Picture N-Back task behavioural findings.

Patients in the cognitive remediation intervention group showed an increase in d' from time 1 (T_1 , mean 2.62, s.d. = 0.60) to time 2 (T_2 , mean 3.15, s.d. = 0.82) on the 2-back trials of the picture N-back task (results using %-correct can be found in online Table DS2), whereas those in the computer skills training group (CST group) showed no change from T_1 (mean 2.54, s.d. = 0.88) to T_2 (mean 2.47, s.d. = 0.86).

COGNITIVE REMEDIATION INDUCES PLASTIC CHANGES IN SCHIZOPHRENIA (2)

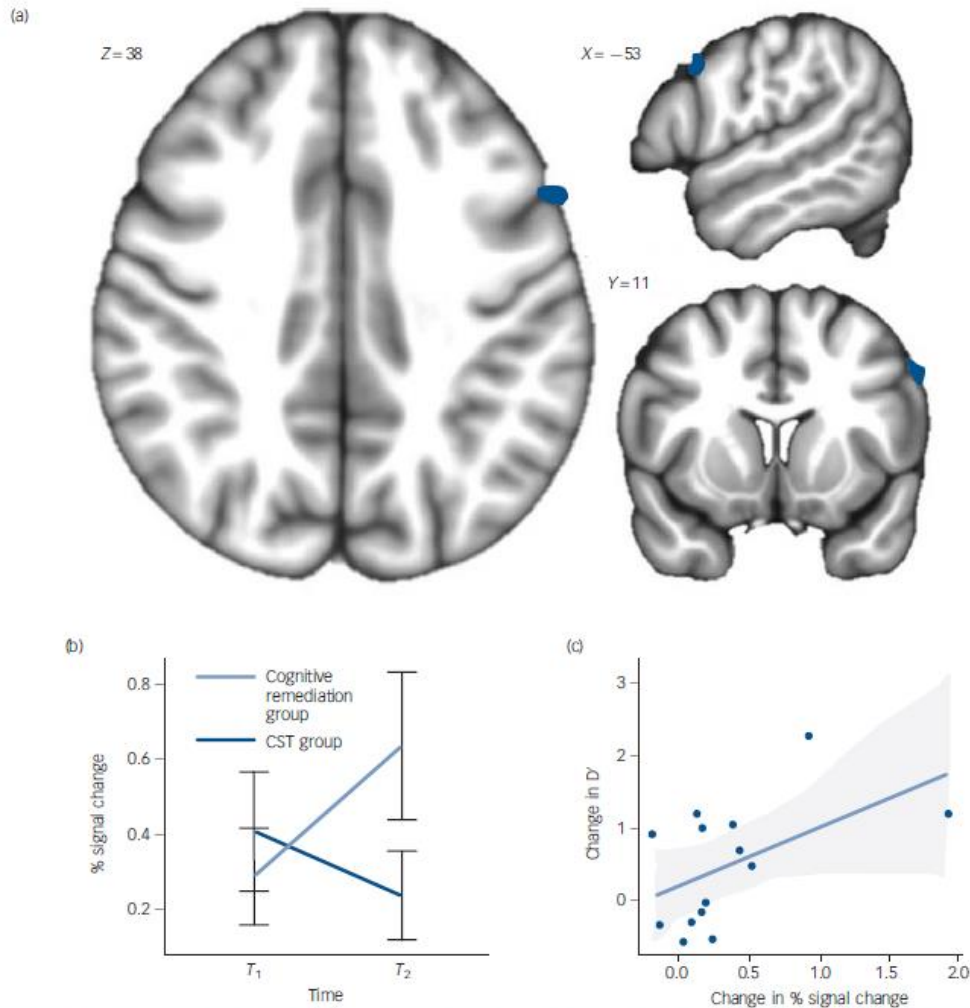


Fig. 2 Group \times time interaction in the left dorsolateral prefrontal cortex (DLPFC) region of interest (ROI) for 2-back v. 0-back blocks (2Bv0B).

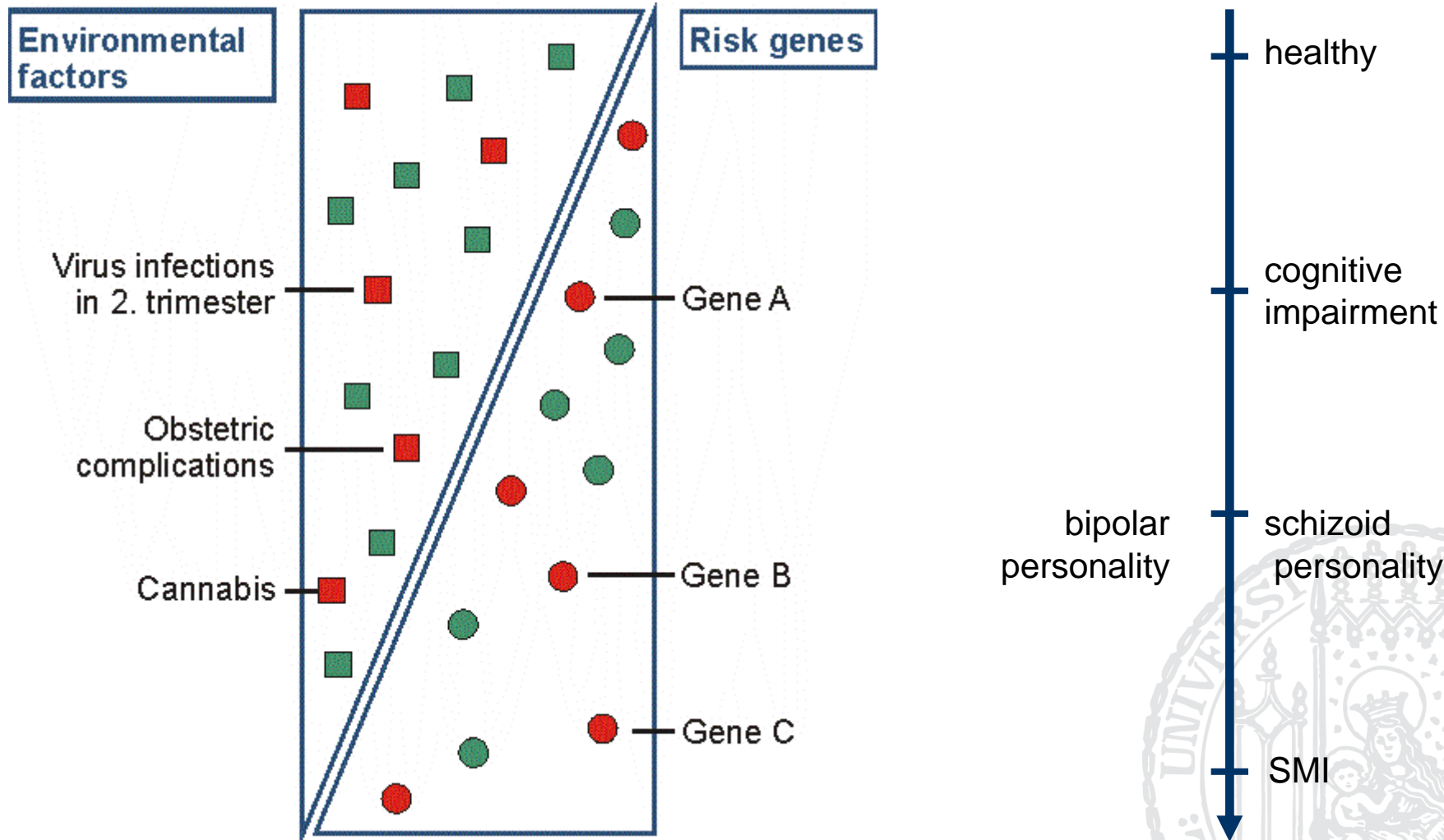
We observed a voxel-wise group \times time interaction in the left DLPFC ROI during the 2Bv0B condition in the cognitive remediation intervention group (a) driven by increases from pre- to post-training in the cognitive remediation group but not the computer skills training group (CST group) (b). (c) Change in per cent signal change extracted from the significant voxels in the left DLPFC were positively correlated with changes in d' on the picture N-back task ($r = 0.51$, $P(\text{hypothesised}) < 0.05$). This relationship held when using a robust linear estimator to control for the effects of outliers ($r = 0.56$, $P(\text{hypothesised}) < 0.05$).

Ramsay I et al. 2017: Br J Psychiatry; 210: 216-222

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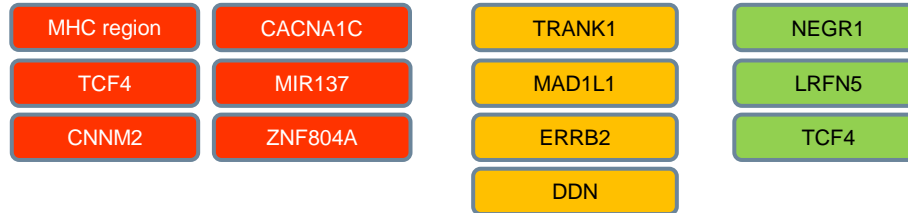
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AETIOLOGY OF AFFECTIVE AND NON-AFFECTIVE PSYCHOSES



GWAS POINT TO NEURAL PLASTICITY AS CANDIDATE SURROGATE OF IMPAIRED RECOVERY

Top SNP hits in disease-specific GWAS

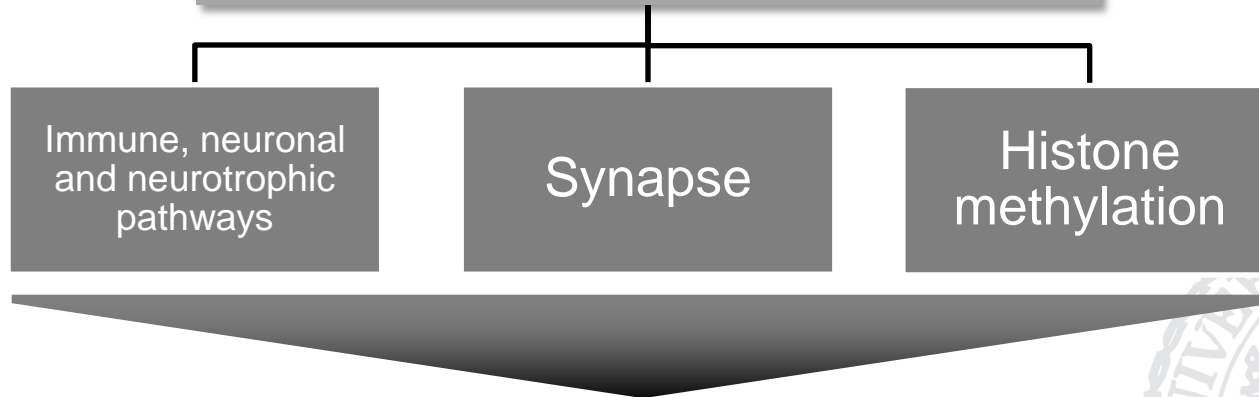


Sullivan et al., Nat Rev Genet, 2012

Cross-disorder approach

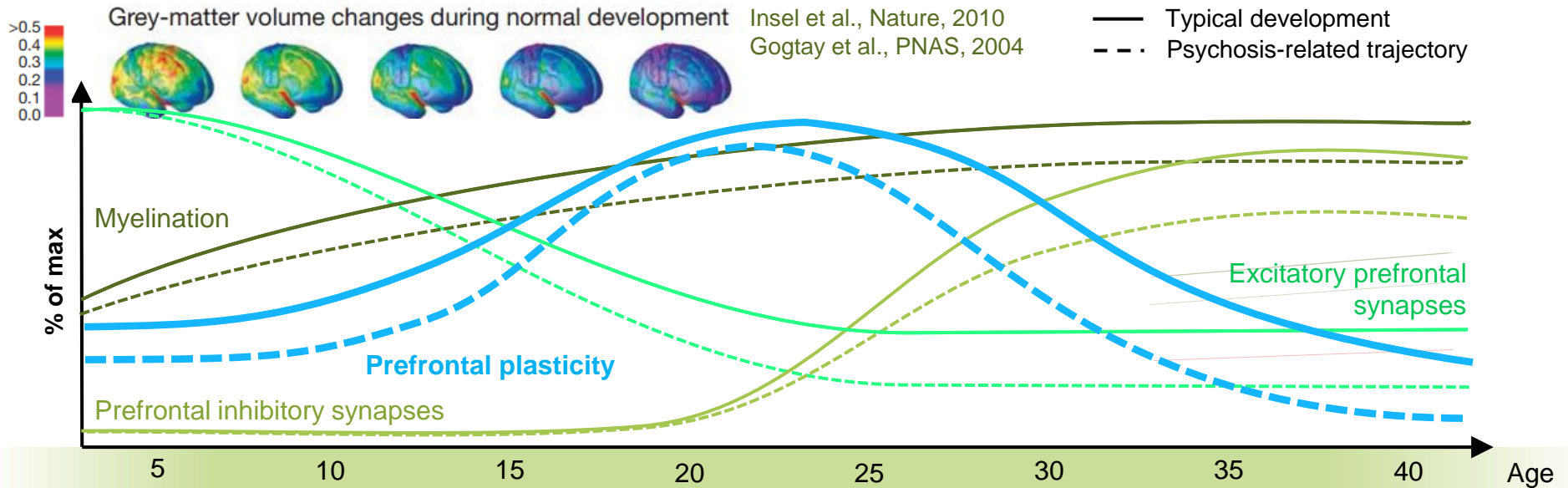
Pathway enrichment analyses based on Psychiatric Genomics Consortium data in severe mental illness

The Network and Pathway Analysis Subgroup of the Psychiatric Genomics Consortium, Nat Neurosci, 2015



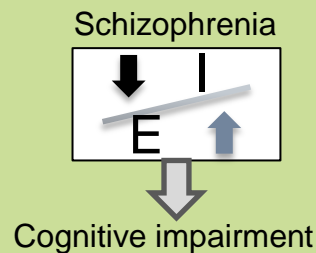
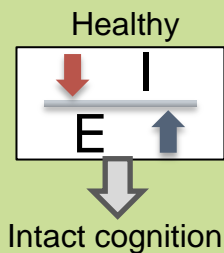
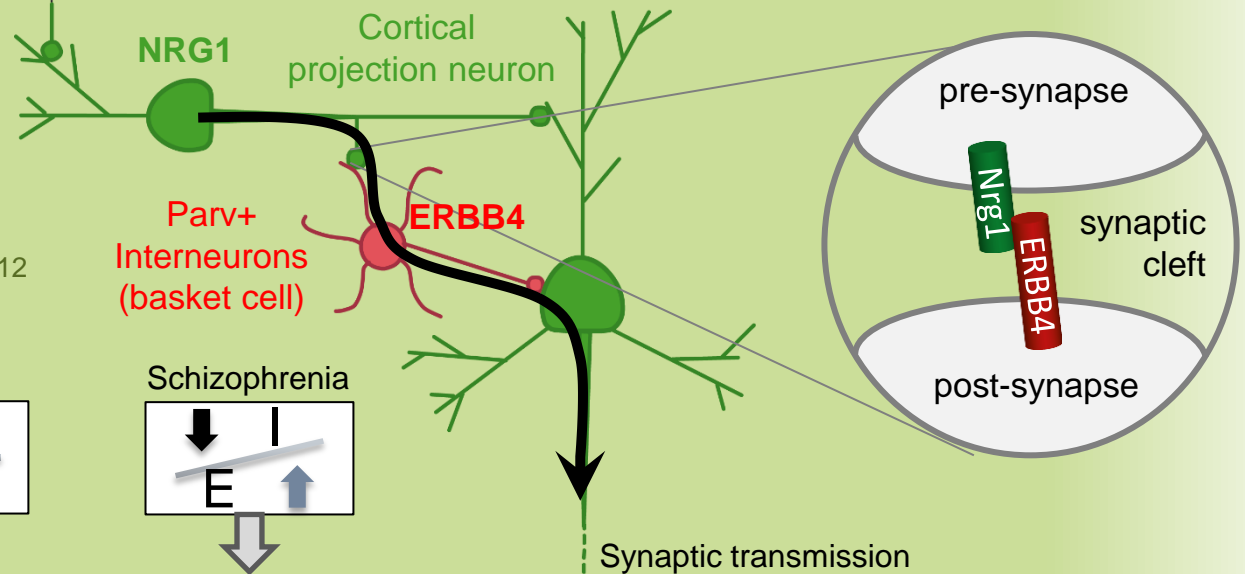
Genetic risk factors relate to cross-disorder disturbances of neural plasticity

Impaired recovery – trajectories of impaired neural plasticity

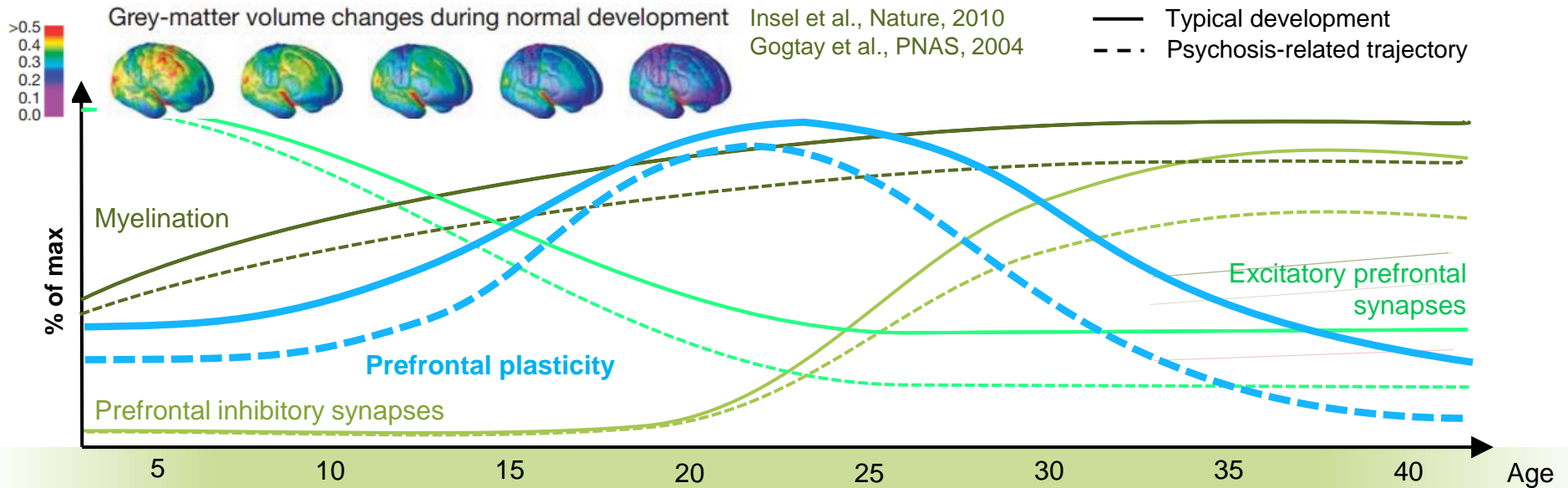


NRG1-ERBB4-related pathway disruption affects neural plasticity

Stefansson et al., Nature 2009
 Ripke et al., Nat Gen 2013
 Agarwal et al., Cell Rep, 2014
 Lewis et al, TINS, 2012
 Weickert et al, Transl Psychiatry 2012
 Hahn et al, Nat Med, 2006



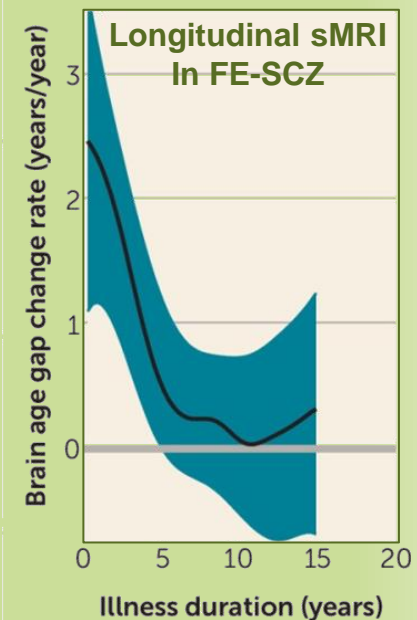
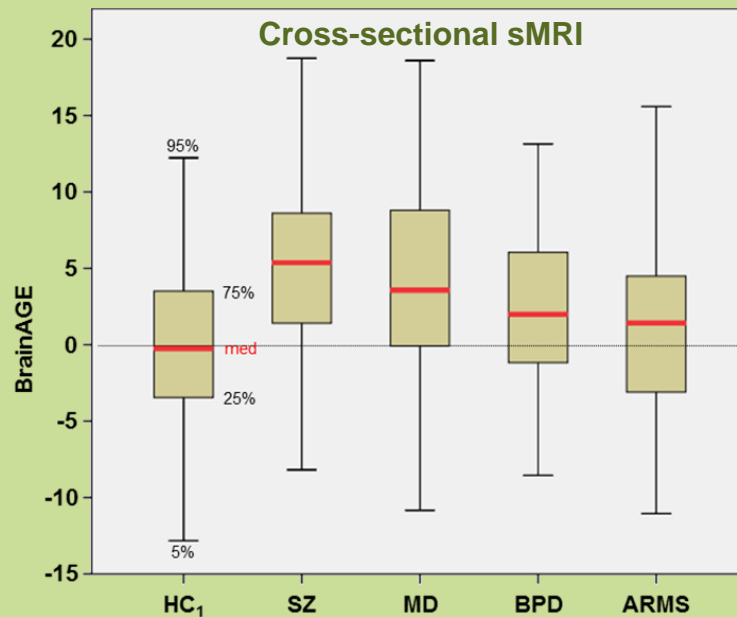
Dysmaturational abnormalities and impaired recovery



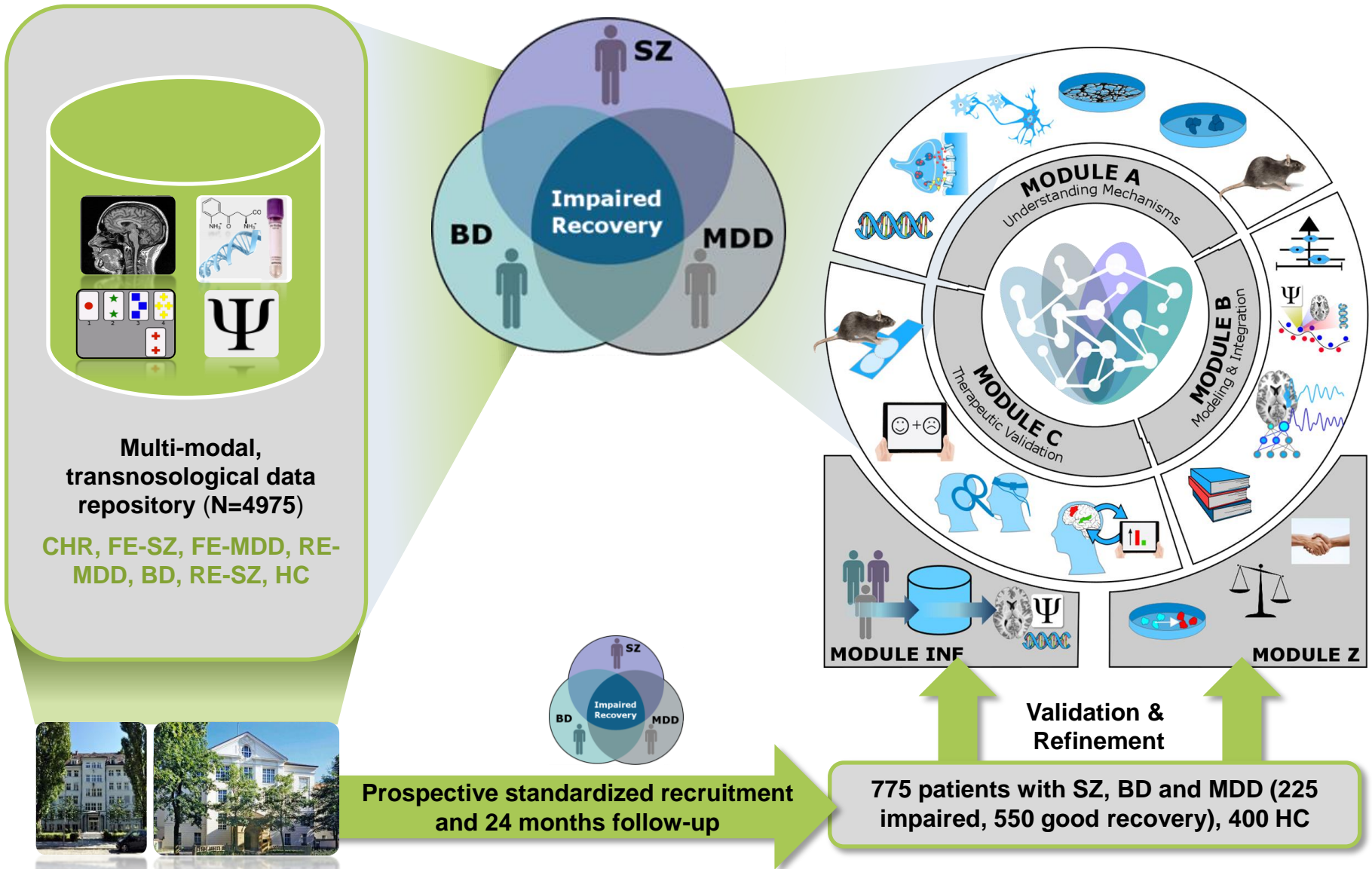
Transnosological BrainAGE analysis using machine learning

Koutsouleris et al., Schizophr Bulletin, 2014

Schnack et al., AJP, 2016

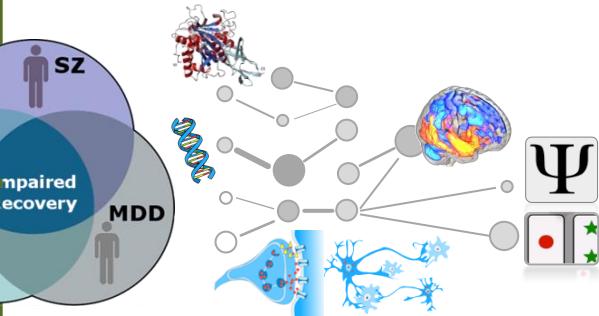


Understanding impaired recovery requires a multi-scale transnosological analysis approach



CRC's 12-year concept from a ,bird's perspective'

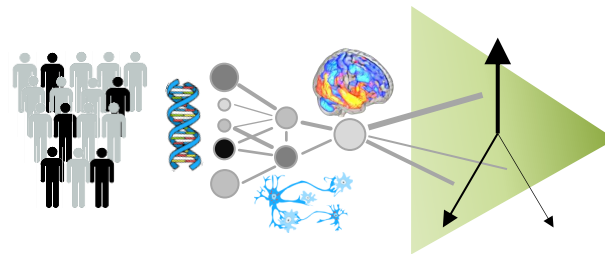
'Multiscale knowledge molecules'



Discover a library of candidate multiscale mechanisms in the existing / new CRC data.

Years 1 – 4

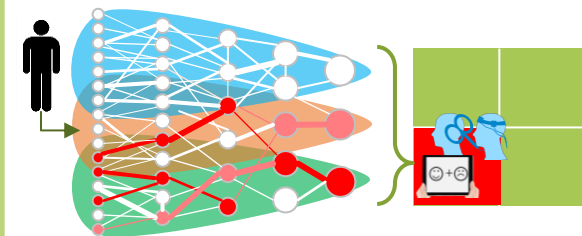
Causal networks



Refine, assemble and therapeutically validate multiscale mechanisms and predictors in new CRC data.

Years 5 – 8

Treatment profiling system

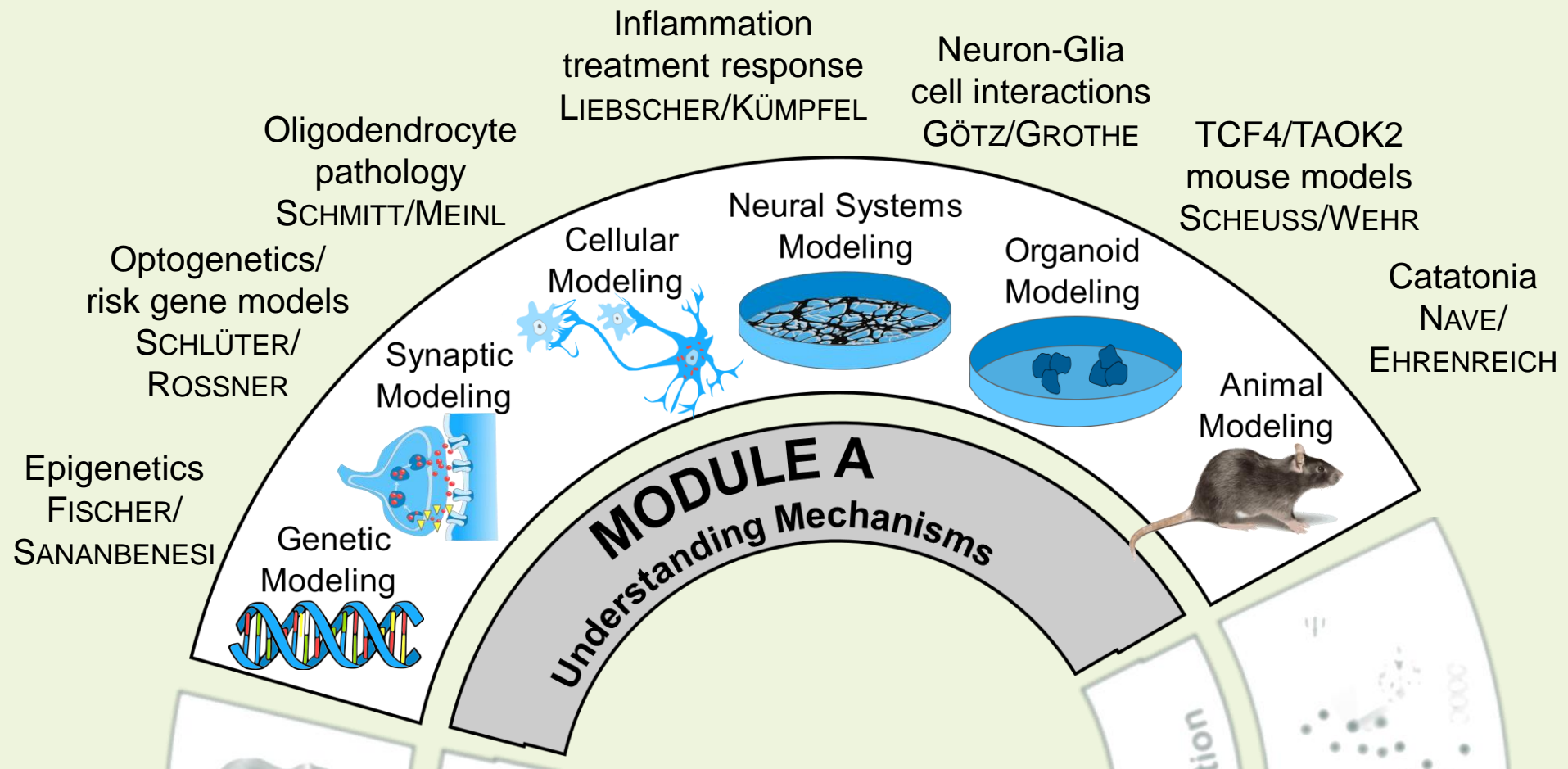


Integrate and validate a treatment profiler:

- Verified mechanisms
- Predictive patterns
- Novel modes of action

Years 9 – 12

MODULE A: A comprehensive toolkit for studying multi-scale mechanisms of recovery



Peleg et al., ... Fischer, **Science**, 2010
Sananbenesi et al., **Nat Neurosci**, 2007

Huang et al., ... Schlüter, **PNAS**, 2015
Botvinnik et al., ... Rossner, **Nat Methods**, 2010

Schmitt et al., **Acta Neuropathol**, 2009
Laurent et al., ... Meinl, **Nat Commun**, 2015

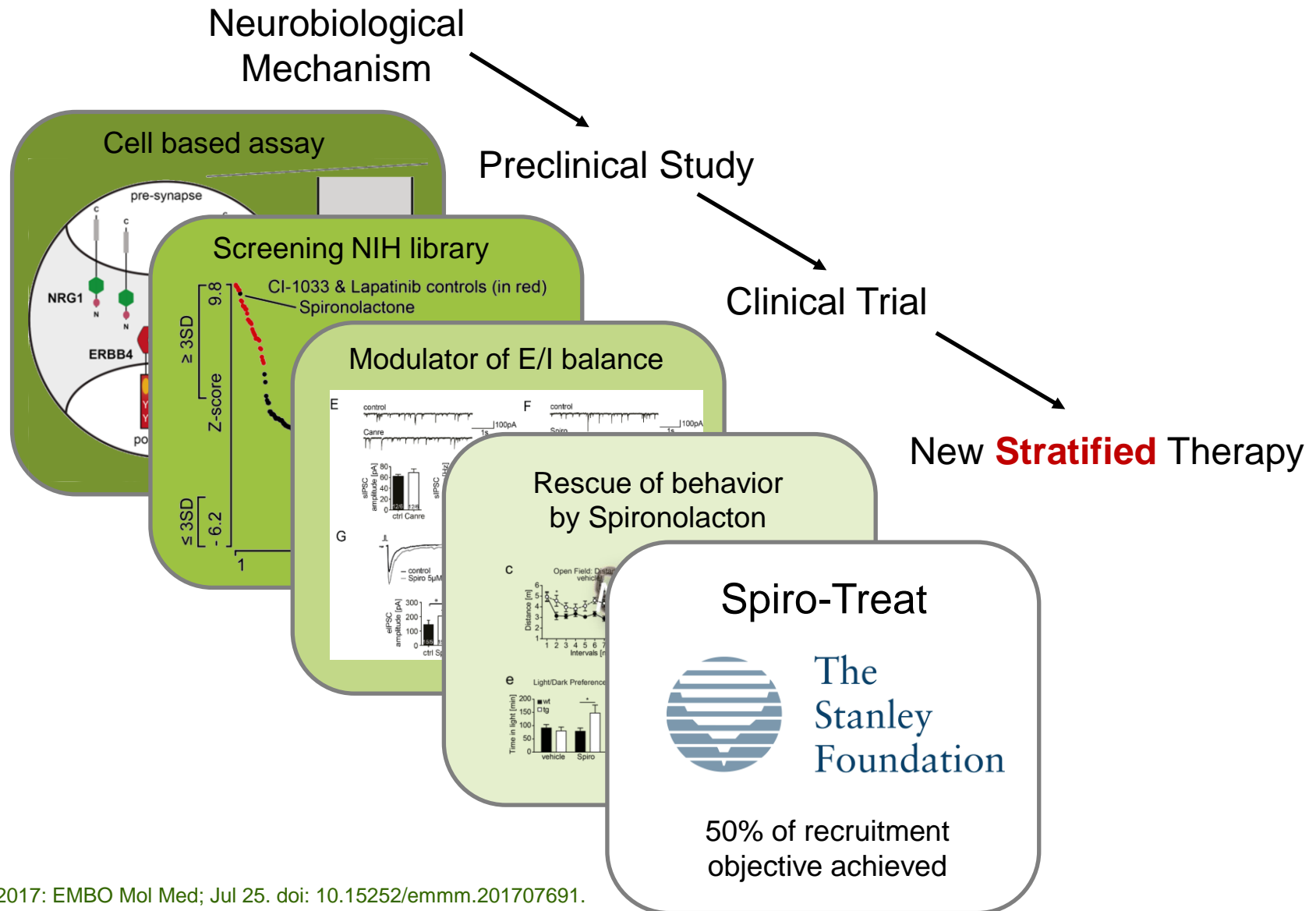
Liebscher et al., **Mol Psychiatry**, 2014
Spadaro et al., ... Kümpfel, **Ann Clin
Tranl Neurol**, 2015

Stahl et al., ... Götz, **Cell**, 2013
Grothe et al., **Nat Neurosci**, 2013

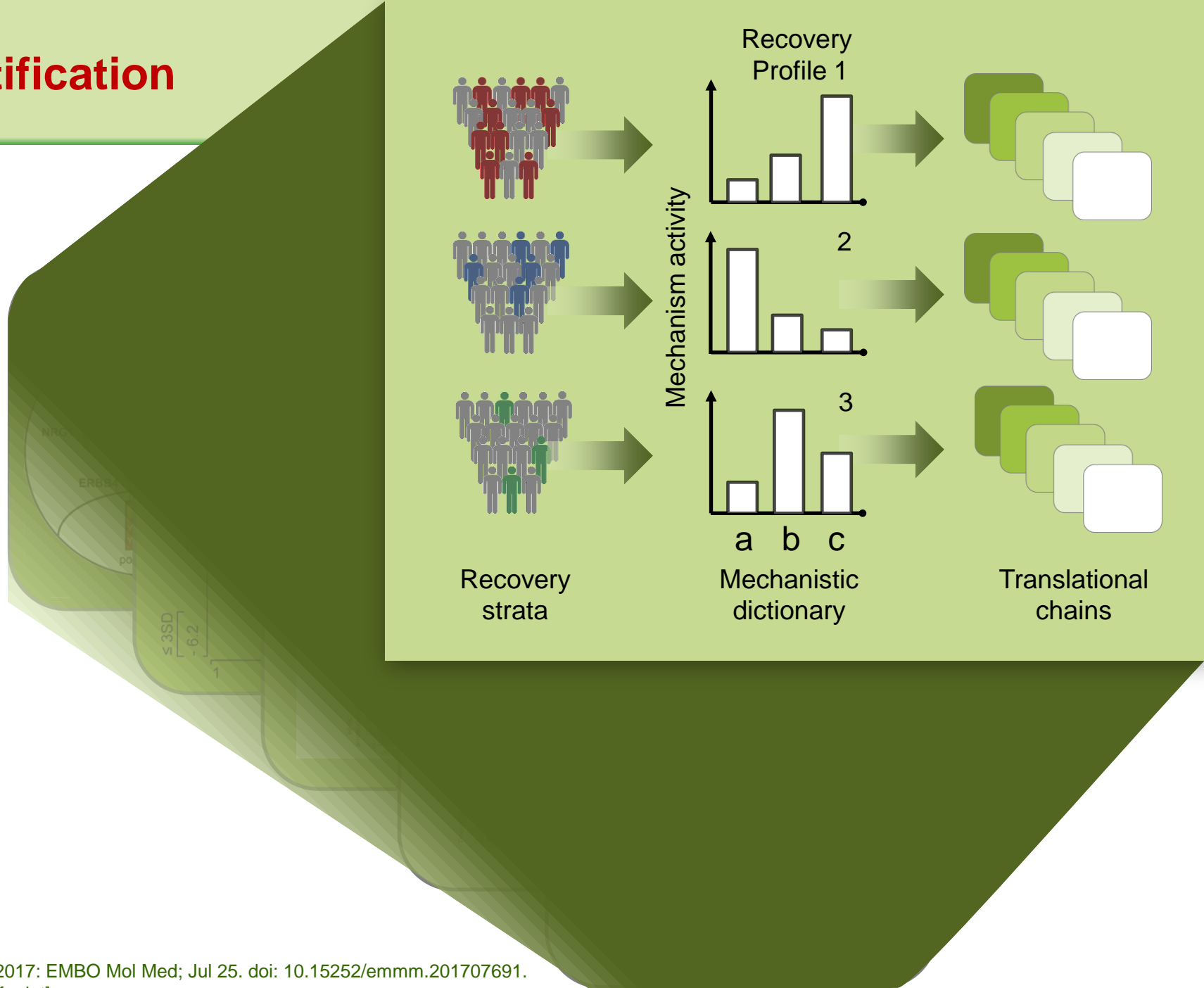
Meyer, Bonhoeffer and Scheuss,
Neuron, 2014
Wehr et al., **Nat Cell Biol**, 2013

Fünfschilling et al., ... Nave, **Nature**, 2012
Hammer et al., ... Ehrenreich, **Mol
Psychiatry**, 2014

An example for the translational chains to be developed by the CRC



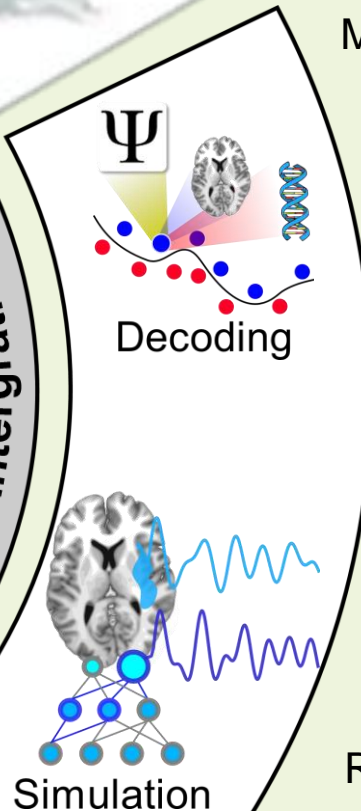
Stratification



MODULE B: From behavior to genes: decoding the multi-scale markers of recovery

Koutsouleris et al., **Arch Gen Psych**, 2009
 Hofmann-Apitius et al., **Nat Rev Drug Discov**, 2015
 Binder et al., **JAMA**, 2008
 Marr, Theis and Schröder, **Nat Biotechnol**, 2016
 Hagemeyer, ..., Papiol et. al., **EMBO Mol Med**, 2012
 Schulze et al., **Lancet**, 2016
 Allebrandt et al., ... Roenneberg, **Mol Psychiatry**, 2013
 Roeske et al., ... Schulte-Körne, **Mol Psychiatry**, 2011
 Bhattacharyya, ..., Kambeitz et al., **Arch Gen Psych**, 2012
 Strube et al., **Neuropsychopharmacology**, 2015
 Schulze et al., **N Engl J Med**, 2014
 Winkelmann, ..., Müller-Myhsok et al., **Nat Genet**, 2007
 Aebersold and Mann, **Nature**, 2016

MODULE B Modelling and Intergration



Multi-scale decoding of recovery using data mining approaches
 KOUTSOULERIS/ HOFMANN-APITIUS

Genetic modelling of risk factors for impaired recovery
 BINDER/THEIS

Multimodal biomarker profiling of treatment response
 PAPIOL/SCHULZE

Circadian rhythm disturbances in impaired recovery
 ROENNEBERG/ SCHULTE-KÖRNE

Modeling recovery using in silico neural and behavioral simulation
 KAMBEITZ/STRUBE

Proteomic stratification of longitudinal recovery phenotypes
 SCHULZE/ MÜLLER-MYHSOK/MANN


 Semantic Data Mining

Validation

Brain Stimulation

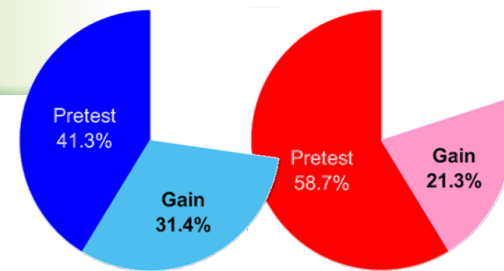
Neuro-feedback

MODULE B: Identifying predictive markers of social functioning outcomes using sMRI

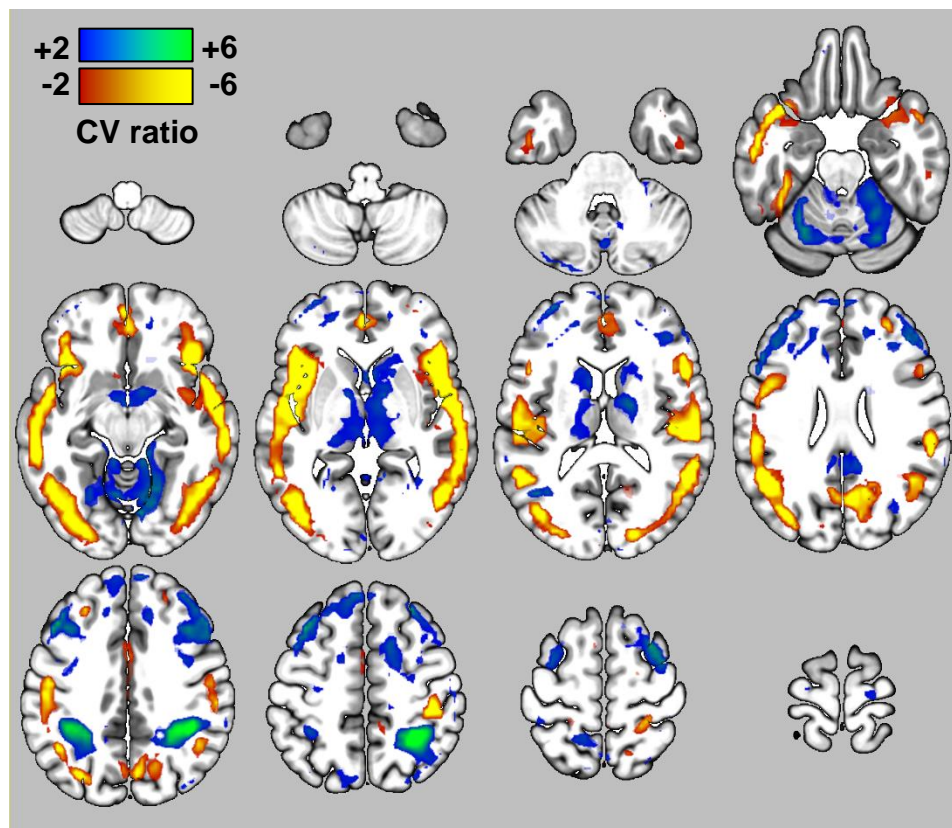
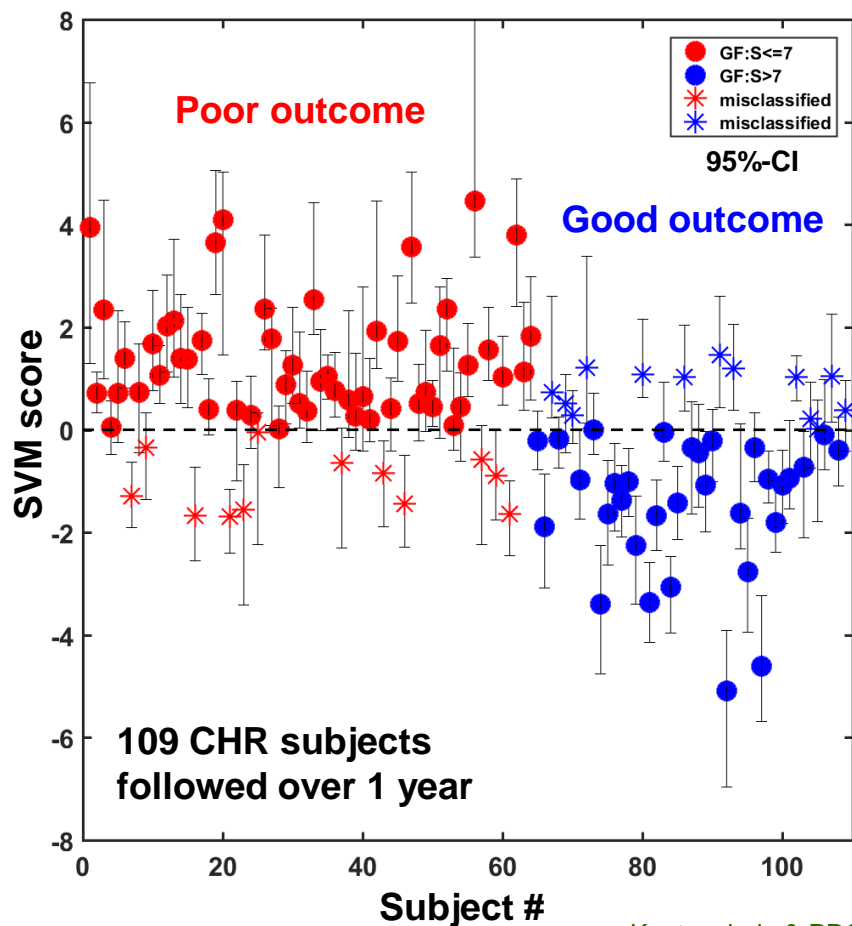


Leave-site-out validation

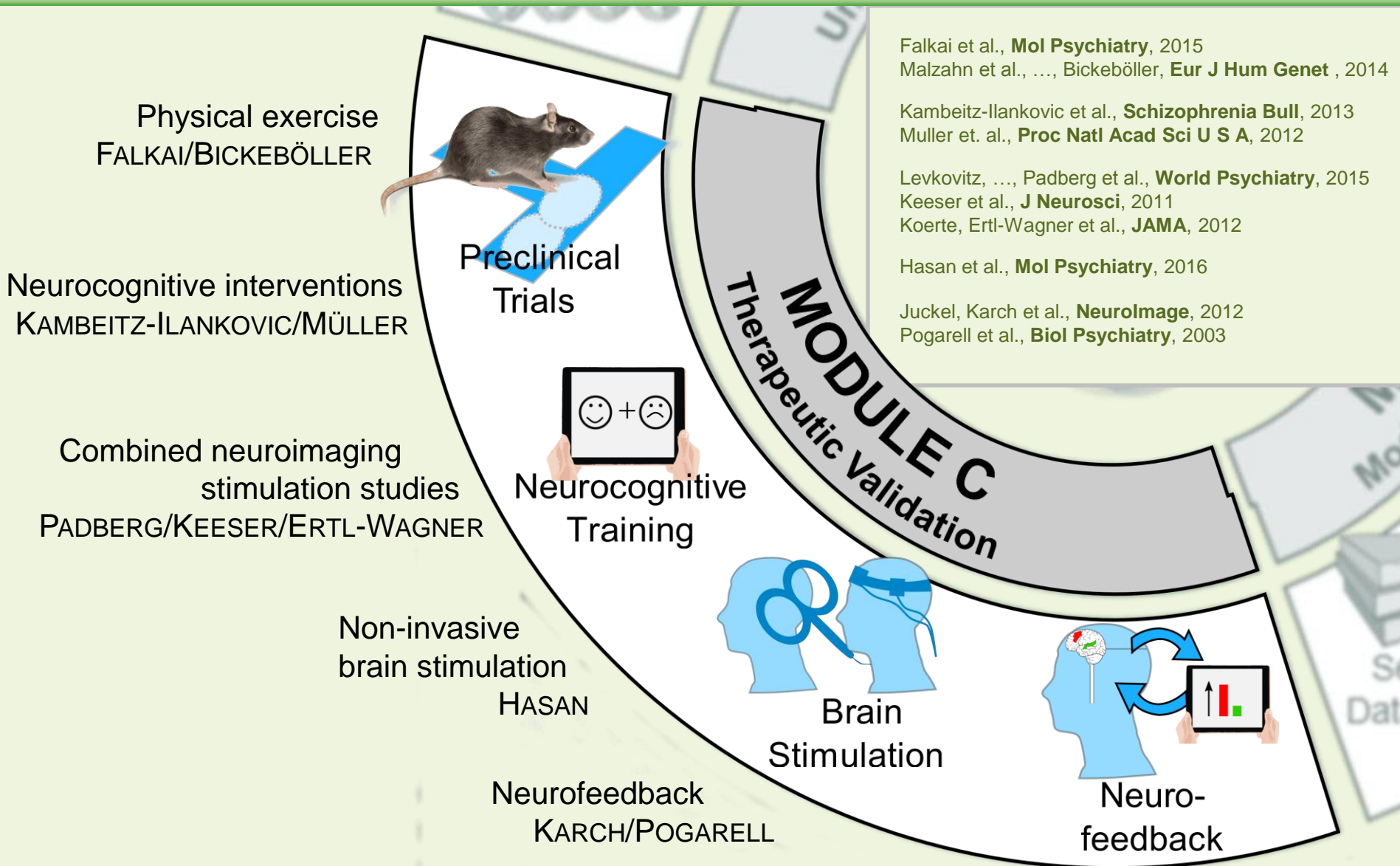
Sensitivity: 81.3%
Specificity: 71.1%



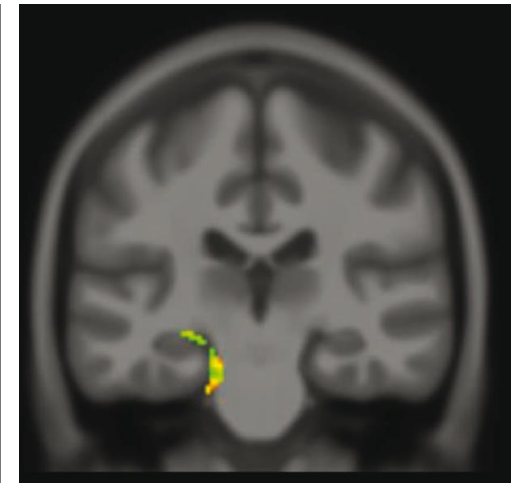
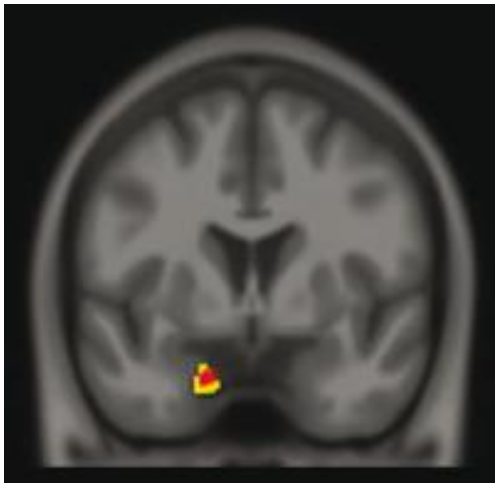
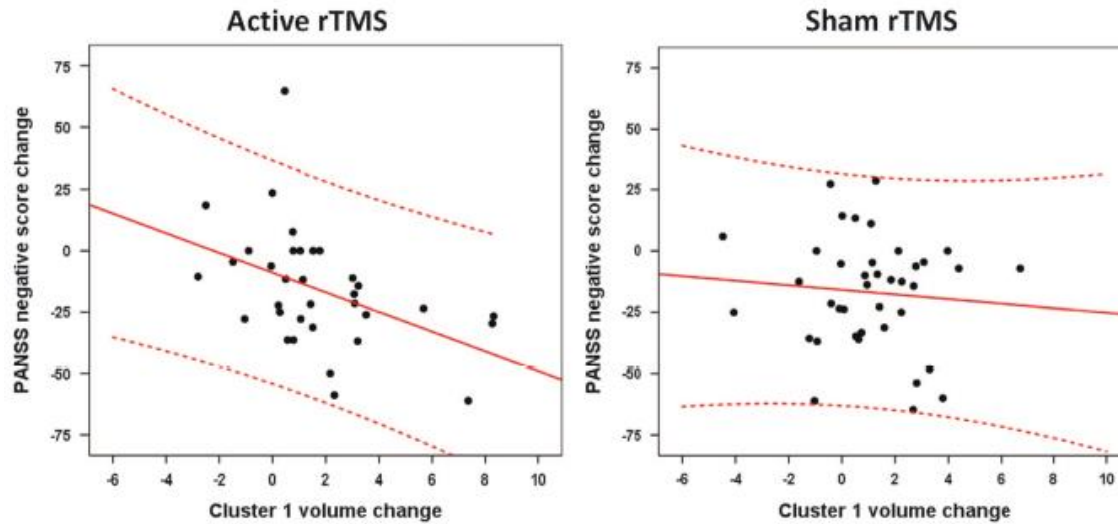
Prognostic Summary Index: 52.7%



MODULE C: Modulating recovery using mechanism-based interventions



MODULE C: Therapeutically validating recovery mechanisms using NIBS



Summary (1)

50% of patients with affective and non-affective psychoses have difficulties in overcoming residual symptomatology of their illness (partial non-recovery)

Recovering implies the reduction of symptoms to a minimum and improvement to a maximum, lasting for a period over 1-2 years

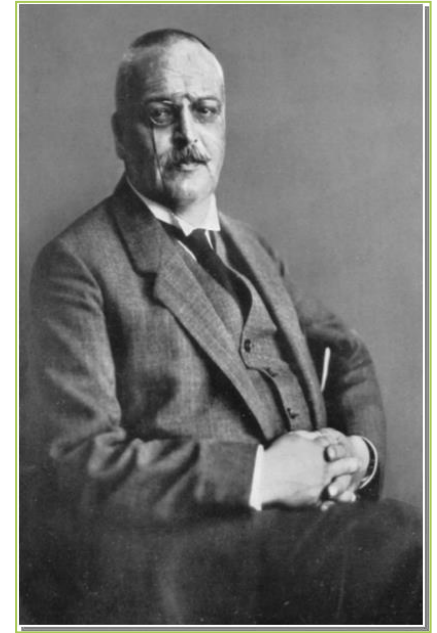
Recovery has an outside view (e.g. measure taken by the GAF, HAMD etc) as well as an inside view (subjective component, Recovery Assessment Scale (RAS)) of the illness

Summary (2)

Recovery oriented therapies contain training modules for strengthening the stress resistance and stress coping skills of patients with affective and non-affective psychoses

Understanding the pathophysiology of recovery defining a model will help to subdivide patient groups due to their long-term outcome at an early stage of the illness

Based on this each subgroup, optimally each patient, will receive optimal treatment which will eventually lead to the best possible level of recovery



**Thank you for your
attention**

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