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Neuroplastizität und Bewegung als Therapieelement bei der Schizophrenie

Psychiatrisches Kolloquium der Universität Zürich

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LMU KLINIKUM
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MAX-PLANCK-INSTITUT
FÜR PSYCHIATRIE

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Peter Falkai received research support/honoraria for lectures or advisory activities from: Boehringer-Ingelheim, Janssen, Lundbeck, Otsuka, Recordati and Richter.
Peter Falkai holds a payed position as chairman of the Psychiatric Department of the University Munich; is full professor at the Psychiatric Department of the University Munich
Peter Falkai has received and is currently receiving grants from several national and international foundations and institutions, e.g. from the “German Science Foundation”, the “German Ministry of Science” and the “German Ministry of Health”

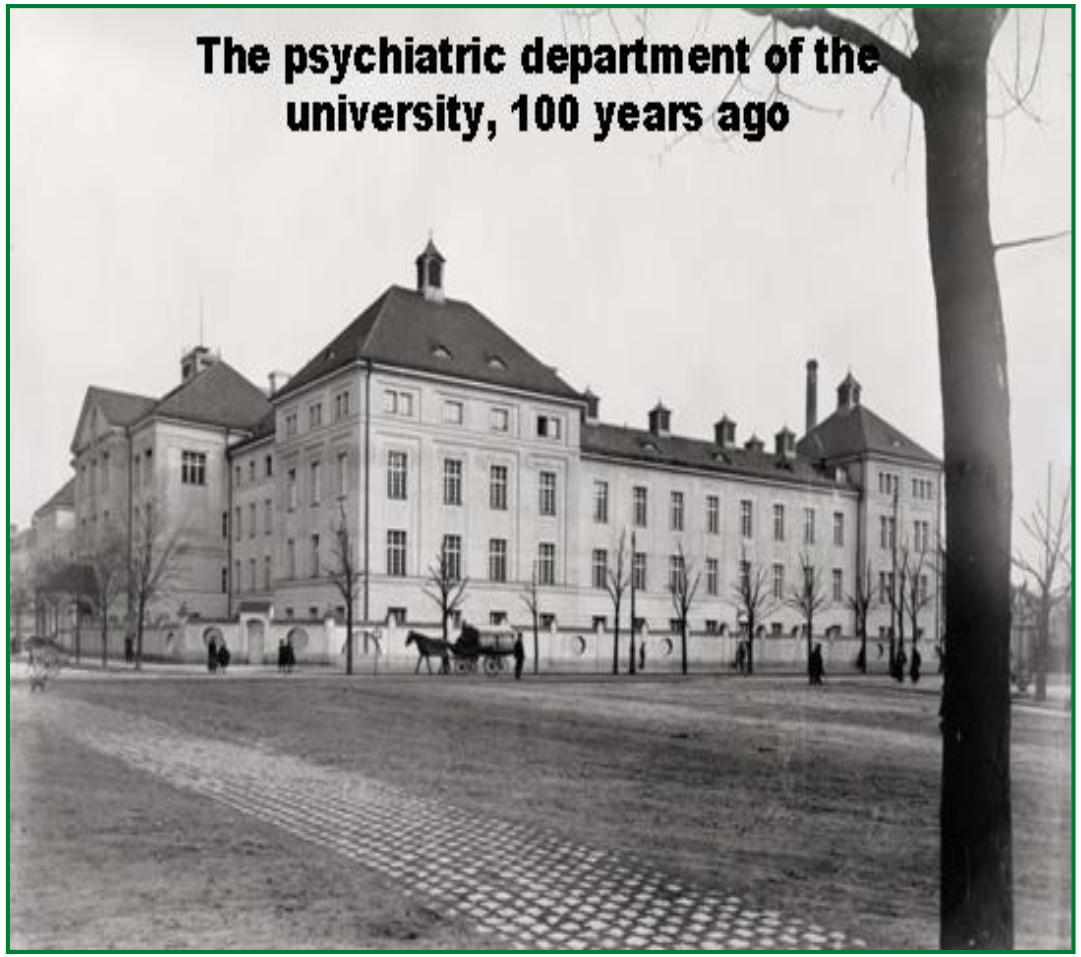
Content

- The pathophysiology of schizophrenia: degeneration or regeneration?
- Aerobic exercise a s a human model for schizophrenia?
- Linking aerobic exercise with symptoms and risk factors
- Translation into the clinic and back
- A biomarker for disturbed myelin plasticity

The pathophysiology of Dementia Praecox (schizophrenia) after Kraepelin

Degeneration vs. Disturbed Regeneration

Emil Kraepelin (1856-1925)



Emil Kraepelin

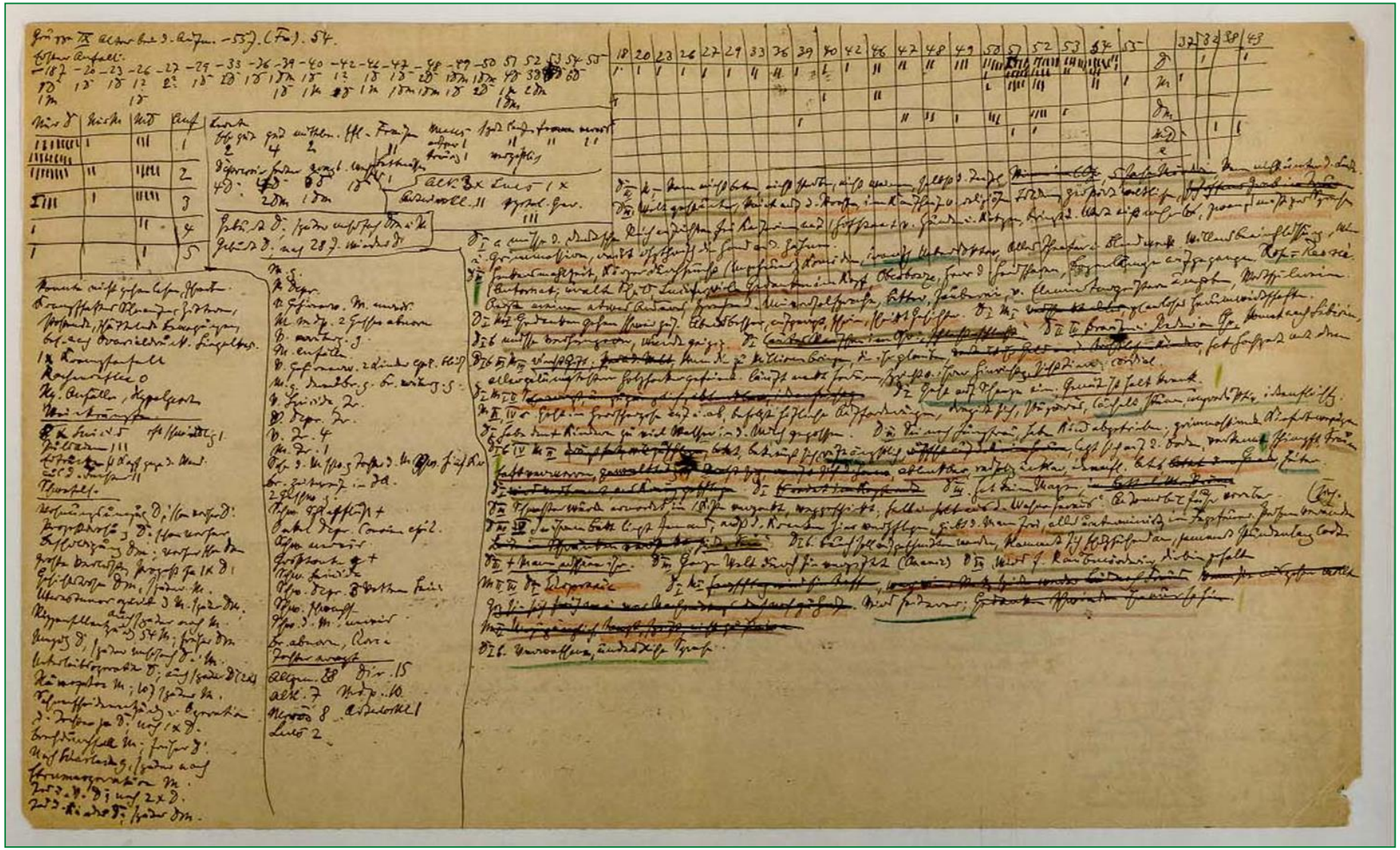
Chairman of the Psychiatric Department of the University of Munich 1903-1922

Emil Kraepelin on his round at the Psychiatric Department of the University of Munich

- **Emil Kraepelin - Chairman of the Psychiatric Department of the University of Munich 1903-1922**
- **In 1891 Kraepelin began a research programme to quantify psychiatric disorders and eliminate any subjective biases on the part of the researcher. His aim was to place psychiatry on a more scientific foundation.**
- **Data were collected about <u>every</u> new patient that was admitted to the clinic and summarized on specially prepared index cards, his famous Zahlkarten.**
- **In his posthumously published Memoirs (first published in German 61 years after his death) Kraepelin described his method:**

„. . . after the first thorough examination of a new patient, each of us had to throw in a note [in a "diagnosis box"] with his diagnosis written on it. After a while, the notes were taken out of the box, the diagnoses were listed, and the case was closed, the final interpretation of the disease was added to the original diagnosis. In this way, we were able to see what kind of mistakes had been made and were able to follow up the reasons for the wrong original diagnosis (p. 61).“

Kraepelin‘s „Zählkarten“ (‚counting cards‘) formed the basis for a psychopathological documentation system



Alzheimer‘s neuroanatomical laboratory in Munich

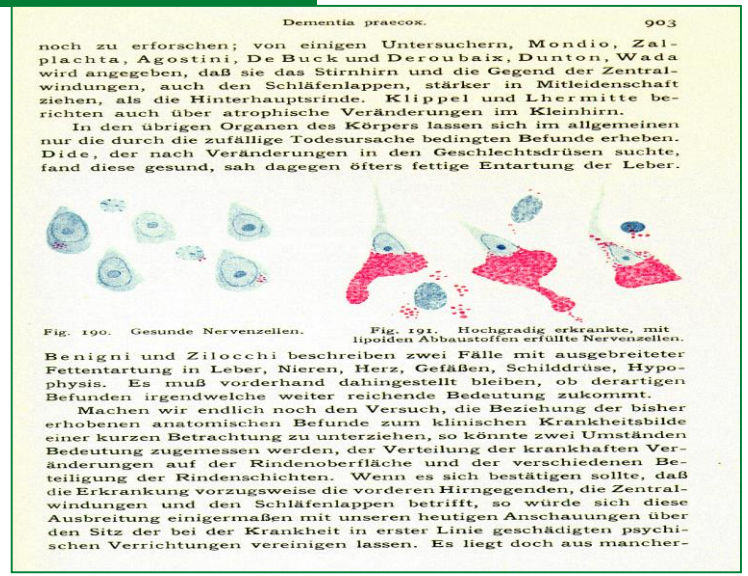
The development of the term ‘Dementia Praecox’

- Dementia praecox (a "premature dementia" or "precocious madness”) refers to chronic, deteriorating psychotic disorder characterized by rapid cognitive disintegration, usually beginning in the late teens or early adulthood. It is a term first used in 1891 in this Latin form by Arnold Pick (1851–1924), a professor of psychiatry at the German branch of Charles University in Prague. It was popularized by Emil Kraepelin in 1893, 1896 and 1899 in his first detailed textbook on descriptions of a condition that would eventually be reframed into a substantially different disease concept and relabeled as schizophrenia by Eugen Bleuler
- In the 6th edition of Psychiatrie (1899), Kraepelin grouped most of the insanities into two large categories, dementia praecox and manic-depressive illness:
- (1) dementia praecox was primarily a disorder of intellectual functioning, manic depressive illness was primarily a disorder of affects or mood;
- (2) dementia praecox had a uniformly deteriorating course and a poor prognosis, manic-depressive insanity had a course of acute exacerbations followed by complete remissions with no lasting deterioration of intellectual functioning; and
- (3) there were no recoveries from dementia praecox, whereas in manic-depressive illness there were many complete recoveries.

Kraepelin‘s words based on Alzheimer’s investigations and drawings

“ These considerations force us to draw the direct conclusion that there must be a manifest destruction of the cortex. In those cases that have been investigated more closely by reliable means, regular alterations have actually been demonstrated for which there is no other explanation..... .

We therefore reach the conclusion that in Dementia praecox there is severe damage to or destruction of the nervous cortical elements, which may be compensated for in individual cases, but which mostly results in a peculiar, persistent impairment of the psyche.”



Dementia praecox. 903

noch zu erforschen; von einigen Untersuchern, Mondio, Zalplachta, Agostini, De Buck und Deroubaix, Dunton, Wada wird angegeben, daß sie das Stirnhirn und die Gegend der Zentralwindungen, auch den Schläfenlappen, stärker in Mitleidenschaft ziehen, als die Hinterhauptsrinde. Klippel und Lhermitte berichten auch über atrophische Veränderungen im Kleinhirn.

In den übrigen Organen des Körpers lassen sich im allgemeinen nur die durch die zufällige Todesursache bedingten Befunde erheben. Dide, der nach Veränderungen in den Geschlechtsdrüsen suchte, fand diese gesund, sah dagegen öfters fettige Entartung der Leber.

Fig. 190. Gesunde Nervenzellen.

Fig. 191. Hochgradig erkrankte, mit lipoiden Abbaustoffen erfüllte Nervenzellen.

Benigni und Zilocchi beschreiben zwei Fälle mit ausgebreiteter Fettentartung in Leber, Nieren, Herz, Gefäßen, Schilddrüse, Hypophysis. Es muß vorderhand dahingestellt bleiben, ob derartigen Befunden irgendwelche weiter reichende Bedeutung zukommt.

Machen wir endlich noch den Versuch, die Beziehung der bisher erhobenen anatomischen Befunde zum klinischen Krankheitsbilde einer kurzen Betrachtung zu unterziehen, so könnte zwei Umständen Bedeutung zugemessen werden, der Verteilung der krankhaften Veränderungen auf der Rindenoberfläche und der verschiedenen Beteiligung der Rindenschichten. Wenn es sich bestätigen sollte, daß die Erkrankung vorzugsweise die vorderen Hirngegenden, die Zentralwindungen und den Schläfenlappen betrifft, so würde sich diese Ausbreitung einigermaßen mit unseren heutigen Anschauungen über den Sitz der bei der Krankheit in erster Linie geschädigten psychischen Verrichtungen vereinigen lassen. Es liegt doch aus mancher-

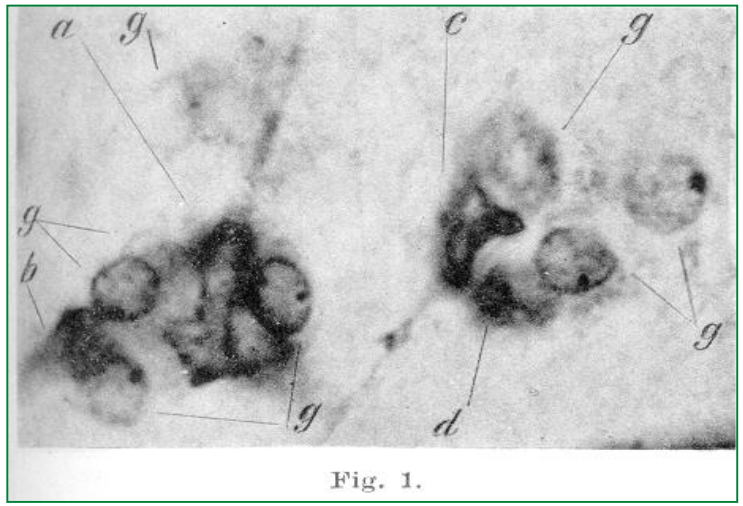


Fig. 1.

E. Kraepelin, Lehrbuch der Psychiatrie (8th ed. Vol 3, part 2), 1913, JA Barth, Leipzig;
Alzheimer A. Neuere Arbeiten über die Dementia senilis [recent works on senile dementia]. Monatsschrift für Psychiatrie und Neurologie 1893; 3: 101–115.

Arguments against a classical neurodegenerative process

Dementia Praecox (Schizophrenia)

1	No Progression of the cognitive deficits	
2	No Loss of neuronal elements	
3	No Astrocytosis or microgliosis indicative for inflammation	
4	Synaptic Changes in schizophrenia	
5	Reversibility of structural and functional changes in schizophrenia	

No progression of cognitive deficits in schizophrenia over 5 years

FIGURE 1. Neuropsychological Summary Scale Scores for the First 5 Years in 42 Patients With First-Episode Schizophrenia and 16 Normal Comparison Subjects

Hoff AL, Am J Psychiatry 156 (1999), 1336-1341

No progression of cognitive deficits after 10 years compared to baseline

Table 3
Neuropsychological test results at baseline and at 10 years

	Patients ($n=21$)		Controls ($n=8$)		F values		
	Baseline	10 years	Baseline	10 years	Group	Time	Group by time
Verbal IQ[a]	97.7 ± 13.6	101.5 ± 11.3	106.1 ± 12.1	113.8 ± 10.6	6.16*	5.07*	.55
WRAT-R reading[b]	97.8 ± 15.4	99.9 ± 16.4	106.4 ± 11.3	106.5 ± 8.1	1.89	.21	.17
Log. Mem.(%)-imm.[c]	25.0 ± 1.1	25.0 ± 1.2	44.0 ± .7	47.0 ± 1.2	27.04**	.62	.38
Log. Mem.(%)-del.[c]	17 ± 1.0	16.5 ± 1.1	34.0 ± .1	38.0 ± 1.5	37.50**	.28	.65
Paired Assoc. total[c]	19.8 ± 7.7	18.1 ± 5.3	24.5 ± 3.9	21.4 ± 5.3	5.79*	1.61	.15
CVLT — total[d]	40.0 ± 12.5	36.2 ± 12.4	56.4 ± 9.7	53.1 ± 9.1	17.93**	1.67	.01
Vis. Rep.(%)-imm.[c]	58.1 ± 2.5	72.2 ± 2.2	86.6 ± 1.3	80.2 ± 3.5	7.15*	.69	4.87*
Vis. Rep.(%)-del.[c]	48.6 ± 2.6	49.2 ± 2.7	81.3 ± 1.5	87.8 ± 1.3	21.65**	.41	.28
Benton VRT—#corr.[e]	5.7 ± 2.2	5.5 ± 3.0	7.9 ± 1.4	7.8 ± 1.8	10.60***	.08	.01
Benton VRT—#err[e]	6.9 ± 4.0	7.0 ± 6.0	2.8 ± 1.9	2.8 ± 2.1	10.67***	.01	.00
WCST—#err[f]	43.0 ± 30.1	36.5 ± 26.8	14.6 ± 6.9	14.6 ± 8.4	8.94***	.32	.32
WCST—#persev. err[f]	27.9 ± 28.5	20.8 ± 15.4	7.6 ± 3.5	8.4 ± 5.2	10.13***	.33	.51
Stroop CW—#corr[g]	29.5 ± 9.5	35.8 ± 8.4	46.4 ± 7.0	53.9 ± 14.0	37.58**	6.66*	.05
Trail Making A—#sec[h]	41.2 ± 30.6	36.0 ± 19.5	21.4 ± 7.7	21.0 ± 3.7	6.64*	.35	.26
Trail Making B—#sec[h]	108.1 ± 67.3	97.7 ± 57.9	68.6 ± 22.0	55.0 ± 25.0	5.41*	2.97	.06
Fing. Tapp.-Dom[h]	41.1 ± 8.8	48.4 ± 6.8	51.4 ± 7.1	53.1 ± 8.4	9.20***	5.85*	2.19
Fing. Tapp.-NonDom[h]	39.6 ± 8.1	44.5 ± 7.9	44.3 ± 7.1	47.3 ± 6.5	1.91	8.75***	.58

[a] Pro-Rated Verbal IQ (Satz and Mogel, 1962); [b] WRAT-R, Wide Range Achievement Test-Revised (Jastak and Wilkinson, 1984); [c] Wechsler Memory Scale Logical Memory and Visual Reproduction, immediate and delayed conditions, Paired Associates (Wechsler, 1945); [d] CVLT, California Verbal Learning Test (Delis et al., 1983); WCST, Wisconsin Card Sorting Test (Heaton and Crowley, 1981); [h] Trail Making Test and Finger Tapping Test, Halstead–Reitan Neuropsychological Battery (Reitan and Wolfson, 1993).

* $p<.05$.
** $p<.005$.
*** $p<.01$.

Hoff AL et al. 2005: Schizophrenia Research 78 (2005) 27– 34

Arguments against a classical neurodegenerative process

Schizophrenia

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The pattern of structural abnormalities in schizophrenia

ENIGMA Consortium

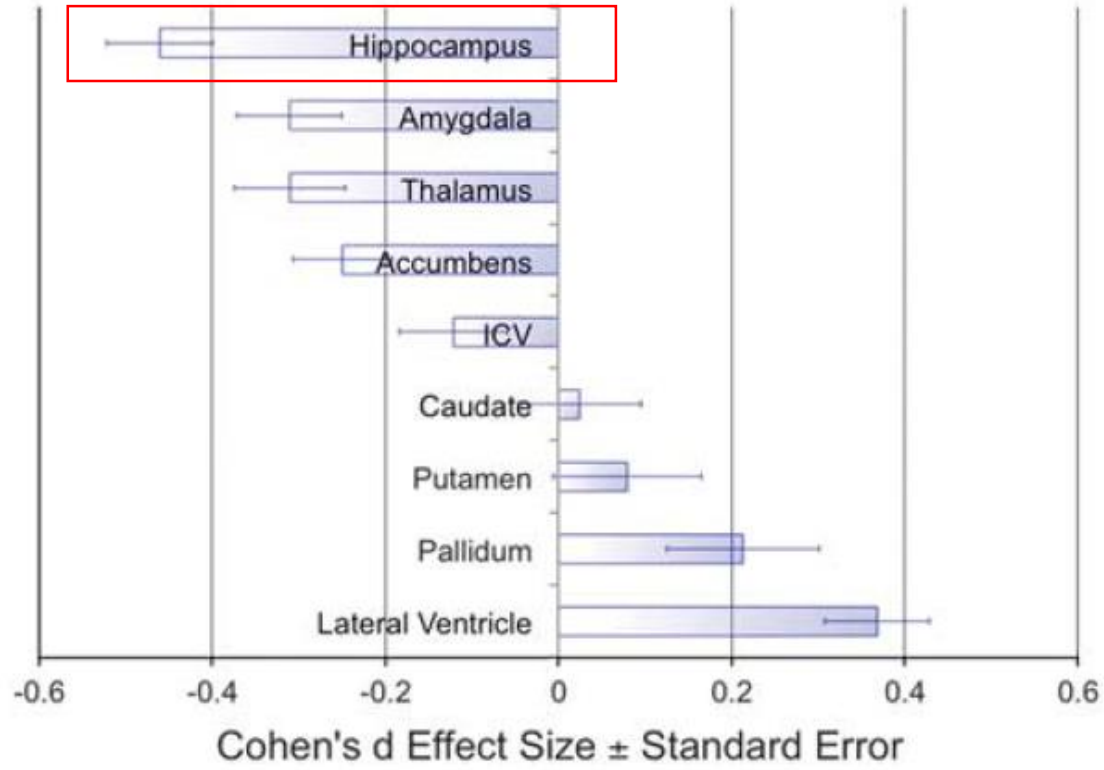
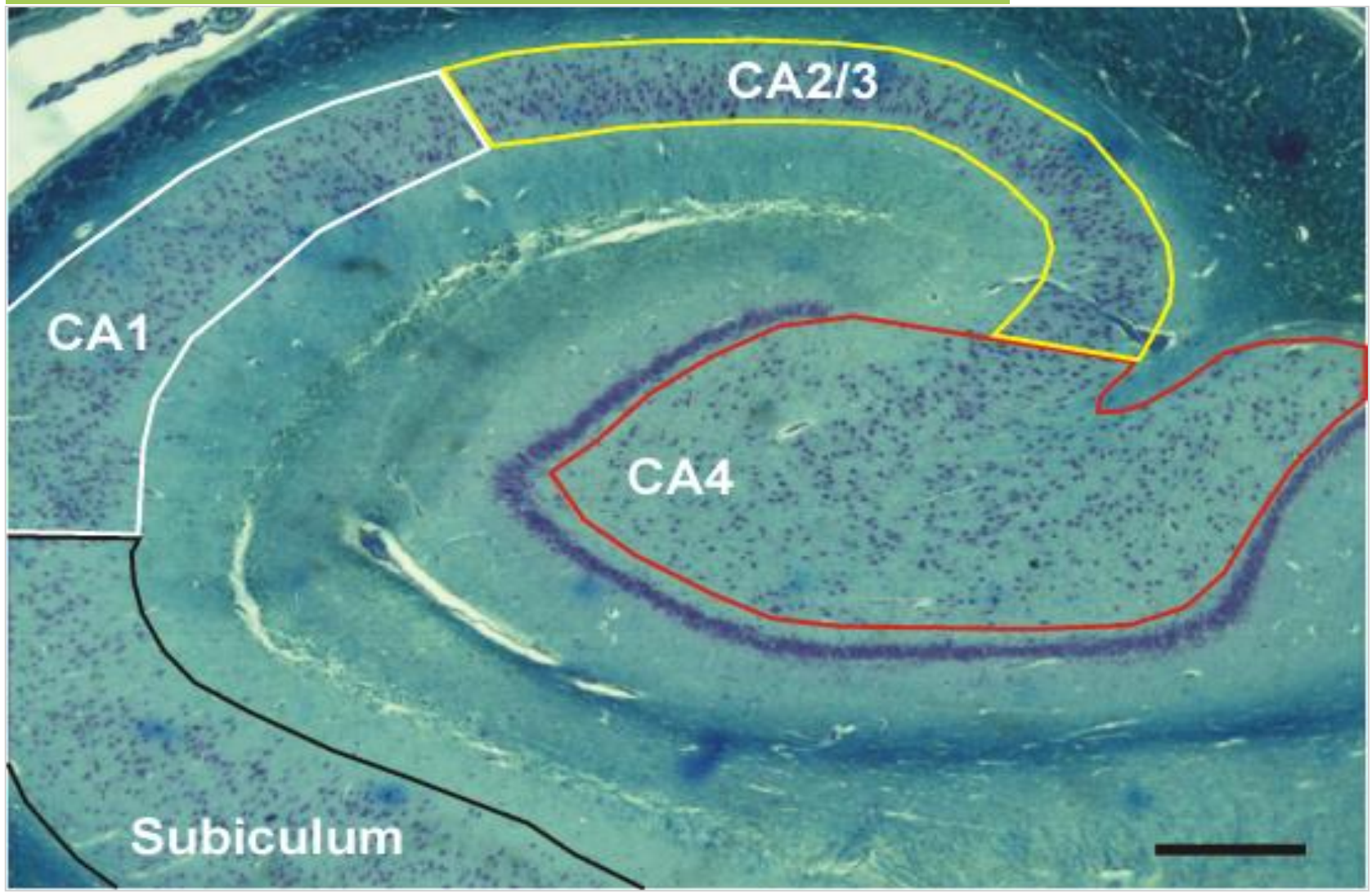


Figure 1. Cohen's *d* effect sizes ± s.e. for regional brain volume differences between Individuals with schizophrenia and healthy controls. Effect sizes for all subcortical volumes depicted were corrected for sex, age and intracranial volume (ICV). The effect size for ICV was corrected for sex and age. The number of independent data points (N_{Sz} and N_{HV}) for each region are listed in Table 1.

Van Erp T et al. 2016: Mol Psychiatry; 21(4): 547-53

The posterior hippocampus in schizophrenia

Analysis of cellular subpopulations via stereology



Schmitt et al. 2009 Acta Neuropathol 117: 395-407

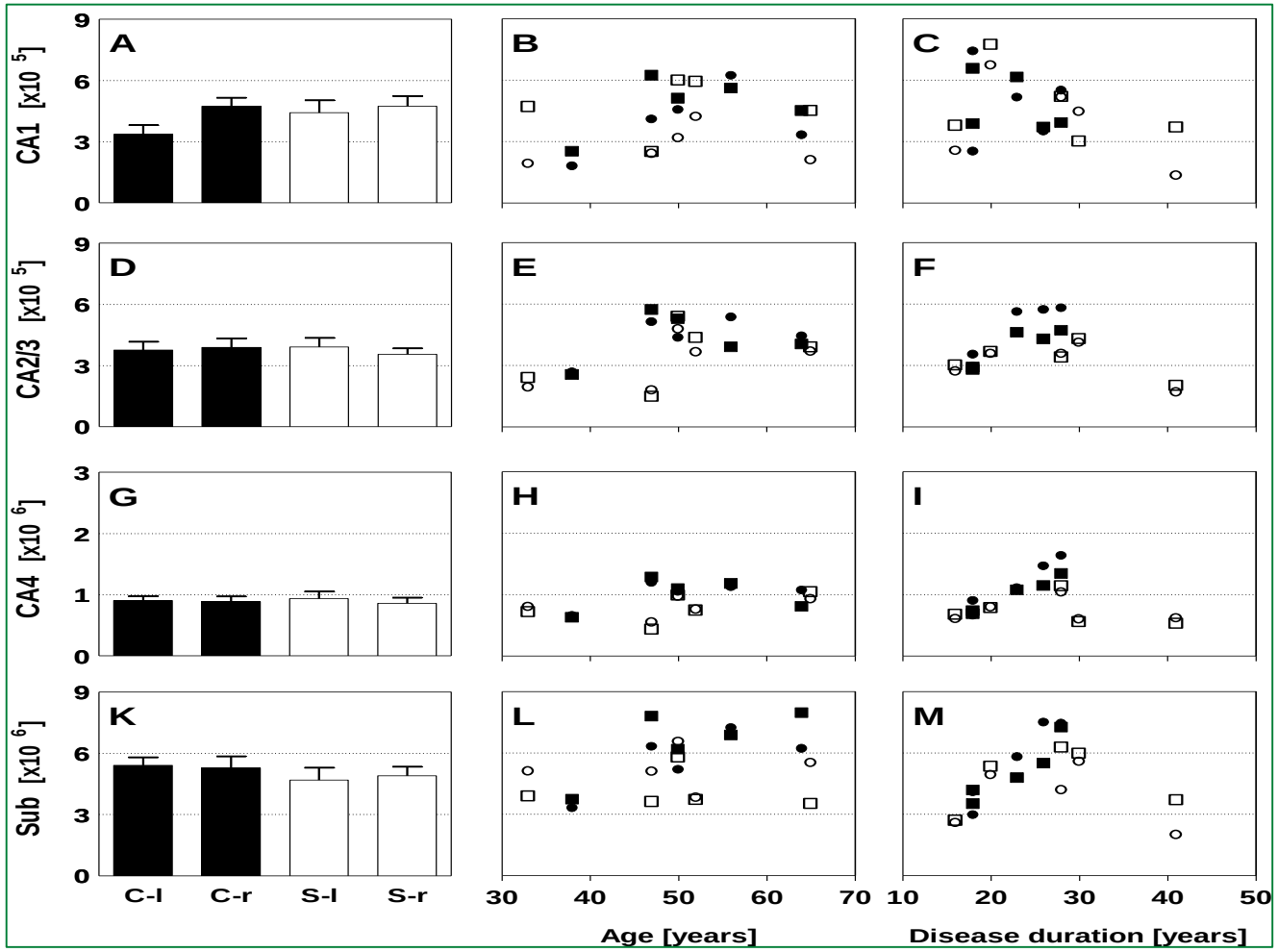
Stereology

Analysis of Neurons

Schmitt et al. 2009 Acta Neuropathol 117: 395-407

No reduction of neuronal numbers in hippocampal subfields in SZ

No sign for a degenerative process



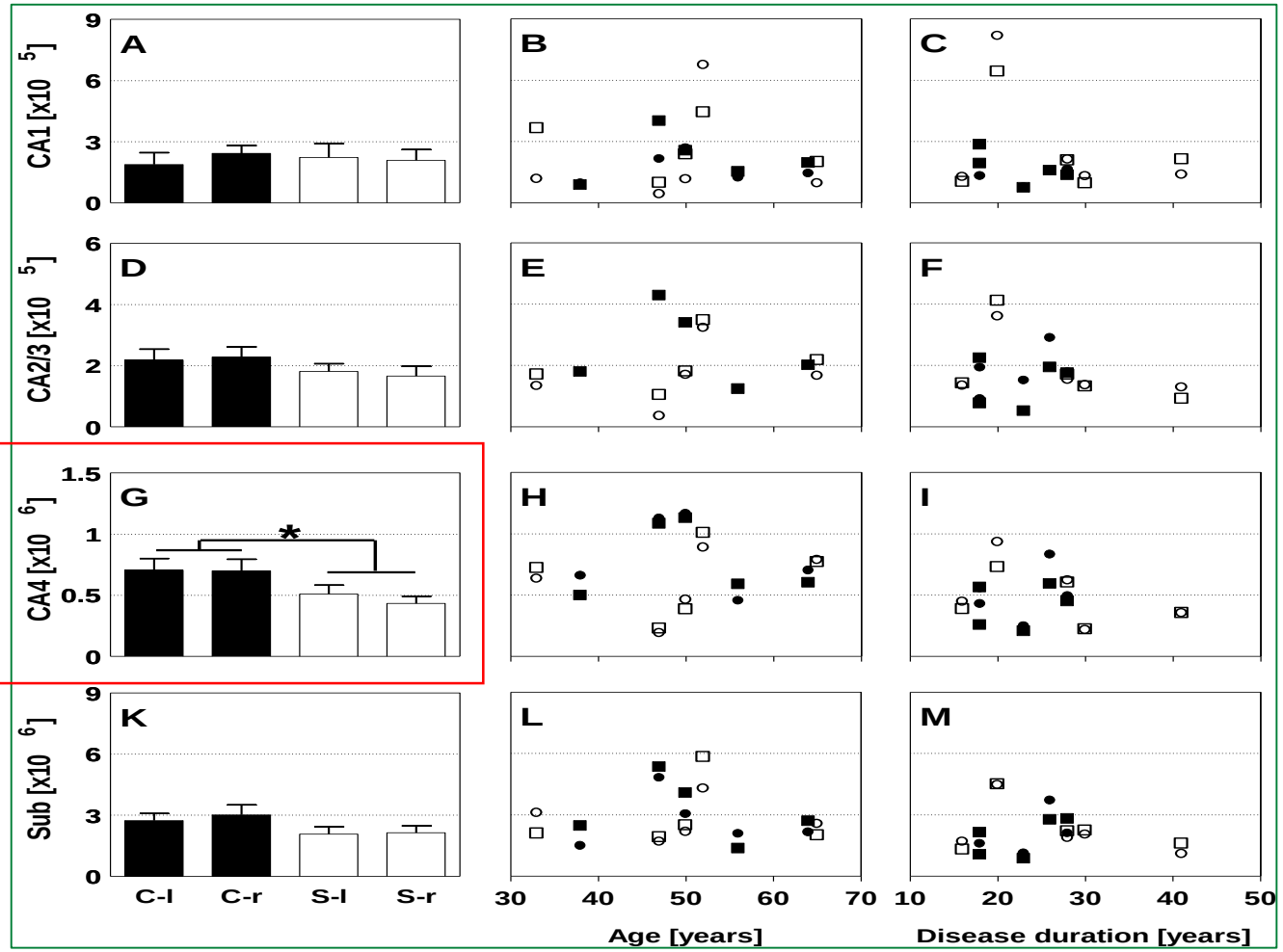
C= controls,

S= schizophrenia,

l= left, r= right hemisphere

Schmitt A et al. 2022: Cells; Oct 15;11(20):3242

Circumscribed reduction of number of oligodendrocytes in CA4



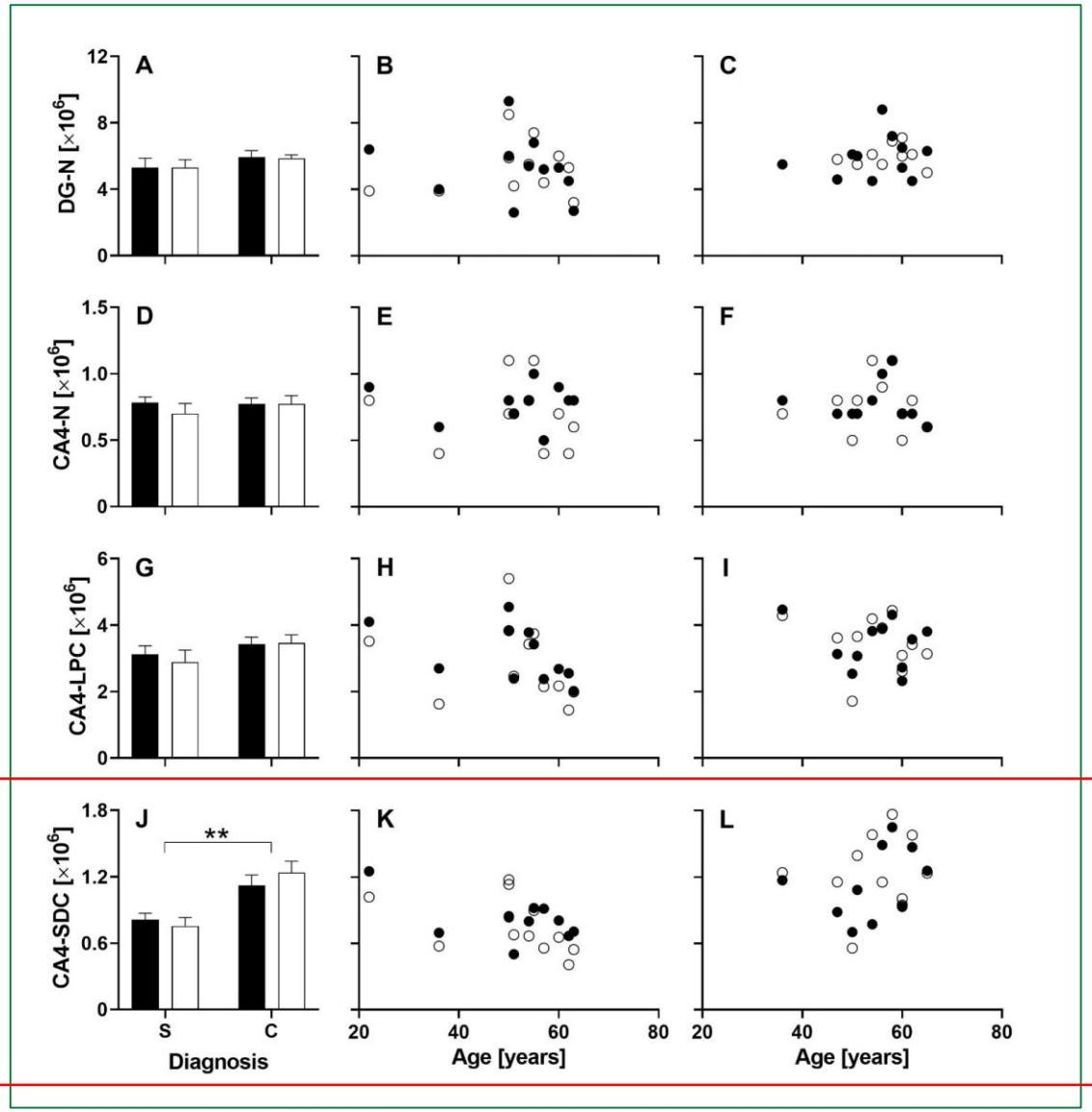
C= controls,

S= schizophrenia,

l= left, r= right hemisphere

Schmitt et al. 2009 Acta Neuropathol 117: 395-407

Replication of the oligodendrocyte reduction in CA4 in an independent sample



Dentate gyrus neurons

CA4 neurons

CA4 astrocytes

CA4 oligodendrocytes

Schmitt A et al. 2022: Cells; Oct 15;11(20):3242

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No Astrocytosis in Schizophrenia

Meta-analysis

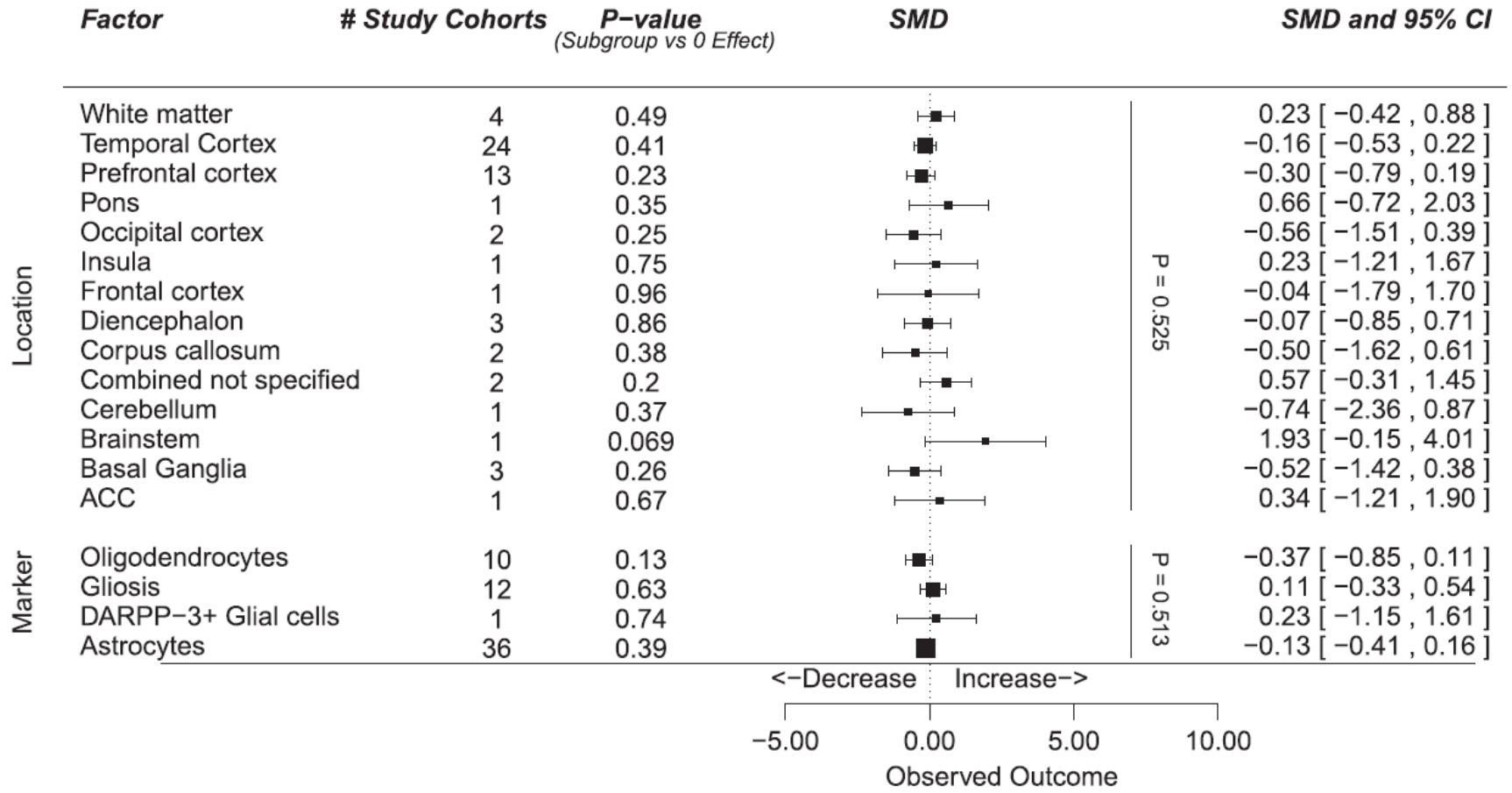
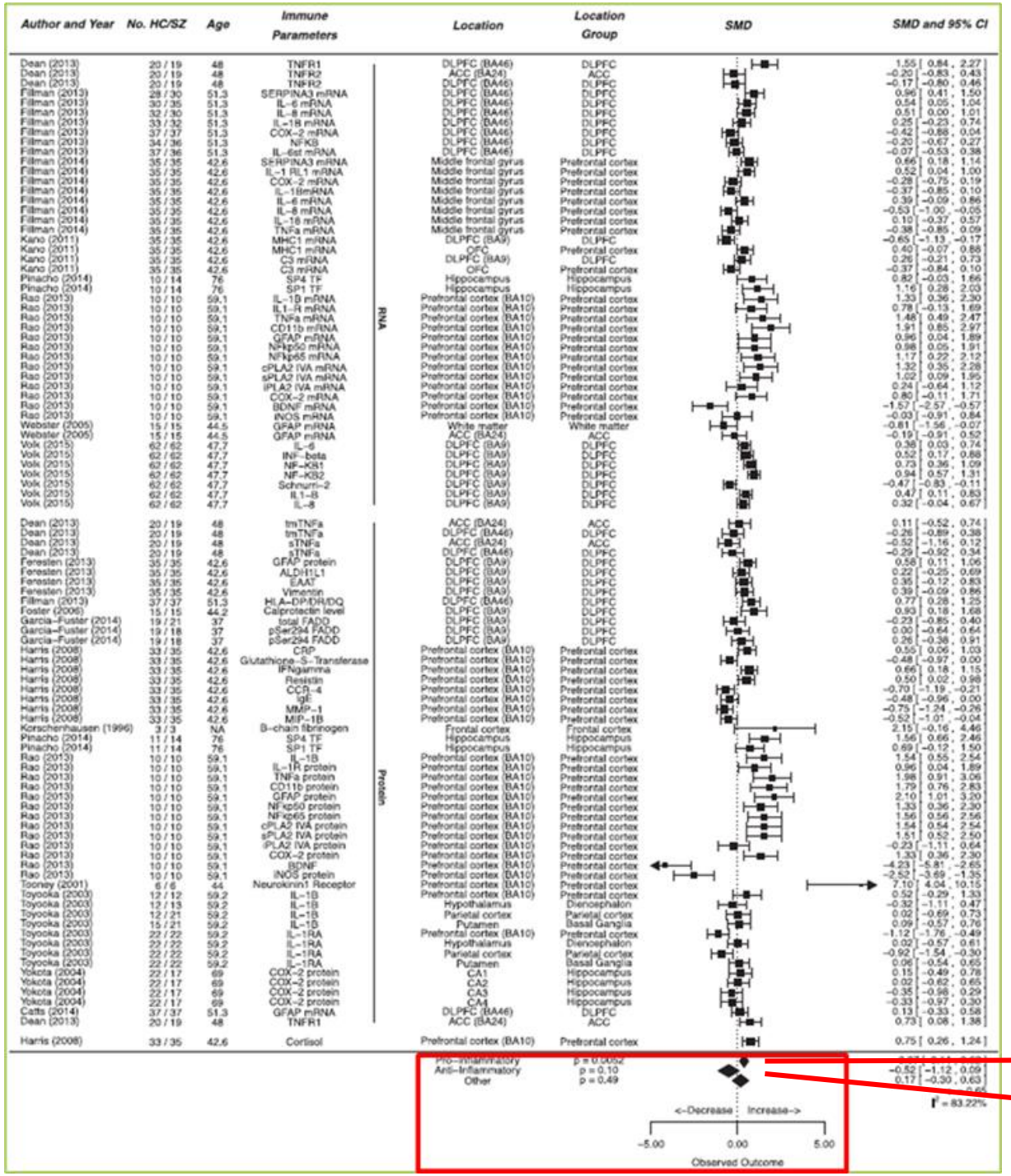


Figure 5. Meta-regression in studies investigating macroglia. Forest plot showing brain region and markers as effect moderators on differences in cellular parameters. '*P*-value (Subgroup vs 0 Effect)' indicates the amount of evidence for alterations in a given brain region or effects observed using a given marker. The vertical *P*-values indicate the added value of the moderators brain region and cell-marker in the meta-regression model. ACC, anterior cingulate cortex; SMD, standardized mean difference.

Van Kesteren CFMG et al. 2017: Transl Psychiatry; 7:e1075



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No Microgliosis in SZ?

Post-mortem evidence

Pro inflammatory ↑

Anti inflammatory ↓

Van Kesteren CFMG et al. 2017: Transl Psychiatry; 7:e1075

Imaging Microglia with PET

Meta-analysis: 4 out of 10 studies ↑, 1 ↓ and 5 no change

TABLE 2 | Positron emission tomography studies with TSPO tracer evaluating microglial activation in schizophrenia patients *versus* controls.

Reference	*n* SZ	*n* C	Tracer	Model; outcome measure	Clinical state Total (T) and positive symptom scale (P) score (PANSS mean ± SD unless otherwise specified)	DOI (years)	Medication % of patients on antipsychotics (AP); (mean CPZ) Benzodiazepines (BZD) excluded (duration)?	Outcome
Van Berckel et al. (56)	10	10	[11C]PK11195	2TCM; BP	Undefined Symptom scores unavailable	3.1 ± 1.7	AP 100% BZD?	SZ > C
Doorduin et al. (57)	7	8	[11C]PK11195	2TCM; BP	Psychosis T 73.6 ± 13.3 *P* 19.7 ± 3.0	5 ± 6	AP 100% BZD excluded (3 × $t_{1/2}$)	SZ > C
Banati and Hickie (66)	16	8	[11C]PK11195	2TCM; BP	Undefined Symptom scores unavailable	Range 0.3–30	Information unavailable	SZ > C
Takano et al. (58)	14	14	[11C]DAA1106	2TCM; BP	Chronic T 77.9 ± 20.1 *P* 19.1 ± 5.3	19 ± 12	AP 100% BZD excluded (<1 m)	SZ = C
Kenk et al. (59)	16	27	[18F]FEPPA	2TCM; V_T	Psychosis T 70.2 ± 9.7 *P* 19.3 ± 2.2	15 ± 9	AP 100%; (300 CPZ) BZD excluded (duration?)	SZ = C
Bloomfield et al. (55)	14	14	[11C]PBR28	2TCM-1K; DVR	Undefined T 63.7 ± 18.1 *P* 17.0 ± 6.1	Undefined	AP?% BZD excluded (duration?)	SZ > C
Coughlin et al. (60)	12	14	[11C]DPA713	Undefined; V_T	Undefined T unavailable *P* (SAPS) 3.8 ± 2.5	2.2 ± 1.4	AP?%; (474.5 CPZ) BZD excluded (6 m)	SZ = C
Van der Doef et al. (61)	19	17	[11C]PK11195	Reference tissue; BP	Undefined T 53 ± 10 *P* 12 ± 4	1.3 ± 1.1	AP 79% BZD excluded (4w)	SZ = C
Collste et al. (64)	16	16	[11C]PBR28	2TCM; V_T	FEP drug naïve T 77.4 ± 18.3 *P* 20.3 ± 4.9	0.7 ± 0.8	AP 0% BZD not excluded	SZ < C
Hafizi et al. (65)	19	20	[18F]FEPPA	2TCM; V_T	FEP unmedicated T 68.6 ± 13.0 *P* 19.2 ± 3.8	2.8 ± 3.3	AP 0% BZD?	SZ = C
Di Biase et al. (62)	33	27	[11C]PK11195	Reference tissue; BP	Recent-onset (*n* = 18) T 68.5[a] *P* (BPRS) 12.6 ± 4.6 Chronic (*n* = 15) T 86.5[a] *P* (BPRS) 19.5 ± 7.8	1.5 ± 1.0 13.6 ± 8.8	AP 78% BZD? AP 100% BZD?	SZ = C SZ = C

SZ, schizophrenia patient group; C, control group; n, number of subjects; FEP, first-episode psychosis patients; DOI, duration of illness; 2TCM, two-tissue compartment model; BP, binding potential; V_T, total volume of distribution; DVR, distribution volume ratio; CPZ, chlorpromazine equivalent; SAPS, Scale for the Assessment of Positive Symptoms; ?, undefined.

SZ > C, increased uptake of tracer in schizophrenia patients compared to controls.

SZ = C, no difference in tracer uptake between schizophrenia patients and controls.

SZ < C, decreased uptake of tracer in schizophrenia patients compared to controls.

[a]Mean Brief Psychiatric Rating Scale total scores were converted to corresponding Positive and Negative Syndrome Scale total scores using the equipercentile linking method (67).

De Picker L et al. 2017: Frontiers in Psy; 8(238)

Microglia in Schizophrenia
Interpretation

Microglial but no astroglial activation: No acute inflammatory state
If the blood-brain barrier is intact: Local process in the CNS
Immune processes are involved in inflammatory processes, but also in tissue repair, homeostasis, neuroplasticity, synaptic pruning and other neurodevelopmental processes

Sellgren C et al. 2019: Nat Neurosci; 22(3): 374-85

Arguments against a classical neurodegenerative process

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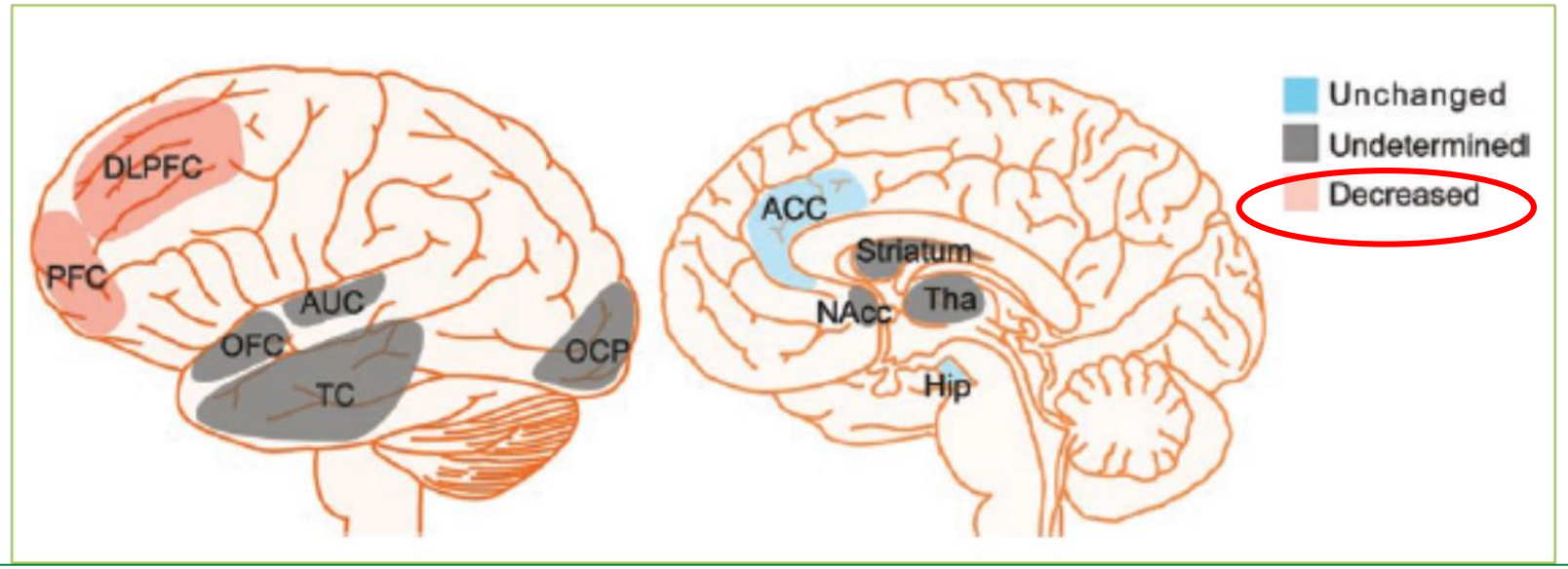
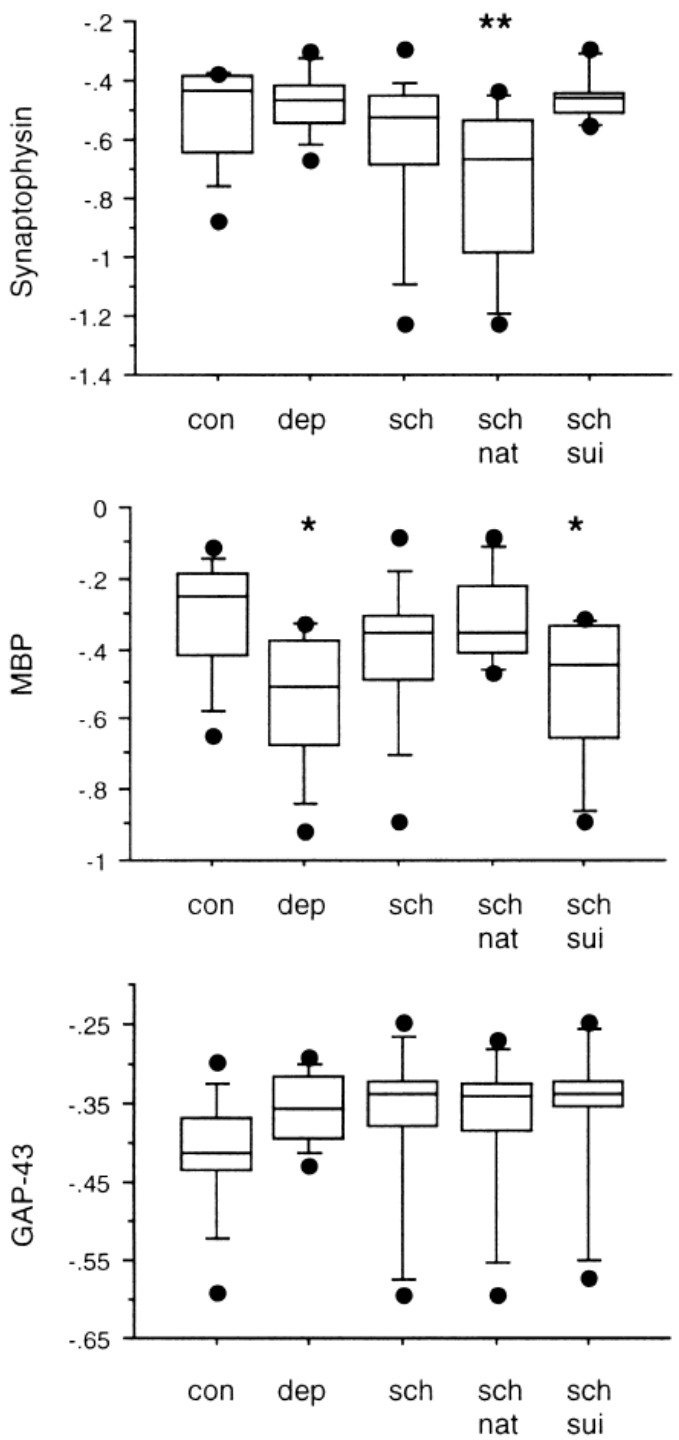
Schematic representation of changes in postsynaptic elements in SZ

The schematic represents changes in postsynaptic elements in SCZ for brain regions tested with meta-analyses (unchanged or decreased) and shows which brain regions could not be tested (undetermined)





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Synaptic and plasticity-associated proteins in anterior frontal cortex in severe mental illness

Box plots of immunoreactivities of synaptophysin, MBP and GAP-43

Fig. 4. Box plots of immunoreactivities of synaptophysin, MBP and GAP-43 in controls (con), depression (dep) and schizophrenia (sch). The schizophrenia results are also shown separated into schizophrenics who died by natural causes (sch/nat), and by suicide (sch/sui). Results represent the amount of brain protein homogenate in micrograms resulting in an optical density signal of 0.5, and are multiplied by −1 as larger amounts of protein indicate less antigen. Percentiles are indicated by boxes (25, 50, 75) and bars (10, 90) with points outside these ranges also shown. Significant reductions compared with controls; $^{**}P = 0.01$, $^{*}P = 0.05$ (Student–Newman–Keuls test).

Honer WG et al. 1999: Neuroscience. 1999;91(4):1247-55.

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Exercise in Rodents

Improves plasticity and learning (“cognition”)

Exercise improved the Water Maze performance, enhanced the number of Bromodeoxyuridin-positive cells and extended alternatively the long-term-potentiation of the Gyrus dentate in mice

Physical Activity has the capacity regulate neuroneogenesis of the hippocampus, equally **synaptic plasticity** and **learning**

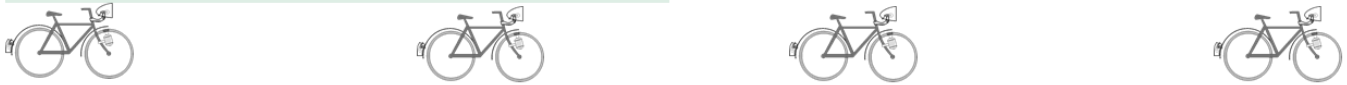
Van Praag et al. 1999: Nature Neurosci 2(3): 366-70

Exercise I Study –

Design

Group: Patients with schizophrenia

Exercise: Cycling



Frequency: 3 times/week à 30 min

Duration: 3 months

Group: Patients with schizophrenia

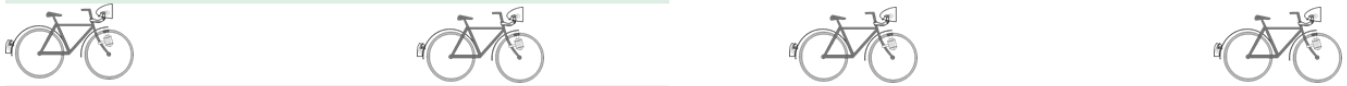
Exercise: table soccer

Frequency: 3 times/week à 30 min

Duration: 3 months

Group: Controls

Exercise: Cycling



Frequency: 3 times/week à 30 min

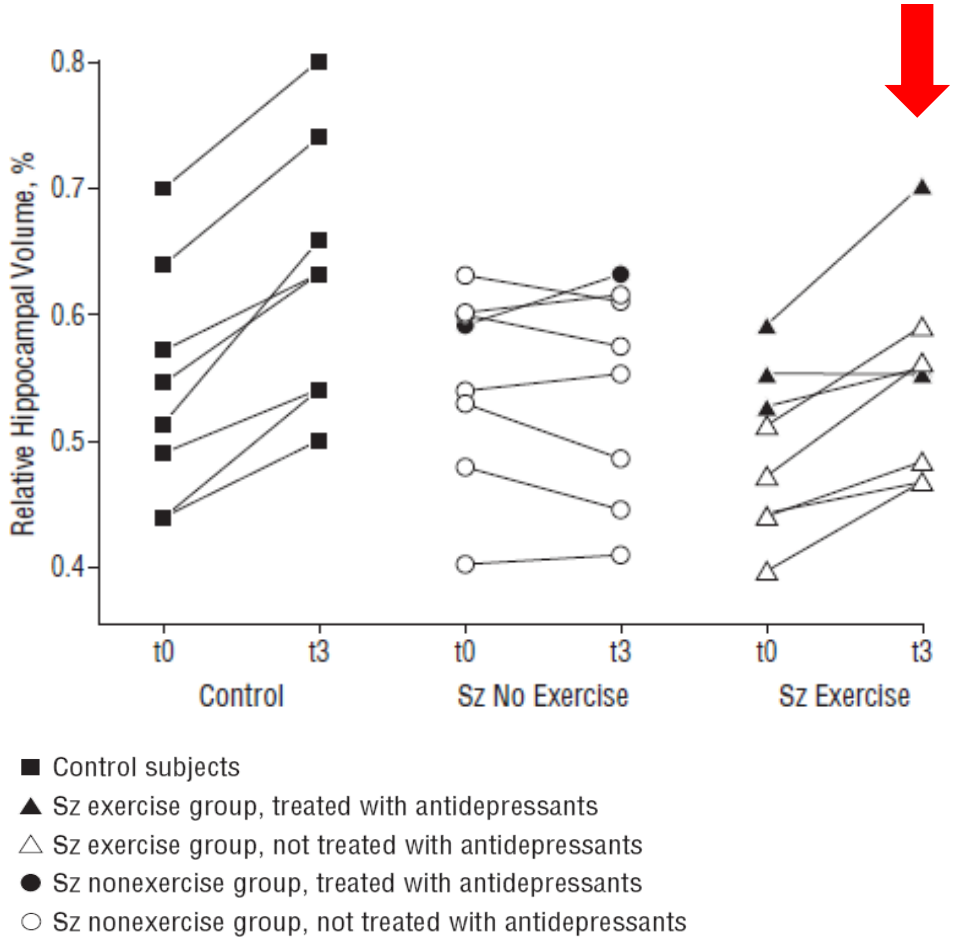
Duration: 3 months

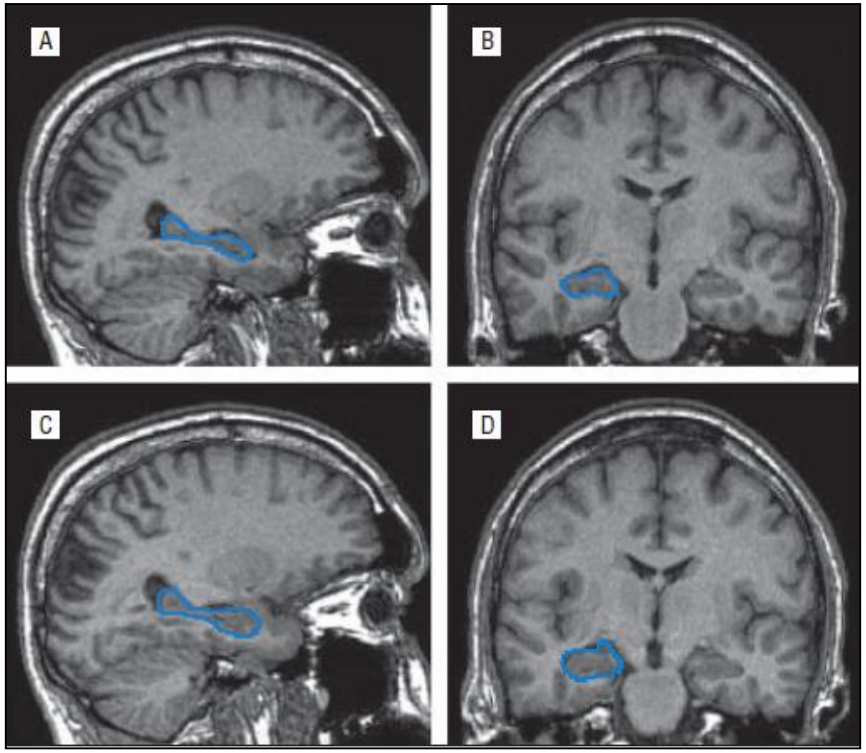
Effects of Exercise on Physical capacity, cognition and neurobiology

Pajonk FG et al. 2010: Arch Gen Psy; 67(2):133-43

Exercise I Study

Results





- **Improvement of negative symptoms and short-term memory**
- **Normalization of hippocampal volume**

Pajonk FG et al. 2010: Arch Gen Psy; 67(2):133-43

Arguments against a classical neurodegenerative process

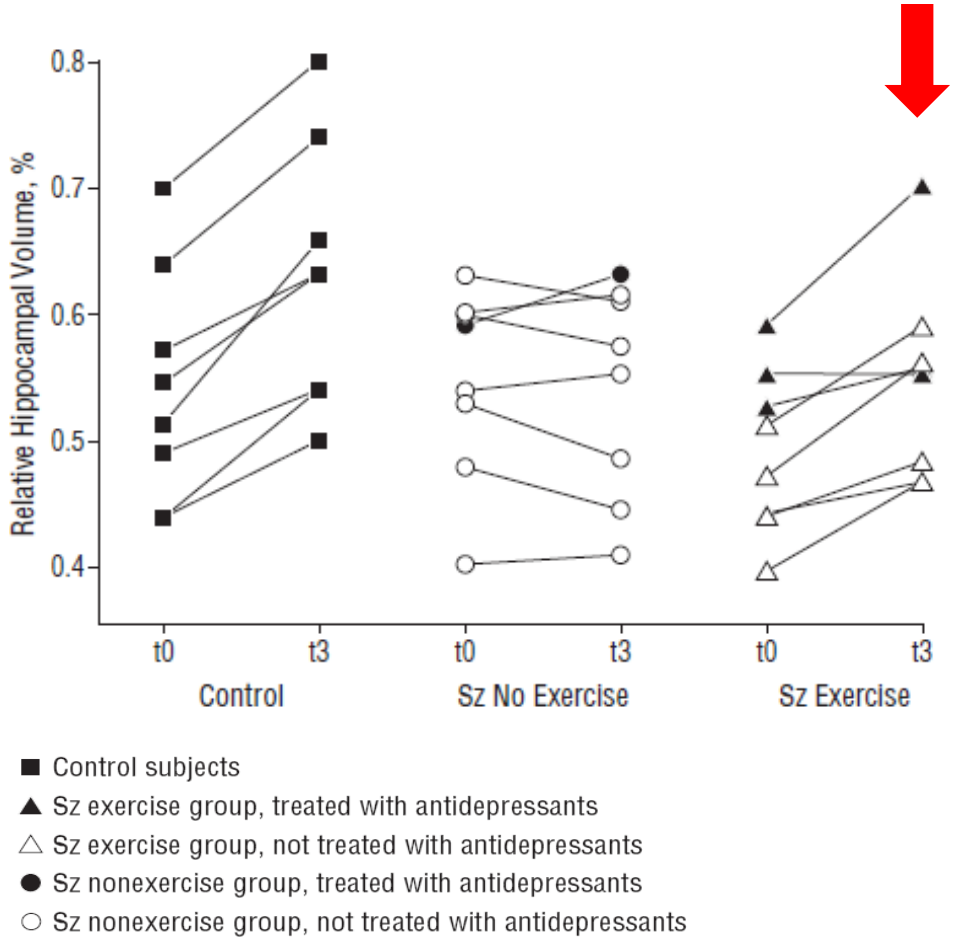
Schizophrenia

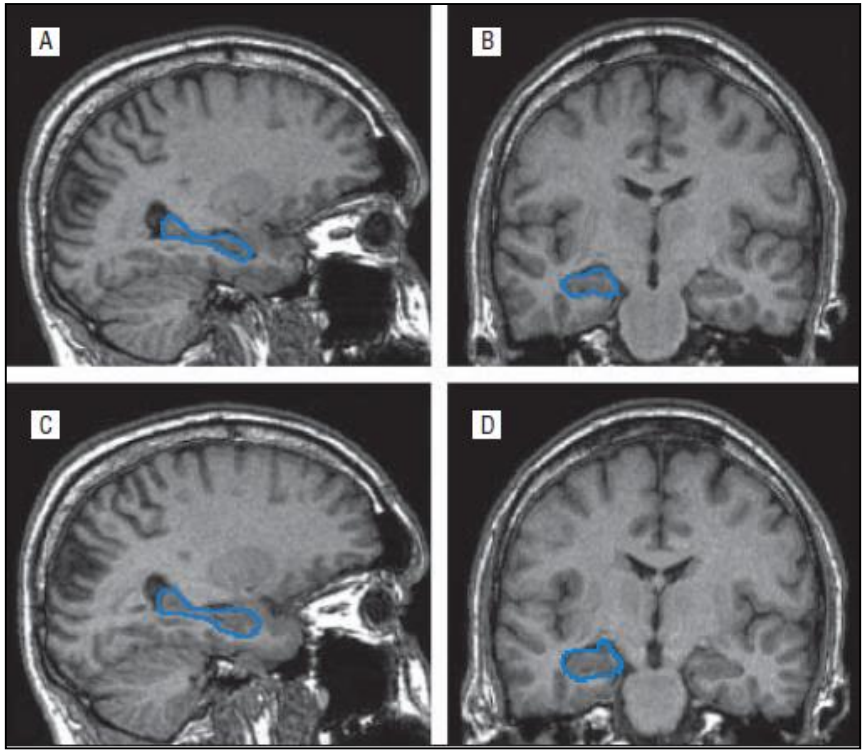
1	No Progression of the cognitive deficits	
2	No Loss of neuronal elements	
3	No Astrocytosis or microgliosis indicative for inflammation	
4	Synaptic Changes in schizophrenia	
5	Reversibility of structural and functional changes in schizophrenia	✓

AEROBIC EXERCISE AS A HUMAN MODEL FOR SZ?

Exercise I Study

Results





- **Improvement of negative symptoms and short-term memory**
- **Normalization of hippocampal volume**

Pajonk FG et al. 2010: Arch Gen Psy; 67(2):133-43

Exercise II Hypothesis

Combining exercise and cognitive remediation

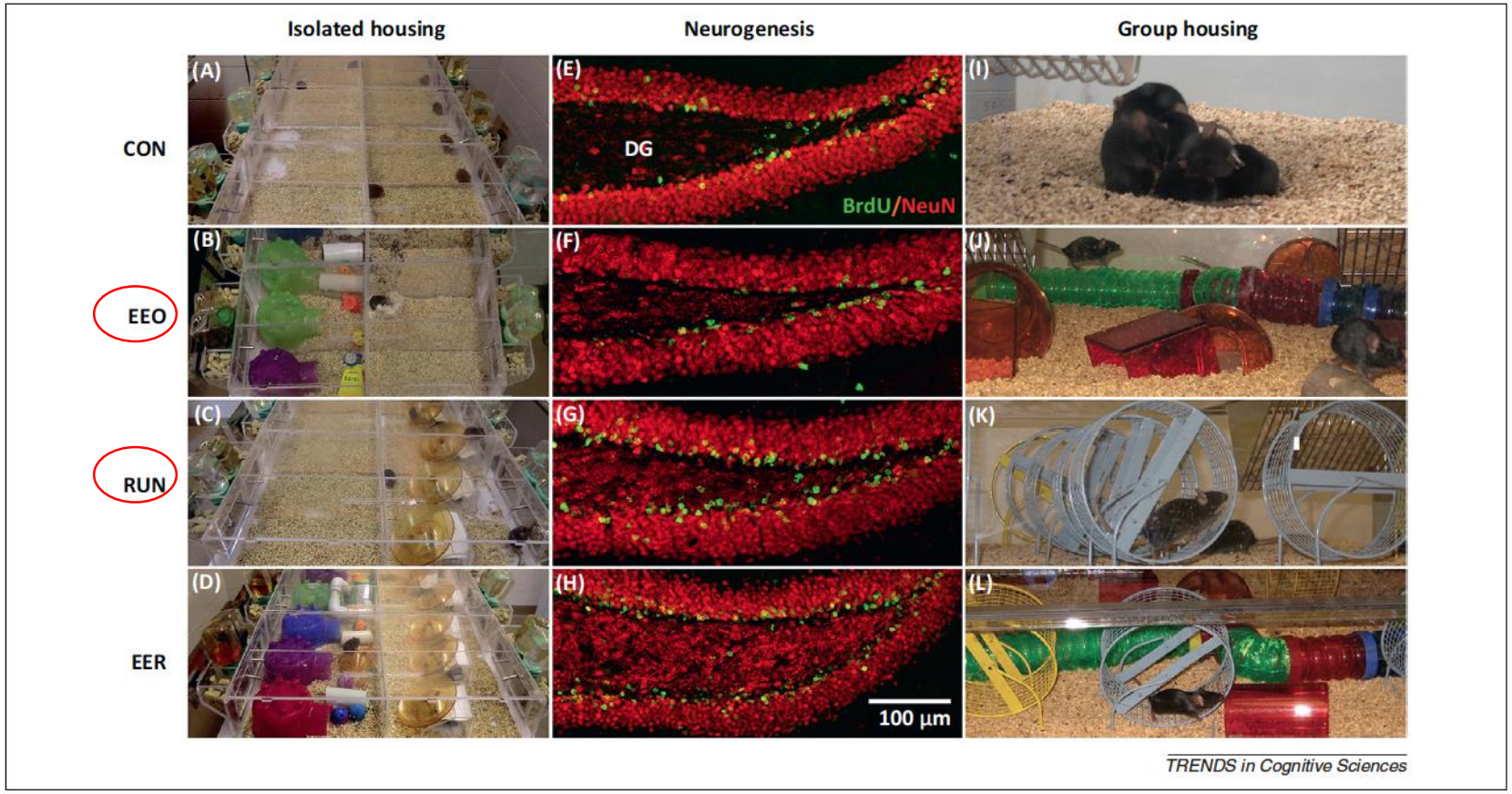


Figure 1. Exercise increases the production of new neurons in the dentate gyrus (DG) of the hippocampus. In two independent studies [18,19], mice were housed under (**A,I**) control (CON), (**B,J**) enriched environment only (EEO), (**C,K**) running (RUN), or (**D,L**) enriched environment and running (EER) conditions in (A–D) single or (I–L) group housing. Confocal images of bromodeoxyuridine (BrdU)-positive cells in the DG in sections derived from mice housed under (**E**) CON, (**F**) EEO (**G**) RUN, and (**H**) EER conditions. Sections were immunofluorescently double-labeled for BrdU (green) and NeuN (red) indicating neuronal phenotype (adapted from [18]). Panels (A–D) are reproduced with permission from [19]. Both studies show that adult DG neurogenesis is increased under the RUN and EER conditions but not under CON or EEO, indicating that running is the neurogenic stimulus.

Hypothesis:
The combination of aerobic exercise and cognitive remediation (=enriched environment) improves functioning better than aerobic exercise alone

Voss MW et al. 2013: Trends Cogn Sci; 10:525-44

Exercise II

Design

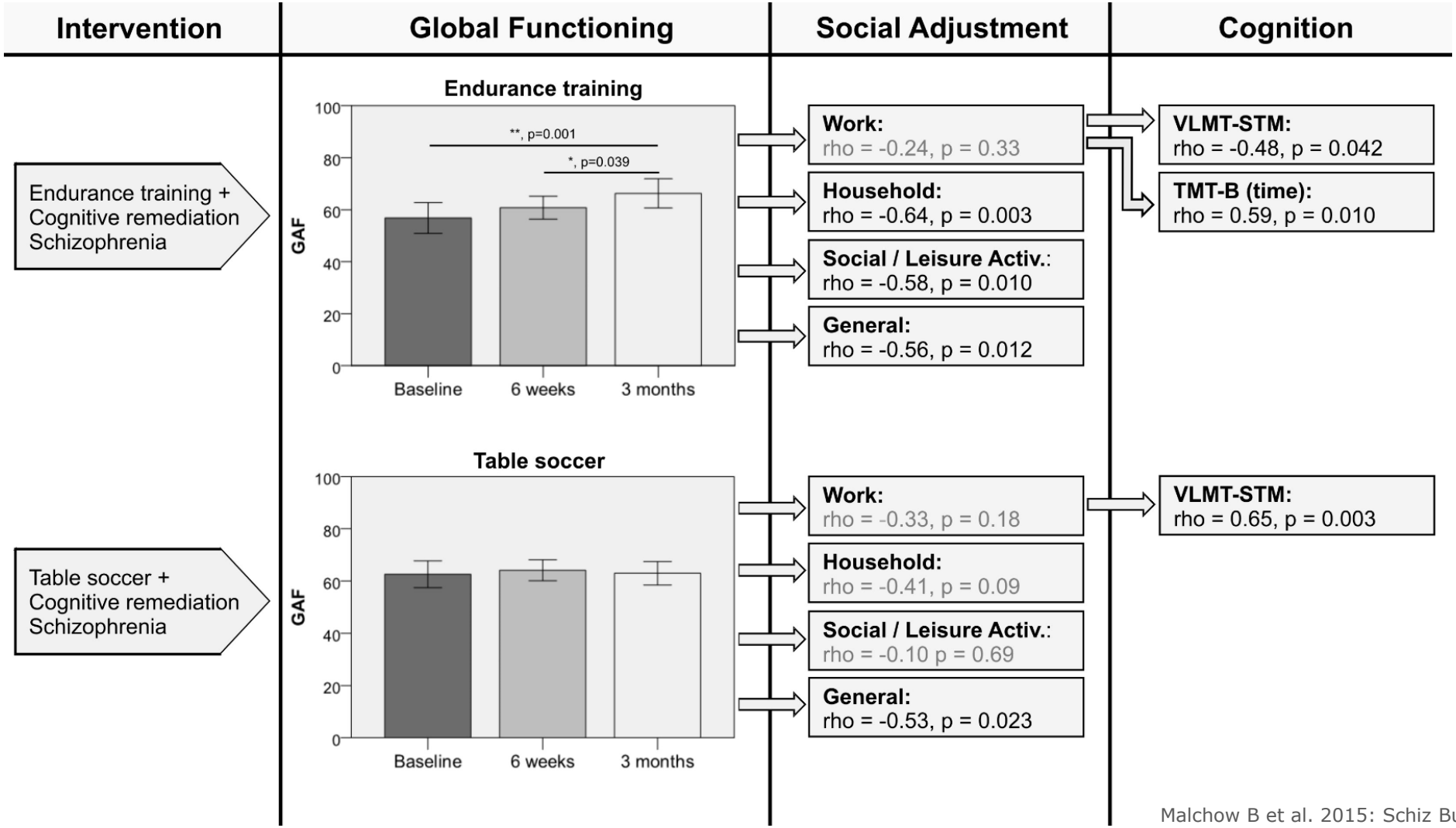



Timeline	Screening	Baseline/Intervention		Follow-up		
Visit-number	**Visit 0**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
Time point (Day)	**-14**	**0 ± 2**	**42 ± 7**	**84 ± 7**	**182 ± 14**	**365 ± 14**
Group 1 (SZ)		**CYCLING**				
			COGPACK			
Group 2 (SZ)		**TABLE SOCCER**				
			COGPACK			
Group 3 (Controls)		**CYCLING**				
			COGPACK			

Malchow B et al. 2016: Schiz Res; 173(3):182-191

Exercise II

Results: Exercise has a bigger effect than cog-remediation



- **Daily functioning (GAF) ↑**
- **Social adjustment (SAS) ↑**

due to exercise and to a lesser extent to cognitive remedia-tion.

Malchow B et al. 2015: Schiz Bull; 41(4):847-58

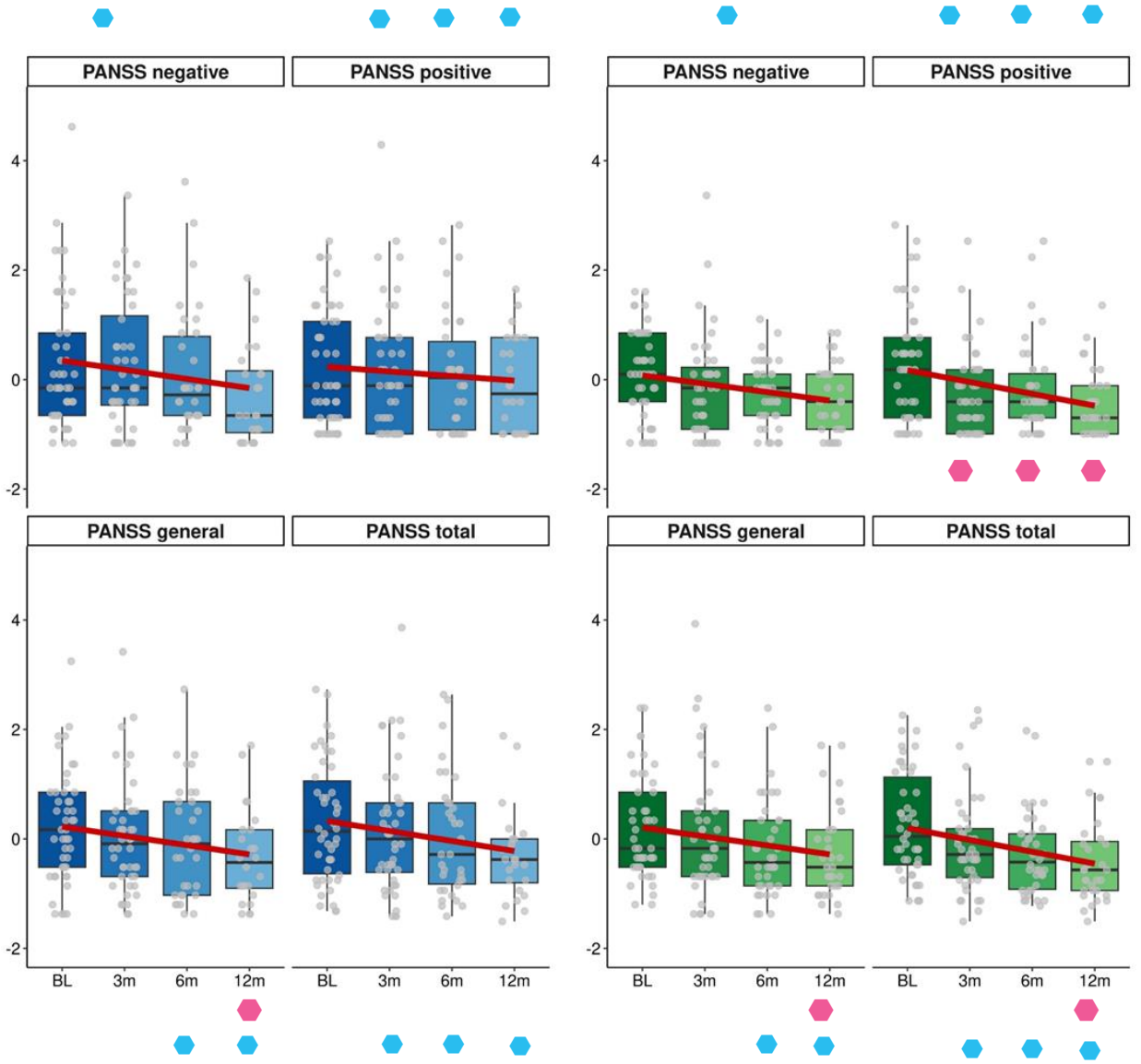
Exercise III study in Schizophrenia (1)

Clinical symptoms

- Significant (ITT)
- Significant (PP sample)

AET
N=90

FSBT
N=90



- **AET : Aerobic exercise training**
- **FSBT: Flexibility Strengthening Balance Training**

- **Effect of AET and FSBT on positive and negative symptomatology**
- **Significance related to BL**

Maurus I et al. 2023: Psych Res; Oct;328:115480

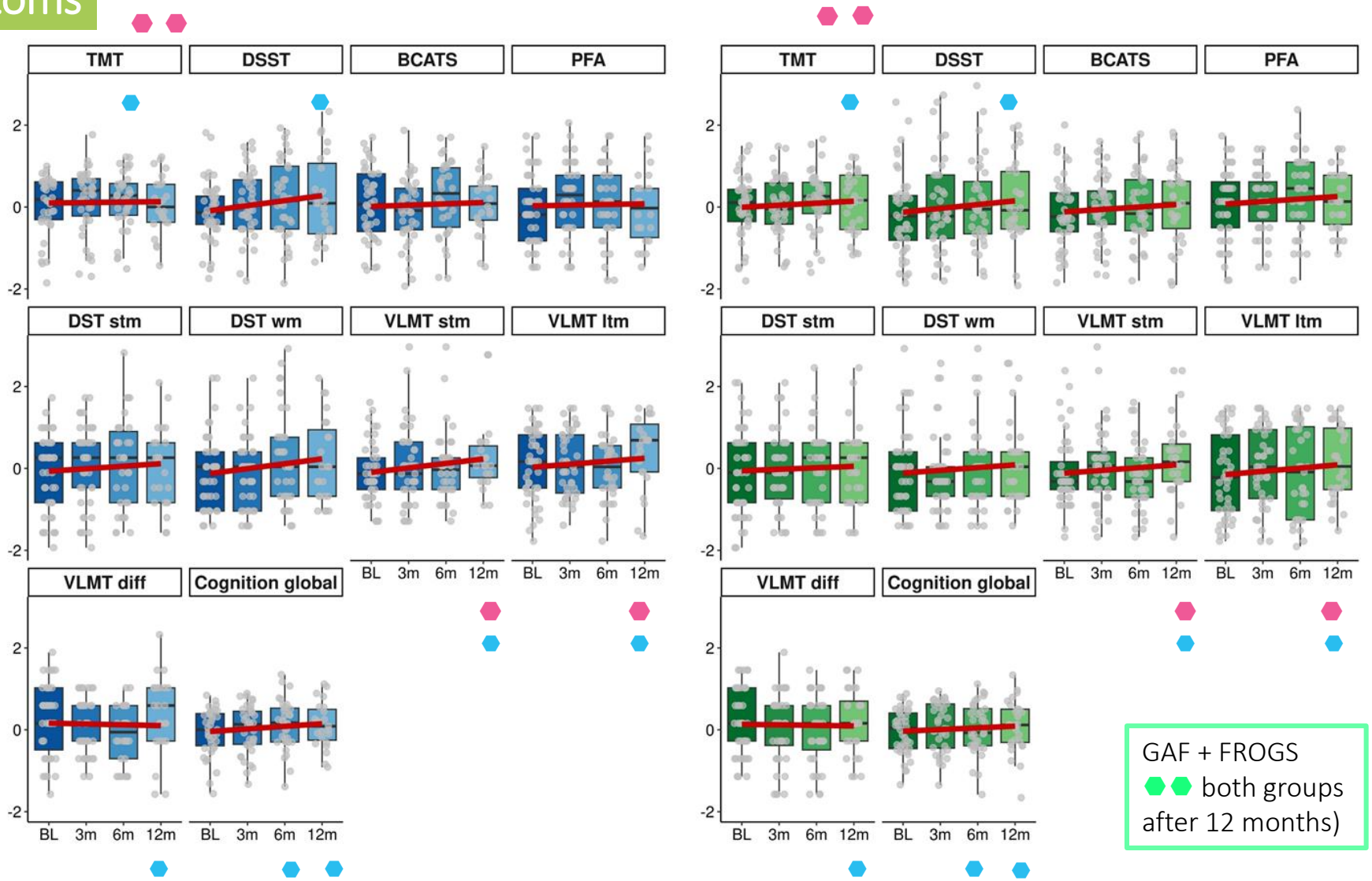
Exercise III study in Schizophrenia (2)

Cognitive symptoms

- Significant (ITT)
- Significant (PP sample)

AET
N=90

FSBT
N=90



- **Improvement in TMT; DSST, VLMT st, lt and gobal cognition**
- **Improvement of GAF and FROGS after 12 months in AET + FSBT**

GAF + FROGS
both groups after 12 months)

Maurus I et al. 2023: Psych Res; Oct;328:115480

Why Exercise in Schizophrenia?

Improvements of positive symptom severity: g = 0.17 – 0.54

(Firth et al., 2015, *Psychol Med*; Dauwan et al., 2016, *Schizophr Bull;* Wei et al., 2020, *Front Psychiatry;* Fernandenz-Abascal et al., 2021, *Neurosci Biobehav Rev;* Bredin et al., 2021, *Front Cardiovasc Med*; Ziebart et al., 2022, *Front Psychiatry*; Gallardo-Gomez et al., 2023, *European Psychiatry*; Maurus et al., 2023, *Psychiatry Res*; Guo et al., 2024, *Schizophrenia*; Rißmayer et al., 2024, *Schizophr Bull*)

Improvements of negative symptom severity: g = 0.30 – 0.65

(Firth et al., 2015, *Psychol Med*; Dauwan et al., 2016, *Schizophr Bull;* Vogel et al. (2019), *Psychiatry Res*; Sabe et al., 2020, *Gen Hosp Psychiatry*; Wei et al., 2020, *Front Psychiatry;* Fernandenz-Abascal et al., 2021, *Neurosci Biobehav Rev;* Bredin et al., 2021, *Front Cardiovasc Med*; Ziebart et al., 2022, *Front Psychiatry*; Kim et al., 2023, *Int J Environ Res Public Health*; Gallardo-Gomez et al., 2023, *European Psychiatry*; Maurus et al., 2023, *Psychiatry Res*; Guo et al., 2024, *Schizophrenia*; Rißmayer et al., 2024, *Schizophr Bull*)

Improvements of global cognition: g = 0.21 – 0.33

(Firth et al., 2017, *Schizophr Bull*; Shimada et al., 2022, Psychiatry Res; Xu et al., 2022, *Psychiatry Res*; Maurus et al., 2023, *Psychiatry Res*)

Improvements of daily life functioning: g = 0.32 – 0.40

(Dauwan et al., 2016, *Schizophr Bull;* Fernandenz-Abascal et al., 2021, *Neurosci Biobehav Rev;* Kormann et al., 2023, *Schizophr Res*)

Röll L 2024 Dissertation. 2025 Nervenarzt, in print

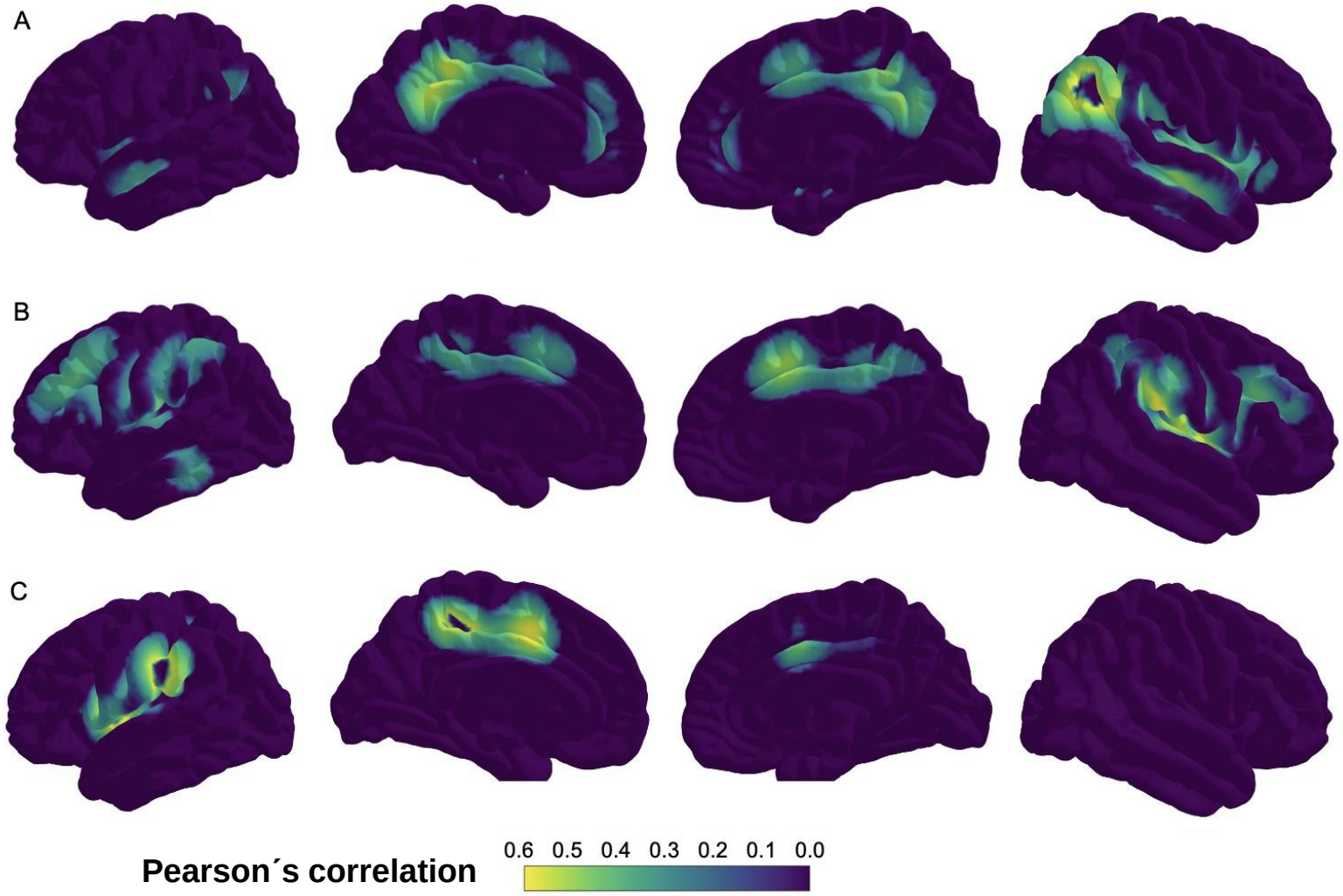
Exercise restores network functioning in Schizophrenia (1)

Functional Dysconnectivity; N=23; Link to the clinic

Δ GAF ⟷ **Δ DCI in DMN**

Δ PANSS ⟷ **Δ DCI in SAL**

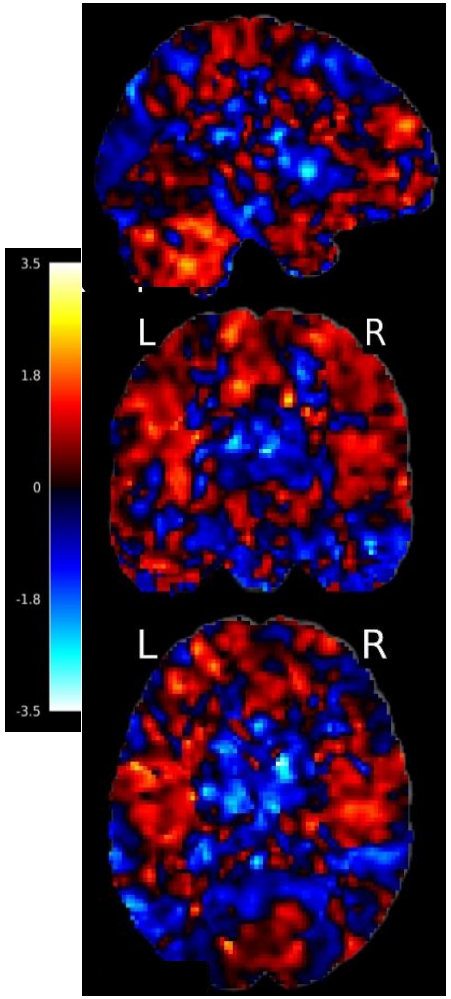
Δ Cognition ⟷ **Δ DCI in Broca + SMN**



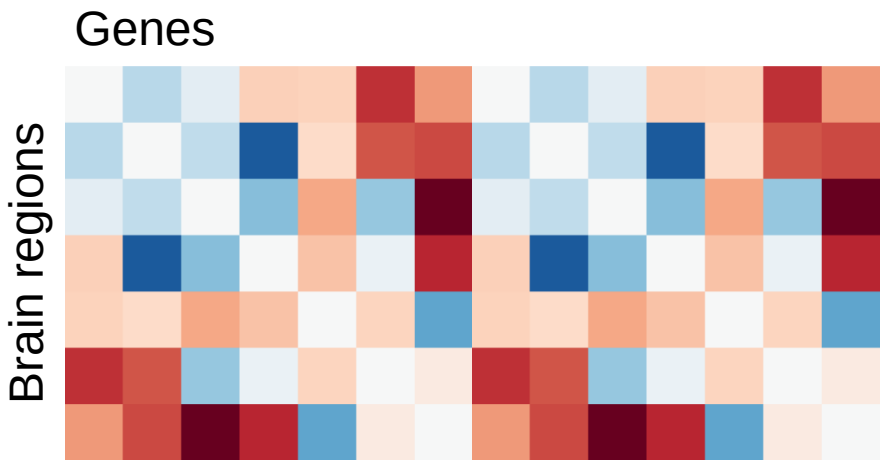
Wunderlich, …, Roell (2025), [under review]

Exercise restores network functioning in Schizophrenia (2)

Imaging Transcriptomics



Functional dysconnectivity



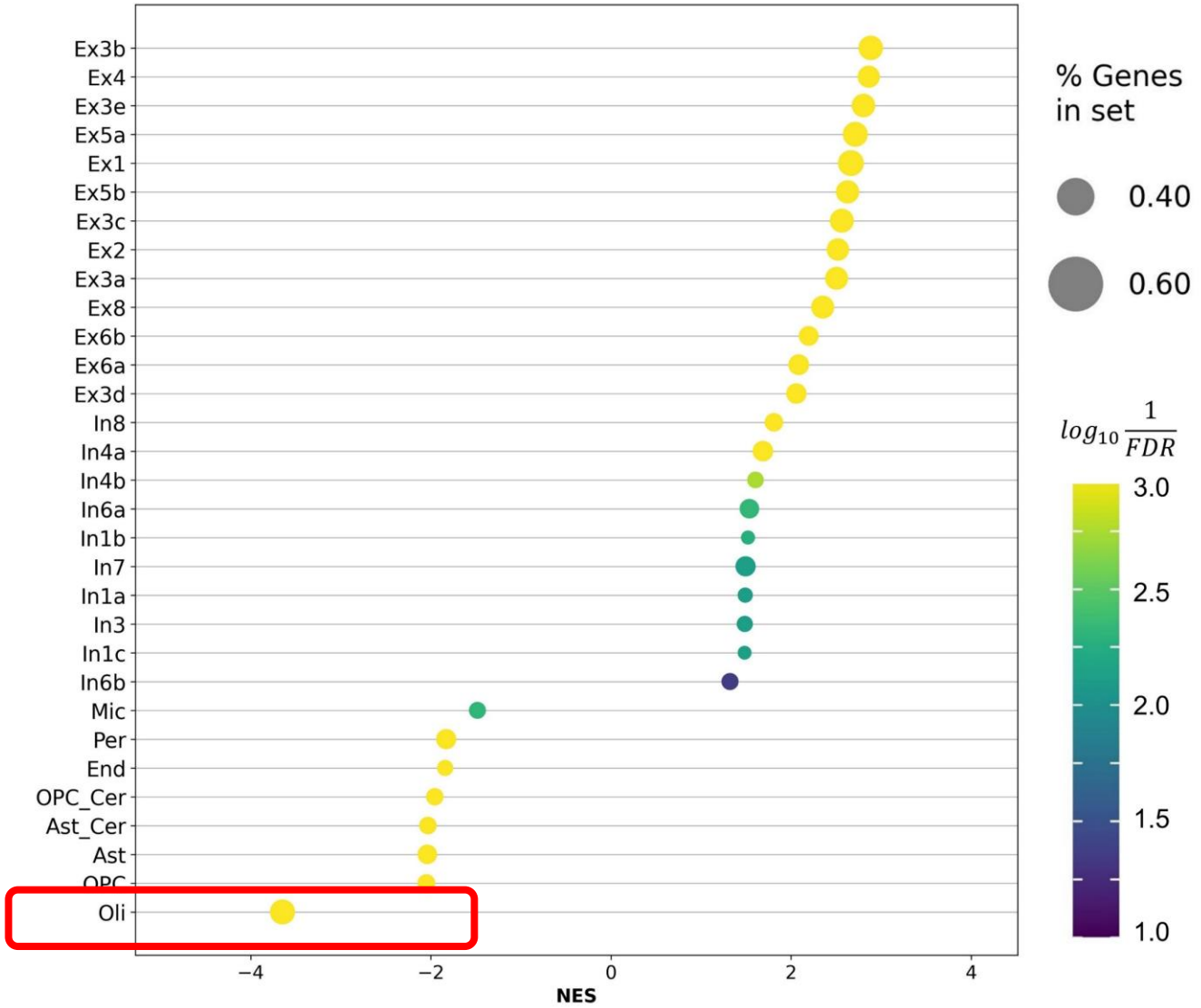
Allen Human Brain Atlas

(Hawrylycz et al. (2012), Nature)

r_s between DCI change and gene expression

Exercise restores network functioning in Schizophrenia (3)

Imaging Transcriptomics; N=23; Link to myelin plasticity



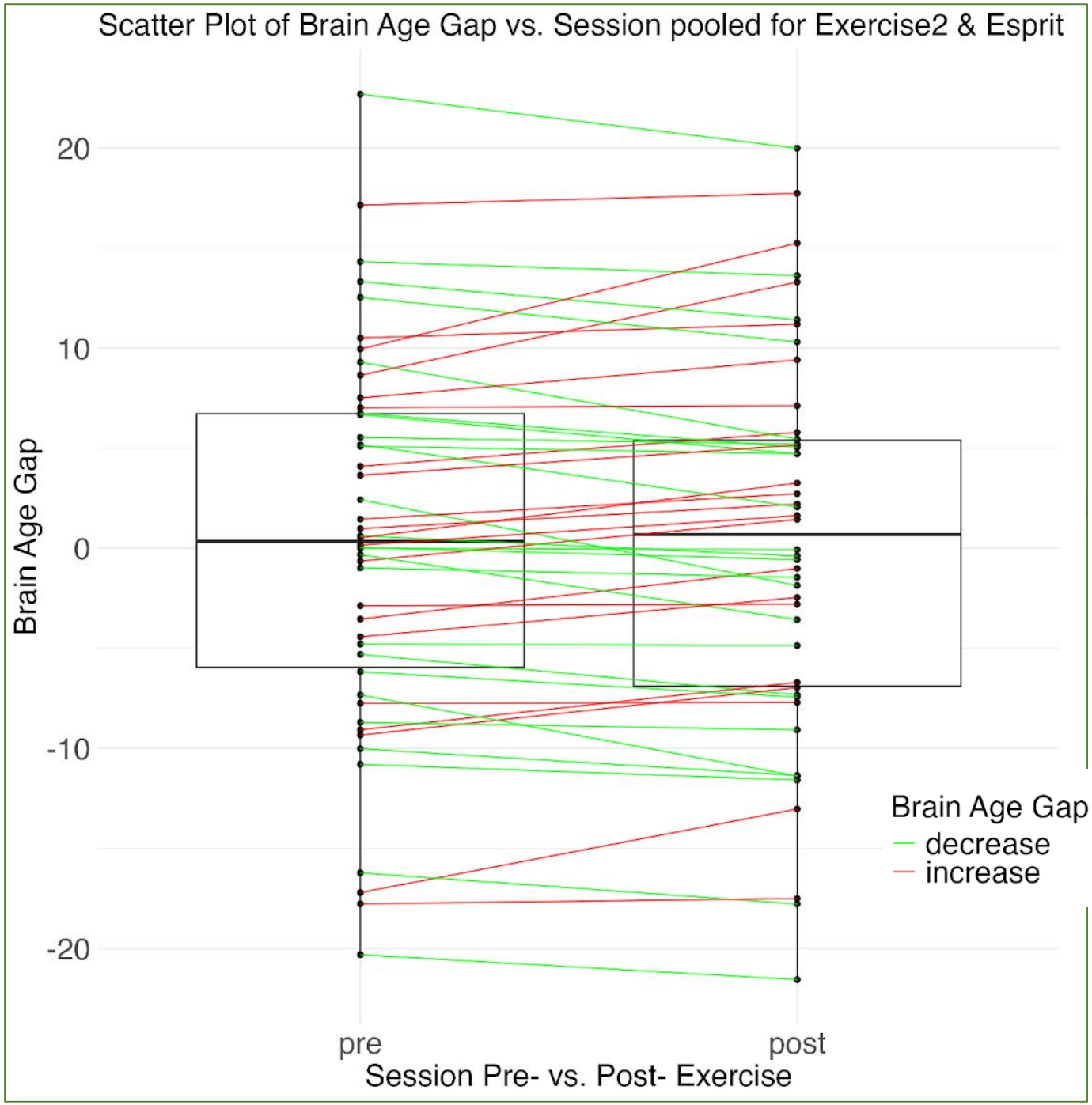
DCI reductions

⇕

Higher expression of genes prominent in

➢ **Oligodendrocytes**

Wunderlich, …, Roell (2025), [under review]



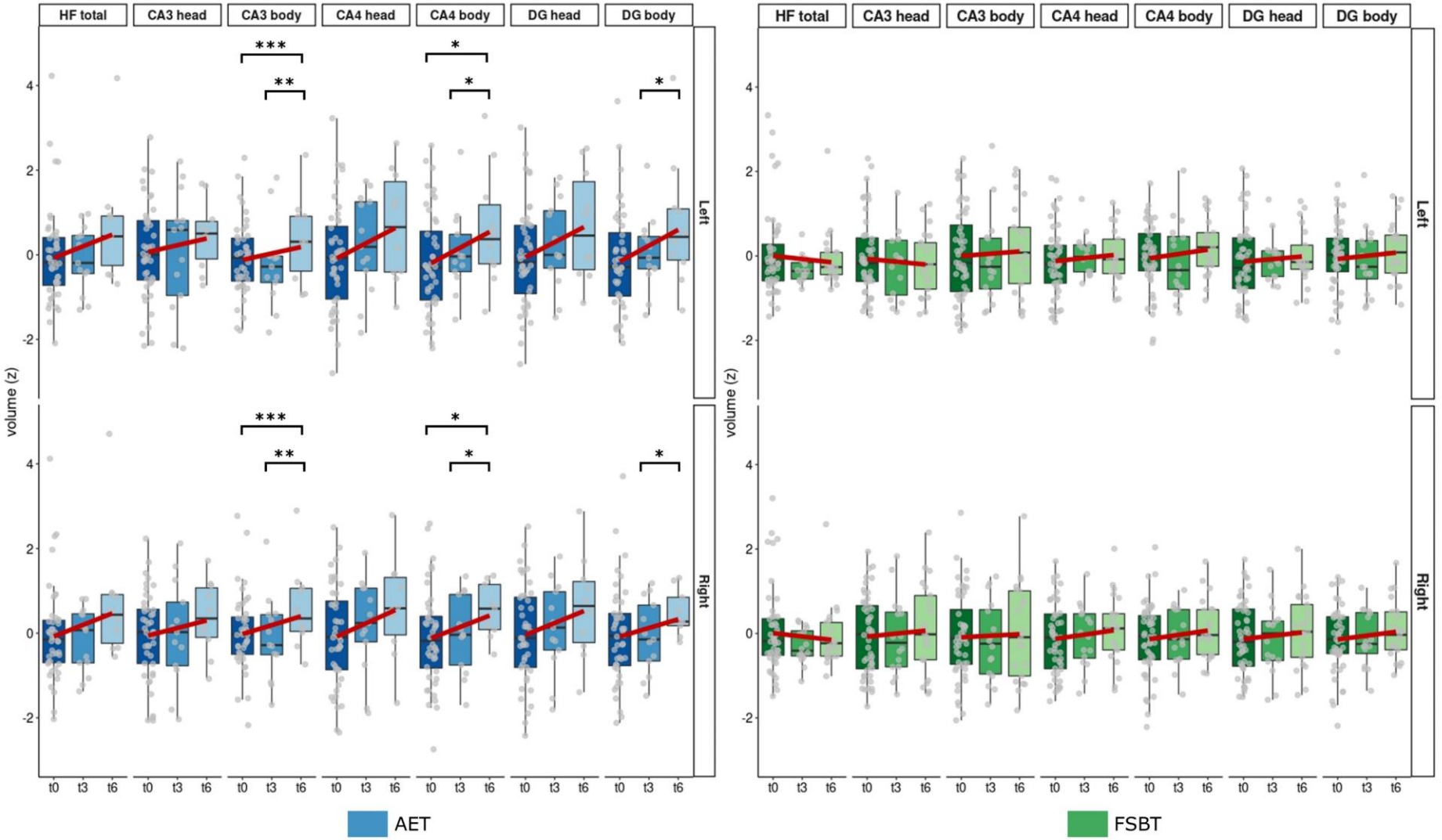
Approx. 50 % of patients show reduction of brain age after physical exercise treatment (no group effect!)

Yilmaz et al. (2025), [under review]

Exercise III study in Schizophrenia (3)

The hippocampus: Volume increase in CA3/CA4

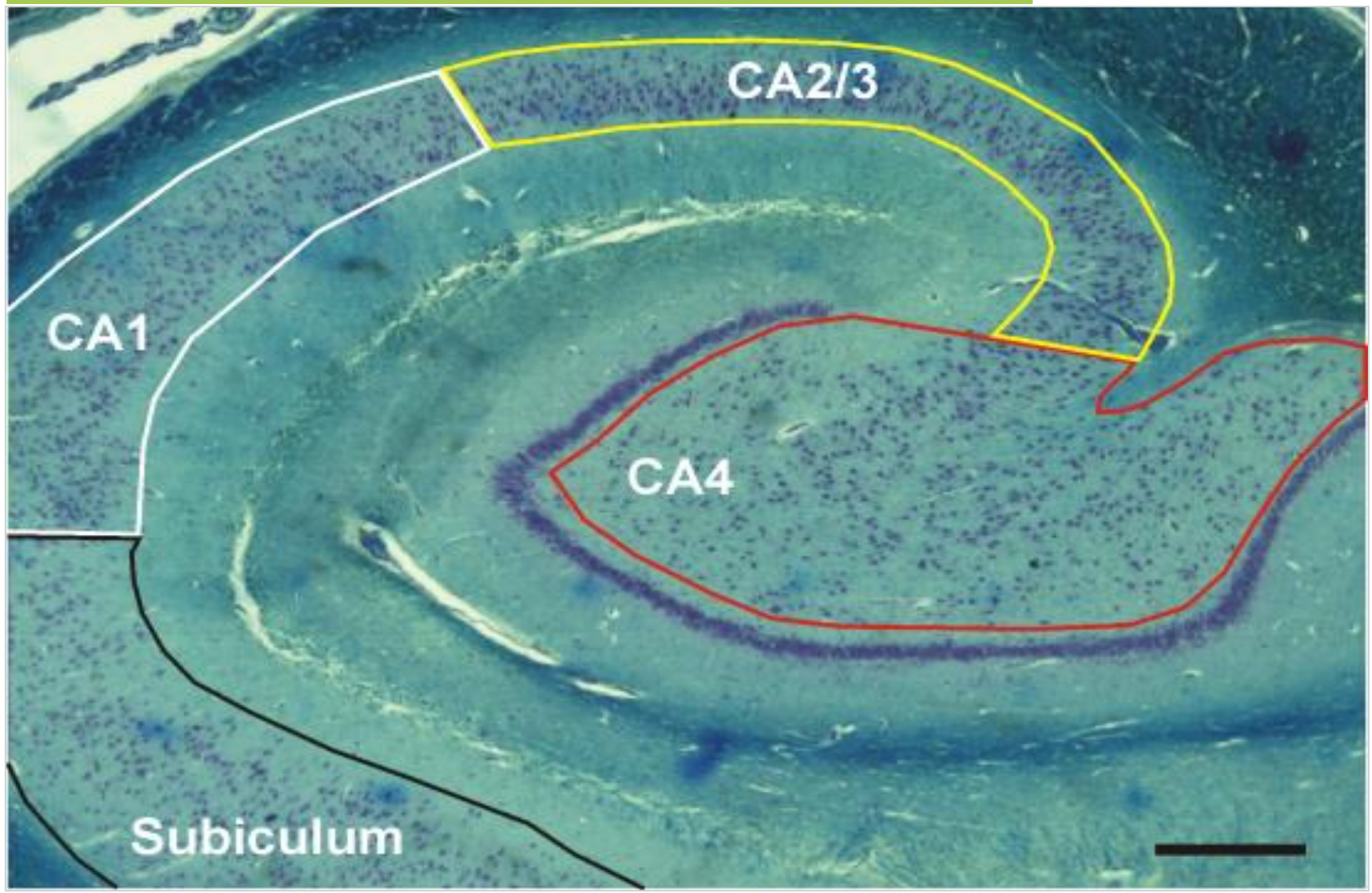
- **Volume increase in CA3 body, CA4 body and DG body *only in AET* not in FSBT**



Roell L et all. 2024: Br J Psychiatry; preprint version available

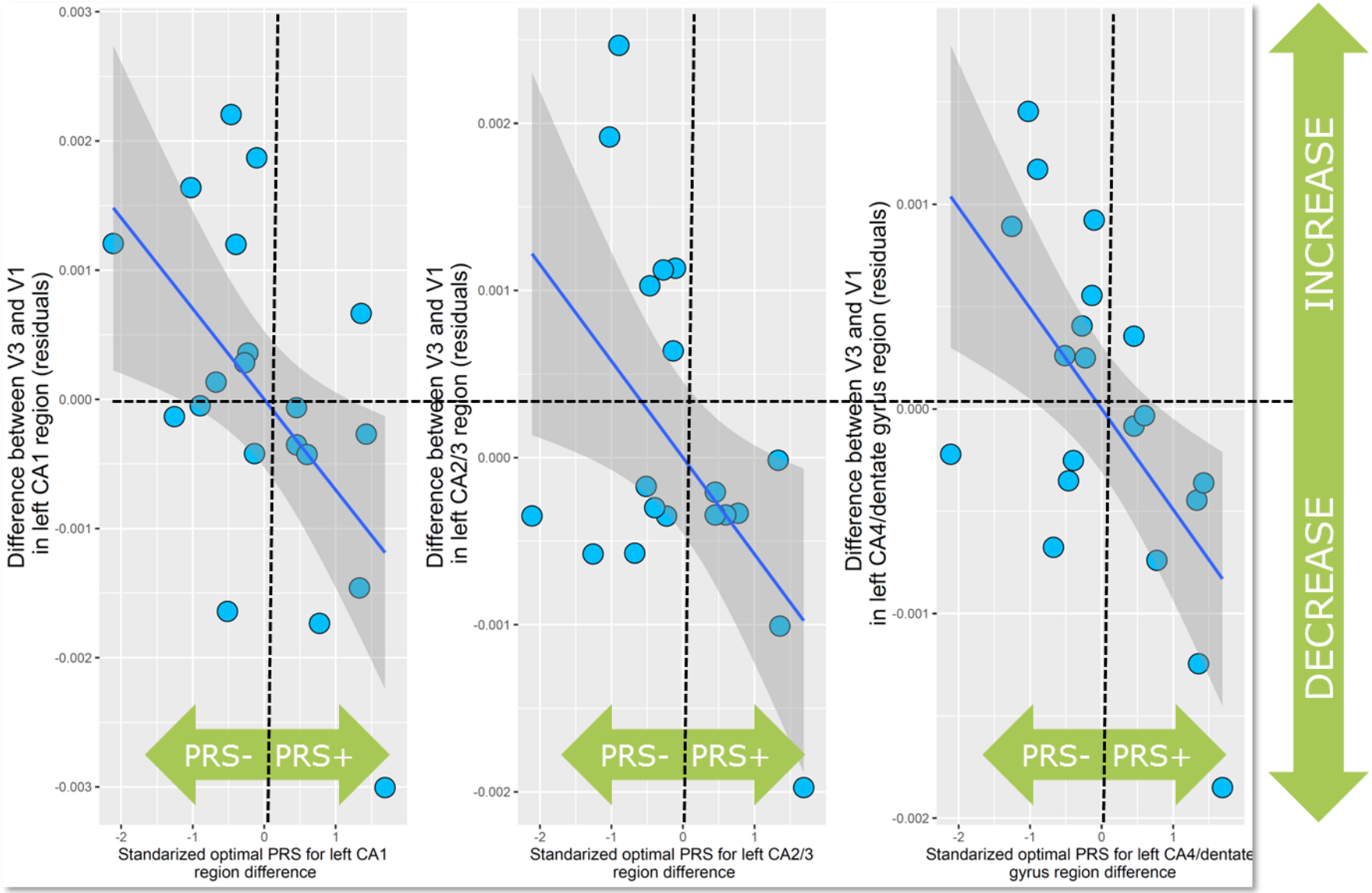
The posterior hippocampus in schizophrenia

The subcompartments CA1 – 4 and the subiculum



Schmitt et al. 2009 Acta Neuropathol 117: 395-407

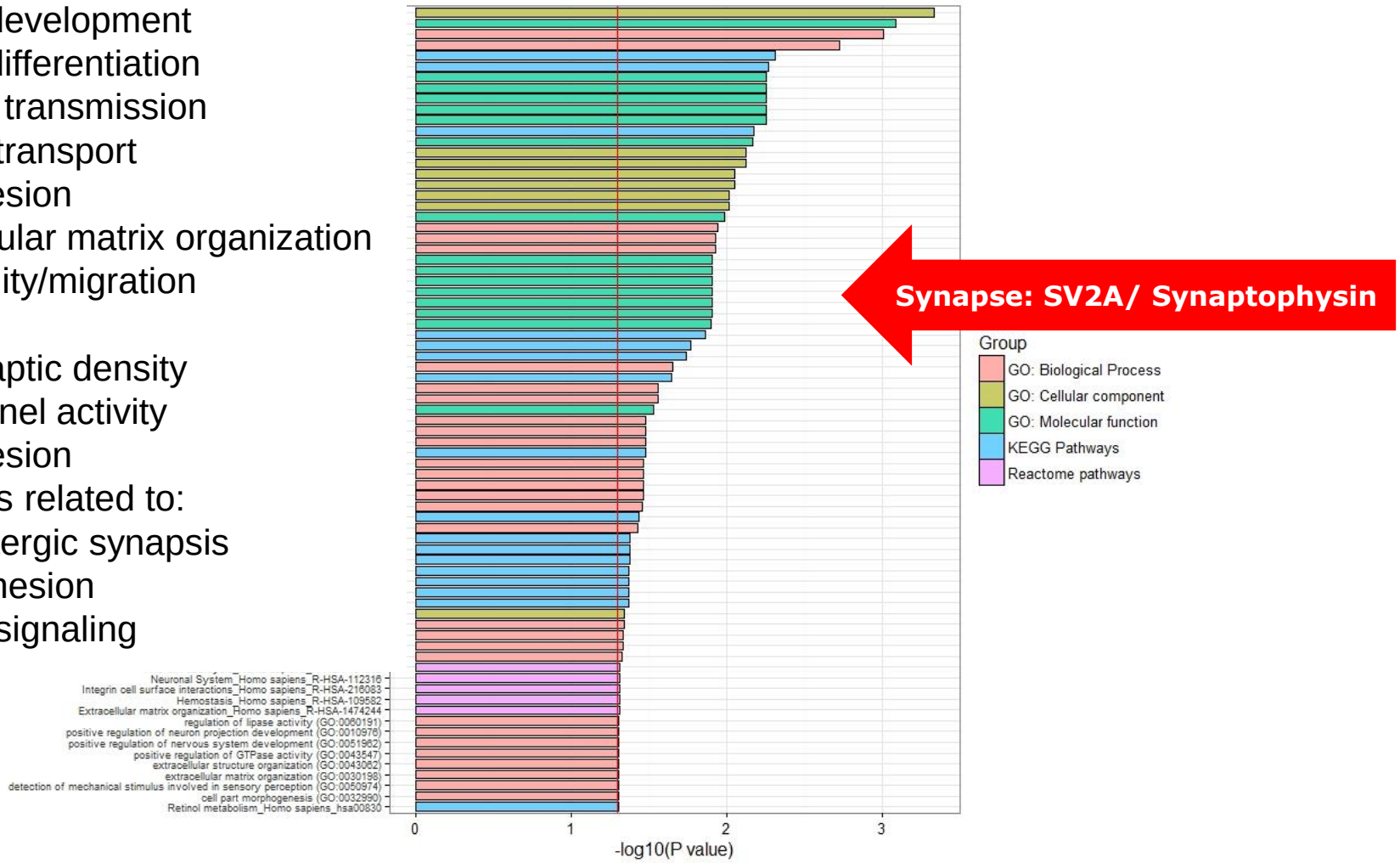
Exercise increases the volume of the hippocampal subfield C4, which is negatively correlated with the burden of risk genes of CA4/Dentate Gyrus



One of the Major Pathways targeted

"Synapse" Pathway with Synaptic Vesicle Protein 2A (SV2A)

- neuron development
- neuron differentiation
- synaptic transmission
- calcium transport
- cell adhesion
- extracellular matrix organization
- cell motility/migration
- synapse
- postsynaptic density
- ion channel activity
- cell adhesion
- pathways related to:
- glutamatergic synapsis
- focal adhesion
- calcium signaling



Papiol S et al. 2017: Translational Psychiatry; 7(6):e1159

Polygenic burden associated to oligodendrocyte precursor cells and radial glia influences the hippocampal volume changes induced by aerobic exercise in SZ patients

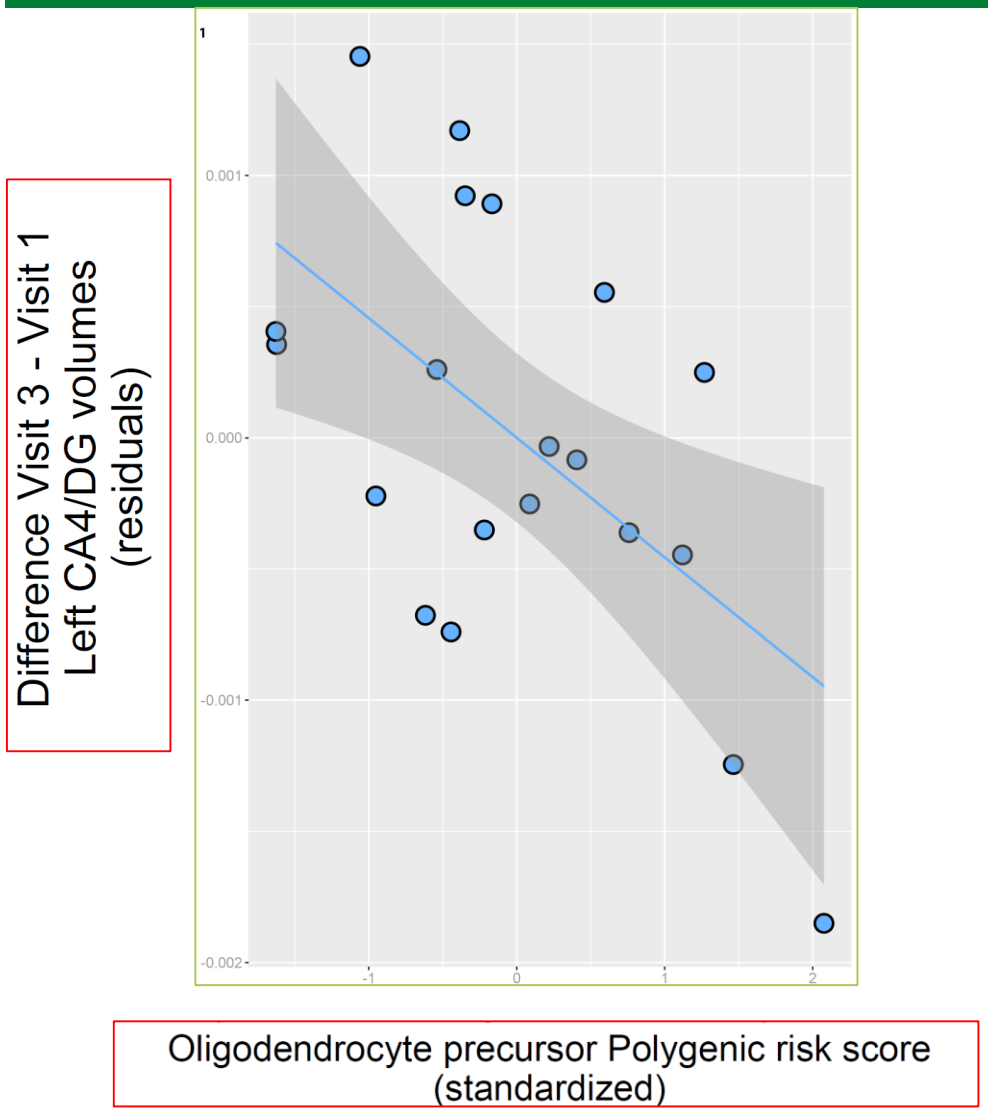
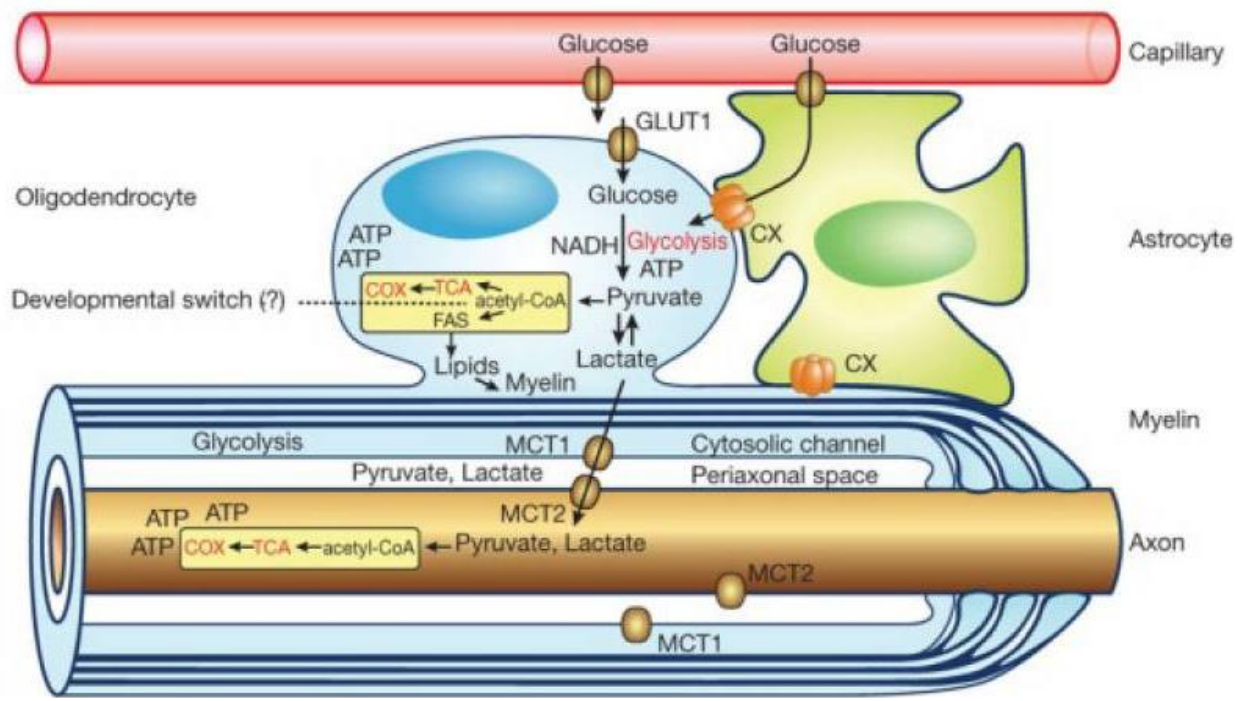


Figure 1. Scatterplot showing the relationship between the optimal (p-value threshold = 0.01) oligodendrocyte precursor polygenic score (PRS^{OPC}; x-axis, standardized) and the change from baseline (V1) in the volume of the left hippocampal subfields CA4/dentate gyrus (right panel) after 3 months of aerobic exercise (V3) (y-axis, corrected residuals). Positive values in the y-axis indicate a gain in volume after 3 months; and positive values in the x-axis, a higher genetic risk burden. Also shown are regression line and 95% confidence intervals based on the predicted means from the regression line.

Papiol S et al. 2017: Translational Psychiatry; 7(6):e1159; Papiol S et al. 2024:Eur Arch Psychiatry Clin Neurosci; 274(6):1241-1244 [replication]

Oligodendrocytes and schizophrenia? Does that match?

Basis of dysconnectivity and disturbed energy supply in schizophrenia

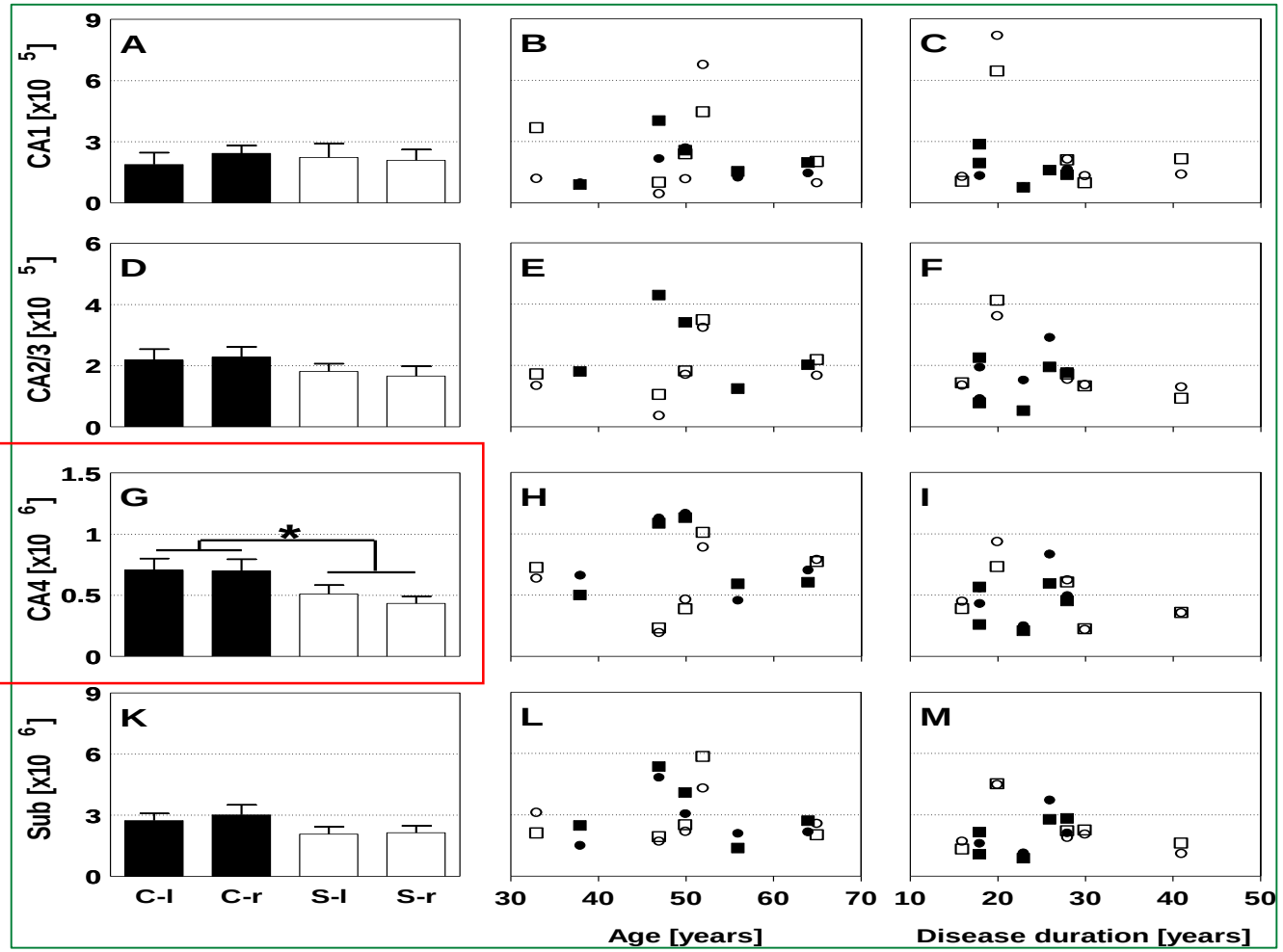


Nature. 2012 Apr 29;485(7399):517-21. doi: 10.1038/nature11007.

Glycolytic oligodendrocytes maintain myelin and long-term axonal integrity.

Fünfschilling U, Supplie LM, Mahad D, Boretius S, Saab AS, Edgar J, Brinkmann BG, Kassmann CM, Tzvetanova ID, Möbius W, Diaz F, Meijer D, Suter U, Hamprecht B, Sereda MW, Moraes CT, Frahm J, Goebbels S, Nave KA.

Circumscribed reduction of number of oligodendrocytes in CA4



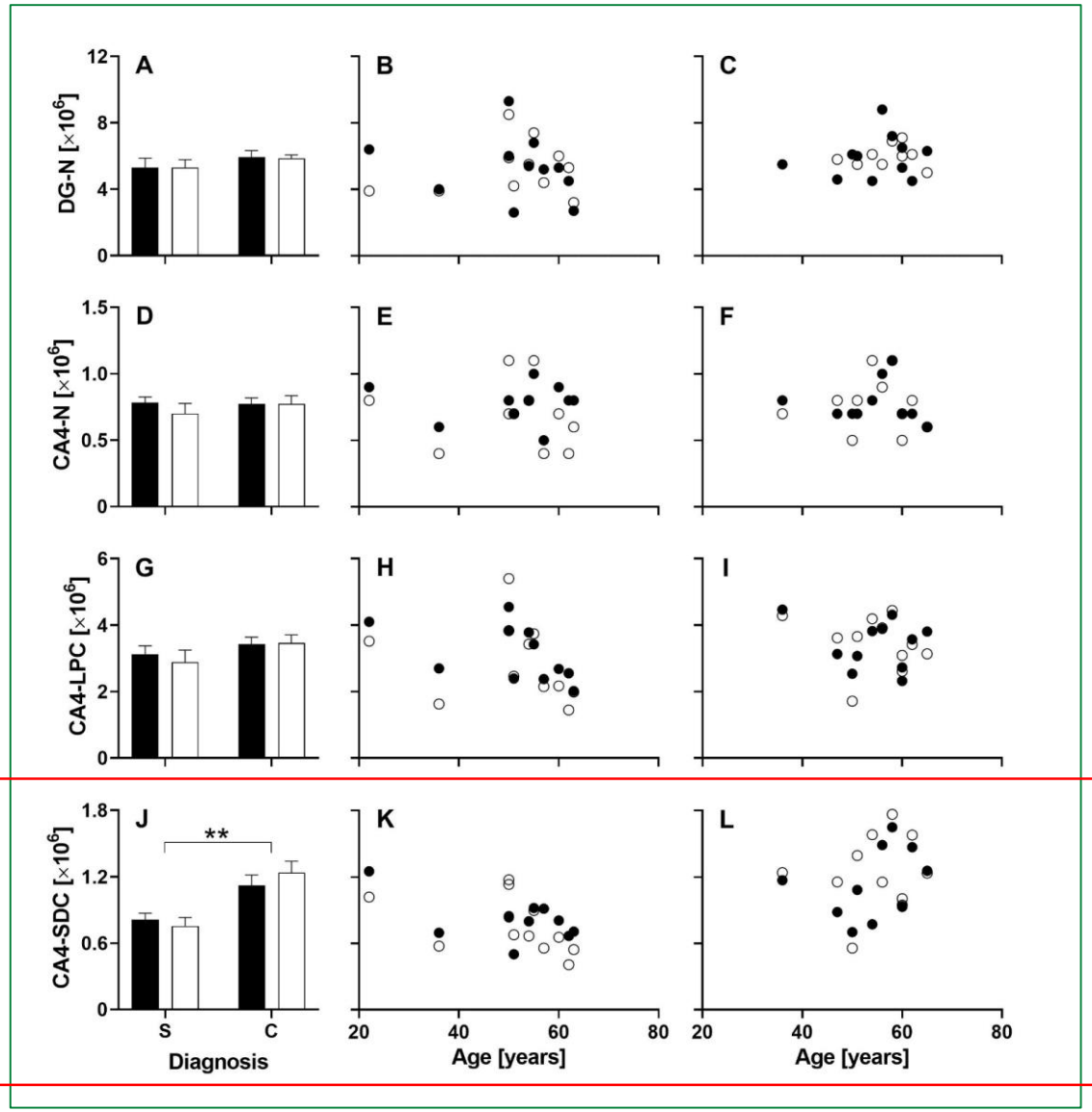
C= controls,

S= schizophrenia,

l= left, r= right hemisphere

Schmitt et al. 2009 Acta Neuropathol 117: 395-407

Replication of the oligodendrocyte reduction in CA4 in an independent sample



Dentate gyrus neurons

CA4 neurons

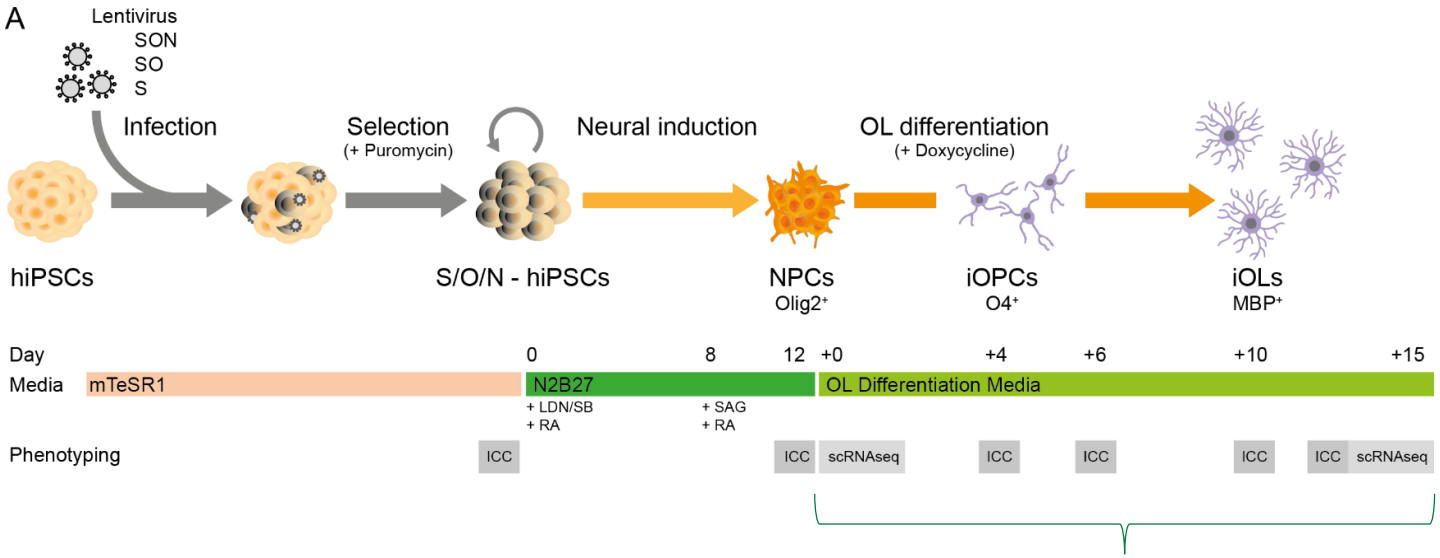
CA4 astrocytes

CA4 oligodendrocytes

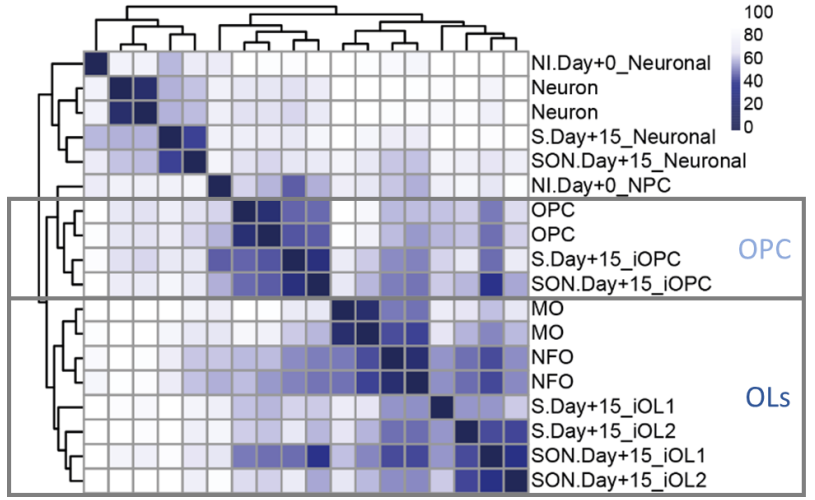
Schmitt A et al. (2022) Cells; 11(20):3242

hiPSCs-derived OPC/Ols – A model for oligodendrocyte dysfunction in SZ (1)

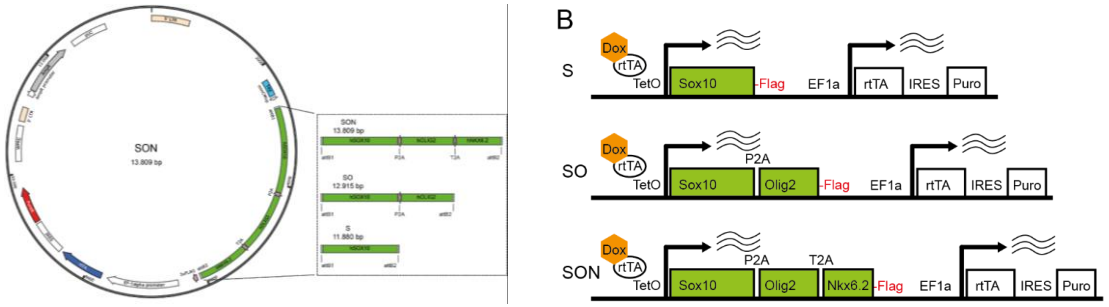
2D human iOL cultures

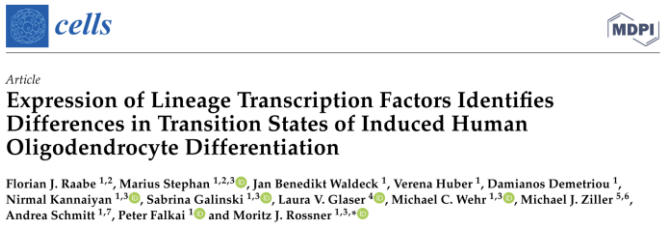


+ Doxycycline induction: overexpression lineage determining transcription factors



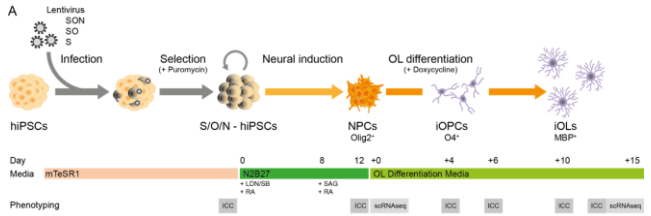
hiPSCs-derived OPC/OLs cluster with primary cells

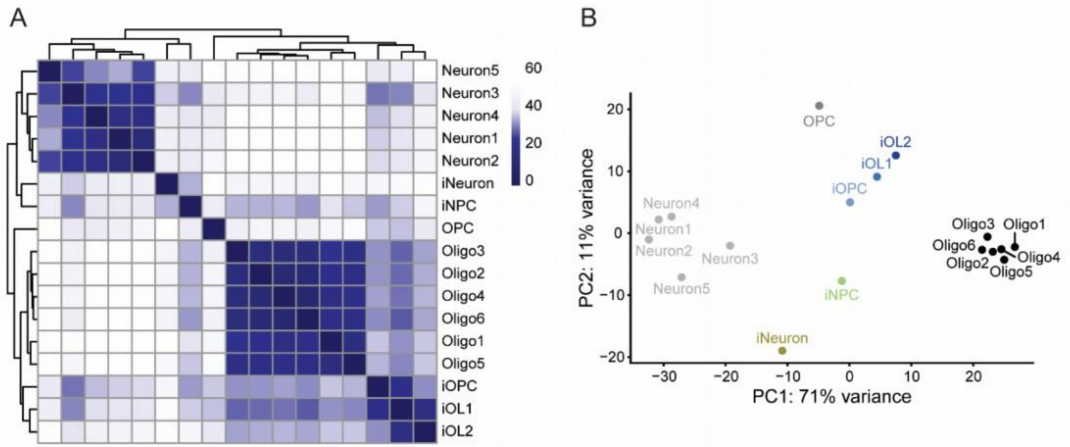



cells
MDPI
Article
Expression of Lineage Transcription Factors Identifies Differences in Transition States of Induced Human Oligodendrocyte Differentiation
Florian J. Raabe [1,2], Marius Stephan [1,2,3], Jan Benedikt Waldeck [1], Verena Huber [1], Damianos Demetriou [1], Nirmal Kannaiyan [1,3], Sabrina Galinski [1,3], Laura V. Glaser [4], Michael C. Wehr [1,3], Michael J. Ziller [5,6], Andrea Schmitt [1,7], Peter Falkai [1] and Moritz J. Rossner [1,3,*]

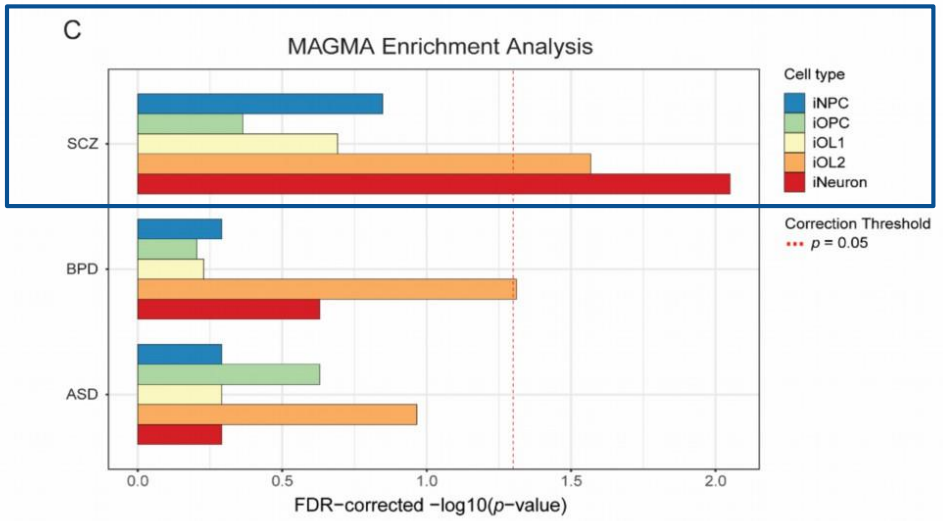
Raabe, F. J., Stephan, M., Waldeck, J. B., … Ziller, M. J., Schmitt, A., Falkai, P., & Rossner, M. J. 2022: Cells

hiPSCs-derived OPC/OIs – A model for oligodendrocyte dysfunction in SZ (2): Genetic analyis



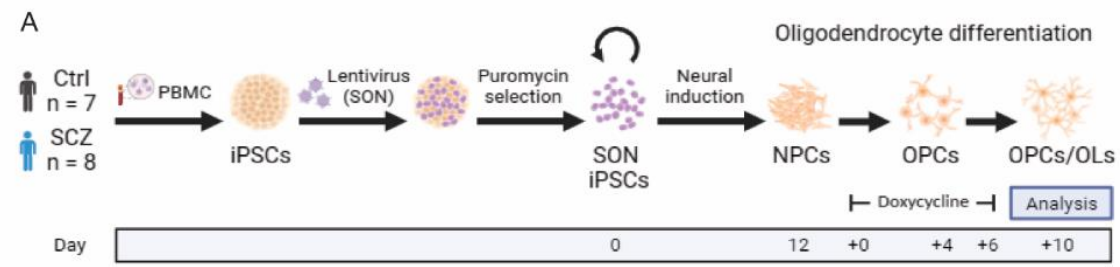


hiPSC-derived iOPCs and iOLs
- cluster with human postmortem OPCs/ OLs
- genes of mature iOLs are enriched in schizophrenia (SCZ) GWAS

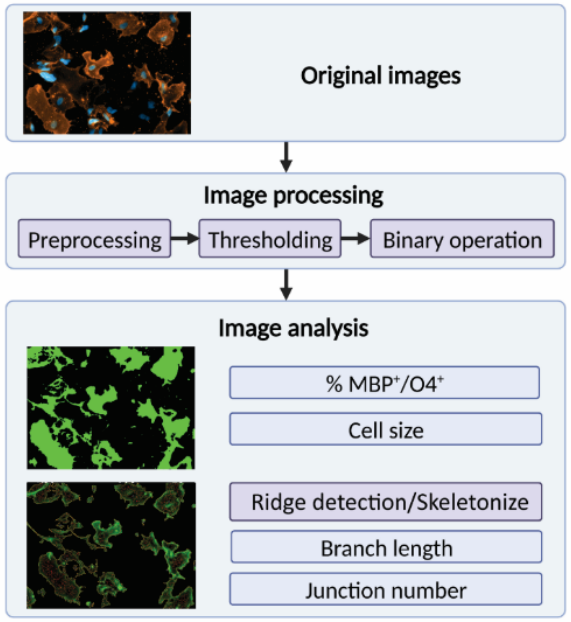


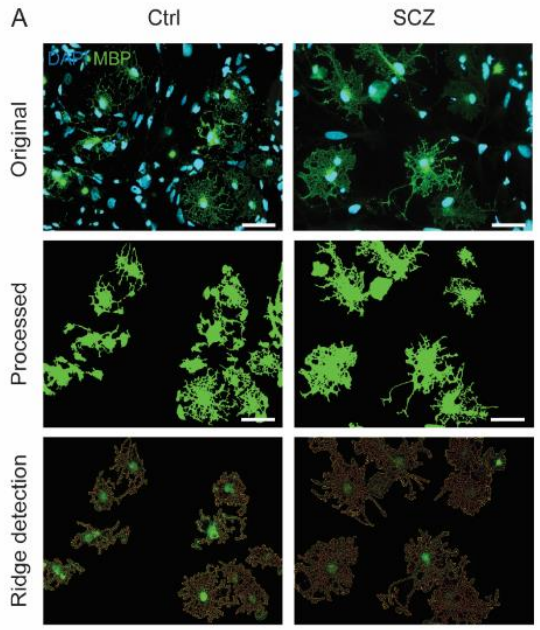
Chang, Waldeck et al. ... Falkai, Rossner, Raabe, revision in review

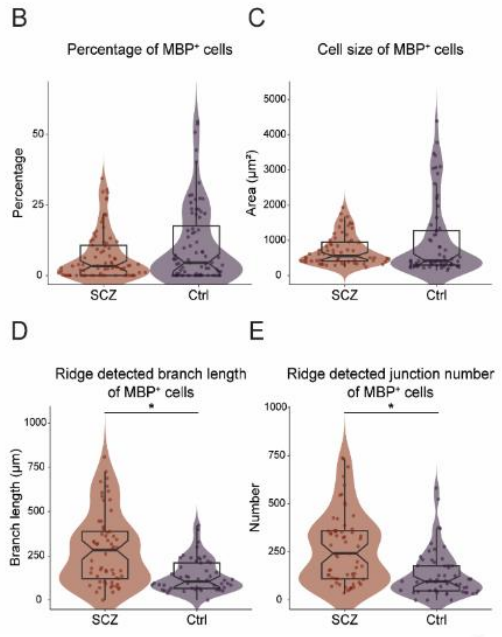
hiPSCs-derived OPC/OIs – A model for oligodendrocyte dysfunction in SZ (3): Case Control study in 2D

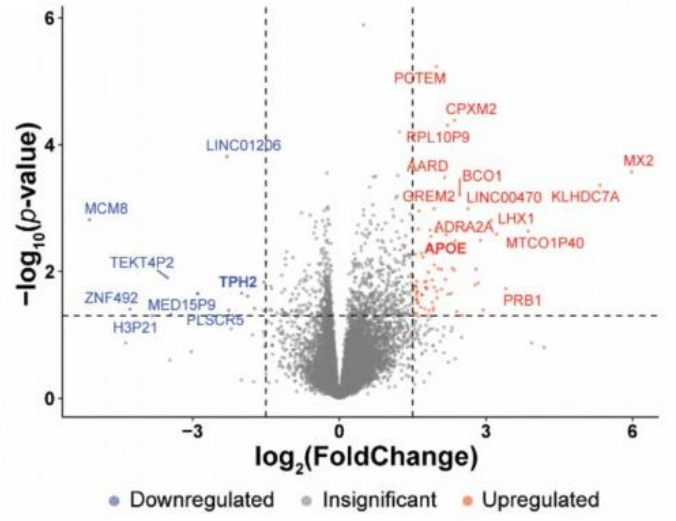


iPSC-derived OPC/OLs from patients with SCZ (cell autonomous)
- Disturbed morphology of MBP⁺ - OLs in SCZ
- Disturbed gene expression





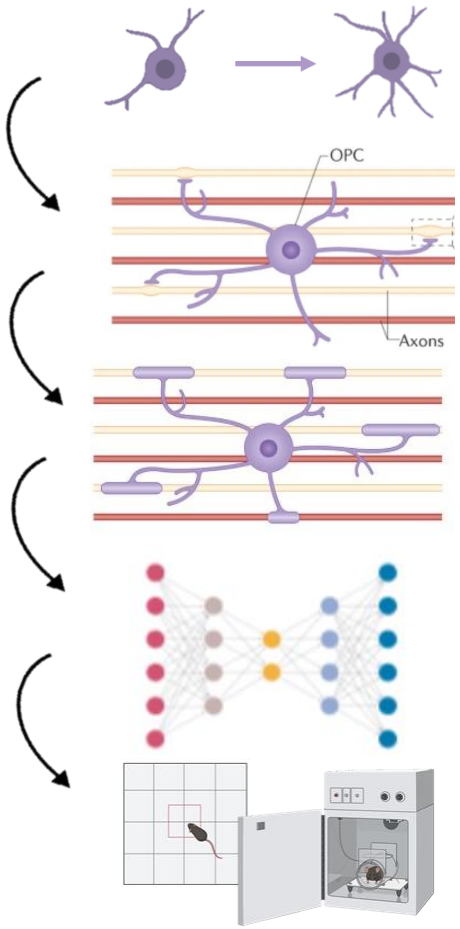




Chang, Waldeck et al. ... Falkai, Rossner, Raabe, revision in review

hiPSCs-derived OPC/Ols – A model for oligodendrocyte dysfunction in SZ (5)

Mechanistic cascade of OL dysfunction in SZ?



OL differentiation ▶ SCZ-iOLs 2D culture

Myelination initiation

Myelination dynamic

Impacts on neural networks

Needed (WIP): Myelinating human cellular 3D Model

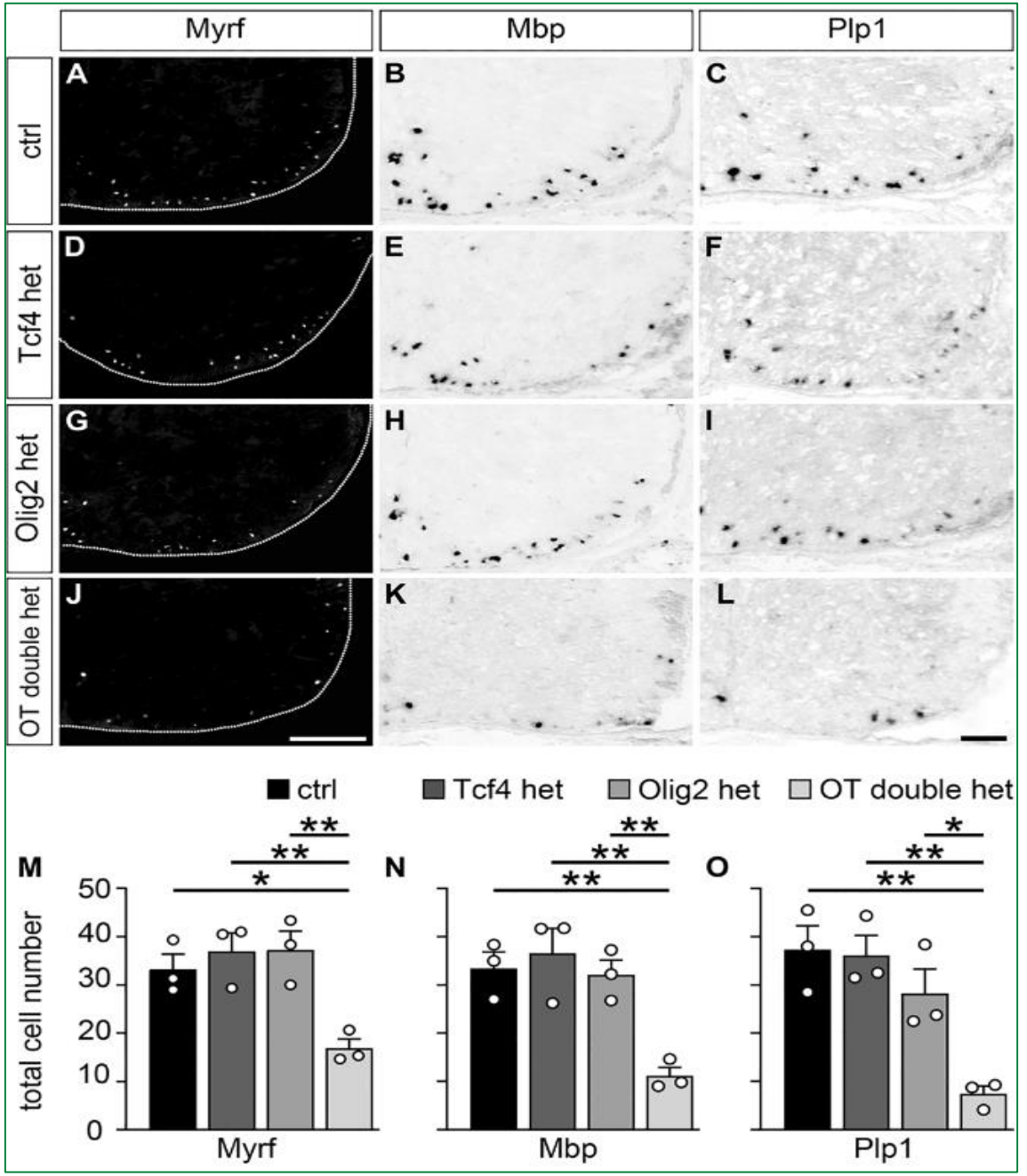
Behavioral outcomes ▶ Proper Mouse Model

Fields RD. A new mechanism of nervous system plasticity: activity-dependent myelination. Nat Rev Neurosci. 2015 Dec;16(12):756-67.
Knowles JK, Batra A, Xu H, Monje M. Adaptive and maladaptive myelination in health and disease. Nat Rev Neurol. 2022 Dec;18(12):735-746.

Impaired oligodendrocytes differentiation in mutant mice ($Olig2^{+/-}/Tcf4^{+/-}$)

A model for oligodendrocyte dysfunction in SZ

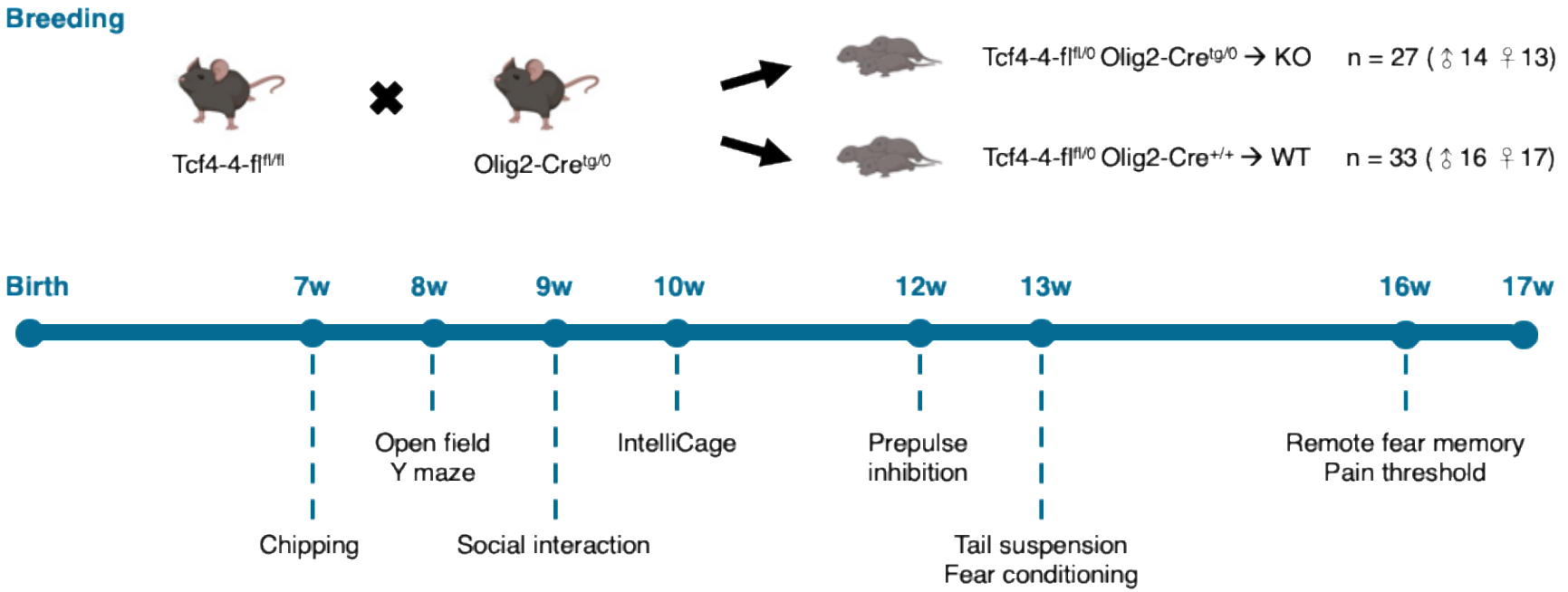
At E18.5, a few Myrf-positive cells appear.
The differentiation process can be visualized by immunohisto-chemical detection of Myrf as the central transcriptional regulator of the myelination process, whereas Mbp and Plp1 are markers of mature Ols.



Wedel et al. 2020 Nucleic Acids Research, 2020, Vol. 48, No. 9

Behavioral deficits in Olig2/Tcf4 double heterozygous mice

A model for oligodendrocyte dysfunction in SZ

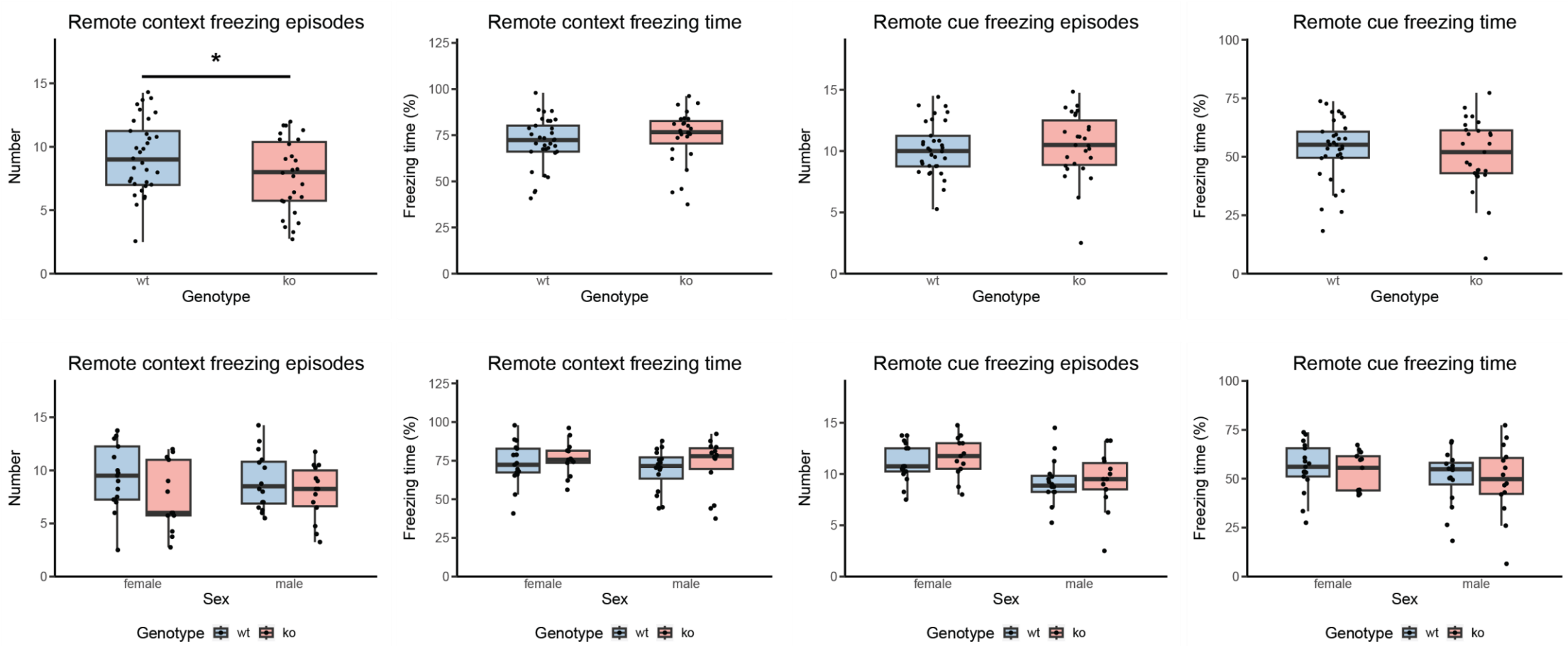


studying Anxiety, Learning, Long-Term-Memory among other behaviors

Note: 1) CNP1-KO mice display altered anxiety, Edgar et al., Transl Psychiatry, 2011
2) MYRF-KO: Preservation of a remote fear memory requires new myelin formation. Pan S, et al. Nat Neurosci. 2020

KO mice showed significantly decreased freezing episodes in context stage

=> Impaired remote fear memory

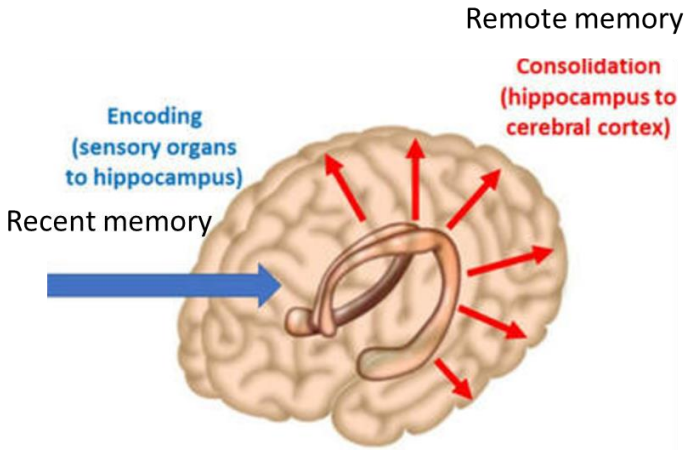


Shapiro-Wilk test, Levene's Test → t test (Context freezing episode, cue freezing episode), Wilcoxon/Mann-Whitney test

*p < 0.05

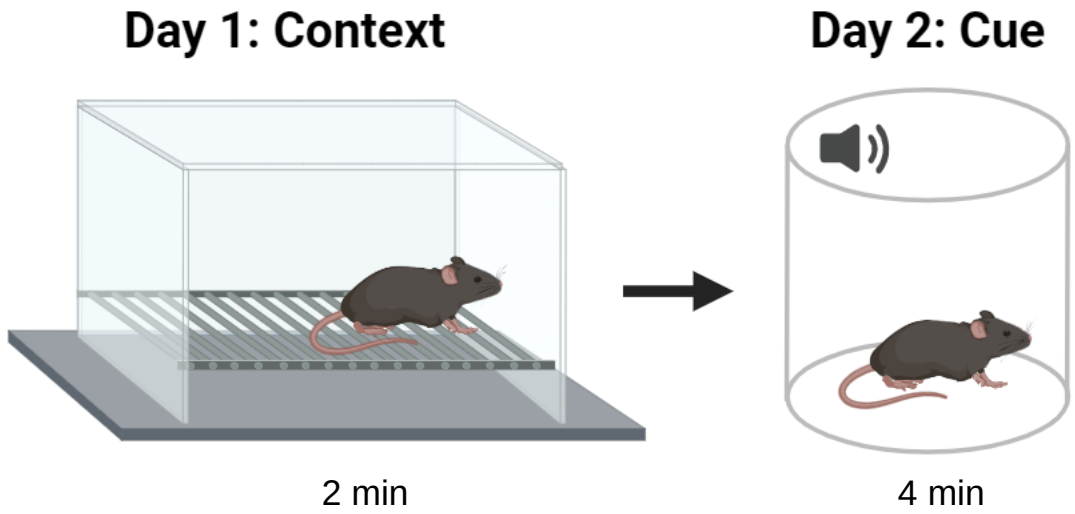
Remote fear memory test

Measure the retention of fear memory
Freezing: index of fear memory



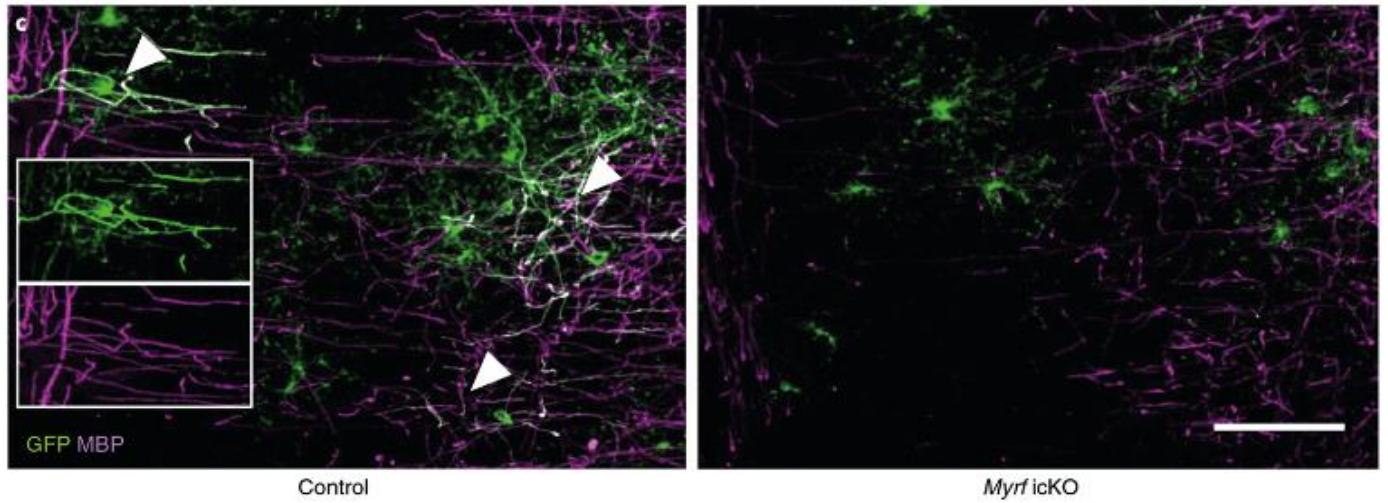
Fear conditioning

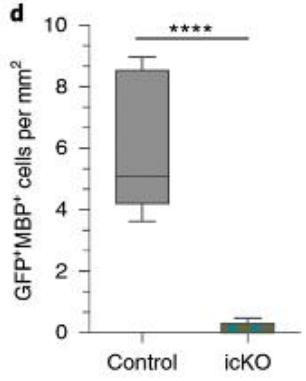
~20 days

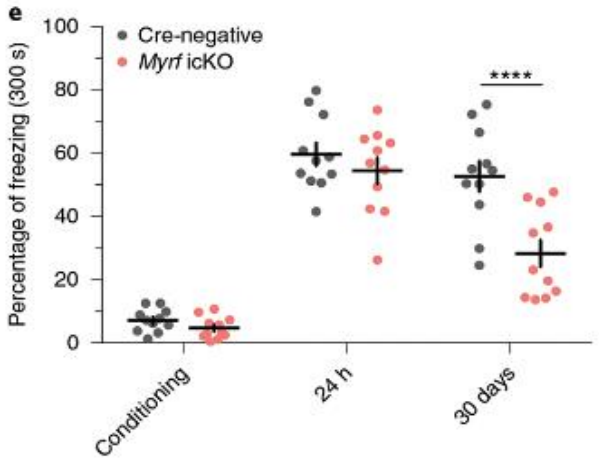


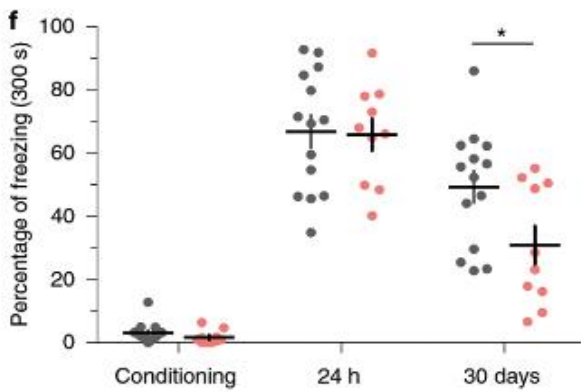
https://biotech.iitm.ac.in/Faculty/CNS_LAB/memory-team/home.php

Myelin-impaired mice exhibit deficient remote, but not recent, fear memory recall









Myelin regulatory factor (MyRF)

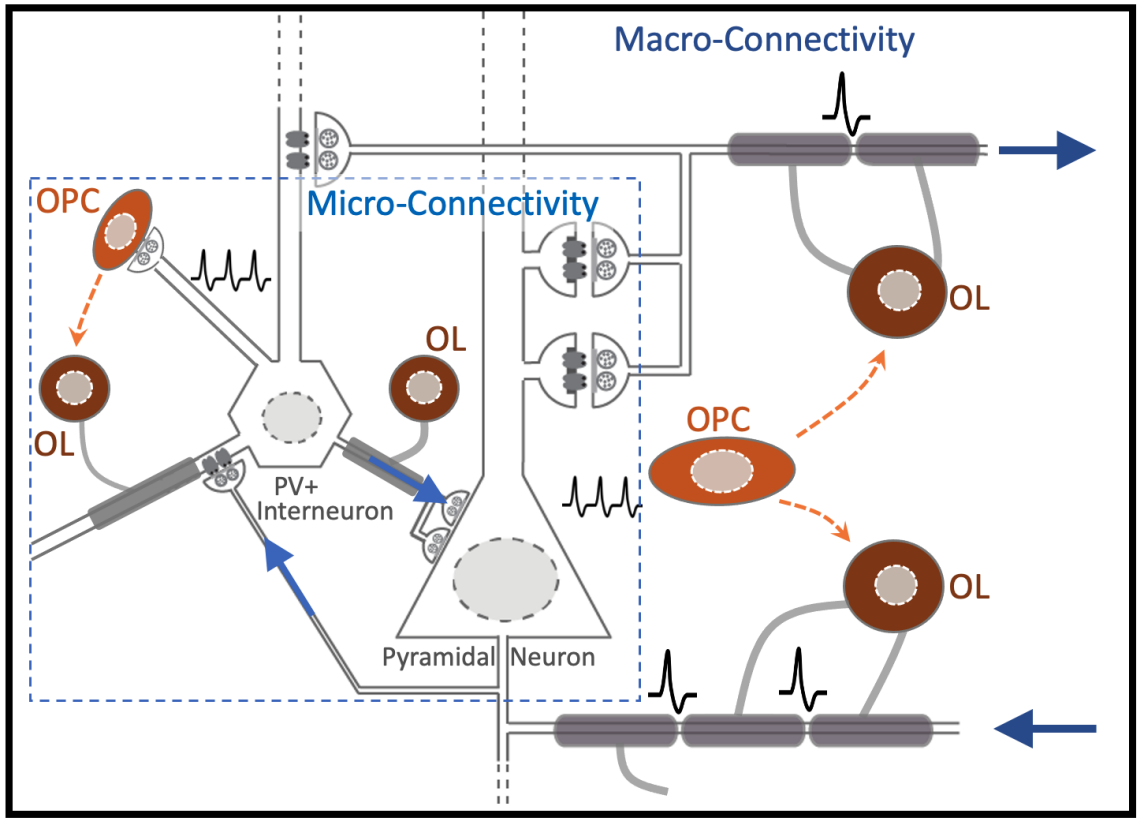
Simon Pan et al., Nat Neurosci., 2020

DISTURBED MYELIN PLASTICITY IN SZ

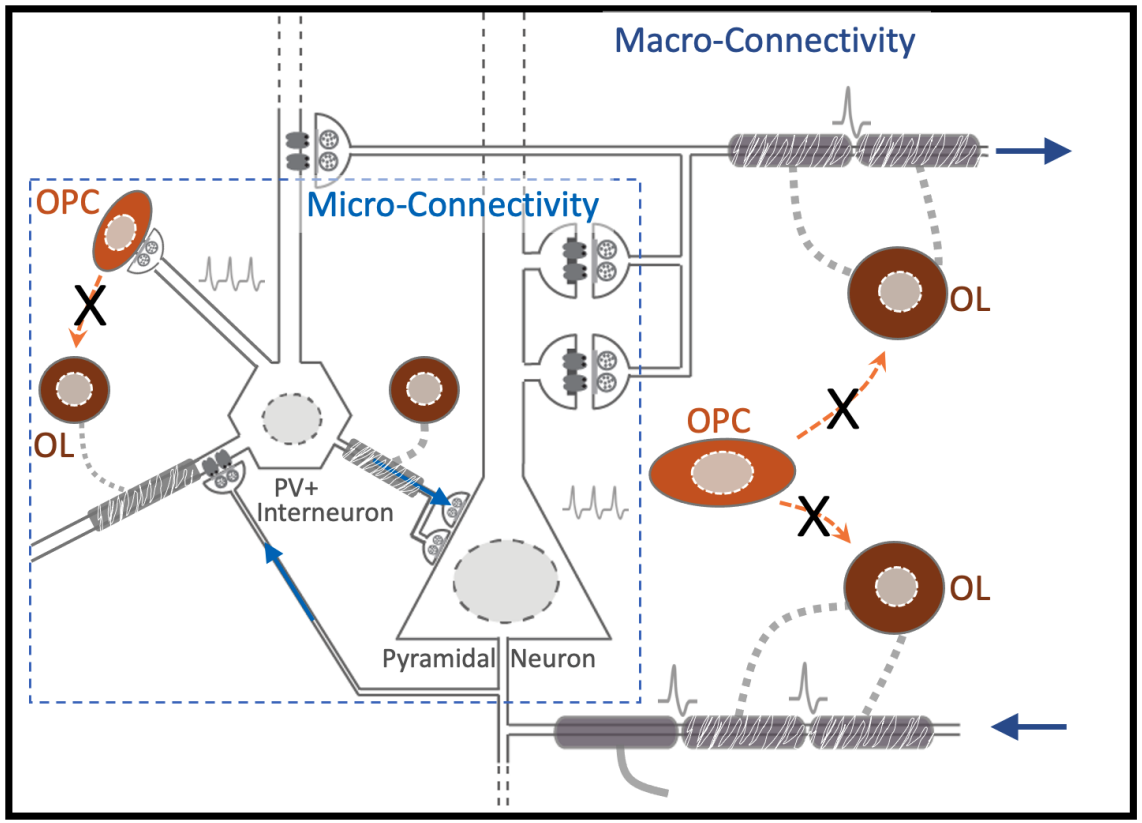
TRANSLATION INTO THE CLINIC AND BACK

Hypothesis: Decreased myelination and oligodendrocyte (OL) differentiation lead to impaired connectivity in schizophrenia

Controls: OLs myelinate interneurons and projections

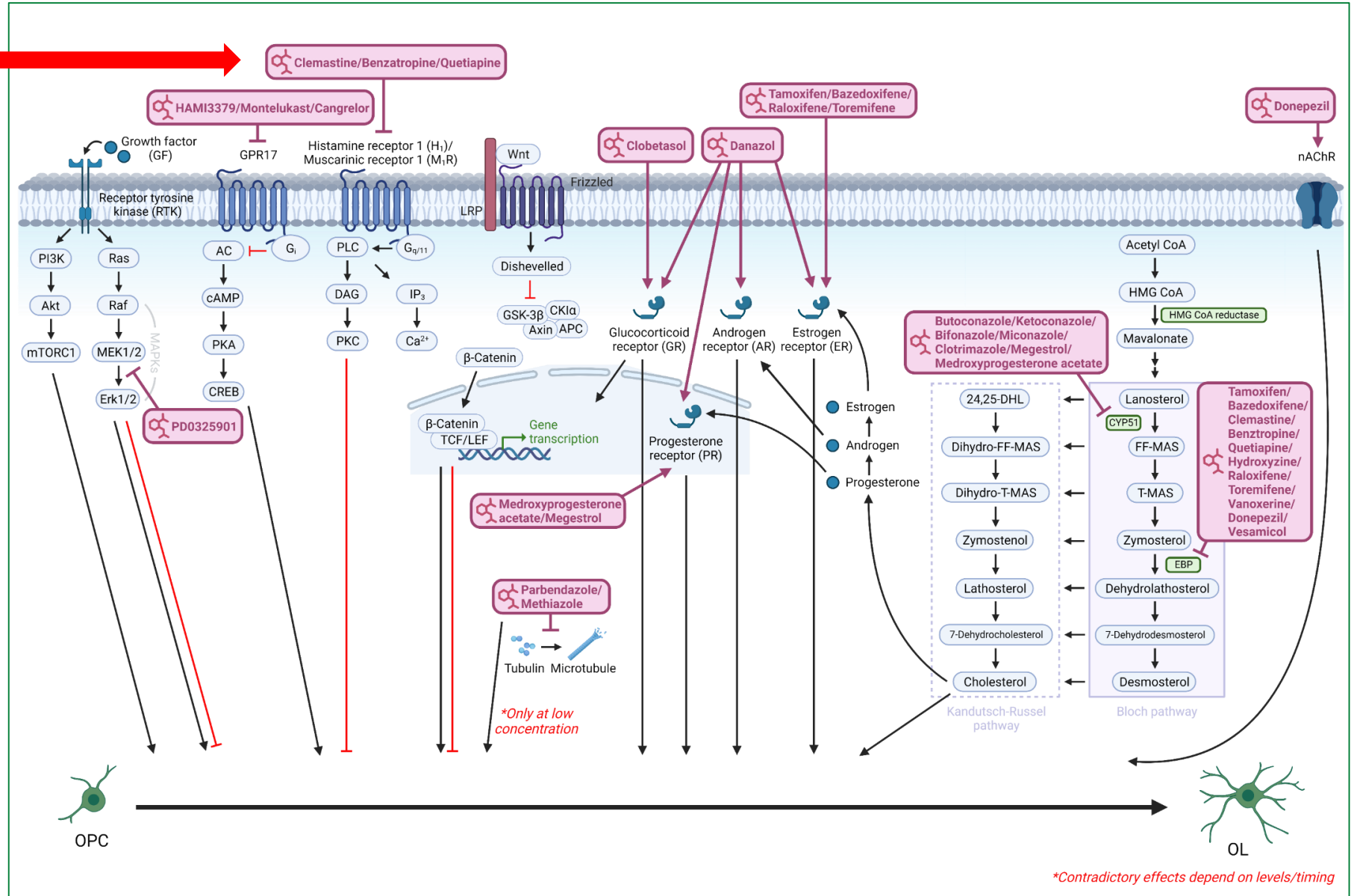


Schizophrenia: impaired myelination and OL differentiation



Falkai et al. Schizophr Bull. 2023 Nov 29;49(6):1614-1624

OL differentiation stimulation pathways



Personal Comminucation
with Emily Chang, AG Molecular and Behavioural Neurobiology
Department of Psychiatry,
Munich University Hospital

Pharmacological treatment of disturbed myelin plasticity

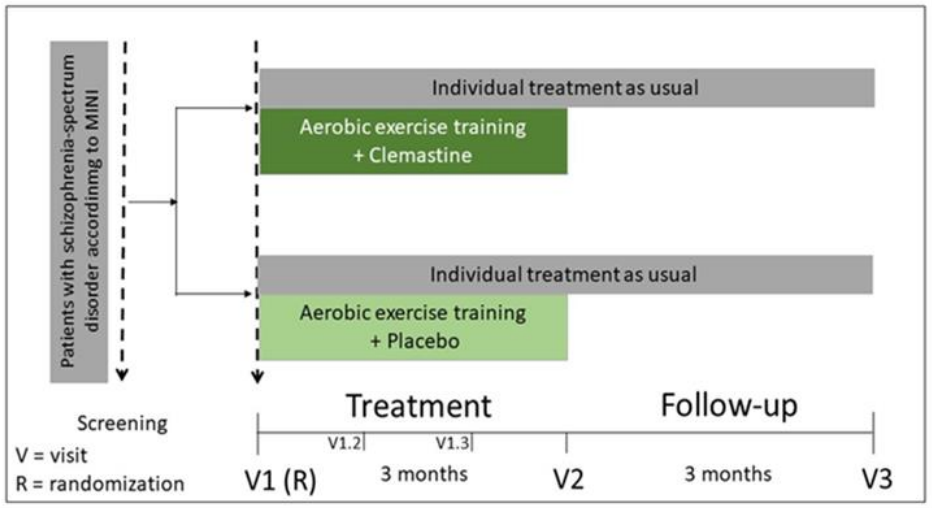
Clemastine

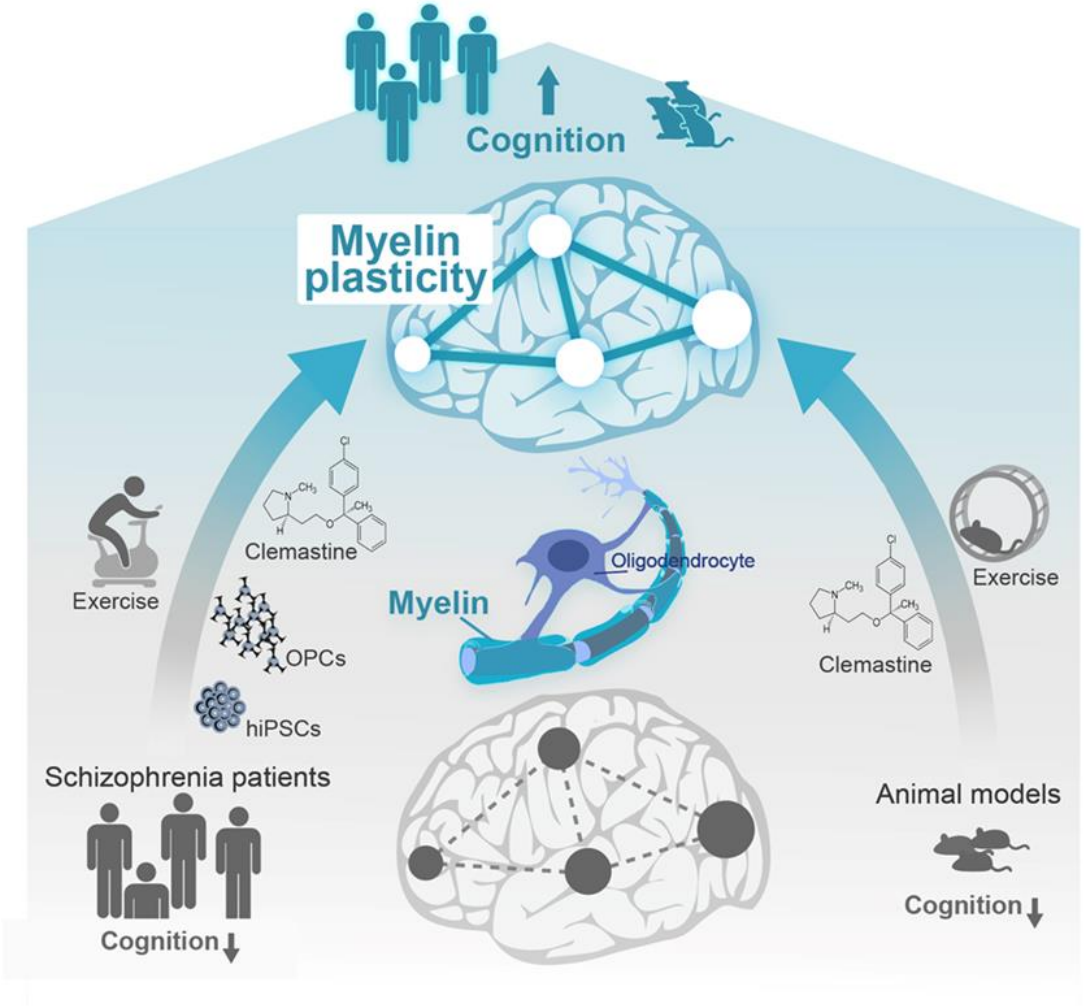
- Histamine H1 antagonist
- P2X7 receptor positive allosteric modulator. *Wolfgang Nörenberg et al., J Biol Chem., 2011 (10.1074/jbc.M110.198879)*
- Muscarinic M1 receptors (M1Rs) antagonist
- M1Rs are expressed by oligodendroglial cells and may modulate OPC proliferation and differentiation. *Federica De Angelis et al., Developmental Neurobiology, 2011 (doi.org/10.1002/dneu.20976)*

The OligoTreat Study

Combining Clemastine with Aerobic Exercise

The OligoTreat Study:
Aerobic exercise combined with clemastine tre
and cognition in schizophrenia patients

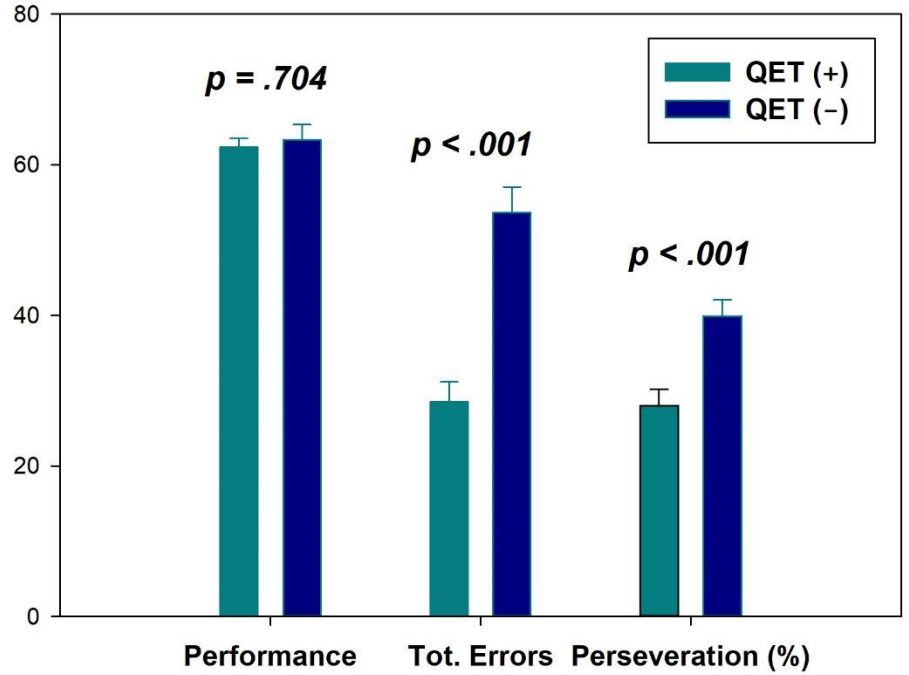




Falkai et al. Schizophr Bull. 2023 Nov 29;49(6):1614-1624

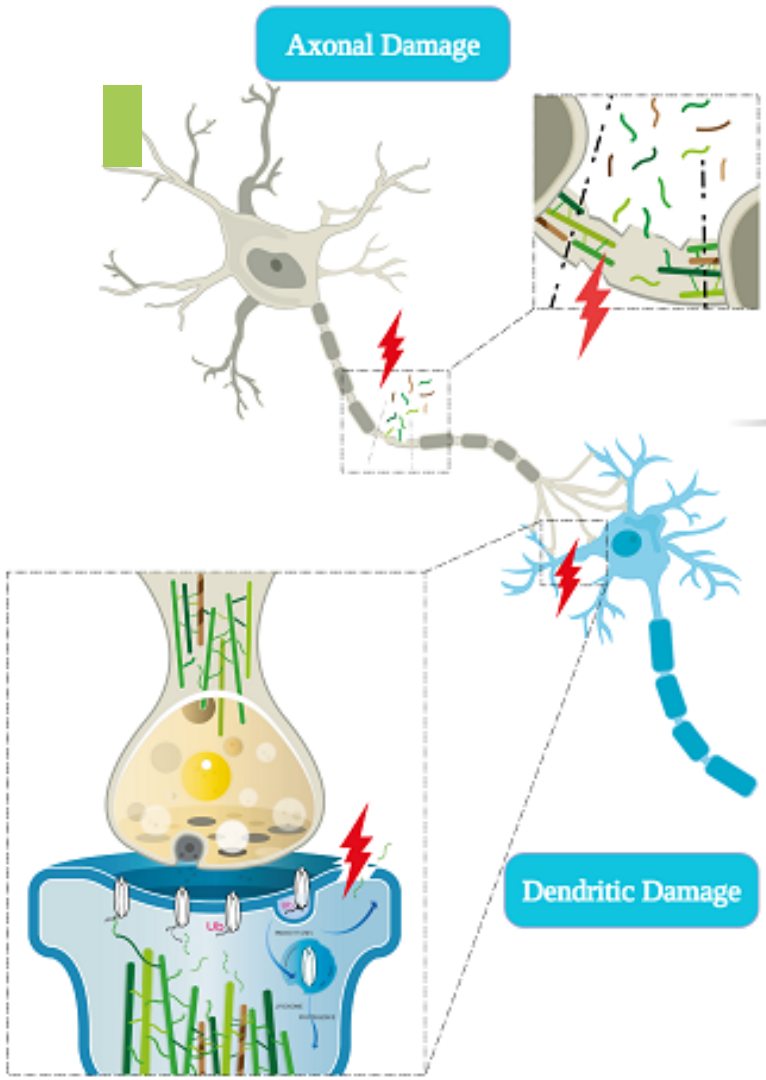
MARS – Effects of Quetiapine Augmentation on Cognitive Flexibility in Depression

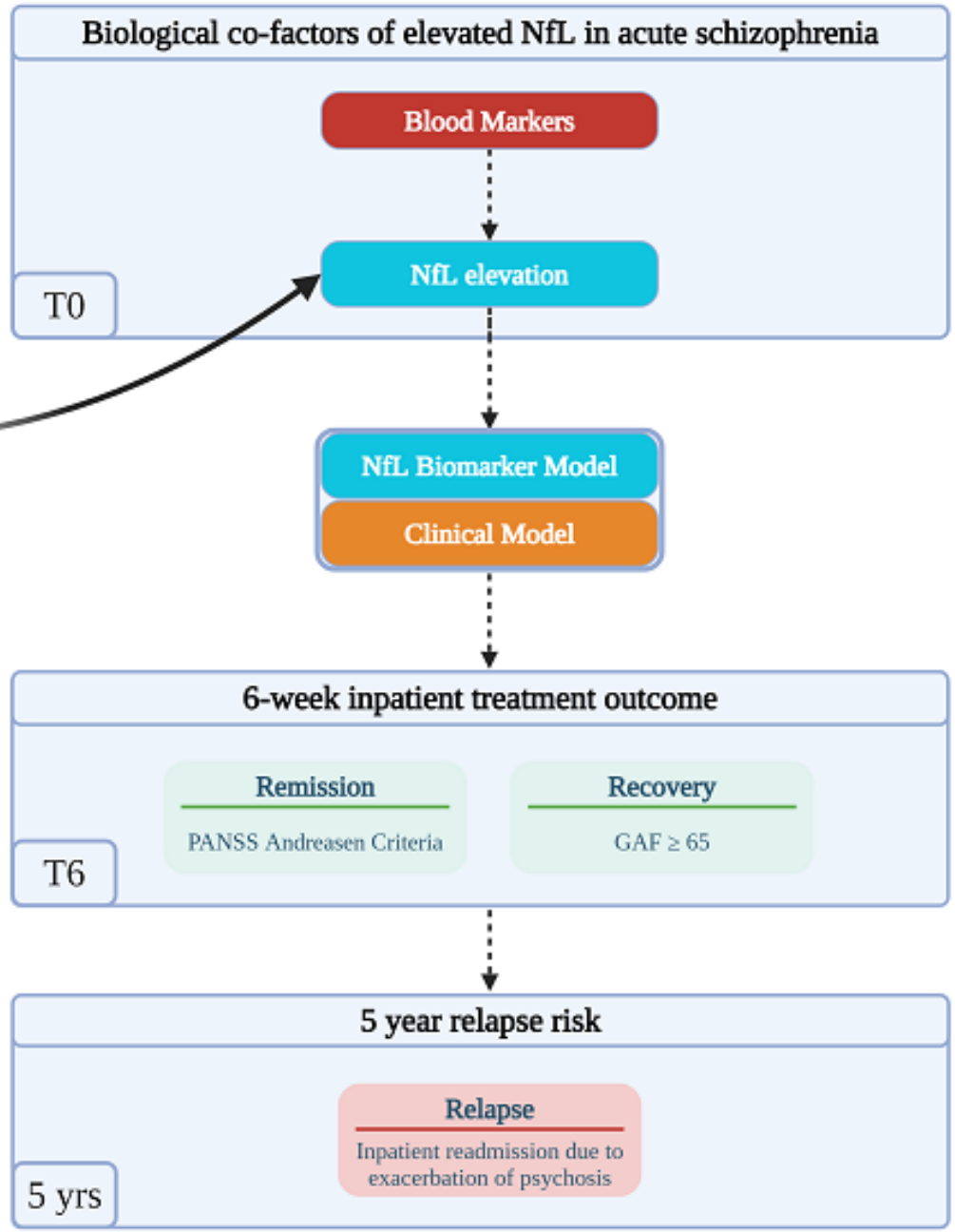
3) WCST: Cognitive Flexibility prior to Discharge



- While general performance in the WCST (number of identified sorting rules) was similar, QET (+) showed substantially higher cognitive flexibility indicated by a lower error rate, and specifically, by a lower rate of perseveration errors in this test. This effect remains significant after correcting for residual depression symptoms at the time of the test. The number of QET (+) treatment weeks - but not the average daily dosage - correlates significantly with low perseveration errors: **r = −.385 (p < .001)**.

DEVELOPING A BIOMARKER FOR SUBTYPING THE LONGITUDINAL COURSE OF SCHIZOPHRENIA



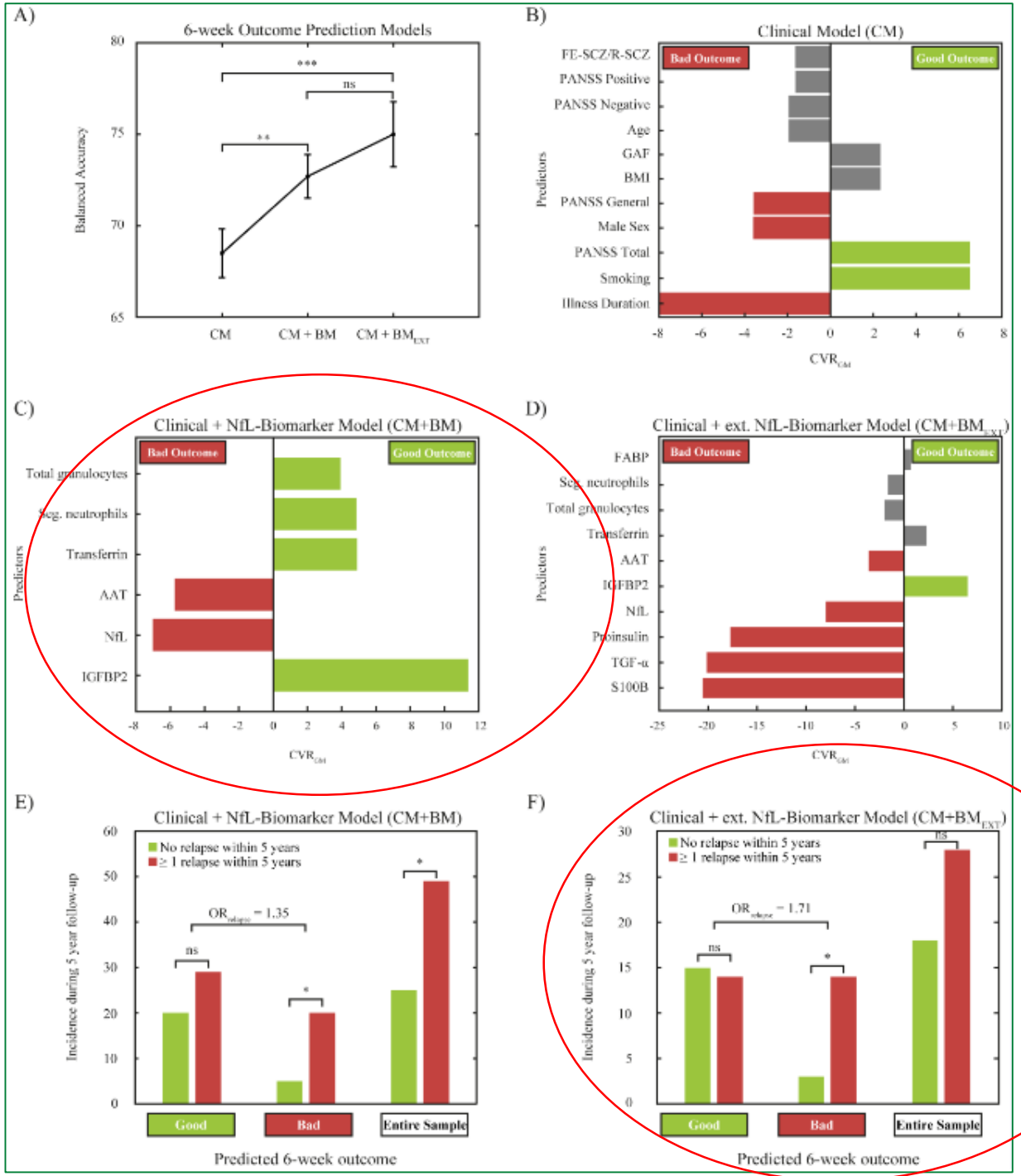


LMU KLINIKUM

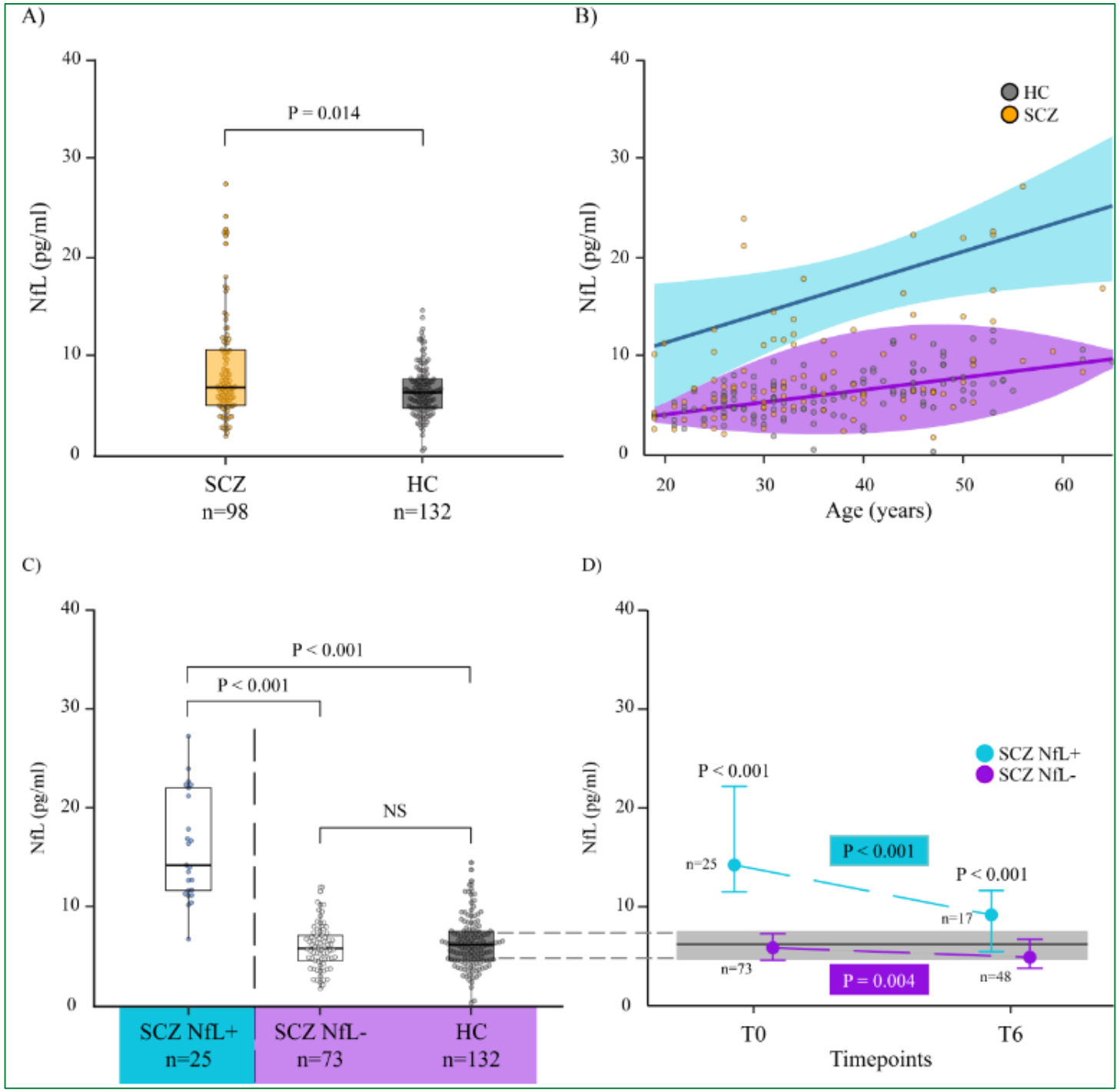
NfL as a marker for short- and long-term outcome in SZ

Popovic, D & Steiner, J, SIRS 2024/2025

Normal and extended NfL biomarker model



NfL in SZ (vs. controls), aging, subtypes and longitudinal course



Popovic, D & Steiner, J, SIRS 2024/2025

Focus on ultrasound to stimulate connectome hubs individually

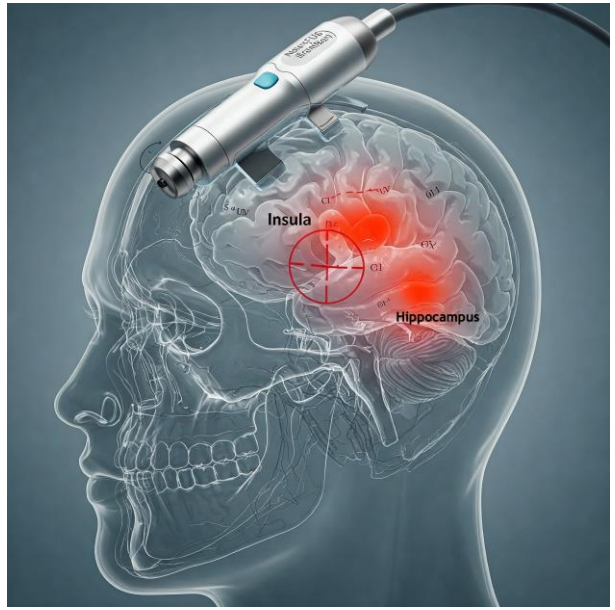
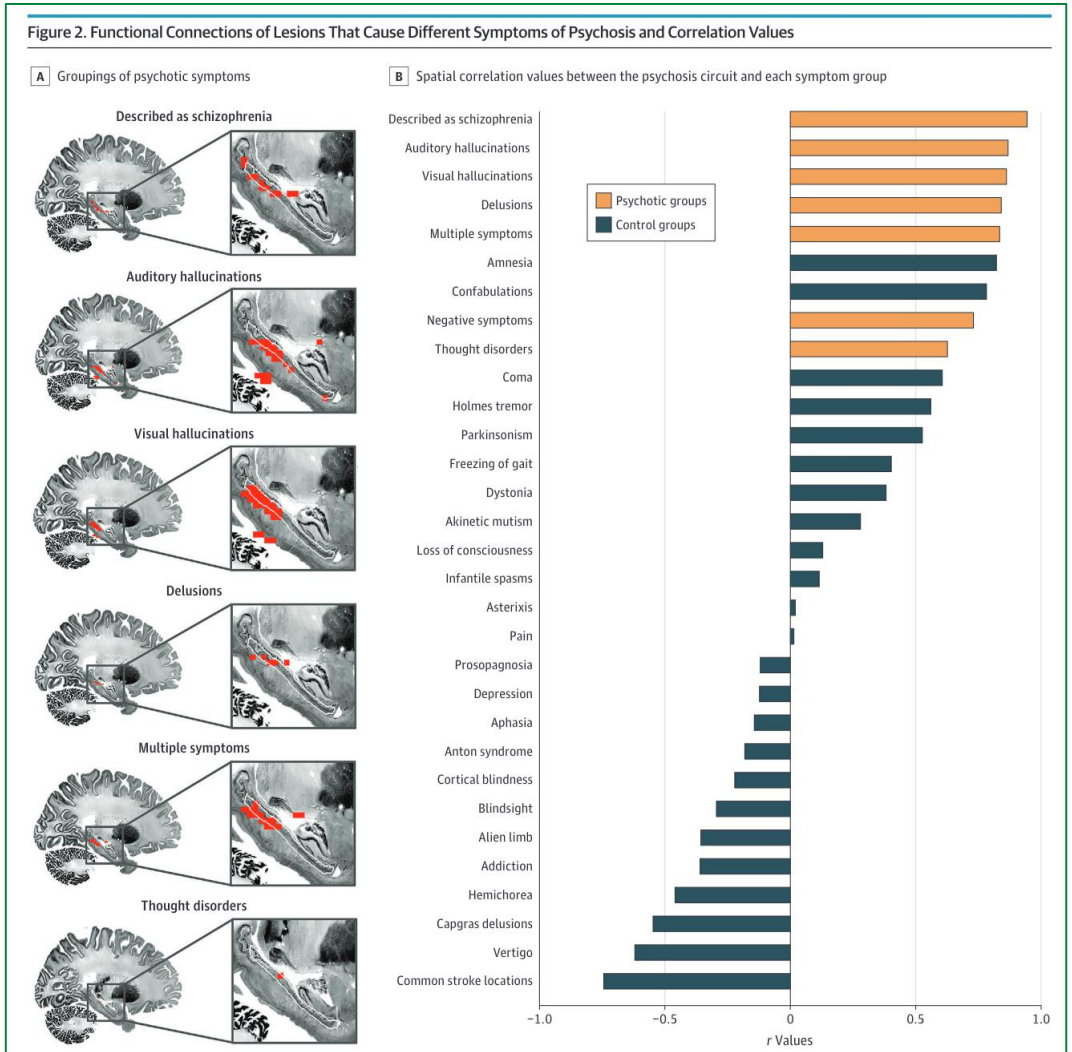


Figure 2. Functional Connections of Lesions That Cause Different Symptoms of Psychosis and Correlation Values



Functional connections of lesions that cause different symptoms of psychosis share a common functional connection to the posterior subiculum of the hippocampus, and are more correlated with each other. A, Each grouping of psychotic symptoms had peak sensitivity (overlap >75%) and specificity (*P* for family-wise error<5×10^{-4}) in the posterior subiculum of the hippocampus (outlined in white). No individual voxels from the negative symptoms subgroup remained significant after correcting for multiple comparisons. B, Spatial correlation values between the psychosis circuit and each symptom group. When correlating between the psychosis circuit and each psychotic symptom group, lesions from the psychotic group being examined were excluded from the psychosis circuit they were being correlated with.

Pines AR et al. 2025: JAMA Psychiatry. Published online February 12, 2025

Summary

- The pathophysiology of schizophrenia: disturbed plasticity instead of degeneration
- Aerobic exercise: Understanding an cure
- From the human to the animal model: e.g. tg TCF4/Olig II
- From mechanism to clinic: e.g. Clemastine, Quetiapine, aerobic exercise
- NFL plus: A tentative biomarker for disturbed myelin plasticity to subtype the longitudinal course of SZ => “instable plastic vs. stable plastic subtype”

People contributing to the work

Andrea Schmitt

Post-mortem studies

Moritz Rossner

Animal models

Sergi Papiol

Genetics

Isabel Maurus

Sport Psych.

Lukas Röll

Sport Psych.

Florian Raabe

iPSCs

LMU KLINIKUM
Gemeinsam. Fürsorglich. Wegweisend.

Top row, left to right: Lotmar (1), Rosenthal (3), Allers (4), Alzheimer (6), Achucarro (7), Lewy (8)

Seated: Grombach (1), Cerletti (2), Bonfiglio (4), Perusini (5)

Thank you

for your attention