KU LEUVEN

The Leuven Late-Life Depression Study

UPC KU Leuven Congres Ouderenpsychiatrie

Multimodale beeldvorming en neuromodulatie in depressie bij ouderen: resultaten van de Leuven Late-Life depression study

26 oktober 2023
Provinciehuis Leuven

Depressie op late leeftijd

- > 60 jaar
- Prevalentie 9-18%

- Therapie resistent
- Suïcidaal
- Psychotisch
- Psychomotorisch
- Somatische comorbiditeiten

- Nood aan efficiënte en snelle behandeling

Depressie op late leeftijd

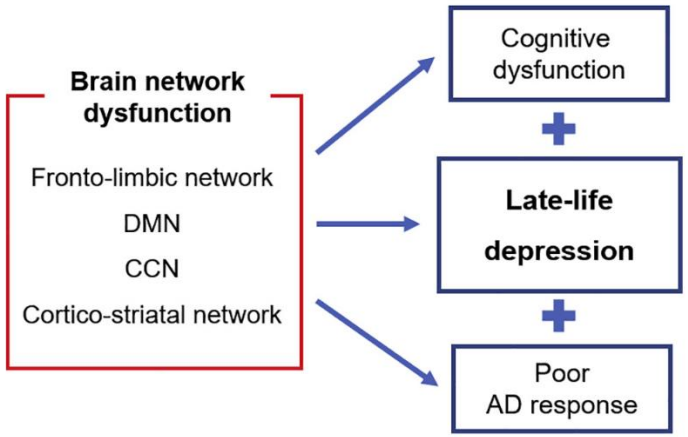
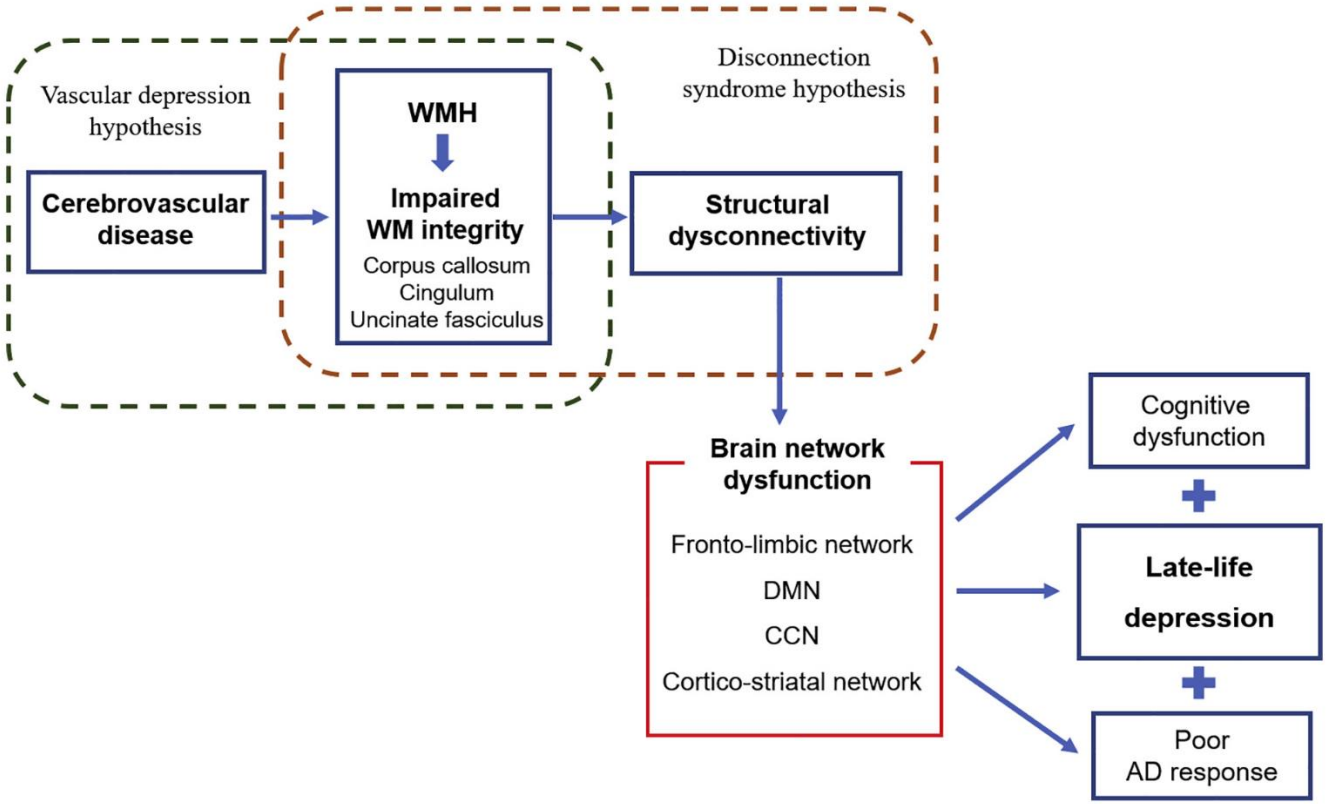


Fig 1: Kim YK, Han KM. Neural substrates for late-life depression: A selective review of structural neuroimaging studies. Prog Neuropsy Biol Psychiatry. 2021. doi: 10.1016/j.pnpbp.2020.110010

Depressie op late leeftijd



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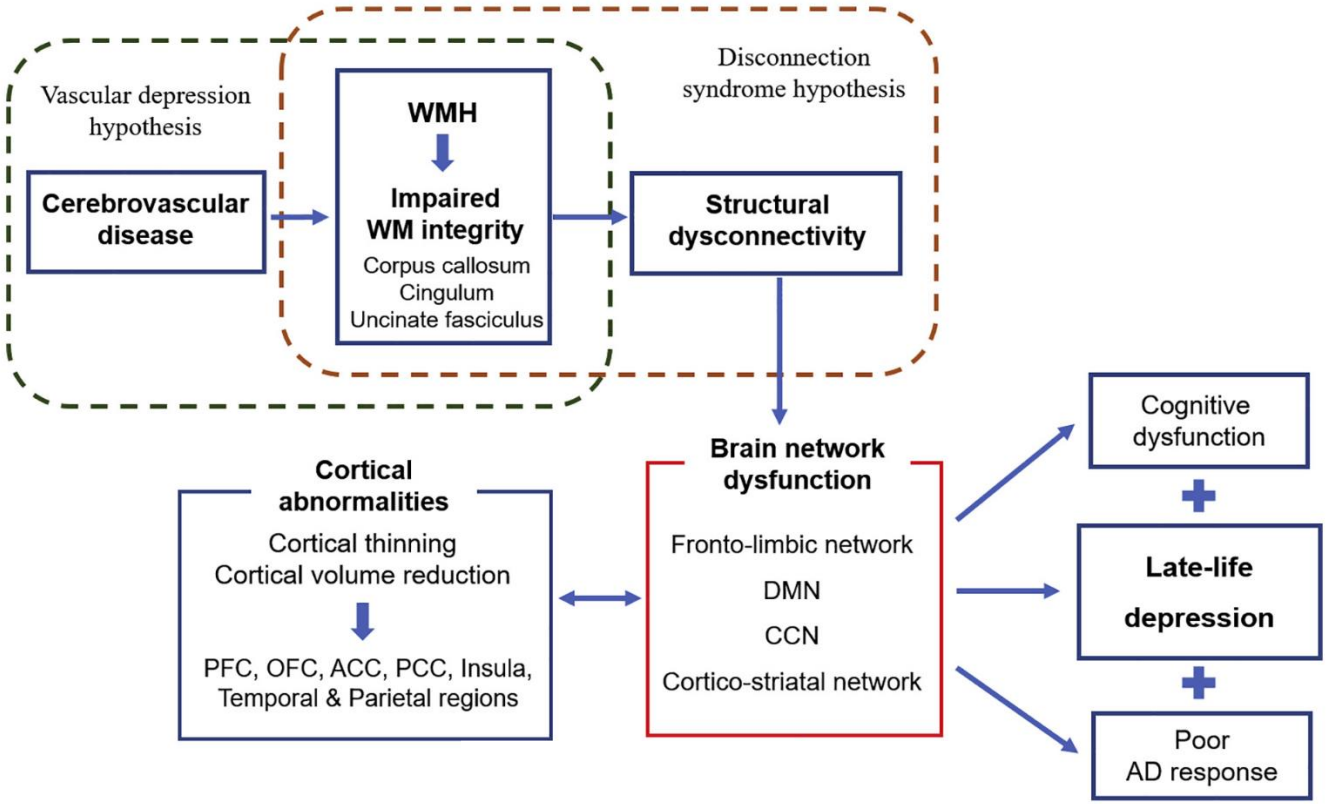

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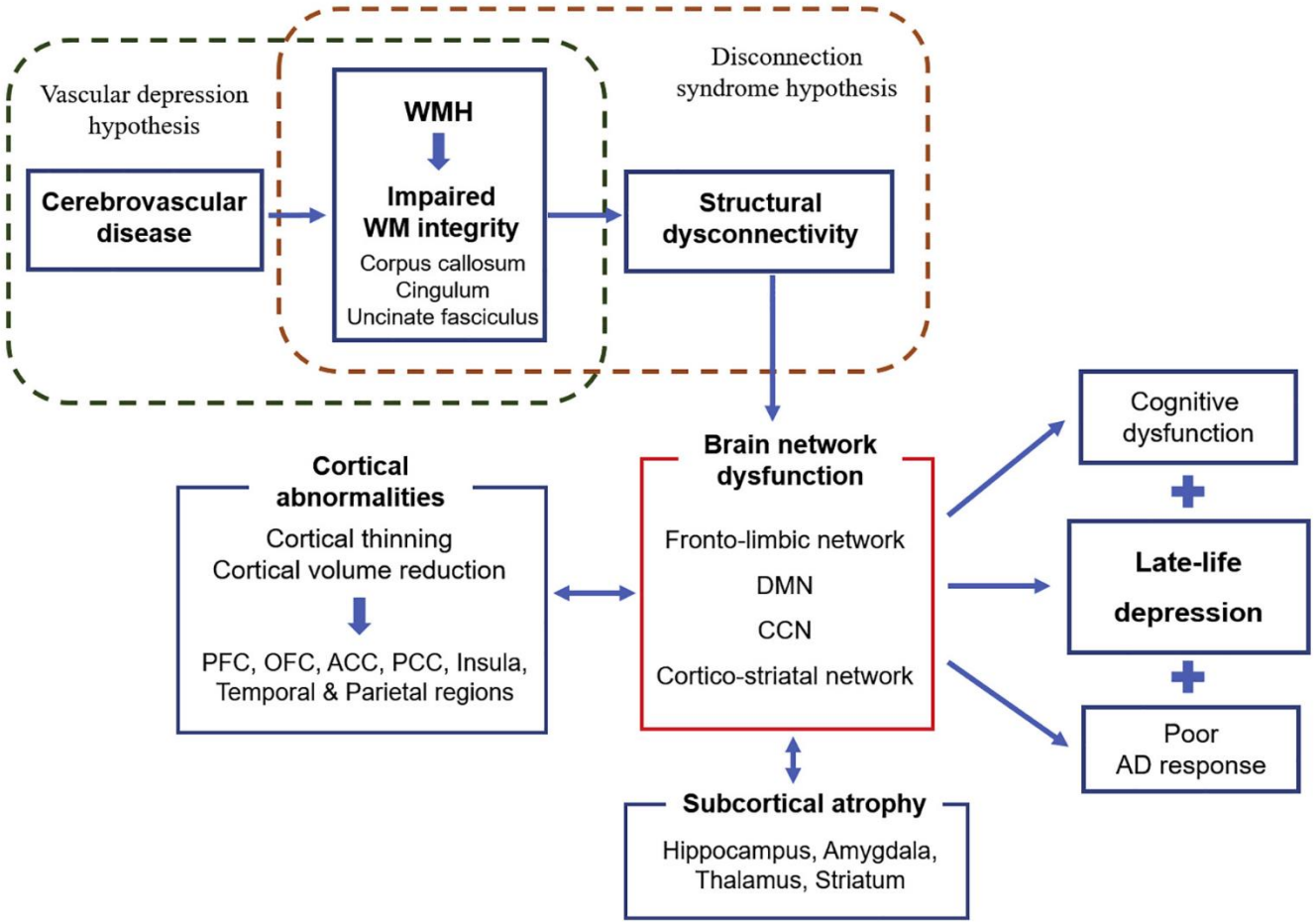
Depressie op late leeftijd



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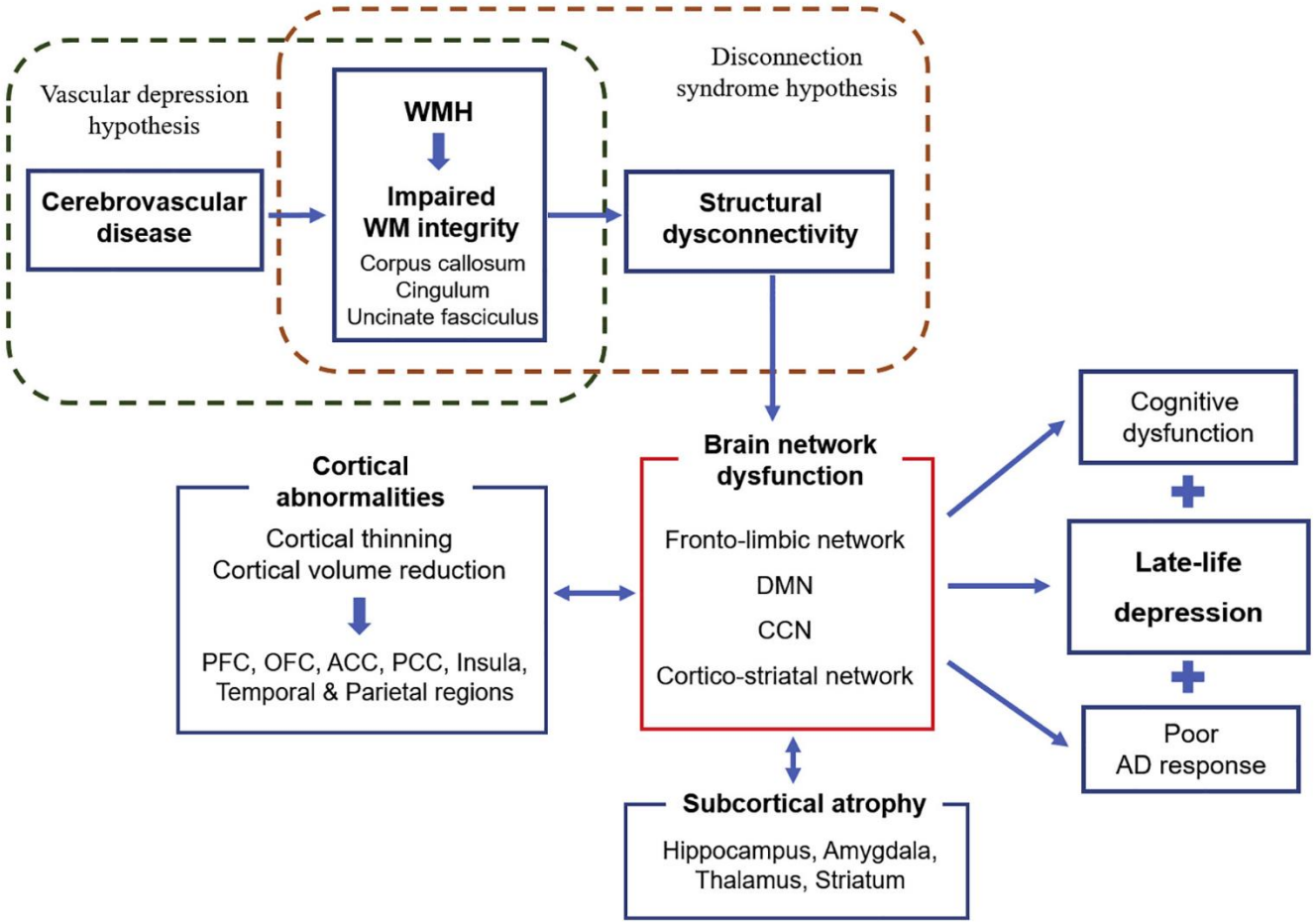


Pathologische veroudering

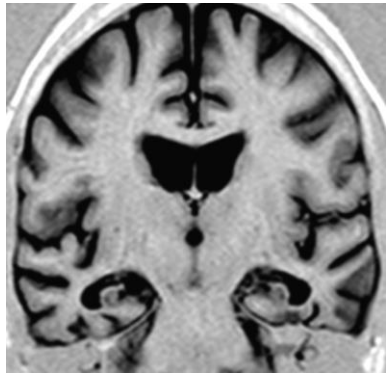
Levensstijl

Stress

Fig 1: Kim YK, Han KM. Neural substrates for late-life depression: A selective review of structural neuroimaging studies. Prog Neuropsy Biol Psychiatry. 2021. doi: 10.1016/j.pnpbp.2020.110010

Pathologische veroudering

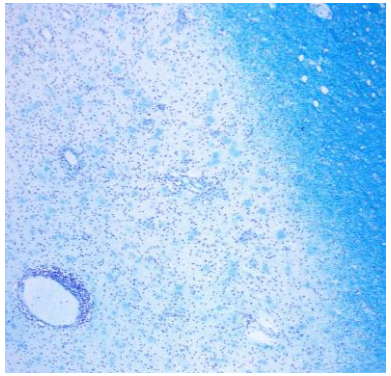
Grey matter loss



01.

Global neural loss in the cerebral cortex and hippocampal atrophy leads to emotional, behavioral and cognitive problems

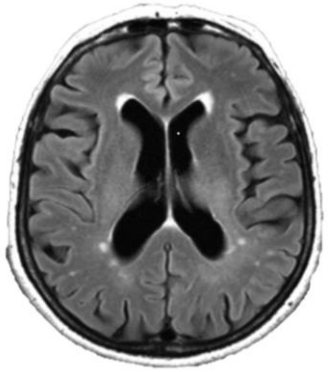
White matter damage



02.

Regional brain connectivity is disrupted leading to impaired neural communication which impacts brain function

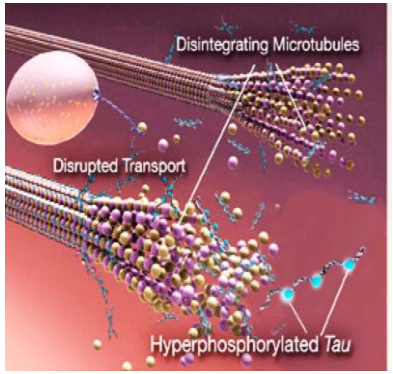
Vascular damage



03.

Vascular deterioration causes tissue damage by starving tissues of oxygen and eliciting neuroinflammatory processes

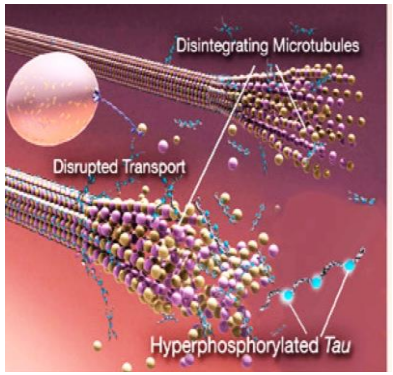
Proteinopathies



04.

The microtubule stabilizing protein tau becomes dysfunctional leading to neuronal damage

Proteinopathies



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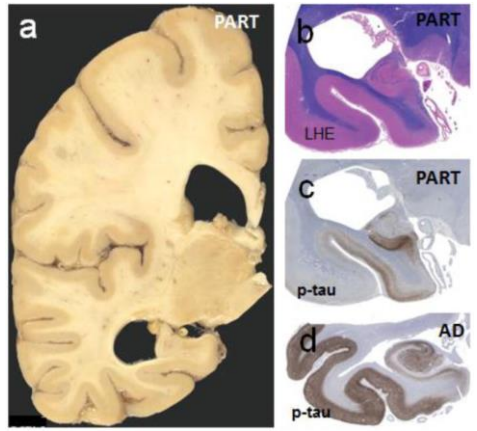
The microtubule stabilizing protein tau becomes dysfunctional leading to neuronal damage

Acta Neuropathol (2014) 128:755–766
DOI 10.1007/s00401-014-1349-0

CONSENSUS PAPER

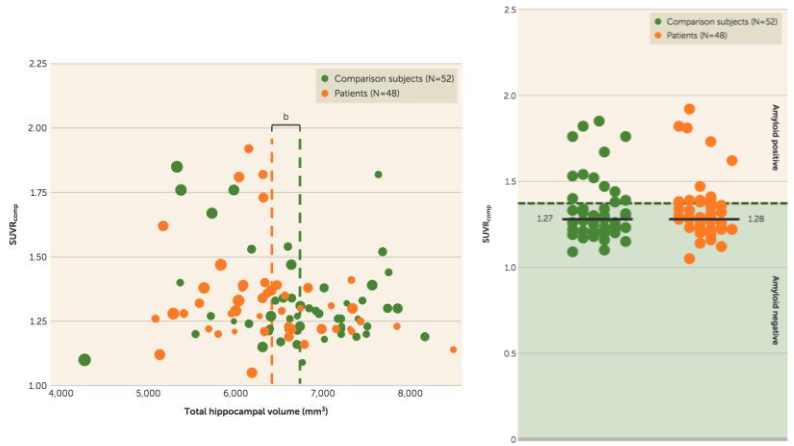
Primary age-related tauopathy (PART): a common pathology associated with human aging

Presence of NFT in absence of Aβ



PART: Primary Age Related Tauopathy

SNAP: Suspected Non Amyloid Disease



No Association of Lower Hippocampal Volume With Alzheimer's Disease Pathology in Late-Life Depression

François-Laurent De Winter, M.D., Louise Emsell, Ph.D., Filip Bouckaert, M.D., Lene Claes, M.Sc., Saurabh Jain, M.Sc., Gill Farrar, Ph.D., Thibo Billiet, Ph.D., Stephan Evers, M.Sc., Jan Van den Stock, Ph.D., Pascal Sienaert, M.D., Ph.D., Jasmien Obbels, M.Sc., Stefan Sunaert, M.D., Ph.D., Katarzyna Adamczuk, Ph.D., Rik Vandenberghe, M.D., Ph.D., Koen Van Laere, M.D., Ph.D., Mathieu Vandenbulcke, M.D., Ph.D.

Leuven Late-Life Depression Study

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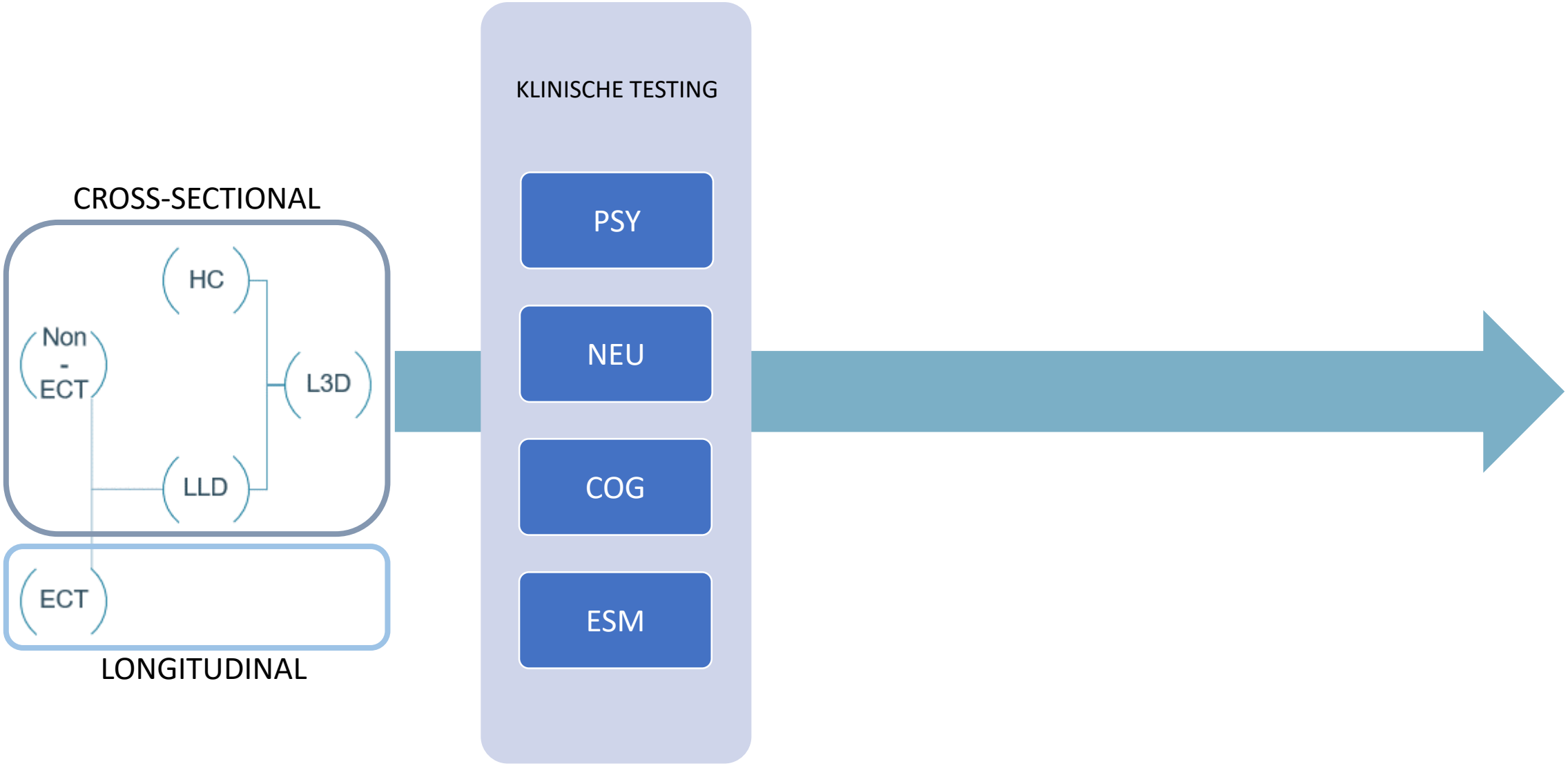

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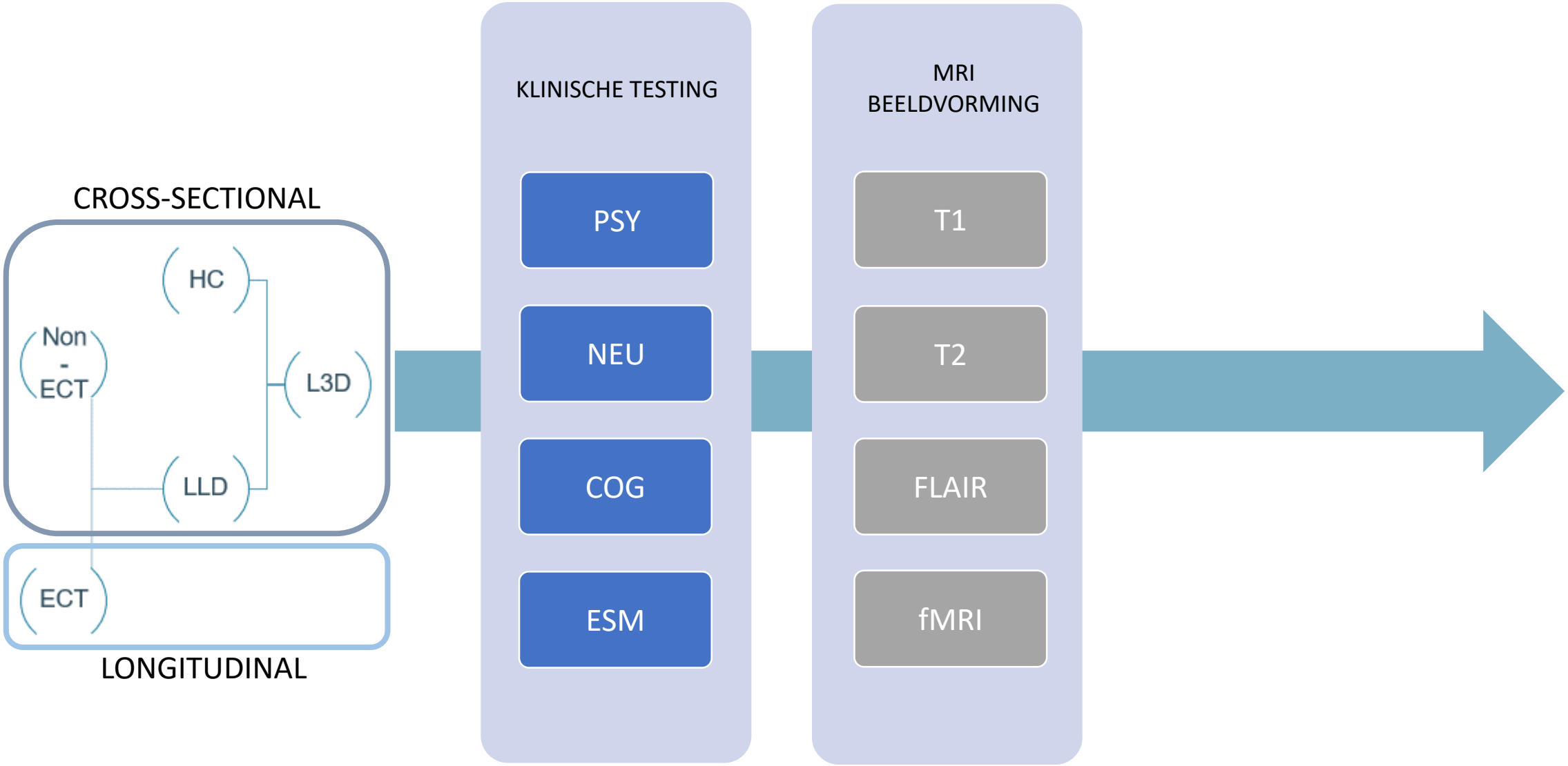

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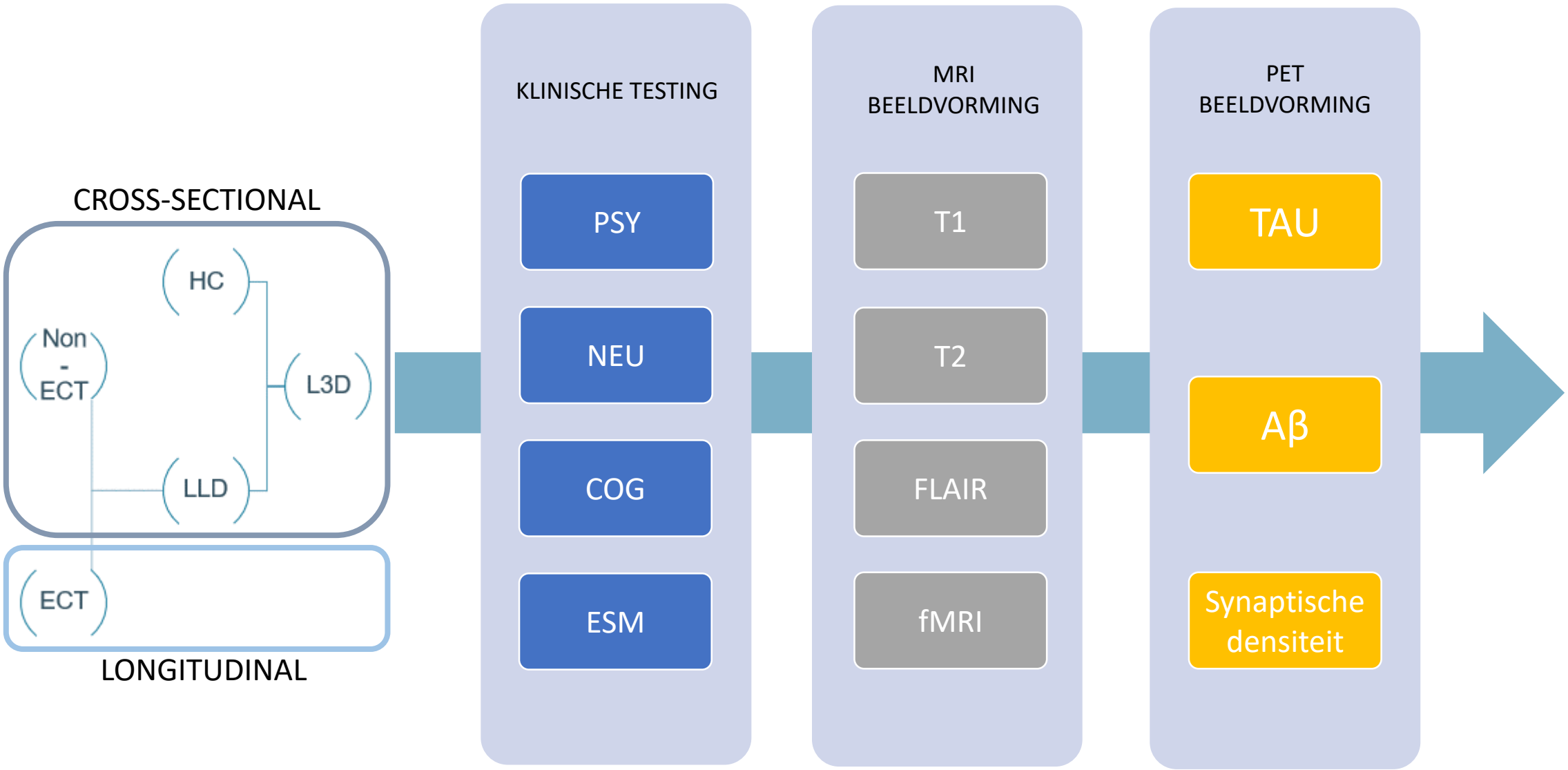
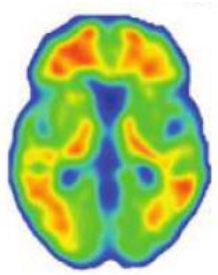
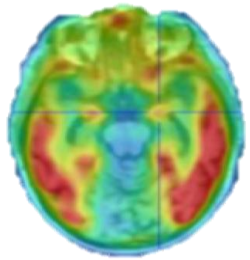
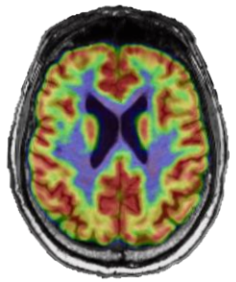
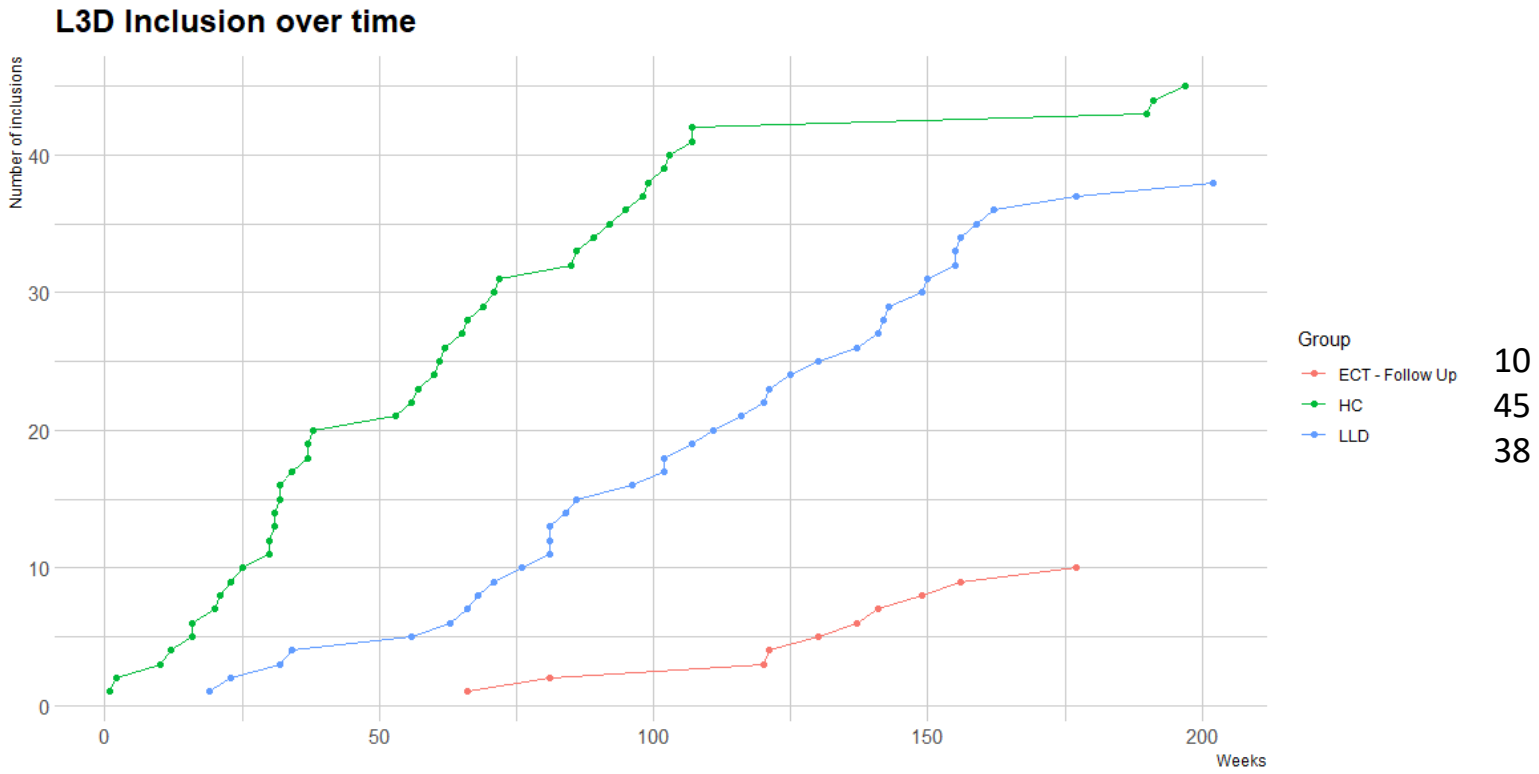


	Amyloid	Tau	Synaptic density
			
Radioligand	^{18}F-Flutemetamol	^{18}F-MK-6240	^{11}C-UCB-J
Target	B-amyloid	NFT	SV2A
PET Findings in LLD to date	Mixed: No difference, lower in LLD, positive corr with mild depressive symptoms in healthy older adults	Limited inconclusive	No studies in LLD, recent report of lower SD in mild depression/PTSD

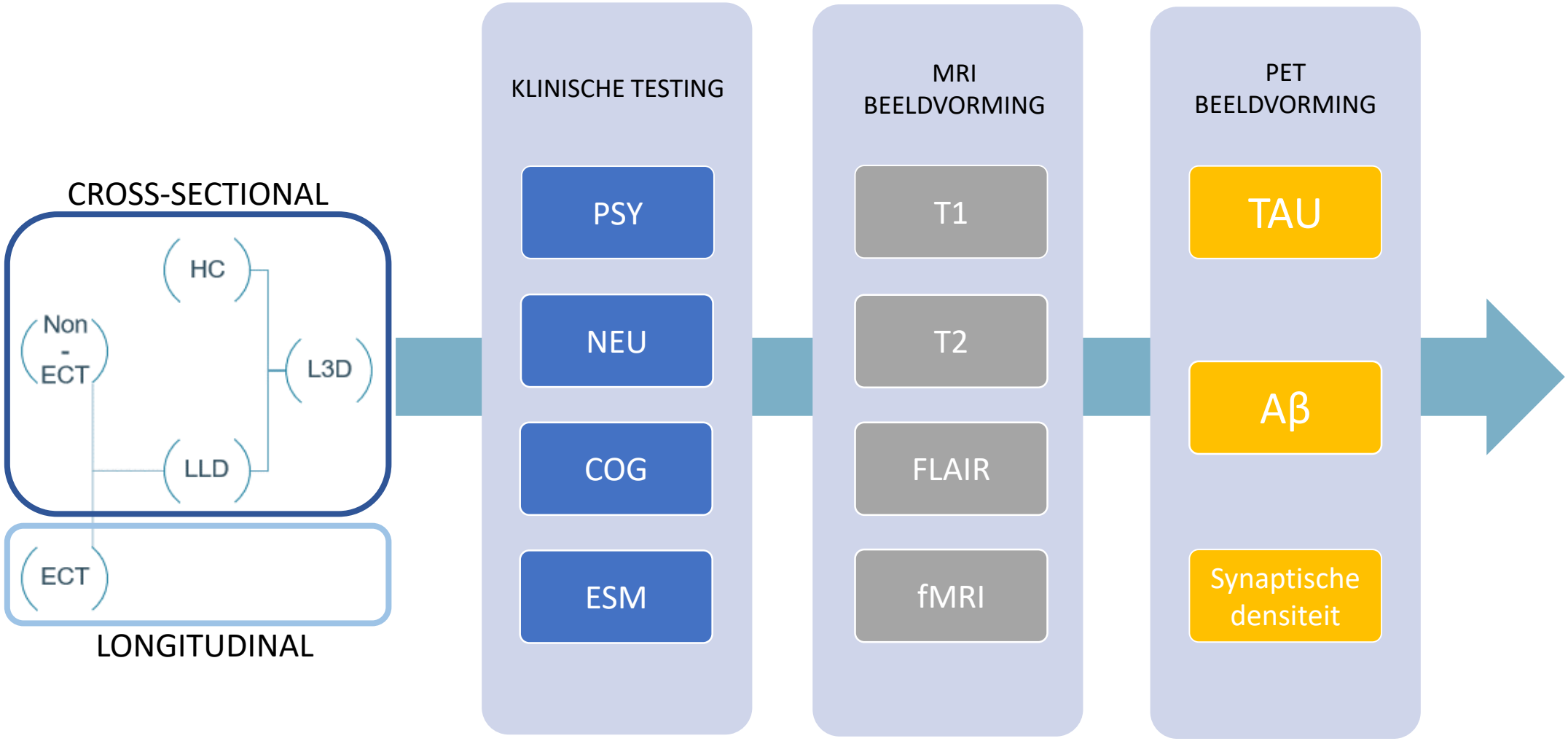
GE Signa 3T PET-MR system



10
45
38

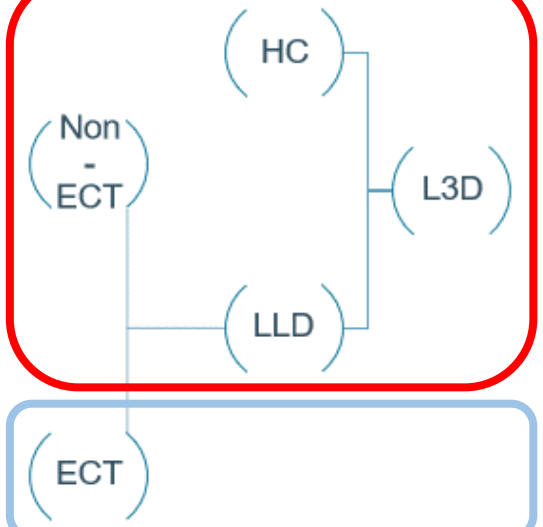
	n	Age (years)	Gender (M/F)	Education (primary/high school/college/university)	Depressive symptoms (GDS)	Apathy (AES)	General cognition (MMSE)	Memory + Learning (RAVLT_A)	Psychomotor function (CORE)
LLD	38	72.9 (6.04)	11/26	6/17/11/2	21.08 (6.47)	45.92 (11.7)	26.0 (2.88)	25.6 (9.8)	18.34 (9.54)
Controls	45	70.88 (6.20	17/25	4/19/14/5	2.71 (2.88)	22.2 (5.15)	28.9 (1.34)	39.6 (9.29)	1.21 (1.77)
Statistical comparison P-value	-	0.194	0.319	0.636	**<0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***
Interpretation	-	No difference	No difference	No difference	LLD more depressed	LLD more apathy	LLD worse general cognition	LLD worse recall	LLD less interaction, more retardation, agitation

L3D Study


CROSS-SECTIONAL
HC
Non - ECT
L3D
LLD
ECT
LONGITUDINAL
KLINISCHE TESTING
PSY
NEU
COG
ESM
MRI BEELDVORMING
T1
T2
FLAIR
fMRI
PET BEELDVORMING
TAU
Aβ
Synaptische densiteit

Multimodal neuroimaging investigation of brain ageing biomarkers in LLD

CROSS-SECTIONAL



LONGITUDINAL

KLINISCHE TESTING

- PSY
- NEU
- COG
- ESM

MRI BEELDVORMING

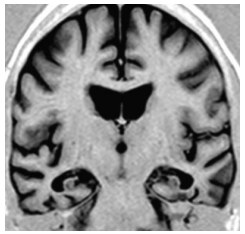
- T1
- T2
- FLAIR
- fMRI

PET BEELDVORMING

- TAU
- Aβ
- Synaptische densiteit

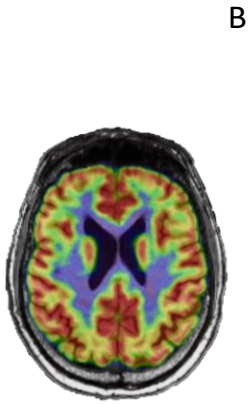
Dr. Thomas Vande Casteele

Synaptic Density in LLD

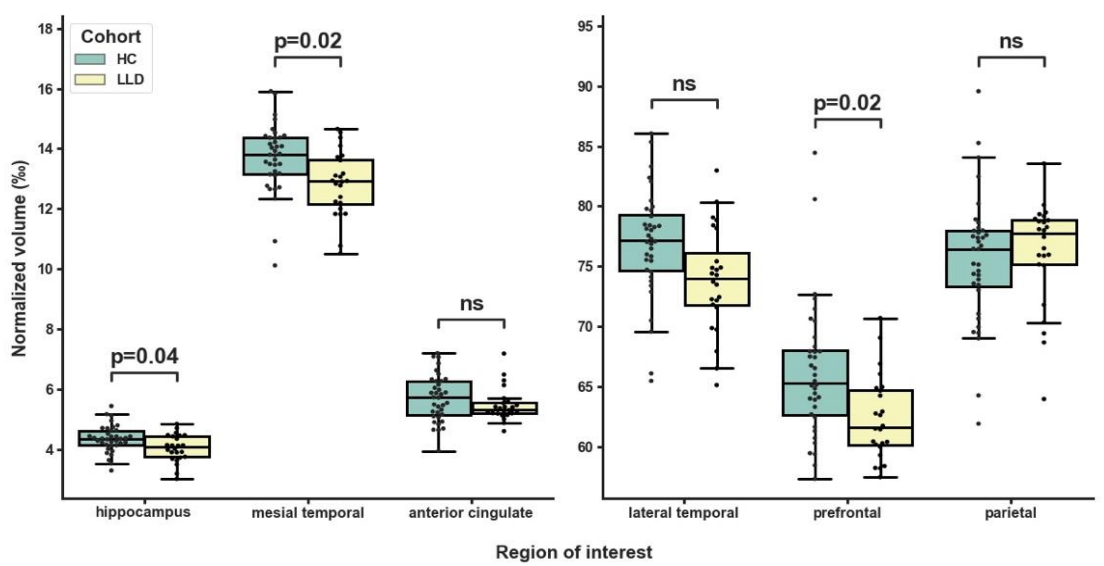


Synaptic density is preserved in LLD:

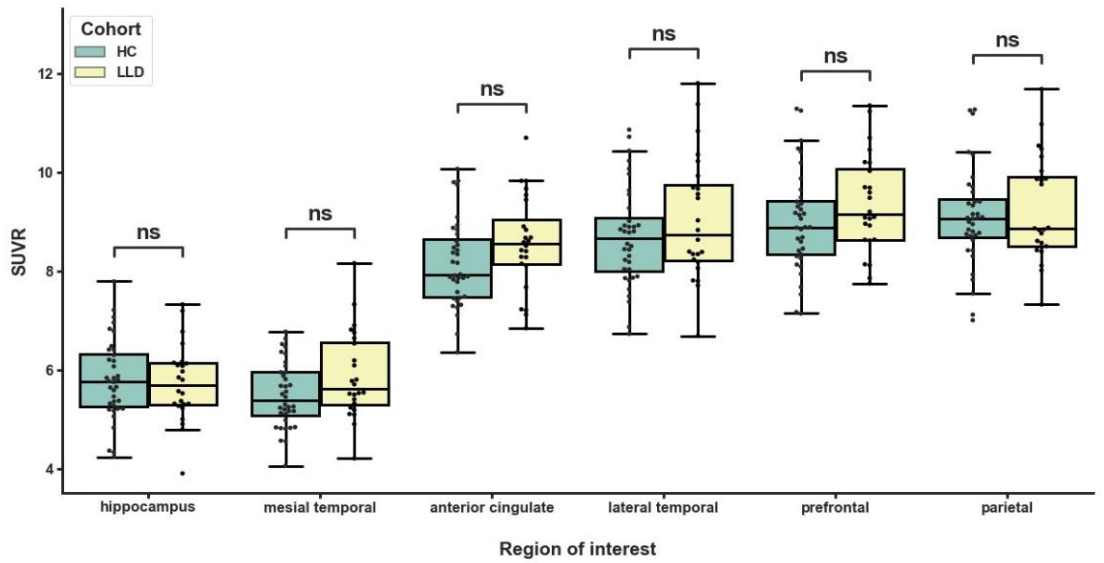
- No evidence for altered synaptic density as measured by ^{11}C-UCB-J
- lower grey matter volumes (hippocampus, mesial temporal cortex, prefrontal cortex)



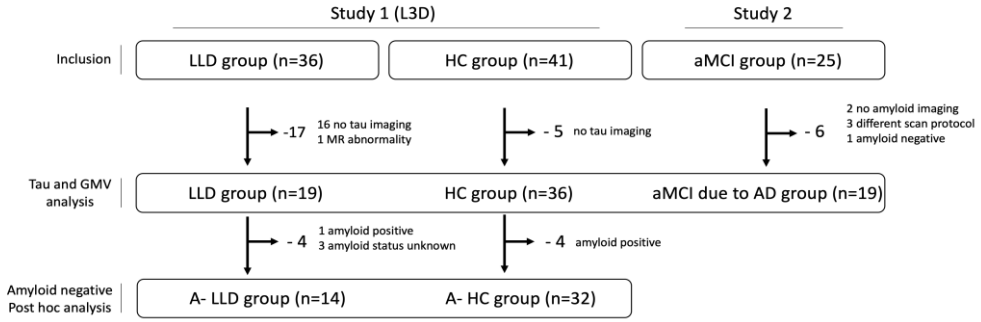
A



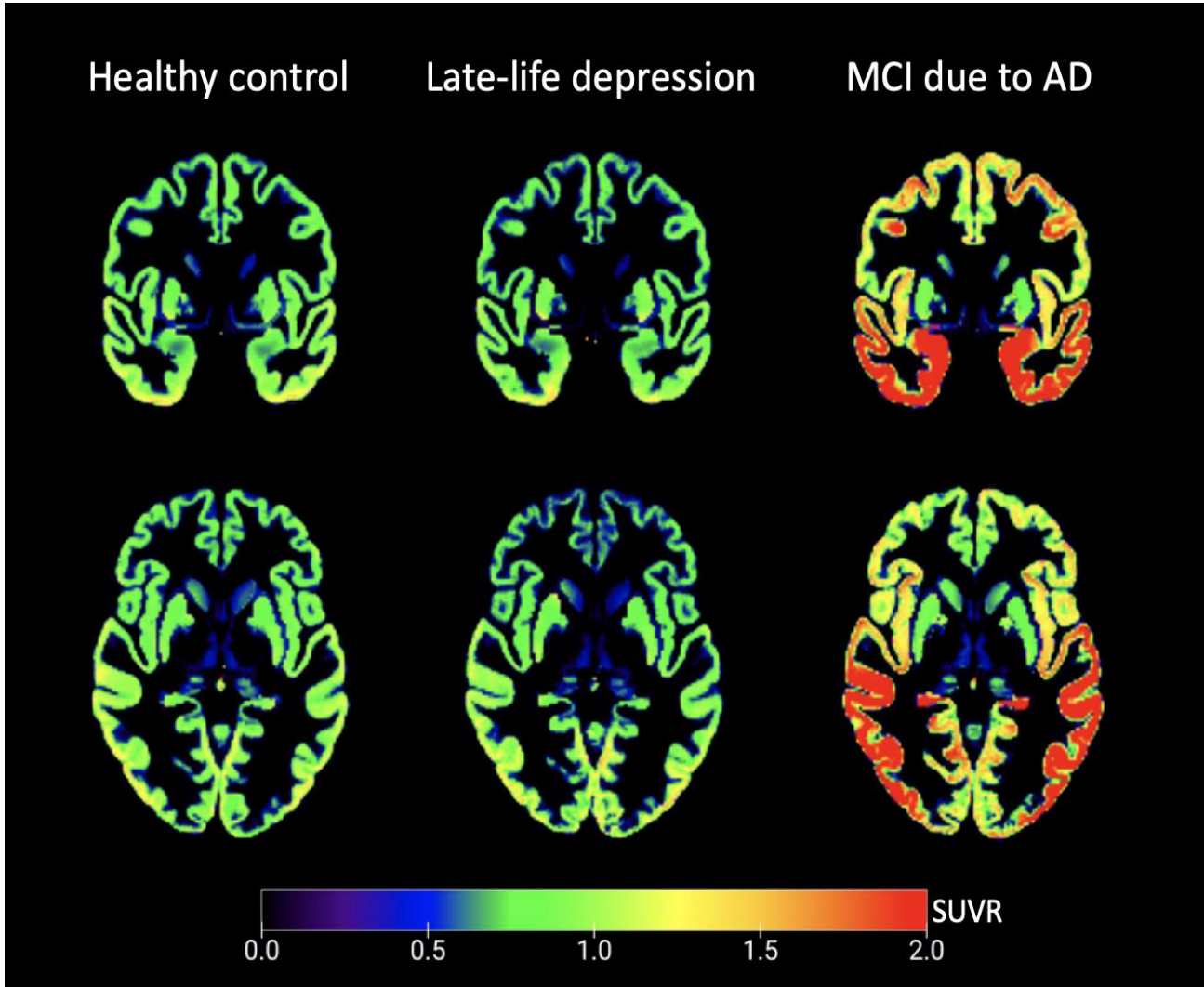
B



TAU accumulation in LLD

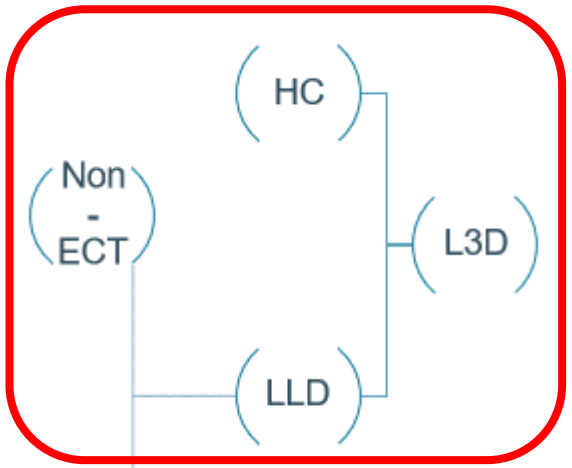


No difference in tau in depression



Neurobiologie van psychomotore symptomen in late life depressie

CROSS-SECTIONAL



LONGITUDINAL

KLINISCHE TESTING

- PSY
- NEU
- COG
- ESM

MRI BEELDVORMING

- T1
- T2
- FLAIR
- fMRI

PET BEELDVORMING

- TAU
- Aβ
- Synaptische densiteit

NEUROBIOLOGIE van PMS in LLD

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PMS = psychomotore retardatie + agitatie

20-50% van MDD

NEUROBIOLOGIE van PMS in LLD

PMS = psychomotore retardatie + agitatie

20-50% van MDD < LLD → ADL impact, vallen, chroniciteit

NEUROBIOLOGIE van PMS in LLD

PMS = psychomotore retardatie + agitatie

20-50% van MDD < LLD → ADL impact, vallen, chroniciteit

<1990 Response op antidepressiva/ECT

NEUROBIOLOGIE van PMS in LLD

PMS = psychomotore retardatie + agitatie

20-50% van MDD[3] < LLD[4] → ADL impact, vallen, chroniciteit

<1990 Response op antidepressiva, ECT[5]

>1990 ↓ Frontostriataal dopamine vs verspreid ↓ CBF, GMV & ↑WML

[3] Calligiuri et al. 2000; [5]Reijnders et al. Mov dis 2008, [4]Rogers et al. 2002

NEUROBIOLOGIE van PMS in LLD

PMS = psychomotore retardatie + agitatie

20-50% van MDD[3] < LLD prodr/MMS[4] → ADL impact, vallen

<1990 Response op antidepressiva, ECT[5]

>1990 ↓ Frontostriataal dopamine vs verspreid ↓ CBF, GMV & ↑WML

? MDD – 'normale' hersenveroudering – prodromale hersenziekte

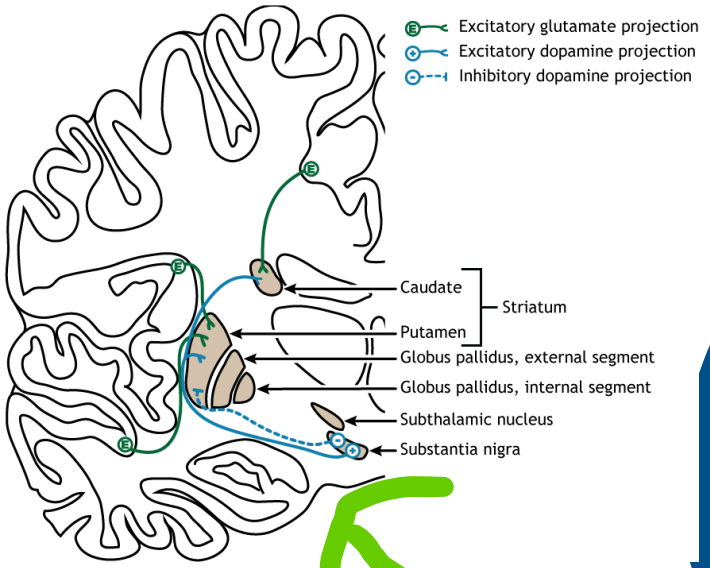
[3] Calligiuri et al. 2000; [5]Reijnders et al. Mov dis 2008, [4]Rogers et al. 2002
For review see: *Liberg et al. 2015, Bennabi et al. 2013, Buyukdura et al. 2011*

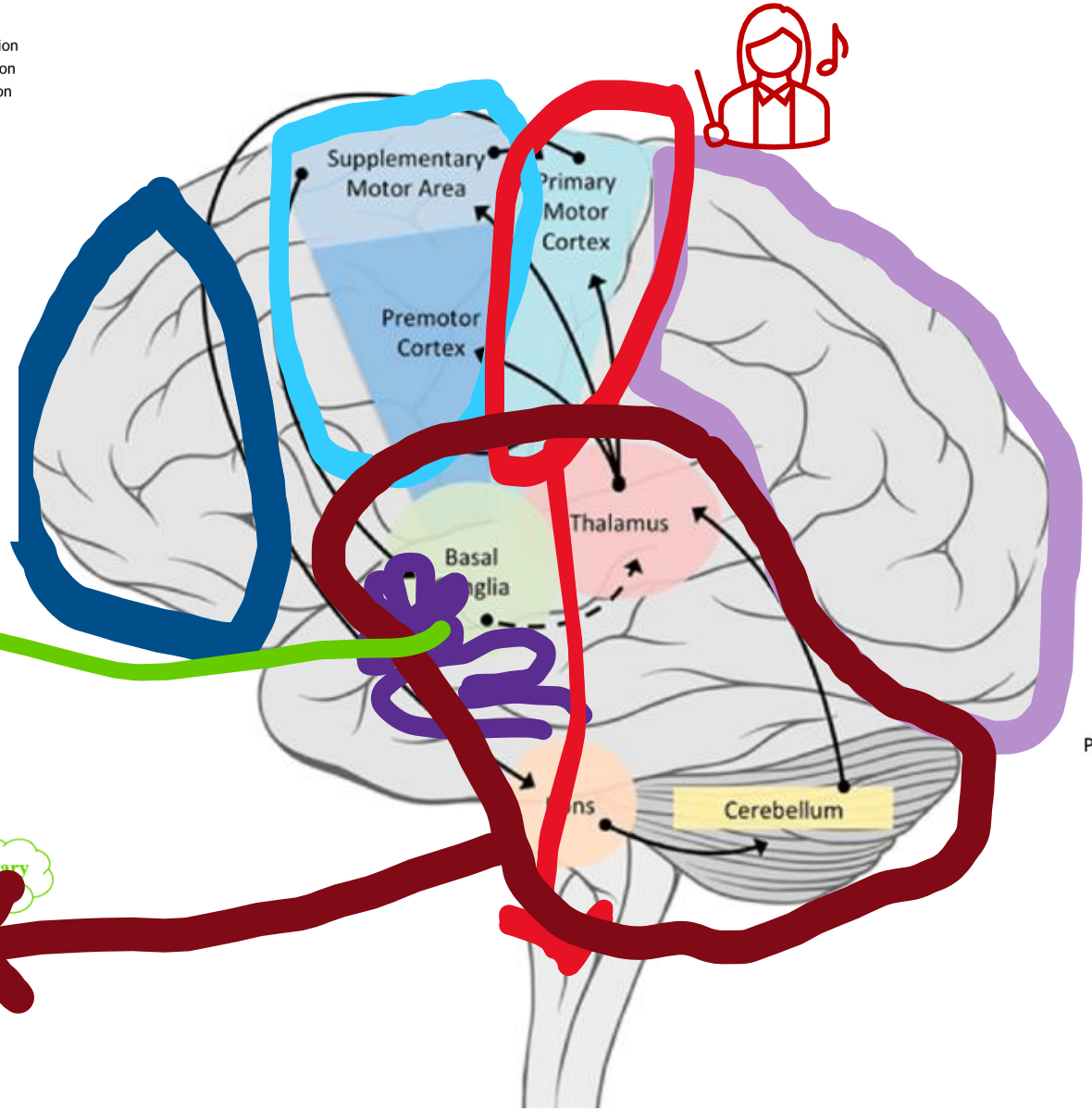
Onderzoeksvragen

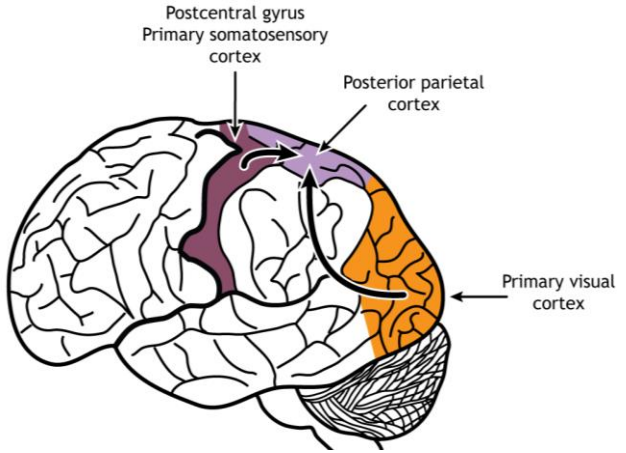
1. PMS fenotypering → hersenregio's? (*waar?*)

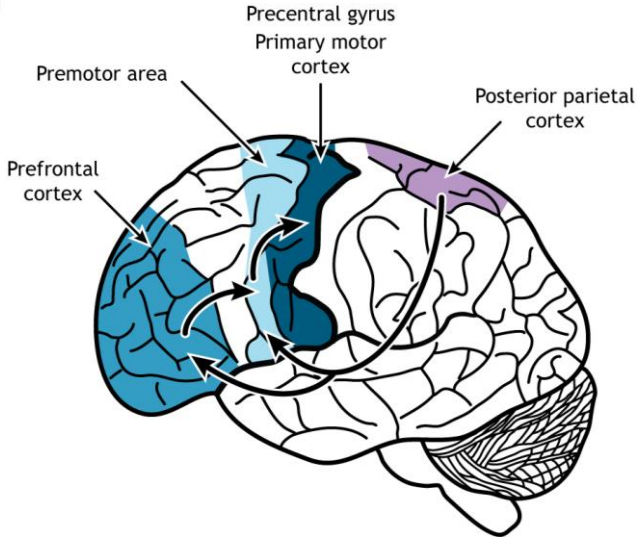
2. PMS // stemming, motivatie- of cognitie? (*hoe?)*

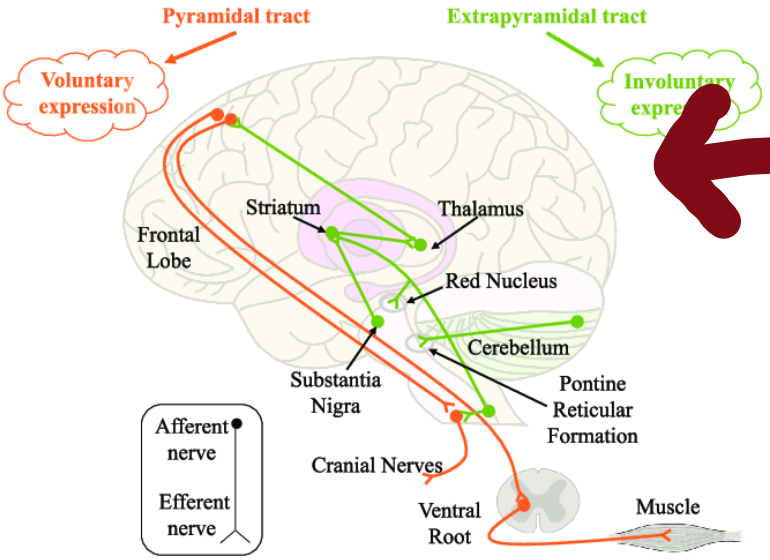
3. PMS // MMS in kader van "natuurlijke hersenveroudering"? (*wat?)*











Source: Sanders et al. Brain Sci. **2020**, *10*, 215

KU LEUVEN

1 Non-interactiveness

For what proportion of the interview doe
or fail to interact with or "stay with" the i
interviewer has "not been registered"? *A
show an impairment of concentration.*

0 — Consistently interactive

1 — Not interactive some of the time
2 — Not interactive much of the time
3 — Not interactive almost all of the tim

2 Facial immobility

The rater should assess the lack of mom
sion. The depth of expression is import
mere social reactions should not be give
in your assessment.

0 — Mobility within normal limits

1 — Somewhat restricted facial mobility
2 — Moderately restricted facial mobilit
3 — Fixed and immobile face

3 Postural slumping

Judge the presence and severity of post
rolled forward) relevant to the patient's a
sitting, standing and walking.

0 — No slumping

1 — Slightly slumped posture
2 — Moderately slumped posture
3 — Markedly slumped posture

4 Non-reactivity

Assess any failure by the patient to show
thing pleasing, or to your attempts at ch
neous reactivity, test for it formally (e.g.,
able event, compliment the patient about
humour). Spontaneous or unforced smil
rating for non-reactivity. Superficial or f

0 — Appropriately reactive mood

1 — Slightly non-reactive mood
2 — Moderately non-reactive mood
3 — Severely non-reactive mood (neithe

5 Facial apprehension

Rate the extent to which the patient's face shows sustained morbid apprehension, perplexity, bewilderment, fearfulness or tortured concern. The apprehension is unable to be relieved substantially by the interviewer's attempts to provide realistic comfort or reassurance. The item should not be rated unless the apprehension is clearly pathological and persisten

0 — No facial apprehension

1 — Slight facial apprehension
2 — Moderate facial apprehensi
3 — Marked facial apprehension

6 Delay in responding ve

Judge the extent to which the pati
tions. Allow for the patient's educ

0 — No obvious delay in respon

1 — Slight delay in responding
2 — Moderate delay in respondi
3 — Severe delay in responding

7 Length of verbal respor

Rate the extent to which the pati
length in reply to more open-end
culture, age and language.

0 — Responses of appropriate le

1 — Responses distinctly shorte
2 — Responses generally of a fe
3 — Mute

8 Inattentiveness

Inattentiveness is, in effect, an in
server. Rate the extent to which th
interviewer. The patient may have
from non-interactiveness (Item 1) i
be unable to sustain attention to t

0 — Consistently attentive

1 — Inattentive for some of the
2 — Inattentive for much of the
3 — Inattentive almost all of the

9 Facial agitation

Judge the extent to which the patient's facial movements and fluc
sion indicate pathological fearfulness, bewilderment, anguish, pe
torment. Agitation can be commonly expressed in sudden outbu
despair. At other times the patient's face may lack mobility. Do
sis of the patient's complaints of anxiety. Do not rate dyskinetic
are not associated typically with tormented mental features. Do
movements or physical disorders which may produce apparent
guishing from movements associated with anxiety, refer to Poi
guidelines. A 3 rating requires persistent and significant agitati
epochs of severe agitation superimposed on a facial expression
perplexity and/or retardation.

0 — No facial agitation

1 — Slight facial agitation
2 — Moderate facial agitation
3 — Persistent and/or several epochs of marked facial agitation

10 Body immobility (amount, not speed)

Judge the extent to which the patient moves limbs, hands and bo
patient's age and physical status.

0 — Mobility within normal limits

1 — Slightly restricted mobility
2 — Moderately restricted mobility
3 — Virtually no movement (immobile)

11 Motor agitation

Rate persistent, excessive or inappropriate motor activity as mani
teristic inability by the patient to sit or stay still, indicating thwar
energy. Typical movements include slow rubbing, pacing, writhin
tions. The movements may have an autistic quality. Do not rate t
or mannerisms. Note Point 3 in the general guidelines. A 2 rating
sisting agitation of moderate severity or epochs of quite severe a
rating reflects persistent and severe agitation.

0 — No abnormality, or movements more typical of anxiety

1 — Slight motor agitation
2 — Persistent agitation of moderate severity or epochs of moderate
3 — Severe motor agitation, unable to sit still at all

Scoring Sheet for the CORE Assessment of Psychomotor Change

After entering the item ratings in the boxes sum the columns to obtain the scores on the three scales; then sum the three scale scores to obtain the total score.

1. Non-interactiveness	☐		
2. Facial immobility		☐	
3. Postural slumping		☐	
4. Non-reactivity	☐		
5. Facial apprehension			☐
6. Delay in responding verbally		☐	
7. Length of verbal responses	☐		
8. Inattentiveness	☐		
9. Facial agitation			☐
10. Body immobility (amount, not speed)		☐	
11. Motor agitation			☐
12. Poverty of associations	☐		
13. Slowed movement (speed, not amount)		☐	
14. Verbal stereotypy			☐
15. Delay in motor activity		☐	
16. Impaired spontaneity of talk	☐		
17. Slowing of speech rate		☐	
18. Stereotyped movements			☐
	NI	RT	AG

NI = Non-interactiveness
RT = Retardation
AG = Agitation

Total CORE score = NI + RT + AG = ☐

MDS UPDRS Score Sheet

1.A	Source of information	☐ Patient ☐ Caregiver ☐ Patient + Caregiver
Part I		
1.1	Cognitive impairment	
1.2	Hallucinations and psychosis	
1.3	Depressed mood	
1.4	Anxious mood	
1.5	Apathy	
1.6	Features of DDS	
1.6a	Who is filling out questionnaire	☐ Patient ☐ Caregiver ☐ Patient + Caregiver
1.7	Sleep problems	
1.8	Daytime sleepiness	
1.9	Pain and other sensations	
1.10	Urinary problems	
1.11	Constipation problems	
1.12	Light headedness on standing	
1.13	Fatigue	
Part II		
2.1	Speech	
2.2	Saliva and drooling	
2.3	Chewing and swallowing	
2.4	Eating tasks	
2.5	Dressing	
2.6	Hygiene	
2.7	Handwriting	
2.8	Doing hobbies and other activities	
2.9	Turning in bed	
2.10	Tremor	
2.11	Getting out of bed	
2.12	Walking and balance	
2.13	Freezing	
3a	Is the patient on medication?	☐ No ☐ Yes
3b	Patient's clinical state	☐ Off ☐ On
3c	Is the patient on Levodopa?	☐ No ☐ Yes
3.C1	If yes, minutes since last dose:	
Part III		
3.1	Speech	
3.2	Facial expression	
3.3a	Rigidity– Neck	
3.3b	Rigidity– RUE	
3.3c	Rigidity– LUE	
3.3d	Rigidity– RLE	
3.3e	Rigidity– LLE	
3.4a	Finger tapping– Right hand	
3.4b	Finger tapping– Left hand	
3.5a	Hand movements– Right hand	
3.5b	Hand movements– Left hand	
3.6a	Pronation- supination movements– Right hand	
3.6b	Pronation- supination movements– Left hand	
3.7a	Toe tapping–Right foot	
3.7b	Toe tapping– Left foot	
3.8a	Leg agility– Right leg	
3.8b	Leg agility– Left leg	
3.9	Arising from chair	
3.10	Gait	
3.11	Freezing of gait	
3.12	Postural stability	
3.13	Posture	
3.14	Global spontaneity of movement	
3.15a	Postural tremor– Right hand	
3.15b	Postural tremor– Left hand	
3.16a	Kinetic tremor– Right hand	
3.16b	Kinetic tremor– Left hand	
3.17a	Rest tremor amplitude– RUE	
3.17b	Rest tremor amplitude– LUE	
3.17c	Rest tremor amplitude– RLE	
3.17d	Rest tremor amplitude– LLE	
3.17e	Rest tremor amplitude– Lip/jaw	
3.18	Constancy of rest	
	Were dyskinesias presen	☐ No ☐ Yes
	Did these movements interfere with ratings?	☐ No ☐ Yes
	Hoehn and Yahr Stage	
Part IV		
4.1	Time spent with dyskinesias	
4.2	Functional impact of dyskinesias	
4.3	Time spent in the OFF state	
4.4	Functional impact of fluctuations	
4.5	Complexity of motor fluctuations	
4.6	Painful OFF-state dystonia	

Scale for the assessment and rating of ataxia (SARA)

1) Gait

Proband is asked (1) to walk at a safe distance parallel to a wall including a half-turn (turn around to face the opposite direction of gait) and (2) to walk in tandem (heels to toes) without support.

- **0** Normal, no difficulties in walking, turning and walking tandem (up to one misstep allowed)
- **1** Slight difficulties, only visible when walking 10 consecutive steps in tandem
- **2** Clearly abnormal, tandem walking >10 steps not possible
- **3** Considerable staggering, difficulties in half-turn, but without support
- **4** Marked staggering, intermittent support of the wall required
- **5** Severe staggering, permanent support of one stick or light support by one arm required
- **6** Walking > 10 m only with strong support (two special sticks or stroller or accompanying person)
- **7** Walking < 10 m only with strong support (two special sticks or stroller or accompanying person)
- **8** Unable to walk, even supported

Score

2) Stance

Proband is asked to stand (1) in natural position, (2) with feet together in parallel (big toes touching each other) and (3) in tandem (both feet on one line, no space between heel and toe). Proband does not wear shoes, eyes are open. For each condition, three trials are allowed. Best trial is rated.

- **0** Normal, able to stand in tandem for > 10 s
- **1** Able to stand with feet together without sway, but not in tandem for > 10s
- **2** Able to stand with feet together with sway
- **3** Able to stand for > 10 s without position, but not with feet togetl
- **4** Able to stand for >10 s in natur intermittent support
- **5** Able to stand >10 s in natural p constant support of one arm
- **6** Unable to stand for >10 s even v of one arm

Score

3) Sitting

Proband is asked to sit on an examination bed without support of feet, eyes open and arms outstretched to the front.

- **0** Normal, no difficulties sitting >10 sec
- **1** Slight difficulties, intermittent sway
- **2** Constant sway, but able to sit > 10 s without support
- **3** Able to sit for > 10 s only with intermittent support
- **4** Unable to sit for >10 s without continuous support

Score

4) Speech disturbance

Speech is assessed during normal co

- **0** Normal
- **1** Suggestion of speech disturbanc
- **2** Impaired speech, but easy to un
- **3** Occasional words difficult to un
- **4** Many words difficult to underst
- **5** Only single words understandal
- **6** Speech unintelligible / anarthria

Score

5) Finger chase

Rated separately for each side

Proband sits comfortably. If necessary, support of feet and trunk is allowed. Examiner sits in front of proband and performs 5 consecutive sudden and fast pointing movements in unpredictable directions in a frontal plane, at about 50 % of proband´s reach. Movements have an amplitude of 30 cm and a frequency of 1 movement every 2 s. Proband is asked to follow the movements with his index finger, as fast and precisely as possible. Average performance of last 3 movements is rated.

- **0** No dysmetria
- **1** Dysmetria, under/ overshooting target <5 cm
- **2** Dysmetria, under/ overshooting target < 15 cm
- **3** Dysmetria, under/ overshooting target > 15 cm
- **4** Unable to perform 5 pointing movements

Score	Right	Left
mean of both sides (R+L)/2		

6) Nose-finger test

Rated separately for each side

Proband sits comfortably. If necessary, support of feet and trunk is allowed. Proband is asked to point repeatedly with his index finger from his nose to examiner's finger which is in front of the proband at about 90 % of proband's reach. Movements are performed at moderate speed. Average performance of movements is rated according to the amplitude of the kinetic tremor.

- **0** No tremor
- **1** Tremor with an amplitude < 2 cm
- **2** Tremor with an amplitude < 5 cm
- **3** Tremor with an amplitude > 5 cm
- **4** Unable to perform 5 pointing movements

Score	Right	Left
mean of both sides (R+L)/2		

7) Fast alternating hand movements

Rated separately for each side

Proband sits comfortably. If necessary, support of feet and trunk is allowed. Proband is asked to perform 10 cycles of repetitive alternation of pro- and supinations of the hand on his/her thigh as fast and as precise as possible. Movement is demonstrated by examiner at a speed of approx. 10 cycles within 7 s. Exact times for movement execution have to be taken.

- **0** Normal, no irregularities (performs <10s)
- **1** Slightly irregular (performs <10s)
- **2** Clearly irregular, single movements difficult to distinguish or relevant interruptions, but performs <10s
- **3** Very irregular, single movements difficult to distinguish or relevant interruptions, performs >10s
- **4** Unable to complete 10 cycles

Score	Right	Left
mean of both sides (R+L)/2		

8) Heel-shin slide

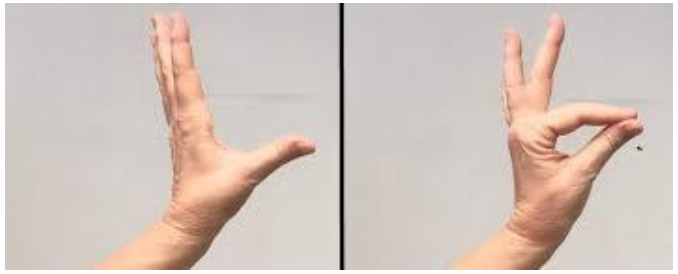
Rated separately for each side

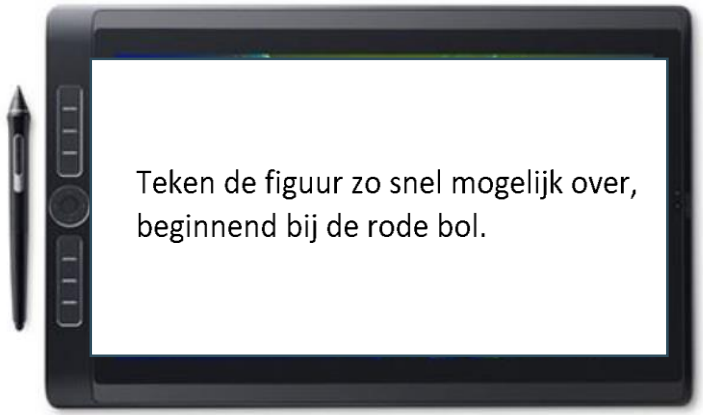
Proband lies on examination bed, without sight of his legs. Proband is asked to lift one leg, point with the heel to the opposite knee, slide down along the shin to the ankle, and lay the leg back on the examination bed. The task is performed 3 times. Slide-down movements should be performed within 1 s. If proband slides down without contact to shin in all three trials, rate 4.

- **0** Normal
- **1** Slightly abnormal, contact to shin maintained
- **2** Clearly abnormal, goes off shin up to 3 times during 3 cycles
- **3** Severely abnormal, goes off shin 4 or more times during 3 cycles
- **4** Unable to perform the task

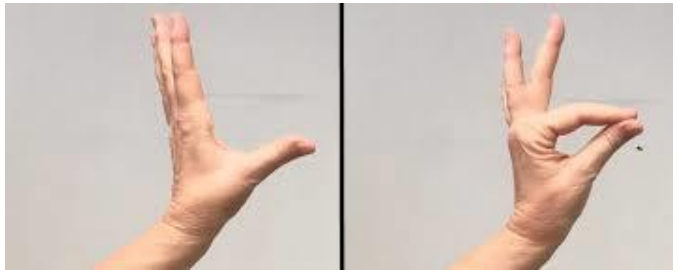
Score	Right	Left
mean of both sides (R+L) / 2		

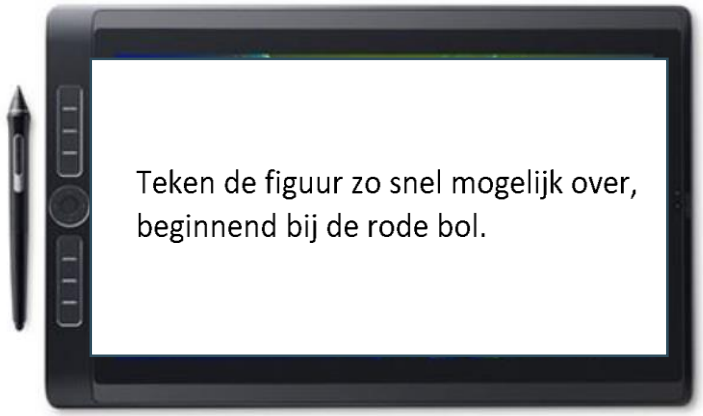
Experimenteel: fijne motoriek @ L3D



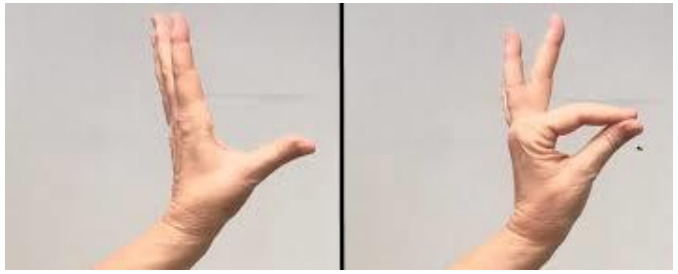


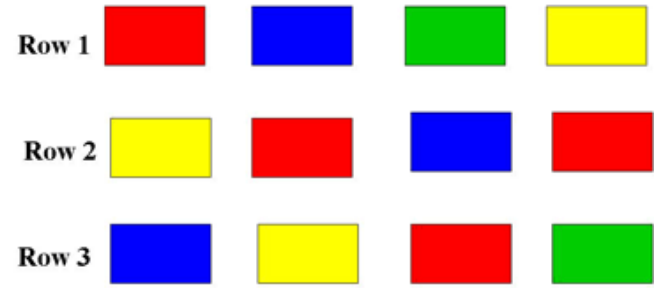
Experimenteel: grove motoriek @ L3D

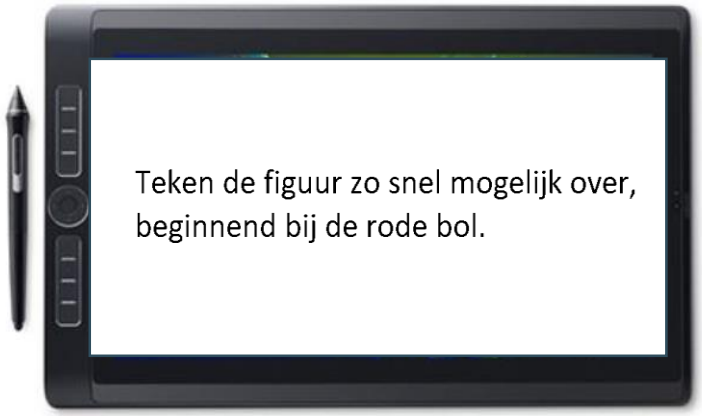


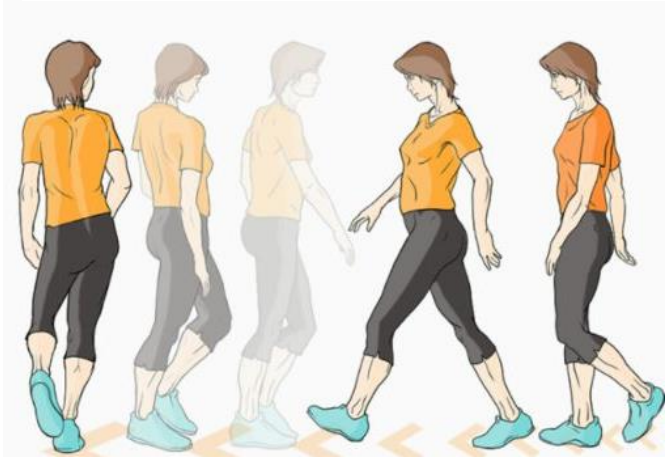


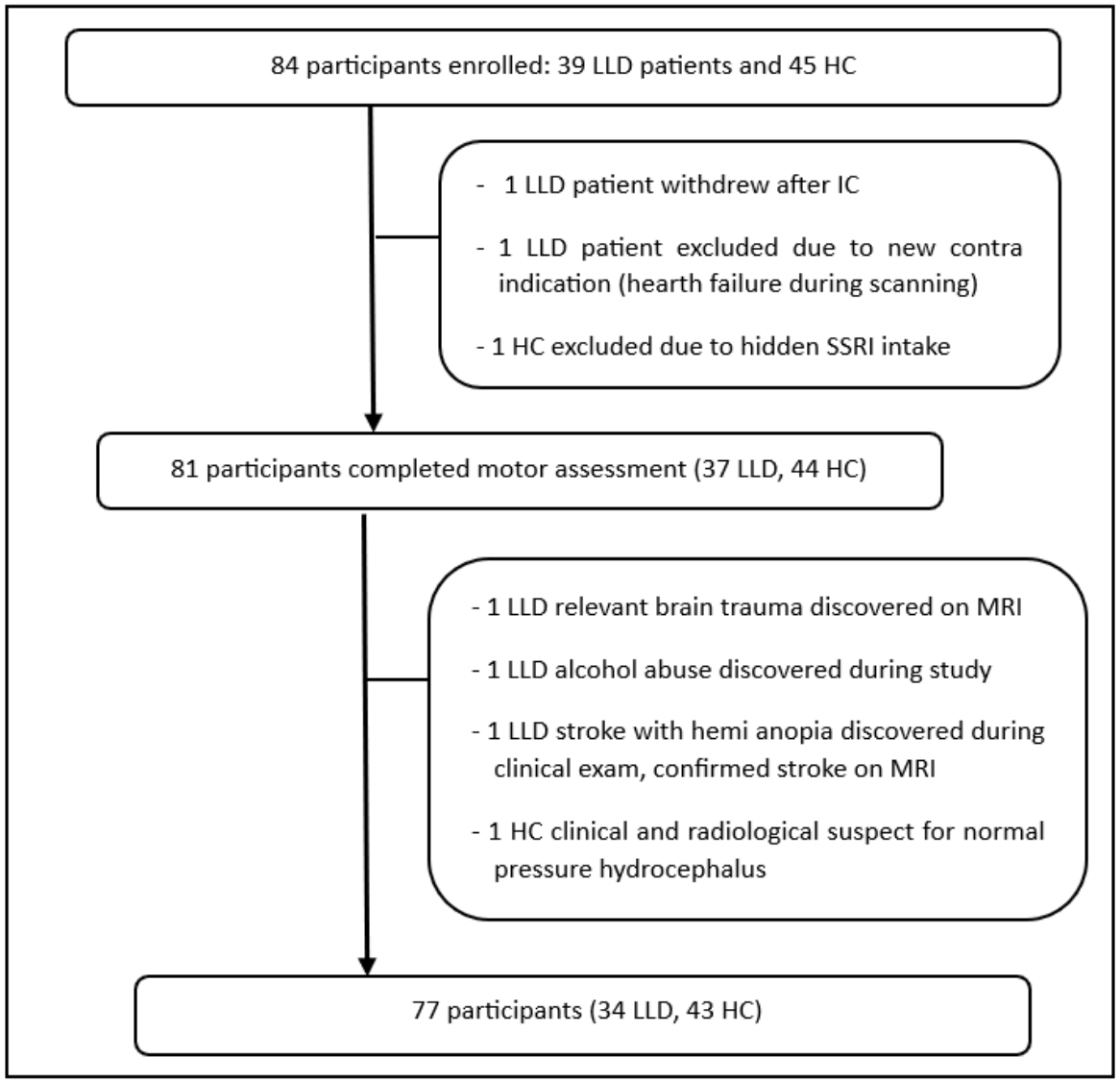
Experimenteel: gang en spraak @ L3D











	n (%)/ mean ±SD/ median [IQR]		*P*
	HC	**LLD**	
Age (years)	70.6 ±5.8	73.3 ±6.0	.046*
Female : male	27:16	23:11	.839
Education (years)	14.3 ±2.7	11.6 ±3.2	<.001*
Exercise last 6 months (times >30min /week)	3 [3]	1 [2]	.002*
Psychotropic drug use			
Antidepressant use	0	32 (94%)	<.001*
Antipsychotics use	0	20 (59%)	
Benzodiazepine use	2 (5%)	18 (53%)	
MADRS	0.9 ±1.7	**27.9** ±11.1	<.001*
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AES	22.0 ±5.1	**45.8** ±11.9	<.001*
MMSE	29.0 ±1.3	**25.8** ±2.9	<.001*
MDS-UPDRS part III	**3.4** ±2.9	**25.6** ±14.7	<.001
Bradykinesia	1.0 ±1.4	12.4 ±7.9	
Tremor	0.6 ±1.1	3.6 ±3.6	
Rigidity	1.1 ±1.2	4.8 ±1.4	
Gait & balance	0.6 ±0.9	3.9 ±2.8	
SARA	**1.3** ±1.6	**6.1** ±4.1	
Gait & balance	0.7 ±1.1	3.1 ±2.3	
Speech	0.1 ±0.4	1.2 ±1.1	<.001*
Upper limb ataxia	0.4 ±0.6	1.6 ±1.3	
Lower limb ataxia	0.0 ±0.0	0.3 ±0.5	
CORE	1.0 ±1.6	18.8 ±9.4	
CORE agitation	0.5 ±0.9	4.3 ±2.8	
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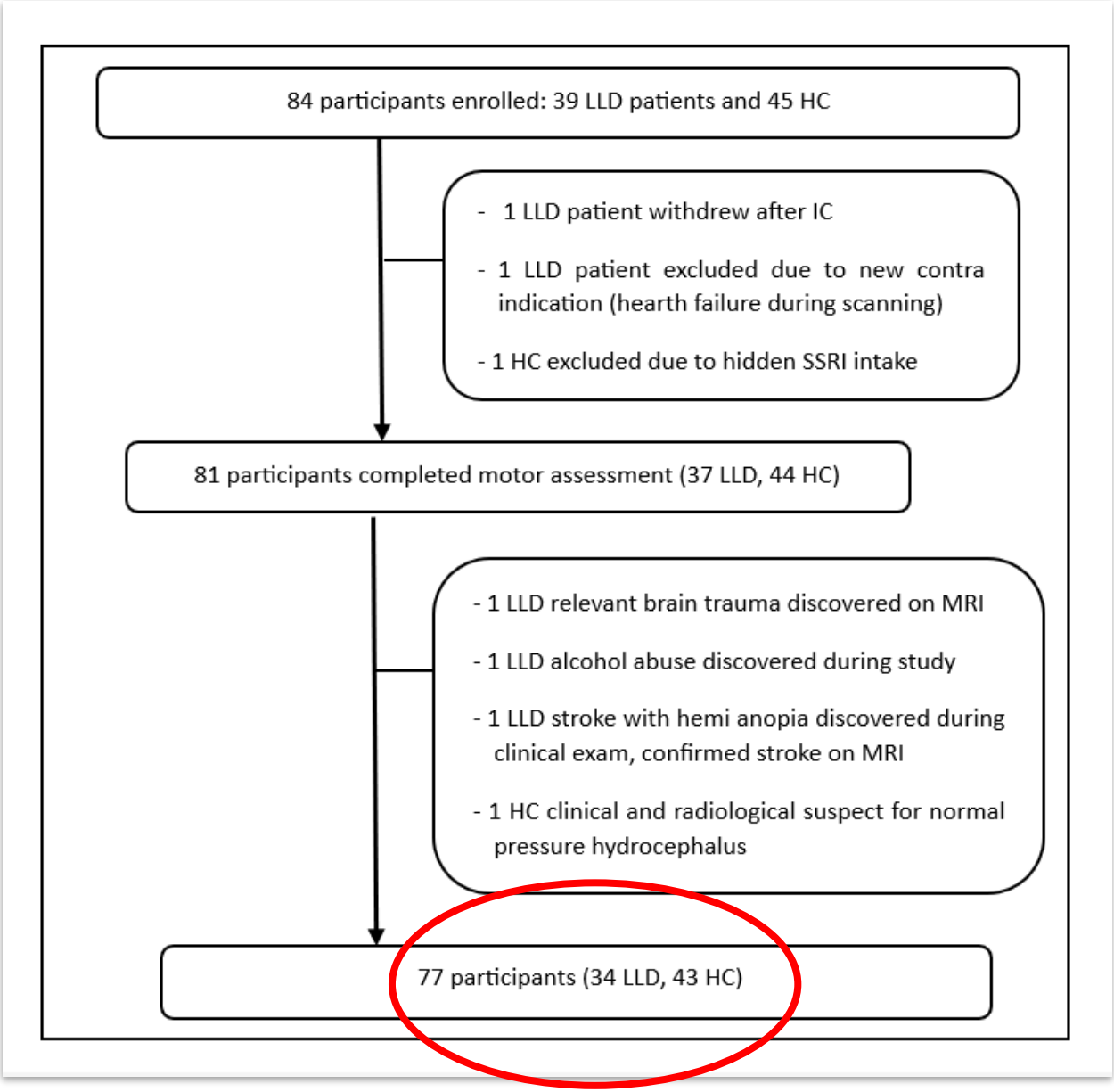

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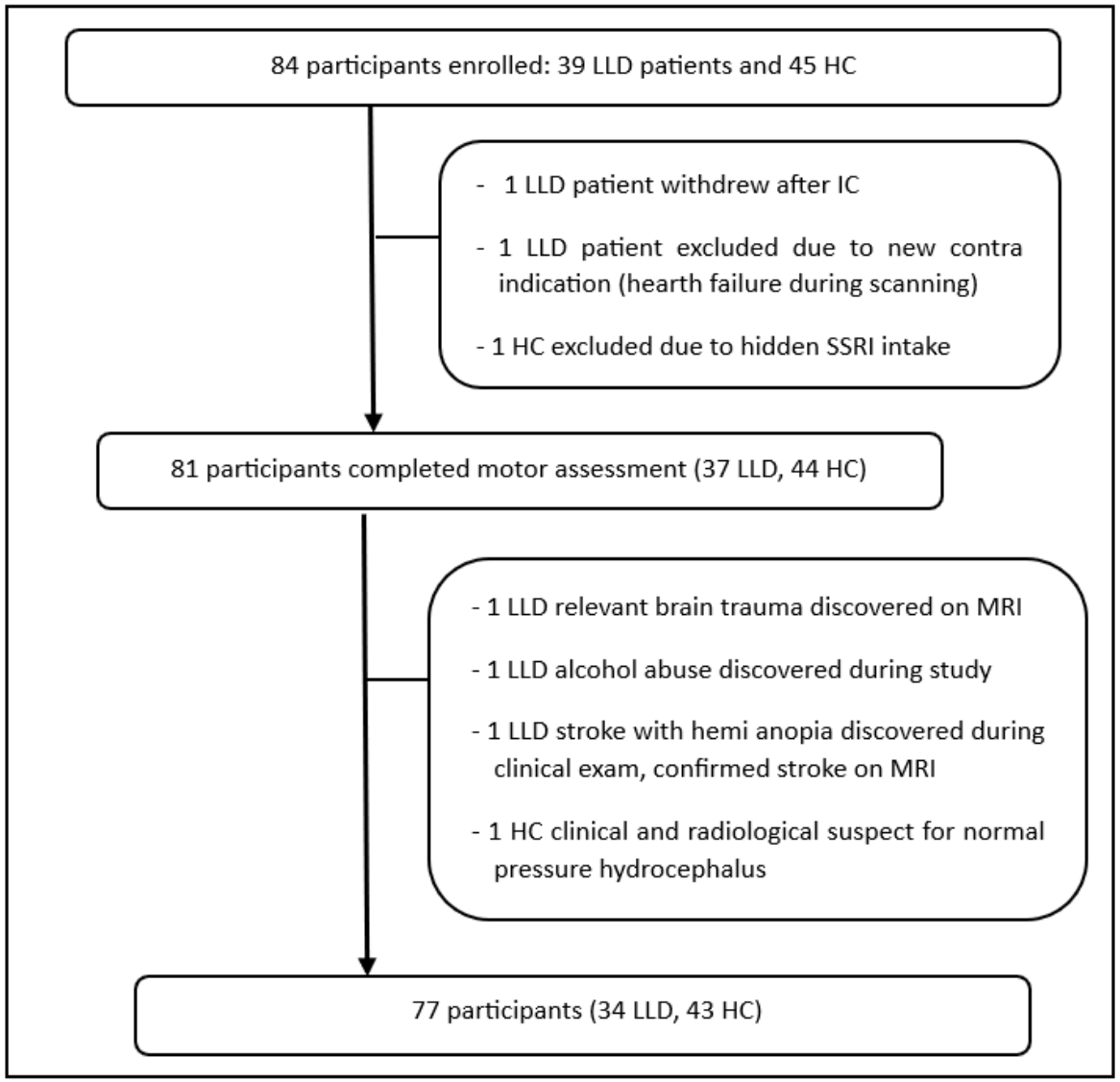

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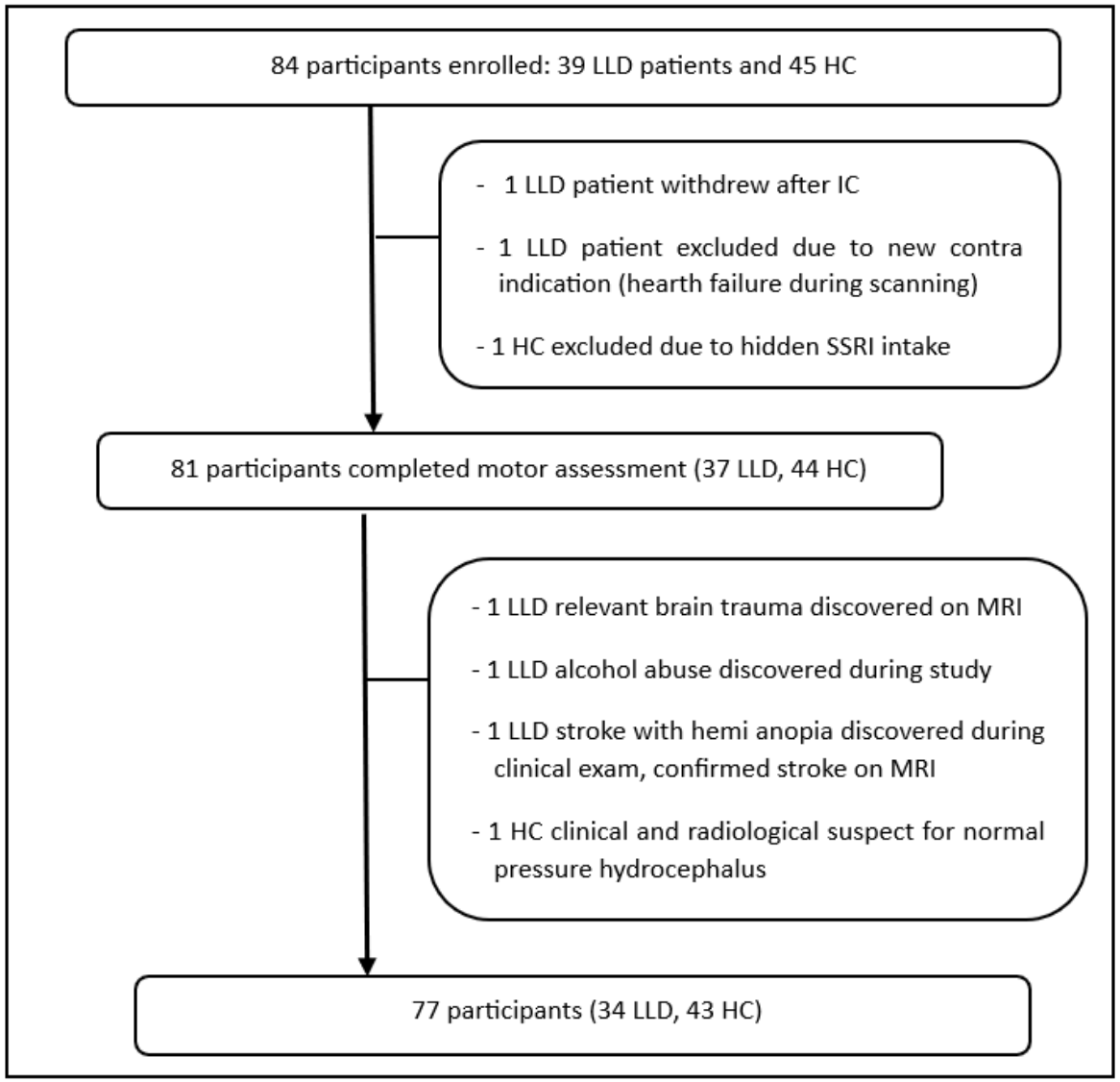

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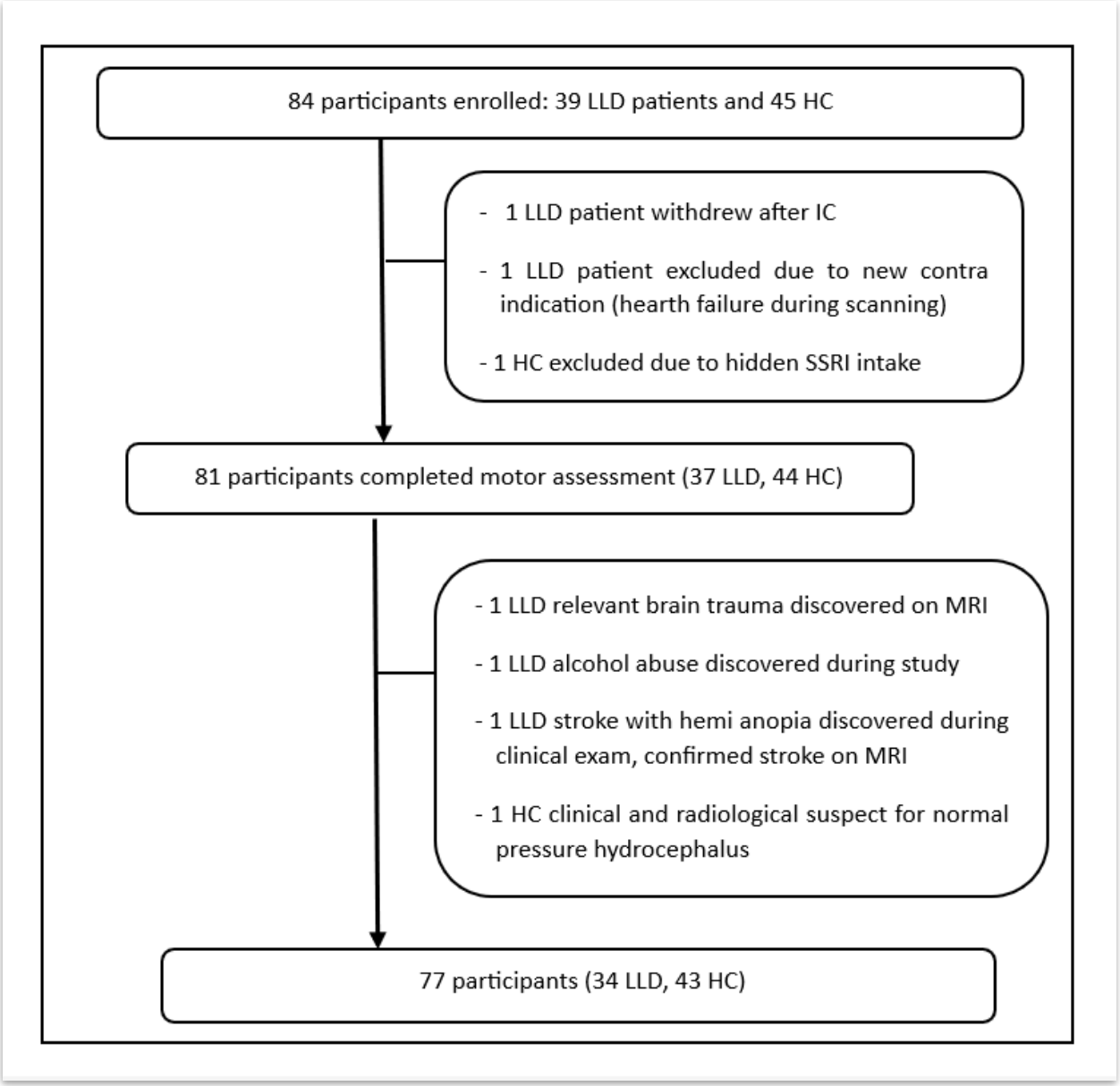

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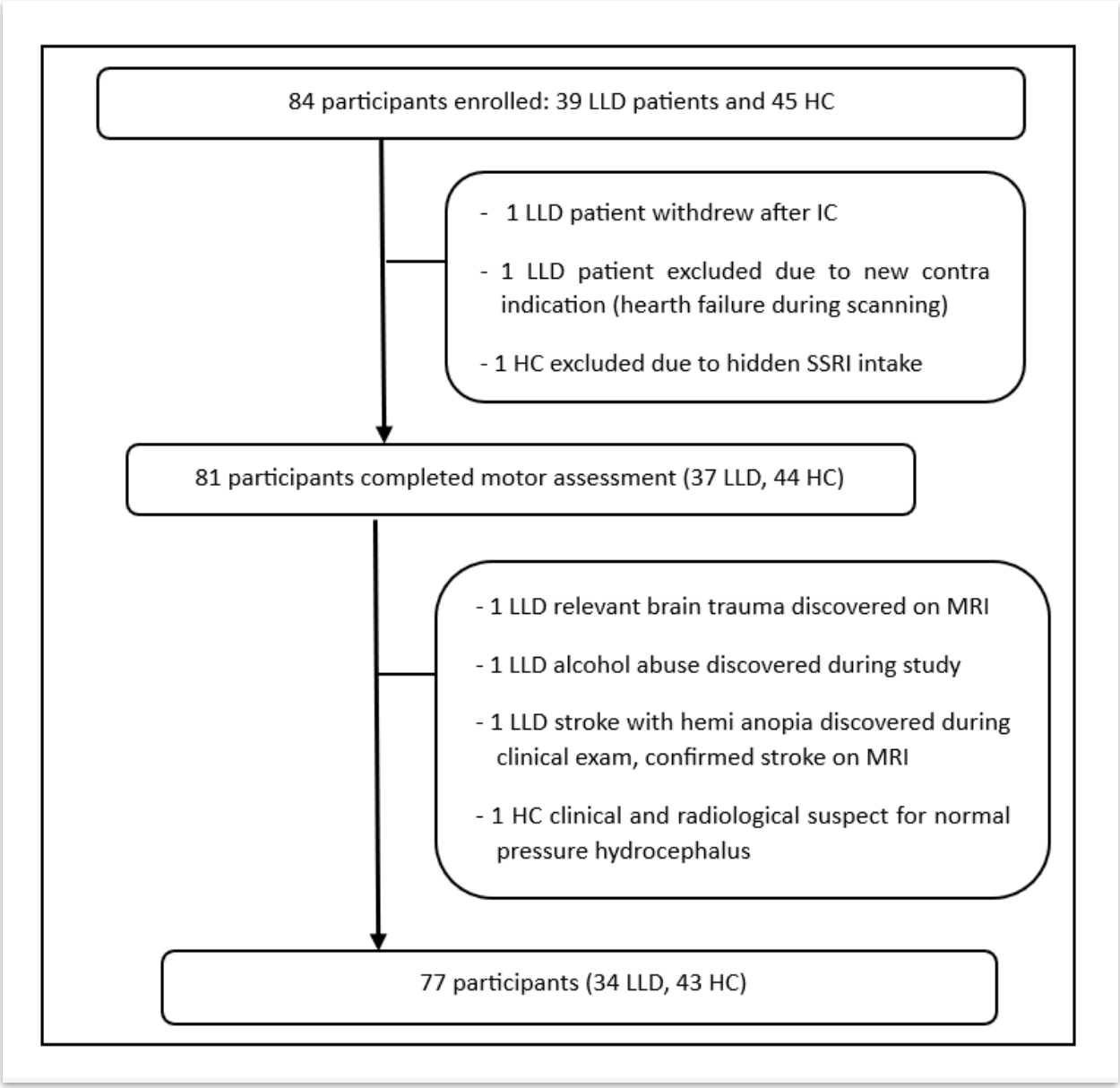

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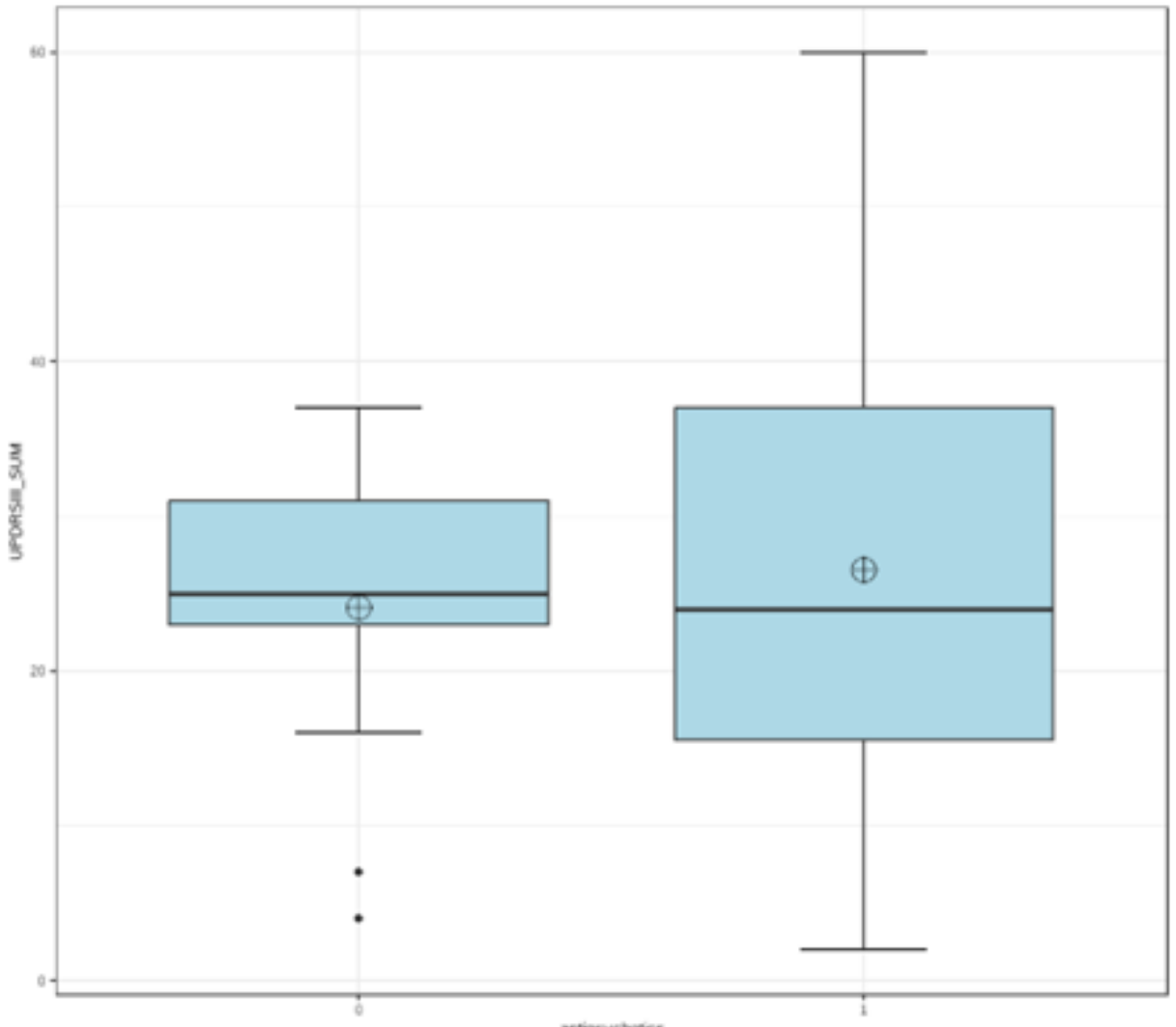
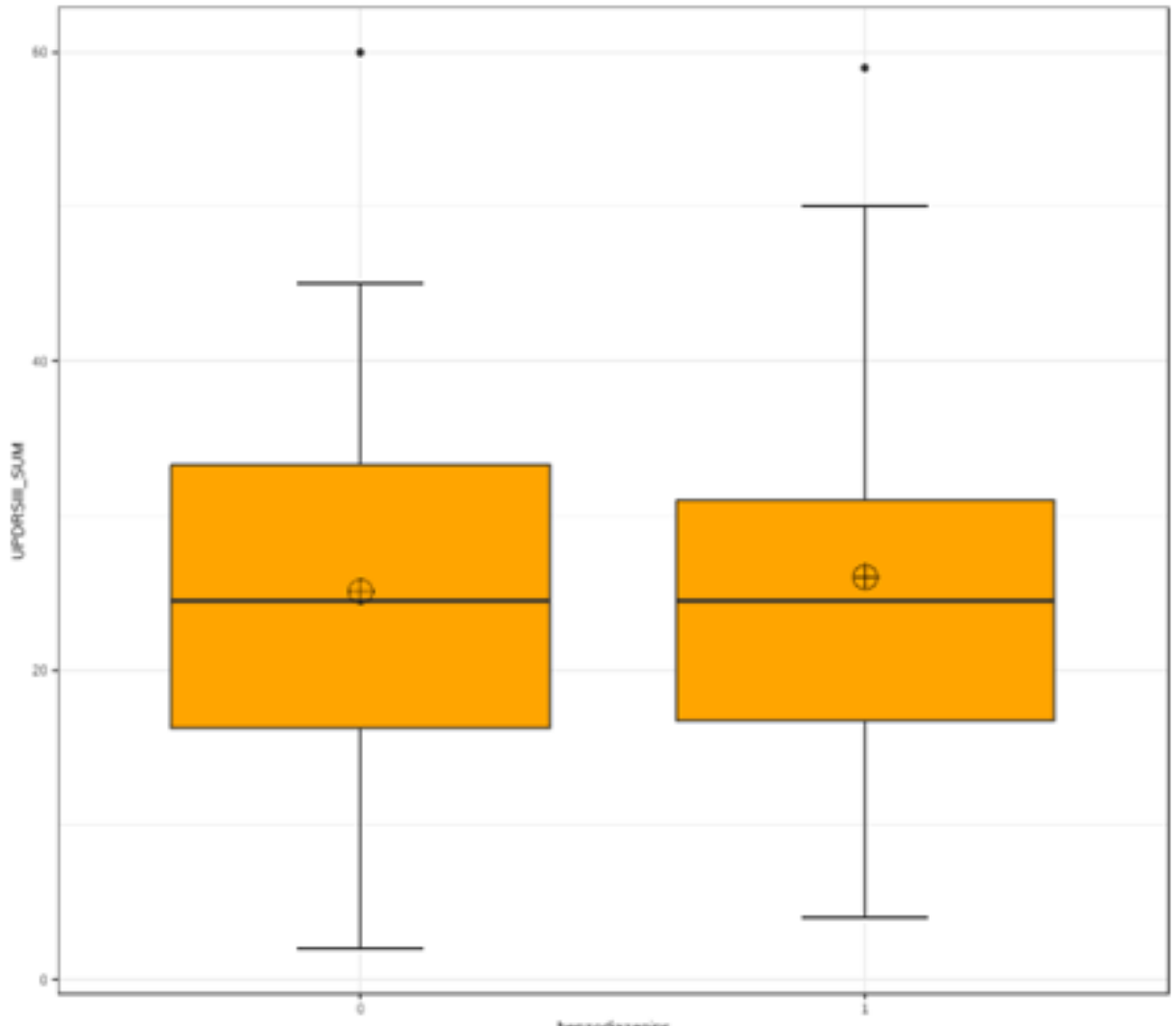
CORE	1.0 ±1.6	18.8 ±9.4	
CORE agitation	0.5 ±0.9	4.3 ±2.8	<.001*
CORE retardation	0.2 ±06	**8.6** ±5.6	
CORE non-interaction	0.4 ±0.9	6.0 ±3.6	

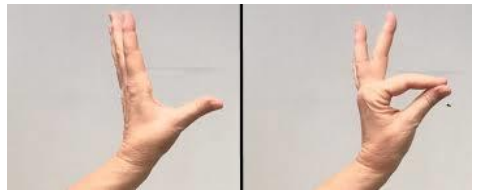
MDS-UPDRSIII



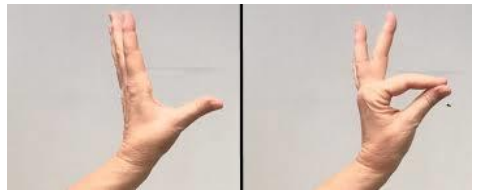
Antipsychotica



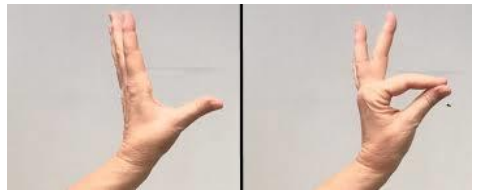
Benzodiazepine



Exp motor task	HC	LLD	P
Fingertapping (taps/s) L	2.95 ±0.77	1.80 ±0.76	<.0001
R	3.03 +0.87	1.96 ±0.74	<.0001



Exp motor task	HC	LLD	P
Fingertapping (taps/s) L	2.95 ±0.77	1.80 ±0.76	<.0001
R	3.03 +0.87	1.96 ±0.74	<.0001
Line (free) MT, mean (s)	3.24 ±1.16	6.47 ±4.22	.001
Diamond (free) MT, mean (s)	7.74 ±2.97	13.34 ±5.94	<.001
Circle (cued) MT, mean (s)	8.32 ±3.35	16.52 ±7.61	<.001
Star (cued) MT, mean (s)	10.51	23.63	<.001
Flags (cued) MT, mean (s)	12.00 ± 4.27	21.13 ±8.74	<.001



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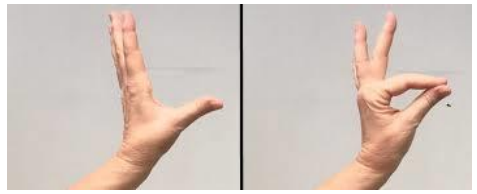
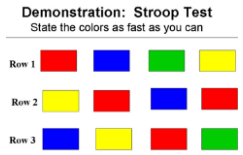
Circle (cued) MT, mean (s)	8.32 ±3.35	16.52 ±7.61	<.001
Star (cued) MT, mean (s)	10.51	23.63	<.001
Flags (cued) MT, mean (s)	12.00 ± 4.27	21.13 ±8.74	<.001
Turns (turns/s) L	1.72 ±0.35	1.21 ±0.31	<.001
R	1.78 ±0.34	1.27 ±0.31	<.001
Stamps (stamps/s) L	2.80 ±0.62	2.25 ±0.59	<.001
R	2.76 ±0.67	2.17 ±0.54	<.001





Exp motor task	HC	LLD	P
Fingertapping (taps/s) L	2.95 ±0.77	1.80 ±0.76	<.0001
R	3.03 +0.87	1.96 ±0.74	<.0001
Line (free) MT, mean (s)	3.24 ±1.16	6.47 ±4.22	.001
Diamond (free) MT, mean (s)	7.74 ±2.97	13.34 ±5.94	<.001
Circle (cued) MT, mean (s)	8.32 ±3.35	16.52 ±7.61	<.001
Star (cued) MT, mean (s)	10.51	23.63	<.001
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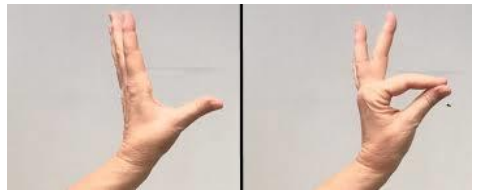
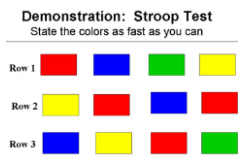
Turns (turns/s) L	1.72 ±0.35	1.21 ±0.31	<.001
R	1.78 ±0.34	1.27 ±0.31	<.001
Stamps (stamps/s) L	2.80 ±0.62	2.25 ±0.59	<.001
R	2.76 ±0.67	2.17 ±0.54	<.001
Speech (time 12 bars)	18.3 ±3.4	23.9 ±7.6	.0035



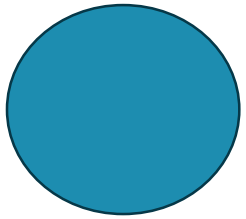


Exp motor task	HC (n=43)	LLD (=34)	P*
Fingertapping (taps/s) L	2.95 ±0.77	1.80 ±0.76	<.0001
R	3.03 +0.87	1.96 ±0.74	<.0001
Line (free) MT, mean (s)	3.24 ±1.16	6.47 ±4.22	.001
Diamond (free) MT, mean (s)	7.74 ±2.97	13.34 ±5.94	<.001
Circle (cued) MT, mean (s)	8.32 ±3.35	16.52 ±7.61	<.001
Star (cued) MT, mean (s)	10.51	23.63	<.001
Flags (cued) MT, mean (s)	12.00 ± 4.27	21.13 ±8.74	<.001
Turns (turns/s) L	1.72 ±0.35	1.21 ±0.31	<.001
R	1.78 ±0.34	1.27 ±0.31	<.001
Stamps (stamps/s) L	2.80 ±0.62	2.25 ±0.59	<.001
R	2.76 ±0.67	2.17 ±0.54	<.001
Speech (time 12 bars)	18.3 ±3.4	23.9 ±7.6	.0035
Mean gait velocity (m/s)	1.14 ±0.18	0.81 ±0.30	<.001
Mean stride length (m)	0.54 ±0.08	0.41 ±0.12	<.001

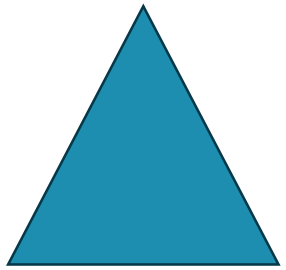
*Student's t test / MWU

Onderzoeksvragen

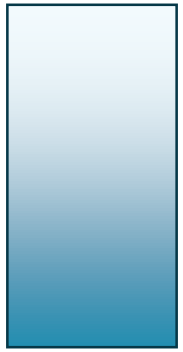
1. PMS fenotypering → **WAAR? ALL OVER THE PLACE**
2. PMS // stemmings-, motivationele- of cognitieve symptomen?
3. PMS // MMS in kader van “natuurlijke hersenveroudering”? (*wat?)*



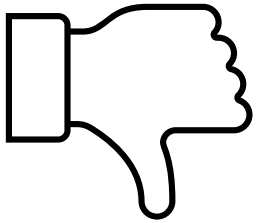
Gezonde controle = HC



Late life depressive patient = LLD

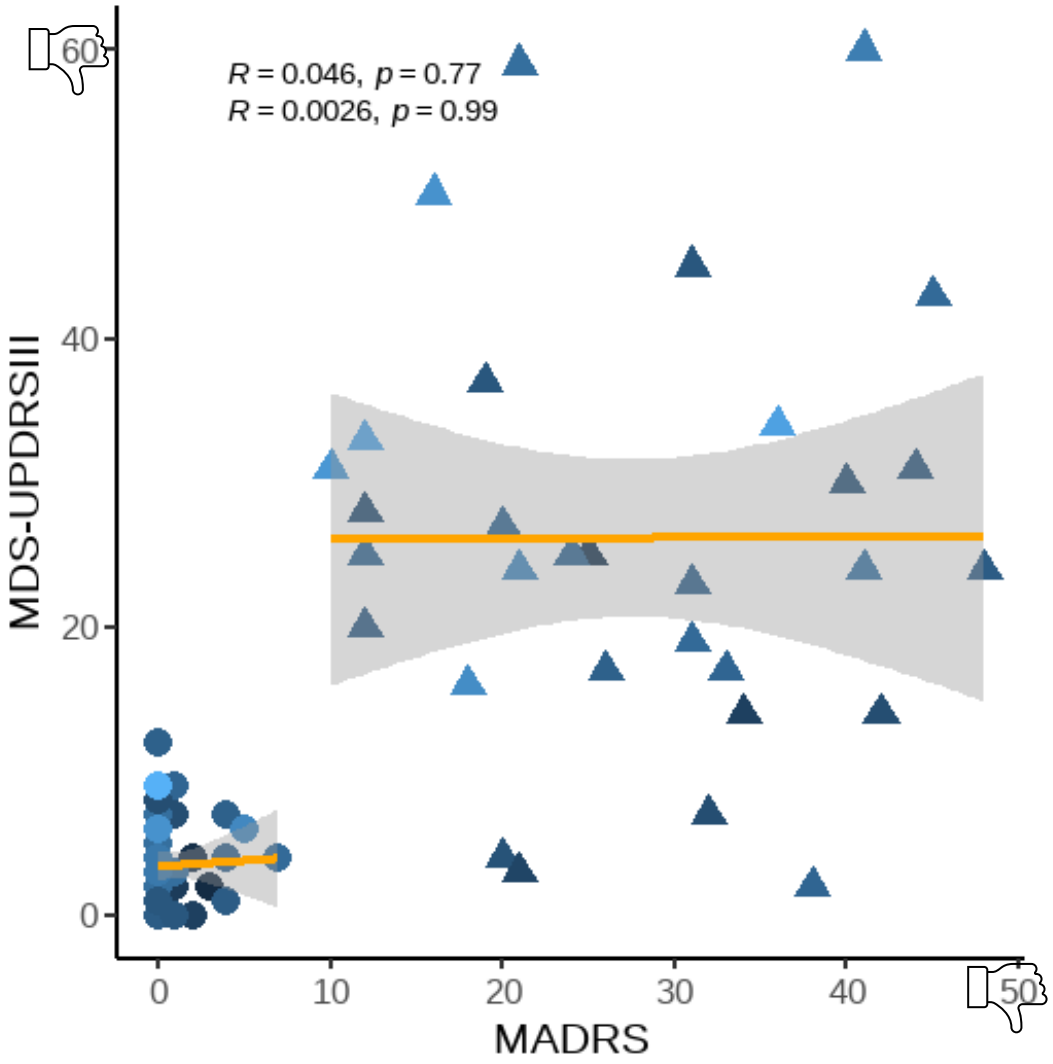


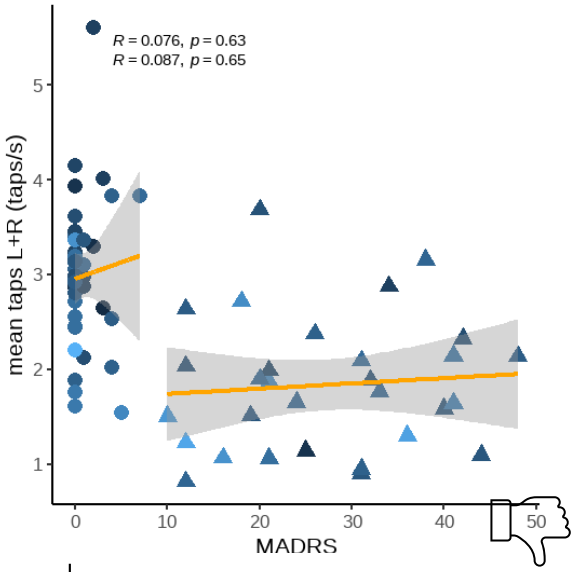
Hogere leeftijd = bleker

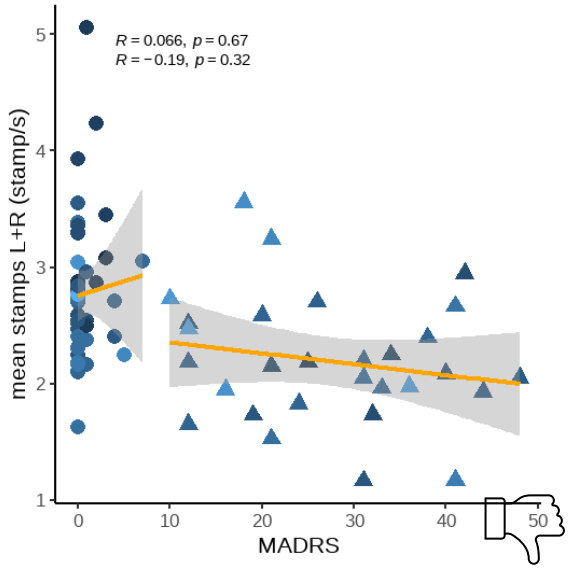


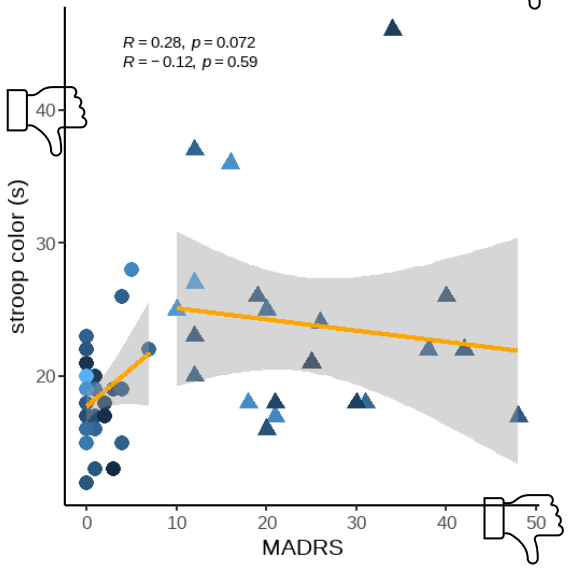
Schaal: hoger = slechtere score

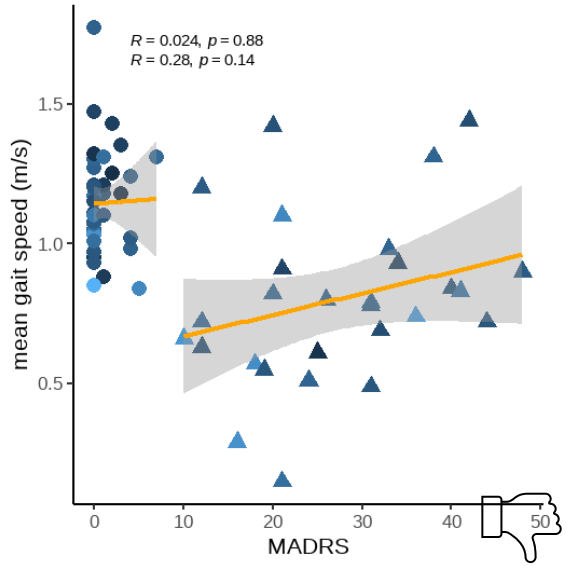
1. PMS // stemming, motivatie en cognitie?







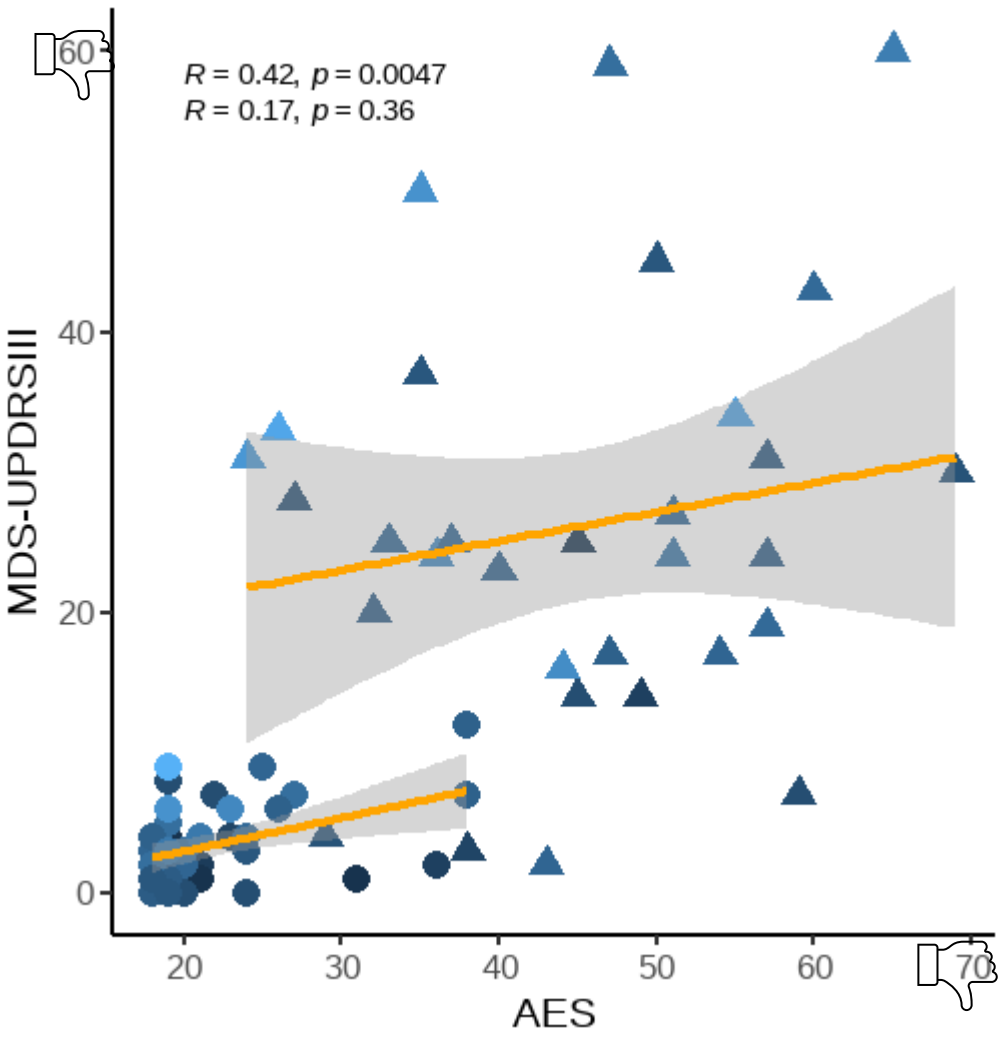


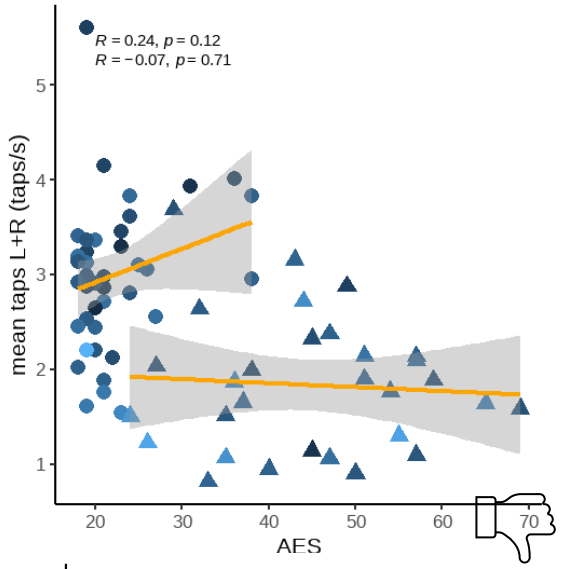


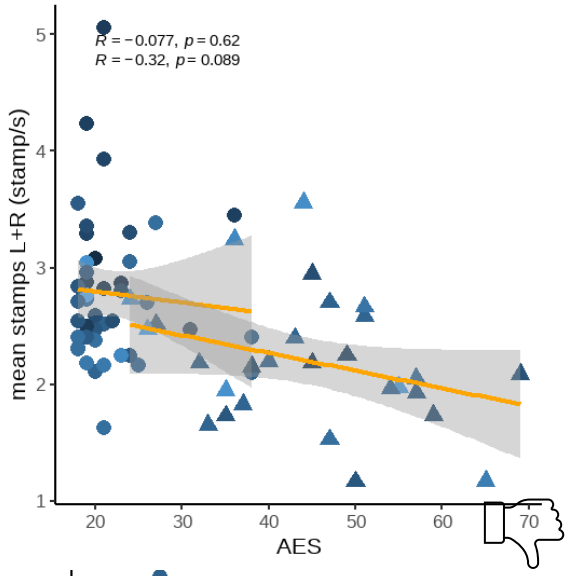
UPDRSIII = Case*** + Exercise* + Age* + Education + MADRS ^{NS} : ($F(5,63)=27$, R^2adj 0.653, $p < .0001$)

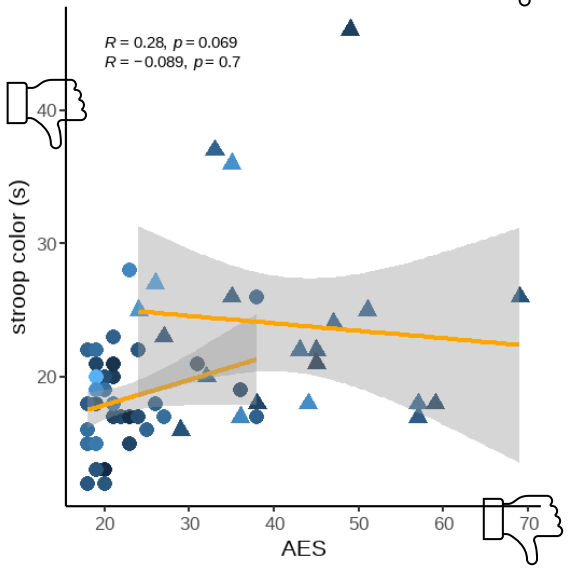
KU LEUVEN

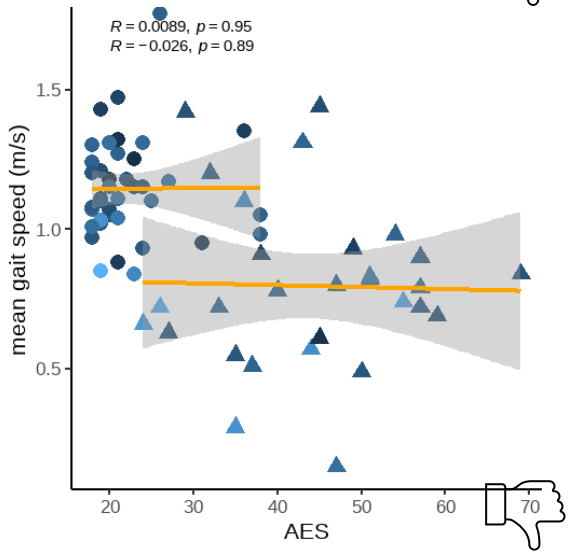
2. PMS // stemming, motivatie en cognitie?







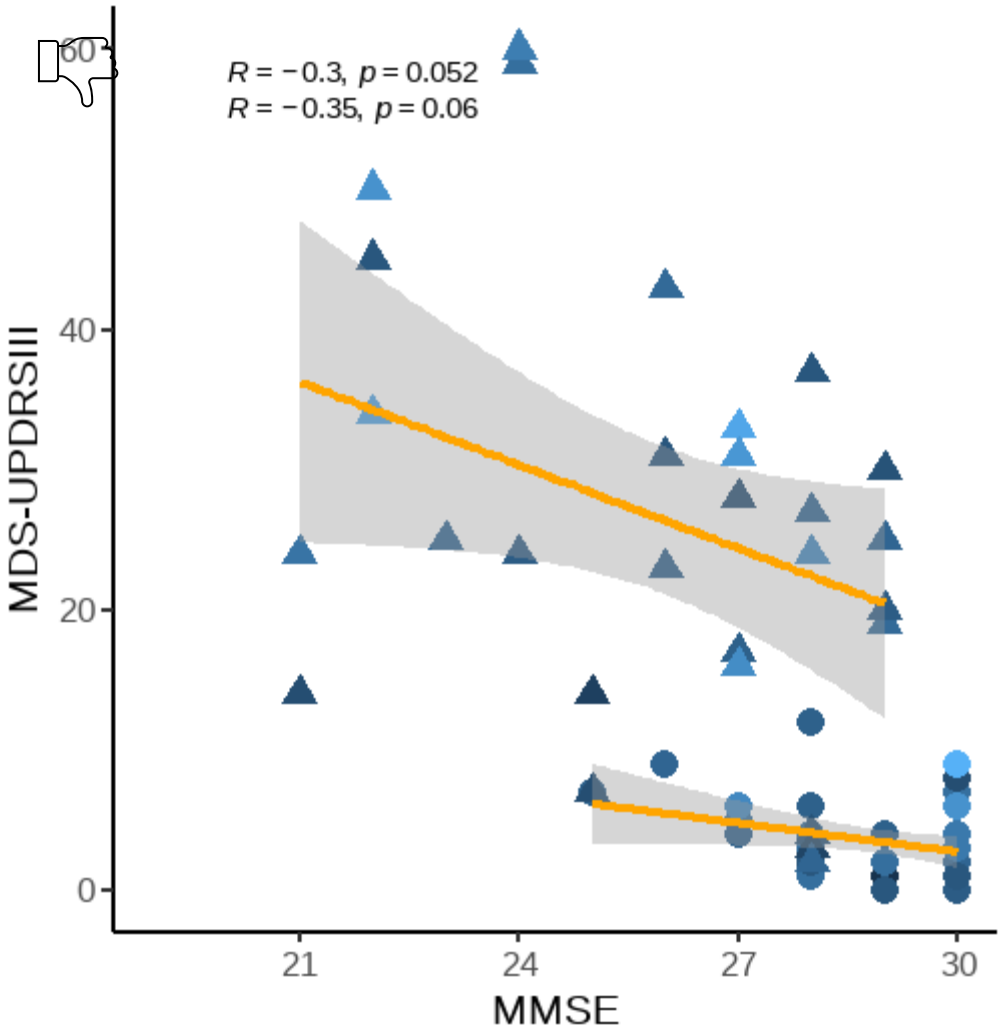


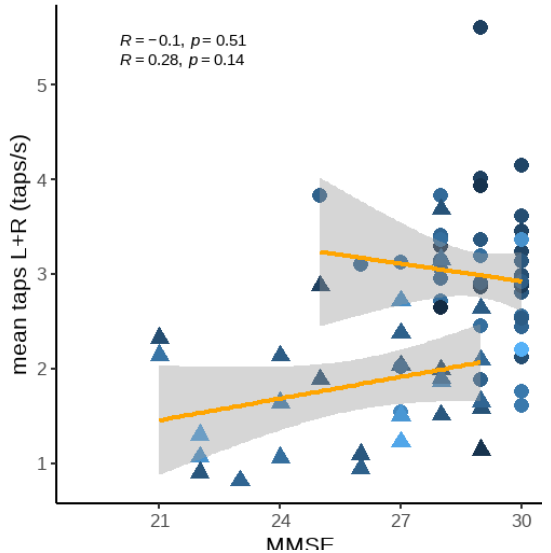


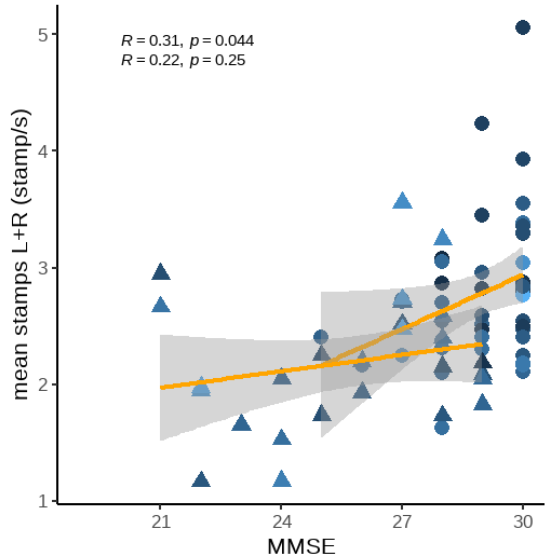
UPDRSIII = Case*** + Exercise* + Age** + Education + AES ^{NS}: (F(5,63)=28, R^2adj 0.665, p <.0001)

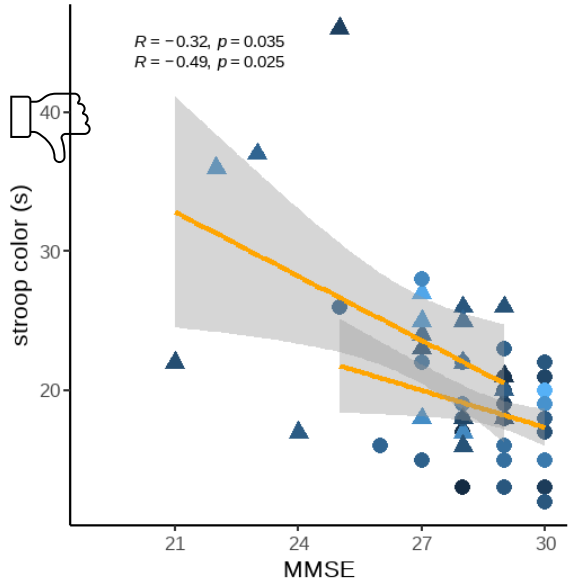
KU LEUVEN

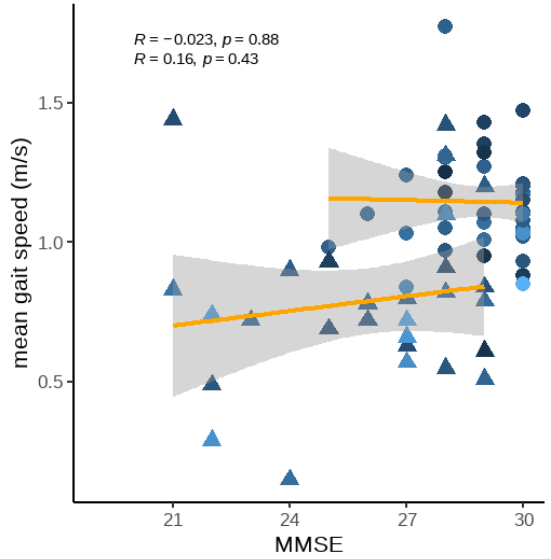
3. PMS // stemming, cognitie en motivatie?











UPDRSIII = Case*** + Exercise** + Age + Education + MMSE*: (F(5,62)=30, R^2adj 0.686, p <.0001)

Case: β= 17.5 (p= 4.62e-09)*** MMSE: β= -1.3 (p=.027)* Age: β= 0.4 (p=.019)* Exercise β= -1.7 (p= 0.006)**

3. PMS// cognitie vervolg…

Cognitieve subdomeinen: executief (TMTB-A), aandacht (DSF/DSB), taal (BNT), geheugen (RAVLT)

Initiatietijd, invloed complexiteit en cueing

Onderzoeksvragen

1. PMS fenotypering → **all over the place**
2. PMS **<-> stemming/motivationele/(cognitieve) symptomen**
3. PMS // MMS in kader van “natuurlijke hersenveroudering”? (*wat?)*

3. PMS // MMS bij “natuurlijke hersenveroudering”?

RESEARCH ARTICLE

Mild Motor Signs in Healthy Aging Are Associated with Lower Synaptic Density in the Brain

Margot G.A. Van Cauwenberge, MD,[1,2*] Aline Delva, MD, PhD,[2,3] Thomas Vande Casteele, MD,[1,4] Maarten Laroy, MSc,[1] Ahmed Radwan, MD, PhD,[5,6] Kristof Vansteelandt, PhD,[1] Jan Van den Stock, PhD,[1,4] Filip Bouckaert, MD, PhD,[1,4] Koen Van Laere, MD, PhD,[7,8] Louise Emsell, MD, PhD,[1,4,5] Wim Vandenberghe, MD, PhD,[2,3] and Mathieu Vandenbulcke, MD, PhD[1,4]

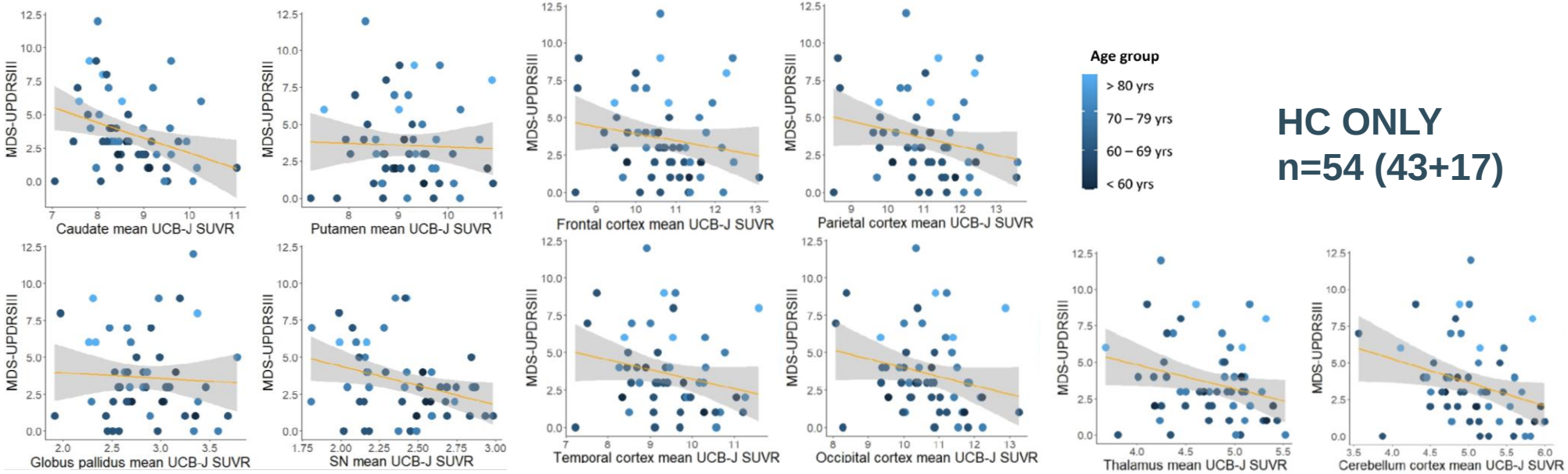
[1]*Department of Neurosciences, Neuropsychiatry, Leuven Brain Institute, KU Leuven, Leuven, Belgium*
[2]*Department of Neurology, University Hospitals Leuven, Leuven, Belgium*
[3]*Department of Neurosciences, Laboratory for Parkinson Research, Leuven Brain Institute, KU Leuven, Leuven, Belgium*
[4]*Geriatric Psychiatry, University Psychiatric Center KU Leuven, Leuven, Belgium*
[5]*Department of Imaging and Pathology, Translational MRI, KU Leuven, Leuven, Belgium*
[6]*Department of Radiology, University Hospitals Leuven, Leuven, Belgium*
[7]*Division of Nuclear Medicine, University Hospitals Leuven, Leuven, Belgium*
[8]*Department of Imaging and Pathology, Nuclear Medicine and Molecular Imaging, KU Leuven, Leuven, Belgium*

ABSTRACT: Objective: To investigate whether mild motor signs (MMS) in old age correlate with synaptic density in the brain.
Background: Normal aging is associated with a decline in movement quality and quantity, commonly termed “mild parkinsonian signs” or more recently MMS. Whether MMS stem from global brain aging or pathology within motor circuits remains unresolved. The synaptic vesicle glycoprotein 2A positron emission tomography (PET) ligand ^{11}C-UCB-J allows the investigation of brain-motor associations at the synaptic level in vivo.
Method: Fifty-eight healthy older adults (≥50 years) were included from two monocentric control cohorts. Brain magnetic resonance imaging and ^{11}C-UCB-J PET data were available in 54 participants. ^{11}C-UCB-J PET binding was quantified by standardized uptake value ratio (SUVR) values in grey matter (GM) volumes of interest (VOIs): caudate, putamen, globus pallidus, substantia nigra, thalamus, cerebellum, and the frontal, parietal, temporal, and occipital cortex. Multiple linear regression analyses were performed with Movement Disorder Society-Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) part III score measuring MMS as the dependent variable and mean SUVR values in each VOI as the independent variable with age, Fazekas score (white matter lesion [WML] load), VOI and cohort as covariates.
Results: Participants (68 ± 7.5 years; 52% female) had an average MDS-UPDRS part III score of 3.3 ± 2.8. The MDS-UPDRS part III score was inversely associated with synaptic density, independently of WML load or GM volume, in the caudate, substantia nigra, thalamus, cerebellum, and parietal, occipital, temporal cortex. Cohen’s f^2 showed moderate effect sizes for subcortical (range, 0.30–0.35), cortical (0.28–0.35) and cerebellar VOIs (0.31).
Conclusion: MMS in healthy aging are associated with lower synaptic density throughout the brain. © 2023 International Parkinson and Movement Disorder Society.

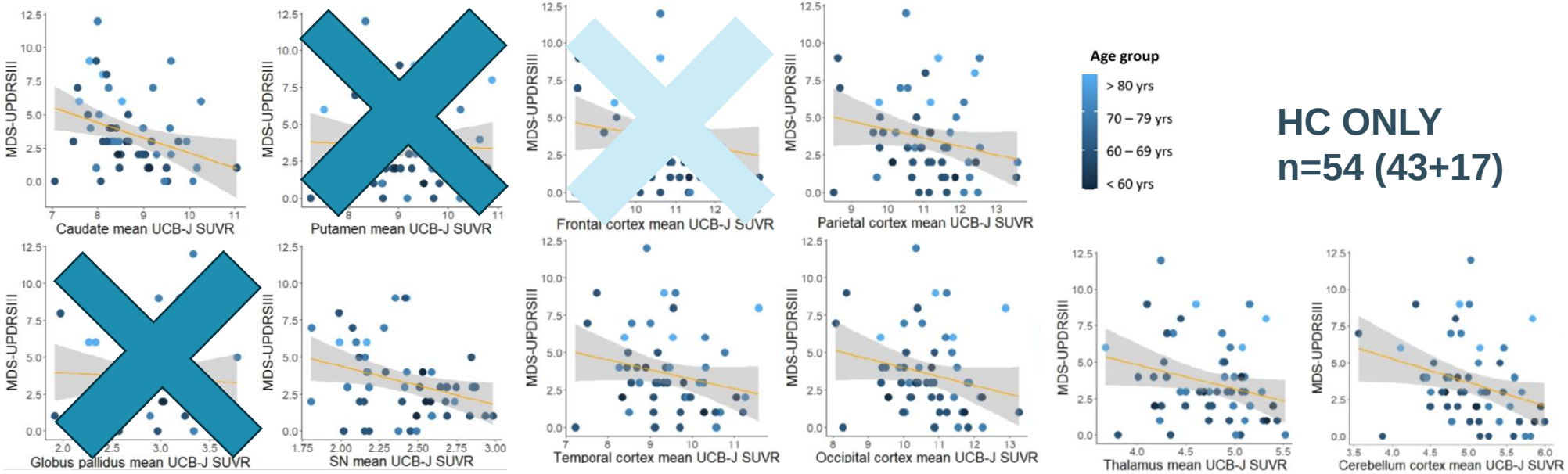
Key Words: mild parkinsonian signs; MRI; PET; synaptic density; aging

Conclusie:
MMS in gezonde ouderen (>50 jaar, n=54) zijn geassocieerd met veralgemeende corticale en subcorticale verminderde synaptische densiteit

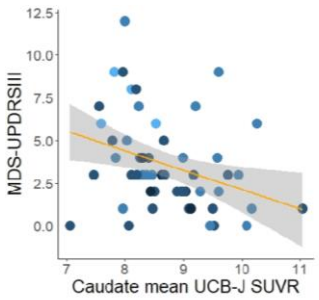
onafhankelijk van GMV
onafhankelijk van WML

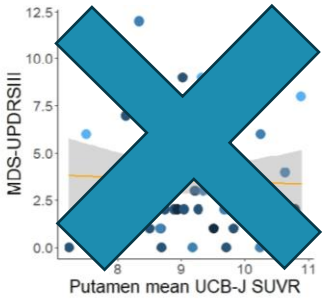


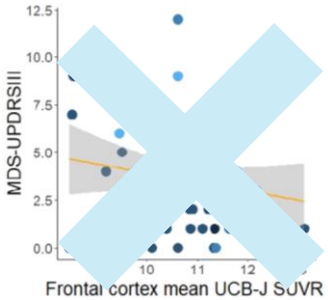
HC ONLY
n=54 (43+17)

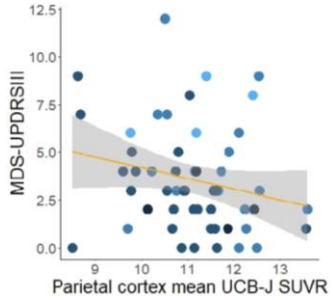


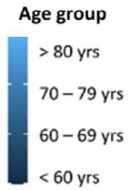
HC ONLY
n=54 (43+17)



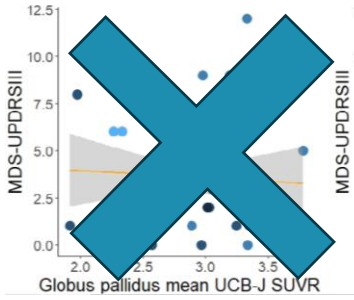


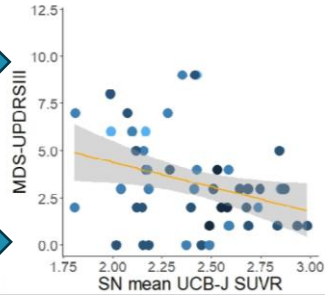


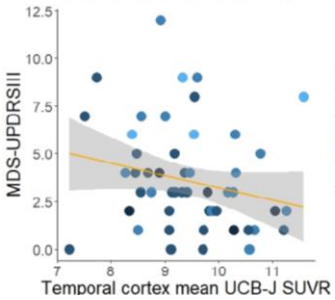


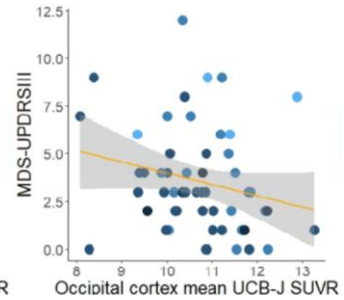


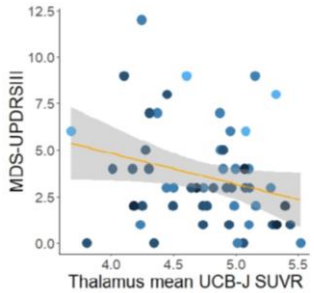
HC ONLY
n=54 (43+17)

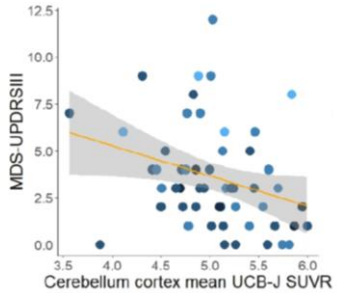


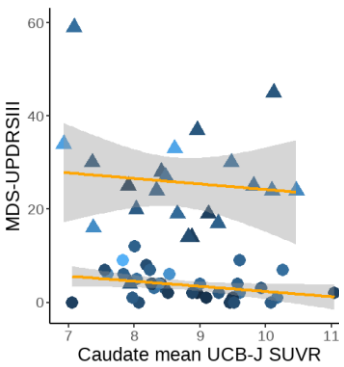


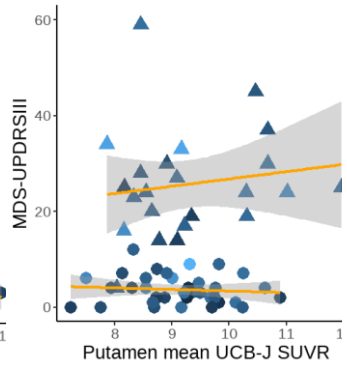


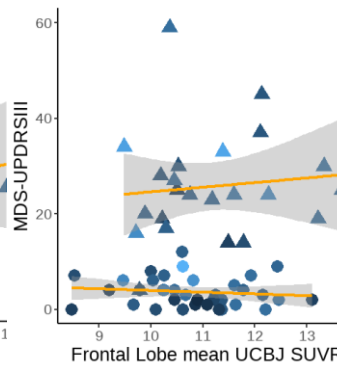


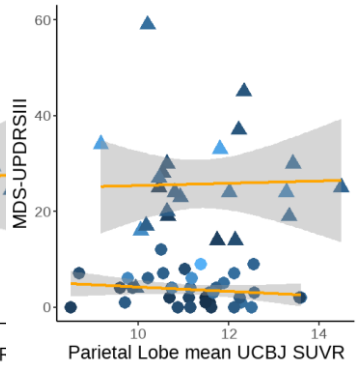




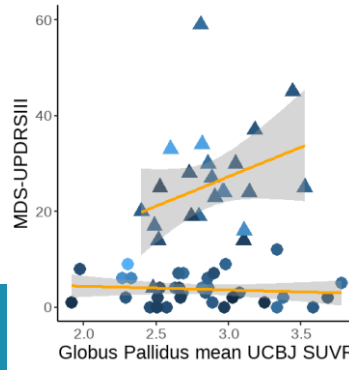


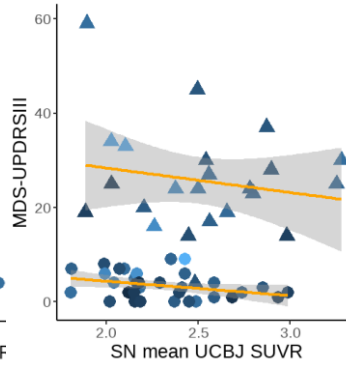


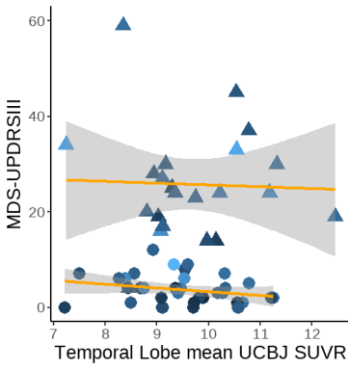


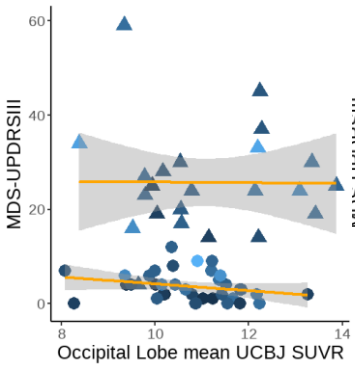


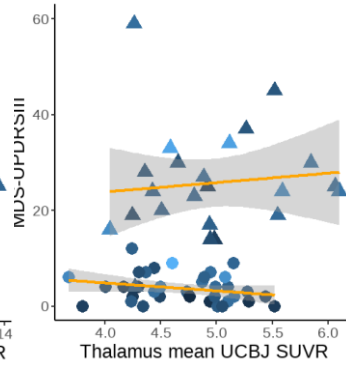
HC + LLD
n= 76 (43+33)

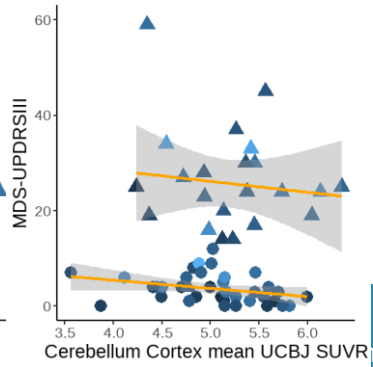


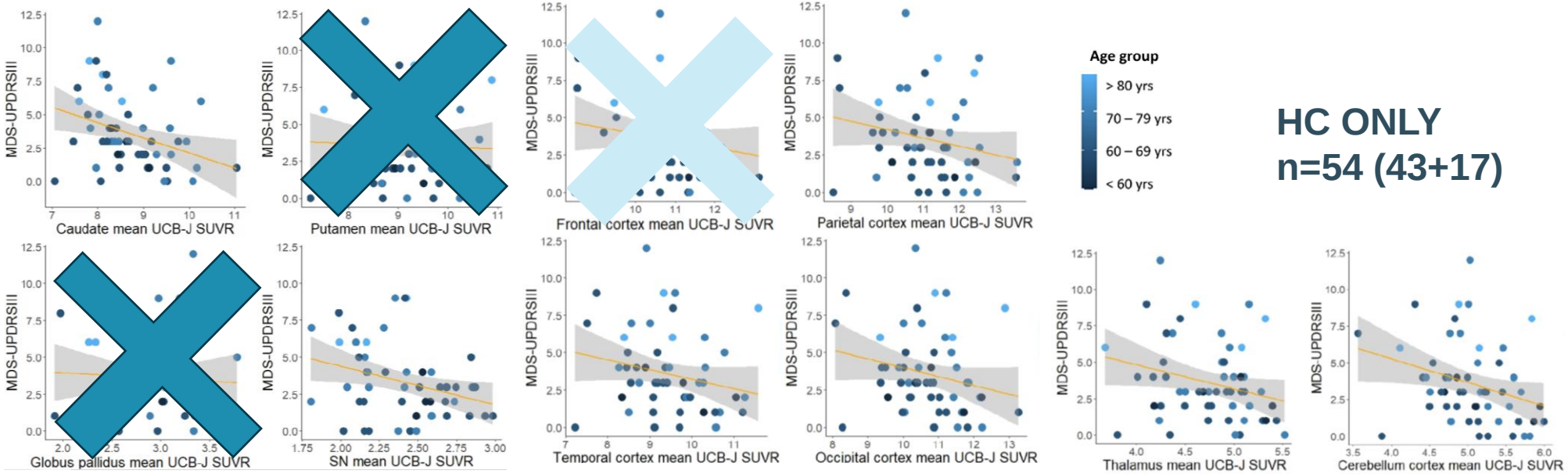




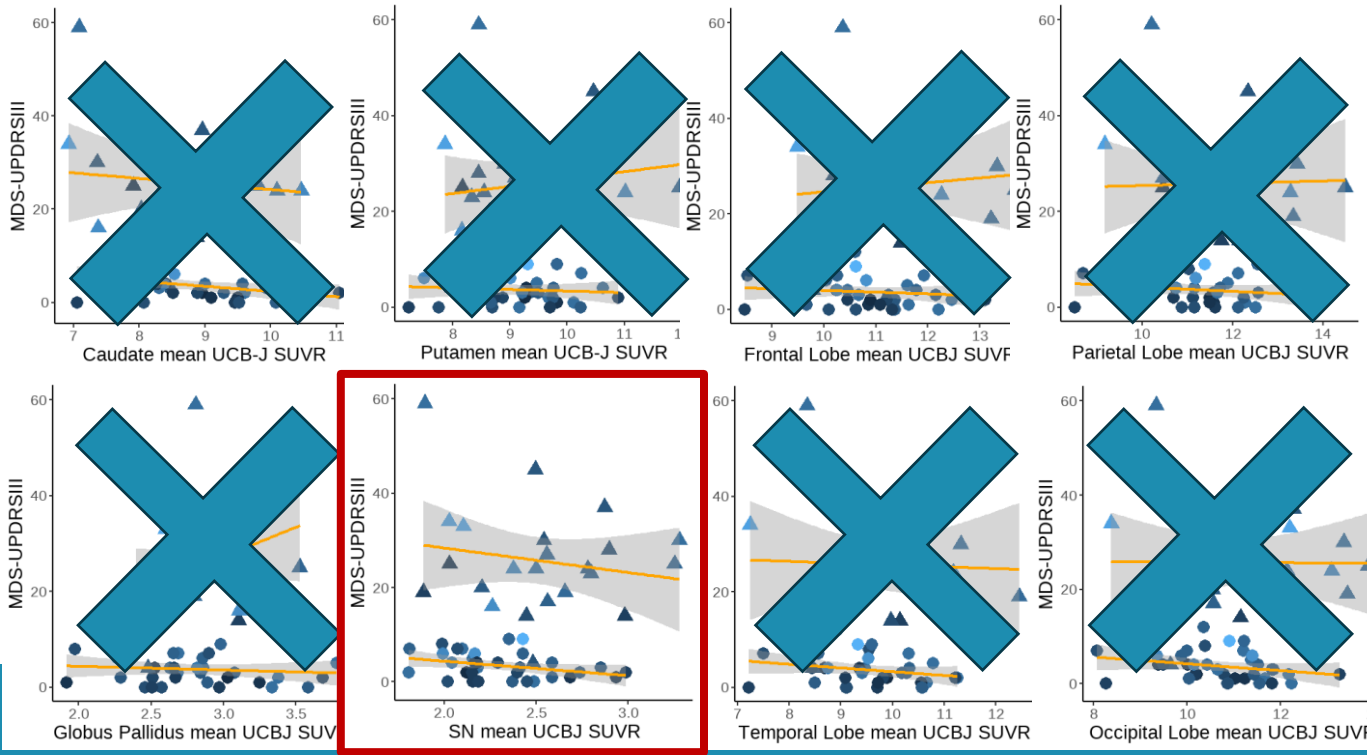








HC ONLY
n=54 (43+17)



HC + LLD
n= 76 (43+33)

Conclusie

1. PMS ~ alle motore domeinen en cortico-subcorticale modaliteiten
2. PMS ≠ antipsychotica of stemming/motivatie/cognitieve symptomen
3. PMS <-> MMS ~ wijdverspreide verminderde syn. densiteit in HC
4. PMS ~ verminderde synaptische densiteit in substantia nigra
5. Limitaties: sample size, WML quantificatie
6. Toekomst: neuropathologische veranderingen?

Resting state functional brain changes in late life depression

CROSS-SECTIONAL

HC

Non - ECT

L3D

LLD

ECT

LONGITUDINAL

KLINISCHE TESTING

PSY

NEU

COG

ESM

MRI BEELDVORMING

T1

T2

FLAIR

fMRI

PET BEELDVORMING

TAU

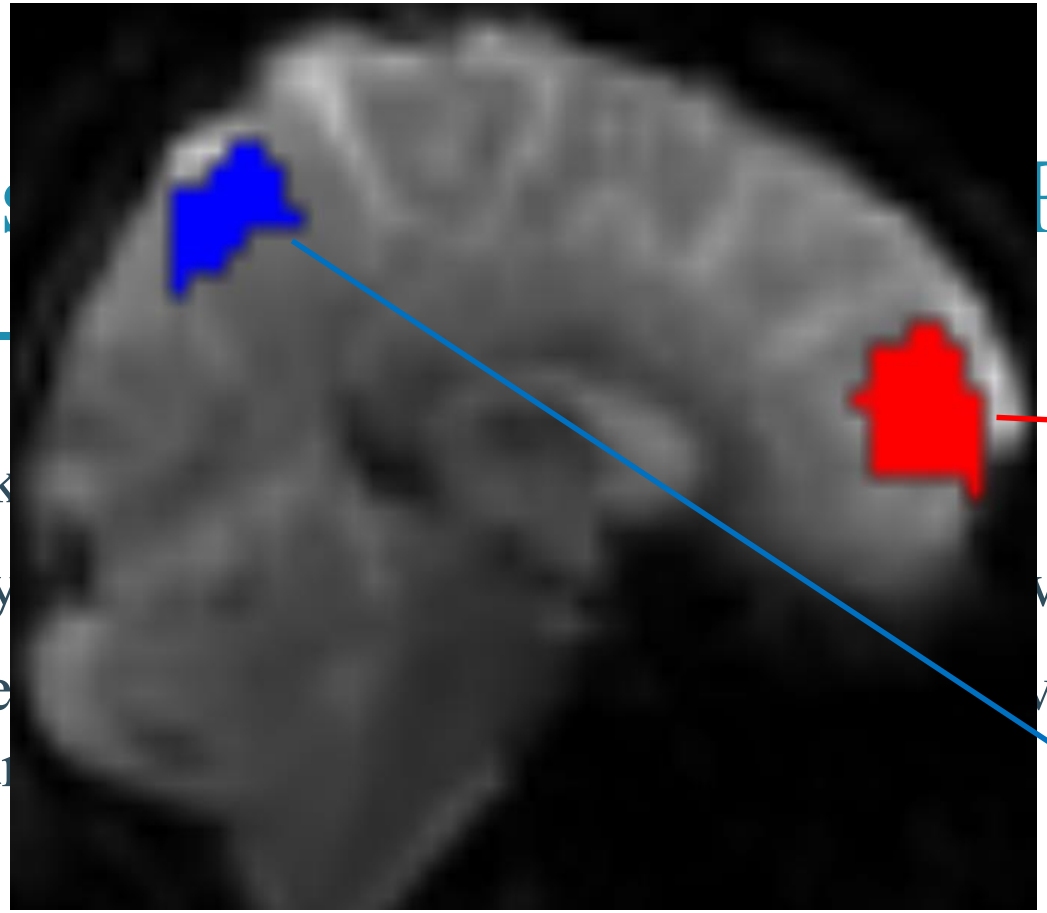
Aβ

Synaptische densiteit

Res RI (rs-

Task

- Ey vake
- Fe ve fu



Functional Connectivity (FC)

- Synchronization of time courses between two brain regions

resting-state fMRI (rs-fMRI): a popular approach for Psychiatric Research

Well-investigated rs-fMRI findings in specific regions:

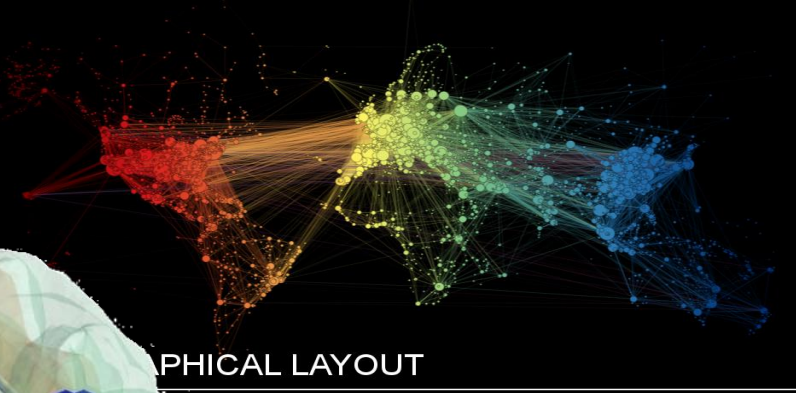
- FC, ReHo, ALFF, … etc
- Across various psychiatric disorders

Shifted Attention to Network-Level Analysis – Graph Theory

- The Global and Nodal levels
- Functional Segregation, Functional Integration, Hub Identification

TRANSPORTATION CLUSTERS

3.200 airports
60.000 routes



PHICAL LAYOUT

Color = Longitude
Size = Number of routes

Alaska

Canada

NORTH AMERICA

LATIN AMERICA

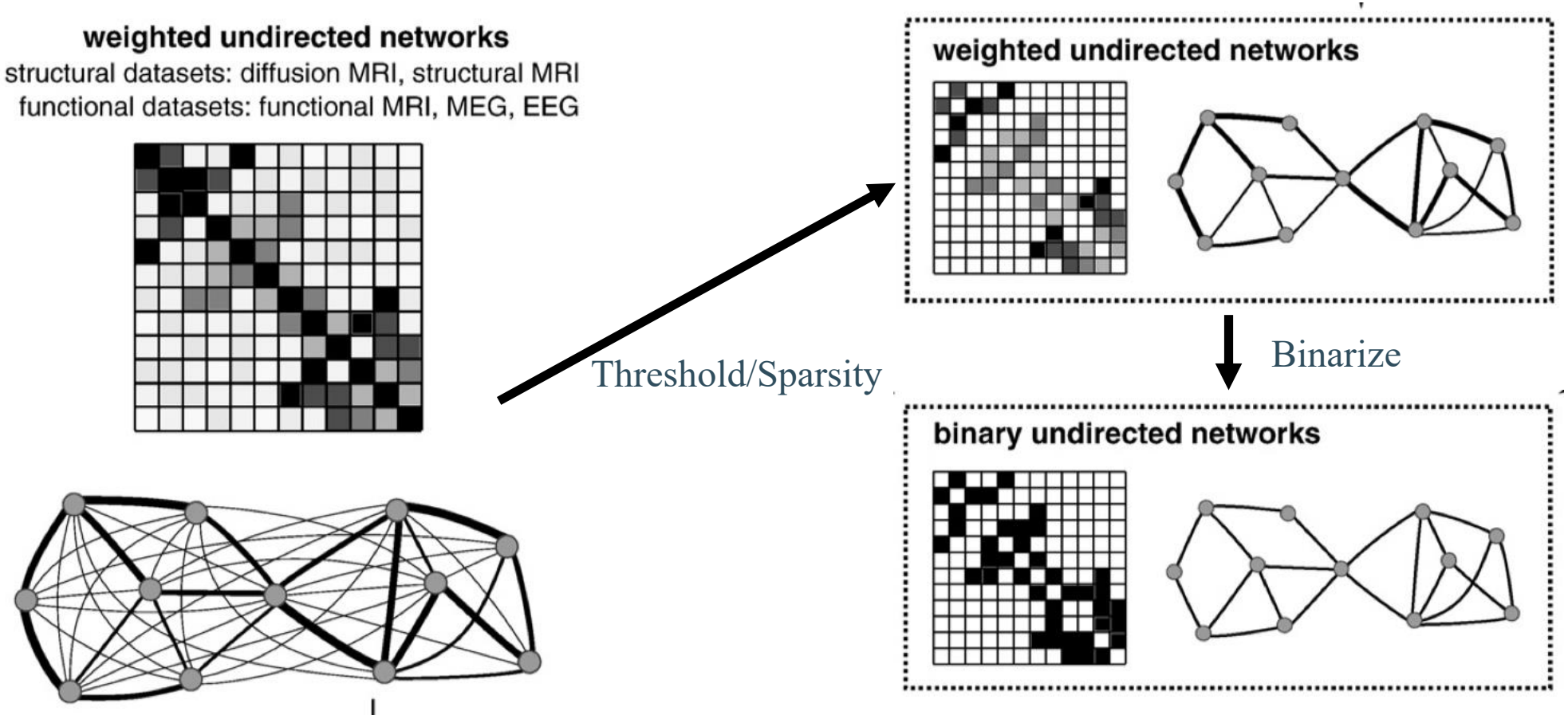
Pacific isla

ASIA

OCEANIA

Data: openflights.org

Network Construction



(Rubinov and Sporns, 2010)

Global Topological Properties

Functional Segregation:

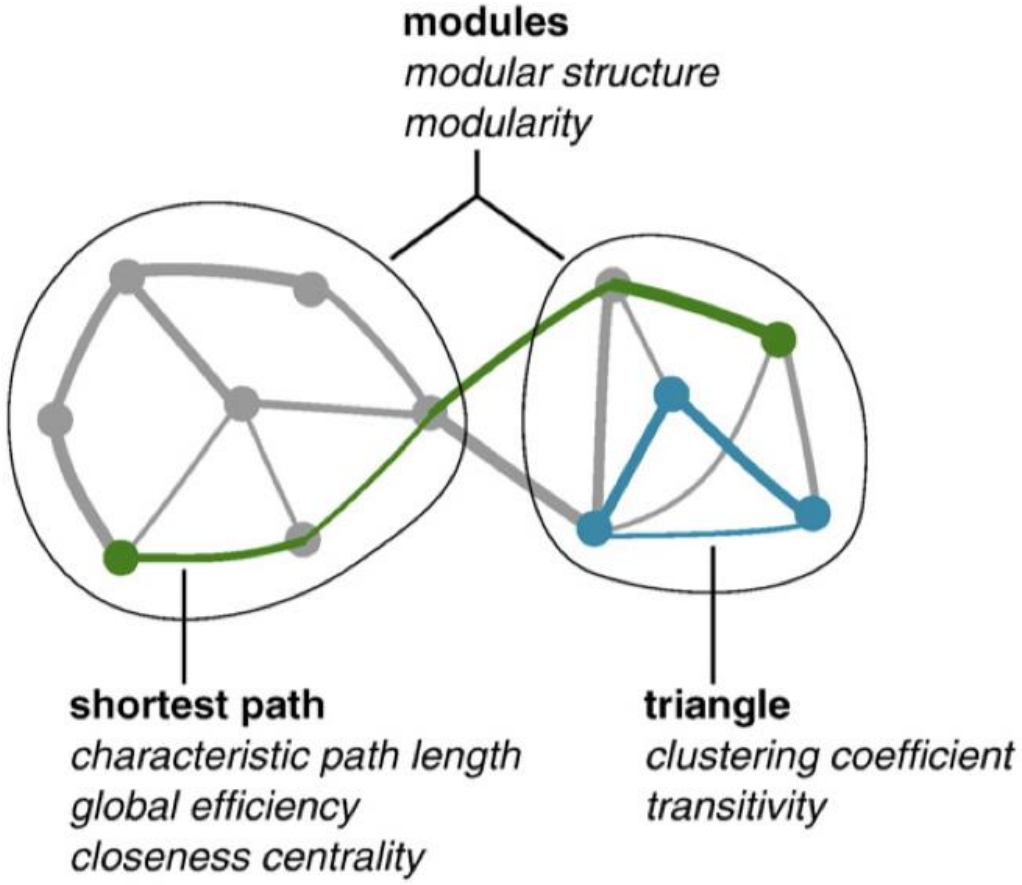
- Clustering Coefficient (CC)

Functional Integration:

- Characteristic Path Length (Lp)

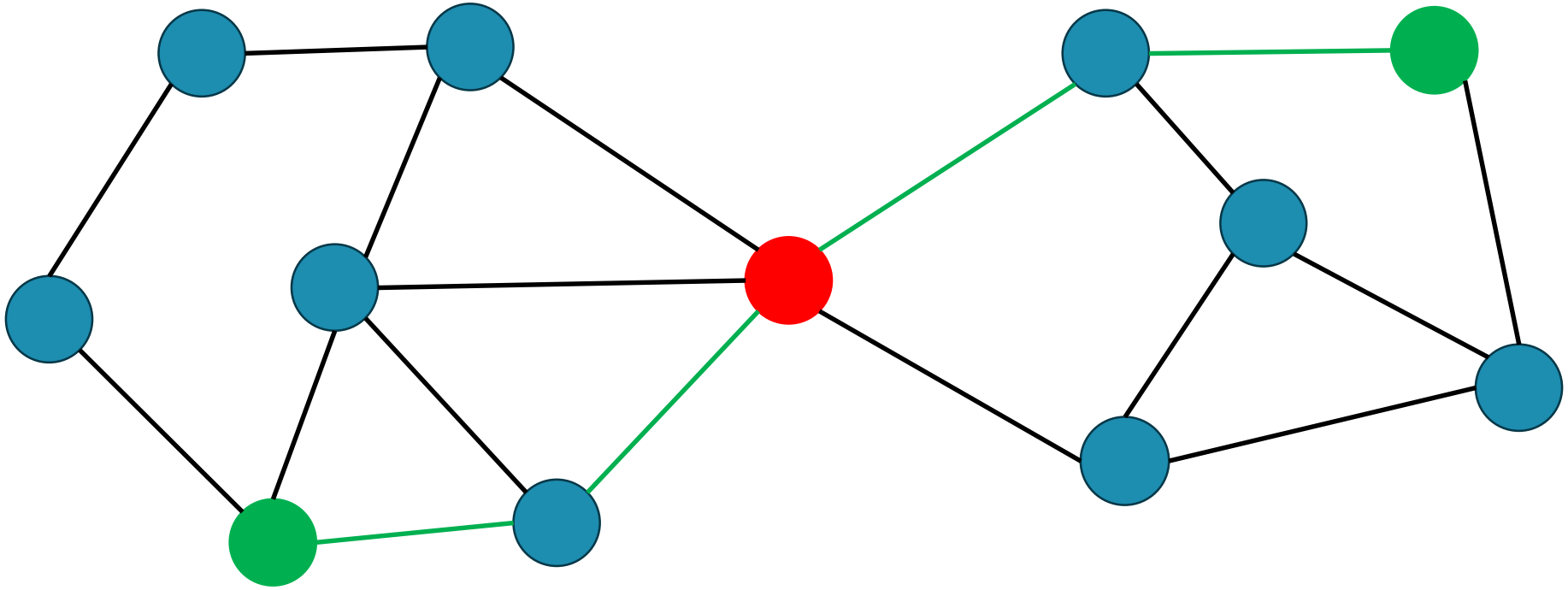
Small-Worldness (σ)

- The balance of CC and Lp



Hub Identification – Betweenness Centrality (BC)

- The extent of shortest paths between all node pairs in the network that pass through a given index node



Gaps in previous studies applying Graph Theory-based approach to LLD patients:

Rare Utilization of Weighted Networks

Exclusion of the Cerebellum from Network Construction

Corresponding changes in Synaptic Density (SD)?

- The association between regional SD and rs-fMRI activities in healthy young adults and depressive patients (Holmes et al., 2019; Fang et al., 2023)

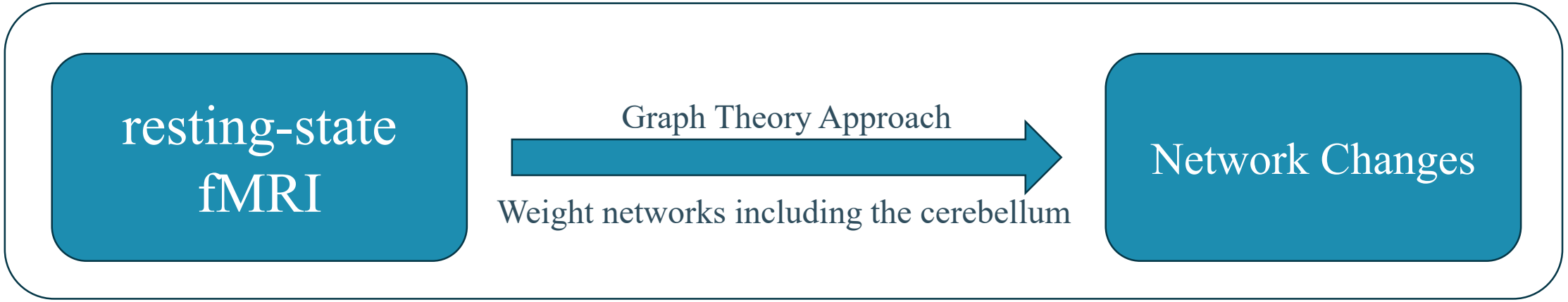
- Unclear relationship between SD and rs-fMRI topological properties in LLD patients

Hypothesis 1: rs-fMRI network changes in LLD patient

rs-fMRI

- Network changes in LLD patients

- Weighted Networks
- Include the cerebrum and cerebellum
- At the global and nodal levels

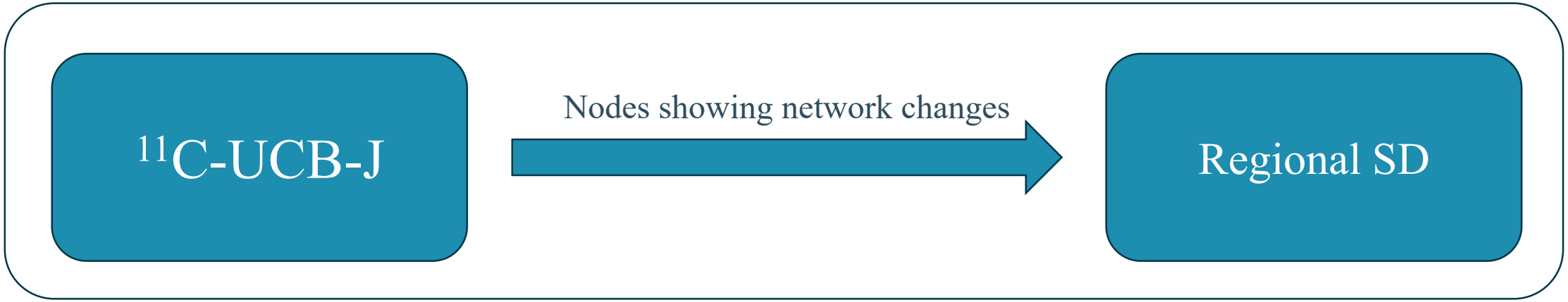


Hypothesis 2: Corresponding changes in regional SD

rs-fMRI

- Network changes in LLD patients

- Weighted Networks
- Include the cerebrum and cerebellum
- At the global and nodal levels



11C-UCB-J

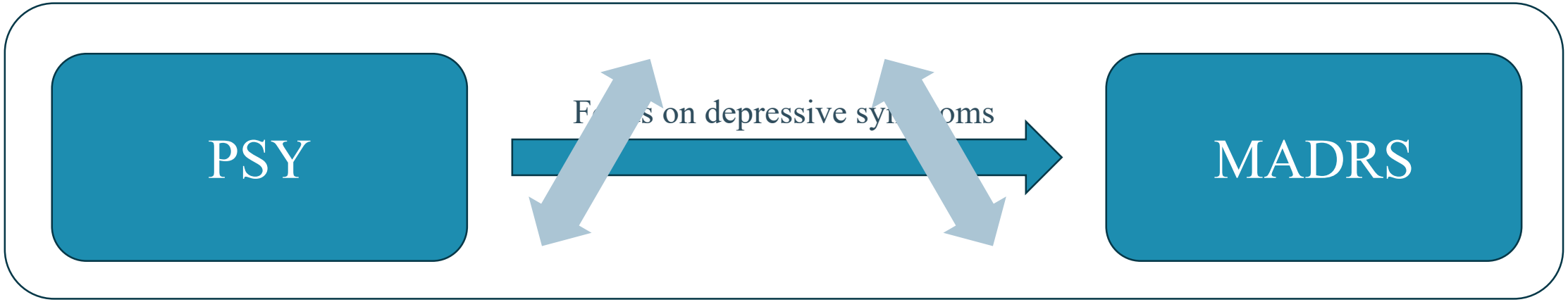
- Regional Synaptic Density (SD) changes

Hypothesis 3: Relationships among SD, BC, and Depression

rs-fMRI

- Network changes in LLD patients

- Weighted Networks
- Include the cerebrum and cerebellum
- At the global and nodal levels



11C-UCB-J

- Regional Synaptic Density (SD) changes

PSY

- Depressive symptoms (MADRS)

	HC (n = 33)	LLD (n = 18)	Group Comparison
Age (Year)	70.48 ± 6.37	71.39 ± 5.77	t = -0.515, p = 0.61
Sex (female/male)	20/13	13/5	x^2 = 0.274, p = 0.601
MMSE	29.09 ± 0.98	26.44 ± 2.99	t = 3.645, p = 0.002**
MADRS	0.88 ± 1.71	26 ± 11.34	t = -9.337, p < 0.001***

Weighted Networks including the cerebrum and cerebellum

272 nodes/ROIs:

- 246 cerebral ROIs from the Brainnetome Atlas
- 26 cerebellar ROIs from the AAL3 Atlas

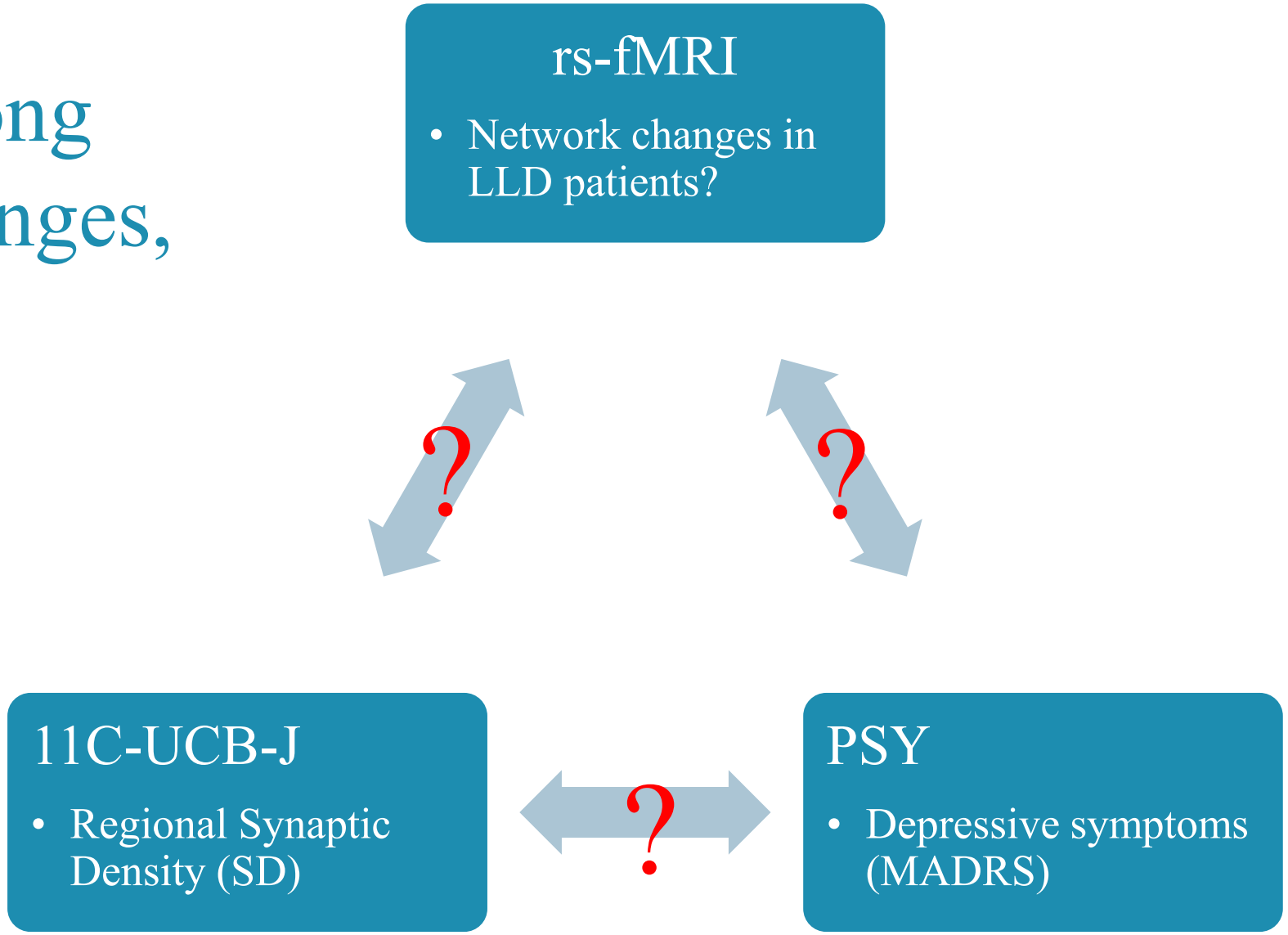
7 sparsity/threshold levels: 10%-40% with steps of 5%

Non-Parametric Permutation Tests with 5000 iterations

The associations among rs-fMRI network changes, Regional SD, and depressive symptoms

Spearman Correlation

- Covariates: age, gender



Criteria for robust results

1. The selected threshold: $p < 0.01$**
   - Network change (BC)
   - Spearman correlations among SD, BC, and MADRS

2. Significant at least 2 continuous sparsity levels

Altered BC & Preserved Global Organization

rs-fMRI

- Network changes in LLD patients?

- Weighted Networks?
- Include the cerebrum and cerebellum
- At the global and nodal levels

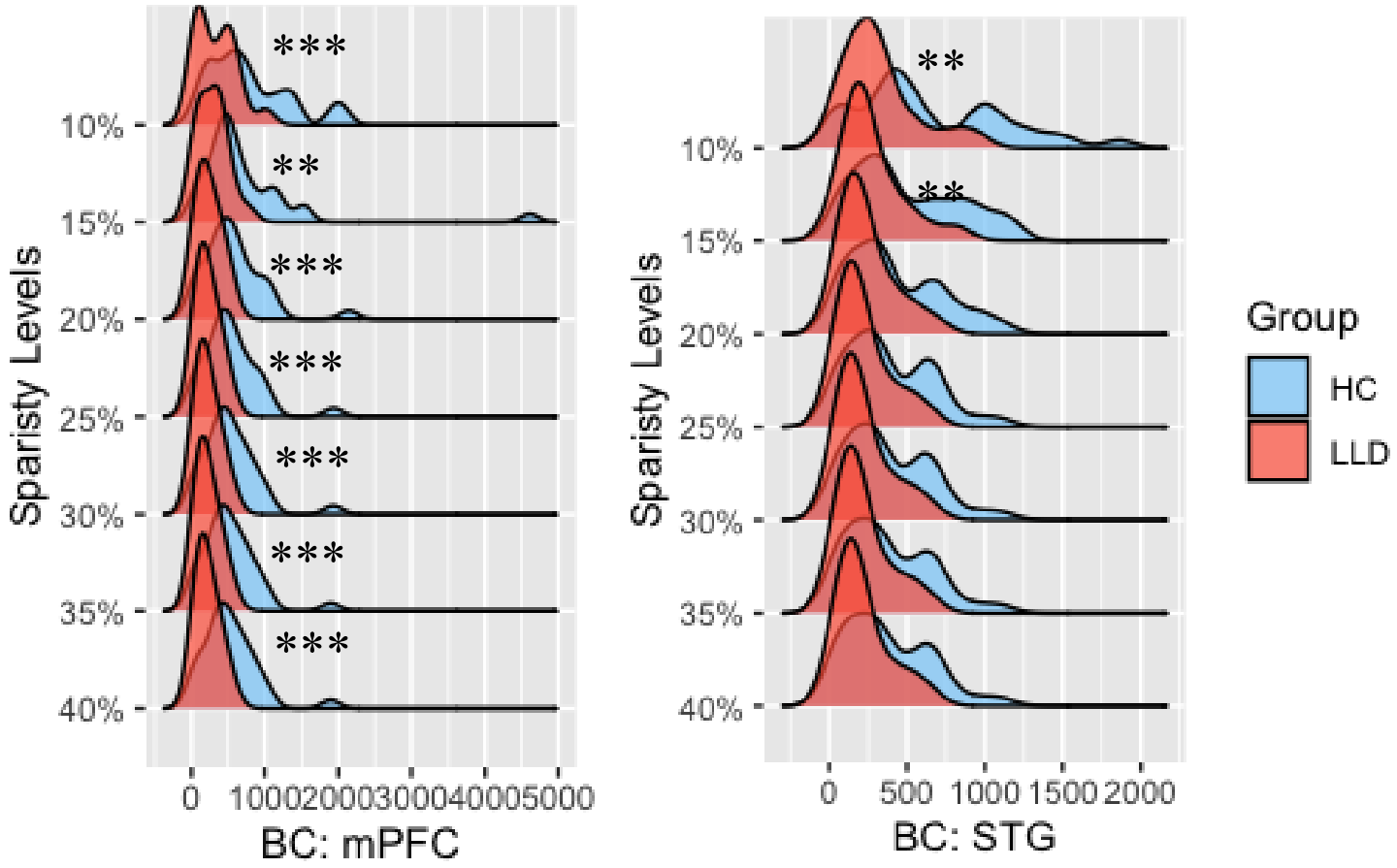
11C-UCB-J

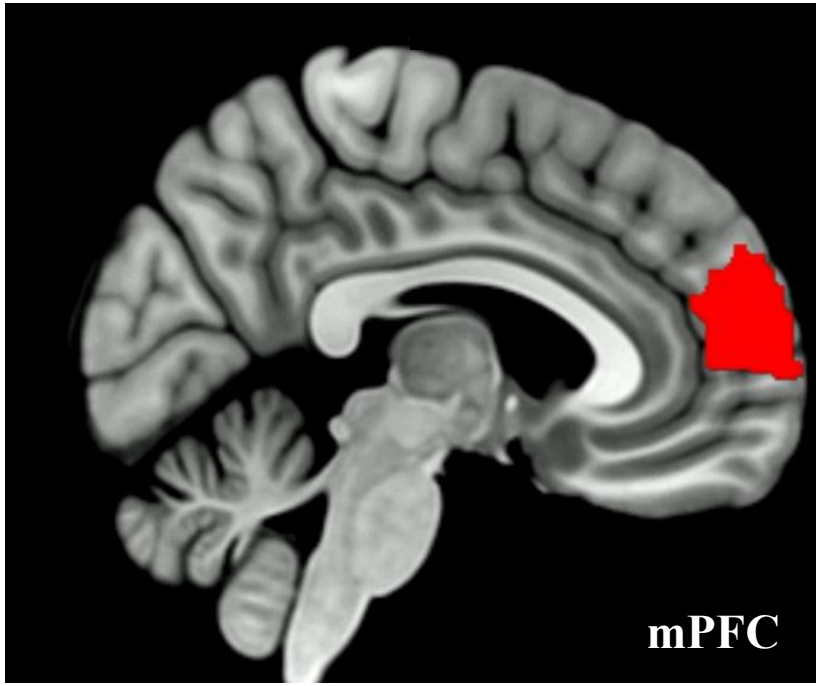
- Regional Synaptic Density (SD)

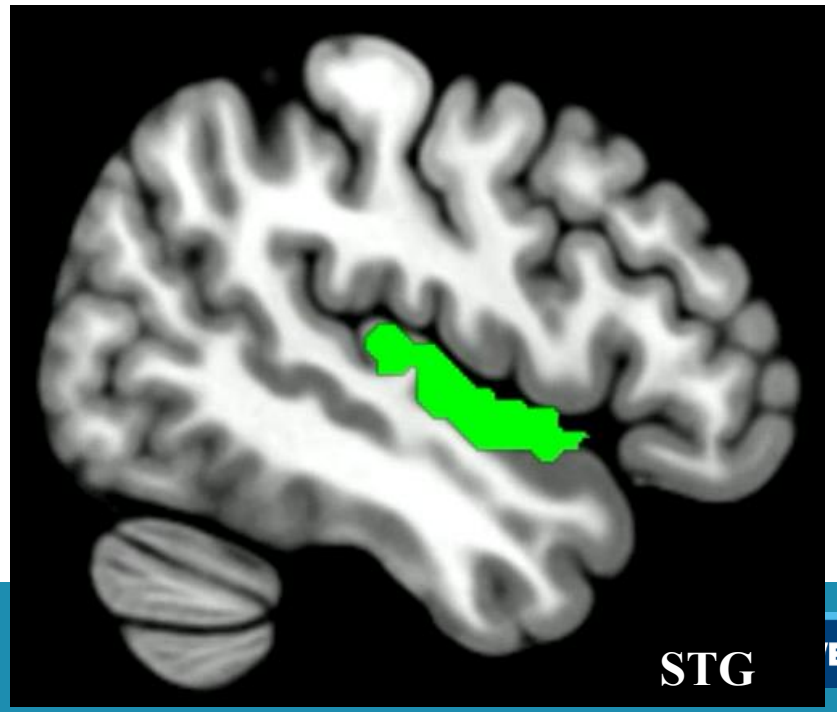
PSY

- Depressive symptoms (MADRS)

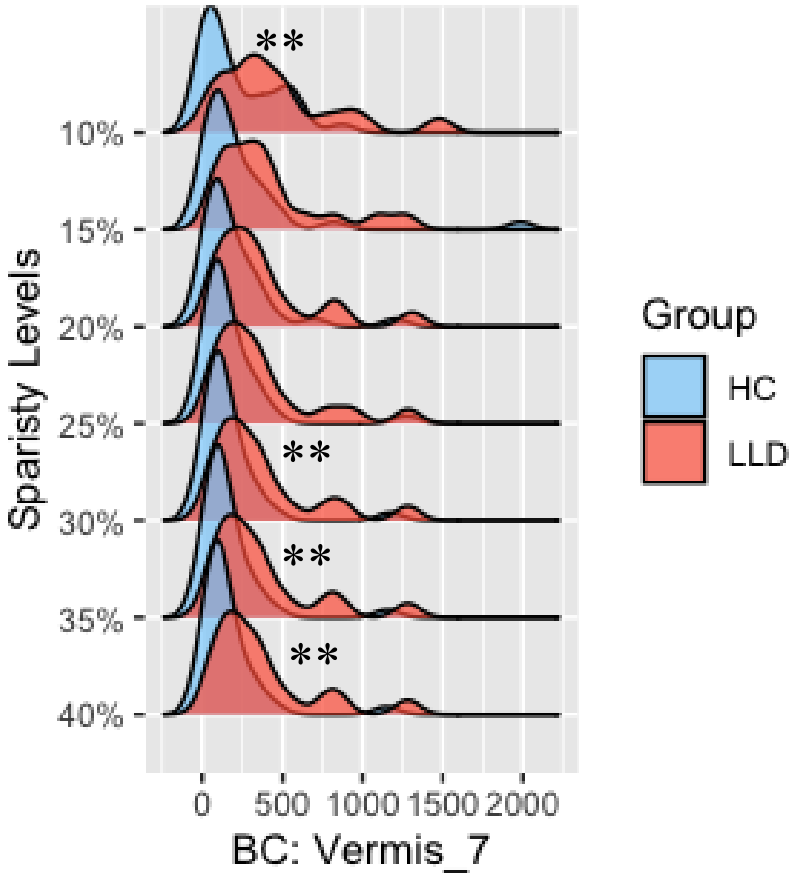
Decreased BC were found in the mPFC and left STG

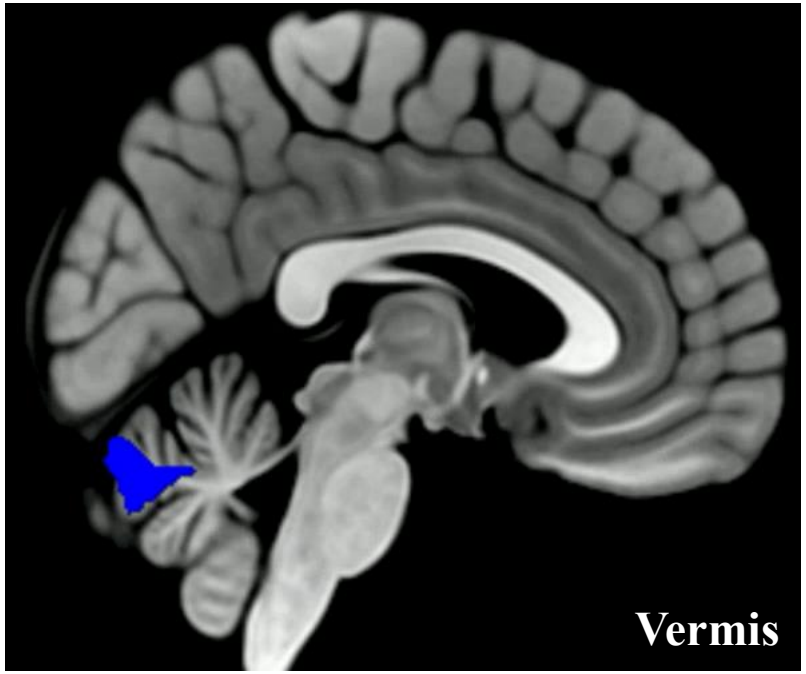


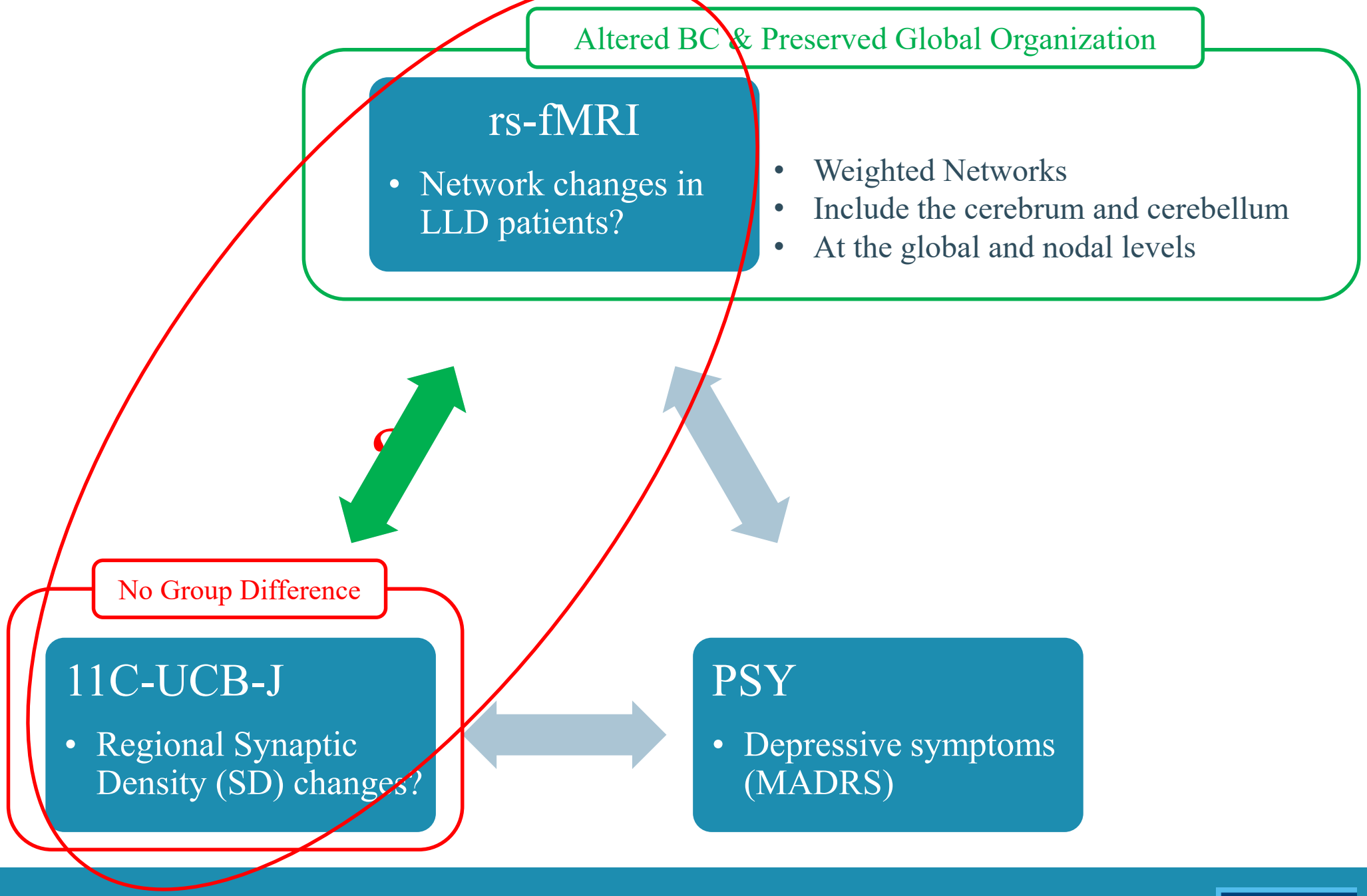




Increased BC was found in the Vermis






Altered BC & Preserved Global Organization
rs-fMRI
• Network changes in LLD patients?
• Weighted Networks
• Include the cerebrum and cerebellum
• At the global and nodal levels
?
No Group Difference
11C-UCB-J
• Regional Synaptic Density (SD) changes?
PSY
• Depressive symptoms (MADRS)

No group difference in regional SD, but correlations between regional SD and BC

No group difference in nodes showing network changes:

- Decreased BC: the mPFC, left STG
- Increased BC: the Vermis

Positive Correlations between regional SD and BC in a cerebellar region across 3 sparsity levels

SD	TP		10%	15%	20%	25%	30%	35%	40%
Vermis_7	BC_117[a]	r	*0.227*				0.761	0.761	0.761
		p	*0.479*				**0.007****	**0.007****	**0.007****

Altered BC & Preserved Global Organization

rs-fMRI

- Network changes in LLD patients

- Weighted Networks
- Include the cerebrum and cerebellum
- At the global and nodal levels

No Group Difference

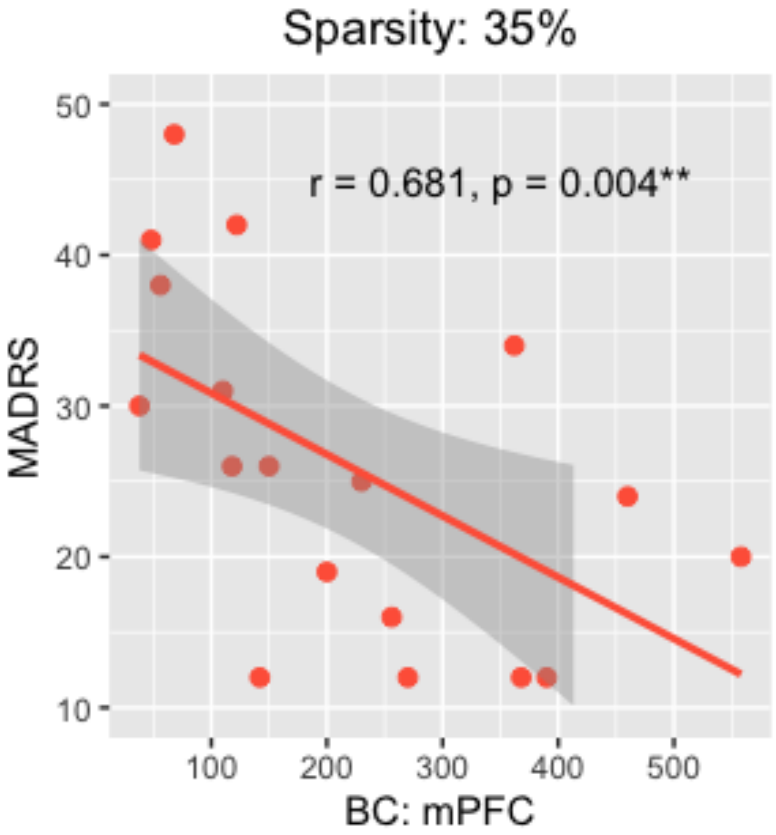
11C-UCB-J

- Regional Synaptic Density (SD)

PSY

- Depressive symptoms (MADRS)

Depressive symptoms are reliably correlated with BC_{mPFC}, but not regional SD



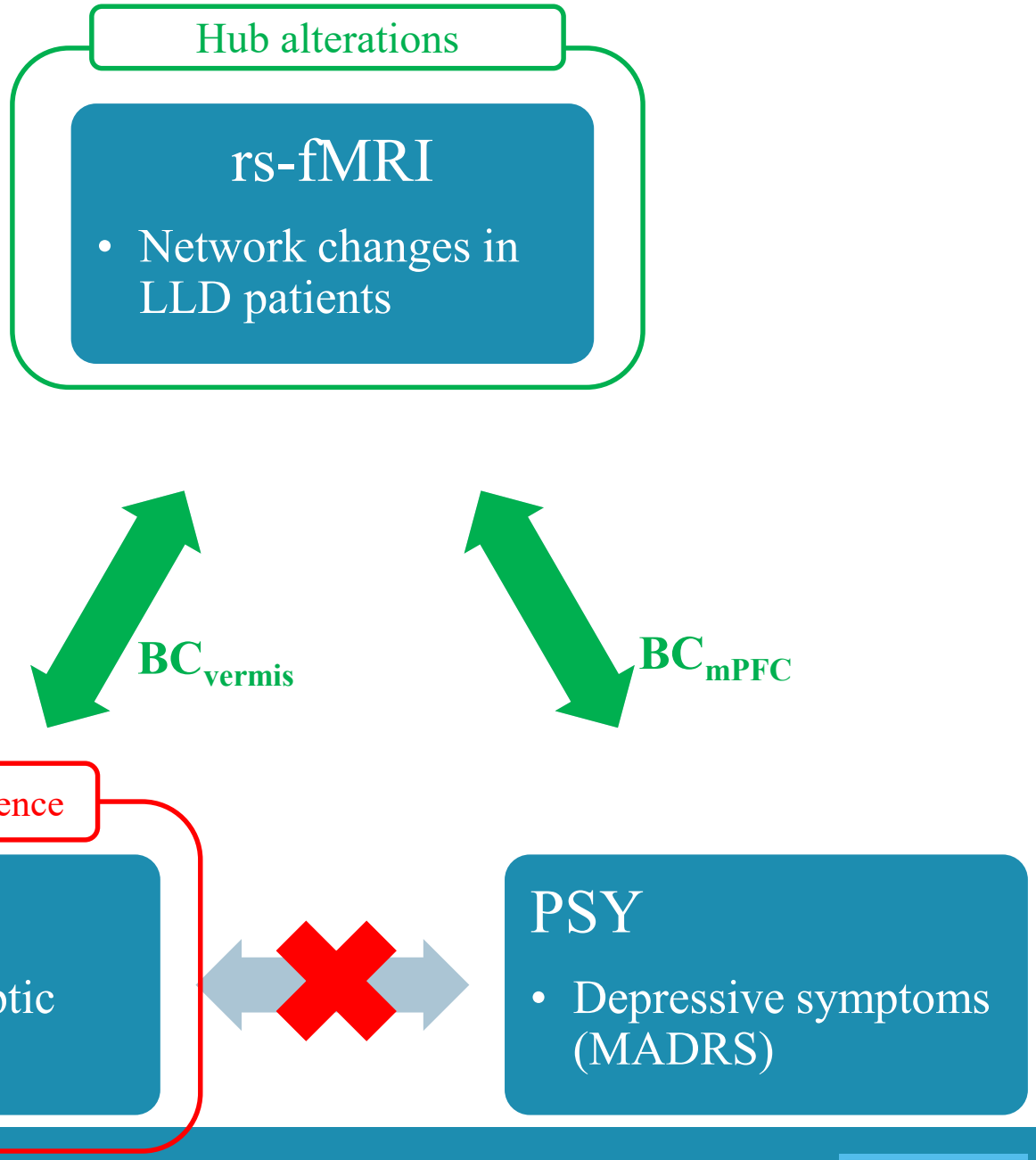
Index	Direction	Label	Score	sig.	10%	15%	20%	25%	30%	35%	40%
BC	Worse	mPFC	MADRS	r	-0.644	-0.572	-0.707	-0.704	-0.681	-0.681	-0.681
				p	**0.007****	**0.02***	**0.002****	**0.002****	**0.004****	**0.004****	**0.004****

Main findings in LLD patients

1. Significant Hub changes in LLD patients

2. Regional SD is correlated to hub changes

3. Robust correlations between BC_{mPFC} and Depressive Symptoms



Conclusion

1. Significant Hub changes in LLD patients

2. Regional SD is correlated to hub changes

3. Robust correlations between BC_{mPFC} and Depressive Symptoms

The Pivotal Role of the mPFC in LLD

The Potential Involvement of the Cerebellum

The Potential Sensitivity of SD for Hub Changes

Synaptische plasticiteit: Een zoektocht naar het mechanisme achter ECT

CROSS-SECTIONAL

HC

Non - ECT

L3D

LLD

ECT

LONGITUDINAL

KLINISCHE TESTING

PSY

NEU

COG

ESM

MRI BEELDVORMING

T1

T2

FLAIR

fMRI

PET BEELDVORMING

TAU

Aβ

Synaptische densiteit

Geschiedenis & Evolutie van ECT

- 1934: Ladislas Meduna (camphor)
- 1938: Ugo Cerletti & Lucio Bini
- 1944: Brief pulse
- 1952: modified ECT (anesthesie)
- 1976: FDA goedkeuring voor MDD

Hoy & Fitzgerald, 2010

ECT & Depressie

Level A: Definite Evidence*

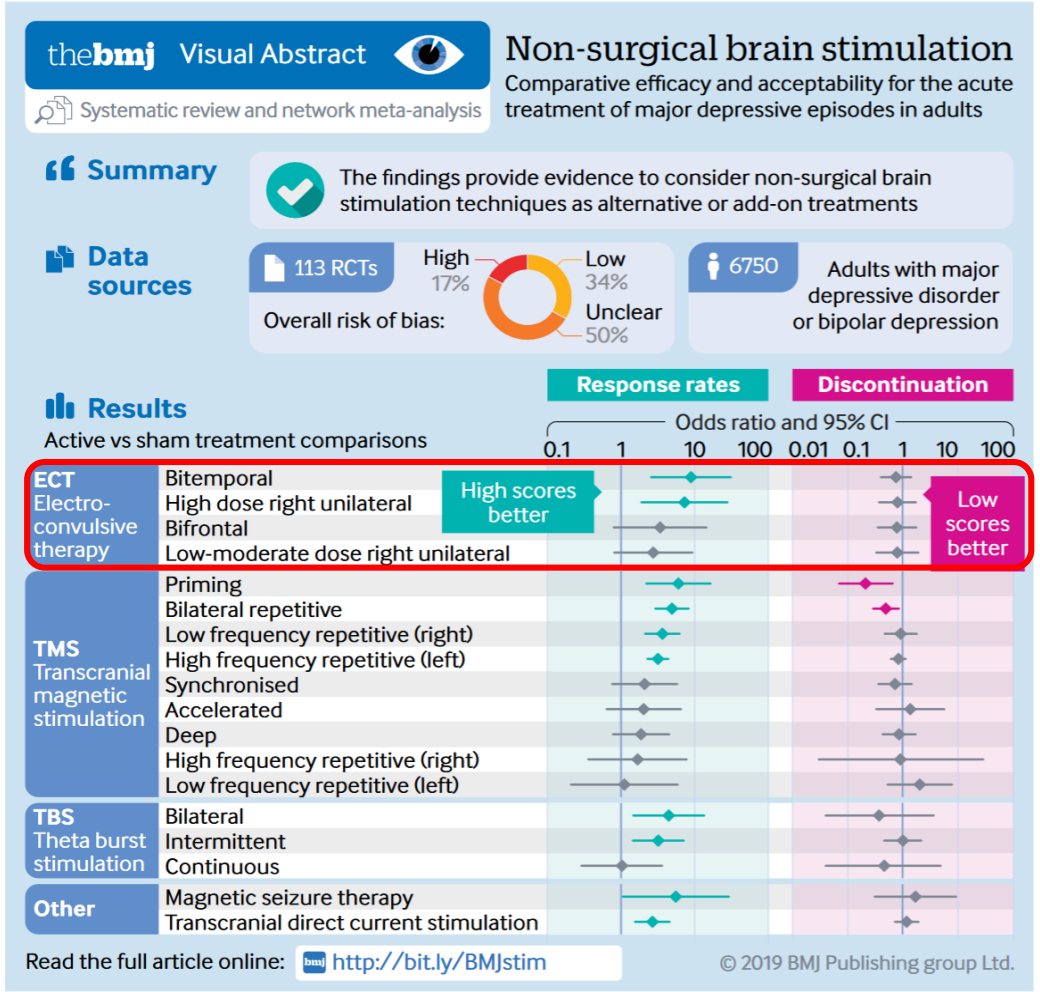
- Acute suicidalieit
- MDD met psychotische kenmerken
- Therapie resistente depressie

Predictors of Response**

- Ernst van de depressie
- Leeftijd
- Psychotische kenmerken

Predictors of Remission**

- Leeftijd
- Psychotische kenmerken

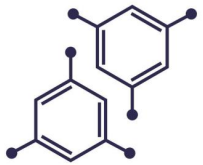


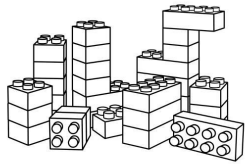
Mutz et al., 2019

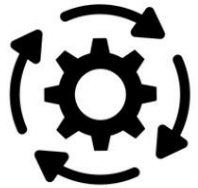
*Kennedy et al. 2009 J Affect Disord (CANMAT)
**Van Diermen et al. Br J Psychiatry

Neurobiologie van ECT

Moleculair	Structureel	Functioneel
Gene Expression Protein Synthesis ...	Neurogenesis Synaptogenesis ...	Long term potentiation Functional connectivity ...



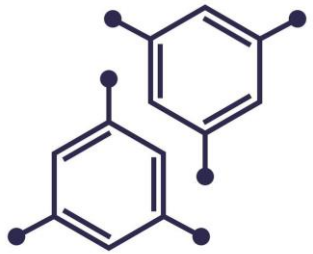




Neurobiologie van ECT

Gene expression
Protein Synthesis
...

Moleculair

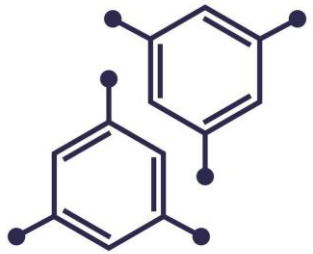


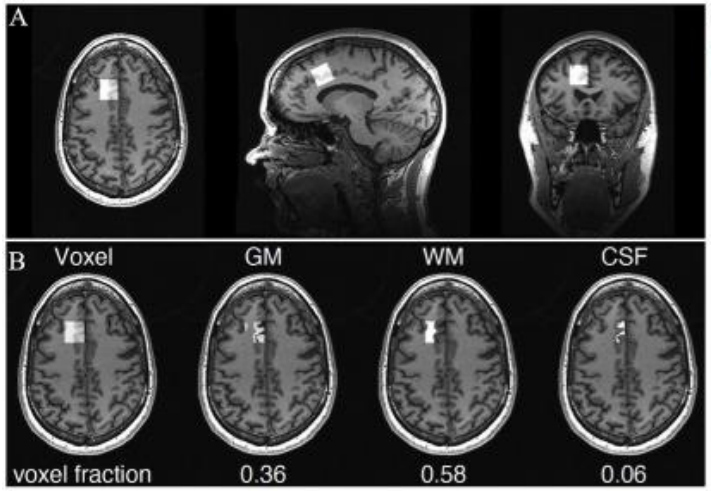
- Neurotrophic Factors
- Cytokines
- Hormones
- Metabolites
- Neurotransmitters
- Enzymes
- Others

Neurobiologie van ECT

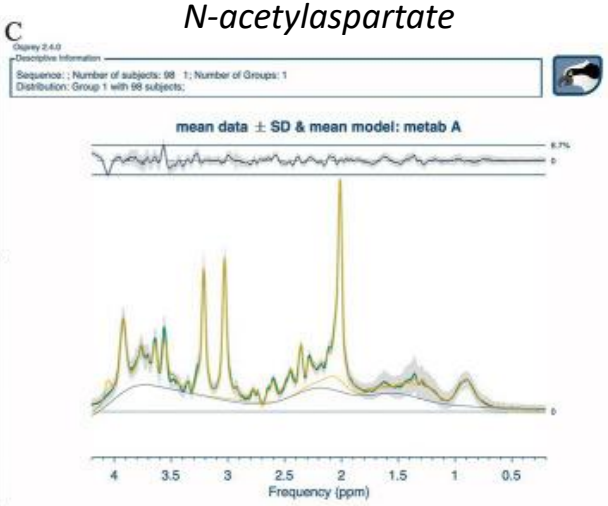
Gene expression
Protein Synthesis
...

Moleculair





N-acetylaspartate



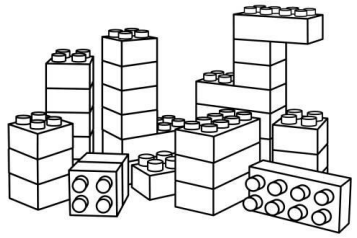
Erchinger et al. 2023

Neurobiologie van ECT

Grijze stof

...

Structureel



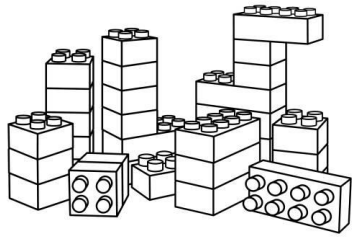
- Grey Matter Volume
- Cortical Thickness
- Morphology, shape & gyrification
- White Matter
- Perfussion Effects
- Edema
- Other

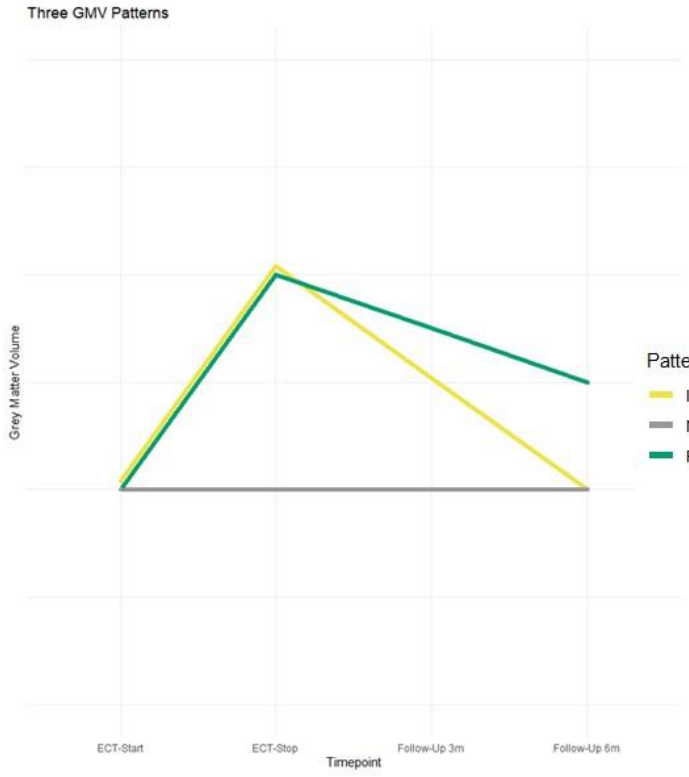
Neurobiologie van ECT

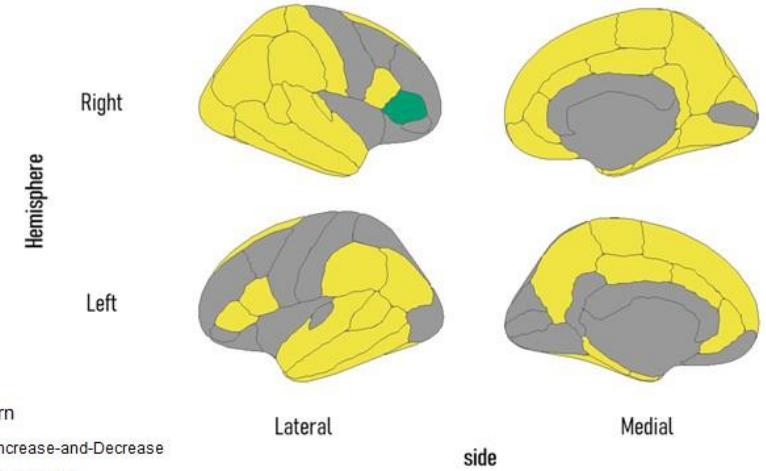
Grijze stof

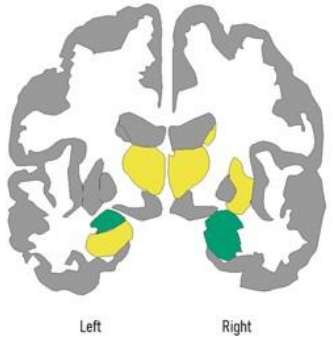
...

Structureel



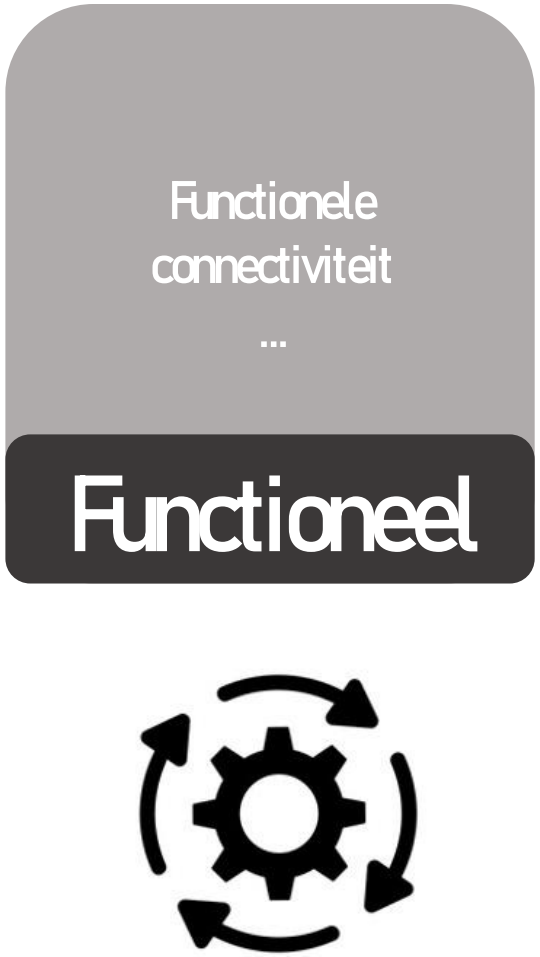






Laroy et al. (in prep)

Neurobiologie van ECT



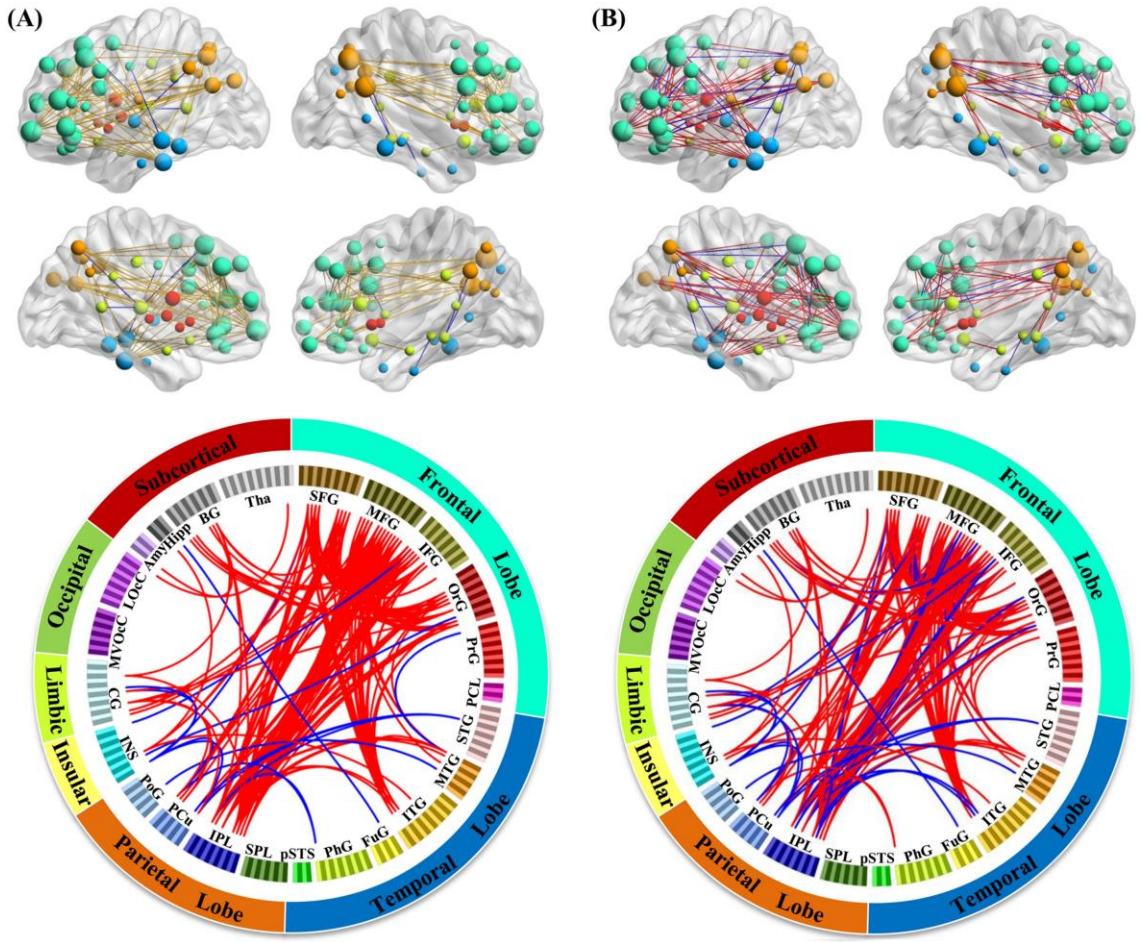
- Functional Connectivity
- (f)ALFF
- Task-based fMRI
- Graph Theory
- Cortical excitability
- Graph Theory

Neurobiologie van ECT

Functionele connectiviteit

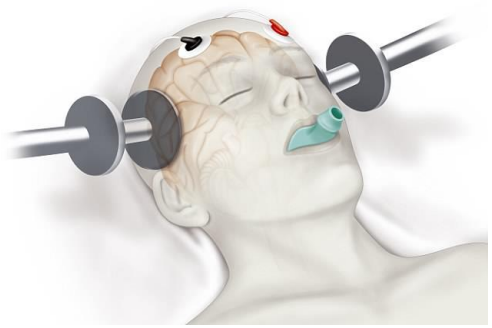
...

Functioneel



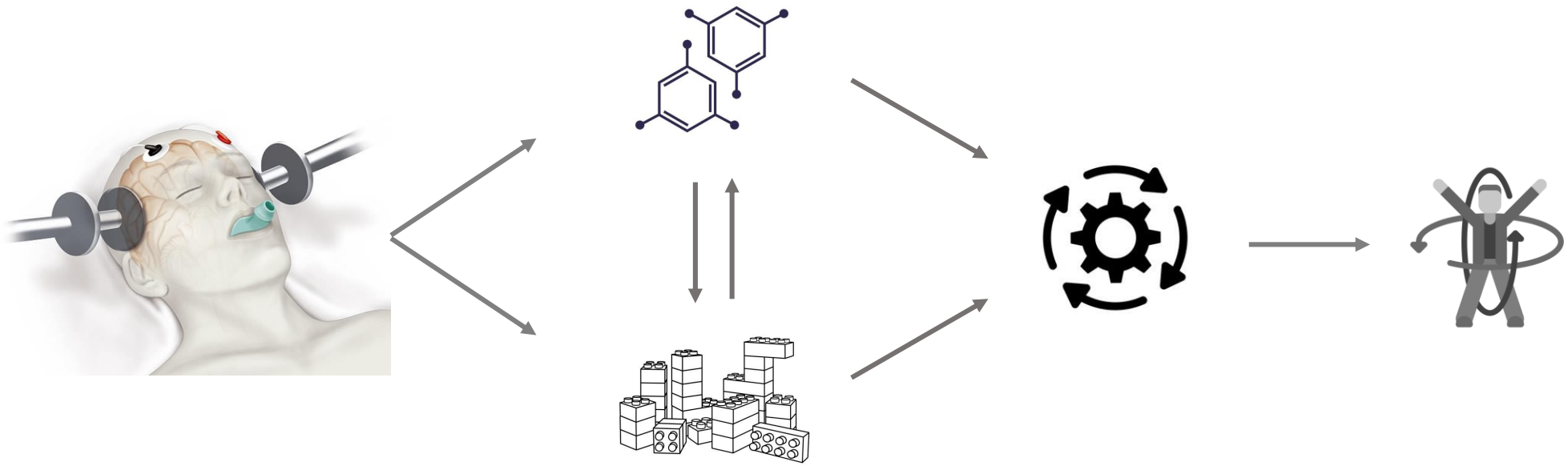
Li et al. 2022

Wat is het werkingsmechanisme?

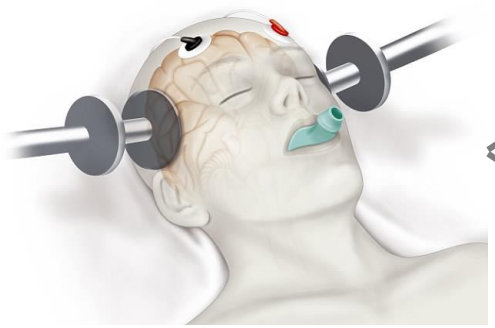


?

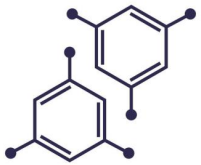
Wat is het werkingsmechanisme?

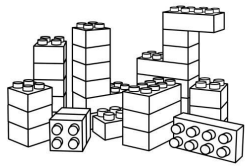


Neurobiologie van ECT



Synaptische densiteit





Grijze stof

COG

PSY

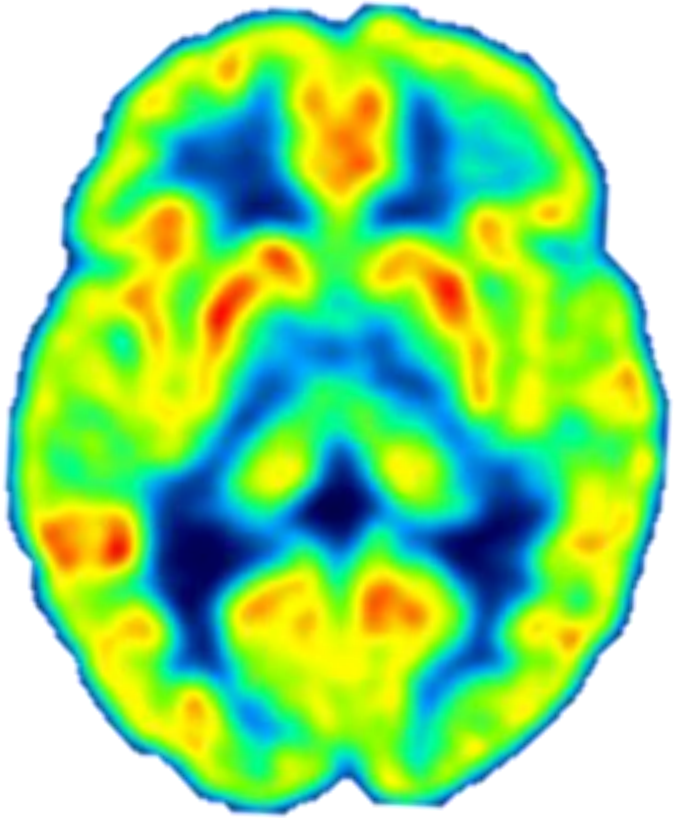
L3D: Synaptische plasticiteit bij ECT

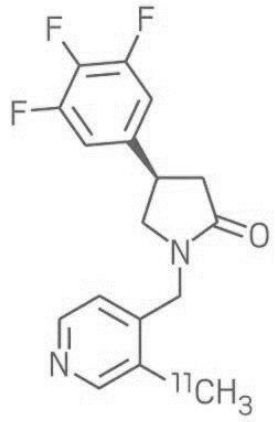
Neuroplasticiteit

Moleculaire Beeldvorming - PET

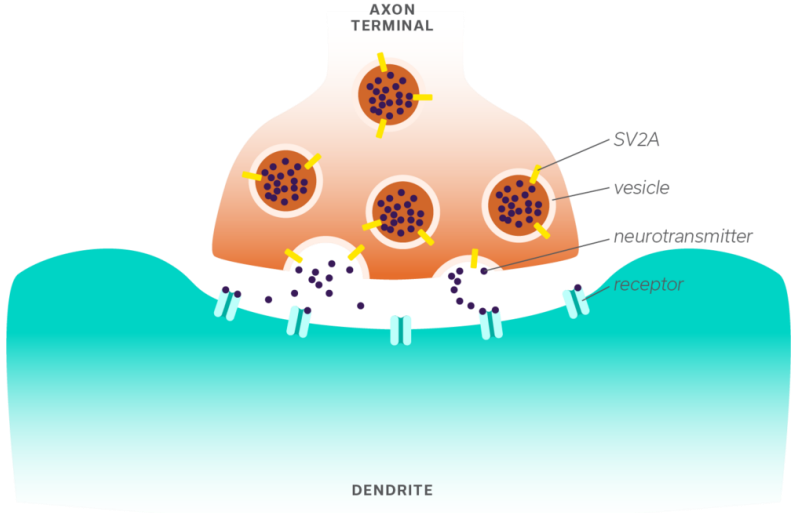
Structurele Beeldvorming - MRI

Longitudinaal design

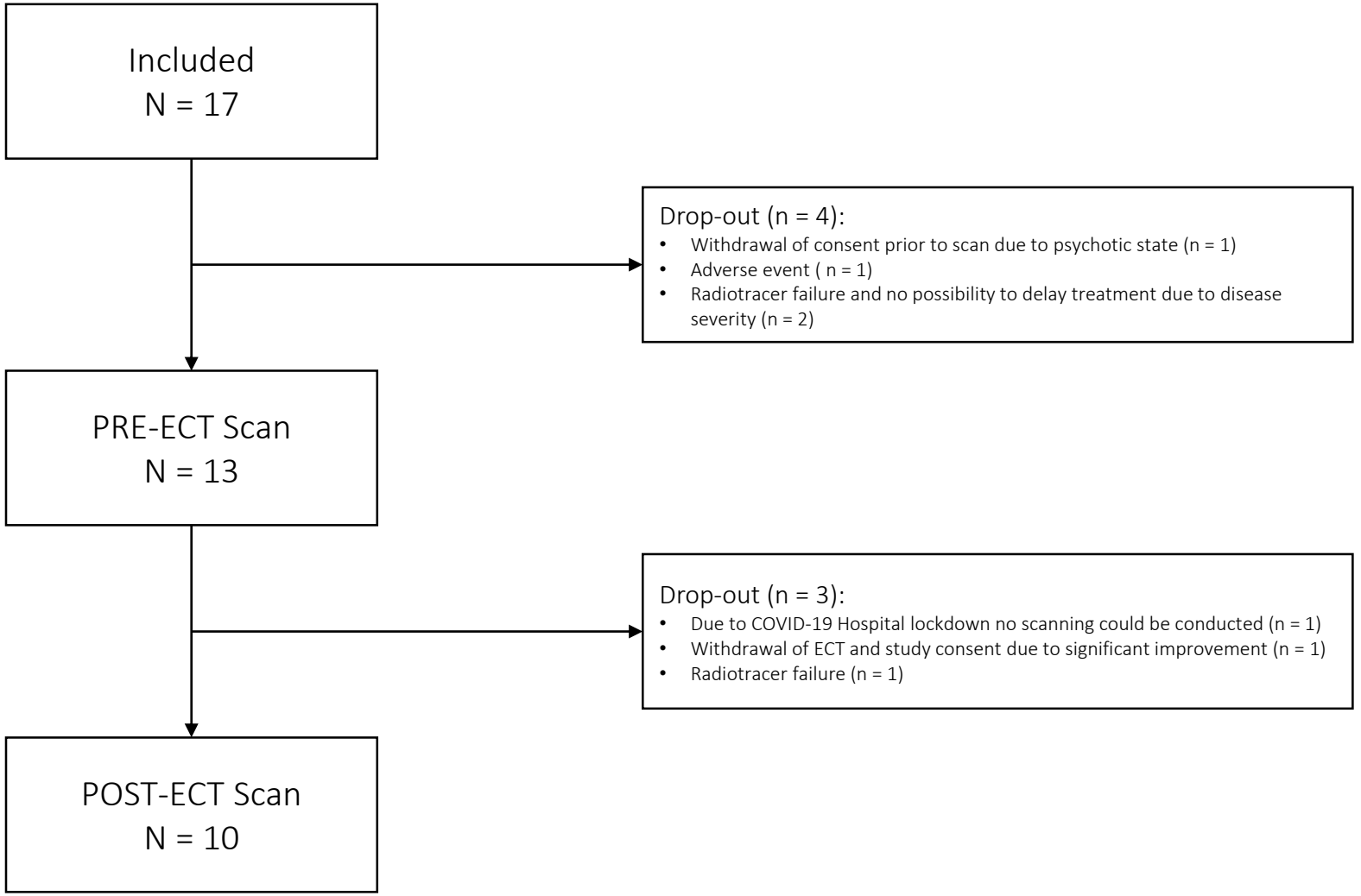




[^{11}C] UCB-J



L3D: Synaptische plasticiteit bij ECT

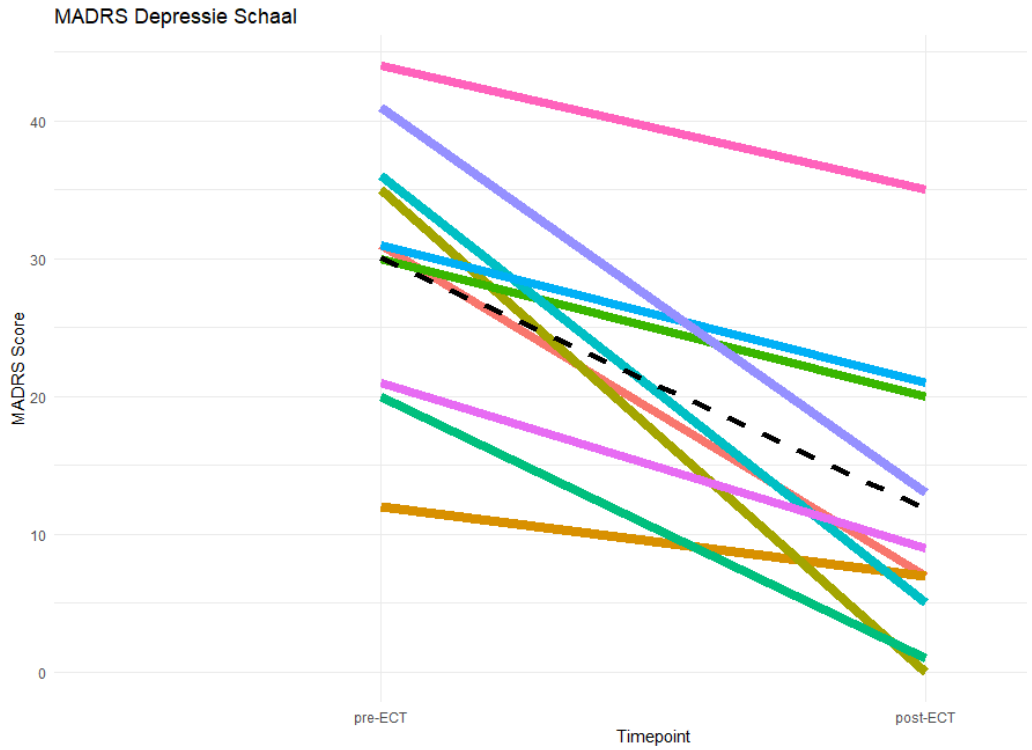


ECT Cohorte

- Leeftijd: 73j
- Sex: 9♀ - 1♂
- Psychotische kenmerken: 40%
- Late Onset Depression: 50%
- Age of onset: 50j
- Duur huidige episode: 27w

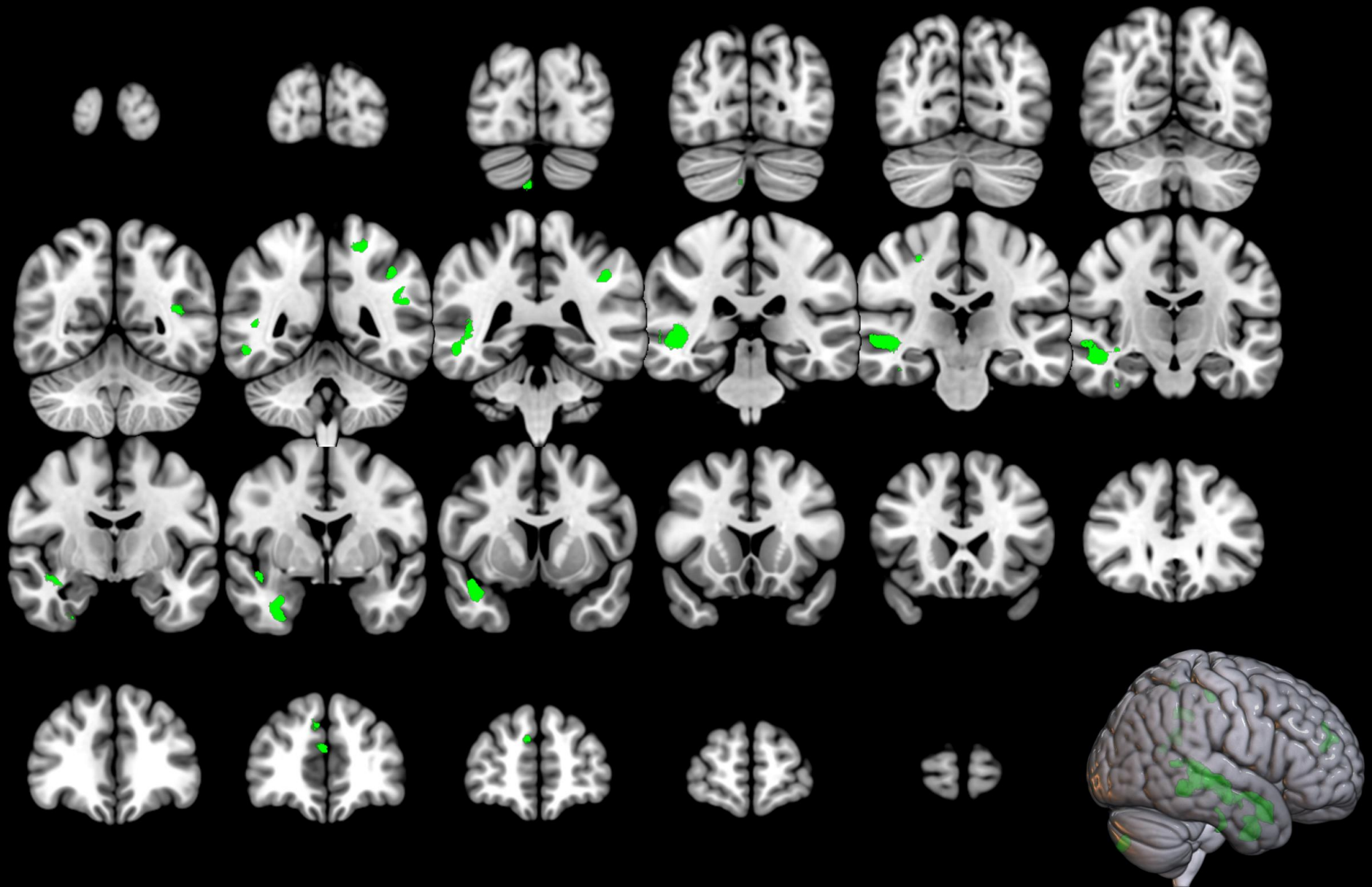
- Aantal ECTs: 10
- Scan Interval post-ECT: 2d17h

- Respons op ECT: 70%
- Remisssie na ECT: 60%



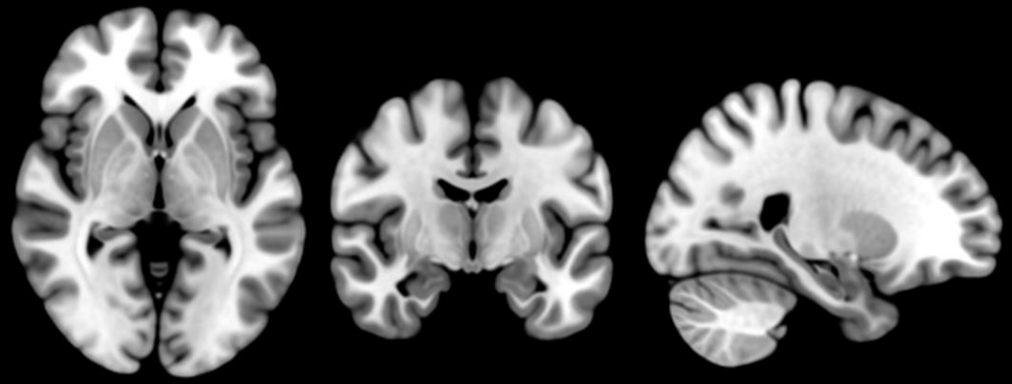
MADRS pre-ECT: 30.1
MADRS post-ECT: 11.8

Structurele veranderingen na ECT

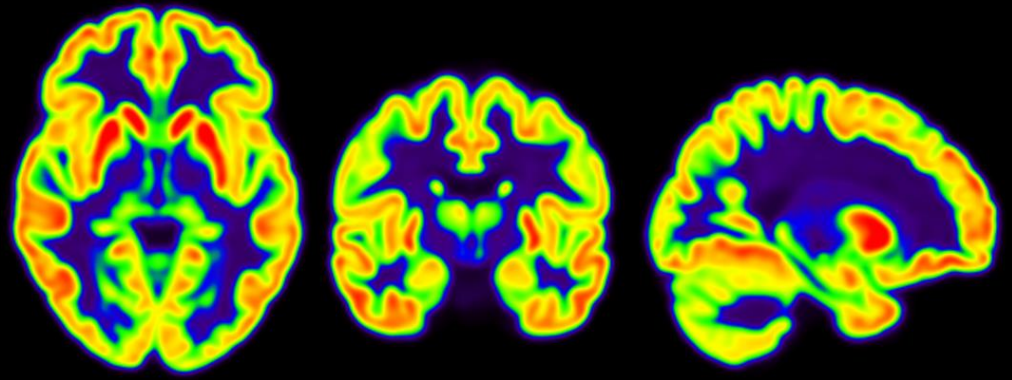


Synaptische veranderingen na ECT

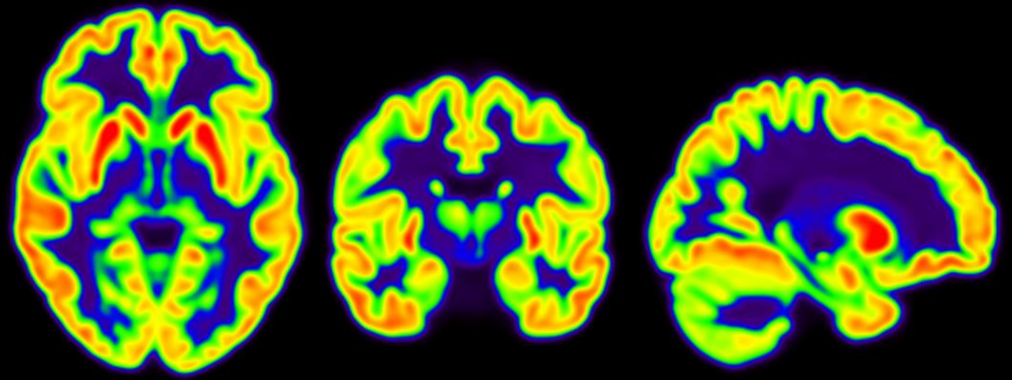
MNI



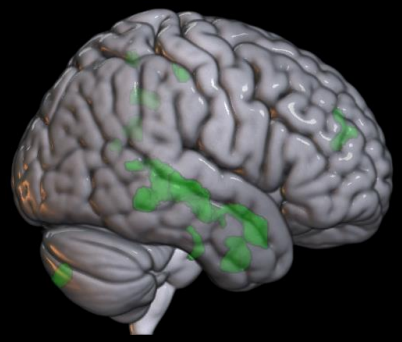
Pre-ECT

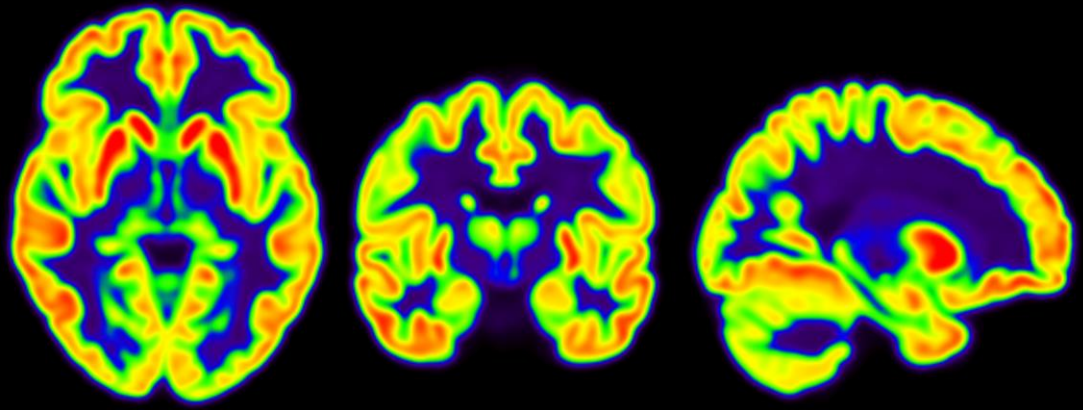


Post-ECT



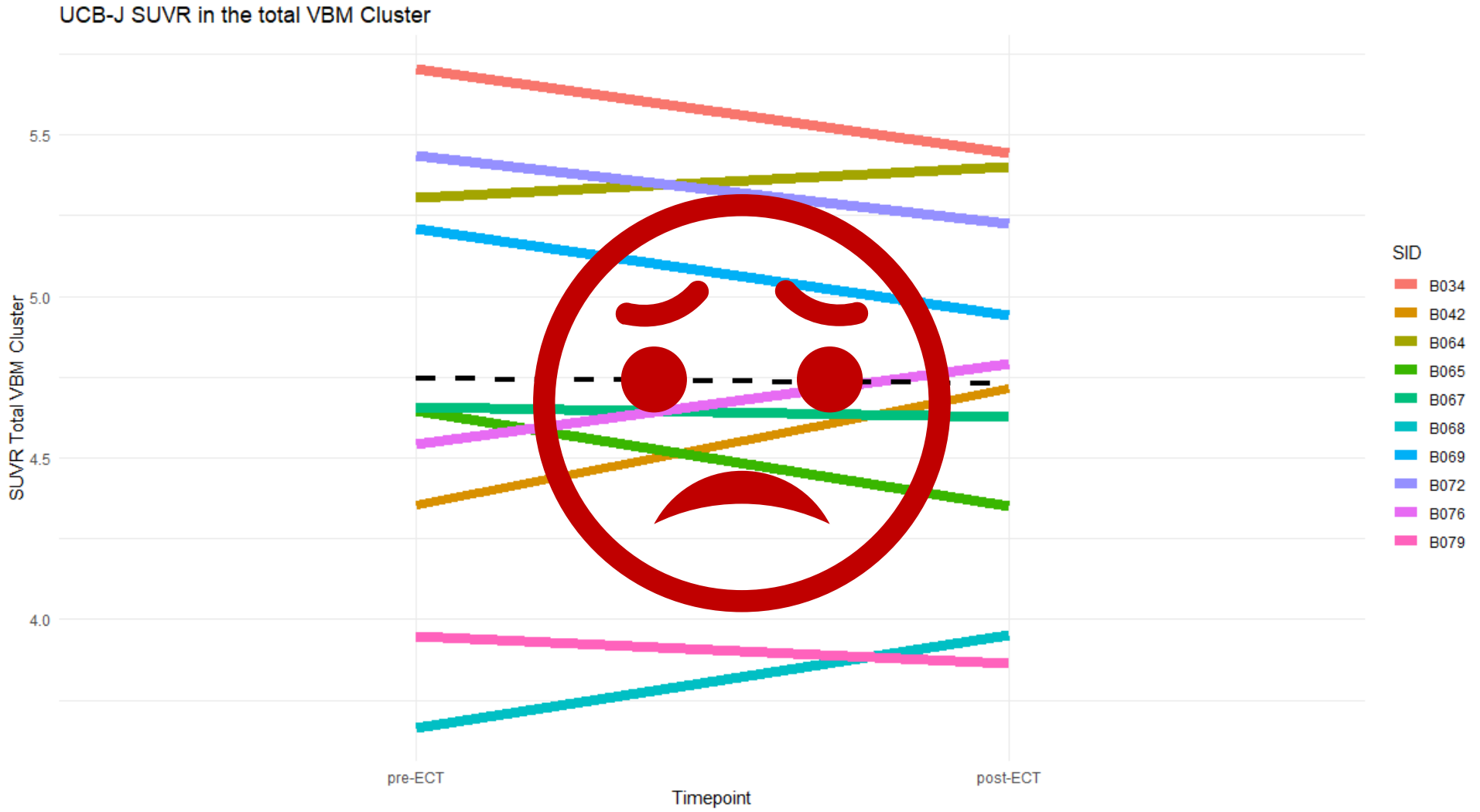
Synaptische veranderingen na ECT



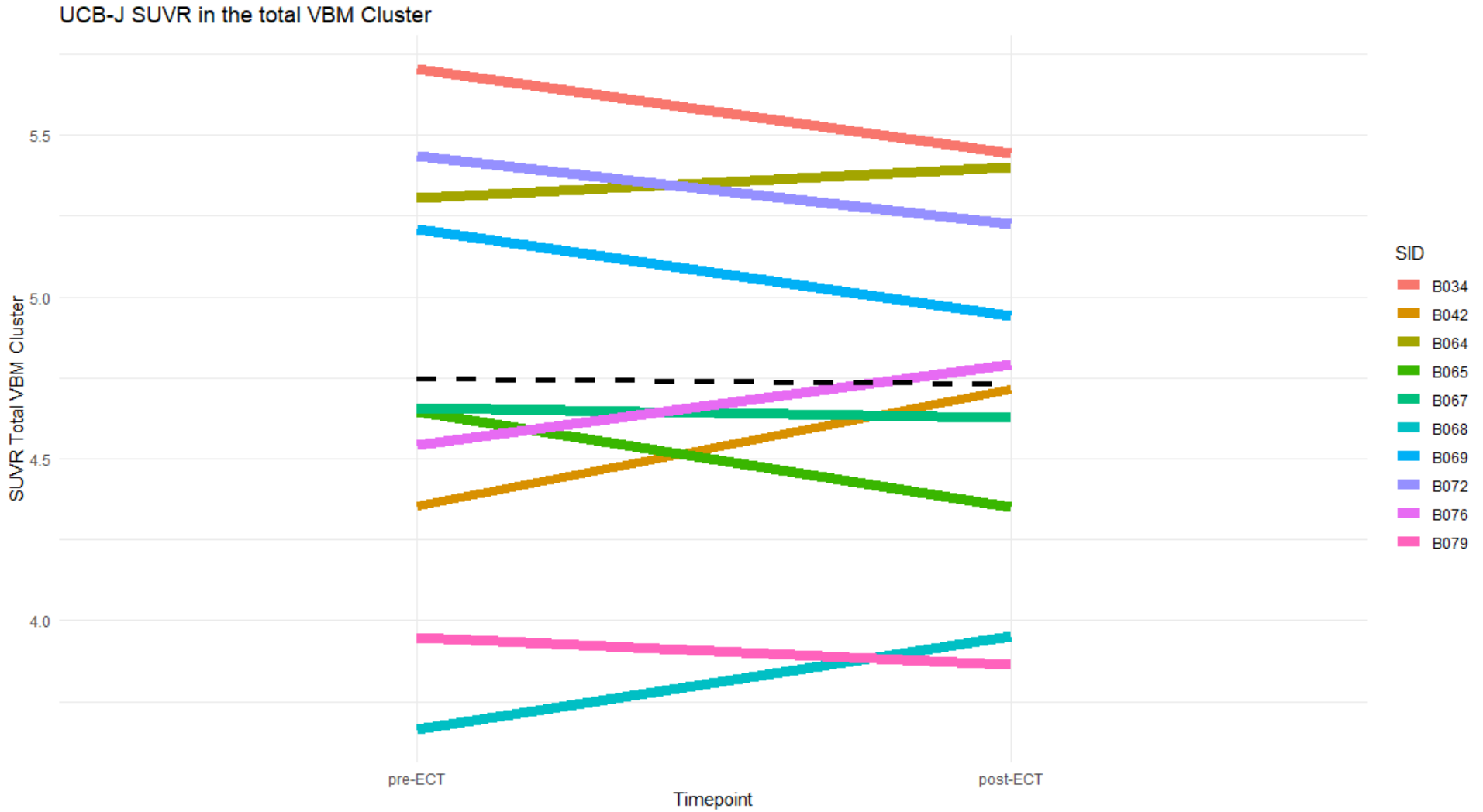


Zijn de structurele veranderingen geassocieerd met synaptische veranderingen?

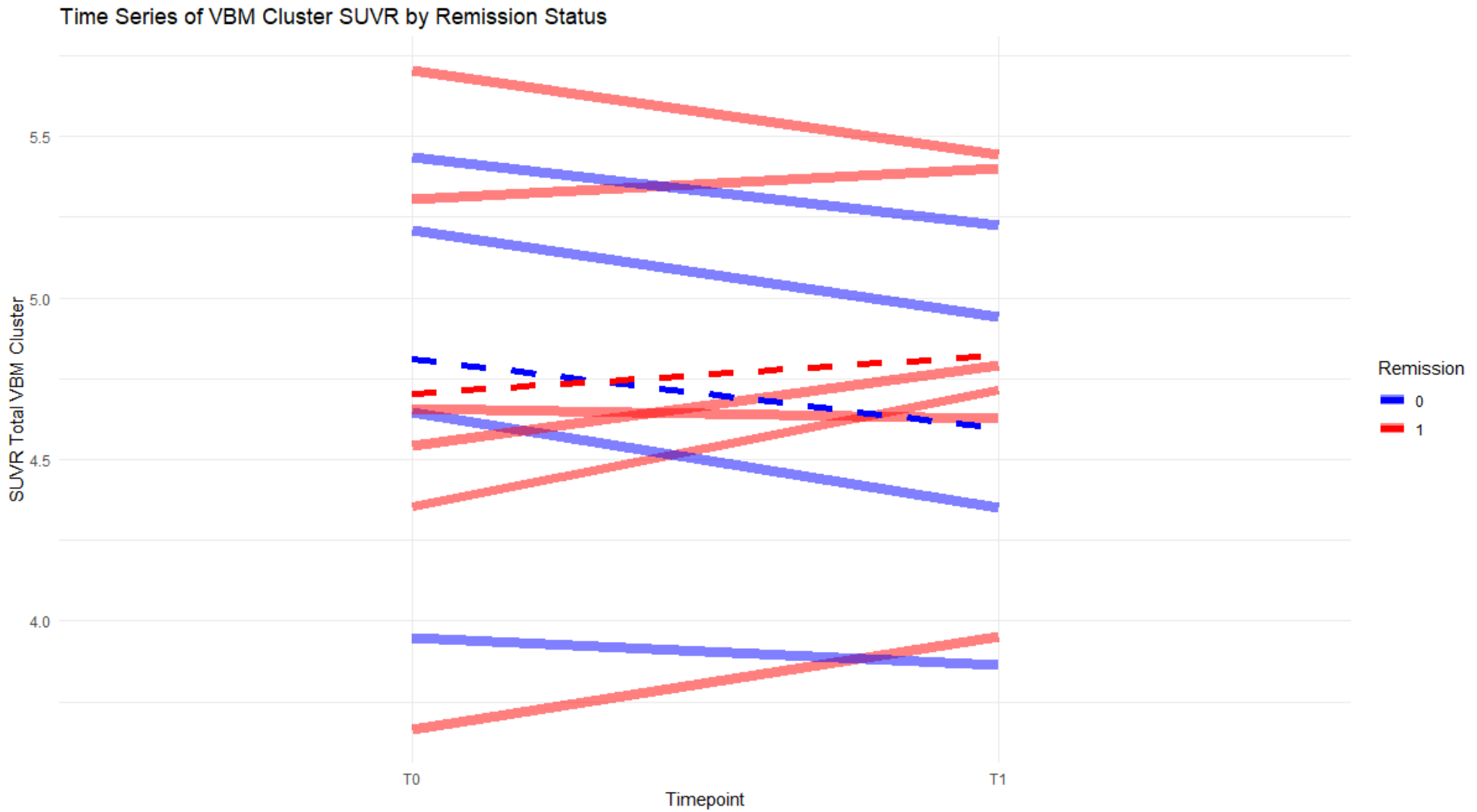
Synaptische veranderingen na ECT



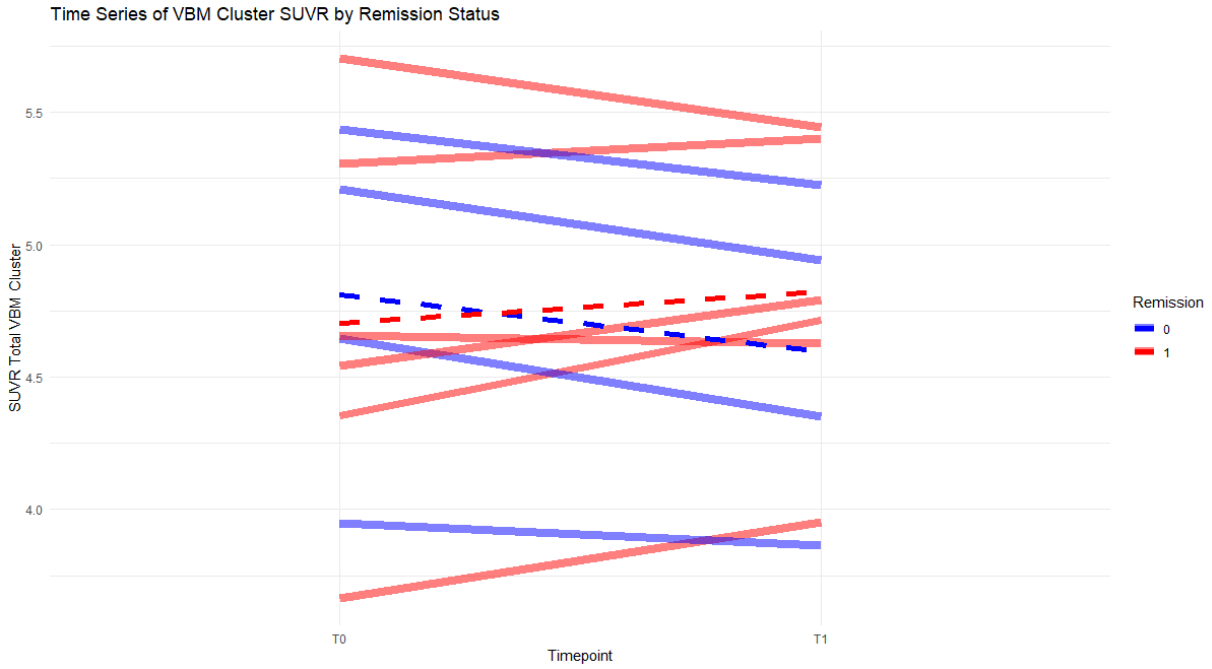
Wat met klinische associaties?

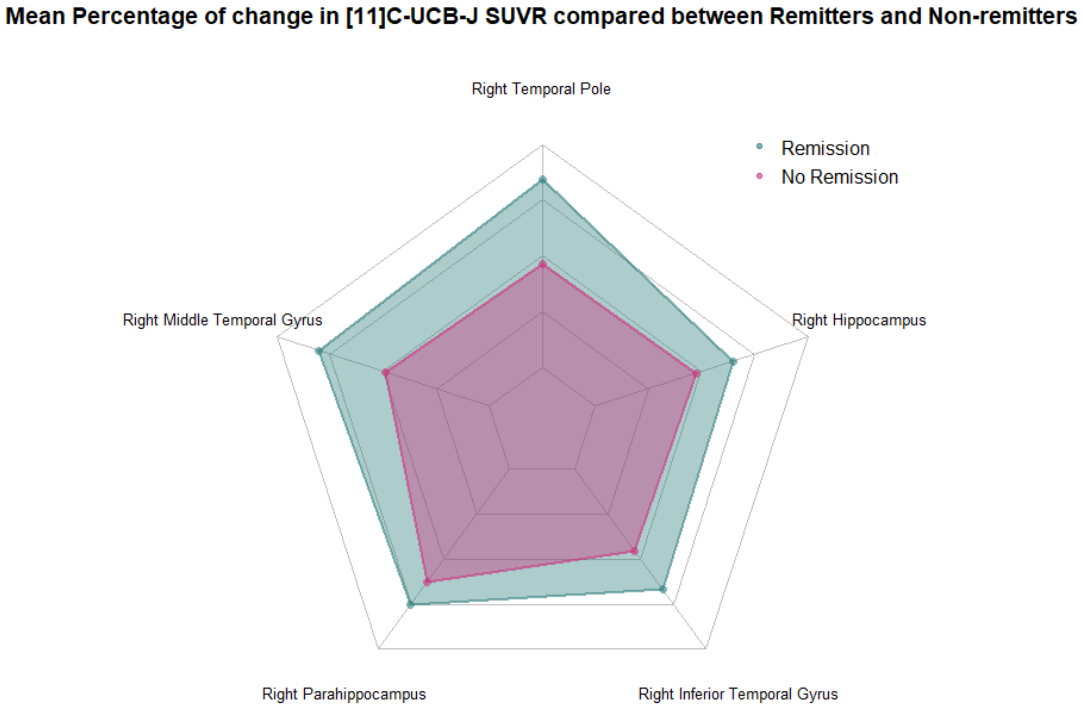


Wat met klinische associaties?

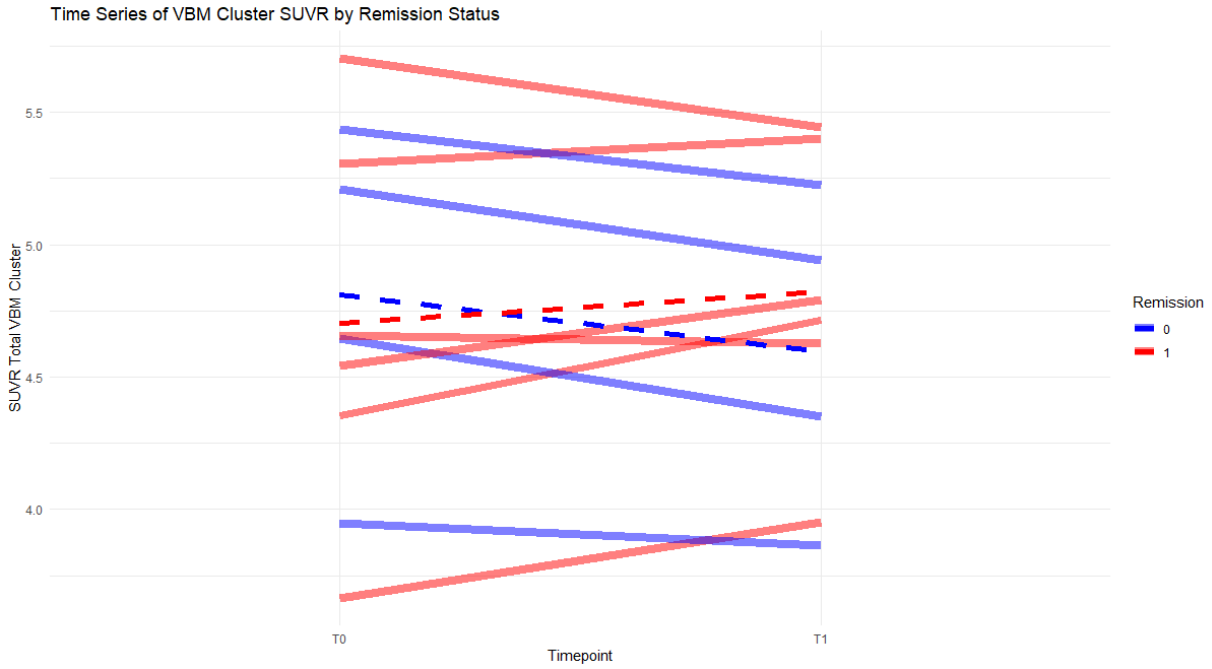


Wat met klinische associaties?

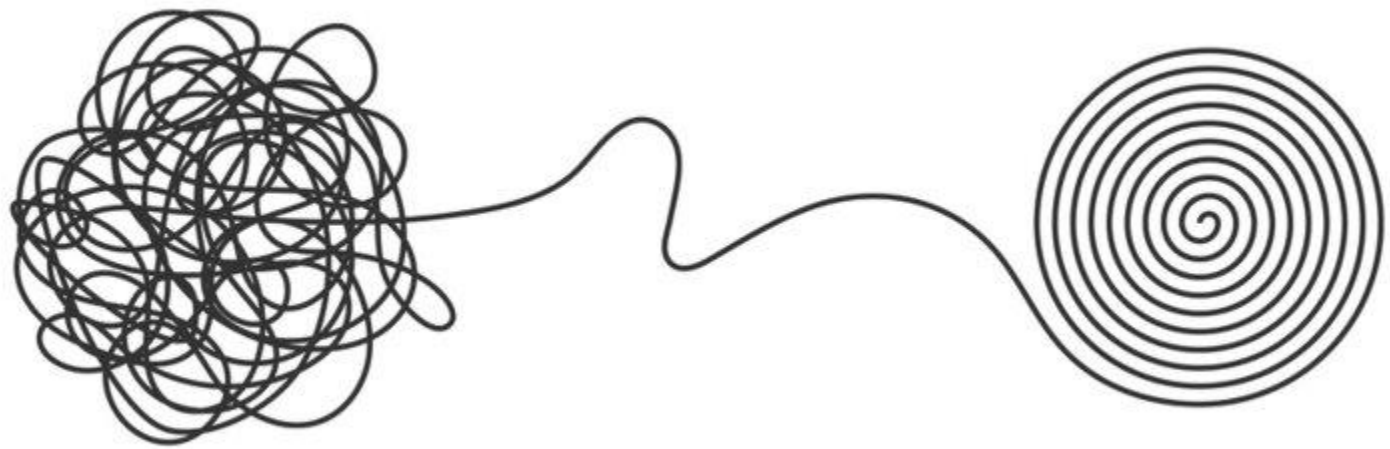


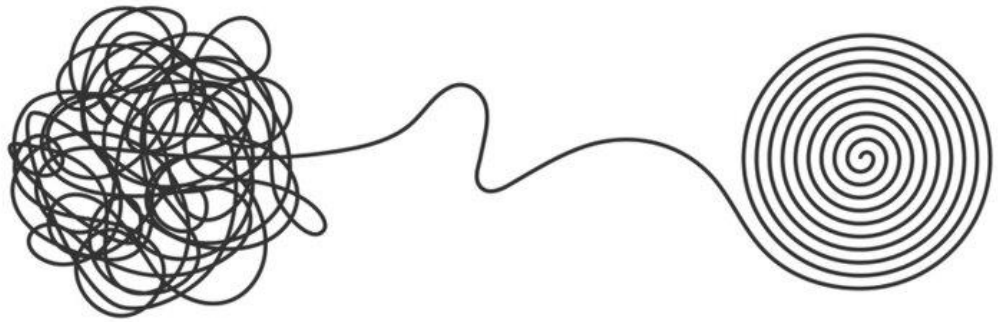


Wat met klinische associaties?



- *Bij Remissie patiënten: Grijze stof toename na ECT gaat gepaard met toename in synaptische densiteit*
- *Bij non-Remissie patiënten: Grijze stof toename na ECT gaat gepaard met afname in synaptische densiteit*





Verschillen in toename grijze stof tussen Remissie vs. non remissie?	**Ja**
Verschillen in grijze stof op baseline tussen Remissie vs. non remissie?	**Nee**
Verschillen in synaptische densiteit op baseline Remissie vs. non remissie?	**Nee**
Verschillen in grijze stof tussen ECT vs. non-ECT?	**Nee**
Verschillen in synaptische densiteit tussen ECT vs. non-ECT?	**Nee**

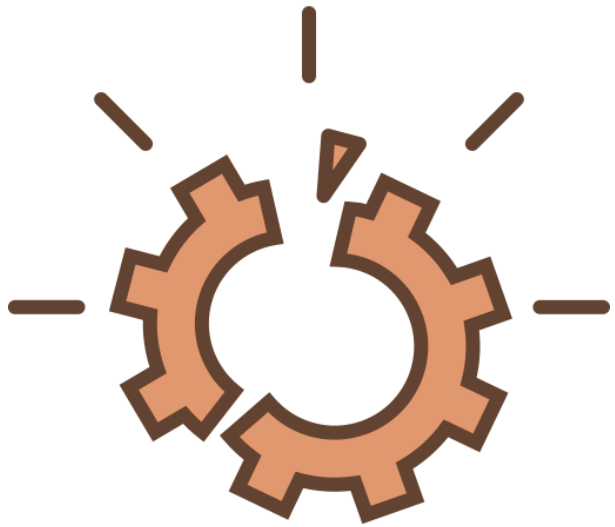
Physiology

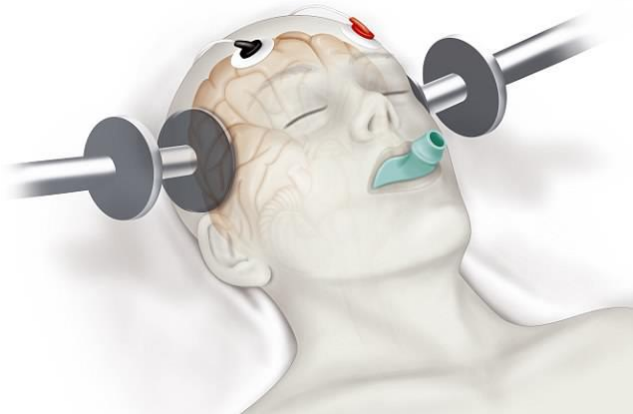
Behaviour

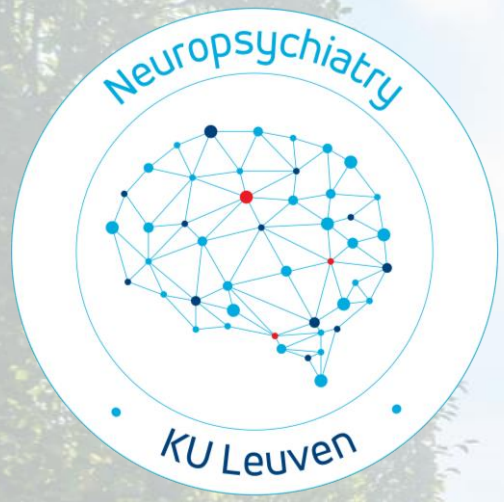
Social network

Society

DISRUPTION







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Akihiro Takamiya
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Jiaze Sun
Laura Van den Bulcke
Laura Van Hove

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Nuclear Medicine: *Koen Van Laere & Michel Koole*
Laboratory for Cognitive Neurology: *Rik Vandenberghe & Patrick Dupont*
TARGID: *Lukas Van Oudenhove*
Center for Contextual Psychiatry: *Inez Germeys*
VIB: *Philip Van Damme*
IMEC: *Chris Van Hoof, Walter De Raedt & Nick Van Helleputte*
Laboratory for Biological Psychology: *Hans Op de Beeck*
Declarative Languages and Artificial Intelligence: *Joost Vennekens*

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University of Sydney, Australia: *Fiona Kumfor*
Maastricht University, The Netherlands: *Beatrice De Gelder*

ResPECT (Research in Psychiatry and ECT Consortium)
GEMRIC (The Global ECT-MRI Research Collaboration)
NIC-FTD (Neuropsychiatric International Consortium FTD)
The Human Affectome Project

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