KU LEUVEN

The Leuven Late-Life Depression Study

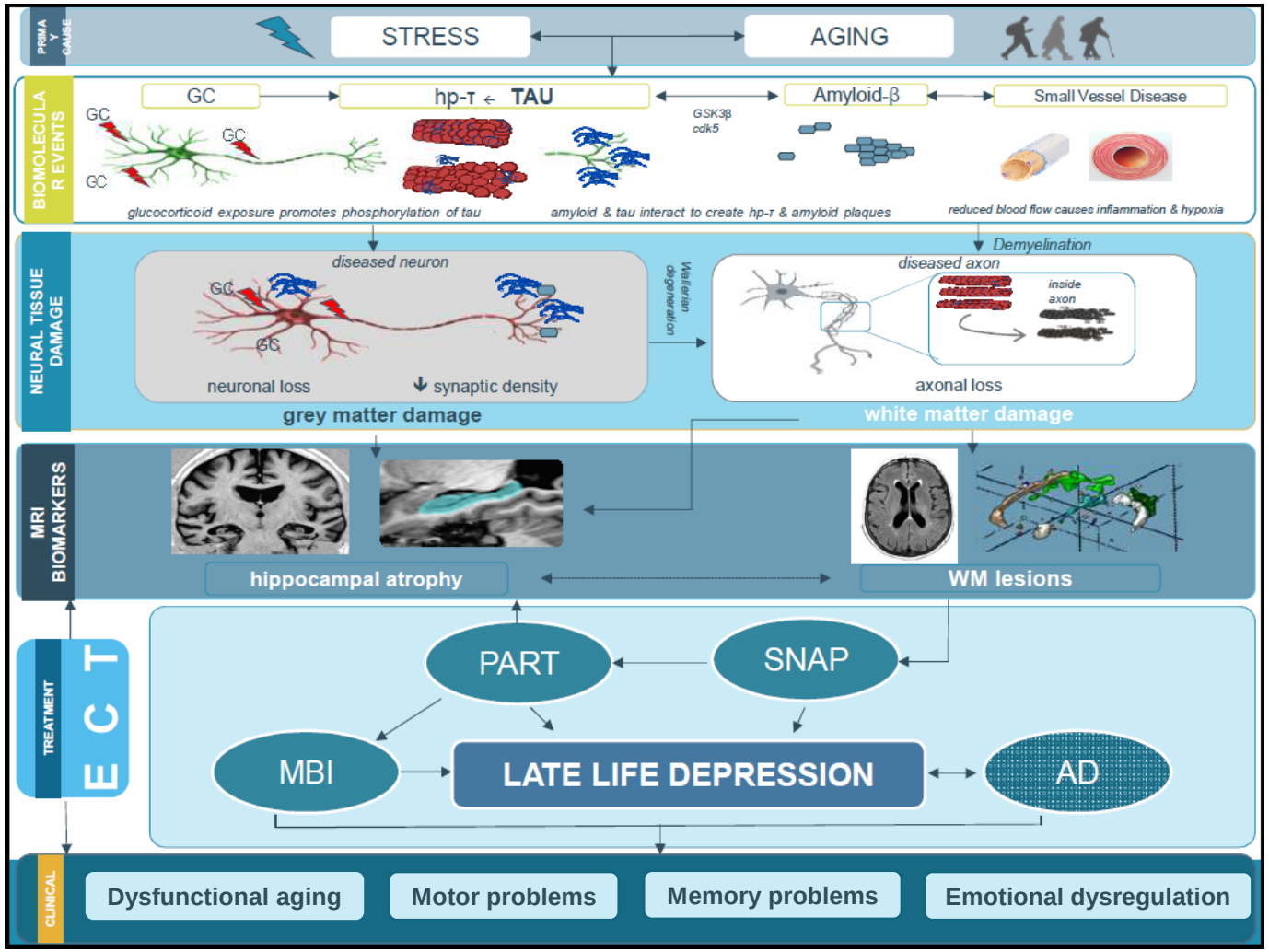
UPC KU Leuven Congres Ouderenpsychiatrie

Uit het oog uit het hart

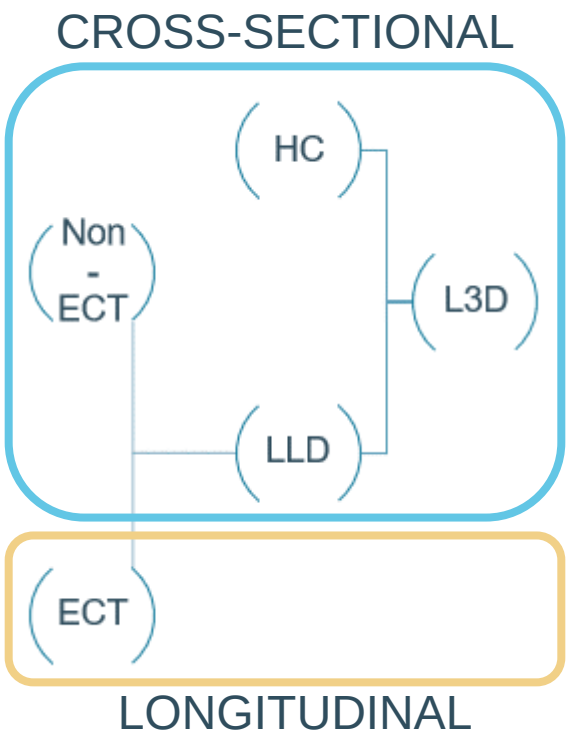
Over eenzaamheid en geestelijke gezondheid bij ouderen

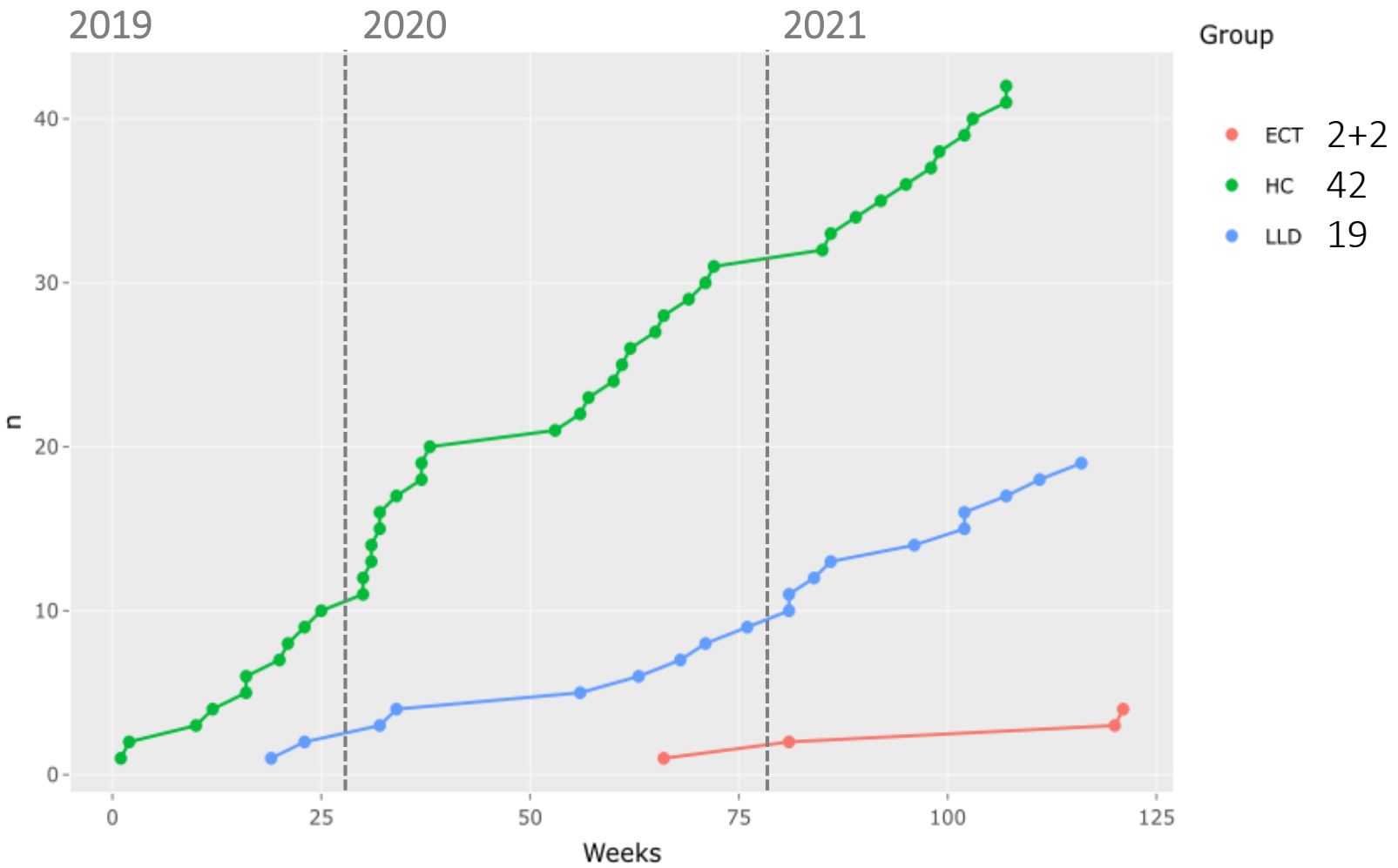
28 oktober 2021
Provinciehuis Leuven

The Leuven Late-Life Depression Study

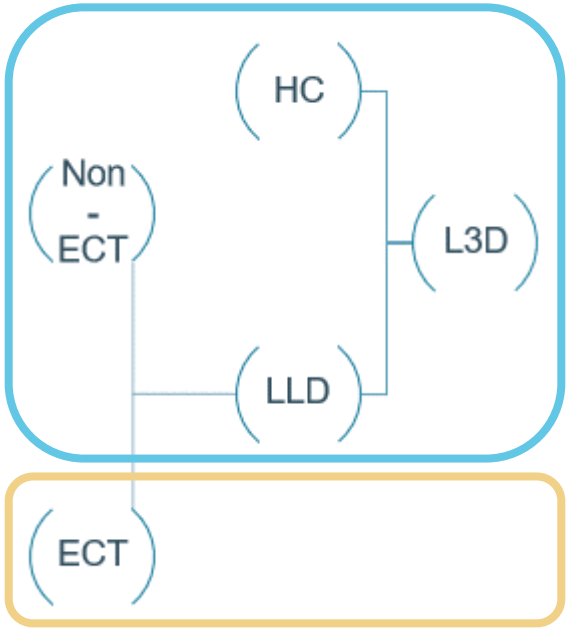


Stand van zaken





CROSS-SECTIONAL



LONGITUDINAL

KLINISCHE TESTING

- PSY
- NEU
- COG
- ESM

STRUCTURELE BEELDVORMING

- T1
- T2
- FLAIR
- DTI

FUNCTIONELE BEELDVORMING

- TAU
- AMY
- Synaptische densiteit
- fMRI

Bevindingen over depressie en het verouderende brein via PET/MR beeldvorming

CROSS-SECTIONAL

HC

Non - ECT

L3D

LLD

ECT

LONGITUDINAL

KLINISCHE TESTING

PSY

NEU

COG

ESM

STRUCTURELE BEELDVORMING

T1

T2

FLAIR

DTI

FUNCTIONELE BEELDVORMING

TAU

AMY

Synaptische densiteit

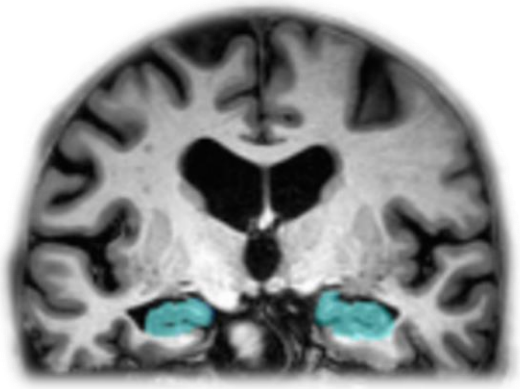
fMRI

Aging

Depressie en het verouderende brein: intro

DEPRESSIE

?



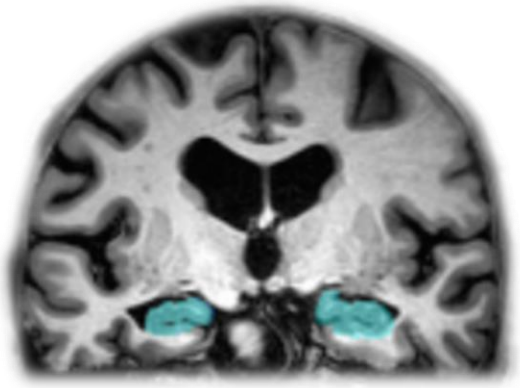
- **Lower hippocampal volume**
- Smaller amygdala
- Larger lateral ventricles

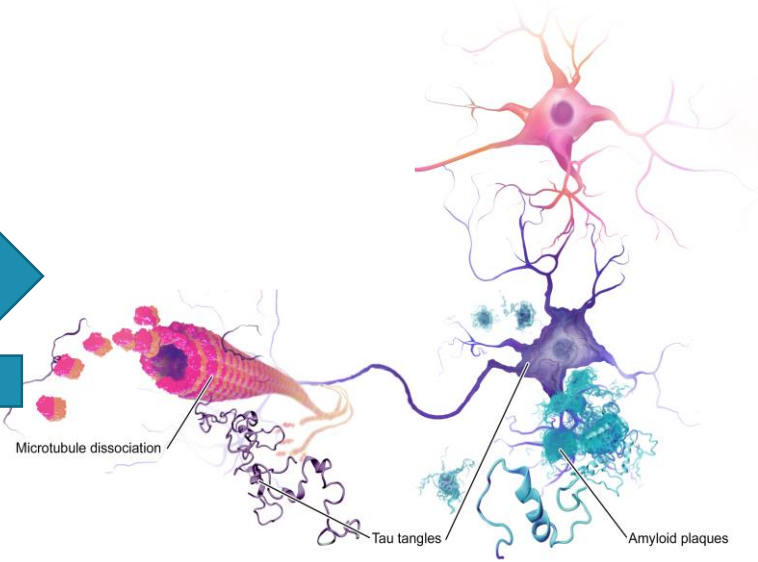
1. Han et al., Molecular Psychiatry 2020
2. Enigma study

Depressie en het verouderende brein: intro

DEPRESSIE

?





- **Lower hippocampal volume**
- Smaller amygdala
- Larger lateral ventricles

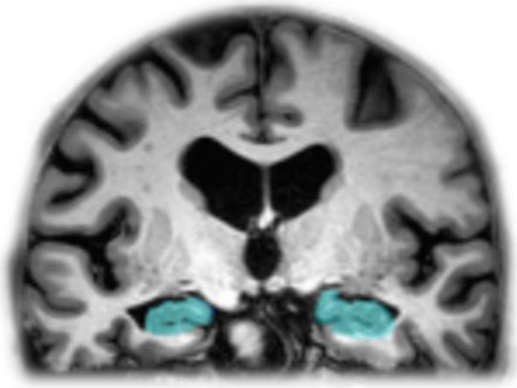
- **TAU**
- **AMYLOID**
- **SD**

1. Han et al., Molecular Psychiatry 2020
2. Enigma study

Depressie en het verouderende brein: intro

DEPRESSIE

?



PET MR

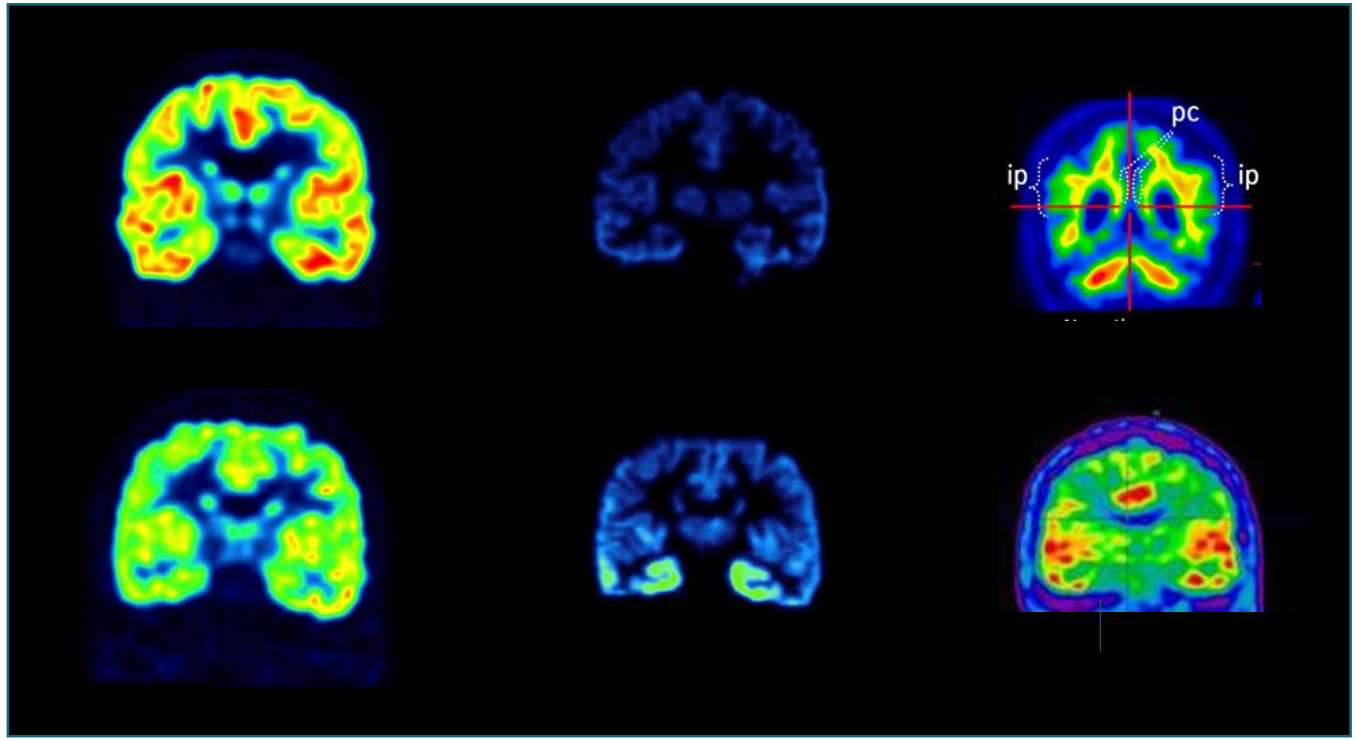
- **Lower hippocampal volume**
- Smaller amygdala
- Larger lateral ventricles

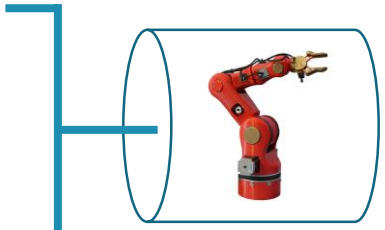
- **TAU : ^{18}F-MK-6240**
- **AMYLOID : ^{18}F-FLUT**
- **SD: ^{11}C-UCB-J**

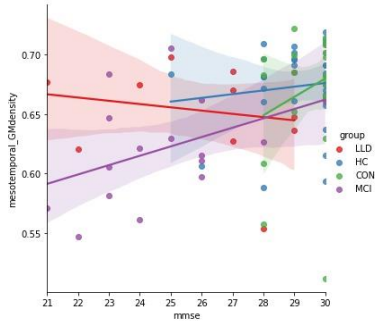
1. Han et al., Molecular Psychiatry 2020
2. Enigma study

Depressie en het verouderende brein: methods

SD: ^{11}C-UCB-J TAU : ^{18}F-MK-6240 AMYLOID : ^{18}F-FLUT



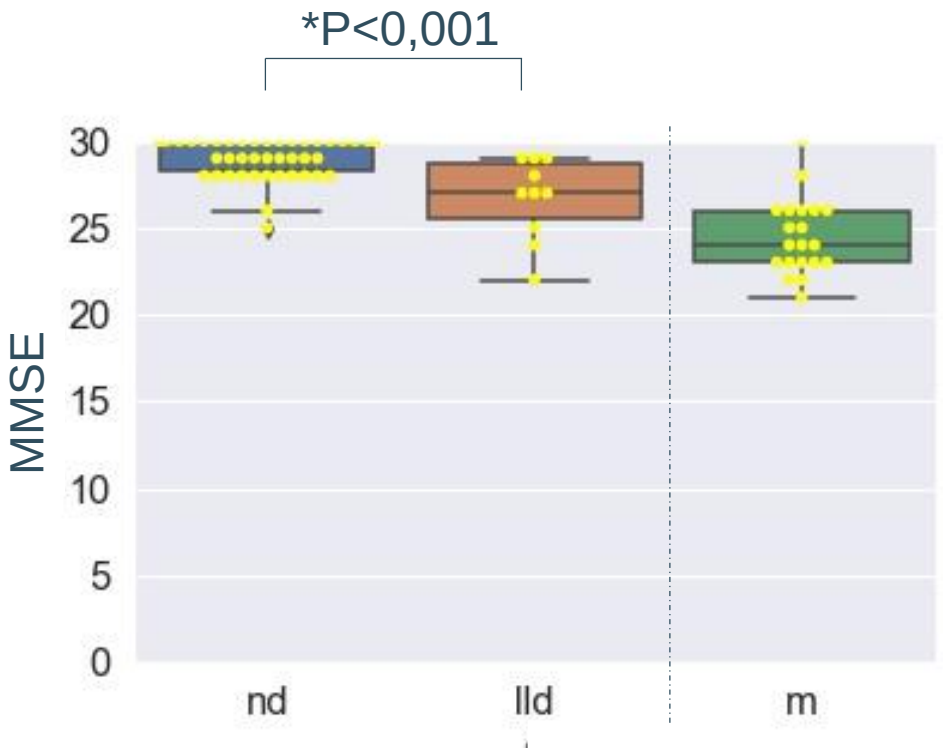


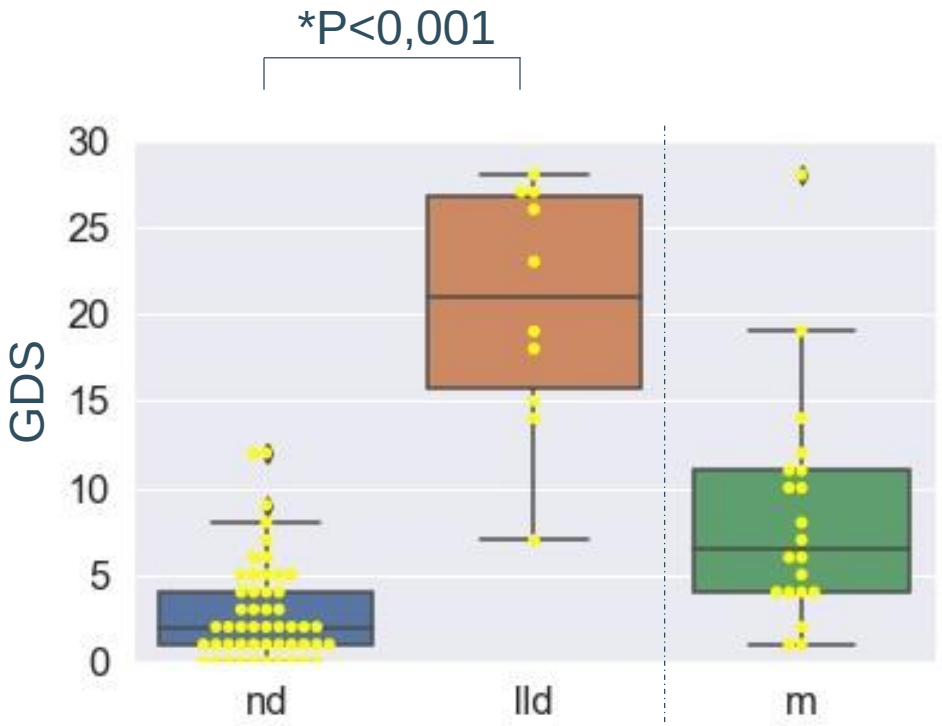


Demografische kenmerken

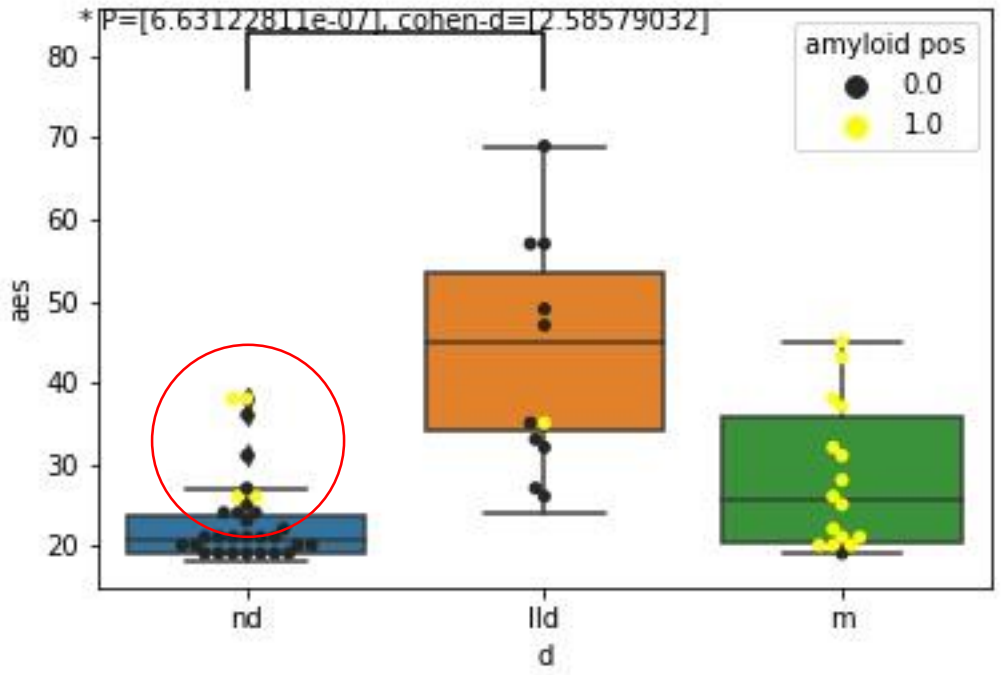
	LLD	CON	MCI	Statistical value	P-value
Number	10	50	20	/	/
Age (mean, sd)	72.8 (6.4)	69.5 (7.7)	70.1 (7.1)	U=295	p=0.38
Female (%)	70%	46%	60%	/	p=0.30
ApoE4 carrier (%)	20%	17%	65%	/	p=0.67
Amyloid Pos	1 (10%)	10 (20%)	95%	/	p=0.67
MMSE (mean, sd)	26.7 (2.4)	29.2 (1.1)	24.5 (2.2)	U=495.5	*<0.001
GDS (mean,sd)	20.4 (7.0)	2.8 (2.8)	8.35 (6.5)	U=66.5	*<0.001

Klinisch verschillende groepen

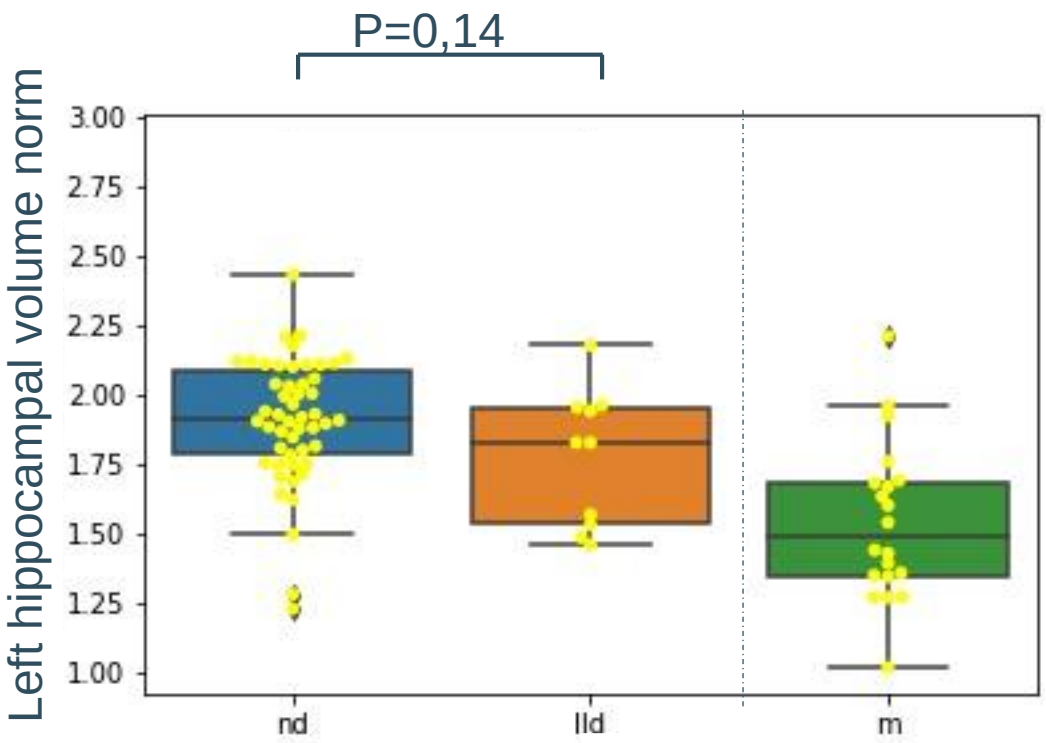


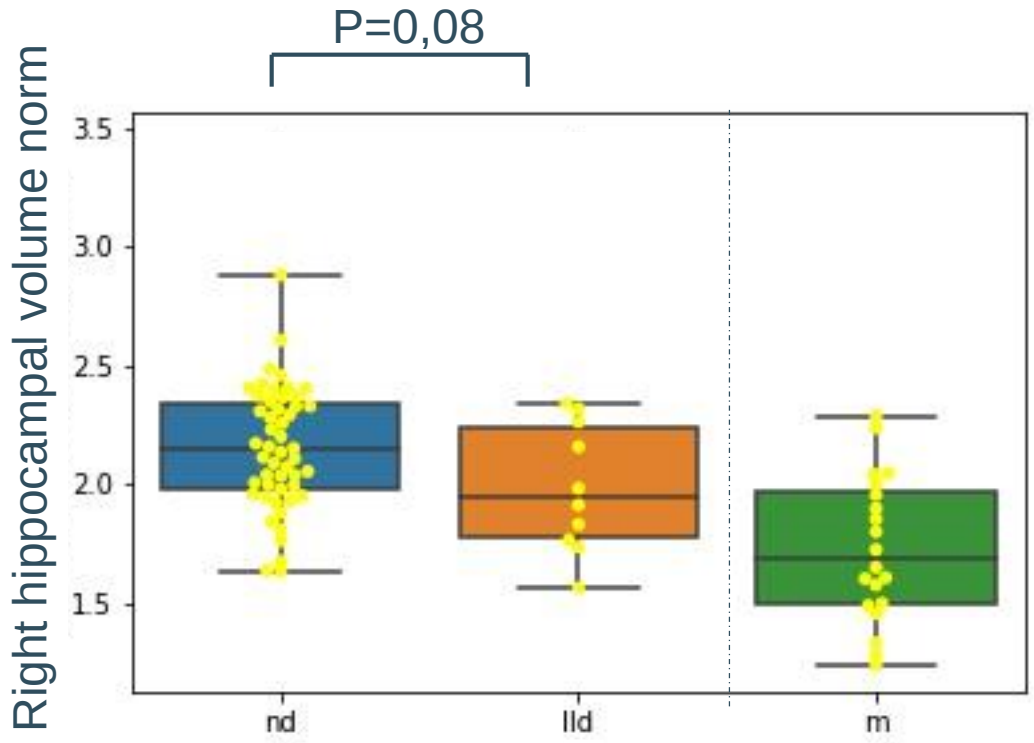


Apathie is hoger bij Aβ-positieve controles

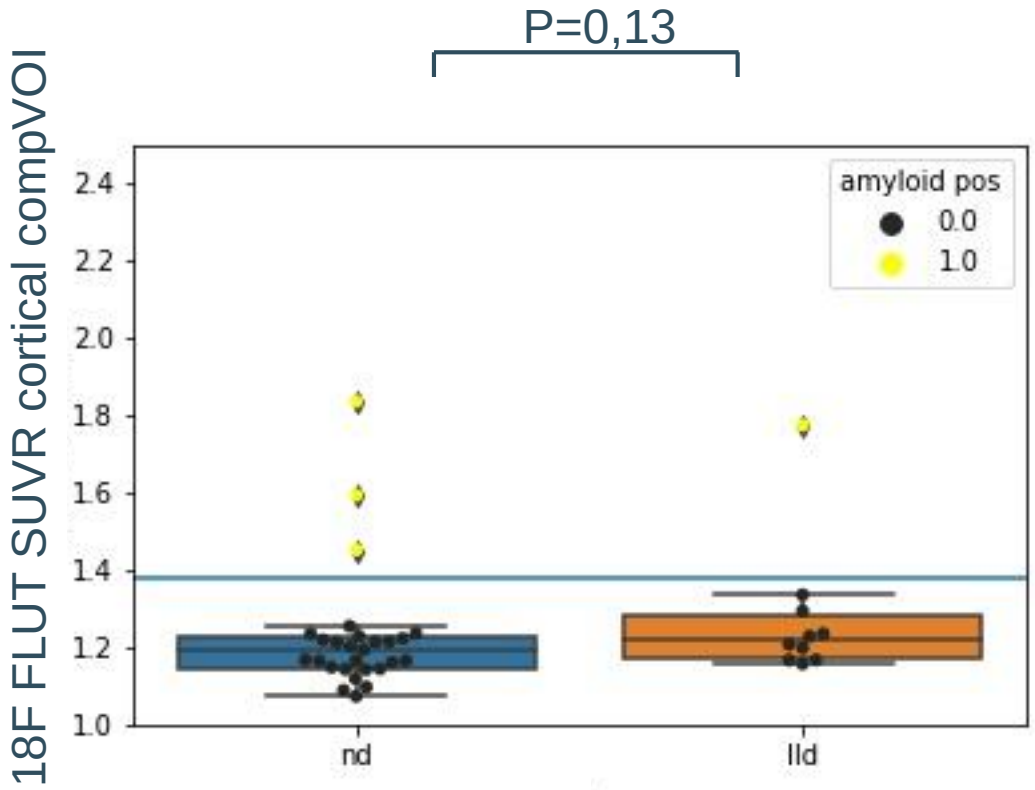


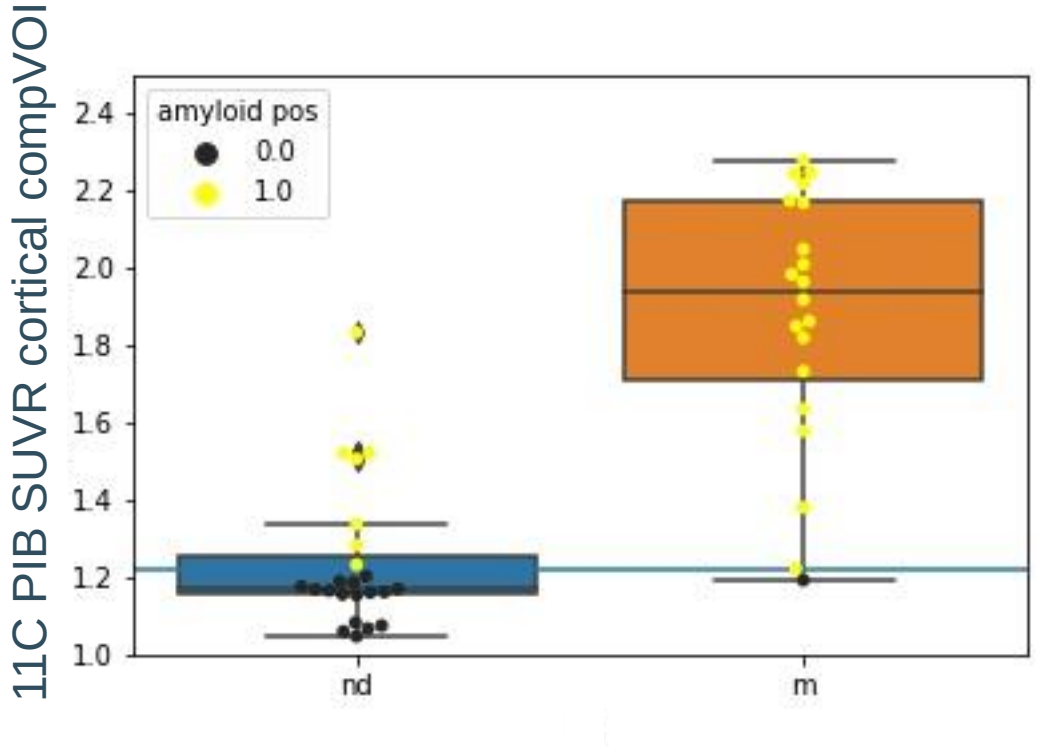
Verschillen in hippocampaal volume



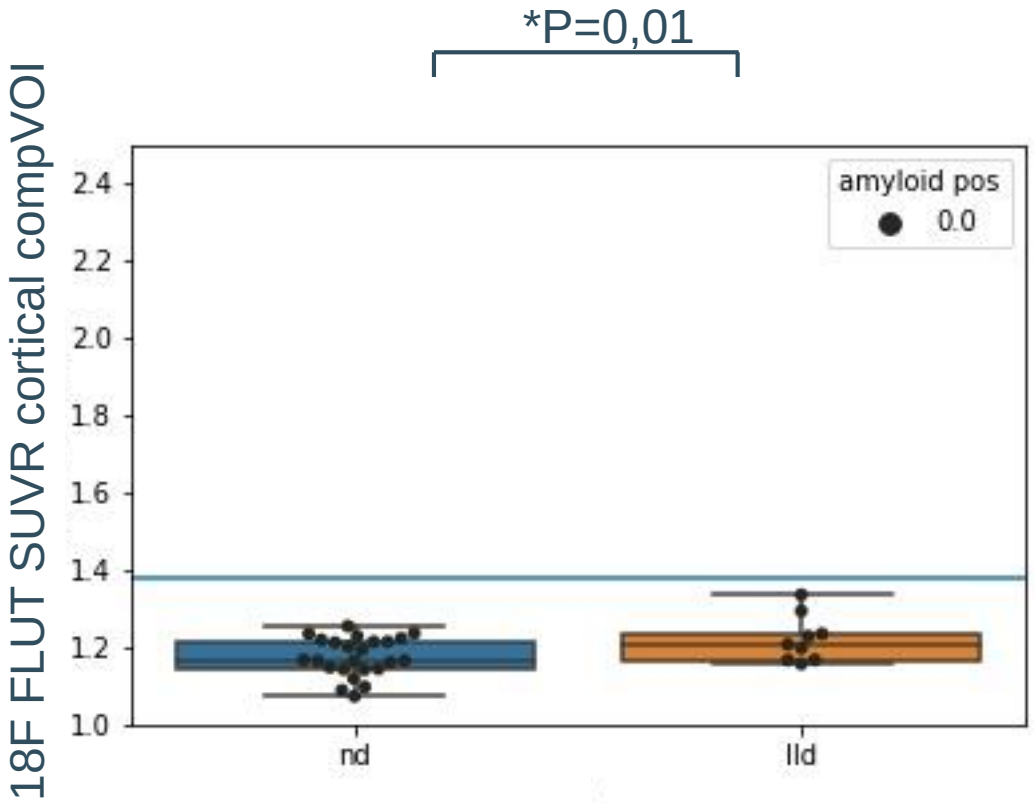


Corticale amyloid neerslag

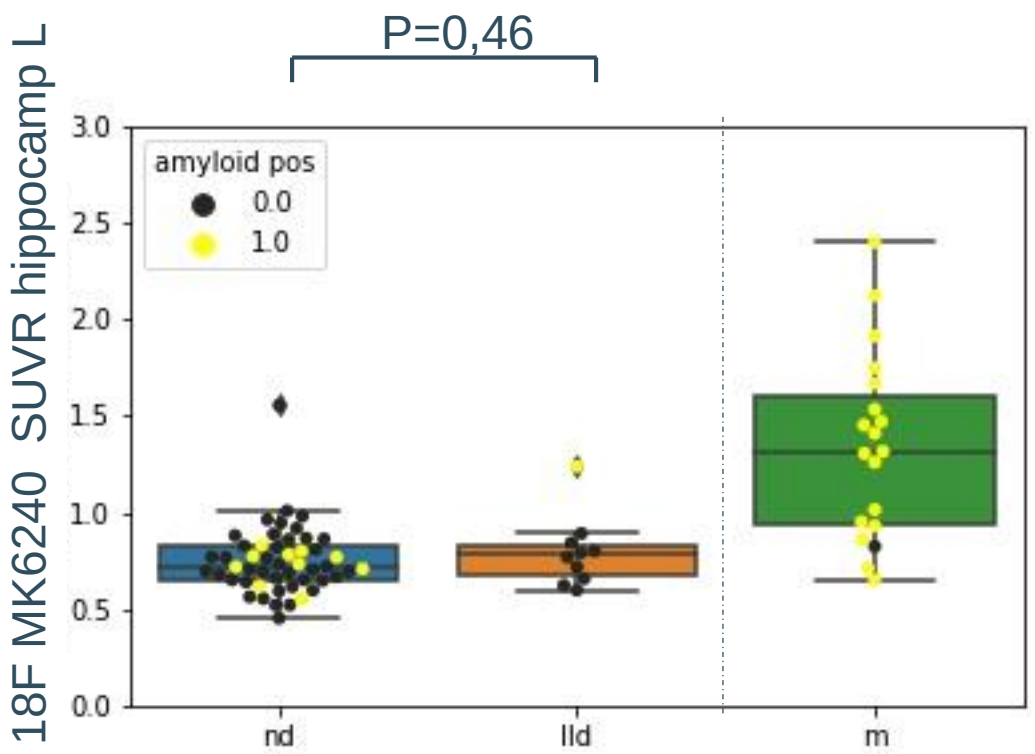


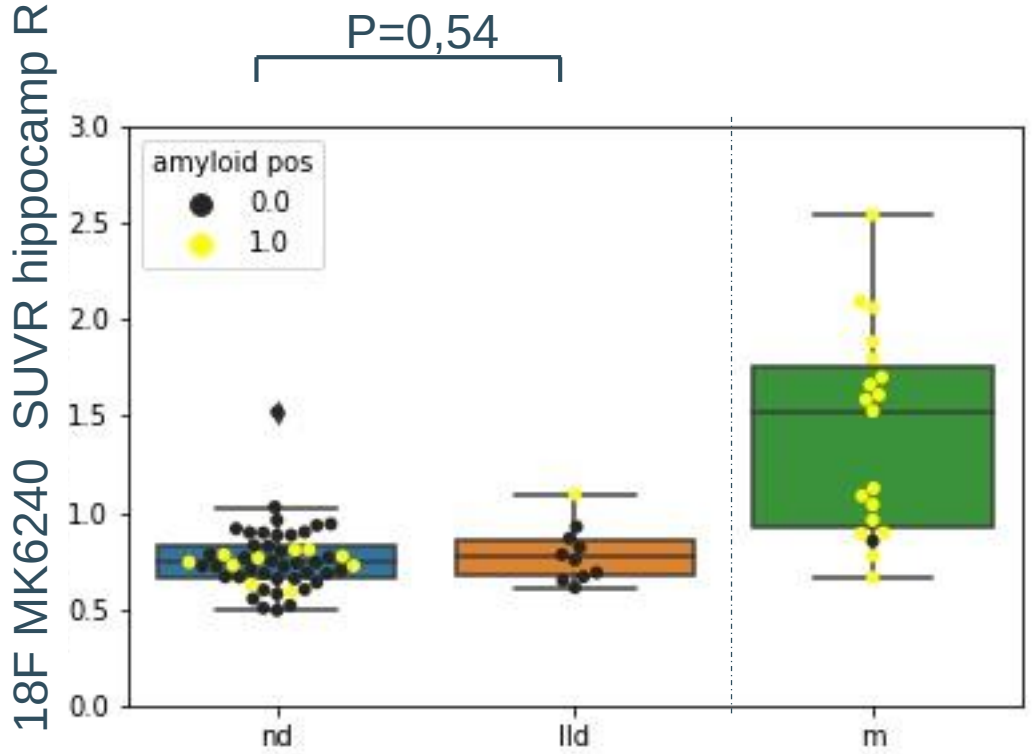


Corticale subthreshold amyloid neerslag



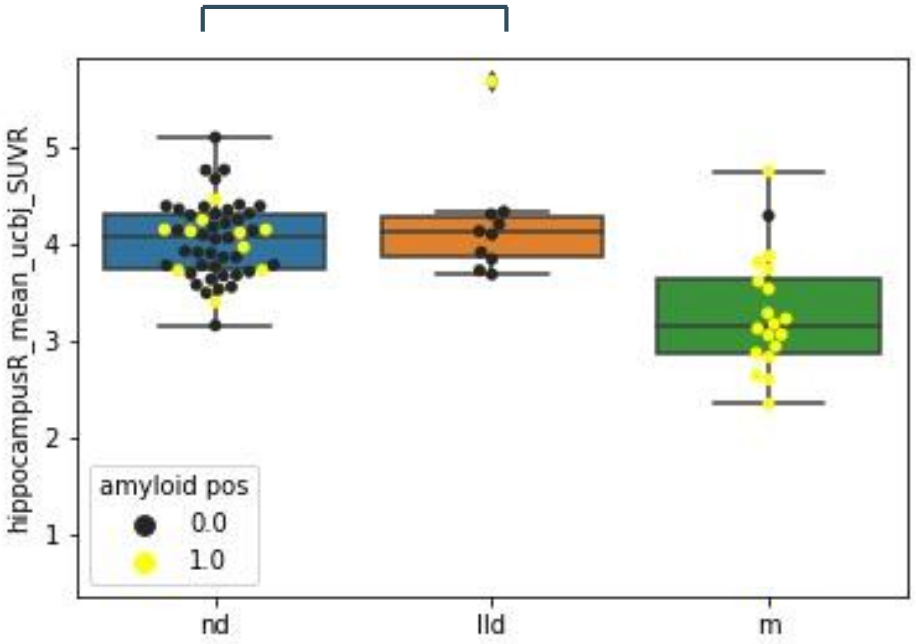
Geen verschil in hippocampale tau neerslag





Geen verschil in hippocampale synaptische densiteit

P=0,78



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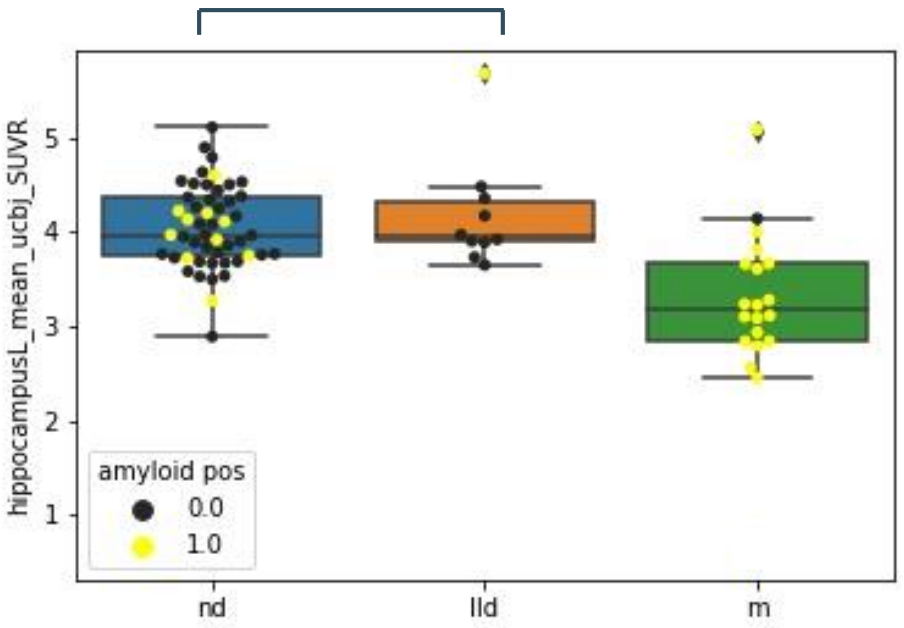
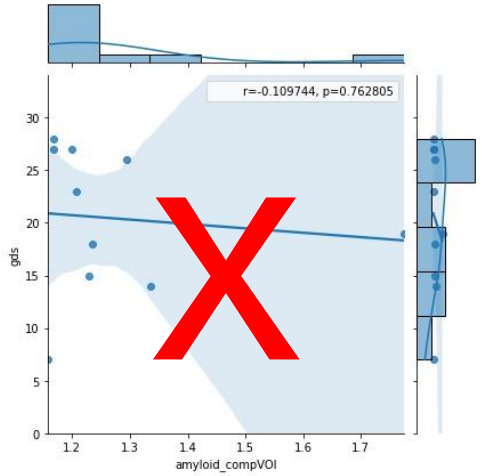


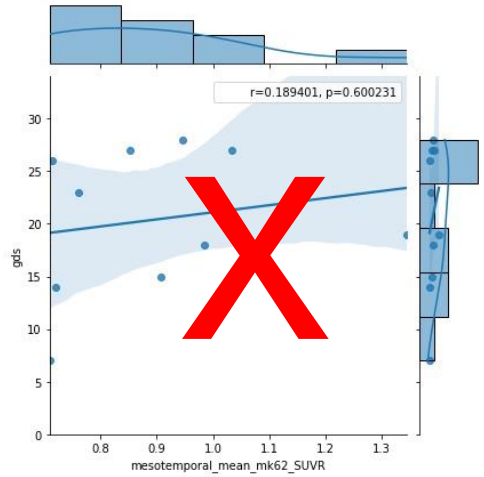
GDS correleert met amyloid neerslag in MCI, niet met tau

AMYLOID

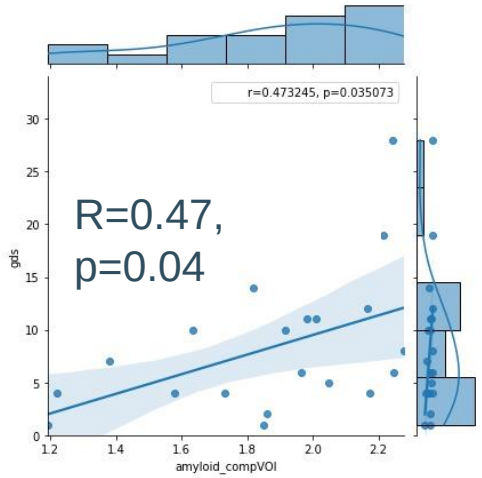
TAU

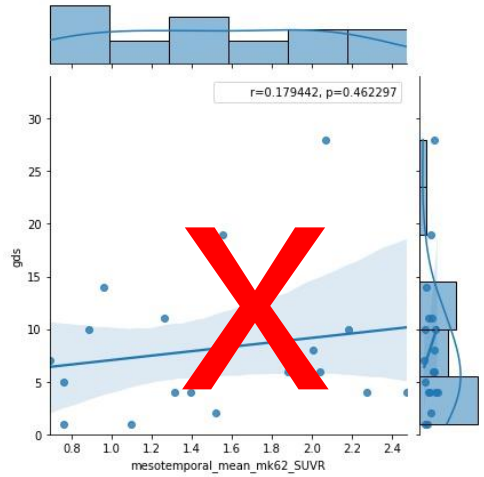
LLD





MCI





Samenvatting

- Geen significant verschil in:
  - Hippocampaal volume (~p=0.14)
  - Corticale amyloid neerslag (~p=0.13)
  - Hippocampale tau neerslag (~p=0.30)
  - Hippocampale synaptische densiteit (~p=0.70)
- GDS correleert met amyloid (niet met tau) in MCI (niet in LLD)

Psychomotore dysfunctie in depressie: een onderzoeksveld in beweging

CROSS-SECTIONAL

HC

Non - ECT

L3D

LLD

ECT

LONGITUDINAL

KLINISCHE TESTING

PSY

NEU

COG

ESM

STRUCTURELE BEELDVORMING

T1

T2

FLAIR

DTI

FUNCTIONELE BEELDVORMING

TAU

AMY

Synaptische densiteit

fMRI

Motor

UZ LEUVEN

Psychomotore dysfunctie (PMD)

Psycho = gerelateerd aan psychiatrische ziekte

Motore= betreft de motoriek

Dysfunctie = het werkt “niet goed”

PMD in 20(-60%) MDD[3] en ↑ leeftijd[5]

PMD responsief op TCA en ECT[4]… maar PD ook

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

Table 1
Overview of the psychomotor assessment techniques employed and main research purposes of the studies reviewed

Type of assessment	Number of studies	Main research purposes
1. Observer-rated assessments		
Clinical evaluation	1	Diagnosis
Single-item observation		
-Hamilton Depression Rating Scale	17	Pathophysiology, predictive capacity, daily-life activity
-Diagnostic interview	1	Study of young patients (preschool-age)
Psychomotor rating scale		
-Salpêtrière Retardation Rating Scale	12	Validity, treatment effect, pathophysiology, measurement, diagnosis
-CORE Assessment of Psychomotor Change	6	Validity, pathophysiology, predictive capacity, diagnosis
-Motor Agitation and Retardation scale	2	Validity, treatment effect
2. Gross motor activity		
Wrist actometer	9	Study of young patients, measurement, treatment effect, pathophysiology
Belt-worn actometer	2	Study in children, measurement
Movement analysis of gait	5	Measurement, treatment effect, daily life activity
Movement-pattern analysis (based on video-tape interview)	1	Diagnosis, pathophysiology
Wrist rotation approach	2	Measurement, predictive capacity
3. Fine motor activity: digitizer		
Copying tasks (lines, simple and complex figures)	5	Treatment effect, measurement, diagnosis,
Fitts' task	5	Diagnosis, measurement, treatment effect, pathophysiology
Symbol Digit Substitution Task	3	Diagnosis, pathophysiology
Sentence writing and drawing superimposed concentric circles	3	Treatment effect, measurement
4. Speech analysis	3	Measurement, prognosis

Schrijvers et al. 2008.

Beeldvorming PMD

- **Structureel** (CT/MRI)

  Ventrikeldilatatie

  Atrofie suppl.motor cortex, prefrontale cortex, basale ganglia

  Witte stofletsels (WML) frontostriataal en paralimbisch

- **Metabool** (Perfusie-, FDG-, RTI-32- and ^{18}F-DOPA - PET/ ^{99m}Tc- and ^{123}I-IBZM- SPECT/ ASL)

  Hyper/hypofunctie in frontostriataal circuit/basale ganglia, prefrontale kwab, cinguli

- **Functioneel** (fMRI, EEG)

  Gedaalde FA in VTA – frontale kwab connecties in fMRI

For review see: *Liberg et al. 2015, Bennabi et al. 2013, Buyukdura et al. 2011*

Hersenbrekers…

- PMD meting:
  - subjectief (schalen) vs objectief (instrumentele taken)
  - contributie stemming, motivatie en cognitie op meting
- PMD neuro beeldvorming: waar en wat? modaliteit? RDoC?
- PMD respons op ECT: hoe?

Motorisch assessment in L3D studie

Psychopathology. 2021;54(2):106-112. doi: 10.1159/000512959. Epub 2021 Mar 1.

Depression Severity Is Related to Less Gross Body Movement: A Motion Energy Analysis

Anna Sandmeir [1], Désirée Schoenherr [2], Uwe Altmann [2], Christoph Nikendei [3], Henning Schauenburg [3], Ulrike Dinger [3]

Klinisch

- CORE schaal
- UPDRS III
- SARA
- (NMSQ-PD)

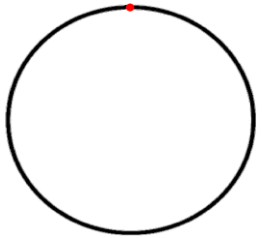
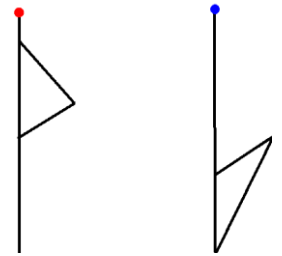
Experimenteel

- Tablet teken en schrijftaak
- Purdue Pegboard test
- Accelerometrie (Chill Band)
- Ganganalyse
- (spraakanalyse)

	HC (n=31) mean (SD)	LLD (n=8) mean (SD)	P*
MADRS	1.1 (1.87)	33.4 (11.09)	<0.001
MMSE	28.7 (1.39)	25.7 (3.35)	0.001
UPDRSIII	3.1 (2.73)	26.5 (11.77)	0.001
CORE	1.2 (1.81)	21.8 (10.20)	<0.001
SARA	1.2 (1.41)	6.0 (2.74)	0.001
PPT both hands (peg/30s)	10.6 (0.32)	8.33 (1.12)	0.012
Gait velocity (m/s)	1.18 (0.184)	0.85 (0.335)	0.001

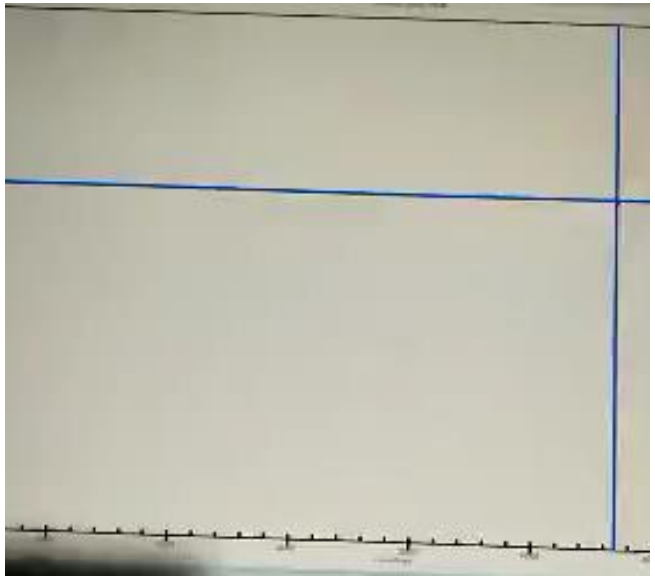
*Student's test with equal variance or [2]with unequal variance, p= 0.05 (2 sided). ns = non significant

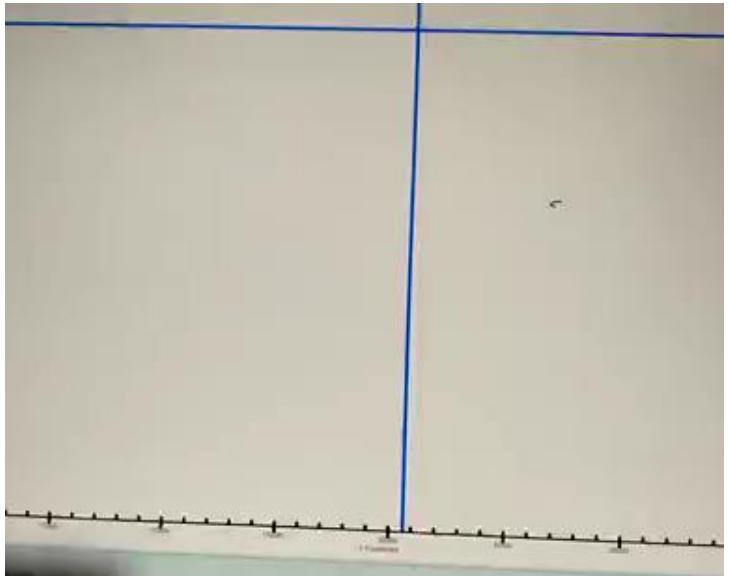
Image drawing[1,2]: MovalyzeR

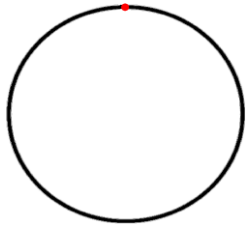
	EASY	COMPLEX
UNCUED		
CUED		

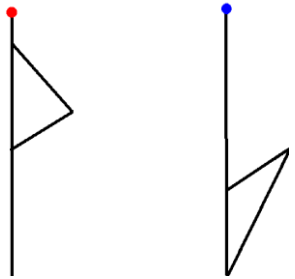
[1] Smits E et al. tandardized Handwriting to Assess Bradykinesia, Micrographia and Tremor in Parkinson's Disease. PLoS ONE 9(5): e97614.
[2] Hoffstaedter F et al. Internally vs. externally triggered movements in patients with major depression. Behav Brain Res. 2012 1;228(1):125-32.

Teken een cirkel, beginnend bij de rode bol…





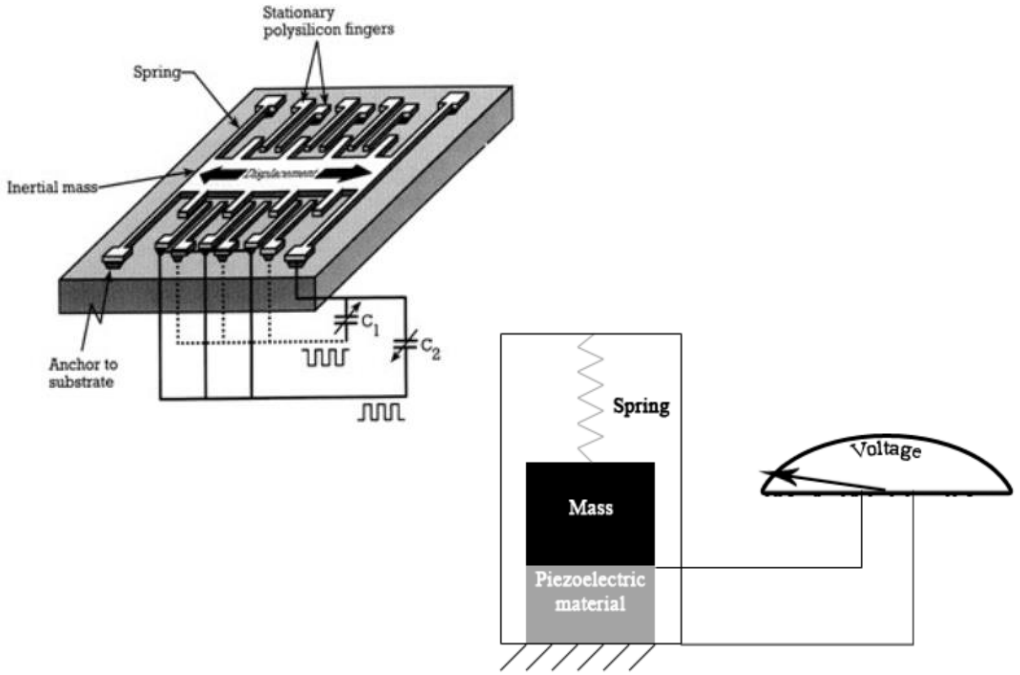


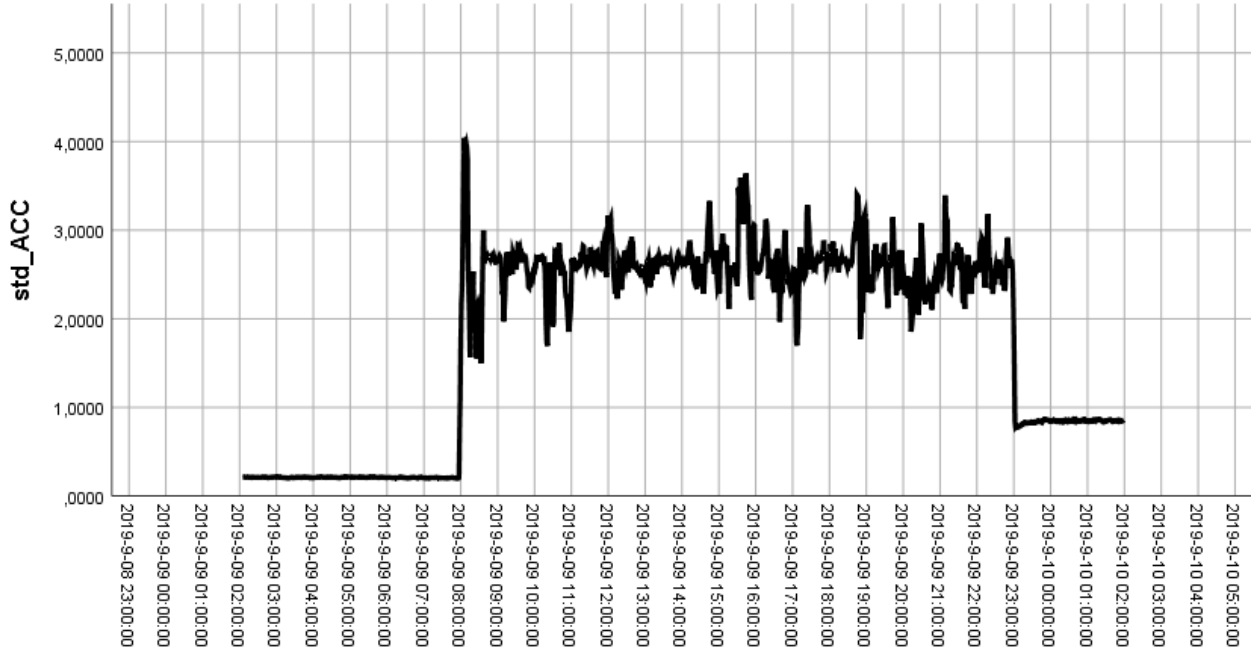


	HC (n=31)	LLD (n=8)	P*
LINE motor time (MT, s)	9.0 (2.62)	13.0 (4.75)	(0.052)
LINE start position (SP, s)	4.8 (1.31)	5.6 (2.42)	n.s.
LINE initiation time (IT, s)	5.8 (1.36)	10.1 (4.22)	n.s.
LINE drawing time (DT, s)	**3.2 (1.84)**	**5.5 (2.46)**	0.005
LINE velocity (cm/s)	**12.2 (6.55)**	**6.1 (2.36)**	0.014
CIRLE MT	18.0 (6.14)	32.6 (7.74)	<0.001
CIRCLE SP	5.2 (1.39)	5.0 (2.06)	n.s.
CIRCLE IT	**6.6 (1.86)**	**9.0 (3.20)**	0.010
CIRCLE DT	**11.3 (5.04)**	**23.8 (5.71)**	<0.001
FLAGS MT	23.4 (7.47)	38.7 (10.31)	< 0.001
FLAGS SP	**6.0 (1.52)**	**4.2 (2.07)**	0.012
FLAGS IT	8.1 (2.27)	9.6 (4.24)	n.s.
FLAGS DT FL 1	**7.7 (3.29)**	**14.3 (2.54)**	<0.001
FLAGS L to R switchtime	1.7 (0.96)	2.5 (0.91)	0.015
FLAGS DT FL 2	**5.9 (2.59)**	**11.5 (2.10)**	<0.001

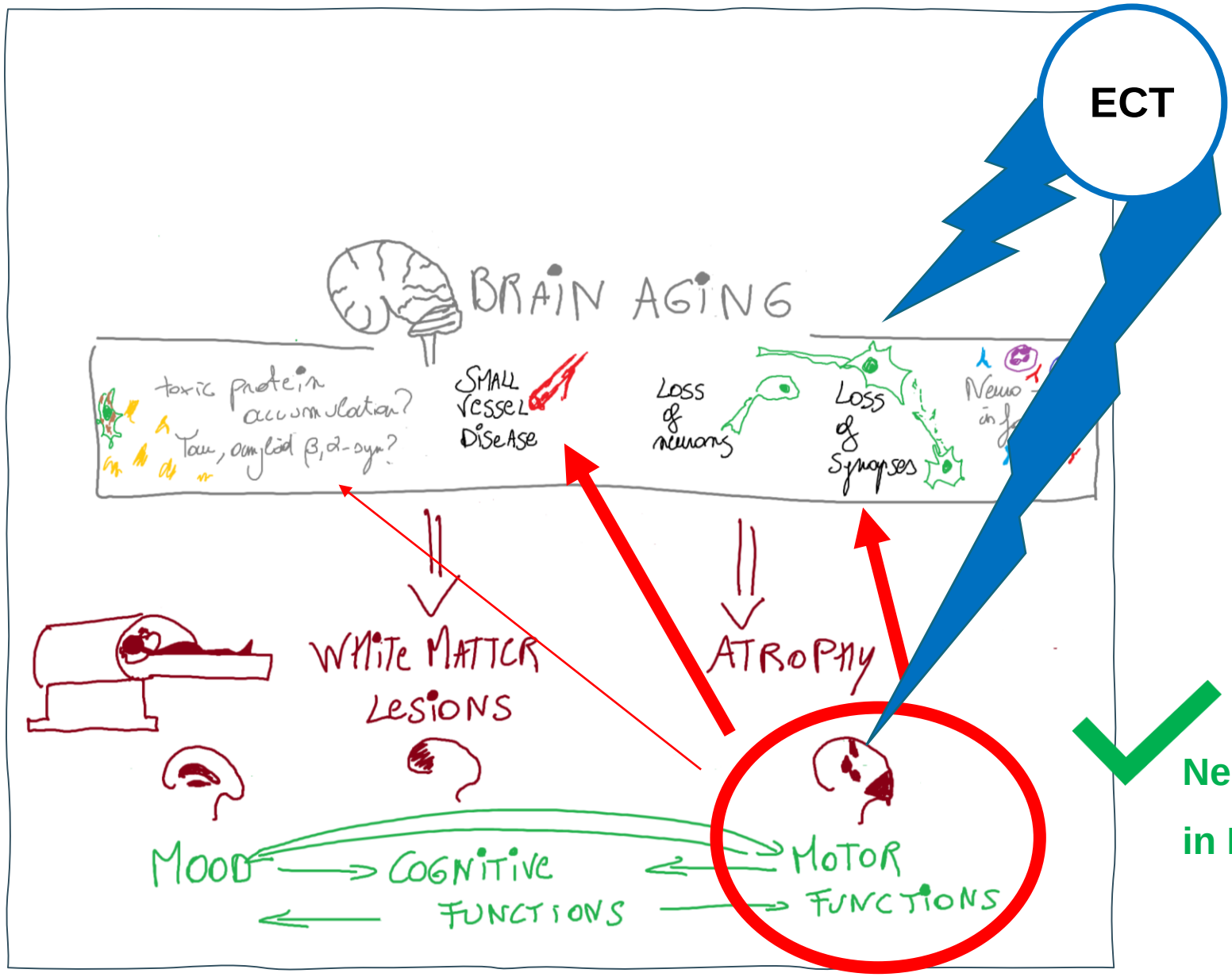
* Student's t test [1]with equal variance or [2]with unequal variance, p= 0.05 (2 sided). n.s. = non significant

Chillband: 3-Axial accelerometer



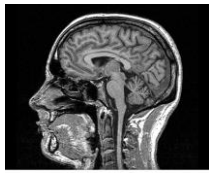


https://learn.sparkfun.com/tutorials/accelerometer-basics/all



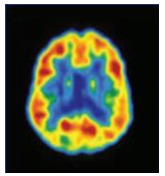
Neurobiology of PMD in LLD (L3D study)

Imaging: MRI & PET



MRI sequences

- **T1**
- **T2 Cube +** T2 High Resolution (hippocampus)
- **FLAIR**
- ASL (Tissue perfusion)
- SWAN (blood vessels, iron)
- DTI (tractography)
- rsMRI (DMN – ACC en pFC)



PET modalities

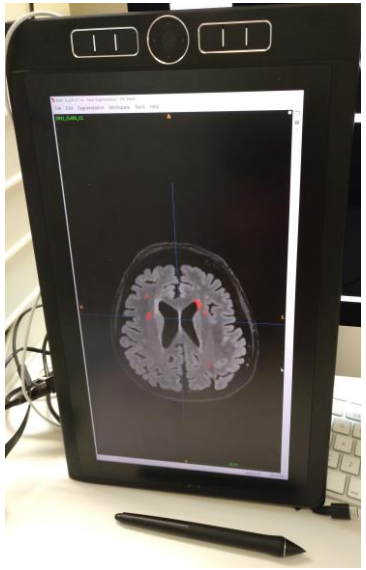
- **UCB-J (11C)** $T_{1/2}$ 20 min

  Target: SV2A (synaptic density)
- MK-6240 (18F) T1/2 110 min.

  Target: Tau (NF tangles)
- Flutemetamol (18F) T1/2 110 min.

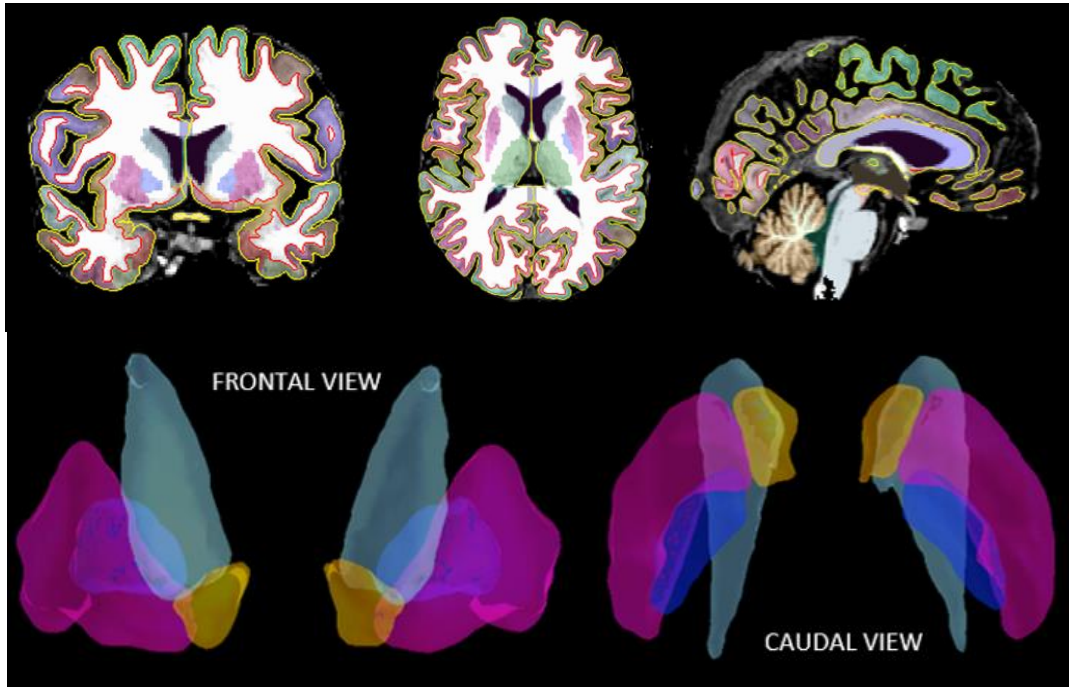
  Target: β-Amyloïd (plaques)

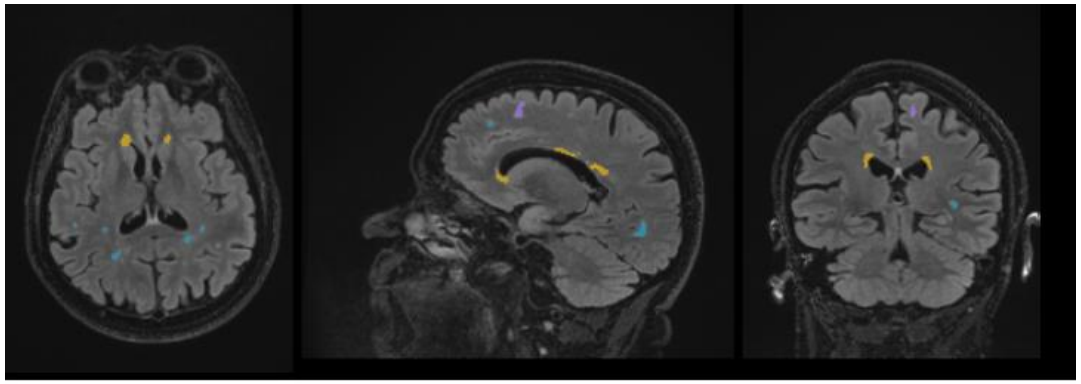
PMD neurobiologie: MRI

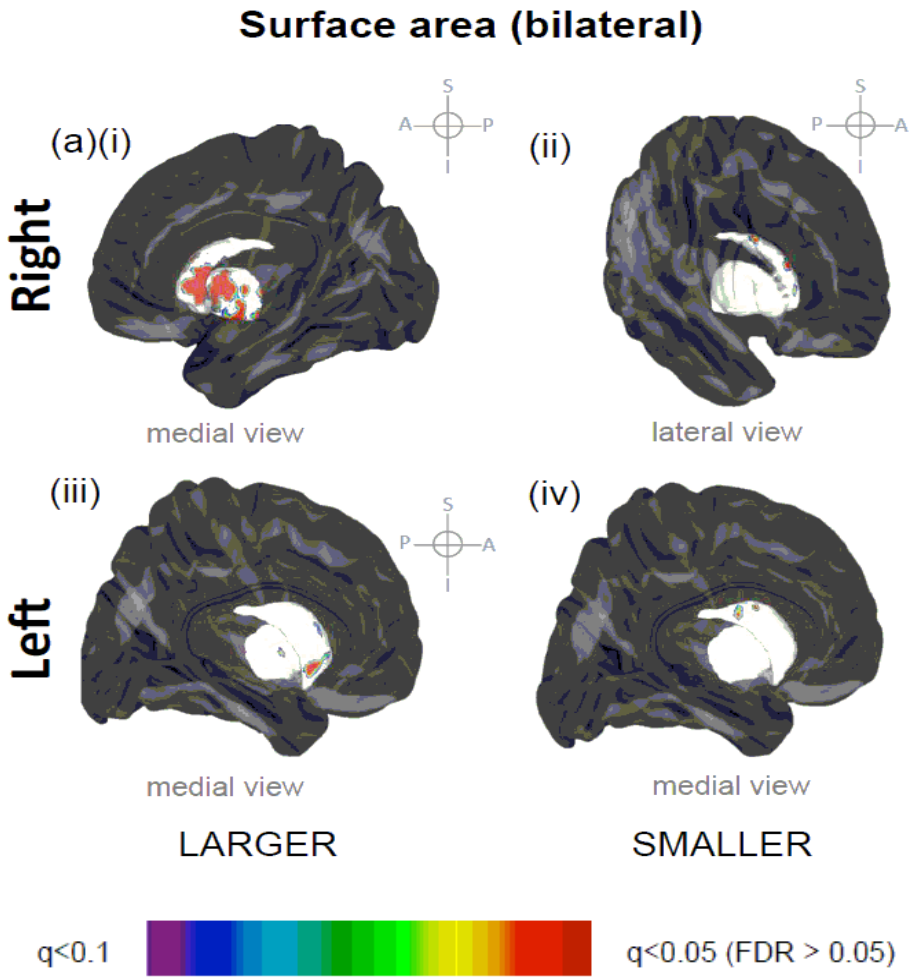


- Volumetrie vs shape analyse vs VBM
- WML quantificatie: Fazekas vs automated vs semi-automated
- WM integriteit analyse: DTI/tractografie → hubs vs connecties
- …

→ Statistisch design met controle voor leeftijd, geslacht, cognitie en stemming = sufficiënte sample size (power analyse)!


FRONTAL VIEW
CAUDAL VIEW



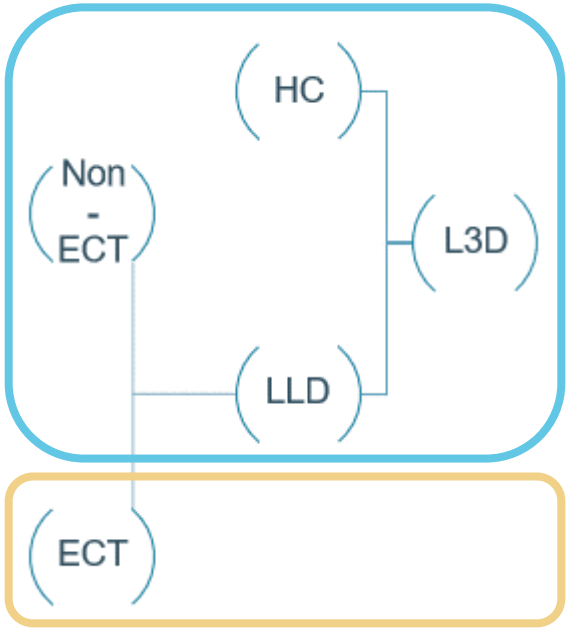

Surface area (bilateral)
(a)(i)
(ii)
Right
S
A
P
I
medial view
lateral view
(iii)
(iv)
Left
medial view
medial view
LARGER
SMALLER
q<0.1
q<0.05 (FDR > 0.05)

Conclusie neurobiologie van PMD

1. Meten van PMD:
   - Objectieve technieken (tablet, 24u-actimetrie)
   - Sample size toename → controle voor cognitie, stemming, apathie
2. Beeldvorming hersenen bij PMD:
   - hybride modaliteiten
3. Neuroplasticiteit basale ganglia bij ECT ….. **?**

Neurobiologische effecten van ECT bij depressie op latere leeftijd

CROSS-SECTIONAL



LONGITUDINAL

KLINISCHE TESTING

- PSY
- NEU
- **COG**
- ESM

STRUCTURELE BEELDVORMING

- **T1**
- T2
- FLAIR
- DTI

FUNCTIONELE BEELDVORMING

- TAU
- AMY
- **Synaptische densiteit**
- fMRI

ECT

Research Foundation Flanders
Opening new horizons


MDD
ECT
MRI
ECS
SHAM
Molecular
Glia
Factor
PET
BDNF
Protein
DTI
Blood
Cell
Imaging
Structural
Serum
Choline
Neurons
mRNA
Bipolar
Kinase
Trh
Serotonin
Plasma
Enzyme
Gaba
Synapses
Adenosine
Proliferation
Glutamate
Astrocyte
Cytokines
Hc
Alff
Fdg
Eeg
Stress
Hippocampal
Spectroscopy
Gene expression
Schizophrenia
Creb
Ltp
Vegf
Oedema
Gray Matter
Transcription
Metabolite
Neurotrophic
Channel
Amygdala
Immune system
White matter
Neuropeptide
Thickness
Neurotransmitter
Interleukin
Hormones
Cortisol
Somatostatin
Dopamine
Kynurenine
Phosphodiesterase
Perfusion
Angiogenesis
Oxidative
Subfields
Sortilin
Proteome
Cortical
Klotho
Peptide
Synthesis
Excitability
Galanin
Ngf
Fgf

Wat zegt de literatuur?

ECT

- Grijze stof toename
- Functionele connectiviteit
- Neurotrofe factoren
- Cytokines
- Metabolites
- Gen expressie

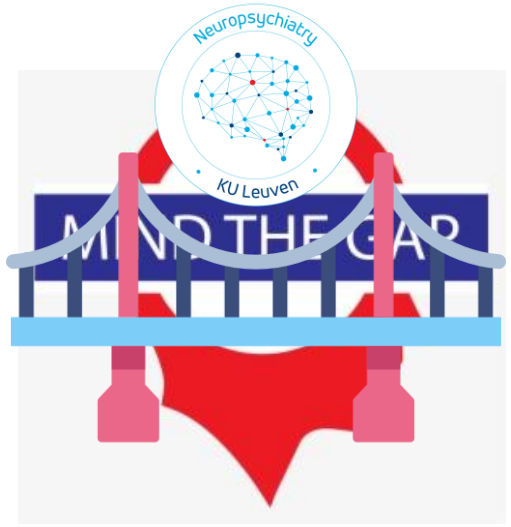
ECS

- Neuroplasticiteit
- synaptogenese
- Angiogenese
- Gen expressie
- Cytokines
- Neurotrofe factoren

Wat zegt de literatuur?

ECT

- Grijze stof toename
- Functionele connectiviteit
- Neurotrofe factoren
- Cytokines
- Metabolites
- Gen expressie



ECS

- Neuroplasticiteit
- synaptogenese
- Angiogenese
- Gen expressie
- Cytokines
- Neurotrofe factoren

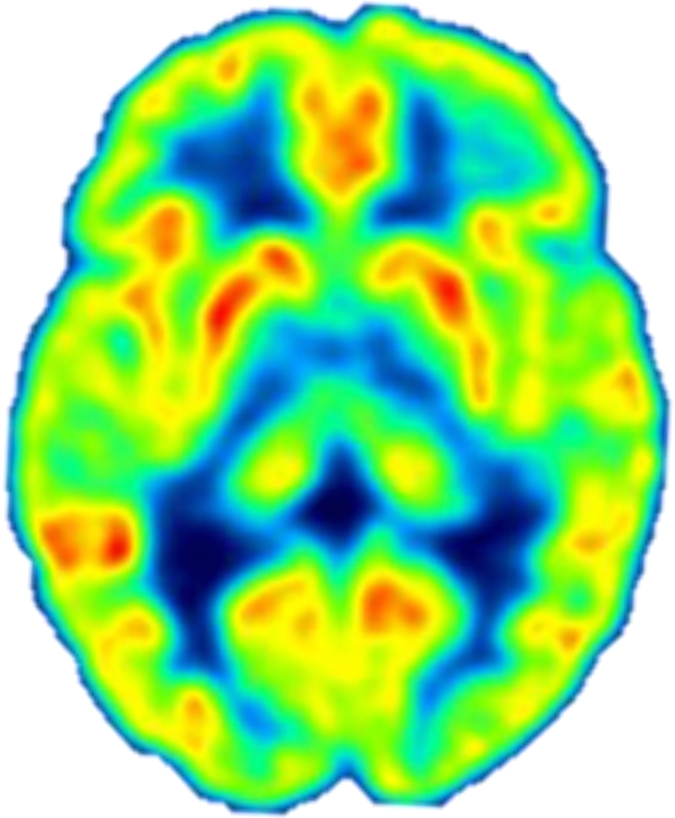
Synaptic plasticity following electroconvulsive therapy

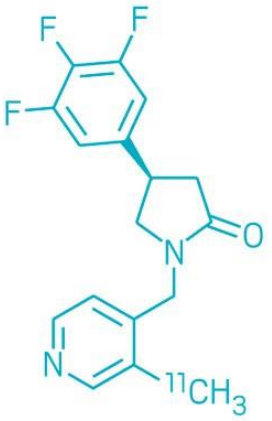
Neuroplasticity

Leuven Late-Life Depression Study

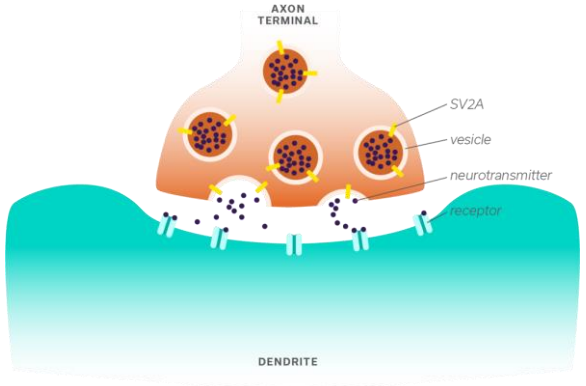
UCB-J radiotracer

Longitudinal design





[11C] UCB-J



ECT Design

Baseline T_1 & post-ECT T_2

Psychiatrische data

- Montgomery-Asberg Depression Rating Scale
- Geriatric Depression Scale
- Apathy Evaluation Scale

Neuropsychologische data

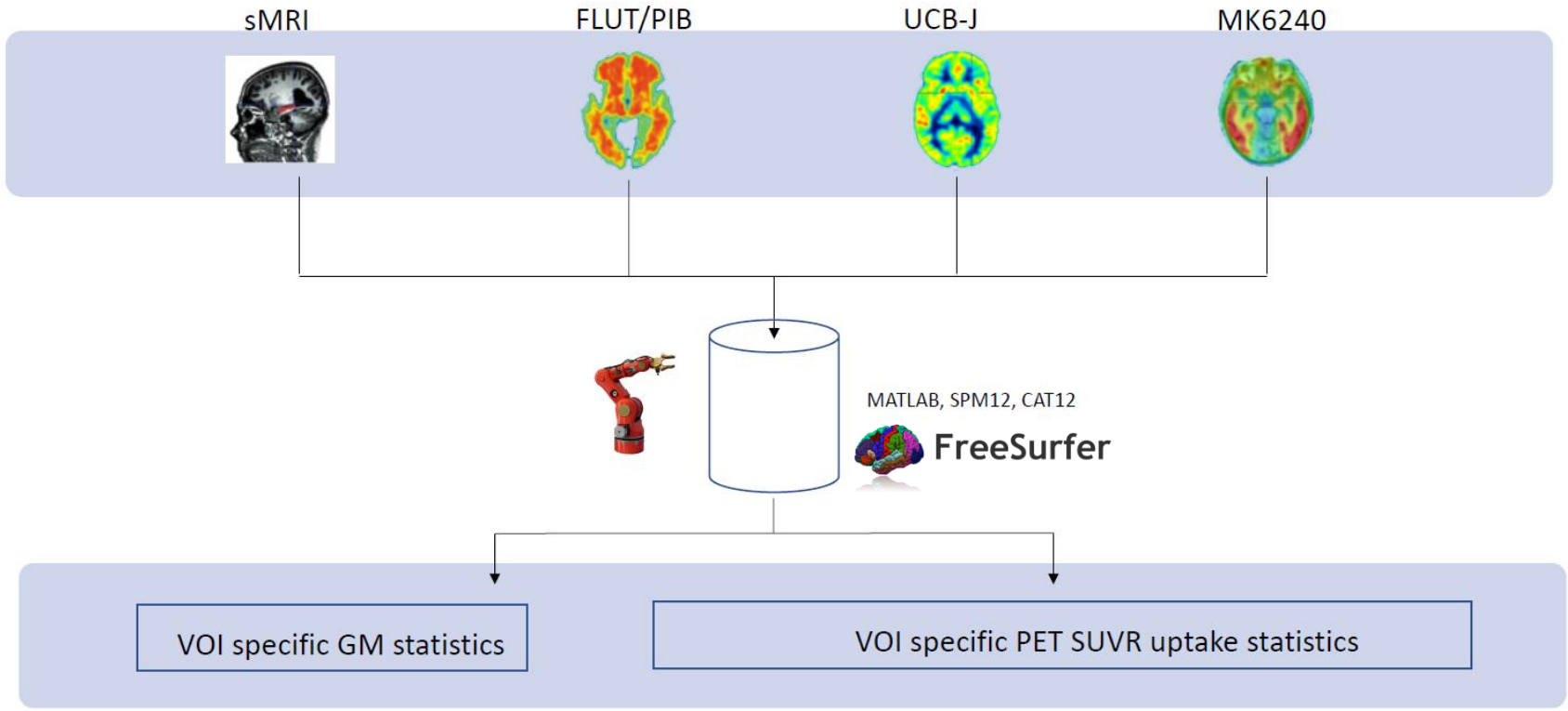
- Mini-Mental State Examination
- Auditory verbal learning test (M)
- Raven's Coloured Progressive Matrices (EF)
- Trail Making Test (A)
- Stroop Task (EF)
- Boston Naming Test (M)
- Verbal fluency
- Digit span (M)
- Autobiographical memory interview (M)

M: memory ; EF: Executive Functioning ; A: Attention

PET-MRI imaging

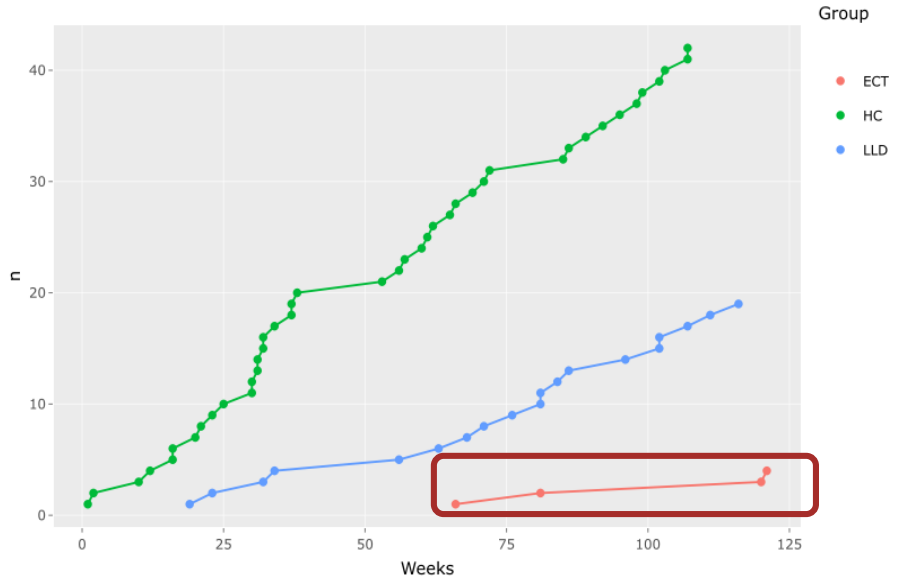
- PET
  - Synaptic Density (11C-UCB-J)
- MRI
  - T1
  - High Resolution T2
  - Resting fMRI

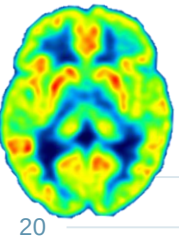
Processing


sMRI
FLUT/PIB
UCB-J
MK6240
MATLAB, SPM12, CAT12
FreeSurfer
VOI specific GM statistics
VOI specific PET SUVR uptake statistics

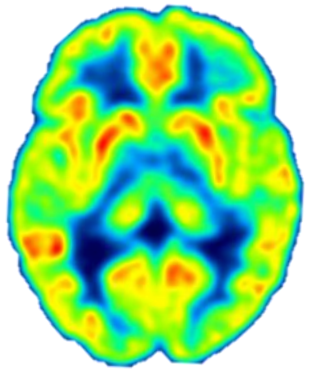
Kenmerken

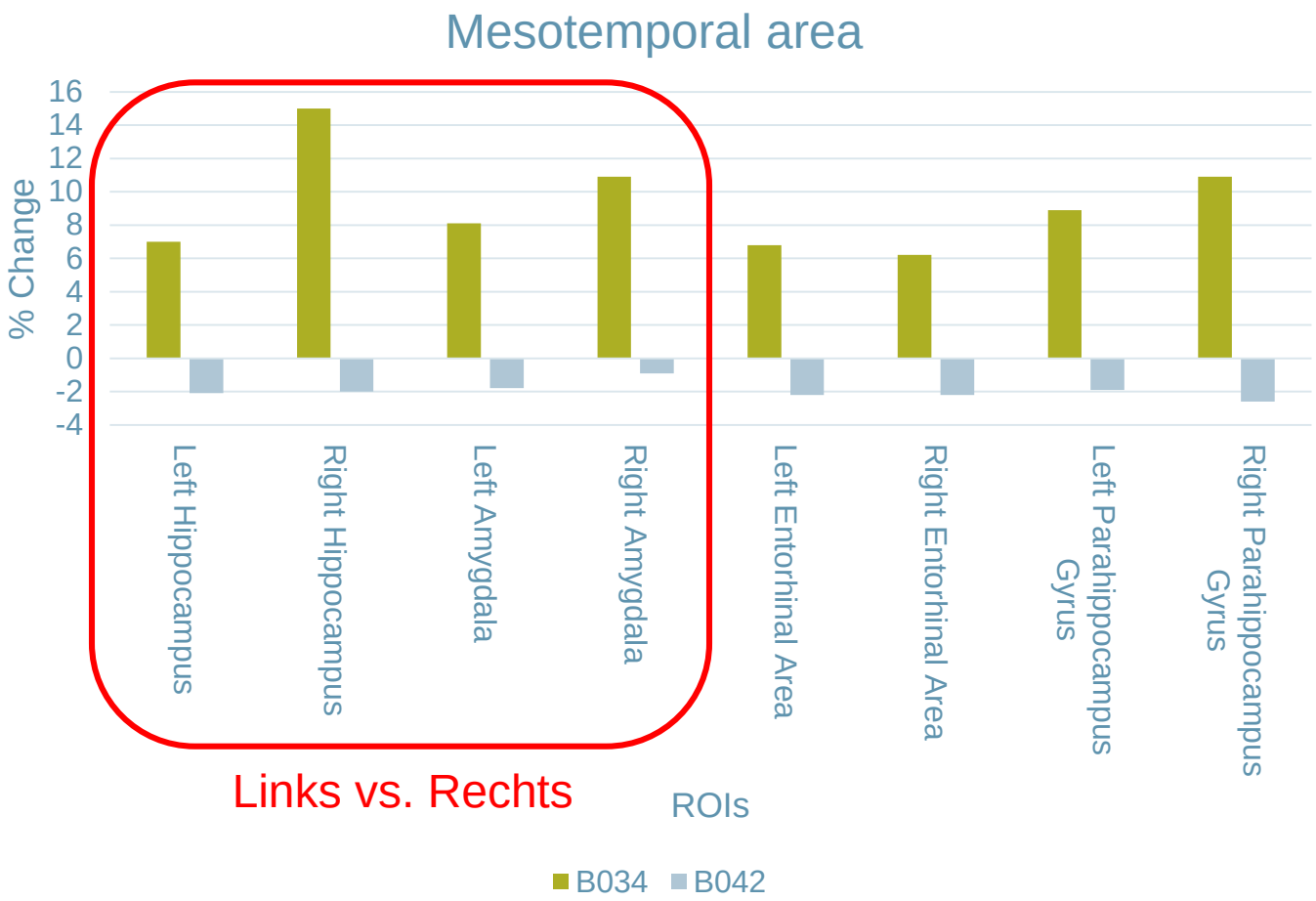
	B034	B042
Leeftijd	74	71
Geslacht	V	V
Opleiding (jaren)	12	16
BMI	34	18
MMSE	29	29
Voorgaande MDD episodes	2	4
Psychotische kenmerken	Afwezig	Afwezig
Onset leeftijd	45	33
Vroegere ECT	Nee	Ja
Stimulatie	RUL	RUL



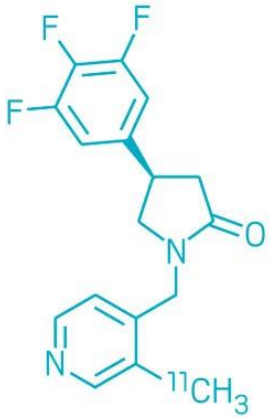


Left Hemisphere
20
15
10
5
0
-5
Right Hemisphere
30
25
20
15
10
5
0
-5
-10
Accumbens
Amygdala
Brainstem
Caudate
Hippocampus
Lateral Ventricle
Pallidum
Putamen
Thalamus Proper
Ventral DC
Basal Forebrain
Anterior Cingulate Gyrus
Anterior Insula
Anterior Orbital Gyrus
Angular Gyrus
Calcarine Cortex
Central Operculum
Cuneus
Entorhinal Area
Frontal Operculum
Frontal Pole
Fusiform Gyrus
Gyrus Rectus
Inferior Occipital Gyrus
Inferior Temporal Gyrus
Lingual Gyrus
Lateral Orbital Gyrus
Middle Cingulate Gyrus
Medial Frontal Cortex
Middle Frontal Gyrus
Middle Occipital Gyrus
Medial Orbital Gyrus
Postcentral Gyrus Medial Segment
Precentral Gyrus Medial Segment
Superior Frontal Gyrus Medial...
Middle Temporal Gyrus
Occipital Pole
Occipital Fusiform Gyrus
Opercular Part of the Inferior...
Orbital Part of the Inferior Frontal...
Posterior Cingulate Gyrus
Precuneus
Parahippocampus Gyrus
Posterior Insula
Parietal Operculum
Postcentral Gyrus
Posterior Orbital Gyrus
Planum Polare
Precentral Gyrus
Planum Temporale
Subcallosal Area
Superior Frontal Gyrus
Supplementary Motor Cortex
Supramarginal Gyrus
Superior Occipital Gyrus
Superior Parietal Lobule
Superior Temporal Gyrus
Temporal Pole
Triangular Part of the Inferior...
Transverse Temporal Gyrus
B034
B042

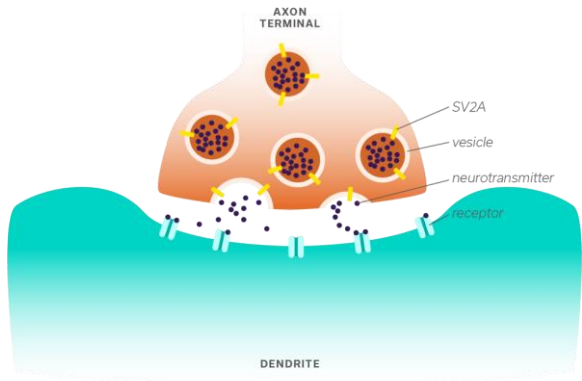




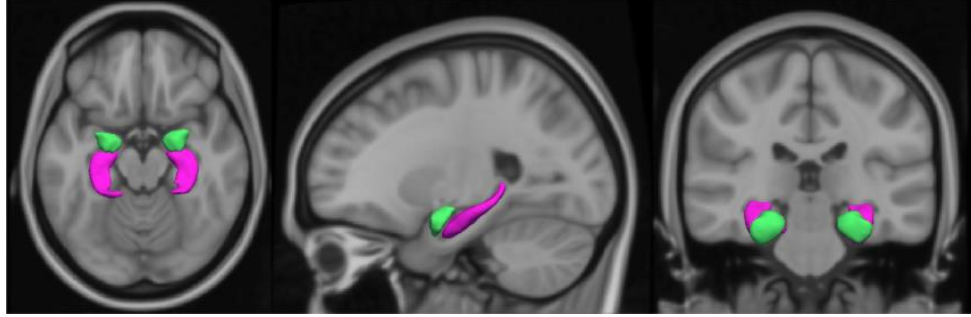
Links vs. Rechts

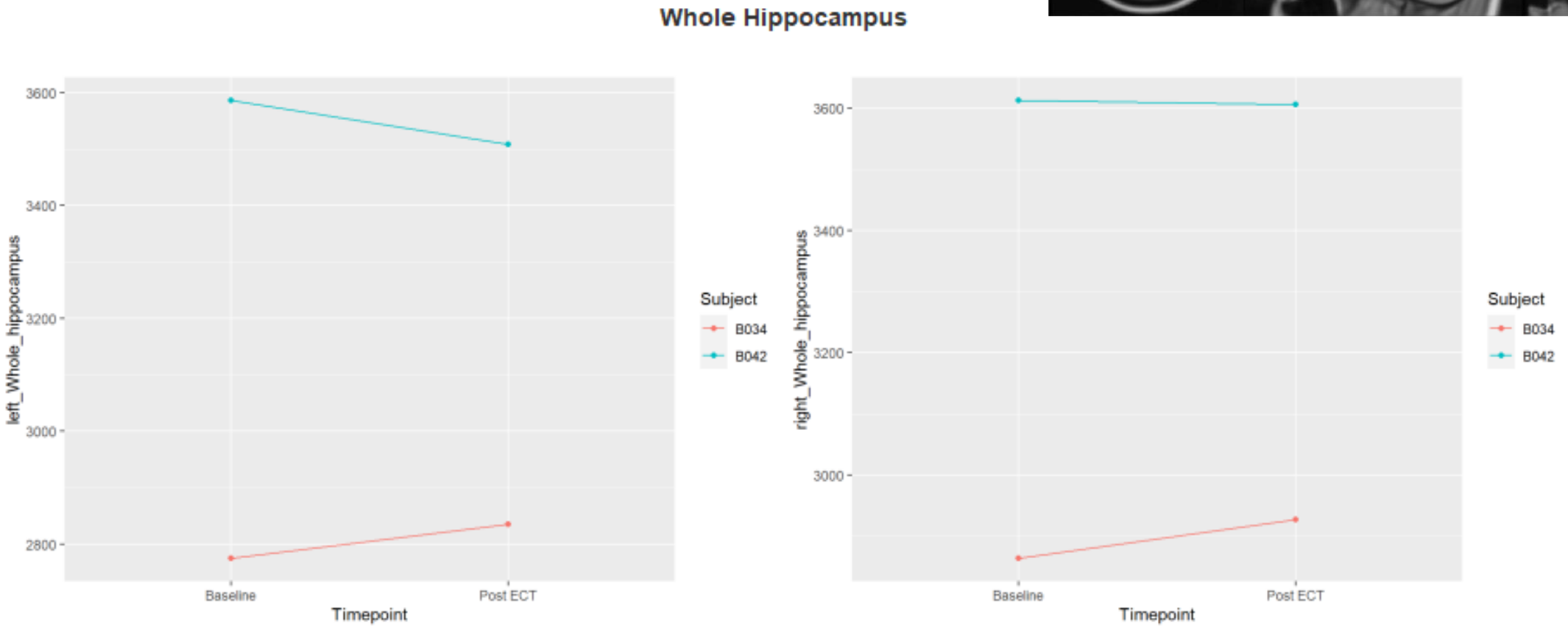


[11C] UCB-J

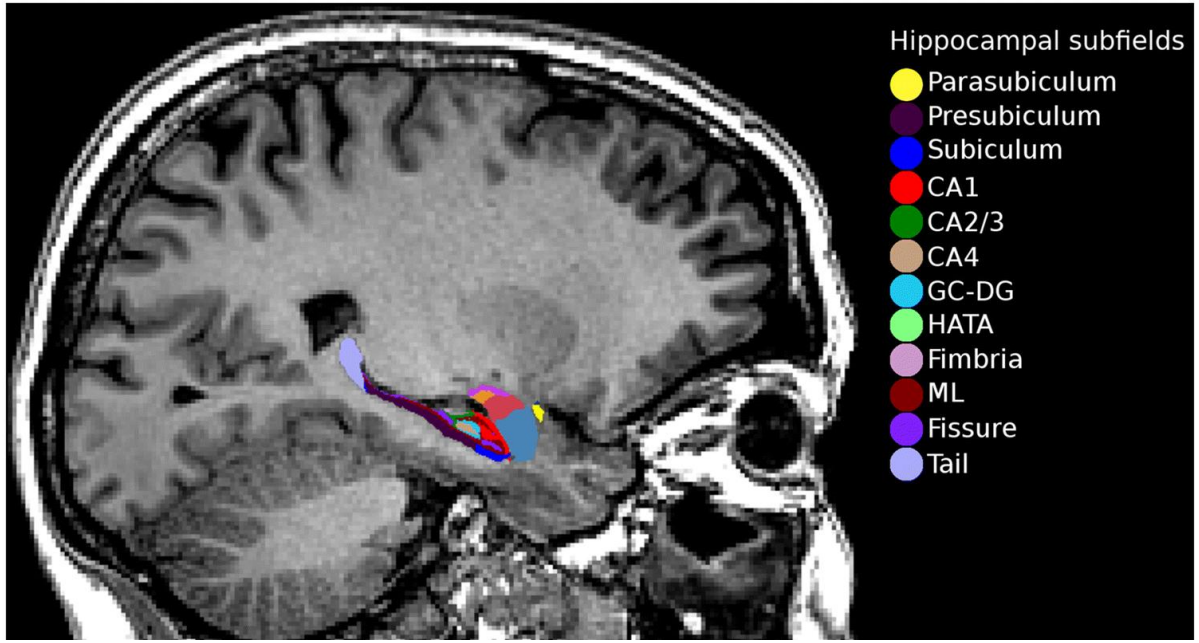


Hippocampus





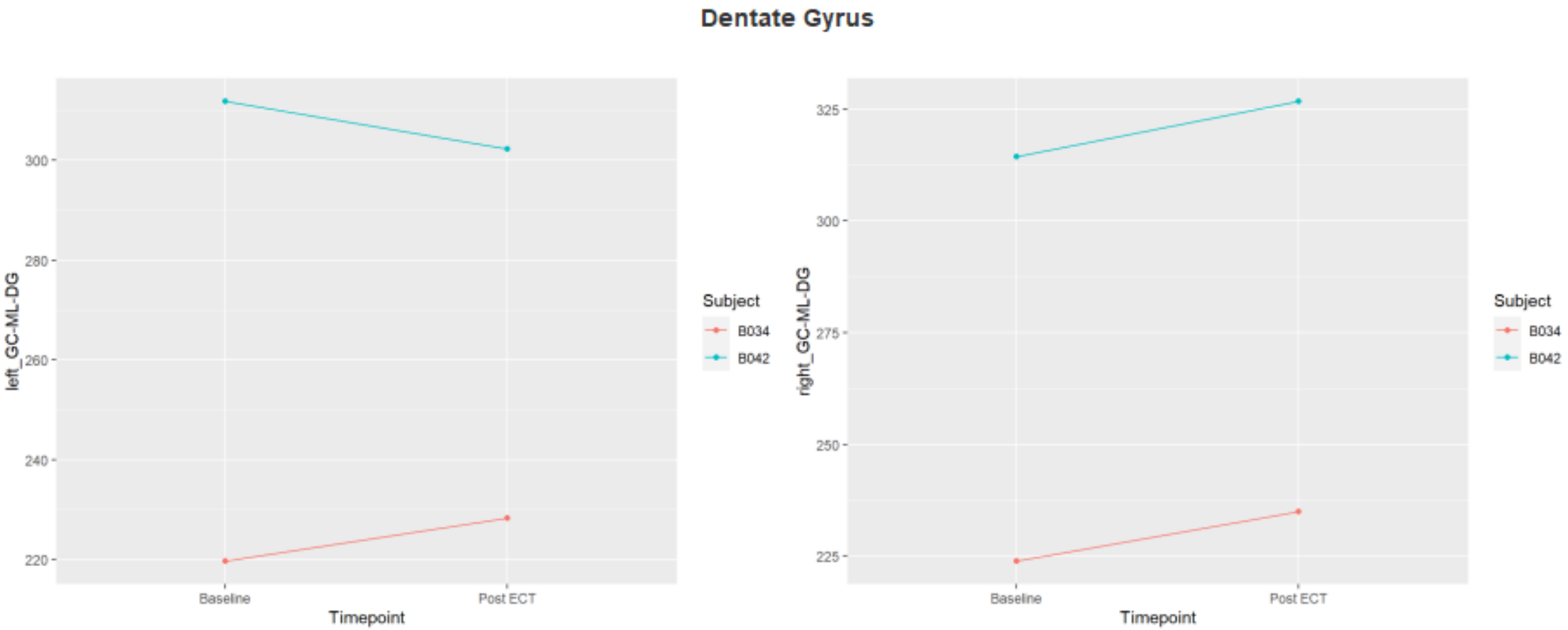
Hippocampus



FreeSurfer

Hippocampus

RUL Stimulatie!



Blinded radiologist ratings

	B034		B042	
Feature	**Baseline**	**Post-ECT**	**Baseline**	**Post-ECT**
Global Cortical Atrophy – Ventricles	2	2	1	1
Clobal Cortical Atrophy – Frontal	1	1	1	1
Clobal Cortical Atrophy – parieto-oc	1	1	1	1
Clobal Cortical Atrophy – Temporal	2	2	0	0
Medial Temporal Lobe Atrophy	2/3	2/**2**	1/0	1/0
Hippocampal edema	No	No	No	No

Dr. Ahmed Radwan

Neuropsychologische veranderingen

- Mini-Mental State Examination
- Auditory verbal learning test (M/A)
- Raven's Coloured Progressive Matrices (EF)
- Trail Making Test (A)
- Stroop Task (EF)
- Boston Naming Test (M)
- Verbal fluency
- Digit span (M)

M: memory ; EF: Executive Functioning ; A: Attention

Boston Naming Test (M)
Raven's Coloured Progressive Matrices (EF)
Digit Span (M)
Stroop Task (EF)

Mini-Mental State Examination
Auditory Verbal Learning Test (M/A)
Trail Making Test (A)
Verbal Fluency

Besluit

Behavioral and neural correlates of the positivity effect in late-life depression

CROSS-SECTIONAL

HC

Non - ECT

L3D

LLD

ECT

LONGITUDINAL

KLINISCHE TESTING

PSY

NEU

COG

ESM

STRUCTURELE BEELDVORMING

T1

T2

FLAIR

DTI

FUNCTIONELE BEELDVORMING

TAU

AMY

Synaptische densiteit

fMRI

EMOTIONS

What's fMRI?

- functional Magnetic Resonance Image (fMRI)
- Blood-Oxygen-Level-Dependent (BOLD) signal
- Correlation, not Causation

Socioemotional Selectivity Theory (SST)

- When time horizon is perceived as limited, people tend to focus on things benefiting well-being (Carstensen et al., 1999).
- Elder adults tend to attend to positive stimuli and adopt emotion regulation strategies automatically when facing negative events (Mather, 2012).
- Increased engagement of emotion-regulation brain regions in elderly

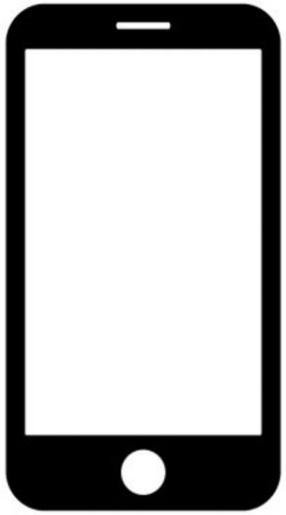

ng
stimulus
stimulus
8s
fM

Chill Band+

- Skin Conductance
- Skin Temperature
- Acceleration (ACC)

Ecological Momentary Assessment (EMA)

- Past Stress
- Current Stress
- Social Stress
- Positive Affect
- Negative Affect
- Interoception



EMA questionnaire

Blok 1: Negatief affect

- Net voor het alarm voelde ik mij onzeker
- Net voor het alarm voelde ik mij angstig
- Net voor het alarm voelde ik mij neerslachtig
- Net voor het alarm voelde ik mij schuldig
- Net voor het alarm voelde ik mij eenzaam

Blok 2: Positief affect

- Net voor het alarm voelde ik mij opgewekt
- Net voor het alarm voelde ik mij ontspannen
- Net voor het alarm voelde ik mij tevreden

Blok 3: Stress:

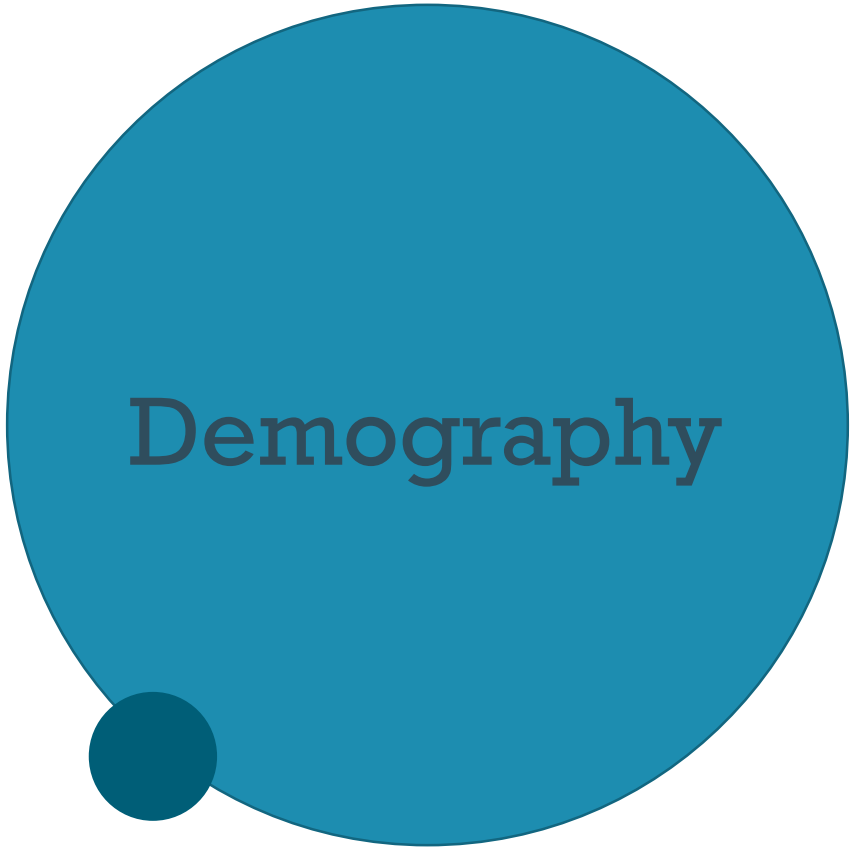
- Denk aan de belangrijkste gebeurtenis die is voorgevallen sinds de vorige rapportering. Hoe aangenaam was deze gebeurtenis?
- Hoeveel stress had u op het moment dat het alarm afging?

Blok 4: Sociale context

- Met wie ben ik op dit moment?
- Ik vind dit gezelschap aangenaam
- Ik zou liever alleen zijn op dit moment
- Ik vind het aangenaam om alleen te zijn op dit moment
- Ik zou liever in het gezelschap van anderen zijn op dit moment

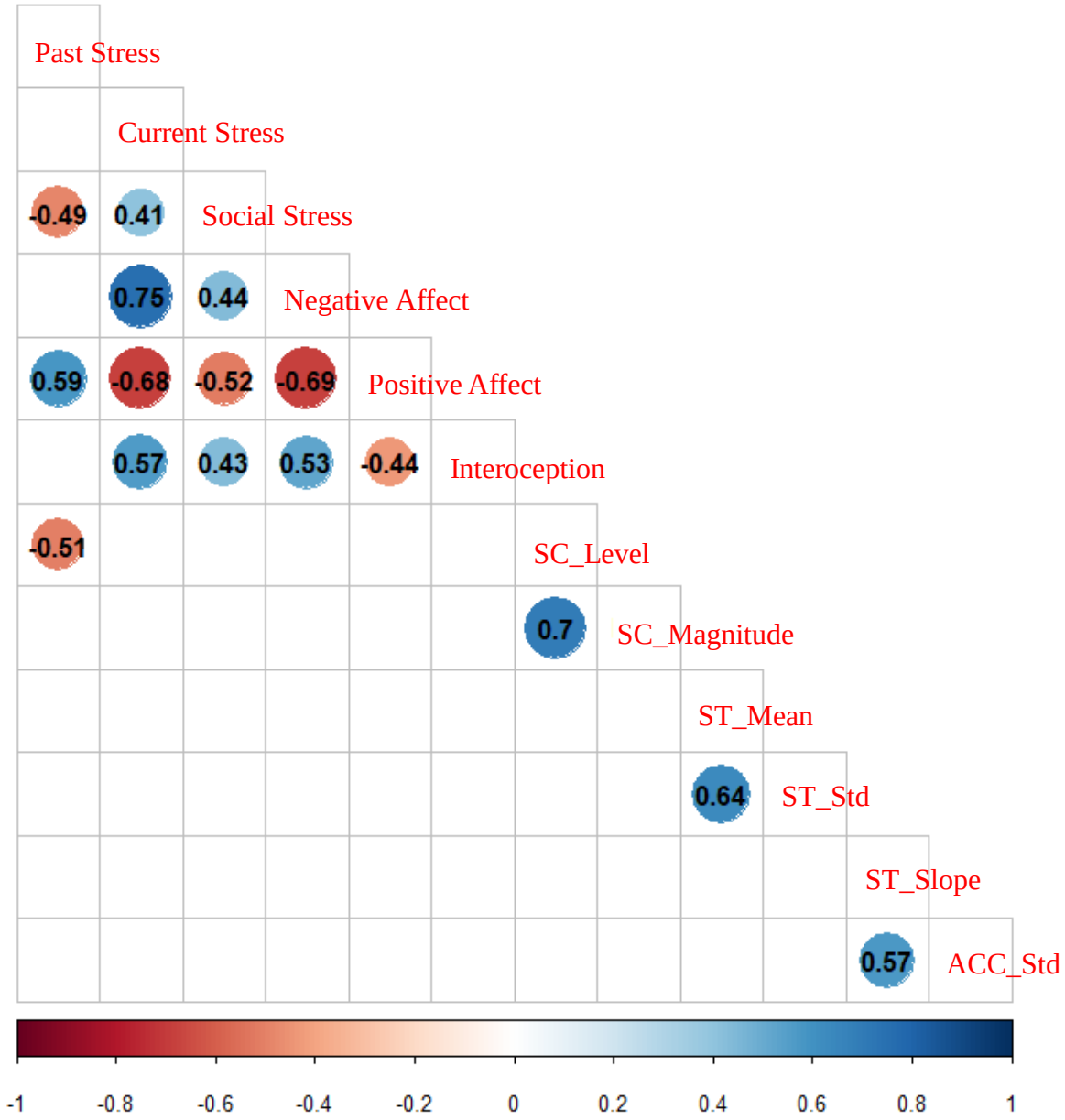
Blok 5: Interoceptie

- Beschrijf op een schaal van 1 tot 10 hoe sterk u interne prikkels op dit eigenste moment ervaart



- 26 Healthy Control
  - 14 Female, 12 Male
  - Age: 60 – 88 (mean: 70.23; SD: 6.483)

Associations between EMA and ChillBand

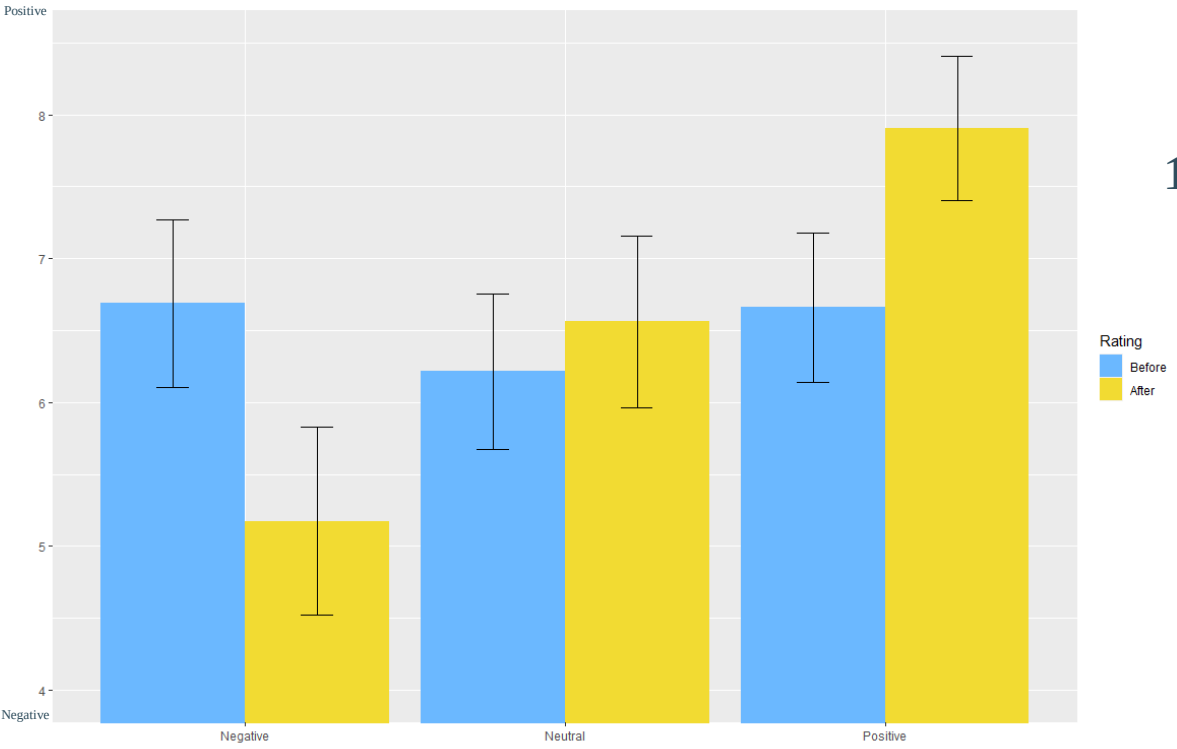


SC: skin conductance; ST: skin temperature; ACC: accelerometer signal.

Mood Rating

17 subjects
- 11 female
- 6 male

Age: 62 – 88
- Mean: 71.53
- SD: 6.938



1: Negative

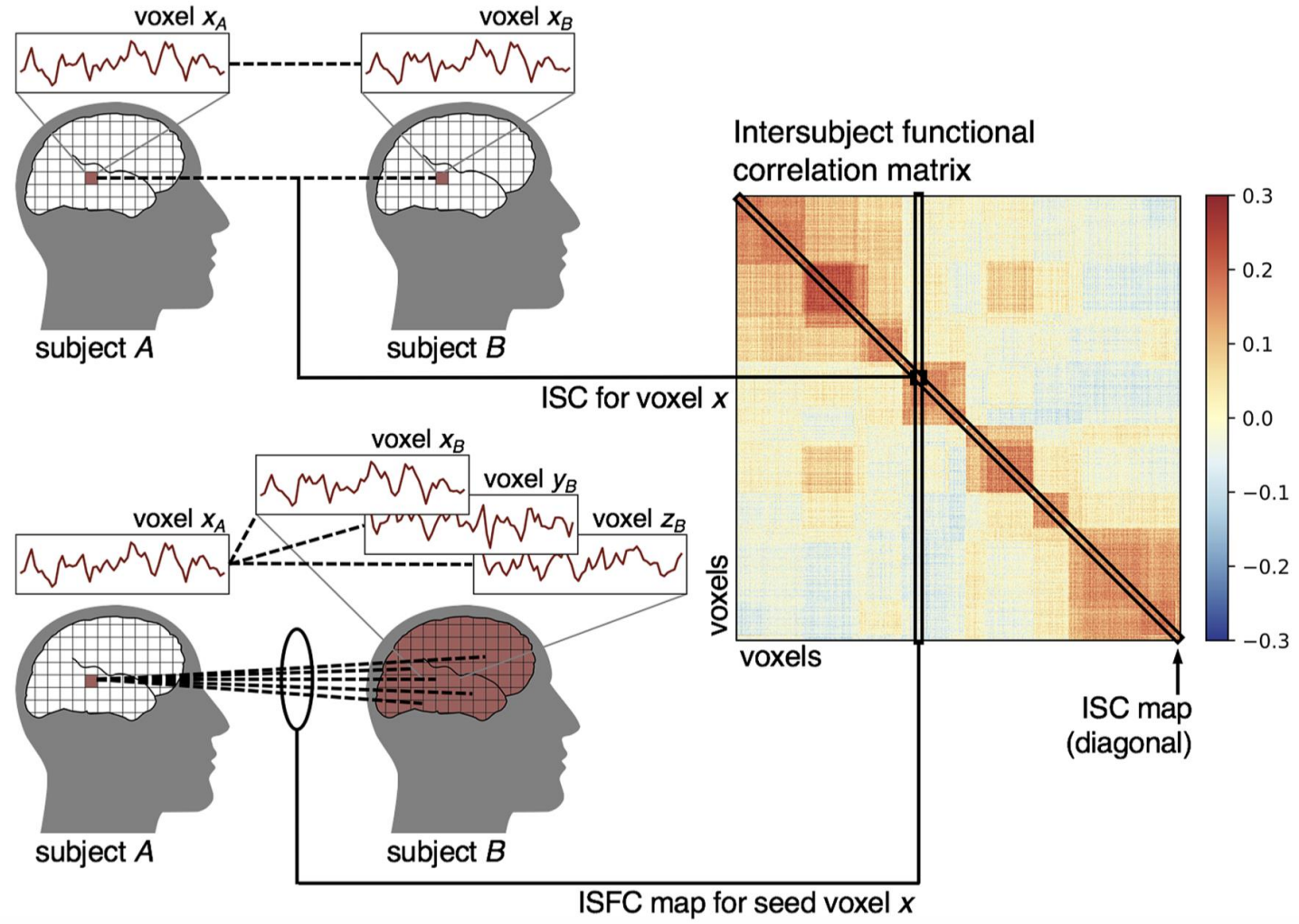
10: Positive

N = 17	Before	After	Difference	p value
Negative	6.686	5.174	-1.512	0.027[a]**
Neutral	6.216	6.563	0.347	.573
Positive	6.661	7.904	1.243	0.009[a]**

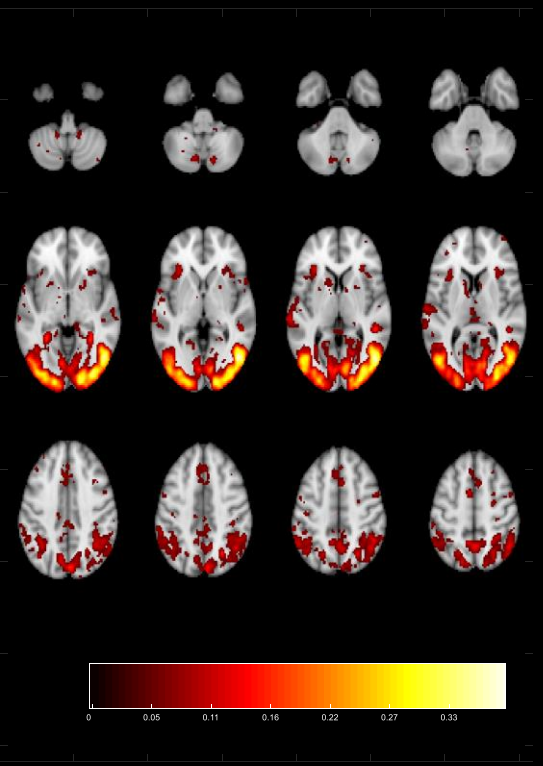
a: Wilcoxon Signed Ranks Tes

Inter-Subject Correlation (ISC)

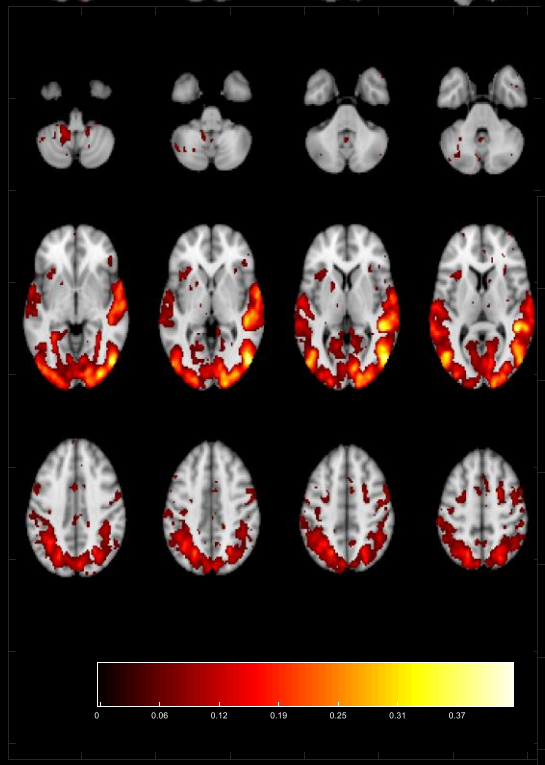
- Hasson et al. (2004)
  - Complex and continuous situations
    - Social interaction
    - Narrative comprehension
    - Movie clips



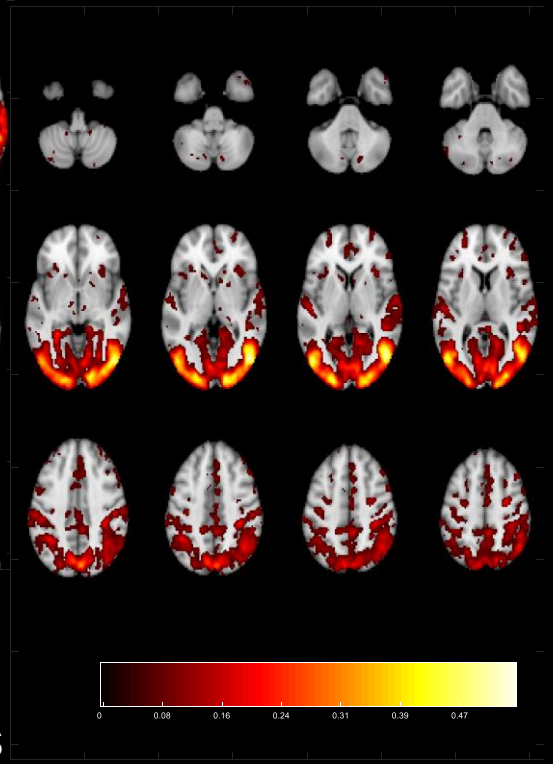
Nastase et al. (2019)



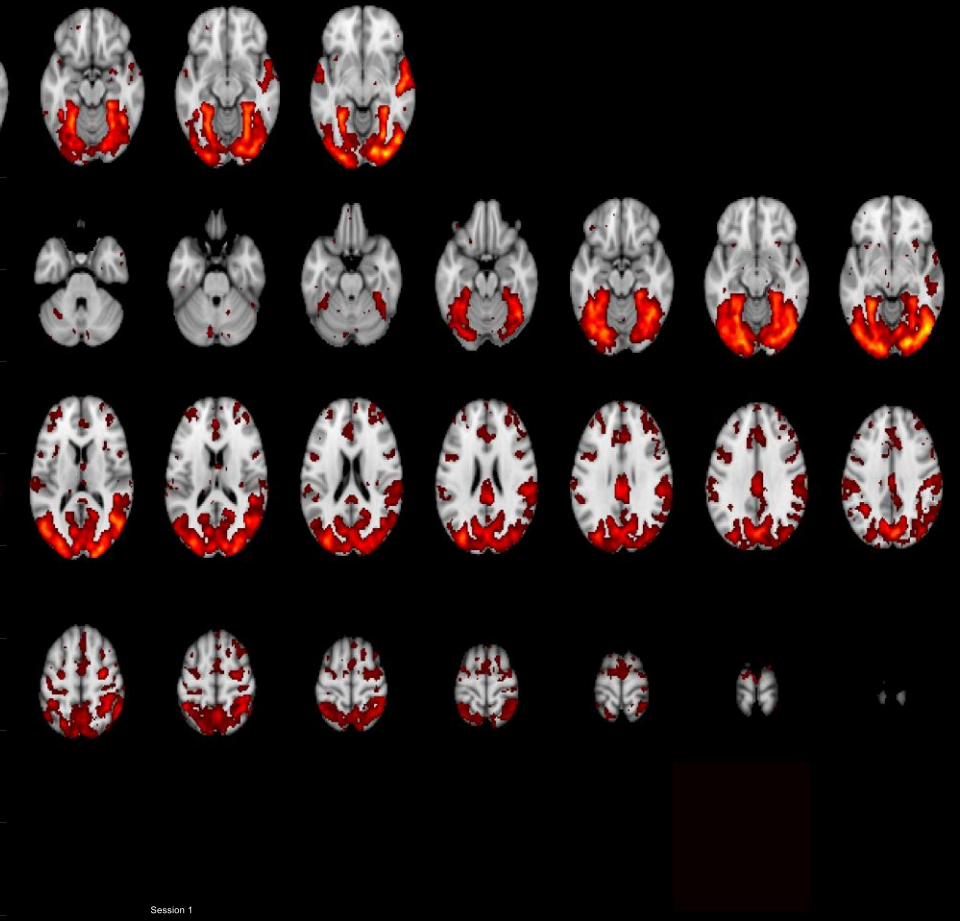
Neutral clips



Negative clips

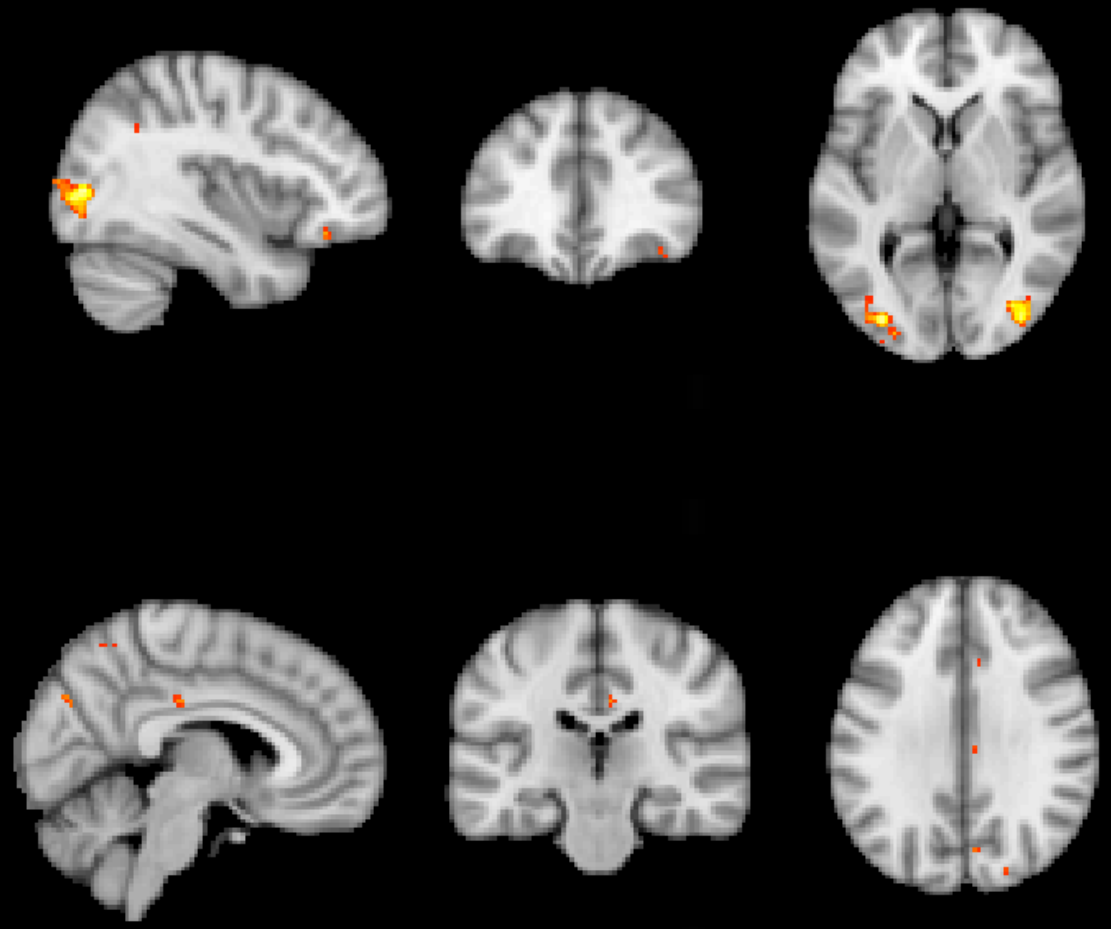


Positive clips



Negative > Neutral

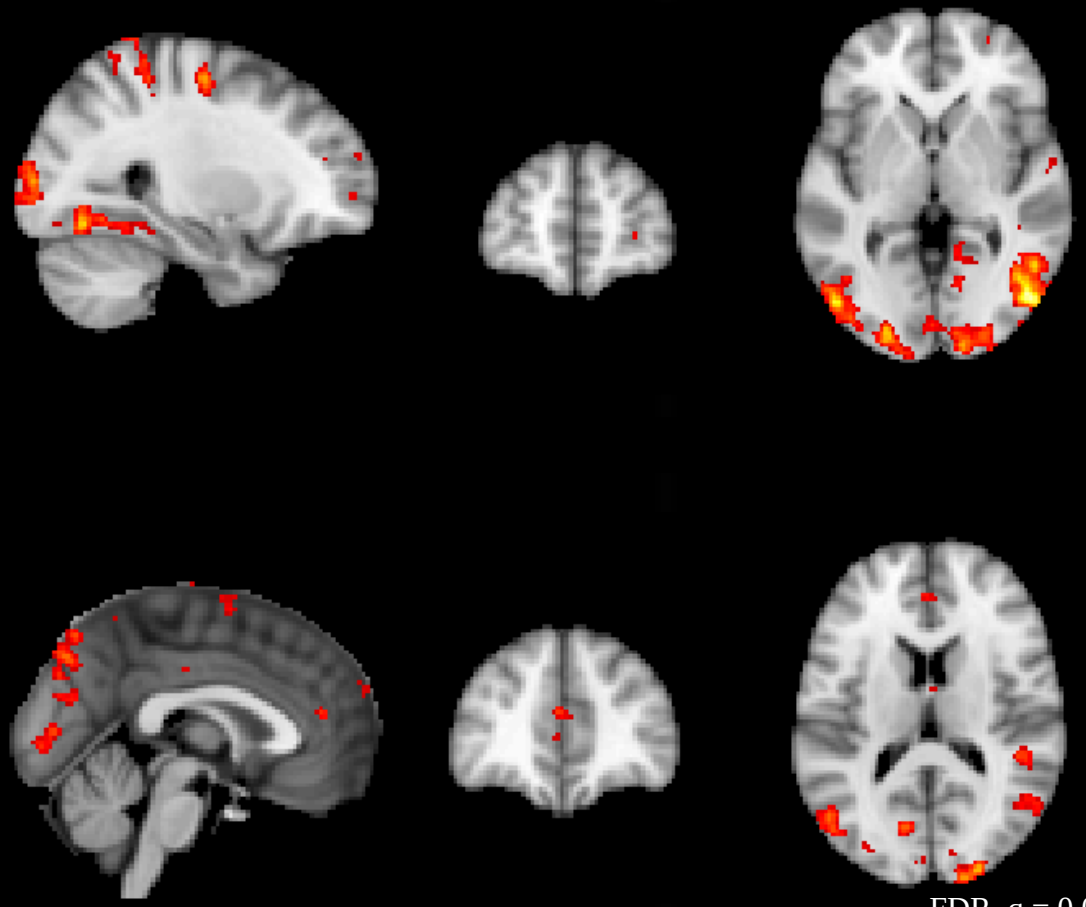
- The right Orbital Frontal Cortex
- The Posterior Cingulate Cortex (PCC)



FDR, q = 0.05

Positive > Negative

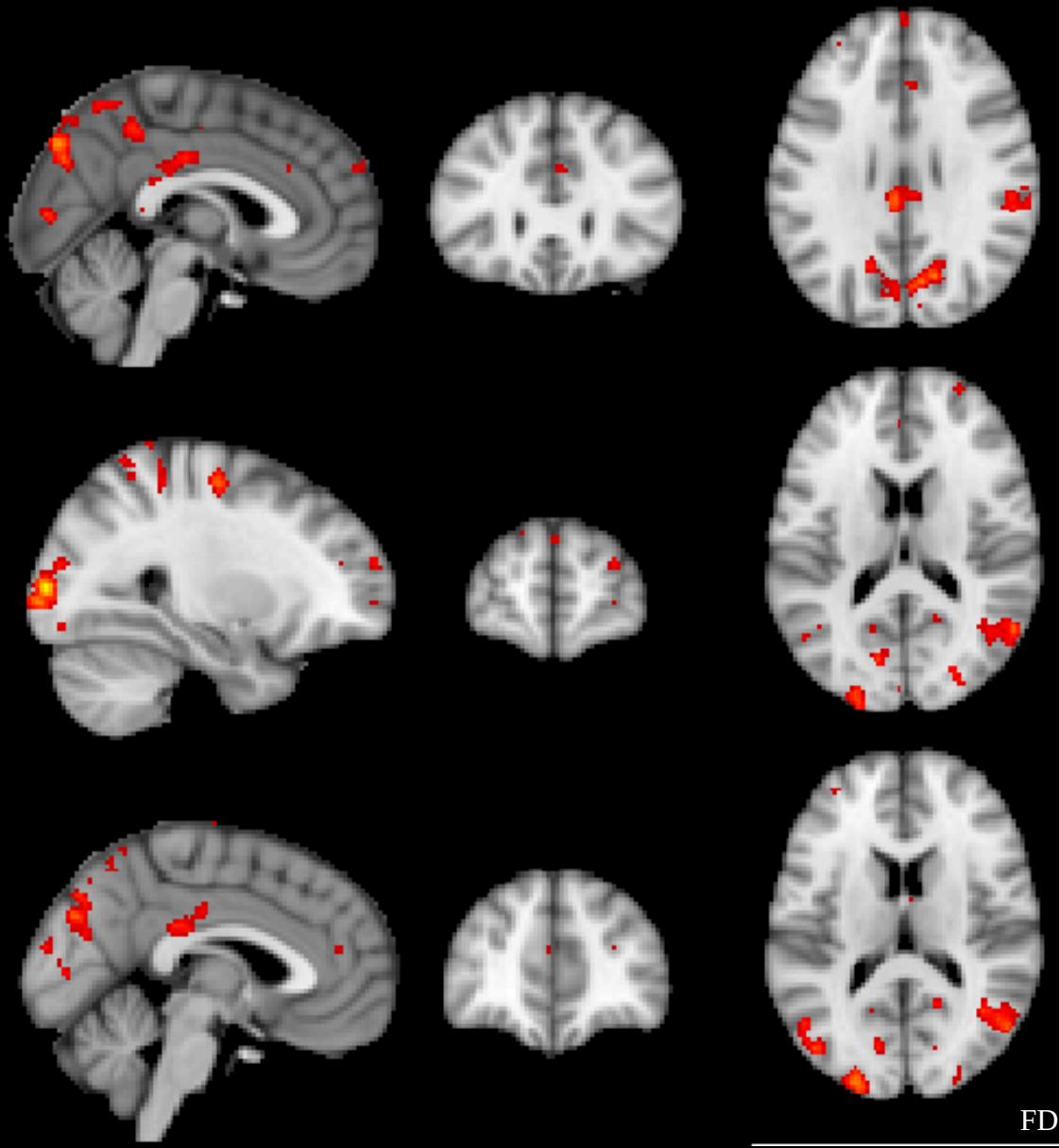
- The ACC, right dlPFC
- The right dmPFC, vmPFC



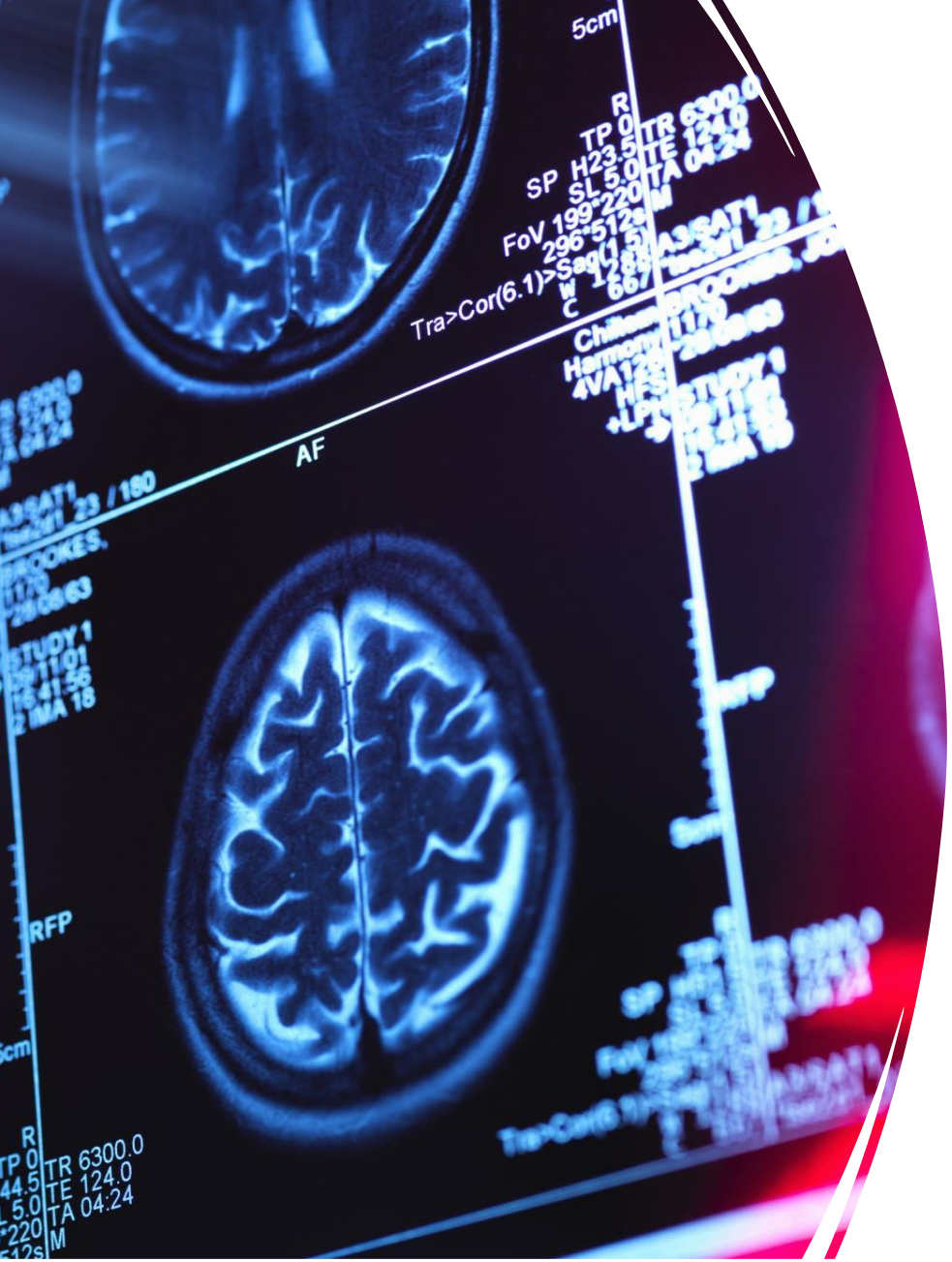
FDR, q = 0.05

Positive > Neutral

- The right vmPFC
- The dmPFC, ACC, PCC

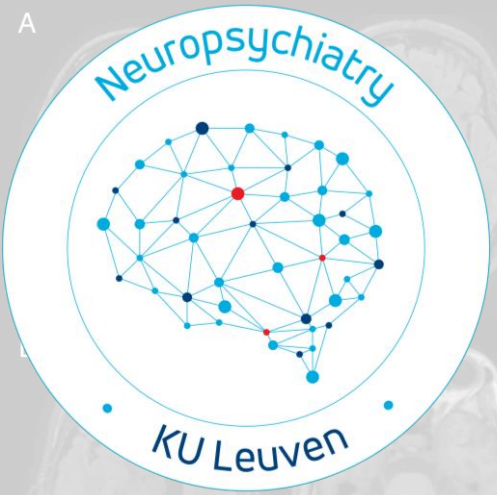


FDR, q = 0.05



Planned analyses

- Investigate group effects
- Link EMA and ChillBand data with brain activation



KU LEUVEN

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