



GGZ Rivierduinen



Neuro–imaging bij bipolaire stoornissen: een overzicht

Max de Leeuw, psychiater en senior onderzoeker GGZ Rivierduinen/LUMC

KenBiS, 17 juni 2016 Leiden

Inhoud

- Emotieverwerking
- Werkgeheugen
- Beloning
- Eerstegraads familieleden

Bipolaire stoornis – DSM

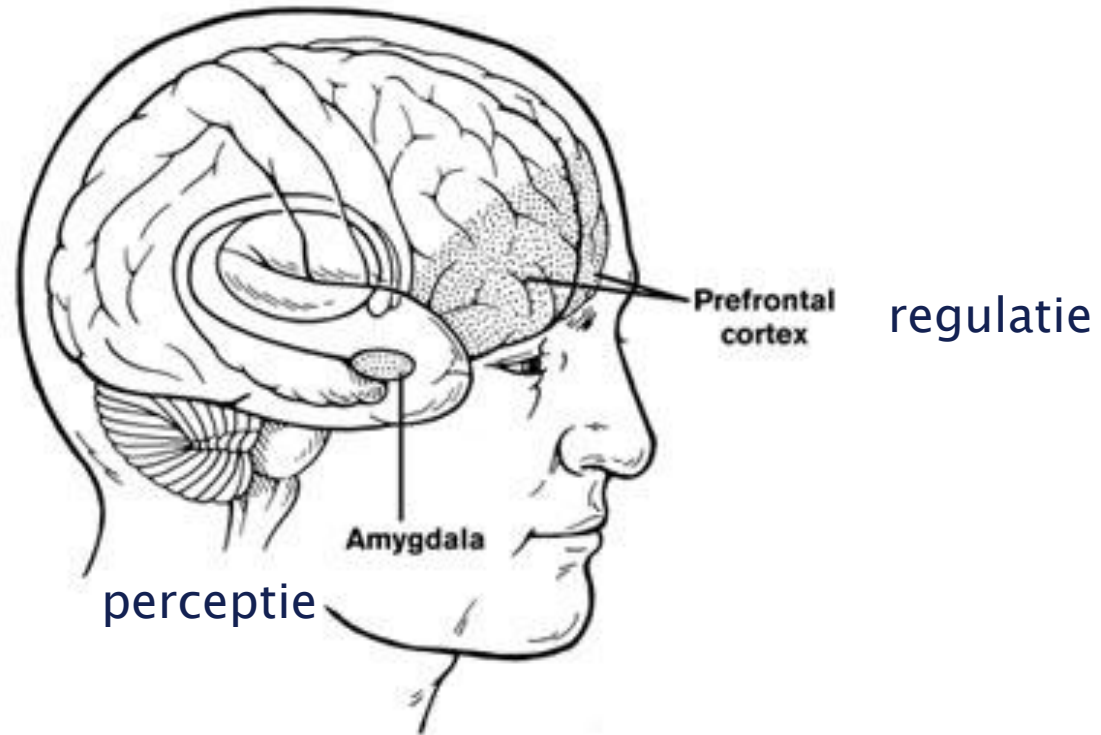
- Manische episode
 - Verhoogde, expansieve of prikkelbare stemming
- Depressieve episode
 - Sombere stemming
- Dus: mogelijk onvermogen om emoties te verwerken
 - Emotie-stoornissen?

Emotieverwerking

Detectie en beoordeling van emotiestimuli, maar ook reguleren van eigen emotionele (affectieve) respons op emotiestimuli

- Model
 - Aandacht en perceptie van informatie dat emotionele respons uitlokken (passief)
 - Emotionele “arousal” op stimuli
 - Reguleren van “arousal” via andere mechanisme (verandering aandacht/perceptie, cognitieve strategieën)

Emotieverwerking



Fronto-limbisch netwerk

Emotieverwerking (aandacht/perceptie)

Amygdala
centrale rol
maar ook:

insula, ACC,
thalamus,
fusiform

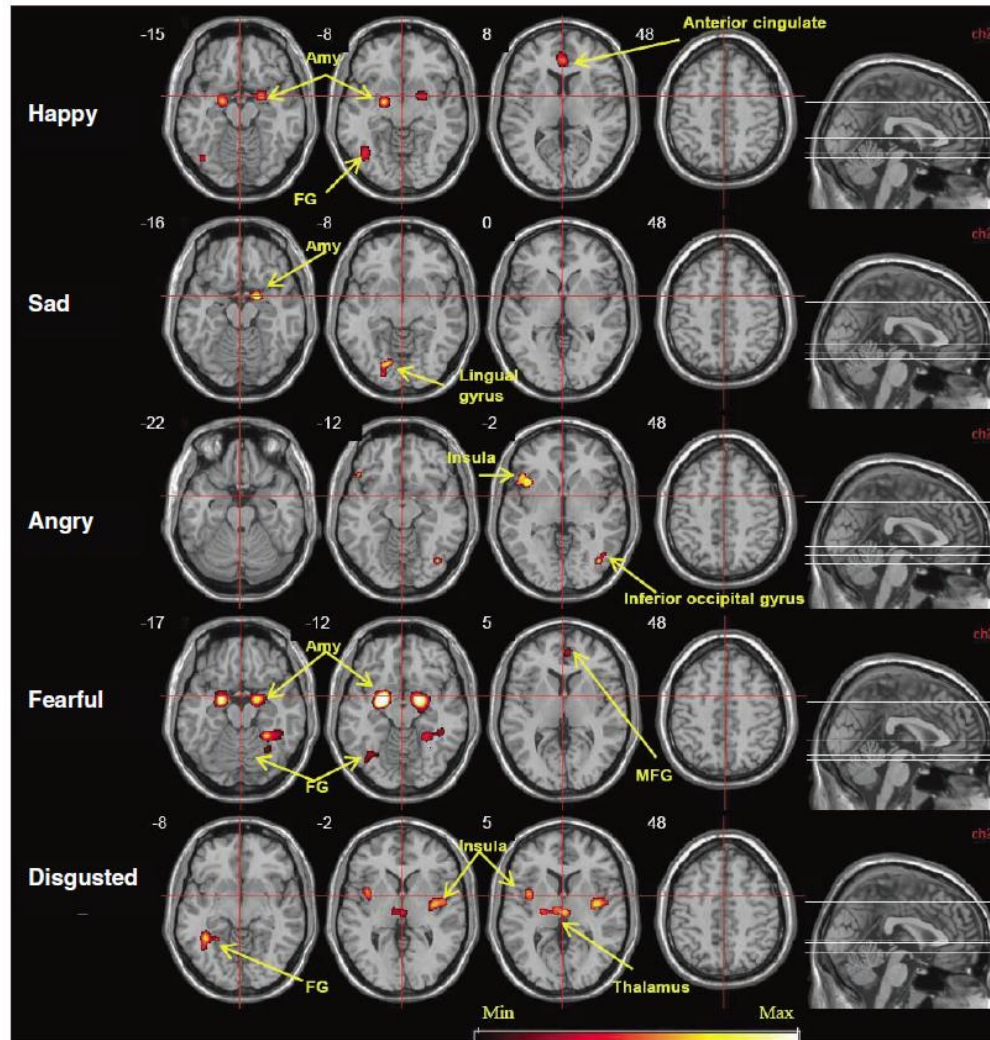
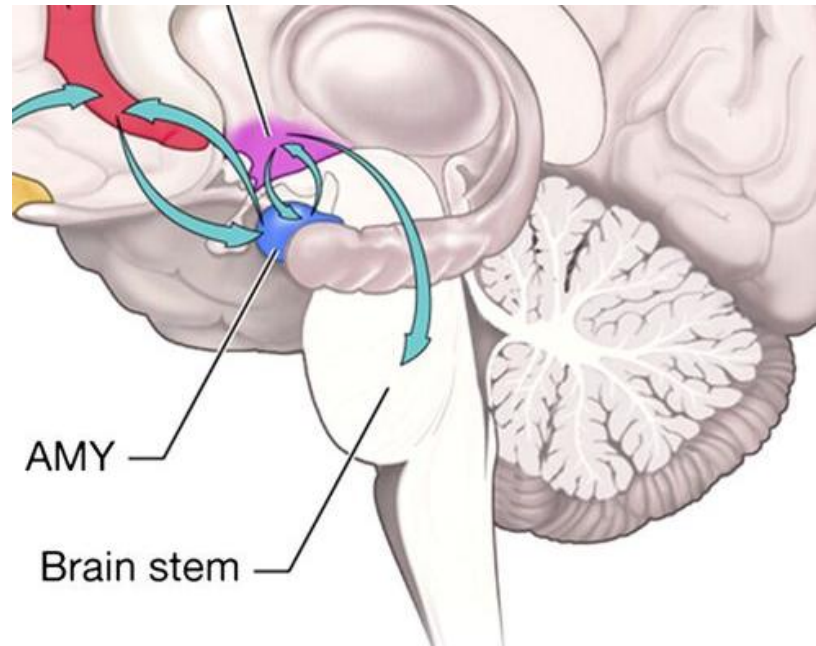
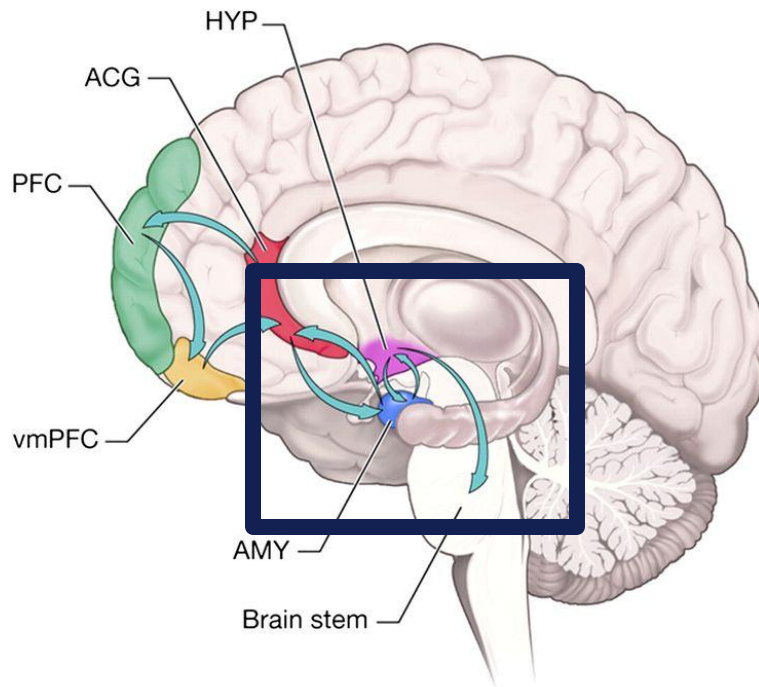


Fig. 2: Brain maps of neural activation in response to happy, sad, angry, fearful and disgusted human faces compared with neutral faces (false discovery rate = 0.001, cluster $p < 0.001$). Amy = amygdala; FG = fusiform gyrus; MFG = medial frontal gyrus.

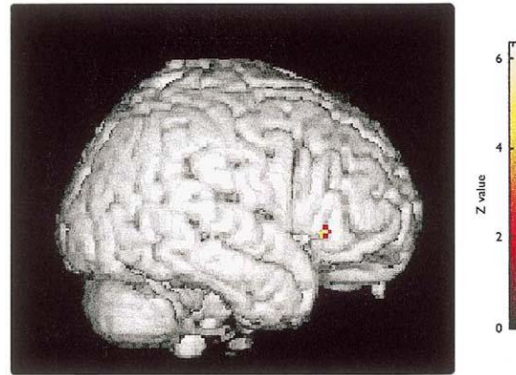
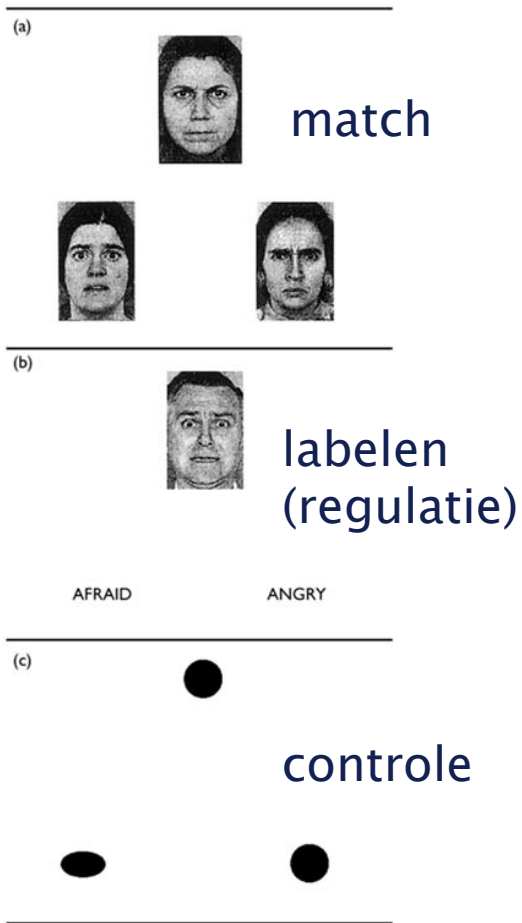
Emotieverwerking (“arousal”)

- Amygdala activiteit
 - Neuronale projectie hersenstam/hypothalamus
 - Stimulatie HPA-as (stress)

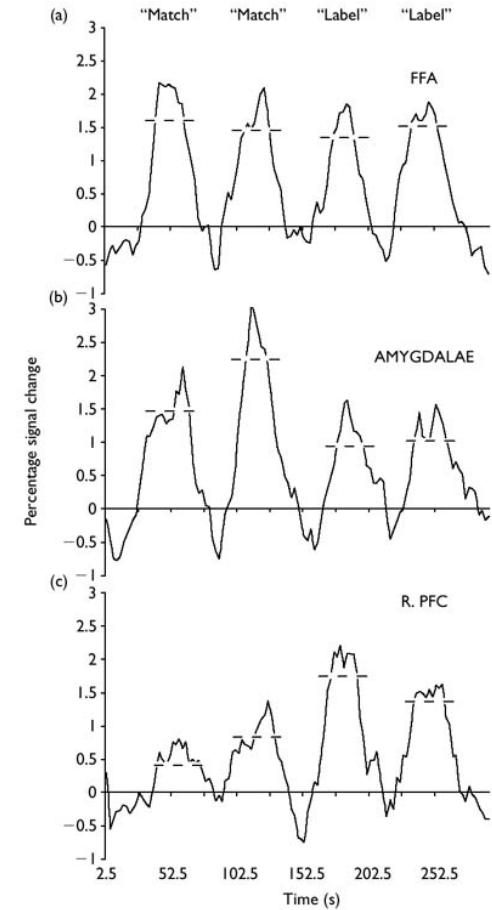


Joels et al., Nat. Rev. Neurosci 2009

Emotieverwerking (regulatie)



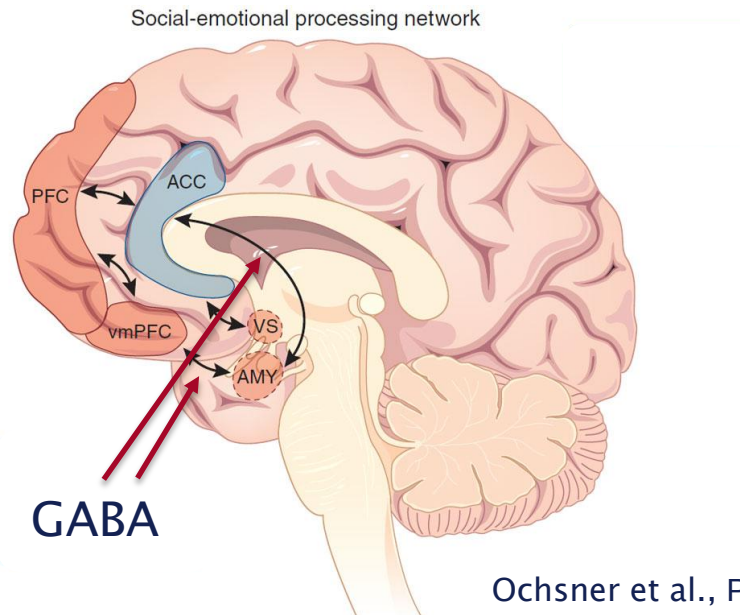
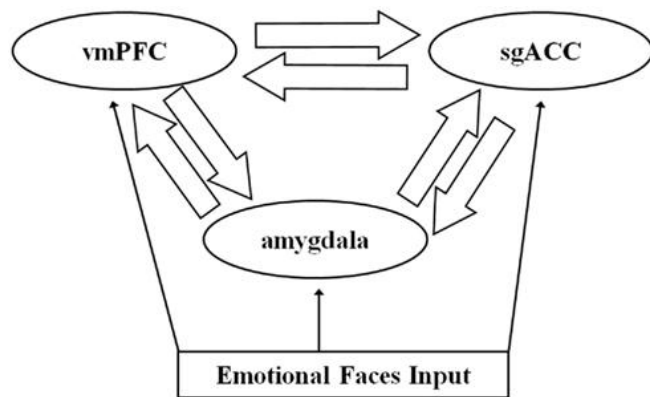
ventro-laterale PFC



Hairiri et al., NeuroReport 2000

Emotieverwerking (regulatie)

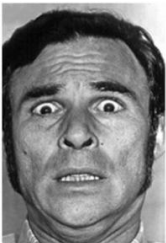
- Frontaal cortex (vlPFC) activiteit
 - cognitieve strategieën
 - remt amygdala, remt “arousal”; dus reguleert emotie
- Anterior cingulate cortex activiteit
 - verandering aandacht/perceptie



Emotieverwerking

Paradigma

- Faces (Ekman et al., 1975)
- International Affective Picture Set (IAPS)



Fearful



Angry



Sad



Happy



Disgusted



Surprised



Awe



Excitement



Anger



Sadness



Contentment



Amusement



Disgust



Fear

Emotieverwerking bipolaire stoornis (manie)

Study	N	Paradigm	Method	Amygdala	vIPFC
Elliot et al. 2004 (71)	M = 8 HS = 11	Emotional Go/NoGo (happy and sad words)	3T Whole-brain	NS	↓ L/R
Lennox et al. 2004 (68)	M = 10 HS = 12	Faces (happy, sad)	3T Whole-brain	NS ^a	NS
Altshuler et al. 2005 (63)	M = 9 HS = 9	Faces (negative): match	3T ROI: amygdala	↑ L	↓ L/R
Chen et al. 2006 (66)	M = 8 D = 8 HS = 8	Faces (fear, sad, happy): implicit and explicit processing	3T Whole-brain	↑ Implicit ↓ Explicit	NS
Foland et al. 2008 (27)	M = 9 HS = 9	Faces (negative): match and label	3T Whole-brain PPI	↑ L	↓ L/R
Killgore et al. 2008 (72)	M = 13 HS = 13	Faces (fear): passive view	1.5T Whole-brain ROI: amygdala	NS	↓ R
Berpohl et al. 2009 (65)	M = 10 HS = 10	IAPS	1.5T Whole-brain	↑ L	NS
Chen et al. 2010 (74)	M = 12 E = 9 HS = 12	Faces (happy, sad, disgust, fear, surprise, anger): rate intensity	1.5T ROI: amygdala, OFC	—	↑ R
Van der Schot et al. 2010 (69)	M = 12 E = 18 D = 12 HS = 18	Faces (neutral, happy, fearful): masked and unmasked	1.5T ROI: amygdala, OFC	↓ L/R	↓ L/R
Strakowski et al. 2011 (64)	M = 40 HS = 36	CPT-END: IAPS	4T ROI: amygdala, vIPFC	↑ L ↓ R ^b	↓ L/R

Emotieverwerking bipolaire stoornis (manie)

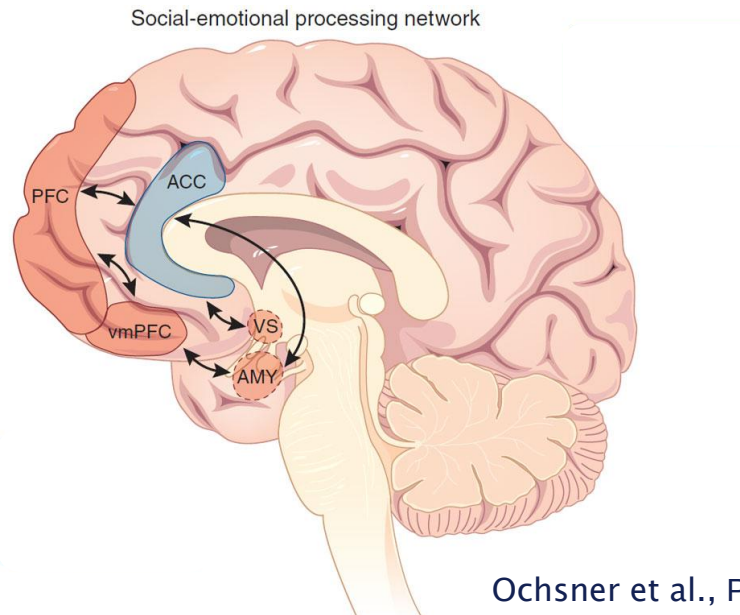
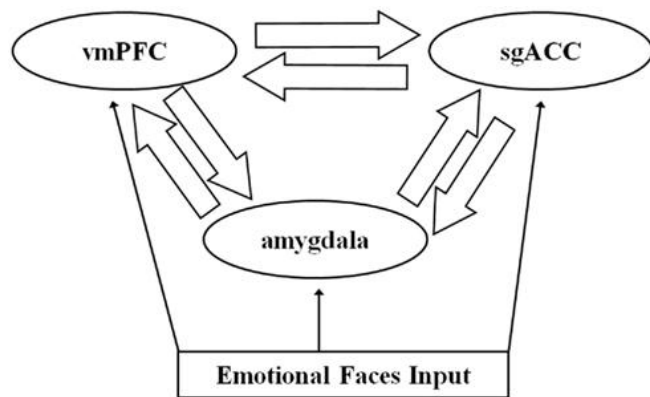
- Verhoogde activiteit amygdala
 - gecorreleerd met Young Mania Rating Scale
 - grotere amygdala

Table 2. Magnetic Resonance Imaging Morphometric Brain Structural Measurements in 24 Patients With Bipolar Disorder (BD) With Mania and 22 Normal Comparison Subjects*

Brain Structure†	Patients With BD	Healthy Volunteers	Effect Size, $f^{\ddagger}$
Total cerebrum	1132 (130)	1110 (98)	0.10
Prefrontal cortex, total	129.6 (14.7)	133.1 (24.4)	0.17
Right	66.2 (8.1)	66.9 (11.9)	
Left	63.4 (7.8)	66.2 (13.1)	
Thalamus, total	15.1 (2.2)	13.5 (1.7)	0.32
Right	7.4 (1.0)	6.6 (0.8)	
Left	7.7 (1.2)	6.9 (0.9)	
Hippocampus, total	8.6 (1.2)	8.4 (0.8)	0.03
Right	4.3 (0.6)	4.2 (0.4)	
Left	4.3 (0.6)	4.2 (0.4)	
Amygdala, total§	7.1 (1.1)	6.3 (0.8)	0.46
Right	3.6 (0.5)	3.2 (0.4)	
Left	3.5 (0.6)	3.1 (0.4)	
Striatum, total	24.2 (2.8)	22.6 (1.8)	0.28
Right	14.2 (1.4)	11.4 (1.0)	
Left	12.0 (1.5)	11.2 (0.9)	
Globus pallidus, total	3.6 (0.5)	3.2 (0.6)	0.31
Right	1.8 (0.3)	1.6 (0.3)	
Left	1.8 (0.2)	1.6 (0.3)	
Left lateral ventricle	5.9 (3.4)	4.6 (2.4)	0.31
Right lateral ventricle	5.4 (2.8)	4.7 (2.1)	0.17
Third ventricle	1.0 (0.3)	0.9 (0.3)	0.05

Emotieverwerking bipolaire stoornis (manie)

- Verlaagde activiteit vIPFC
 - functioneel gecorreleerd aan verhoogde amygdala activiteit (primair?)
 - relatief afgenomen remming



Emotieverwerking bipolaire stoornis (depressie)

Study (depressed)	N	Paradigm	Method	Amygdala	vIPFC
Malhi et al. 2004 (73)	D = 11 HS = 10	Captioned pictures (negative, neutral, positive): passive view	1.5T Whole-brain	↑ L	↓ ^a
Chen et al. 2006 (66)	M = 8 D = 8 HS = 8	Faces (fear, sad, happy): implicit and explicit processing	3T Whole-brain	NS	NS
Altshuler et al. 2008 (82)	D = 11 HS = 17	Faces (negative): match	3T Whole-brain	NS	↓ L/R
Almeida et al. 2010 (84)	D = 15 E = 15 HS = 15	Faces (fear, happy, sad): label	3T ROI: amygdala	NS ^b	N/A
Van der Schot et al. 2010 (69)	M = 12 E = 18 D = 12 HS = 18	Faces (neutral, happy, fearful): masked and unmasked	1.5T ROI: amygdala, OFC	NS	↓ L/R

Emotieverwerking bipolaire stoornis (depressie)

- Activiteit amygdala
 - meer variabiliteit
- Verlaagde activiteit vLPFC
- Weinig studies
 - neuro-anatomisch werkingsmechanisme onduidelijk

Emotieverwerking bipolaire stoornis (euthym)

Study (Euthymic)	N	Paradigm	Method	Amygdala	vIPFC
Malhi et al. 2005 (93)	E = 12 HS = 12	Emotional Stroop: (affective versus neutral)	3T Whole-brain, GSR	↓ L	↓ L
Lagopoulos and Malhi 2007 (91)	E = 10 HS = 10	Emotional Stroop: (negative versus neutral)	3T Whole-brain, GSR	↑ R	↓ L/R (PFC)
Malhi et al. 2007 (89)	E = 10 HS = 10	Faces (fear, disgust, neutral): label	3T Whole-brain	NS	↓ L
Wessa et al. 2007 (101)	E = 17 HS = 17	Emotional Go/NoGo: (fear, happy, and neutral faces)	1.5T Whole-brain	NS	NS
Hassel et al. 2008 (88)	E = 19 HS = 24	Faces (happy, fear, neutral): label	3T Whole-brain ROI: amygdala	NS	↓ L/R (PFC)
Robinson et al. 2008 (90)	E = 15 HS = 16	Faces (negative): match and label	3T Whole-brain ROI: amygdala, vIPFC	NS	↑ R
Almeida et al. 2009 (85)	E = 21 HS = 25	Faces (happy, neutral): label	3T Whole-brain DCM: parahippocampus, vmPFC, dlPFC	NS	NS
Hassel et al. 2009 (87)	E = 14 HS = 16	Faces (happy, fear): label	3T ROI: amygdala, dPFC	NS	↓ R
Almeida et al. 2010 (84)	D = 15 E = 15 HS = 15	Faces (fear, happy, sad): label	3T ROI: amygdala	NS	N/A
Chen et al. 2010 (74)	M = 12 E = 9 HS = 12	Faces (happy, sad, disgust, fear, surprise, anger): rate intensity	1.5T ROI: amygdala, OFC	↑ R	↑ R
Surguladze et al. 2010 (92)	E = 20 HS = 20	Faces (happy, fear): label	Whole-brain ROI: amygdala	↑ L ^a	NS
Van der Schot et al. 2010 (69)	M = 12 E = 18 D = 12 HS = 18	Faces (neutral, happy, fearful): masked and unmasked	1.5T ROI: amygdala, OFC	↓ L/R	↓ L/R
Lagopoulos and Malhi 2011 (99)	E = 11 HS = 11	Faces (neutral or disgust): label	3T fMRI, GSR	NS	NS

Emotieverwerking bipolaire stoornis (euthym)

- Geen verschil in amygdala activiteit
 - alleen studies met negatieve emoties
 - amygdala activiteit meer gerelateerd aan “state” (stemming)
- Verlaagde activiteit vIPFC
 - frontale afwijkingen gerelateerd aan “trait”
 - functionele consequentie (remming van amygdala, “normale activiteit”) vindt alleen plaats tijdens “state”

Bipolaire stoornis – DSM

- Manische episode
 - Verhoogde, expansieve of prikkelbare stemming
 - Depressieve episode
 - Sombere stemming
-

Kenmerken (endofenotype, “trait”, onafhankelijk van episode)

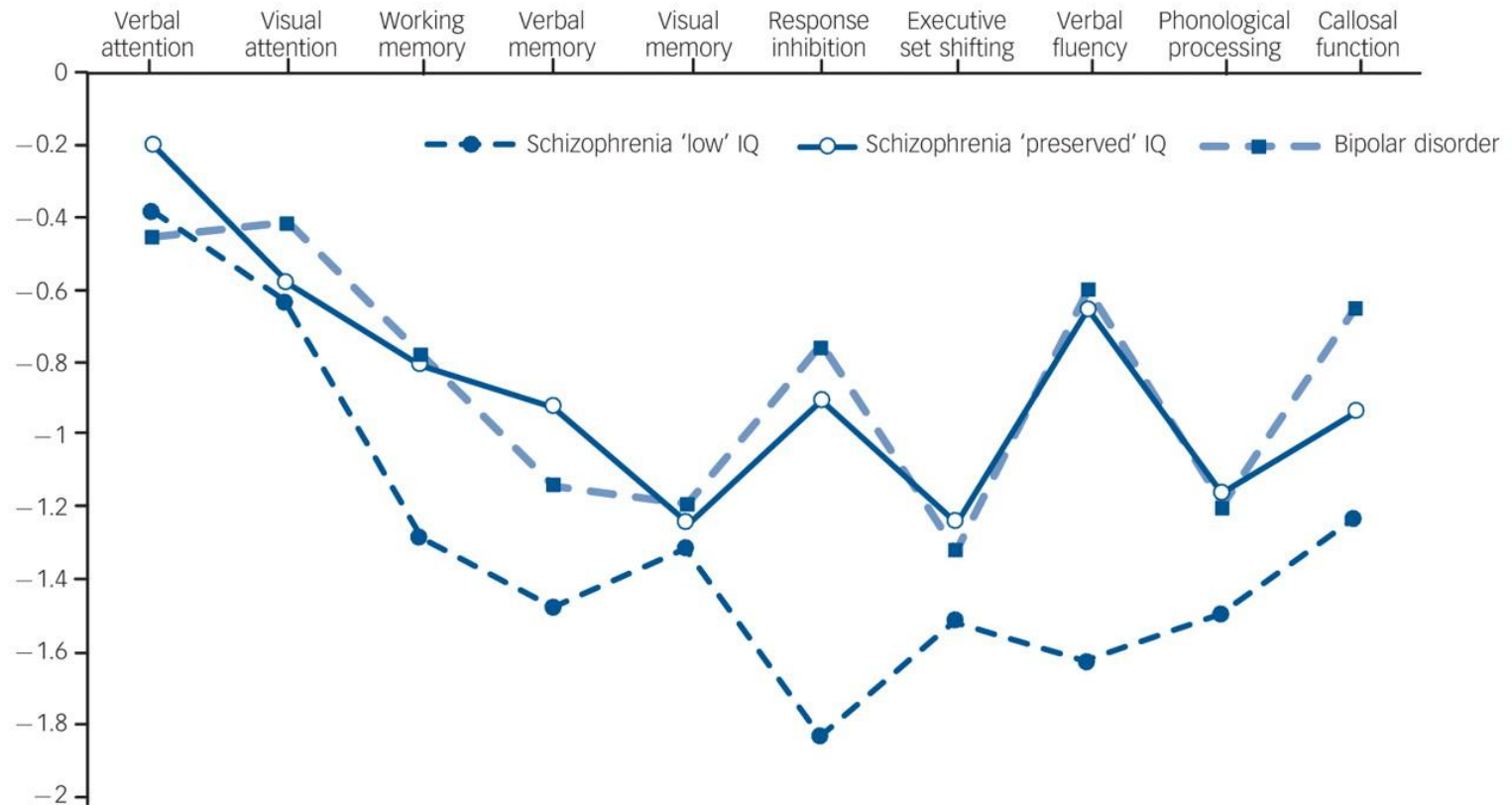
- Cognitieve functiestoornissen

Bipolaire stoornis – neurocognitief

Mean weighted effect sizes for individual tasks and education for relative-control differences

Test	Study	Bipolar relatives	Control relatives	<i>D</i>	95% CI	<i>z</i>	<i>p</i>	Q-test <i>p</i>	Bias
Stroop	6	142	209	0.51	0.27–0.76	4.1	<0.0001	0.37	0.60
TMT-B	8	252	274	0.38	0.20–0.55	4.15	<0.0001	0.52	0.52
WCST per	9	257	312	0.36	0.20–0.54	4.18	<0.0001	0.08	0.71
CPT omission	5	128	153	0.36	0.12–0.60	2.93	0.003	0.95	0.53
Immediate recall	5	151	192	0.33	0.11–0.55	2.94	0.003	0.62	0.86
Learning	8	209	338	0.28	0.09–0.46	2.97	0.003	0.92	0.38
FAS	5	90	117	0.27	–0.01–0.55	1.85	0.06	0.56	0.34
Delayed recall	7	192	321	0.27	0.04–0.50	2.27	0.02	0.21	0.32
WCST cat	7	167	217	0.24	–0.08–0.56	1.48	0.14	0.05	0.22
DSST	5	115	280	0.22	–0.04–0.49	1.69	0.09	0.28	0.52
Digit Span Backwards	7	153	346	0.22	–0.14–0.57	1.21	0.23	0.02	0.24
Memory recognition	5	120	127	0.20	–0.11–0.51	1.27	0.20	0.25	0.96
Current IQ	7	157	242	0.20	–0.24–0.63	0.89	0.37	0.0006	0.36
CPT commission	3	94	92	0.18	–0.11–0.47	1.21	0.23	0.55	0.83
Edu	11	269	576	0.18	–0.05–0.42	1.52	0.13	0.02	0.11
TMT-A	9	277	358	0.17	0–0.33	1.97	0.05	0.82	0.07
Visual memory recall	3	41	173	0.13	–0.39–0.65	0.48	0.63	0.14	0.74
Digit span forwards	6	134	232	0.08	–0.38–0.54	0.32	0.75	0.003	0.44
Premorbid IQ	8	165	441	–0.03	–0.29–0.23	0.23	0.83	0.07	0.45
Visual copy	3	41	173	–0.1	–0.44–0.25	0.56	0.58	0.84	0.84

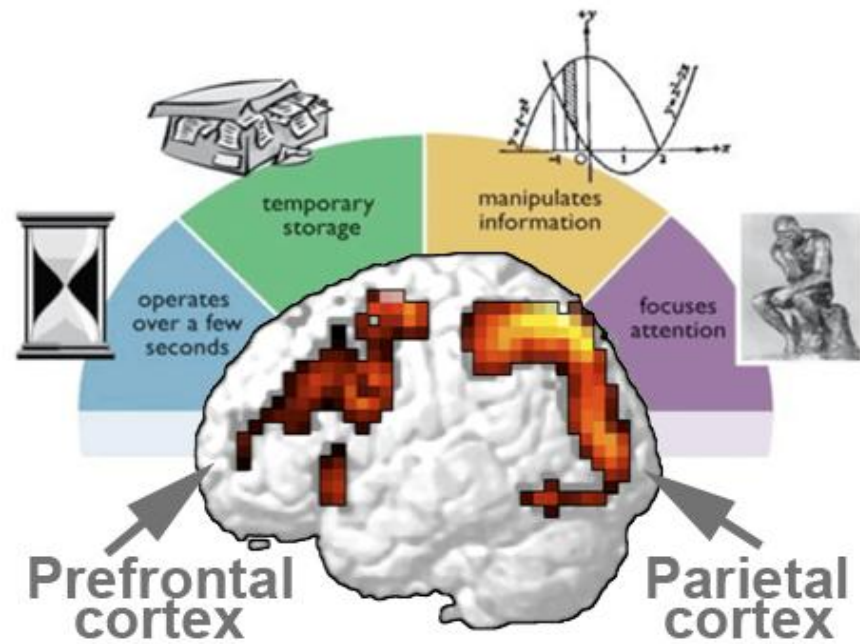
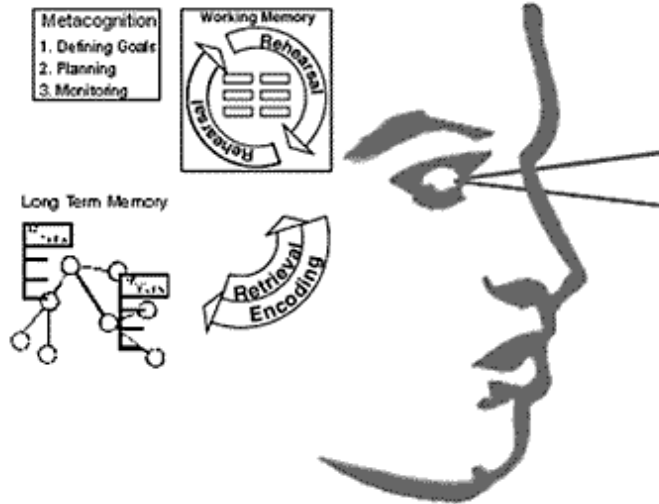
Bipolaire stoornis – neurocognitief



Bipolaire stoornis – neurocognitief

- Persisteren tijdens euthyme fase
- “Trait”
- Werkgeheugen (Thompson et al., 2007)

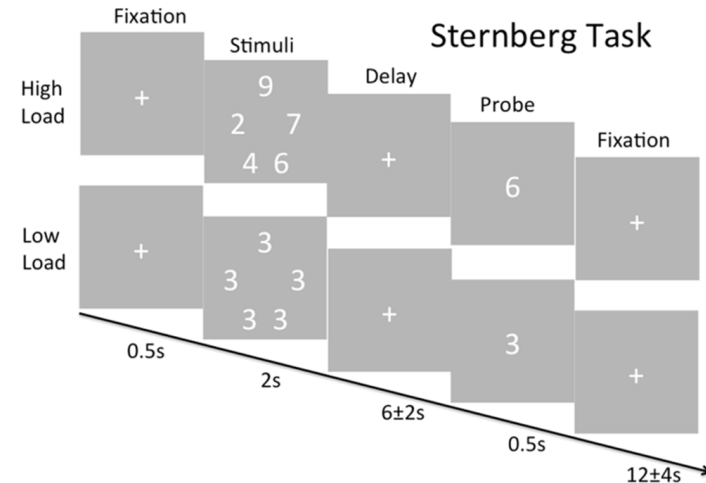
Werkgeheugen



Werkgeheugen

Paradigma

- N-back
- Sternberg



Verbal n-back

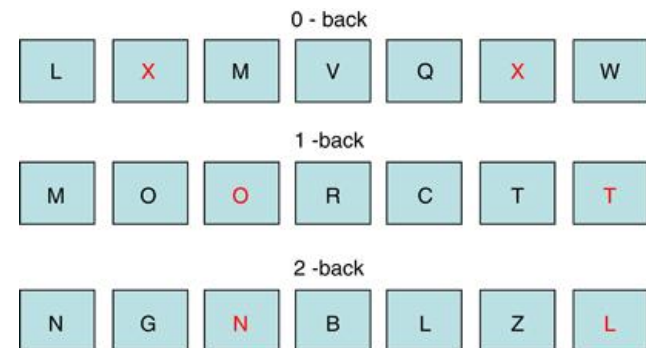
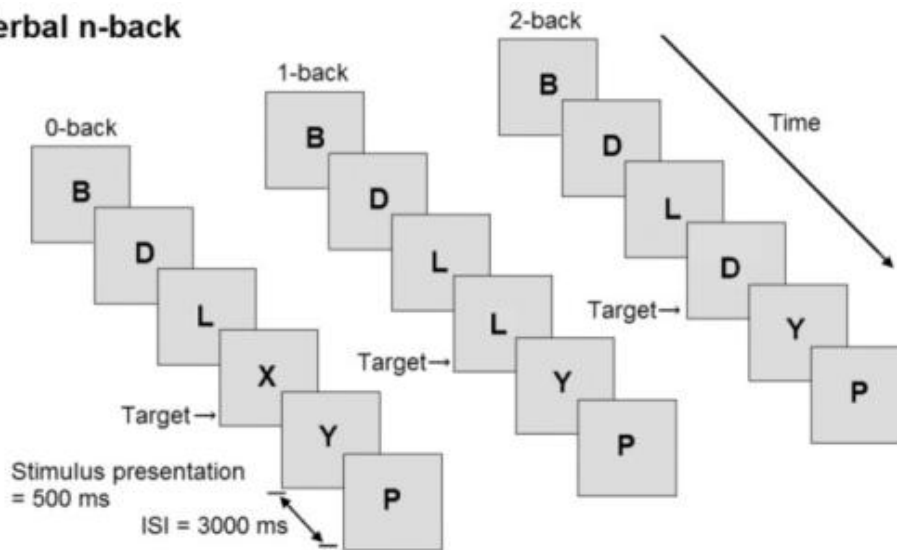


Table 1. Main findings from fMRI studies with N-back task assessing WM in euthymic bipolar patients

Authors	Patients	Controls and comparison groups	Task	fMRI	Findings (behavioral data and neural activation)
Adler et al., 2004 [21]	15 BD I euthymic patients mean age $\pm$ DS: 29 $\pm$ 9	15 controls	0-, 2-back	3.0 T	BD vs. controls: ↓ accuracy, no differences in reaction times; ↑ activation in frontopolar PFC temporal cortex posterior parietal cortex basal ganglia, thalamus
Monks et al., 2004 [22]	12 BD I euthymic patients mean age $\pm$ DS: 45.83 $\pm$ 2.76	12 controls	2-back, Sternberg paradigm	1.5 T	BD vs. controls: no differences in accuracy and reaction times; ↓ activation in left frontal lobe right middle temporal gyrus cuneus/precuneus cerebellum ↑ activation in left precentral cortex right medial frontal gyri left supramarginal gyri
Frangou et al., 2008 [23]	7 BD I euthymic patients mean age $\pm$ DS: 37 $\pm$ 5.88	7 controls	1-, 2-, 3-back, Iowa Gambling task	1.5 T	BD vs. controls: no differences in accuracy and reaction times; ↓ activation in VPFC and DPFC ↑ activation in parietal cortex lateral temporal and polar regions
Drapier et al., 2008 [31]	20 BD I euthymic patients mean age $\pm$ DS: 42.7 $\pm$ 10.4	20 controls 20 first-degree relatives	1-, 2-, 3-back	1.5 T	BD and relatives vs. controls: ↓ accuracy in bipolars vs. relatives and controls (2- and 3-back); ↑ activation in left frontopolar cortex
Hamilton et al., 2009 [33]	21 BD I euthymic patients mean age $\pm$ DS: 36.38 $\pm$ 10.7	38 controls 20 schizophrenic patients	N-back (on and off blocks)	3.0 T	BD vs. controls: no differences in accuracy and reaction times; ↓ activation in DLPFC right primary visual cortex
Thermenos et al., 2010 [24]	19 BD (I) euthymic patients mean age $\pm$ DS: 41.1 $\pm$ 3.1	19 controls 18 first-degree relatives	2-back	1.5 T	BD and relatives vs. controls: ↑ activation in left anterior insula BD vs. controls: ↓ accuracy, ↑ reaction times (2-back) ↓ activation in left frontopolar cortex
Townsend et al., 2010 [34]	42 BD I patients (13 manic, 15 euthymic and 14 depressed) mean age euthymics $\pm$ DS: 37 $\pm$ 10	14 controls	2-back	3.0 T	BD vs controls: no differences in accuracy and reaction times; ↓ activation in right DLPFC posterior parietal cortex ↑ activation in orbitofrontal cortex temporal lobe structures
Jogia et al., 2011 [35]	36 BD I euthymic patients mean age $\pm$ DS: 42.5 $\pm$ 10.6	37 controls	0-, 1-, 2-, 3-back, Iowa Gambling task	1.5 T	BD vs. controls: no differences in accuracy and reaction times; ↓ activation in the VL frontopolar cortex ↑ activation in right superior/middle temporal gyri insular cortex

Werkgeheugen bipolaire stoornis (euthym)

- Verhoogde activiteit prefrontale cortex
 - compensatoir aan gelijke accuratesse
 - heterogeniteit van resultaten
 - kleine groep/medicatie
 - klinische variabelen (ziekteduur, aantal/aard episodes)

Werkgeheugen bipolaire stoornis (euthym, type I/II)

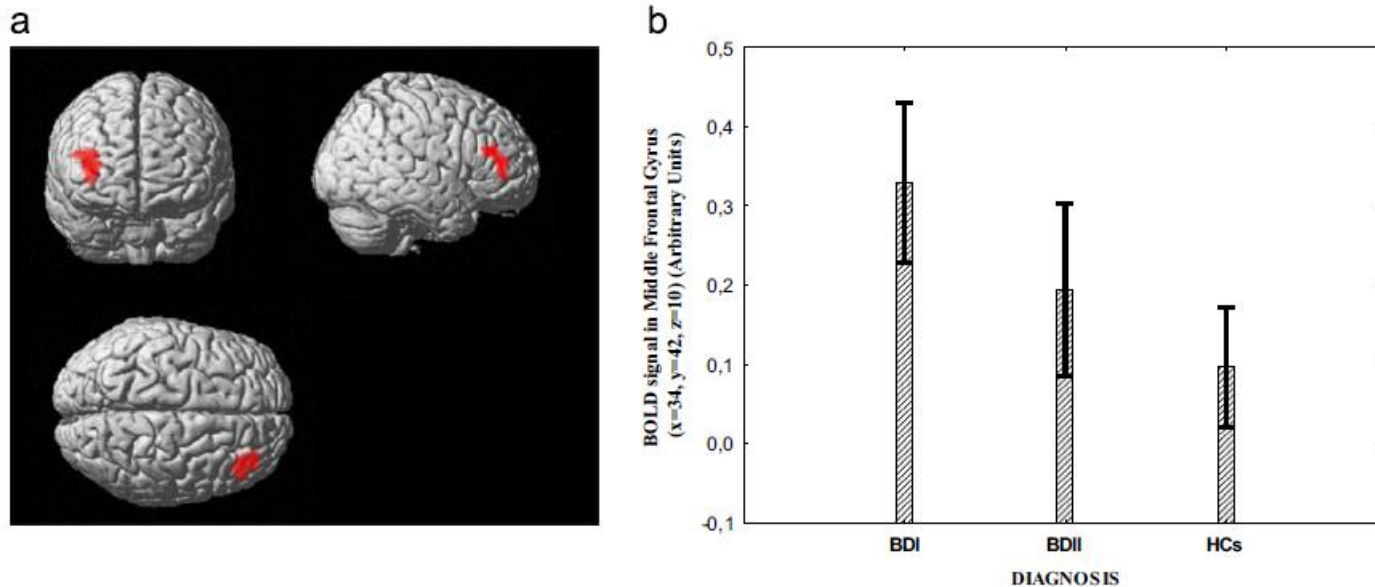


Fig. 1. Effect of diagnosis on prefrontal activity during working memory. (a) 3 Dimensional rendering showing blood oxygenation level-dependent (BOLD) signal difference across diagnostic groups [Bipolar Type I patients, BDI=15, Bipolar Type II patients, BDII= 13, and Healthy Control subjects, HCs=27] in right middle frontal gyrus [MNI, $x=34$, $y=42$, $z=10$; $k=282$, $Z=4.79$]. Images thresholded at $p < 0.05$, FWE corrected. (b) Graph illustrating mean $\pm$ SD of parameter estimates extracted from the significant cluster in right middle frontal gyrus [Bipolar Type I patients=BDI, Bipolar Type II patients=BDII, Healthy Control subjects= HCs].

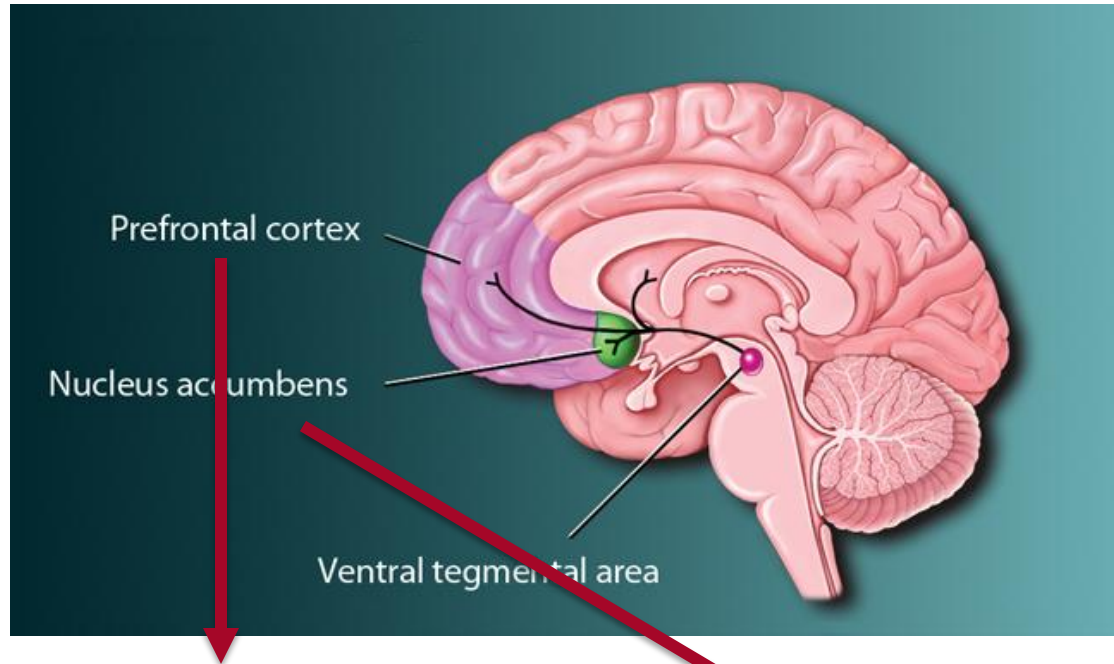
Bipolaire stoornis – DSM

- Manische episode
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 - Depressieve episode
 - Sombere stemming
-

Kenmerken (endofenotype, “trait”, onafhankelijk van episode)

- Cognitieve functiestoornissen
- Stoornissen in beloningsverwerking

Beloning

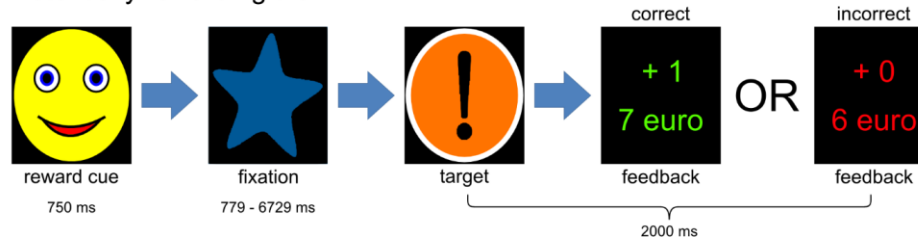


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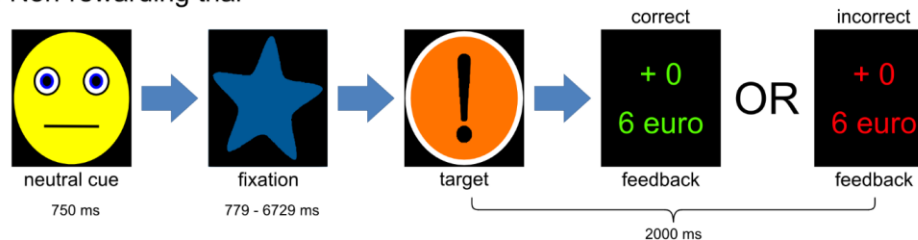
Paradigma

- Monetary Delayed Incentive task

A. Potentially rewarding trial



B. Non-rewarding trial

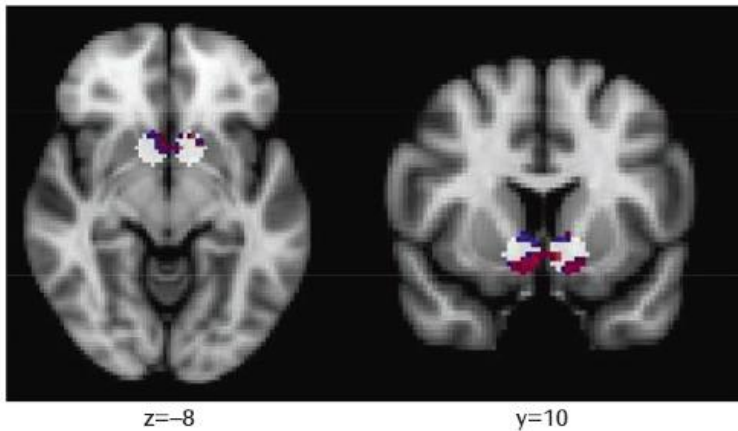


anticipatie

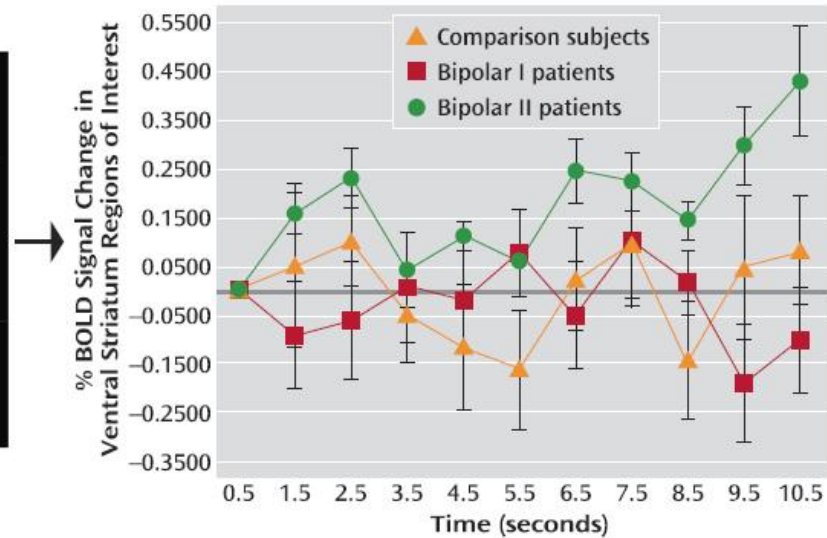
ontvangen

Beloning bipolaire stoornis (euthym)

A. Region-of-Interest Analysis (Ventral Striatum)



B. Whole-Brain Analysis



Beloning bipolaire stoornis (euthym)

- Verhoogde activiteit in ventraal striatum
 - alleen in BP II
 - hogere sensitiviteit voor beloning
 - neuronaal mechanisme voor beloning-
zoekend gedrag?

Bipolaire stoornis erfelijkheid

- Concordantie 45–75 %
- Eerstegraads familieleden hebben 8 keer zo hoge kans (Jones et al. 2002)

Eerstegraads familieleden

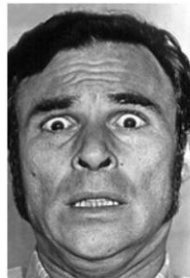
- Delen 50% van genen (dus overlappende “bipolaire” genen)
- Geen ziekte
- Kwetsbaarheid? Risicofactor?



Emotieverwerking

Paradigma

- Faces (Ekman et al., 1975)



Fearful



Angry



Sad



Happy

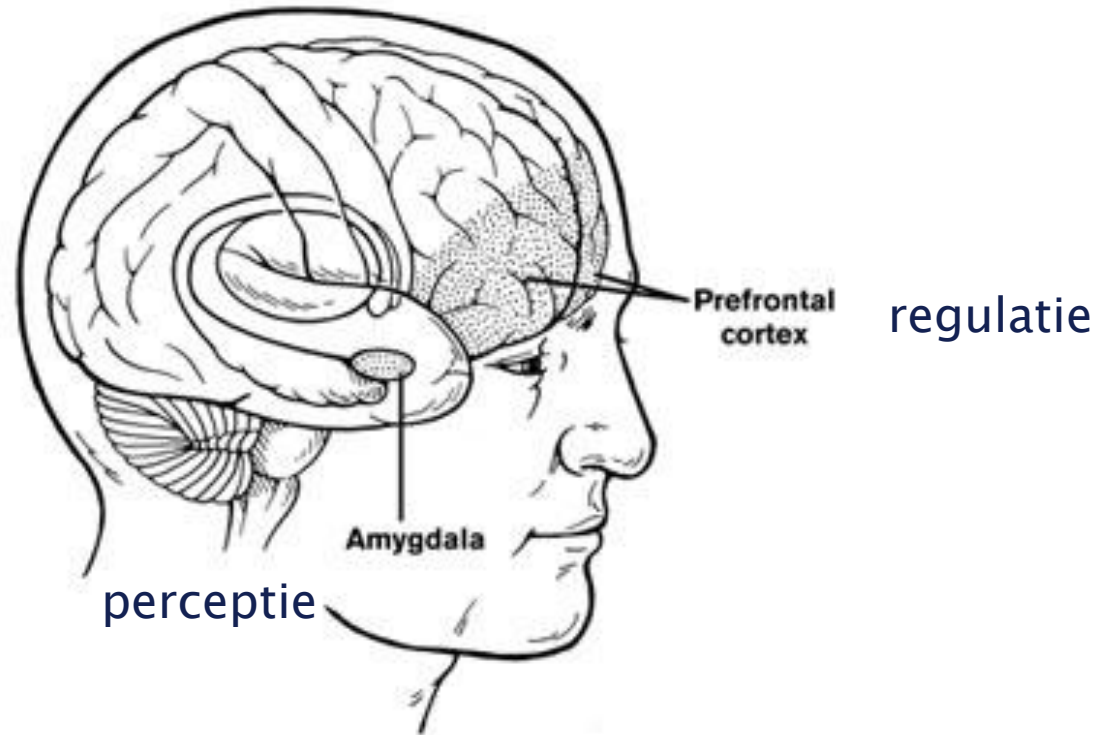


Disgusted



Surprised

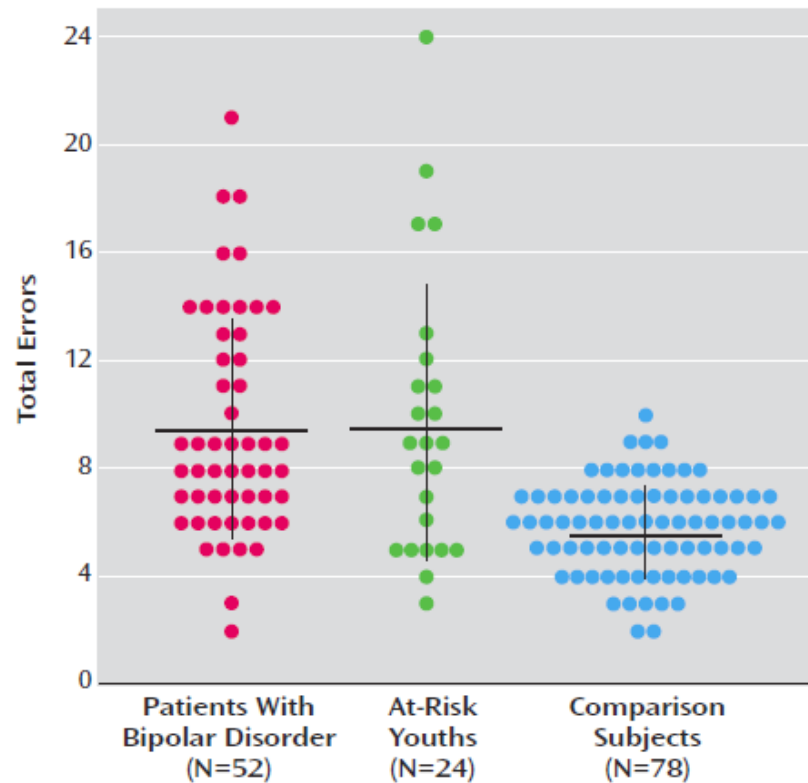
Emotieverwerking



Fronto-limbisch netwerk

Emotieverwerking eerstegraads familieleden (kinderen)

FIGURE 1. Total Number of Facial Emotion Labeling Errors on Both Facial Expressions Subtests of the Diagnostic Analysis of Nonverbal Accuracy Scale, by Group^a



Emotieverwerking eerstegraads familieleden (kinderen)

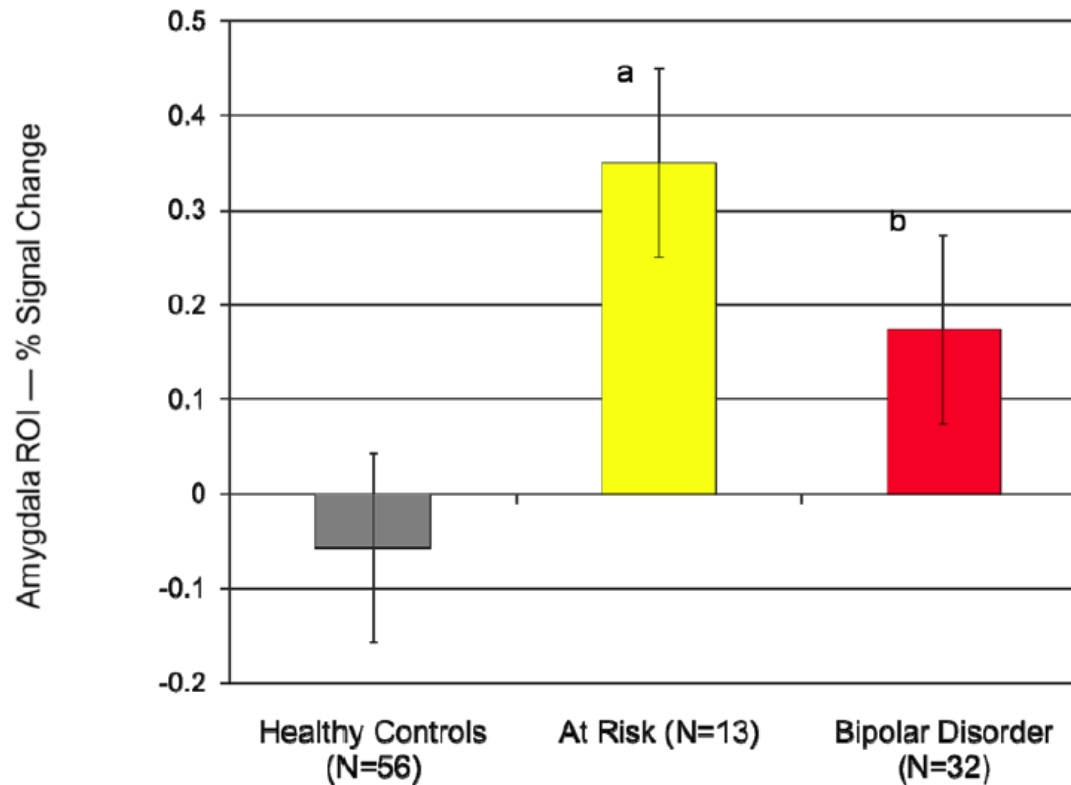
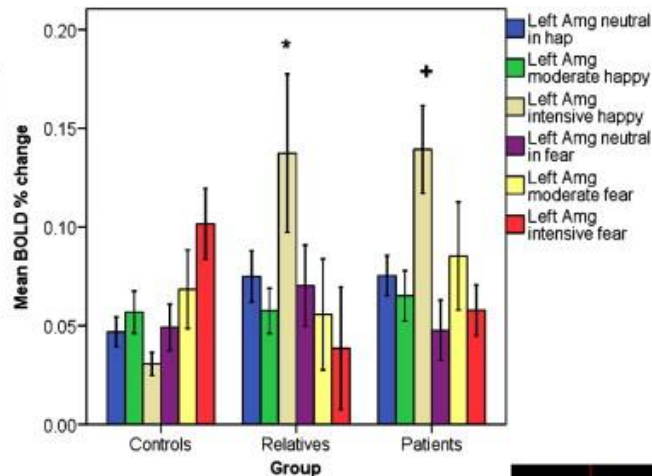
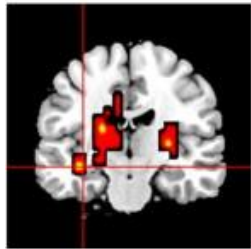


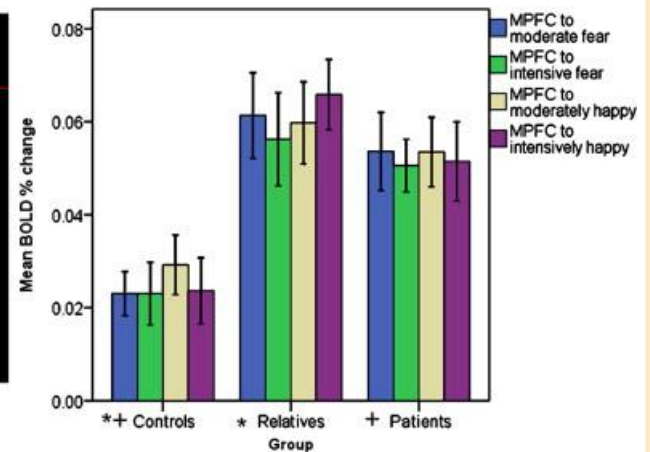
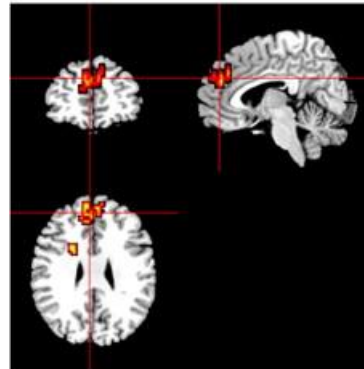
Figure 1. Amygdala Region of Interest Analysis – Fearful Faces: Afraid Rating vs. Passive Viewing

Note: ROI = Region of Interest. ^aAt-risk vs. Healthy Comparisons $p=.01$; ^bBipolar Disorder vs. Healthy Comparisons $p=.05$

Emotieverwerking eerstegraads familieleden (siblings)



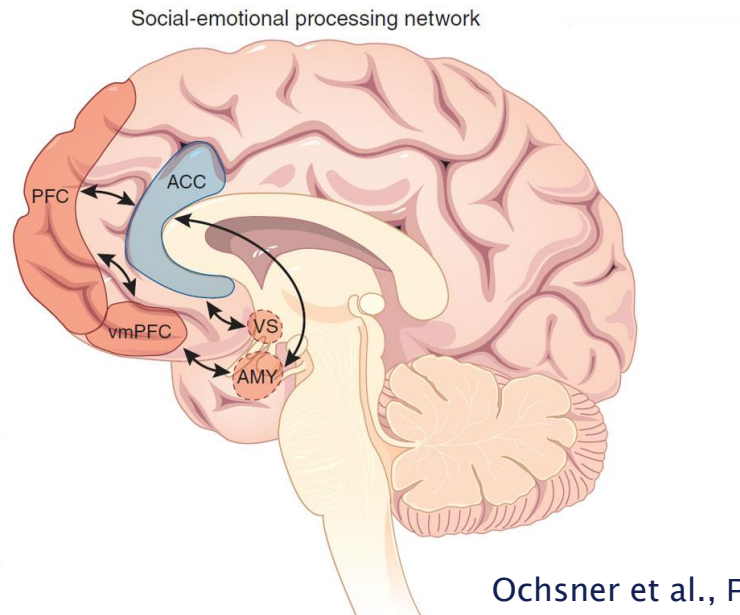
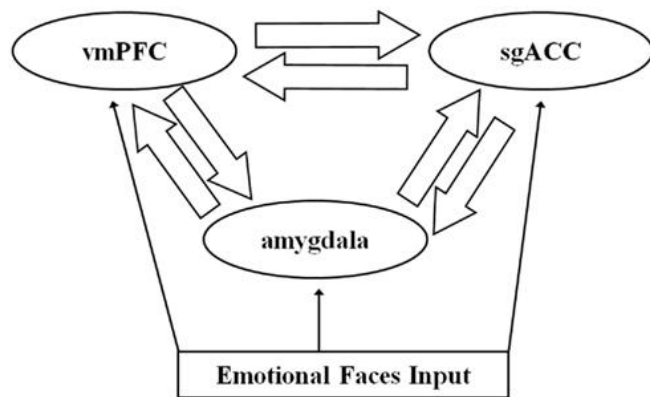
* relatives > controls ($p < 0.05$); + patients > controls ($p < 0.05$)



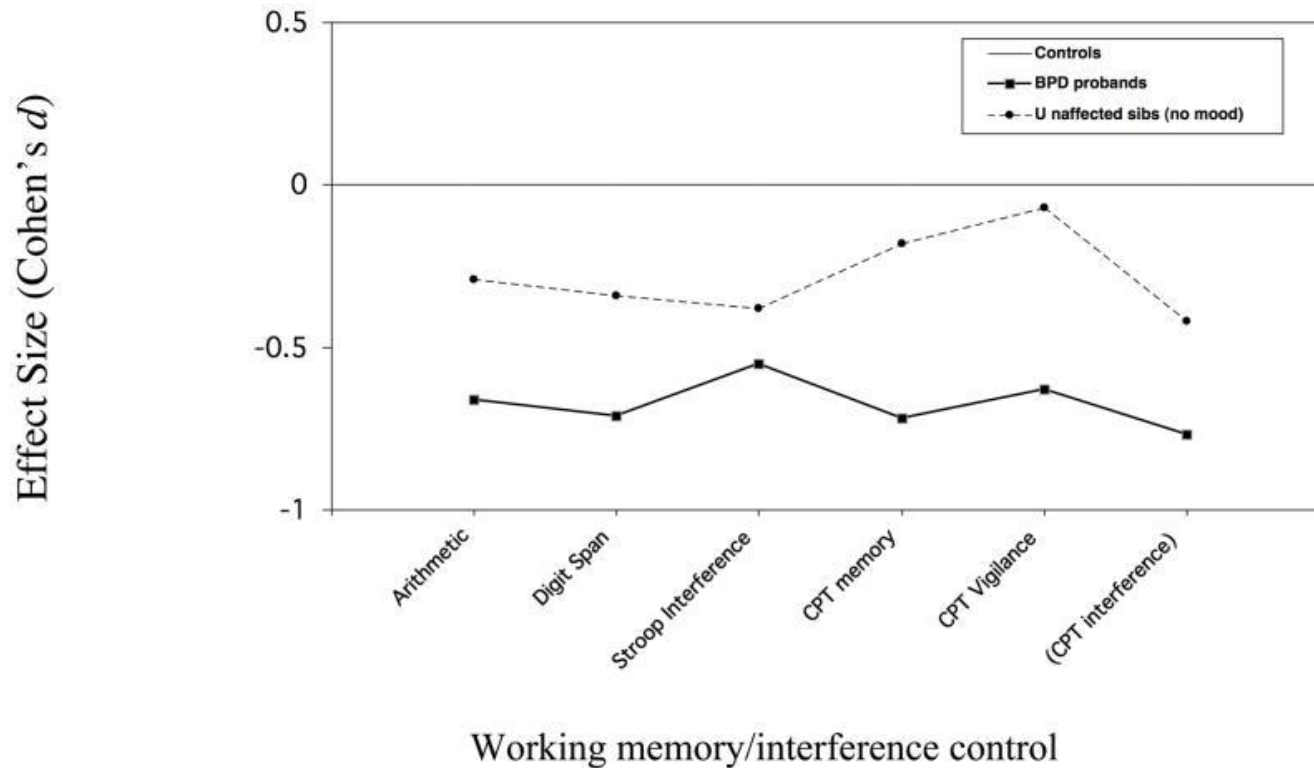
* Relatives > controls ($p < 0.001$); + patients > controls ($p < 0.05$).

Emotieverwerking eerstegraads familieleden

- Verhoogde activiteit amygdala
 - consistent met patiënten
 - kwetsbaarheidsfactor vs. risicofactor
- Verhoogde activiteit frontaal cortex
 - inconsistent met patiënten
 - gezond: remming nog intact echter insufficiënt?



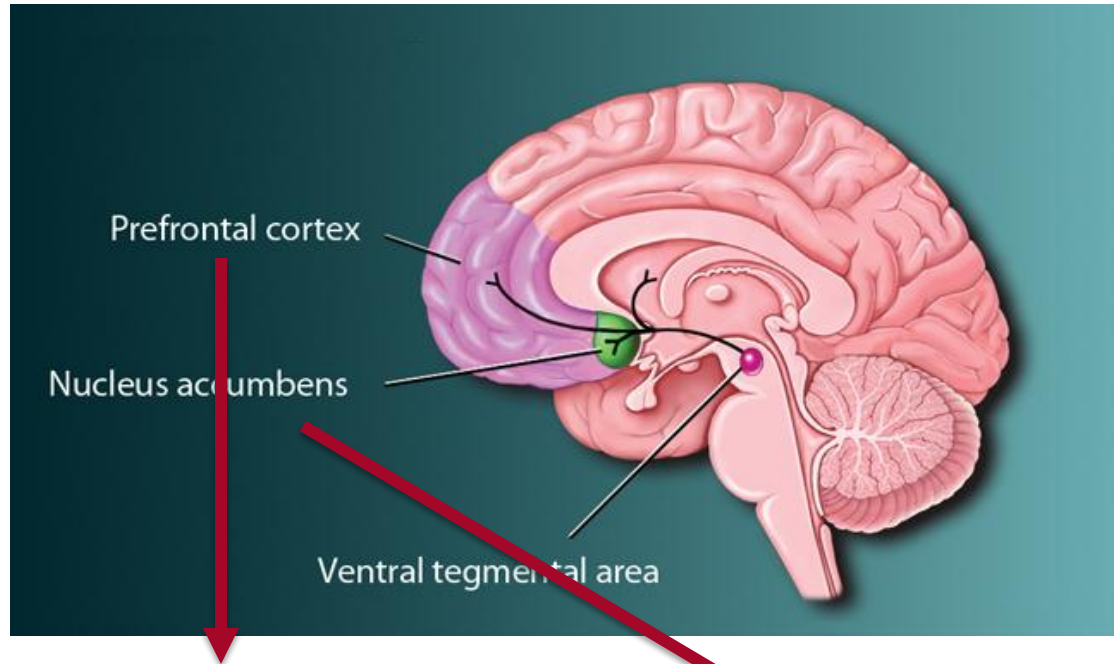
Werkgeheugen



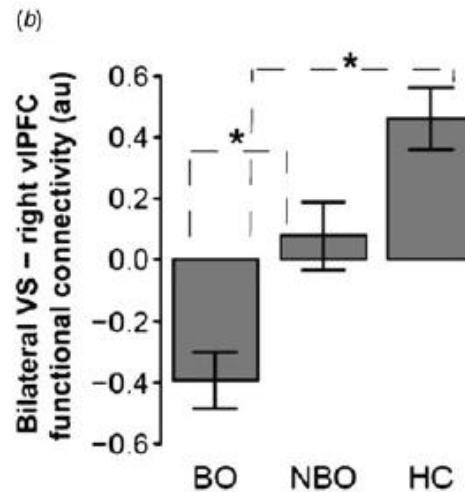
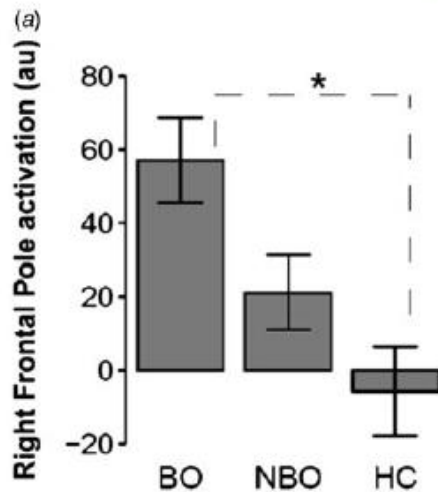
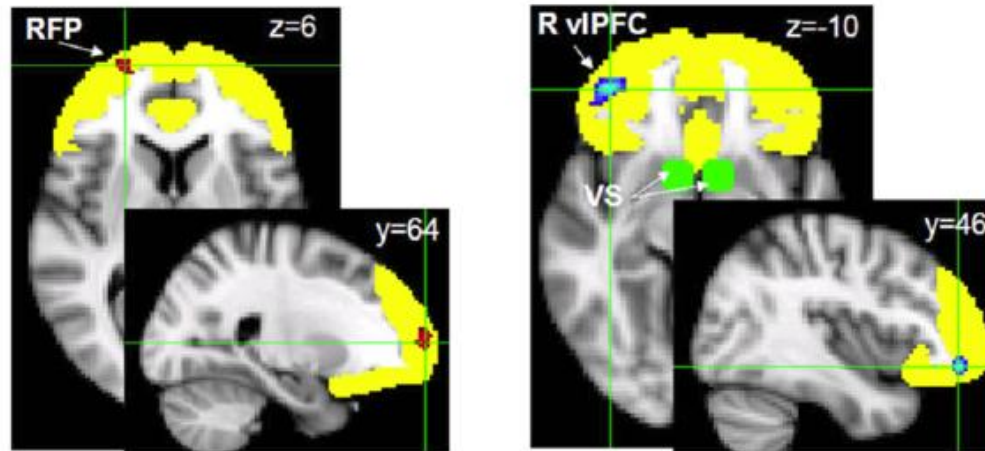
Geen imaging studies

Doyle A et al., Psychol Med. 2009

Beloning



Beloning eerstegraads familieleden (kinderen)



Beloning eerstegraads familieleden (kinderen)

- Verlaagde activiteit in ventraal striatum
 - inconsistent met patiënten
 - geen siblings
 - afgeleide maat
- Verhoogde activiteit in frontaal cortex
 - inconsistent met patiënten (geen activiteitverschil)

Samenvatting

■ Emotieverwerking

■ Patiënten

- amygdala (state) ↑↓
- vIPFC (trait) ↓

■ Eerstegraads familieleden

- amygdala ↑
- vIPFC ↑

■ Werkgeheugen

■ Patiënten

- PFC (trait) ↑

■ Eerstegraads familieleden

- ??

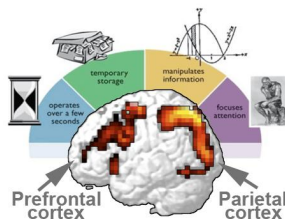
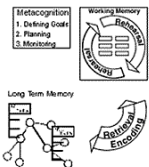
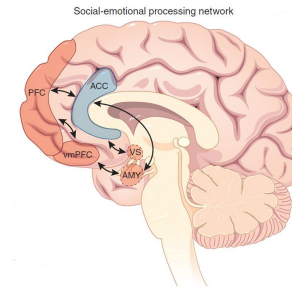
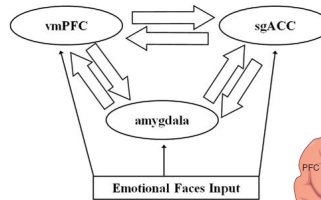
■ Beloning

■ Patiënten

- VS (?) ↑

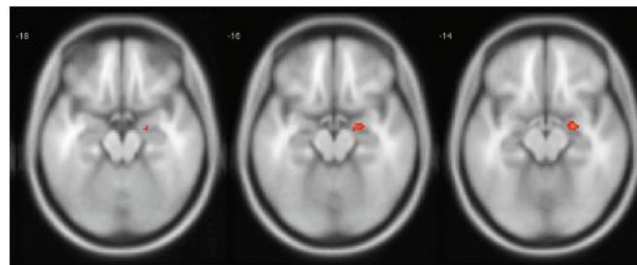
■ Eerstegraads familieleden

- VS ↓
- Frontaal cortex ↑



Toekomstige studies

- Manie versus depressie
- Grote studies patiënten zonder medicatie
- Eerstegraads familieleden
 - werkgeheugen brein-activiteit
 - belonging (siblings)
 - longitudinale studie (kinderen)



A Manic > BP depressed subjects

Discussie



GGZ Rivierduinen

