Bipolar disorder: clinical and neurobiological perspective

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Plan

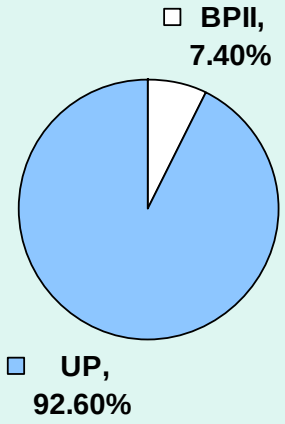
- Bipolar disorder: prevalence
- Intermediate phenotypes/endophenotypes
- Functional anatomy of regions involved in emotion processing
- Neuropathology of BPD
- Some candidate endophenotypes
- Our study

Lifetime prevalence

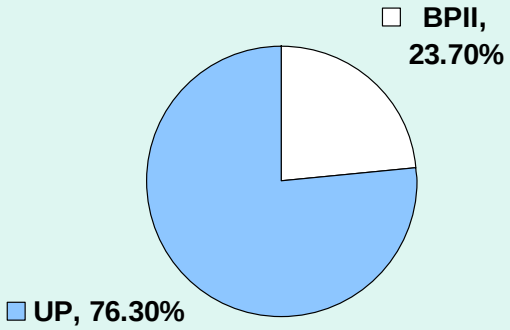
	MDD (%)	**BPD (%)**	**Proportion of BPD**
ECA study 1991	4.9	1.3	21%
NCS study 1994	13.1	1.8	12%
NCS-R study 2003	16.2	4.5	16-28%

Bipolar disorder II as a % of major depressive episodes

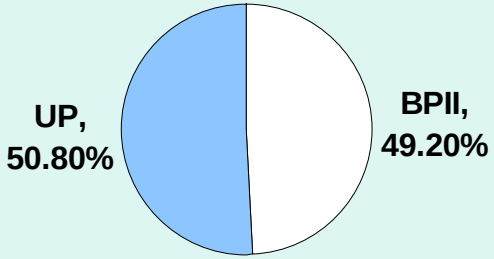
DSM-IV



ZHR strict criteria



ZHR broad criteria



J. Angst *Dialogues in Clin Neurosci* 2008

Recent developments beyond DSM-IV criteria

- DSM-IV criterium of “period of expansive, elevated or irritable mood” presumes that subject is always aware of a mood change
- Behavioural changes could be better detected, eg
  - Periods of increased enterprise, increased activity
  - Less need for sleep than usual
  - Talking more
  - Travelling more and doing more other things
  - Less fatigability

J. Angst *Dialogues in Clin Neurosci* 2008

ICD-10

- persistent elevation of mood
- increased energy and activity
- marked feelings of well-being and both physical and mental efficiency
- increased sociability, talkativeness, over-familiarity
- increased sexual energy
- decreased need for sleep
- irritability, conceit, and boorish behaviour may take the place of the more usual euphoric sociability

Bipolar disorder

Two main dimensions (+/- psychosis)

- Mood instability
  - ✓Depression
  - ✓Mania
  - ✓Irritability
- Cognitive abnormalities
  - ✓Lack of concentration
  - ✓Memory deficits
  - ✓Impaired decision making

Endophenotype: internal, intermediate phenotype (i.e., not obvious to the unaided eye) that fills the gap in the causal chain between genes and distal diseases (Gottesman & Shields, 1973)

- Genetic vulnerability:
  - Concordance in monozygotic twins = 0.67
  - Concordance in dizygotic twins = 0.10-0.20
  - Relative risk in 1st-degree relatives = 0.10-0.20

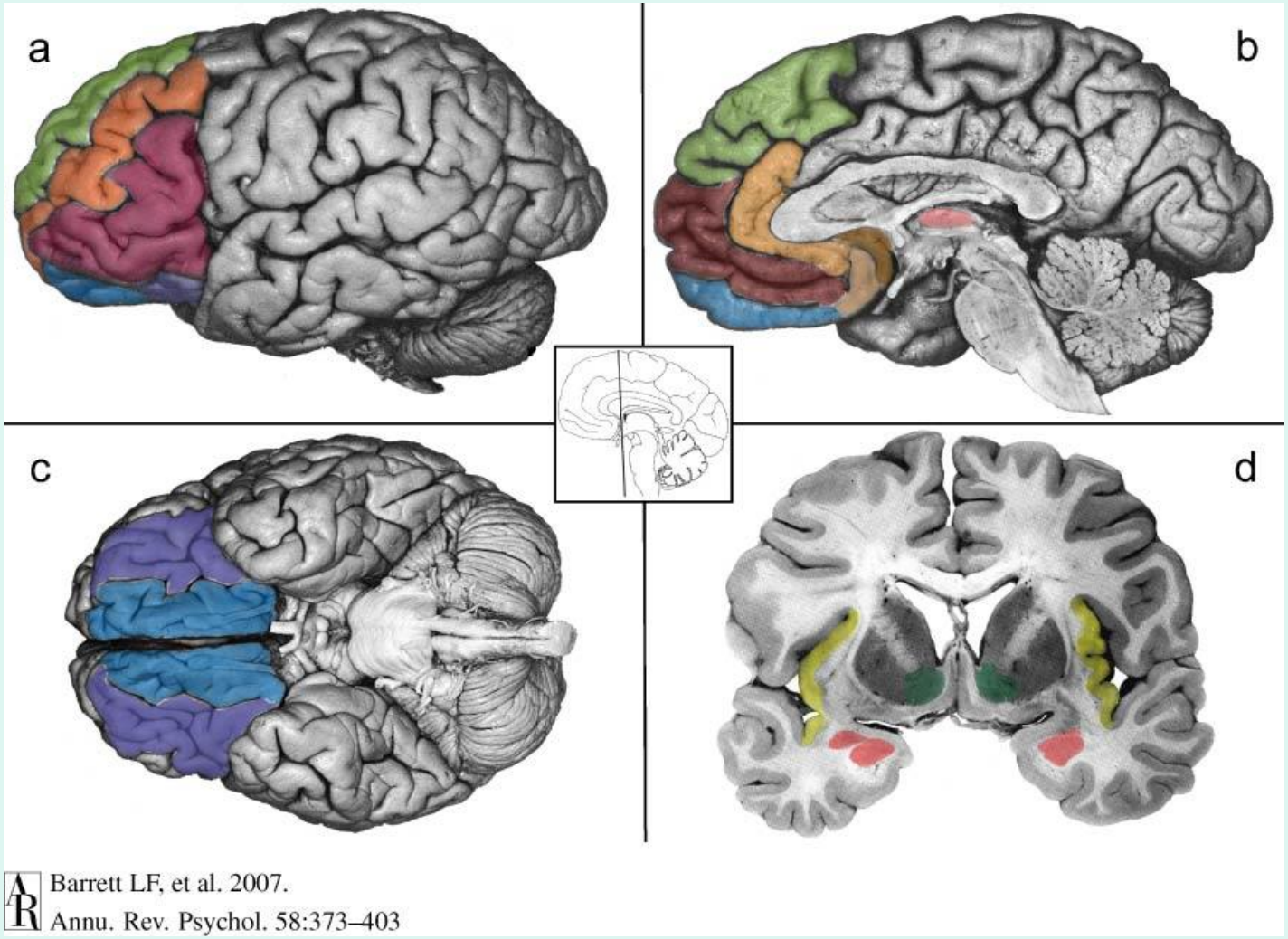
Intermediate phenotypes (endophenotypes) criteria

- Associated with illness in the population
- Heritable
- State independent, but might need to be elicited by a challenge
- Within families, endophenotype and illness co-segregate
- Is found at a higher rate in relatives than in a general population

Intermediate phenotypes (endophenotypes)

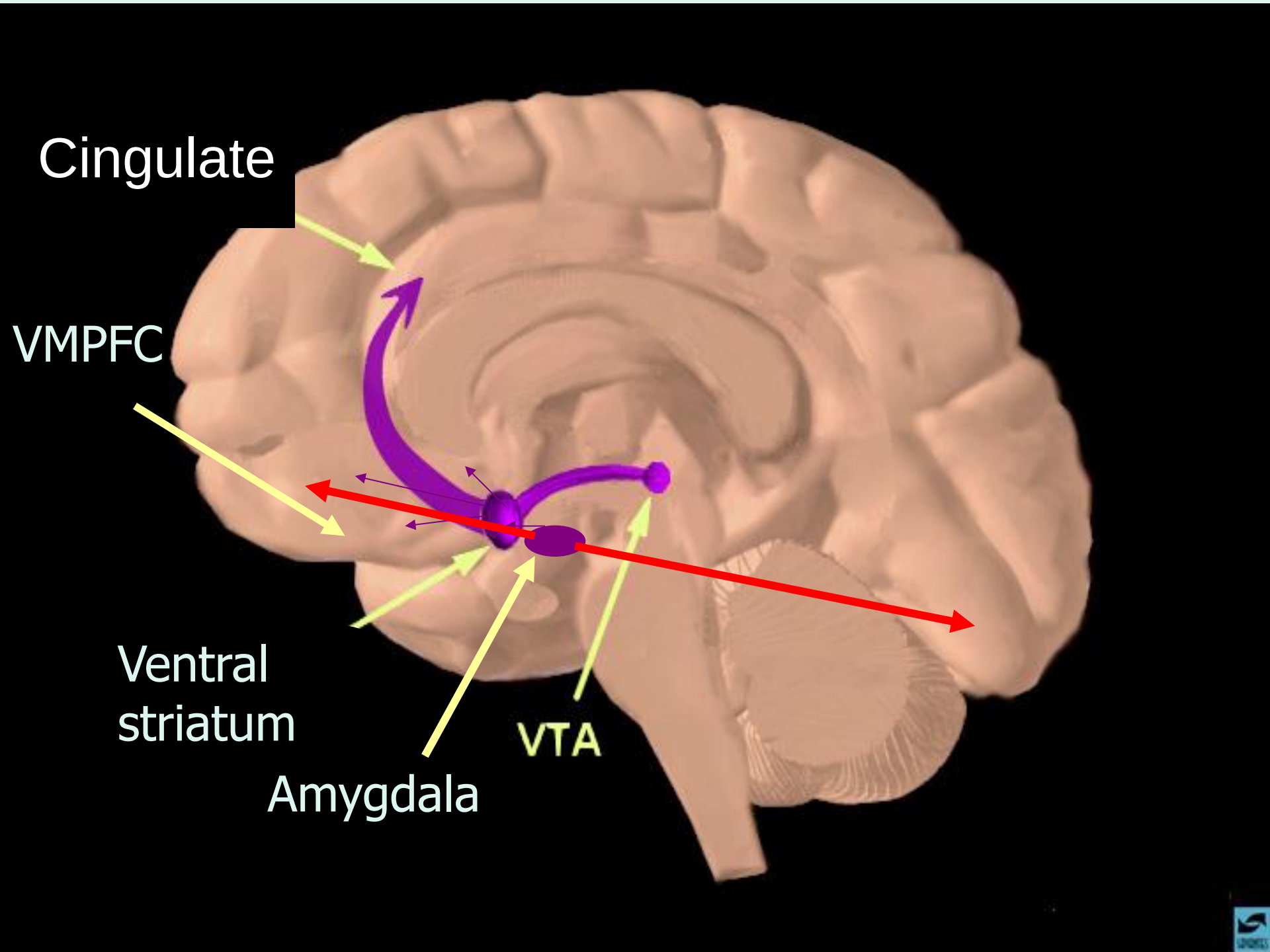
- Neurophysiological
  - Hyperactive amygdala in fMRI
- Neuropsychological
  - Emotion processing
- Cognitive
  - Sustained attention
- Neuroanatomical
  - Grey matter, lateral ventricles
- Biochemical
  - Altered dopaminergic transmission

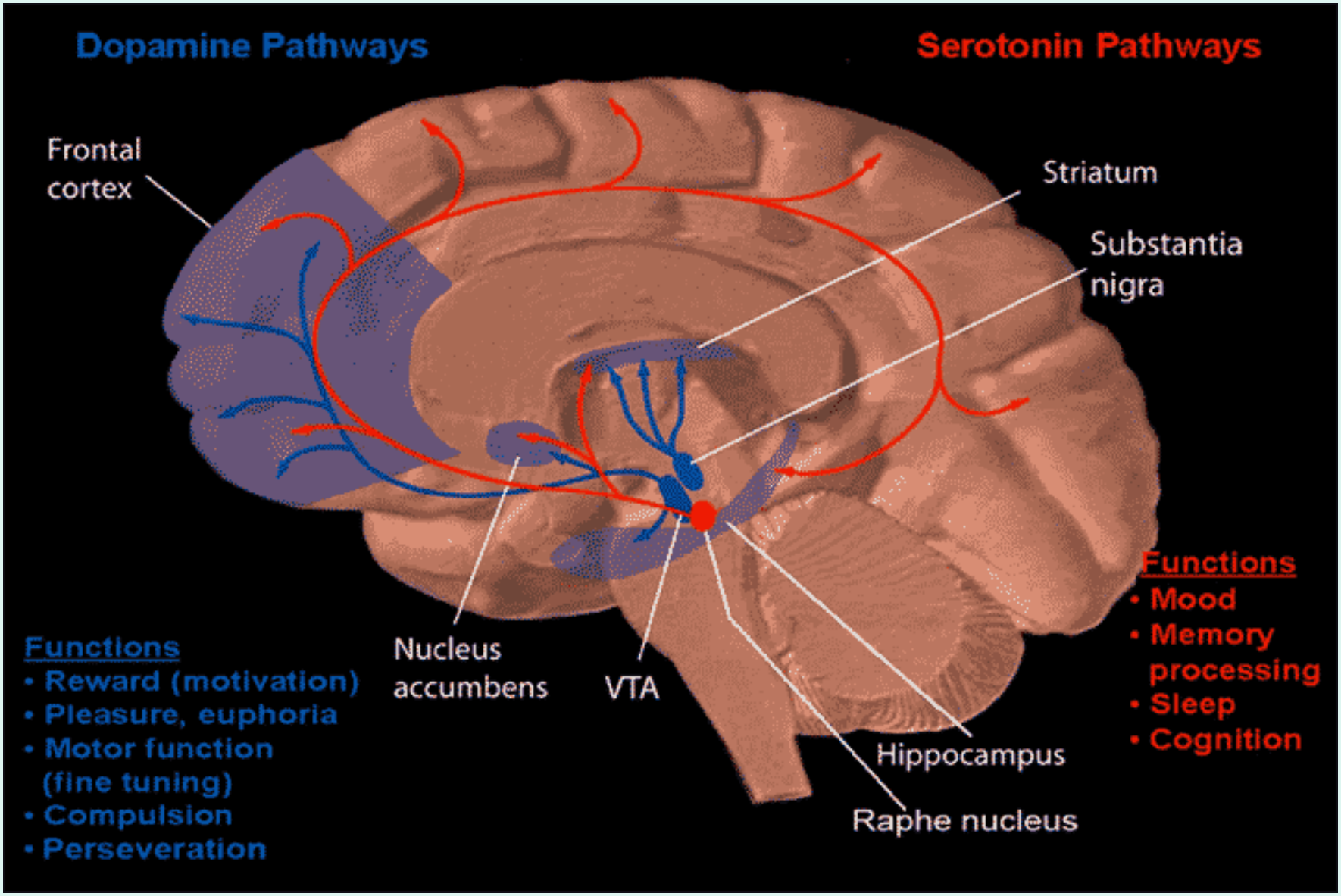
Hasler et al., Biol Psychiatry 2006

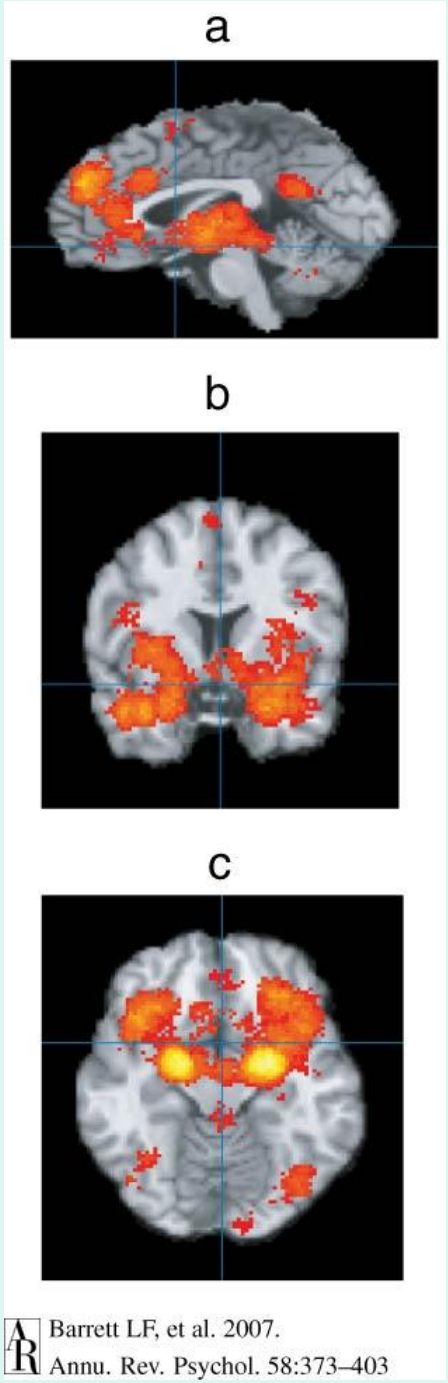


Barrett LF, et al. 2007.
Annu. Rev. Psychol. 58:373–403

Annual Reviews


Cingulate
VMPFC
Ventral
striatum
Amygdala
VTA


Dopamine Pathways
Serotonin Pathways
Frontal cortex
Striatum
Substantia nigra
Nucleus accumbens
VTA
Hippocampus
Raphe nucleus
Functions
• Reward (motivation)
• Pleasure, euphoria
• Motor function (fine tuning)
• Compulsion
• Perseveration
Functions
• Mood
• Memory processing
• Sleep
• Cognition



Barrett LF, et al. 2007.
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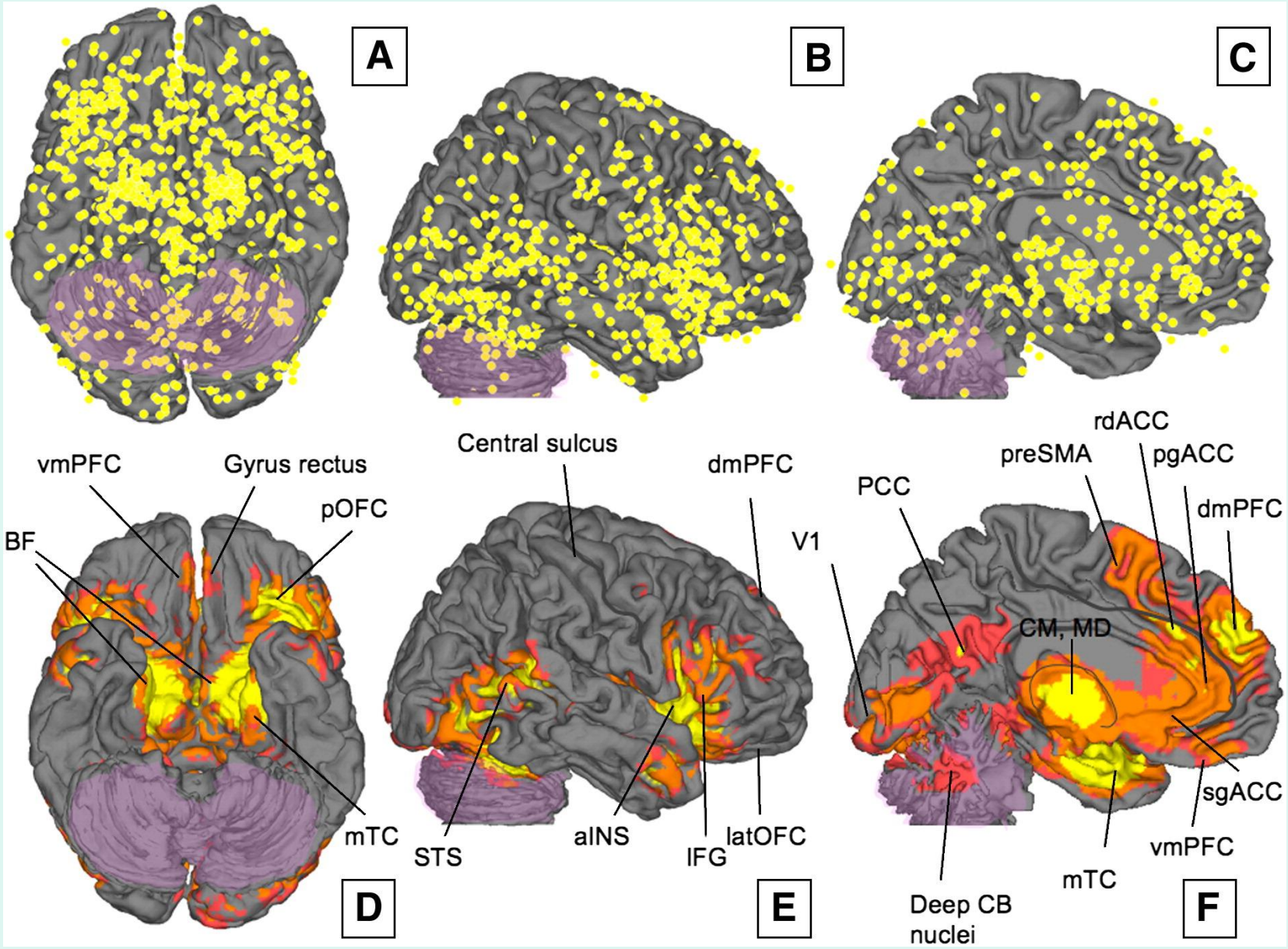
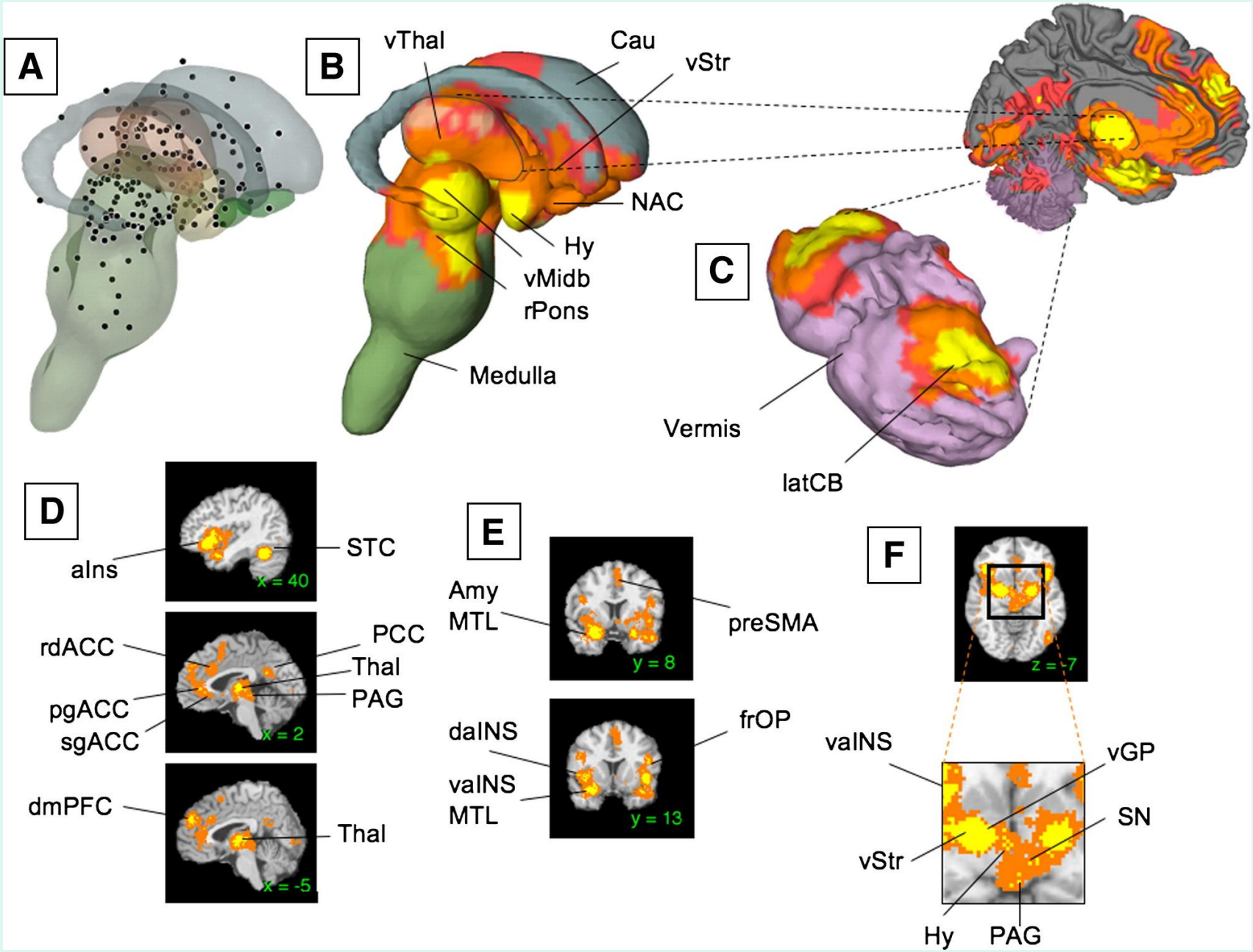
Annual Reviews


A
B
C
vmPFC
Gyrus rectus
pOFC
BF
mTC
D
Central sulcus
dmPFC
STS
aINS
lFG
latOFC
E
rdACC
preSMA
pgACC
PCC
dmPFC
V1
CM, MD
sgACC
vmPFC
mTC
Deep CB
nuclei
F


A
B
vThal
Cau
vStr
NAC
Hy
vMidb
rPons
Medulla
C
Vermis
latCB
D
aIns
STC
x = 40
rdACC
PCC
Thal
pgACC
PAG
sgACC
x = 2
dmPFC
Thal
x = -5
E
Amy
MTL
preSMA
y = 8
daINS
frOP
vaINS
MTL
y = 13
F
z = -7
vaINS
vGP
SN
vStr
Hy
PAG

Amygdala

- Lesions $\rightarrow$ emotional blunting, less fear perception
- Stimulation $\rightarrow$ fear like reaction ($\uparrow$ corticosterone, heart rate)
- Cells in the amygdala respond selectively to faces and eye gaze direction in non-human primates

Ventral Striatum

- Functional Neuroimaging Studies: Ventral striatum – response to happy faces, to drug-related pictures in drug addicts
- Ventral striatum is implicated in REWARD processing (reinforcing stimuli)
- Linking emotionally significant stimuli
  (+ and -) with behavioural responses
- Abnormal activity in depression (Anhedonia)?

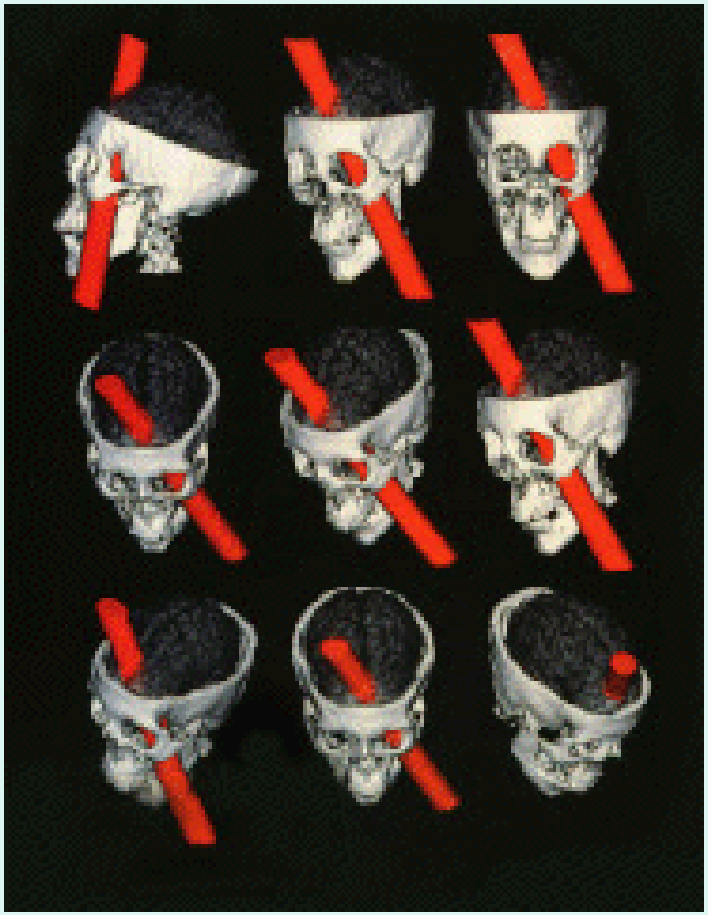
Orbital and medial (ventromedial) prefrontal cortex

- Connections with amygdala
- Important for representation of the reward value of a stimulus to guide goal-directed behaviour

- Lesions $\rightarrow$ impairment of emotional expression identification (visual & auditory), disinhibition, impulsiveness, misinterpretation of other people's moods, impaired performance on gambling tasks

Ventromedial prefrontal cortex cont.

Example: Phineas Gage



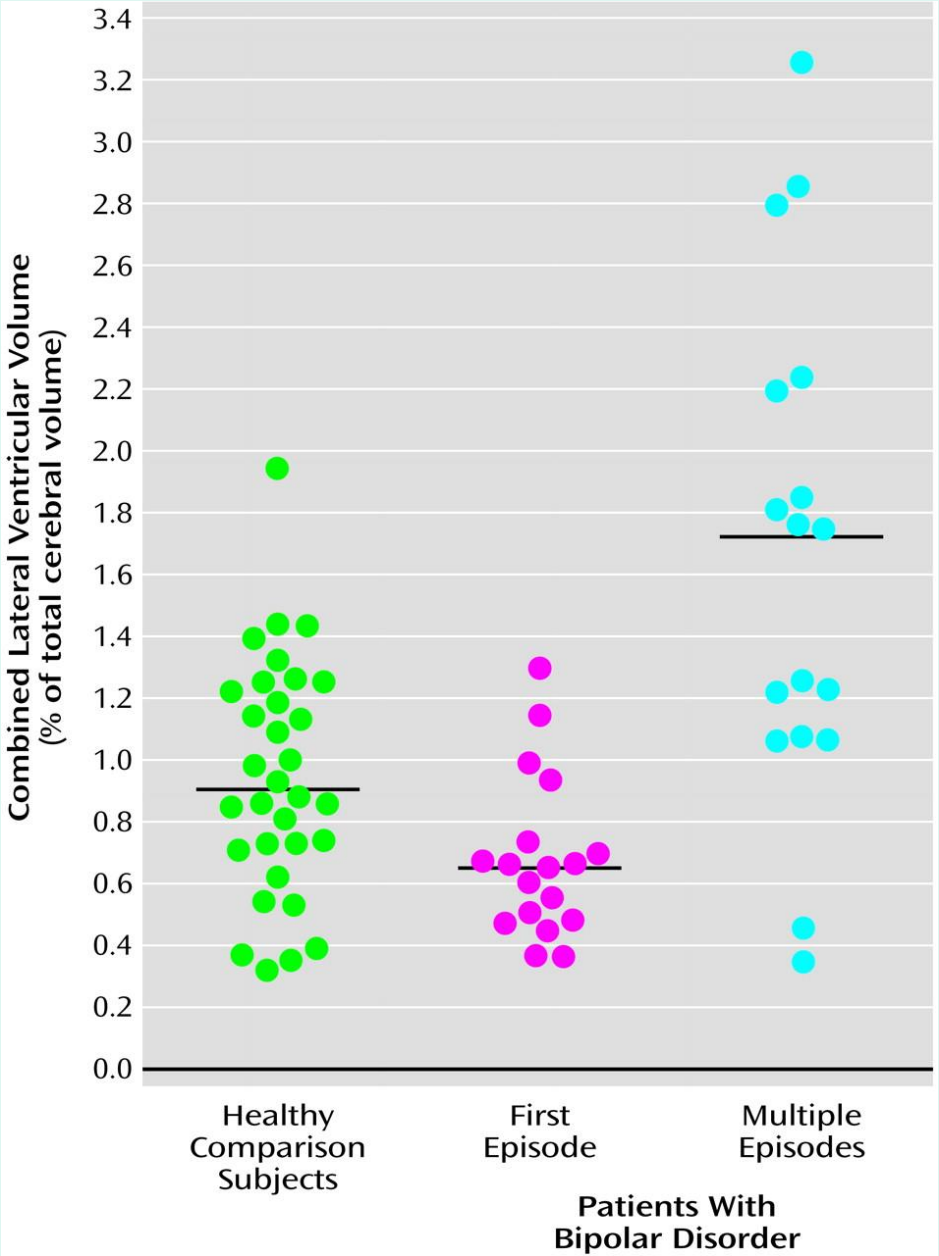
Neuropathology of BPD

- Areas involved:
  - ACC
  - OFC
  - DLPFC
  - Hippocampus
  - Amygdala

Neuropathology

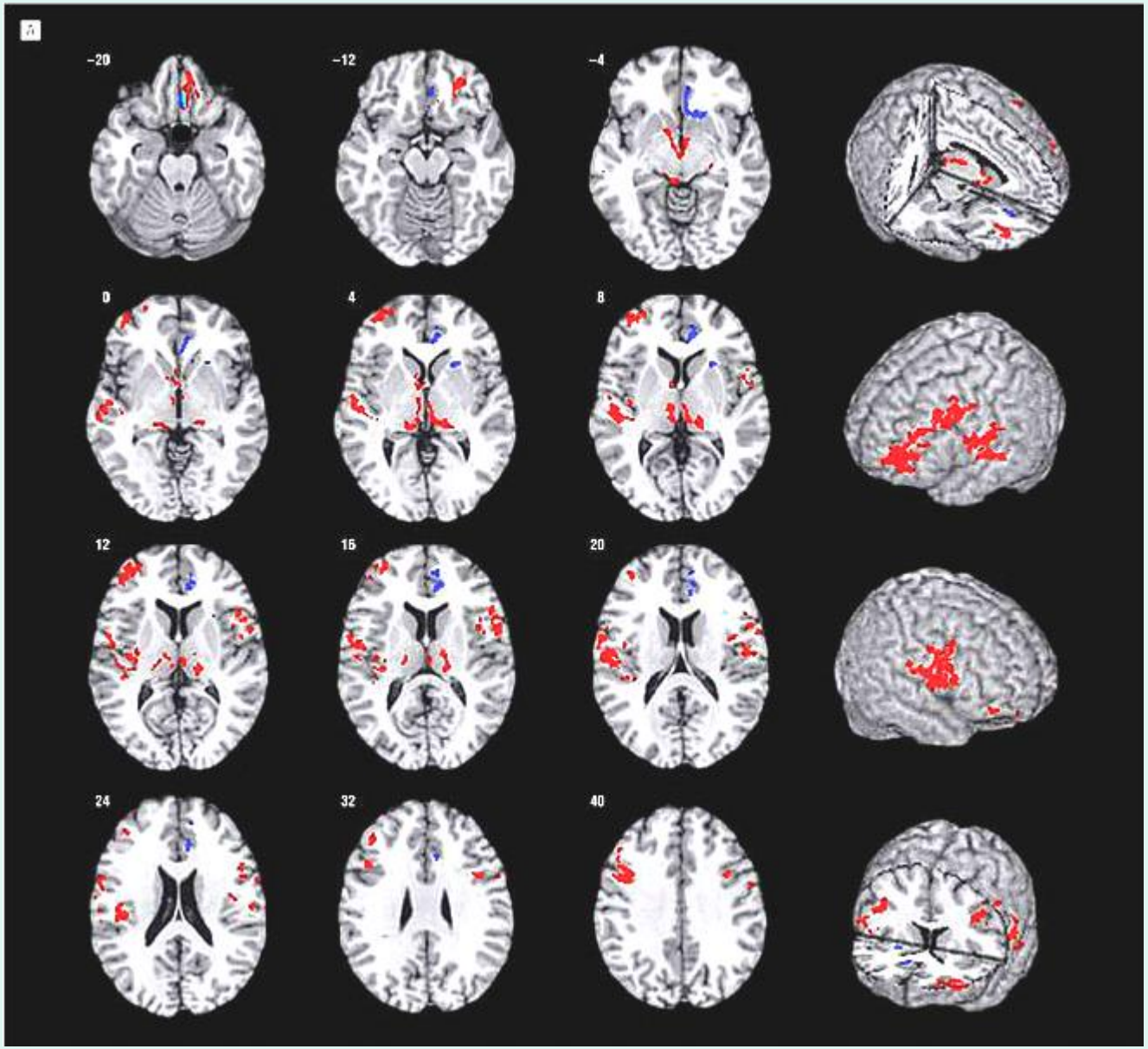
- Main features
  - Reduced number or density of glia (Ongur et al., 1998), esp Oligodendrocytes – myelination (Tkachev et al., 2003)
- Smaller and fewer neurons (Harrison 2002)
- Reduced synaptic markers (Harrison 2002; Eastwood & Harrison 2000)

Ventricular and periventricular structural volumes in first- versus multiple-episode bipolar disorder.



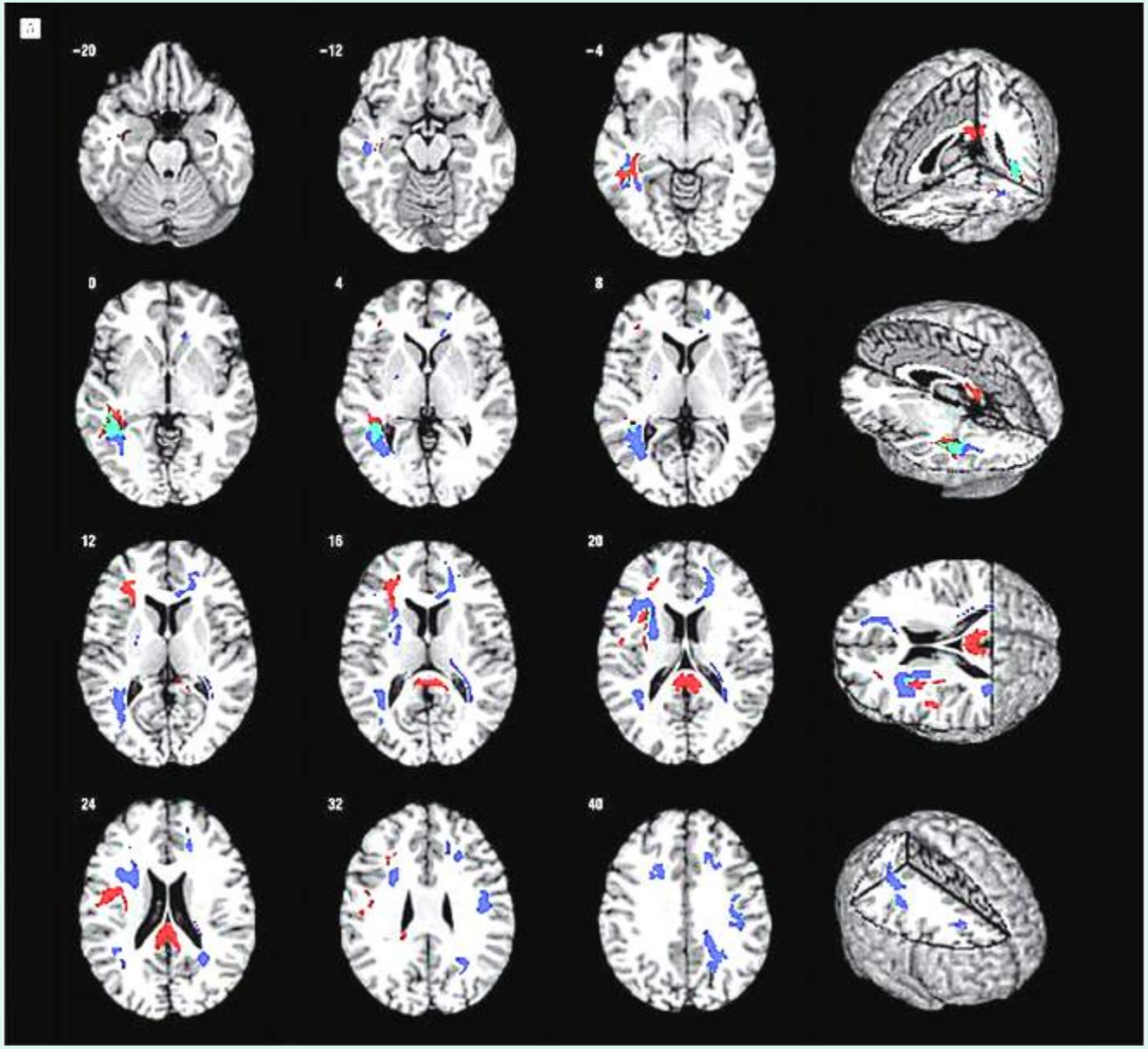
Strakowski et al Am J Psychiatry. 2002 Nov;159(11):1841-7

Gray matter endophenotypes associated with genetic risks for schizophrenia and bipolar disorder



McDonald, C. et al.
Arch Gen Psychiatry
2004;61:974-984.

White matter endophenotypes associated with genetic risks for schizophrenia and bipolar disorder



McDonald, C. et al.
Arch Gen Psychiatry
2004;61:974-984.

Cognitive endophenotypes

- Sustained attention deficit found in remitted states, in mania and depression

- Executive function? Not consistently reported in manic and depressed states, not in remission

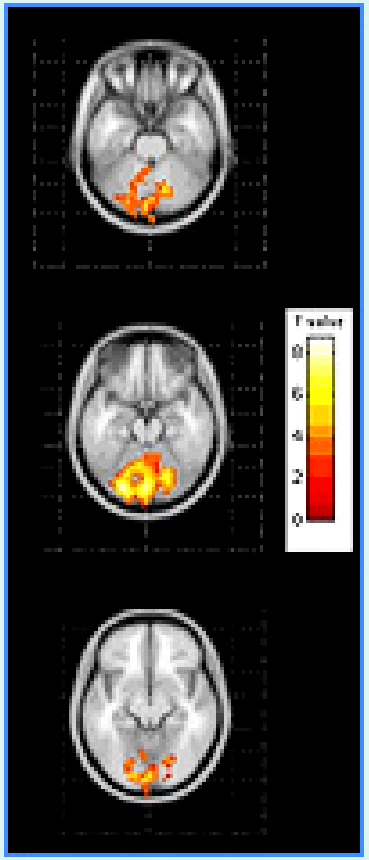
Endophenotype candidates: personality measures

- BPD relatives and patients had higher TEMPS score in dysthymia scale comp with NC (Burdick et al, 2008)

Hasler et al., Biol Psychiatry 2006

How do we measure brain functioning?

- Functional magnetic resonance imaging fMRI
- Positron emission tomography PET
- Single photon emission computed tomography SPECT



Neuroimaging studies

- Manic states
  - in decision making tasks: Dysregulation of medial and orbital prefrontal circuits
- Remission states
  - in Stroop tests: Dysregulation of ACC and orbital prefrontal circuits
  - Emotional faces, sustained attention tasks : overactive limbic areas

Neuroimaging studies

- Bipolar depression
  - Affect generation task: increased limbic and basal ganglia activity
  - Happy faces task: increased limbic activity

Our study

	Pts (20)	Rel (20)	Ctrl (20)	F	p
Age	42.7	43	41.9	0.04	0.95
Yrs educ	14.4	15.8	16	0.93	0.39
BDI	7.3	4.9	3.9	1.6	0.19
ASRM	3.4	2.2	1.9	1.4	0.25

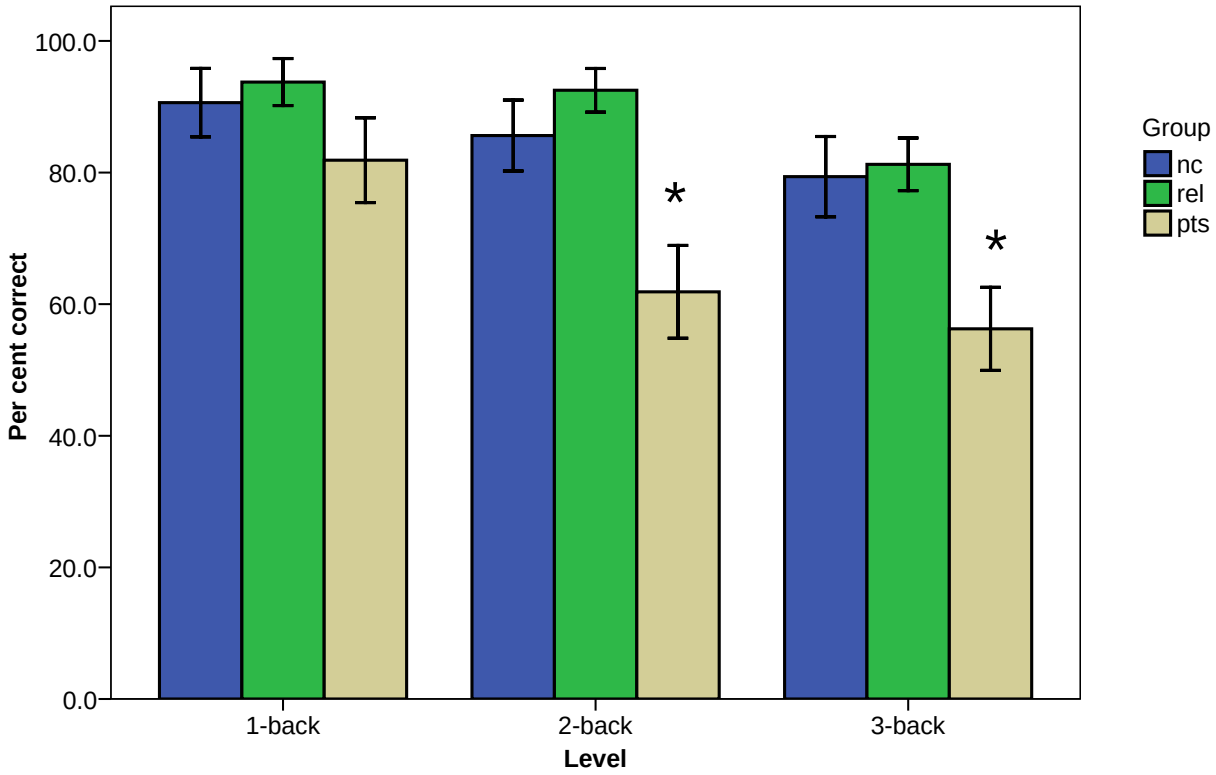
Drapier et al, *Biological Psychiatry 2008*

fMRI experiments

- Working memory
  - X: A Y X I N X
  - 1-back : A C C T U N
  - 2-back: A C T C U N
  - 3-back: A C T Y C U

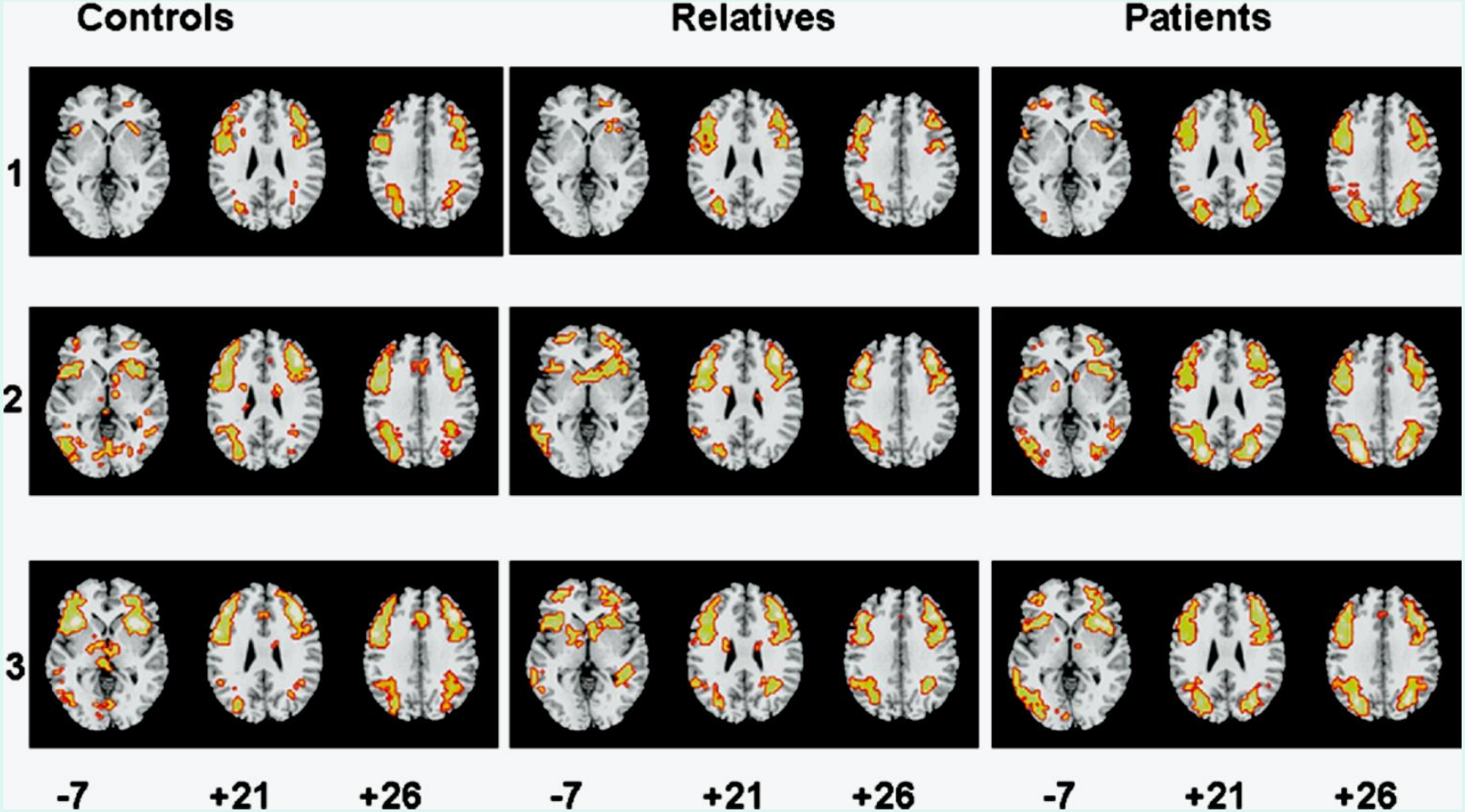
- Emotional expressions
  - Happy faces
  - Fearful faces

Working memory task performance

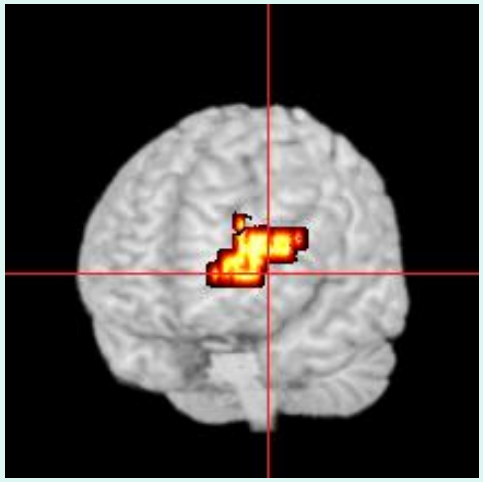


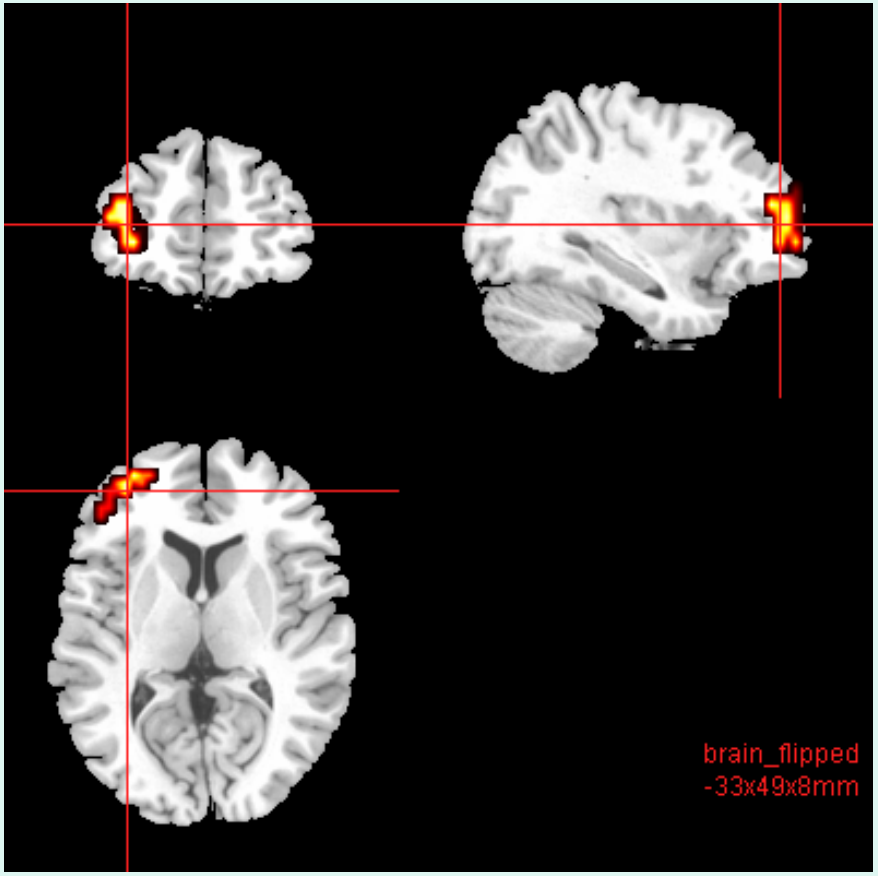
*p < 0.05; a significant difference between bipolar patients and both relatives and controls for performance on 2-back and 3-back tasks

Working memory

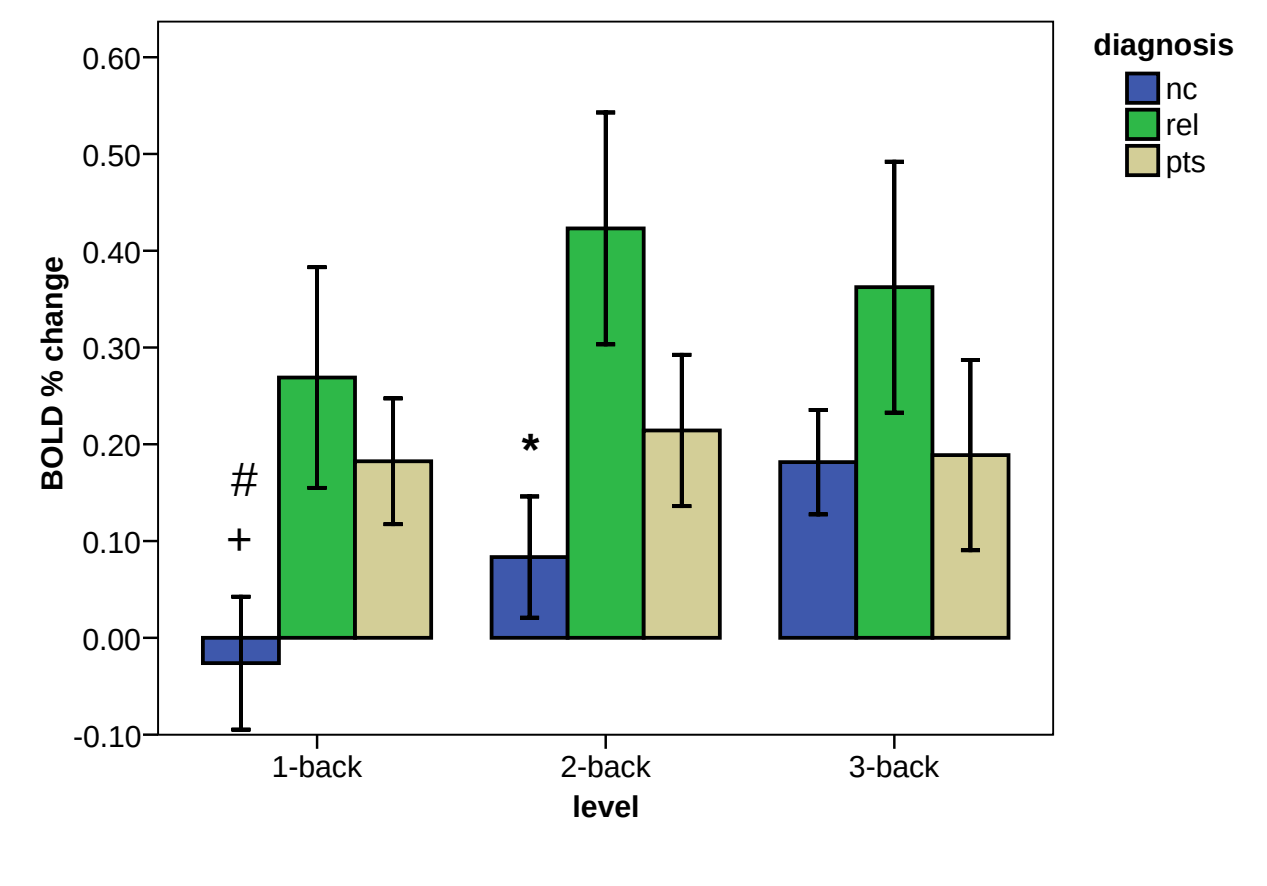


BOLD response to WM task: 3 x 3 repeated measures ANOVA





BOLD response to WM task



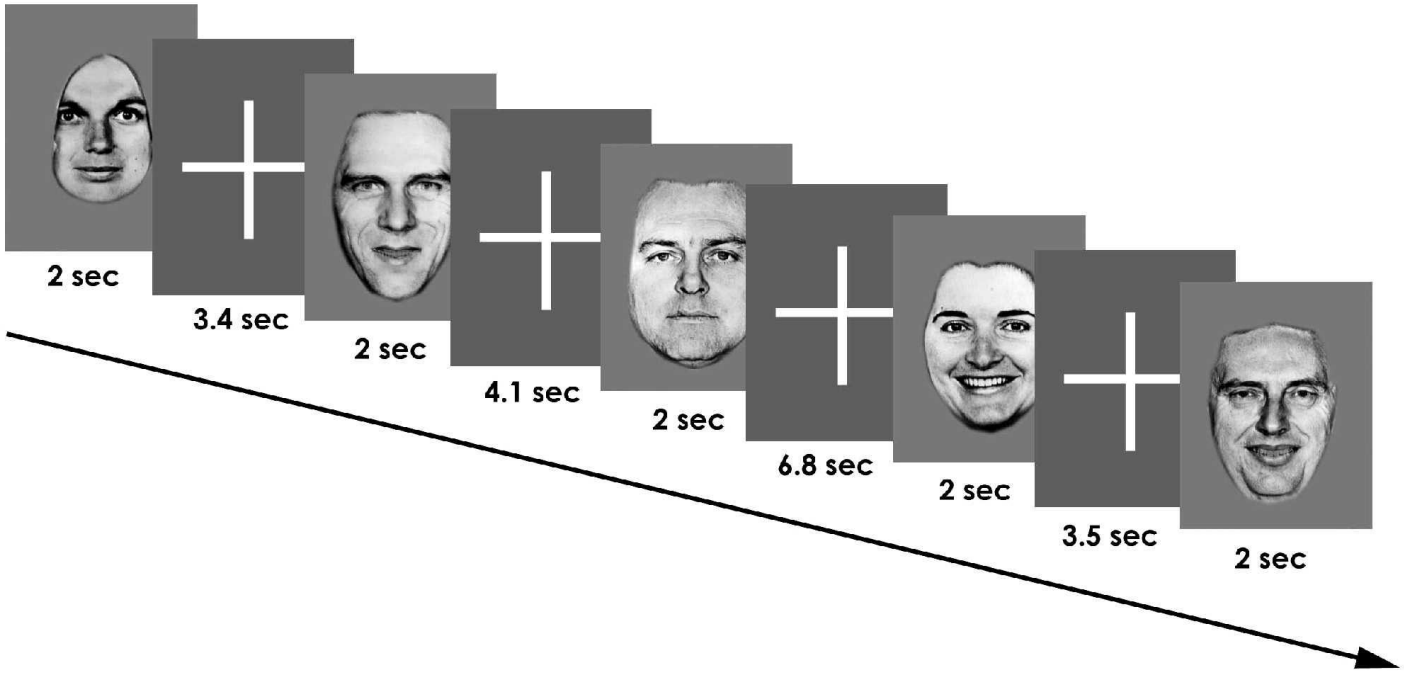
+ significant difference between relatives and controls and
# patients and controls in 1-back task ($p<0.01$);

*significant difference between relatives and controls in 2-back task ($p=0.01$).

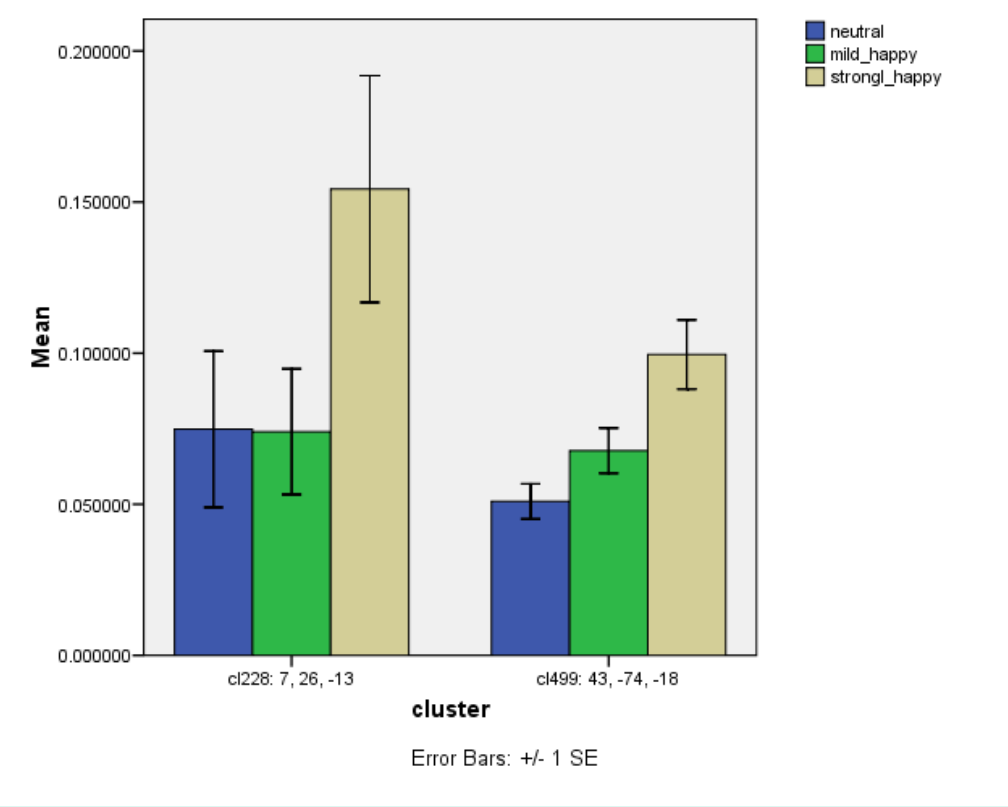
Summary of working memory study

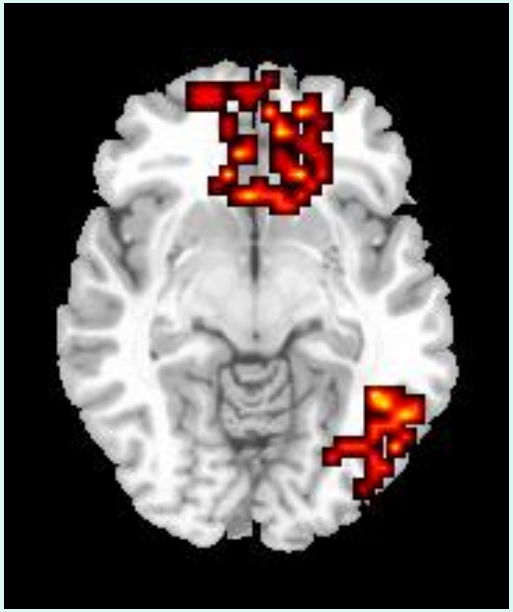
- Left prefrontal hyperactivation during WM task despite normal performance represents a potential intermediate phenotype for BPD.

Experiments with facial emotional expressions

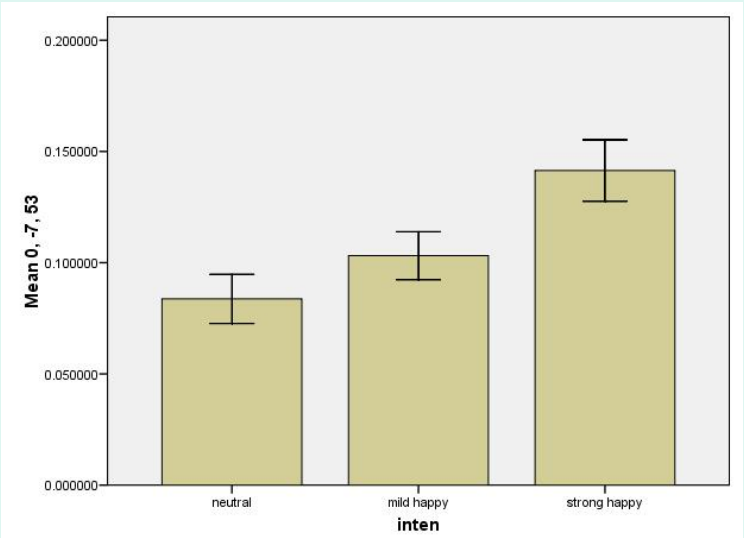


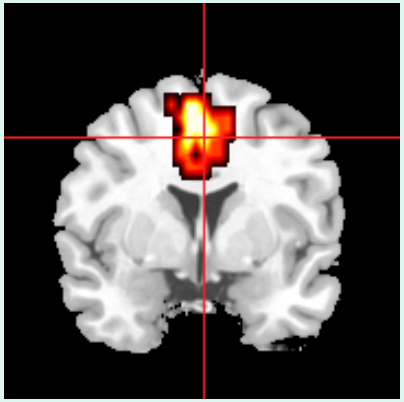
Healthy controls

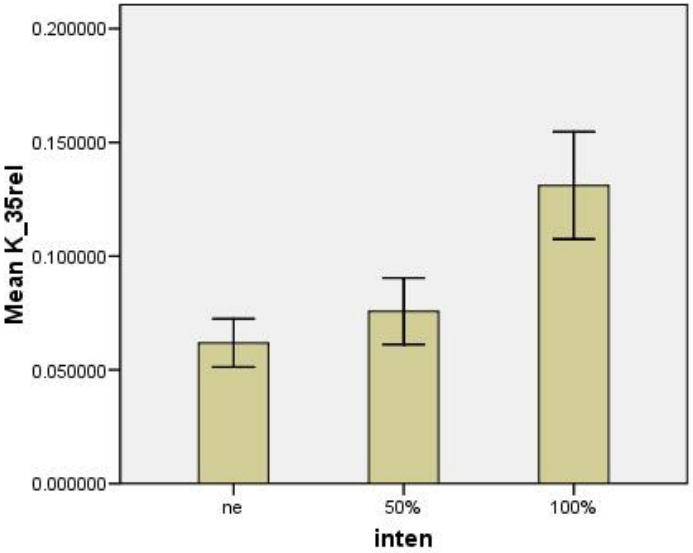




Relatives


0.200000
0.150000
0.100000
0.050000
0.000000
Mean 0, -7, 53
neutral
mild happy
strong happy
inten




0.200000
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Mean K_35rel
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50%
100%
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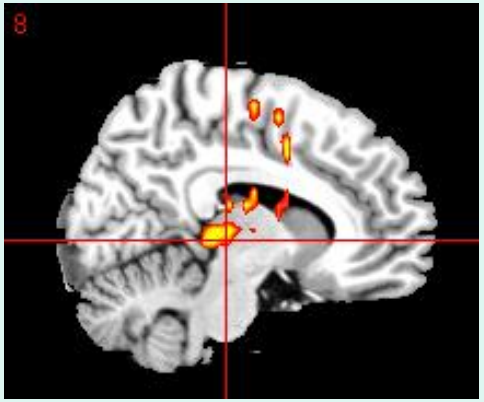
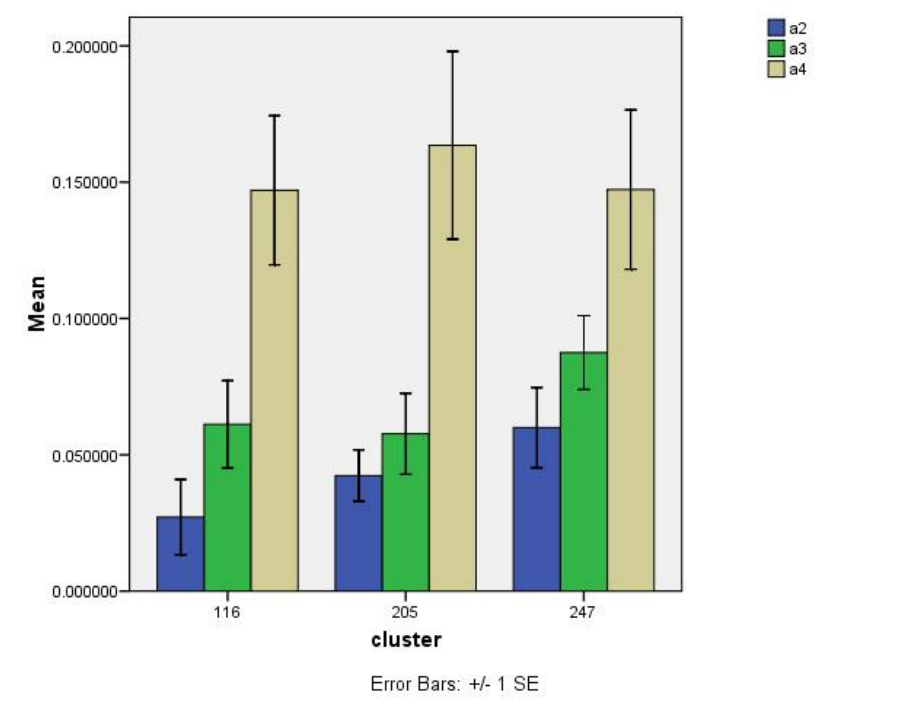
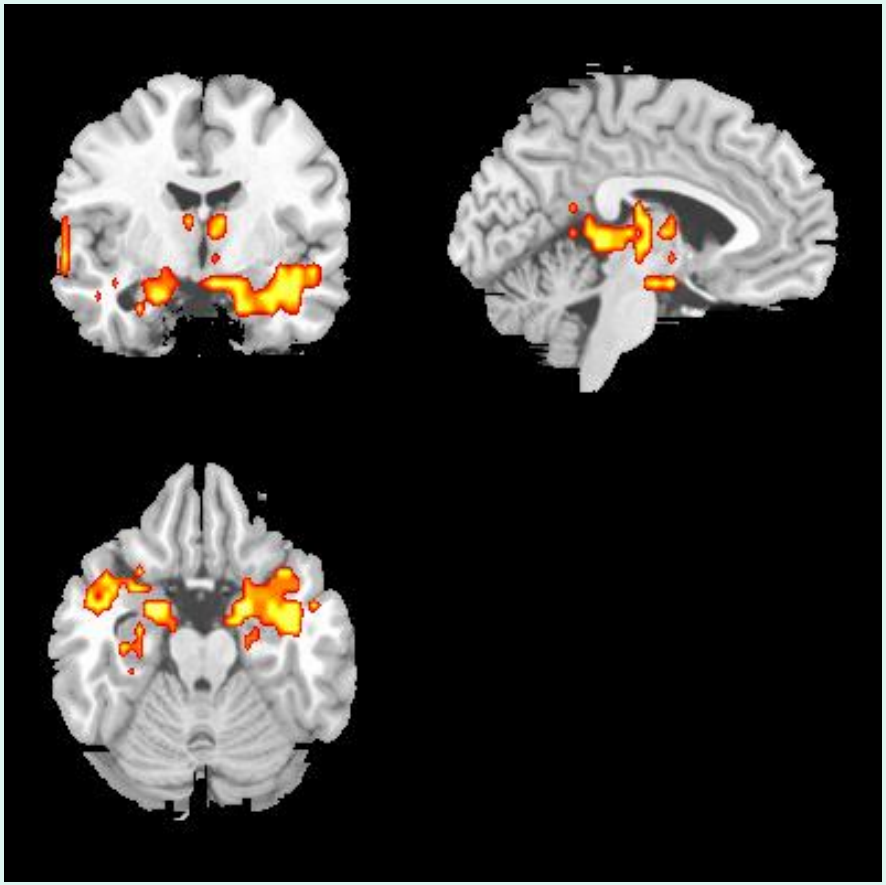
Error Bars: +/- 1 SE


8

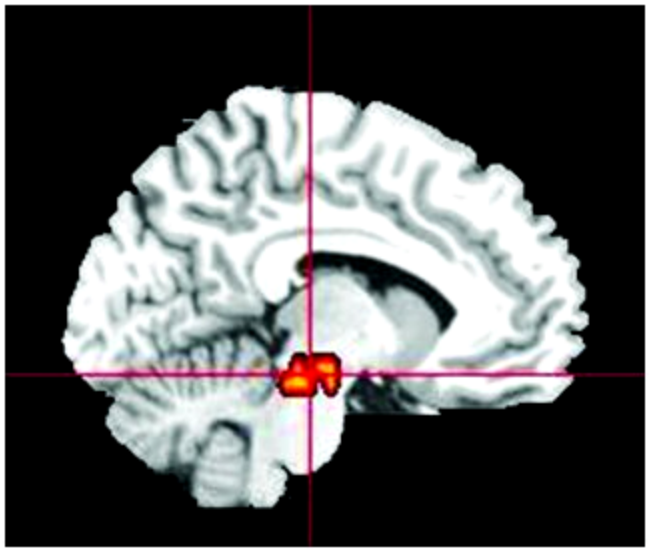
Probands


a2
a3
a4
0.200000
0.150000
0.100000
0.050000
0.000000
Mean
116
205
247
cluster
Error Bars: +/- 1 SE

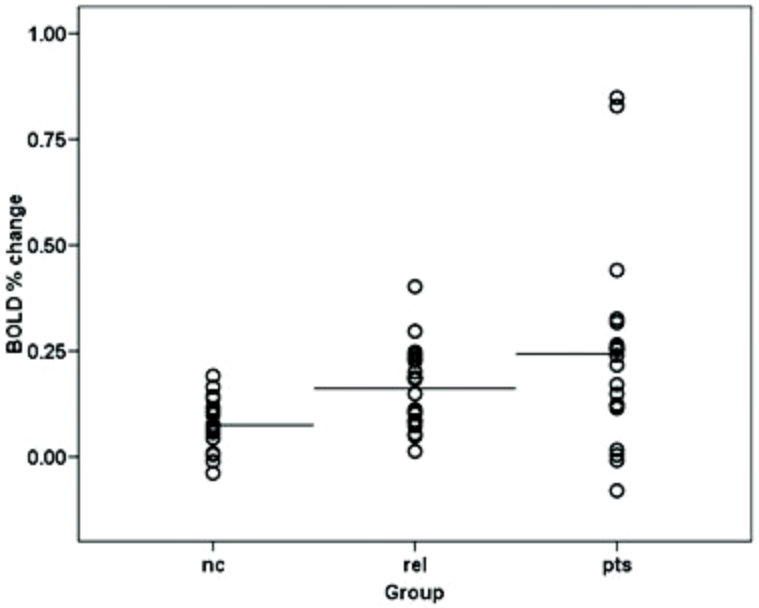


Between-group difference: midbrain

A



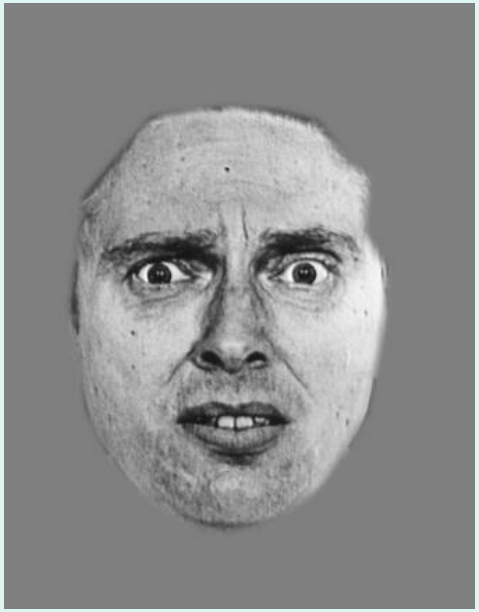
B

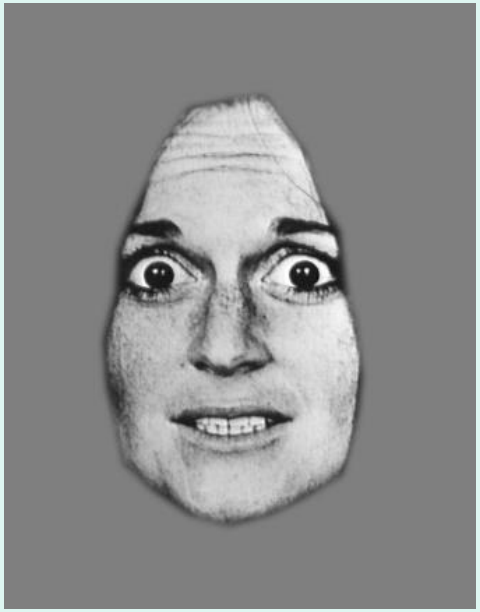


Summary of happy faces experiment

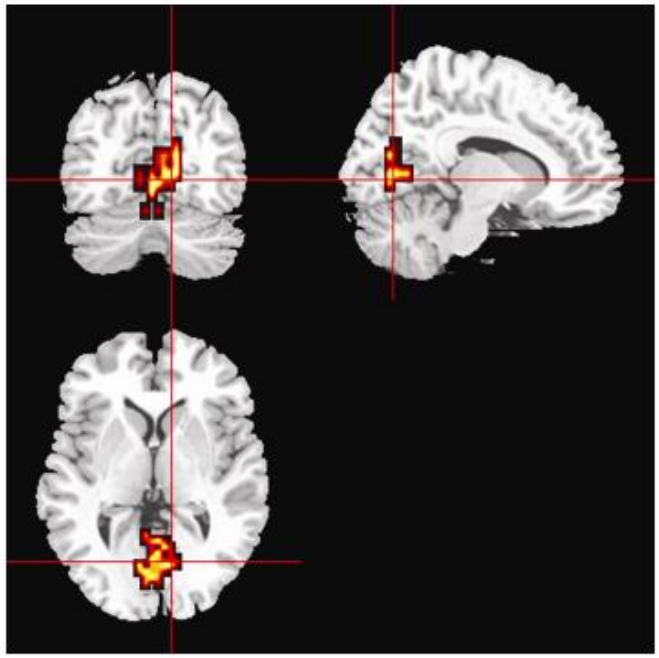
- Midbrain was differentially hyperactive in the patient group vs. controls in response to intensively happy faces
- This may indicate dysregulation of reward-related (dopamine-related) system

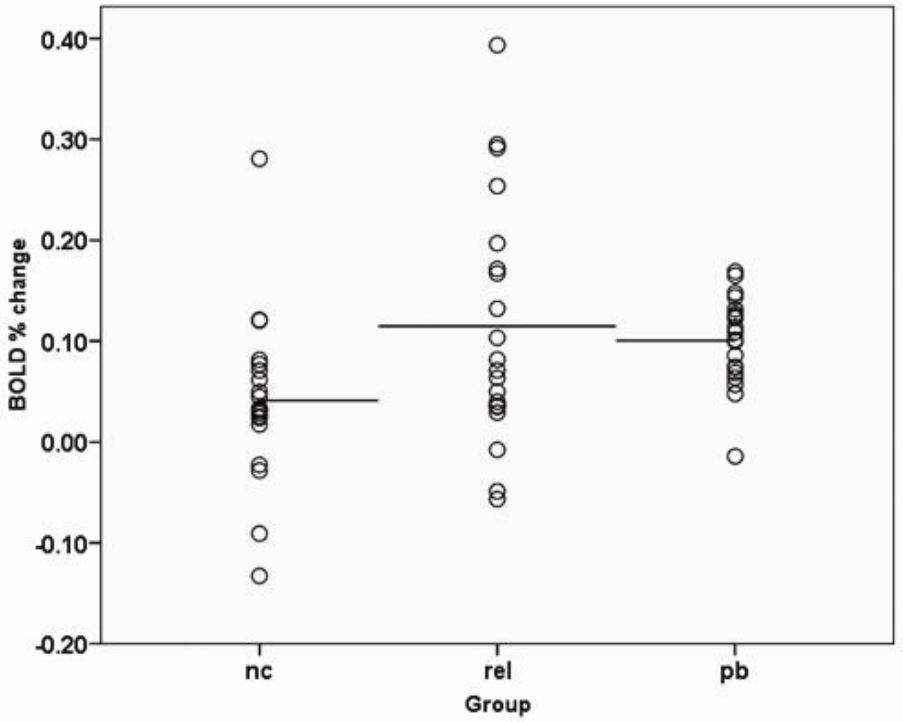
Fear



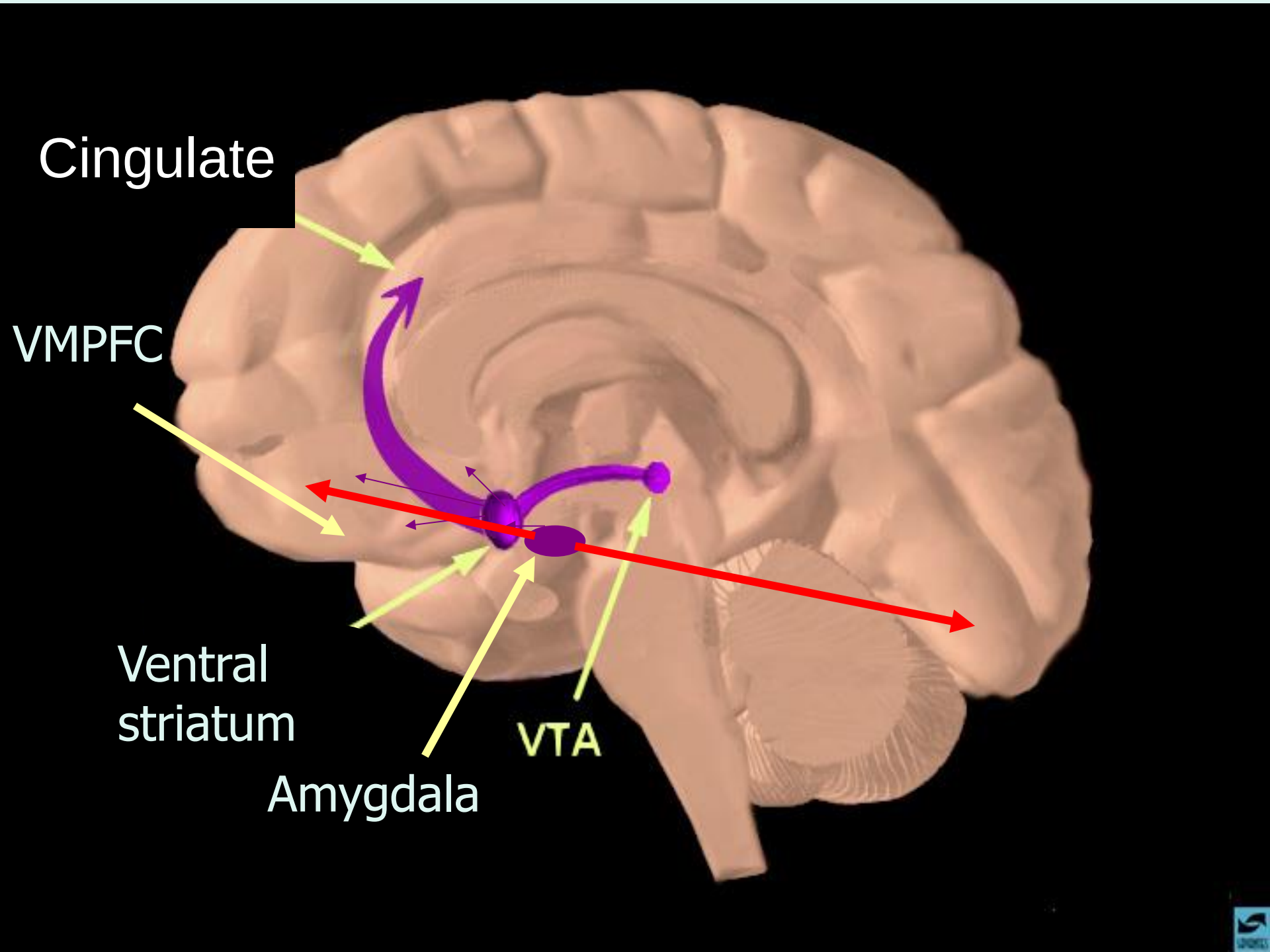


Between-group difference

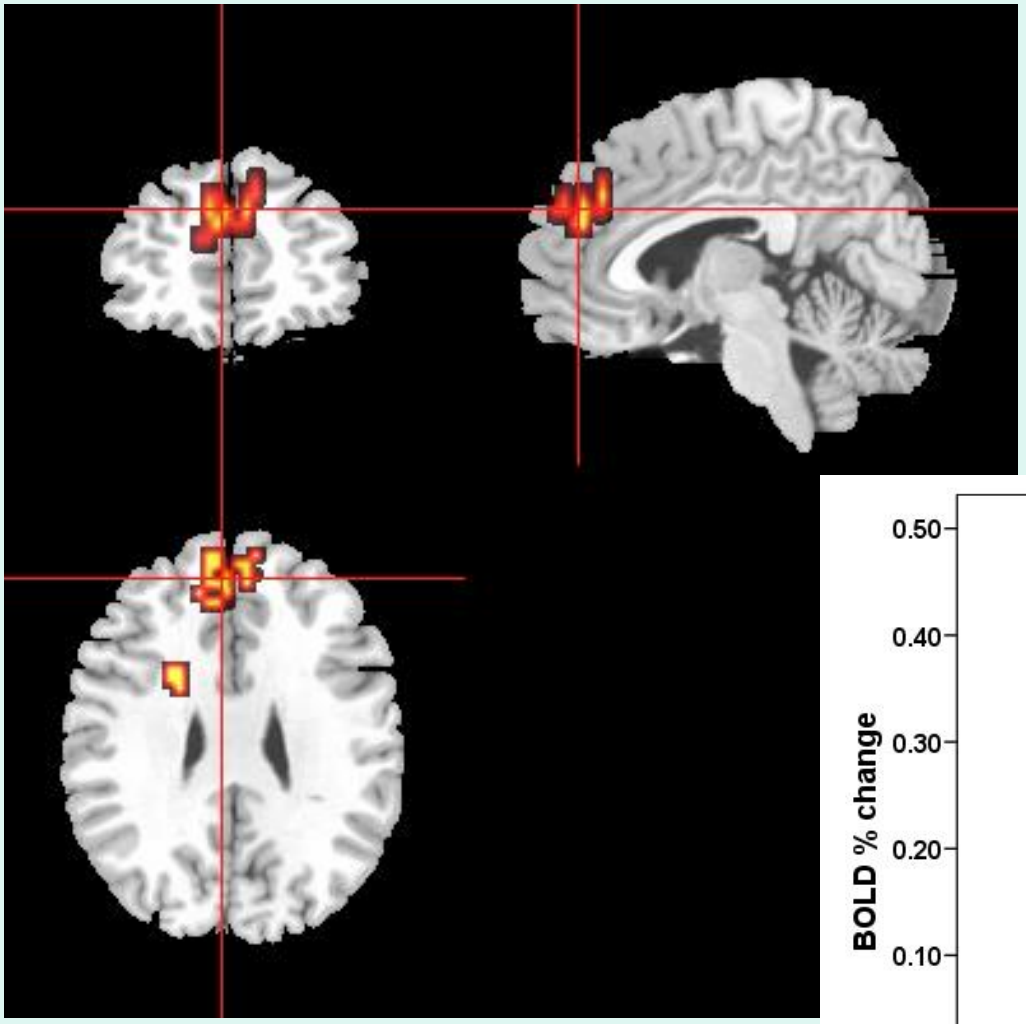


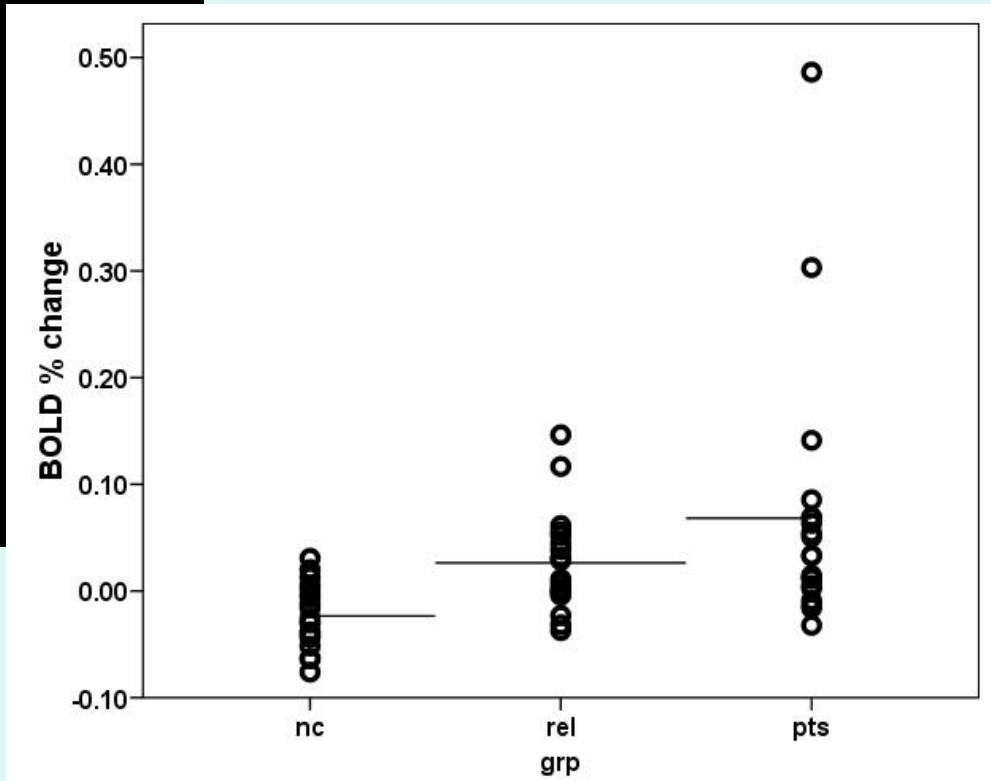


In response to 100% fear, both patients (p=0.04) and relatives (p=0.01) groups activate more than controls

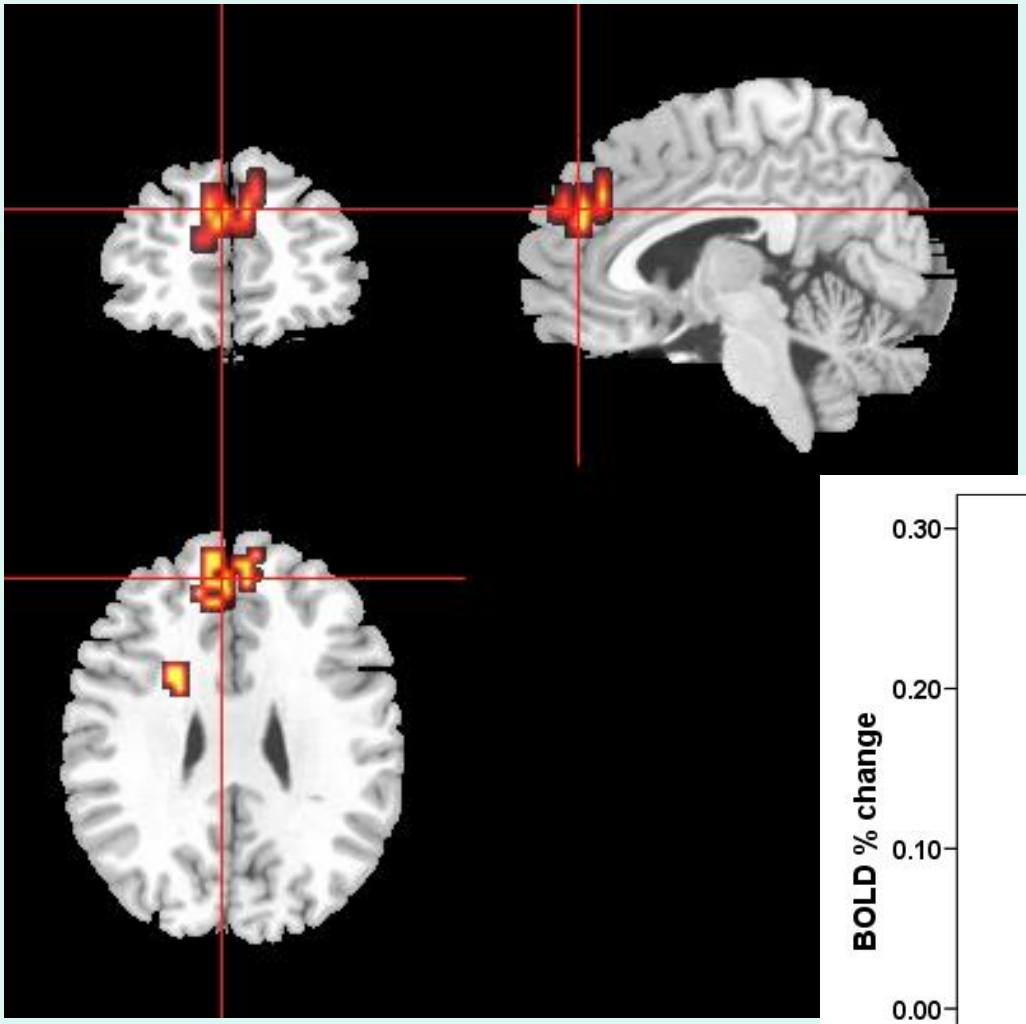

Cingulate
VMPFC
Ventral
striatum
Amygdala
VTA

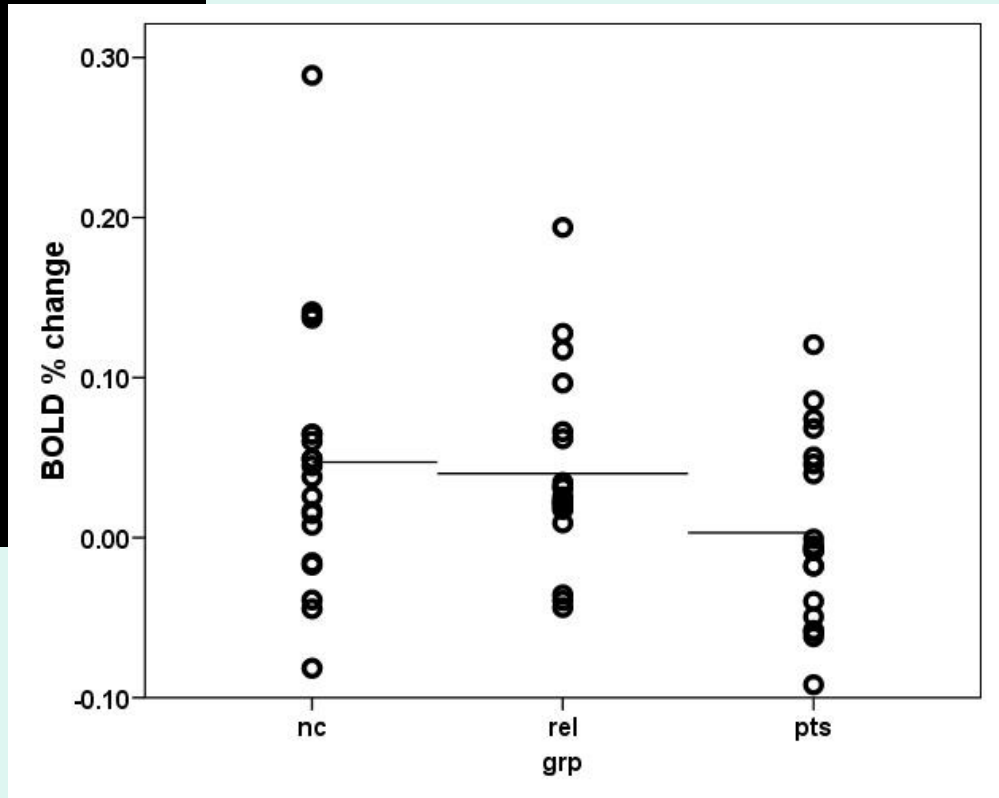
Patients and relatives hyper-activate to mildly happy faces



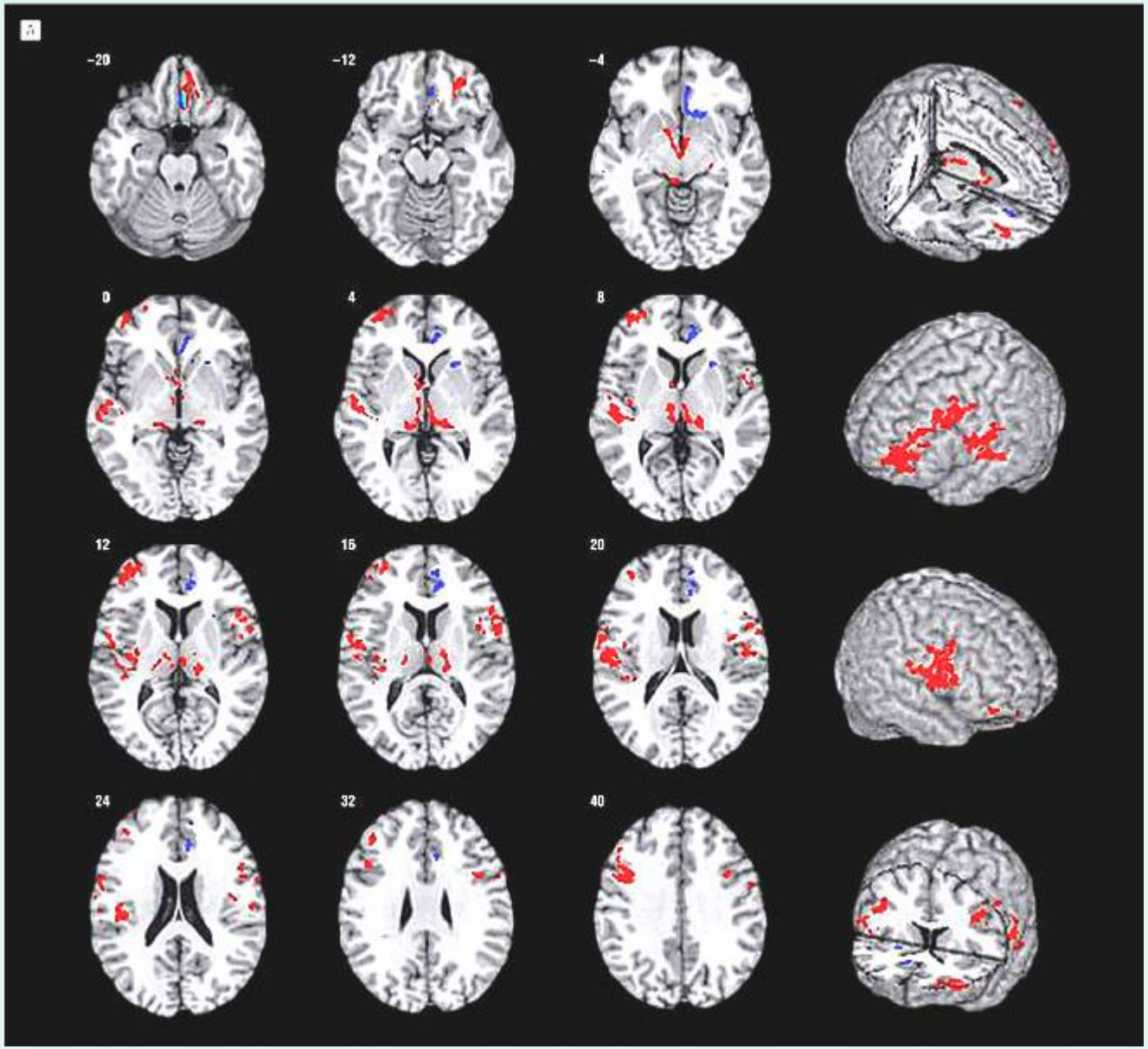


Patients hypo-activate to mildly fearful faces





Gray matter endophenotypes associated with genetic risks for schizophrenia and bipolar disorder



McDonald, C. et al.
Arch Gen Psychiatry
2004;61:974-984.

Summary of fearful faces experiment

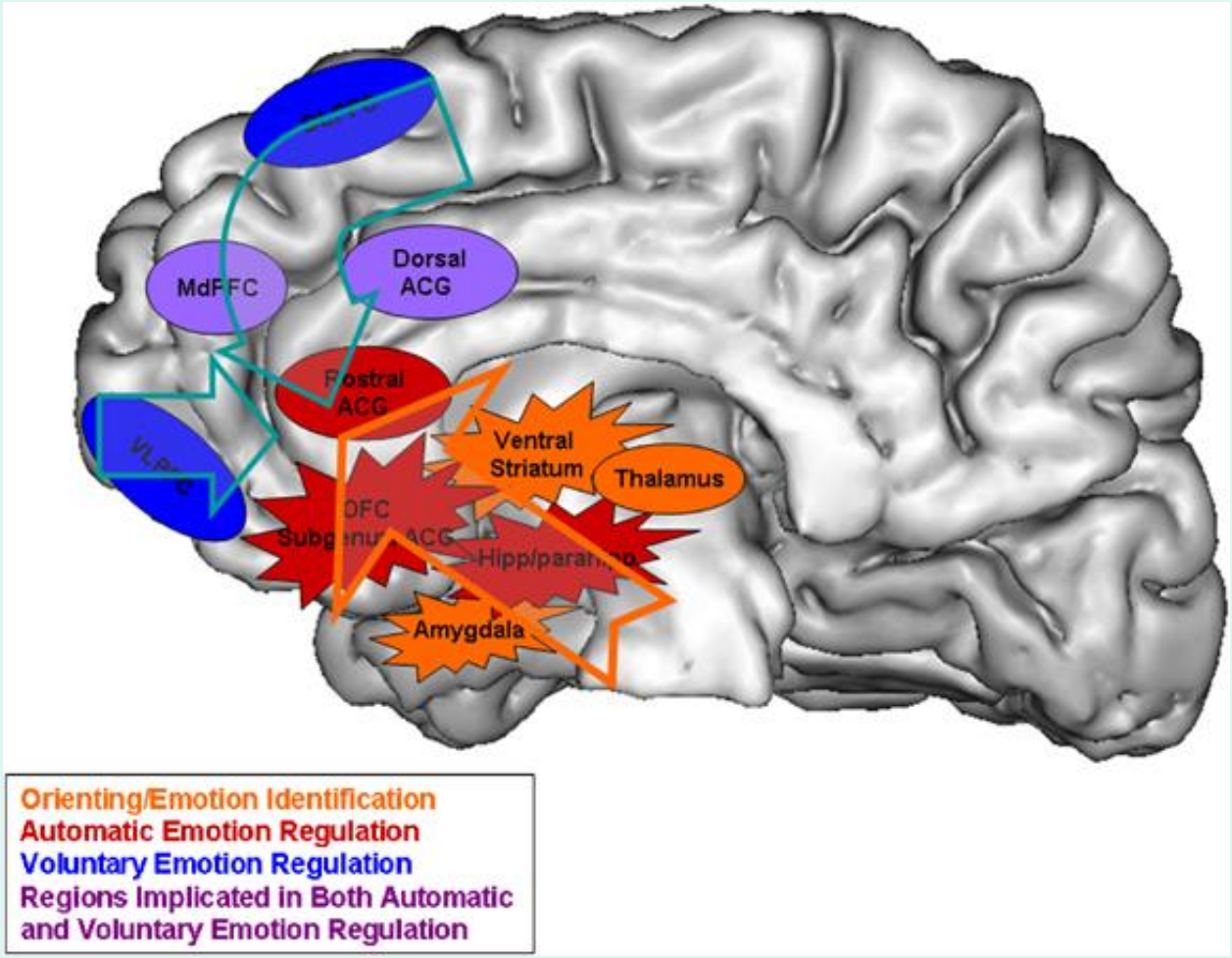
- Patients and their relatives demonstrated hyperactivity in response to fearful stimuli in the right lingual gyrus
- This indicates the greater involvement of visual processing structures

General conclusions

- Differential activations in relatives and patients elicited by functional neuroimaging are task-specific, rather than universally demonstrated in any condition
- Working memory experiments demonstrate hyperactivity (low efficiency) in left prefrontal cortex /ventro-lateral gyrus
- Emotion processing tasks reveal hyperactivity in cortical (lingual gyrus) and subcortical areas (midbrain)

A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder

Phillips, Ladouceur, Drevets, Mol Psychiatry 2008



- Thank you for listening!