



UNIVERSITÄTSMEDIZIN
GÖTTINGEN : UMG



Neue Befunde der funktionellen Hirnbildgebung bei bipolaren Störungen: Differentialdiagnostische Marker, Endophänotypen und Kandidatengene

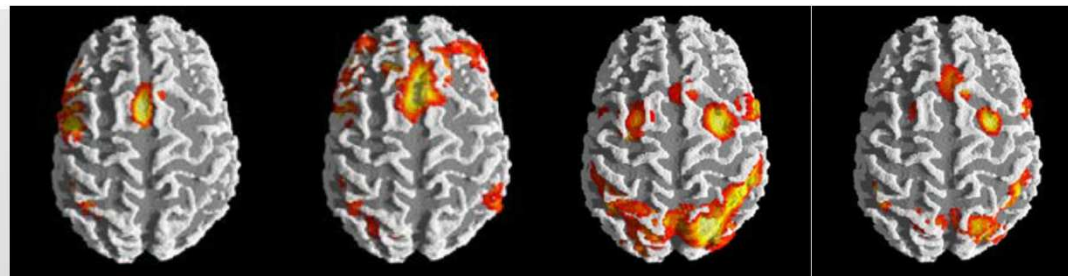
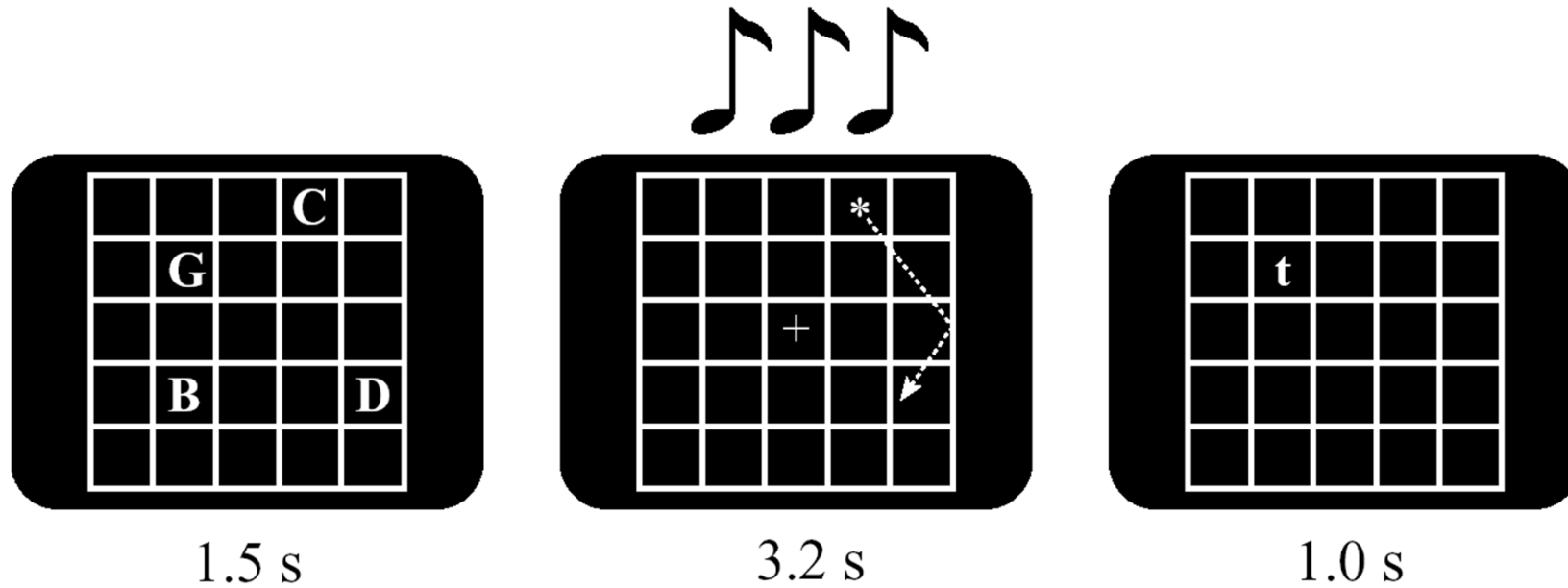
Oliver Gruber
Georg-August-Universität Göttingen

DGBS-Kongress 2012
Hannover, den 29. September 2012

Funktionelle Bildgebung bei bipolaren Störungen: Stand der Forschung

- „Emotionale Aufgaben“: Relativ konsistent Hyperaktivierungen in „limbischen“ Gehirnregionen sowohl bei symptomatischen (manischen/depressiven) als auch bei euthymen Patienten (Blumberg et al. 2005; Lawrence et al. 2004; Malhi et al. 2004; Pavuluri et al. 2007; Rich et al. 2006; Yurgelun-Todd et al. 2000)
- „Kognitive Aufgaben“: Hyper- und Hypoaktivierungen in verschiedenen präfrontalen Subregionen (OFC, ACC, DLPFC) und in Basalganglien (Blumberg et al. 2003a; Blumberg et al. 2003b; Gruber et al. 2003; Gruber et al. 2004; Kronhaus et al. 2006; Strakowski et al. 2005)

Differenzierte Untersuchung der Subkomponenten des Arbeitsgedächtnisses



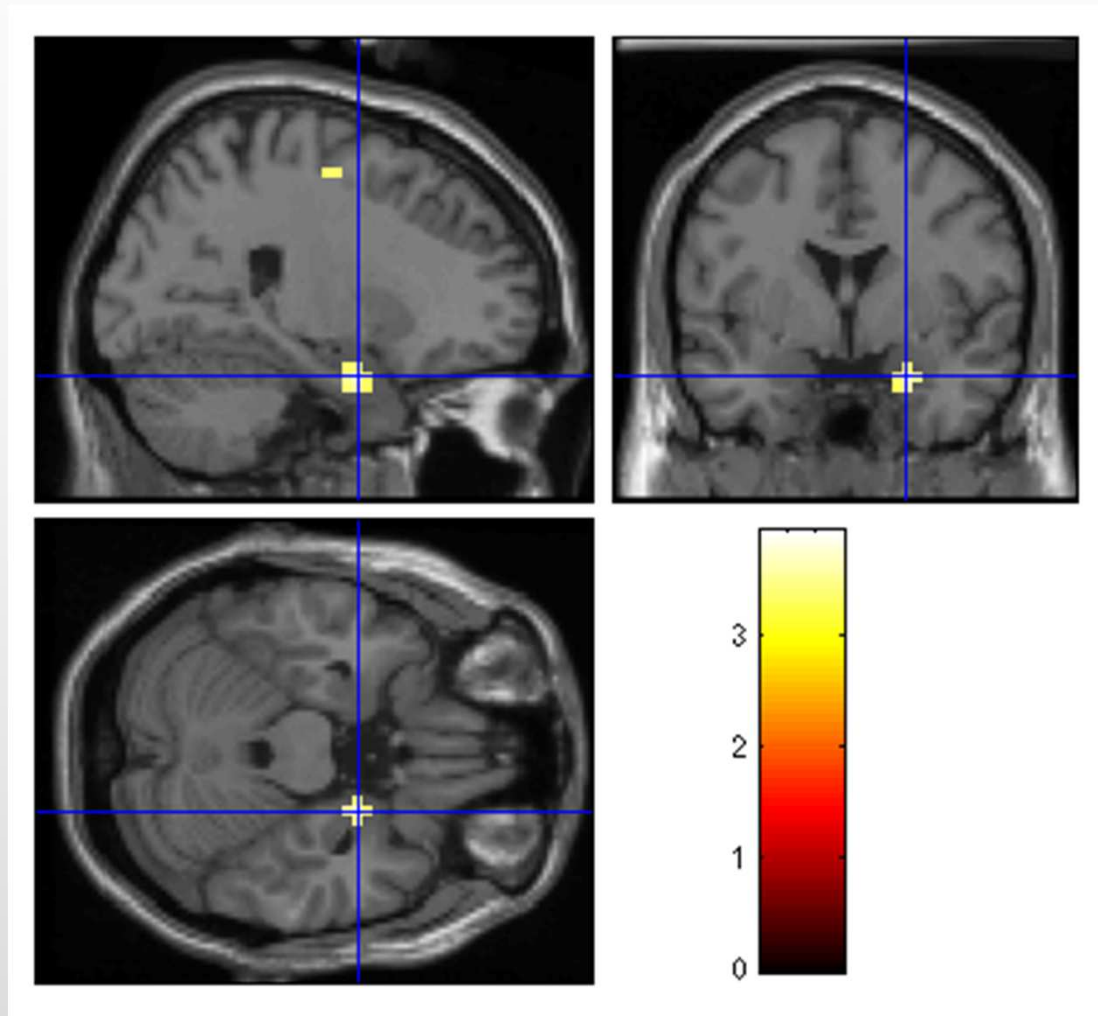
Gruber (2001) *Cerebral Cortex* 11:1047-1055

Gruber & von Cramon (2001) *Neuroscience Letters* 297:29-32

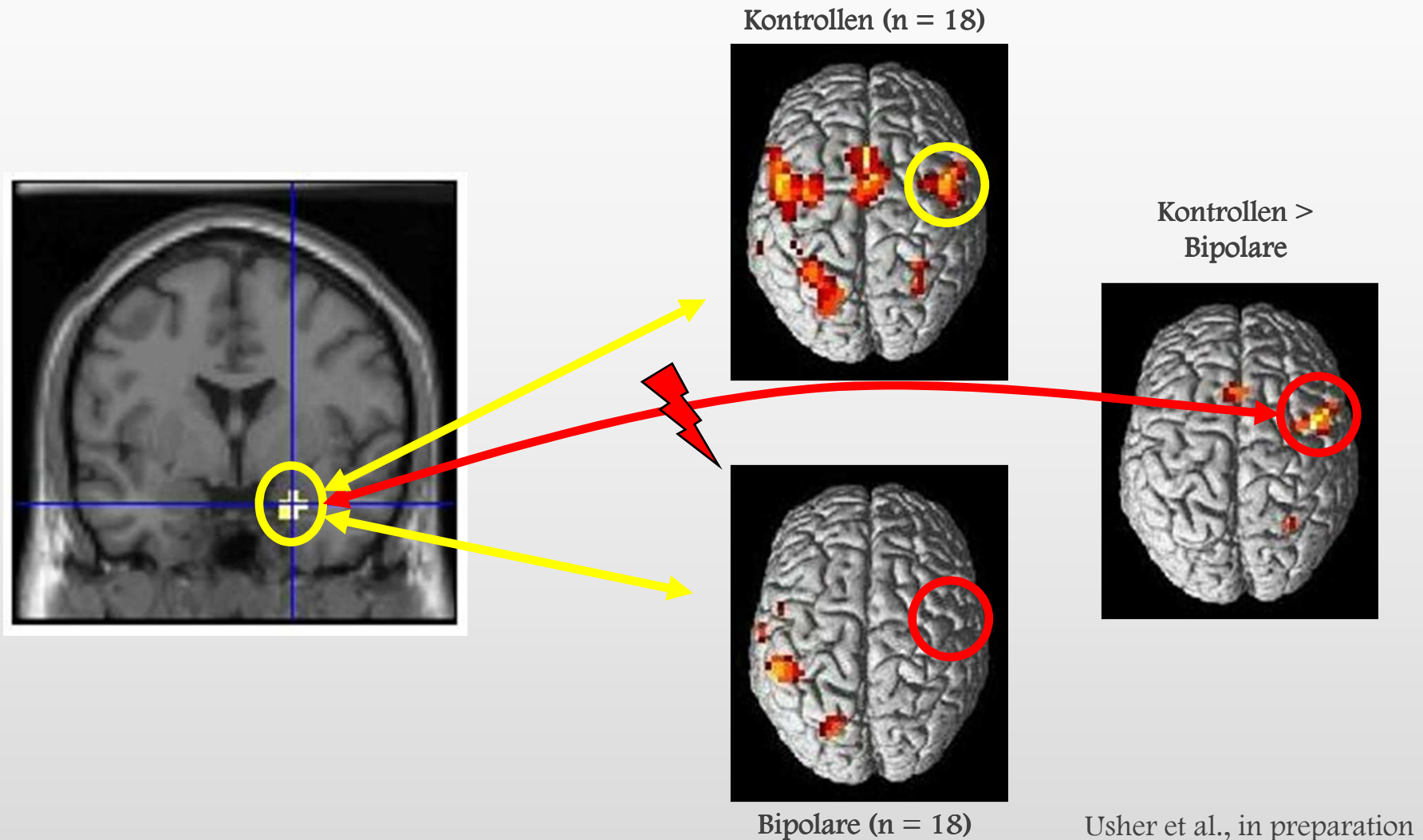
Gruber & von Cramon (2003) *Neuroimage* 19:797-809

Pathologische Amygdala-Aktivierung als Neuroimaging-Marker bei bipolaren Patienten (Subgruppe)

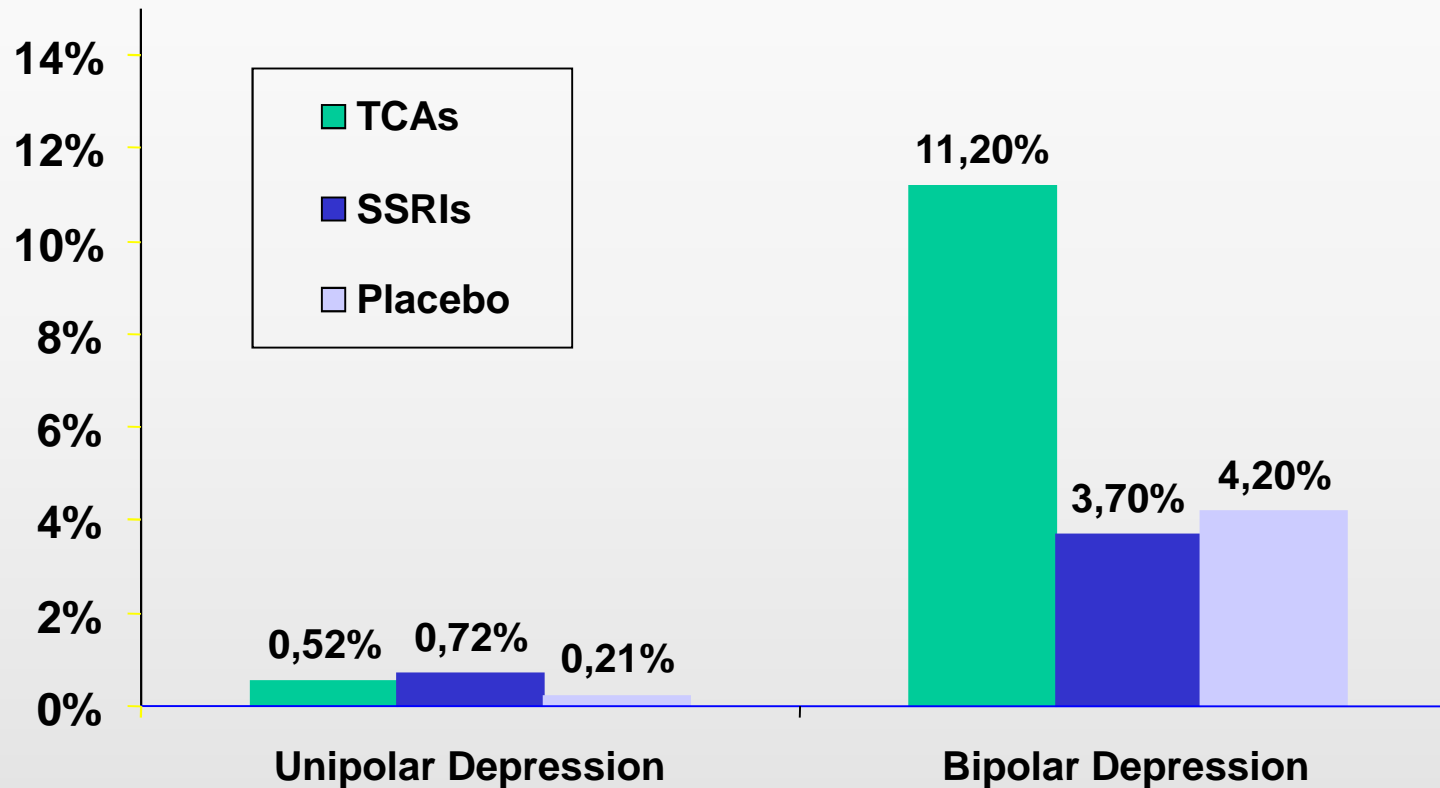
Artikulatorisches Rehearsal:
Bipolare >
Kontrollen = Schizophrene



Gestörte kortiko-amygdaläre Interaktionen bei Patienten mit bipolarer affektiver Störung



Therapeutische Relevanz der Differentialdiagnostik affektiver Störungen



Signifikanz:

TCA = SSRI > Placebo

TCA > SSRI = Placebo

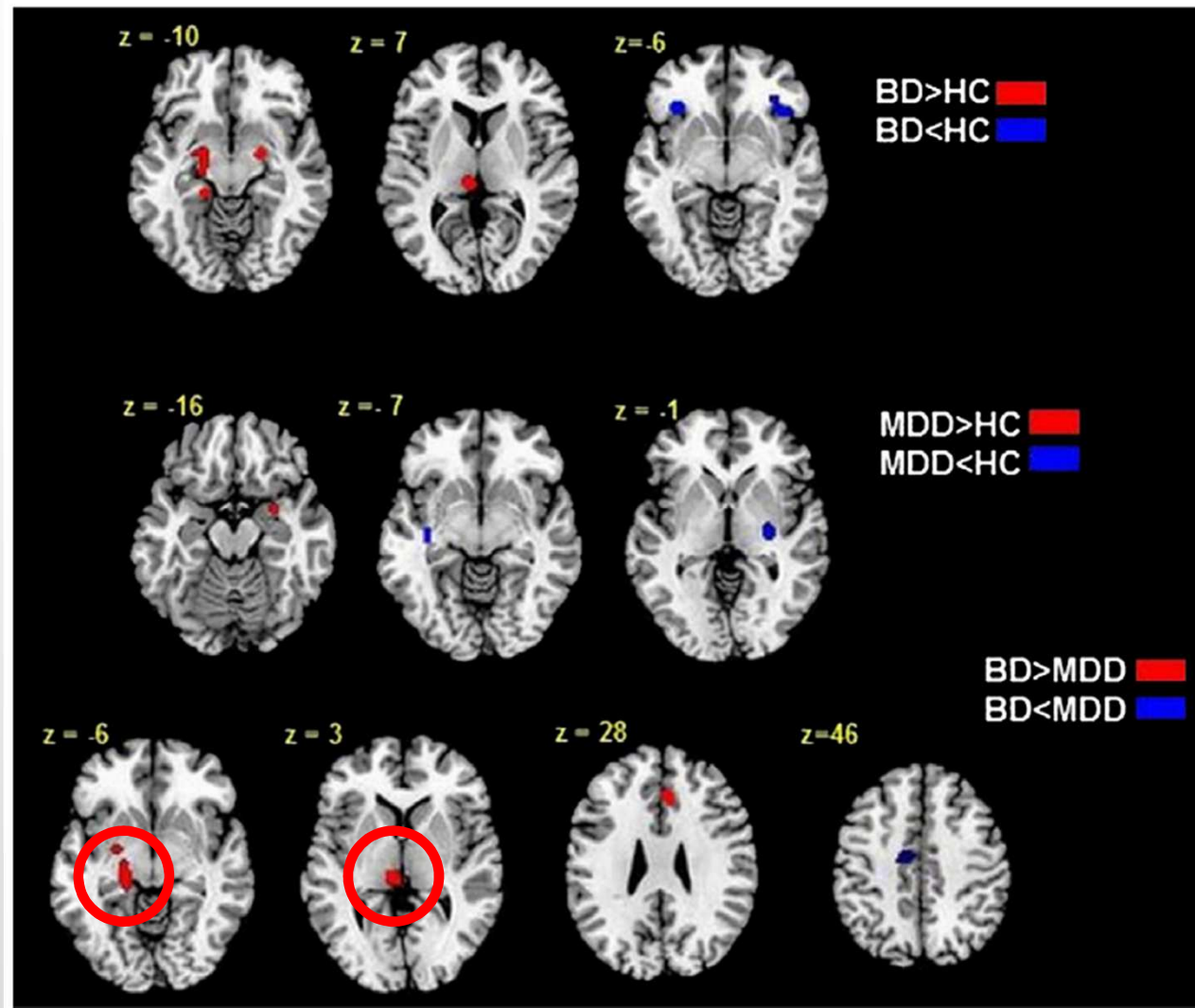
(Peet, 1994)

Metaanalyse zu neuronalen Korrelaten emotionaler Verarbeitung bei Depression und bipolarer Störung

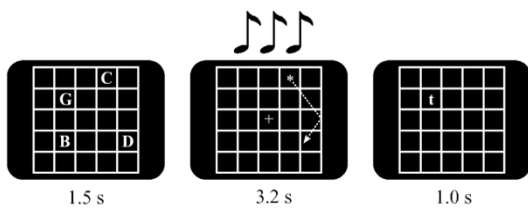
Table 1 Studies included in the meta-analyses (alphabetical order).

Study	Participants (Male/female)	Age Mean, years (standard deviation)	Design	Contrast used in meta-analysis
Almeida et al. (2010)	BD (remitted) 15 (5/10) BD (depressed) 15 (1/14) 15 MDD (2/13) 15 HC (3/12)	BD (remitted): 33.2 (7.8) BD (depressed): 36.5 (11.8) MDD: 32.7 (9.8) HC: 32.6 (8)	Explicit facial affect labelling Event related	Sad> neutral
Altshuler et al. (2008)	11 BD(5/6) 17 HC (9/8)	BD: 32 (7.3) HC: 29.5 (6.6)	Explicit facial affect matching Block	Fear and angry> shapes
Blumberg et al. (2005)	17 BD (10/7) 17HC (7/10)	BD: 40 (12.3) HC: 33.2 (10.8)	Implicit facial affect processing Block	Happy> fixation cross
Chen et al. (2006)	8 BD (depressed) (5/3) 8 BD (manic) (8/0) 8 HC (2/6)	BD (depressed): 41.8 (12) BD (manic): 39 (13.4) HC: 38.7 (12.5)	Explicit and implicit facial affect recognition Event related	Fear> neutral (explicit) Happy> neutral (explicit)
Foland et al. (2008)	9 BD (3/6) 9 HC (3/6)	BD: 34.6 (8.0) HC: 30.4 (7.6)	Explicit facial affect matching Block	Fear and anger> shapes
Fu et al. (2007) ¹	19 MDD (6/13) 19 HC (8/11)	MDD:43.2 HC:42.8	Implicit Facial Affect Processing Event-Related	Happy> fixation
Gotlib et al. (2005)	18 MDD (5/13) 18 HC (5/13)	MDD: 35.2 HC:30.8	Implicit facial affect processing Block	Happy> neutral Sad> neutral
Hassel et al. (2008)	19 BD (10/9) 24 HC (11/13)	BD: 32.47 HC: 27.78	Implicit facial affect processing Event-related	Happy> neutral
Jogia et al. (2008) ¹	12 BD (5/7) 12 HC (5/7)	BD: 42.1 (11.8) HC: 41.8 (10.9)	Explicit facial affect recognition Event-related	Sad> neutral
Killgore et al.(2008)	14 BD (11/3) 13 HC (12/1)	BD: 28.1 (11.2) HC: 25.5 (4.7)	Implicit facial affect processing Block	Fear> fixation

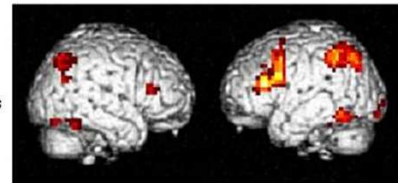
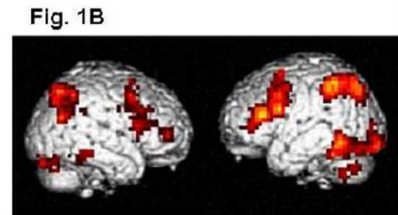
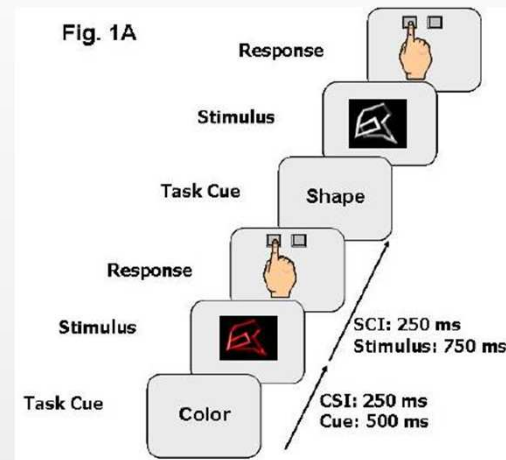
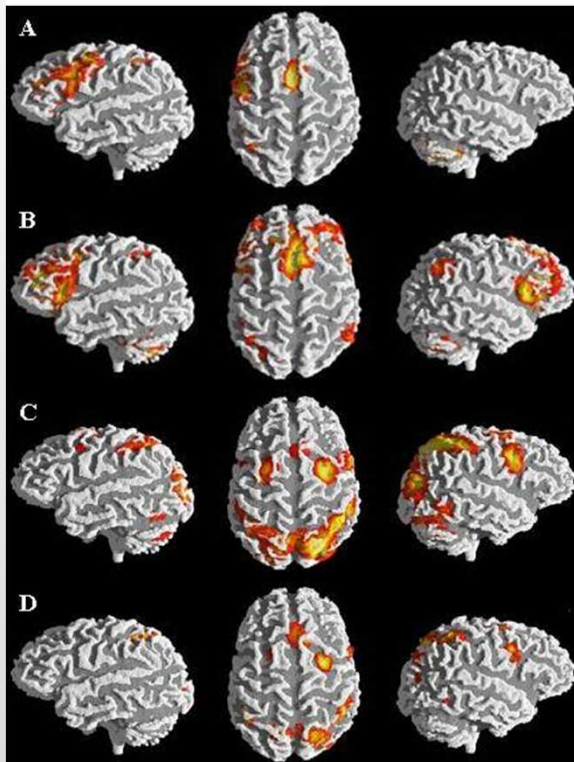
Metaanalyse zu neuronalen Korrelaten emotionaler Verarbeitung bei Depression und bipolarer Störung



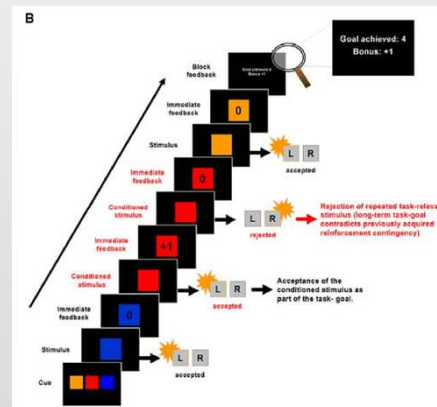
Multifunktionelle MRT-Untersuchung pathophysiologisch relevanter neuronaler Systeme



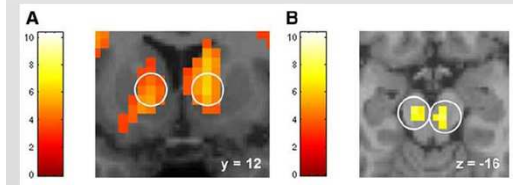
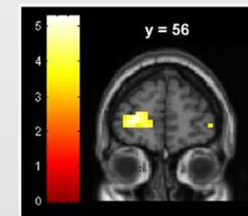
Gruber & von Cramon (2003) Neuroimage



Gruber et al. (2009) Brain and Cognition



Diekhof & Gruber (2010) Journal of Neuroscience



Störungen von Belohnungsverarbeitung und Impulskontrolle bei affektiven Störungen

REVIEW

Reward and Punishment Processing in Depression

Neir Eshel and Jonathan P. Roiser

Depression is a complex and heterogeneous disorder whose cause is poorly understood. Theories on the mechanisms of the disease have often focused on either its neurobiology or its cognitive and behavioral manifestations. Recently, studies exploring how depressed patients process reward and punishment have linked these two facets together. It has been suggested that individuals with a dysfunction in a specialized network of brain regions are unable to exploit affective information to guide behavior. Deficits in this ability might predispose such individuals to develop depression, whereas subsequent restoration of this ability—whether through pharmacological or behavioral treatments—might enable recovery from the disorder. Here we review behavioral, neuroimaging, and computational findings relevant to this hypothesis. There is good evidence that depressed patients exhibit abnormal behavioral responses to rewards and punishments and that these tendencies correspond to aberrant function in frontostriatal systems modulated by the monoamine systems. Furthermore, computational studies have generated testable predictions for how these neural signaling and neurochemical abnormalities might contribute to the symptoms of depression. Combining these approaches—as well as molecular and behavioral work in animals—provides great promise for furthering our understanding of this common and debilitating disease.

BIOL PSYCHIATRY 2010;68:118–124

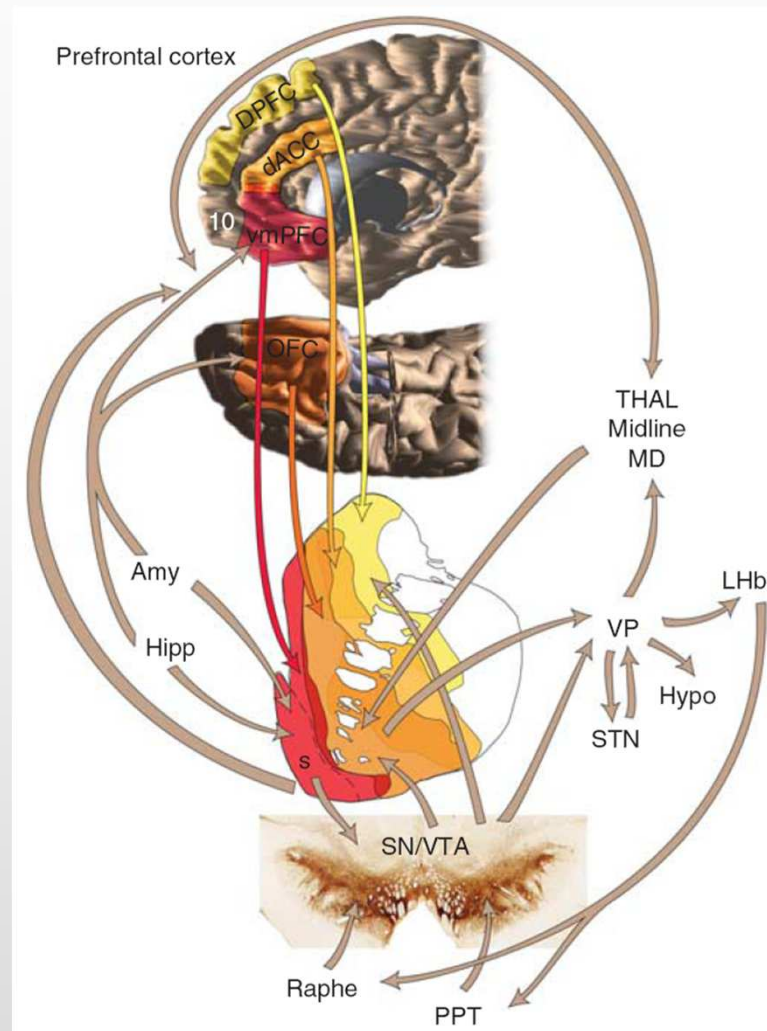
Impulsivity in Mania

Alan C. Swann, MD

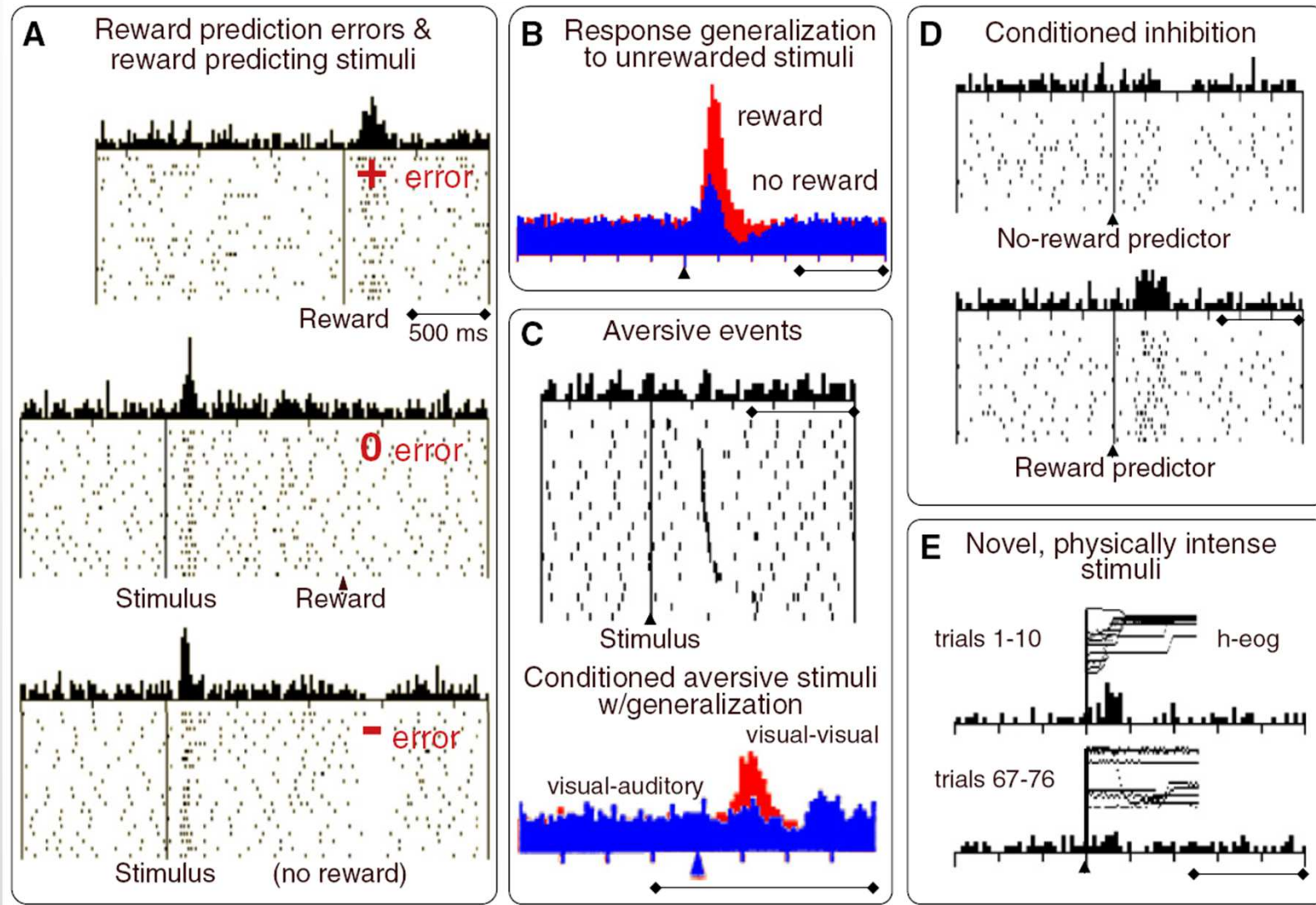
Current Psychiatry Reports 2009, 11:481–487

Impulsivity, a breakdown in the balance between initiation and screening of action that leads to reactions to stimuli without adequate reflection or regard for consequences, is a core feature of bipolar disorder and is prominent in manic episodes. Catecholaminergic function is related to impulsivity and mania. Manic individuals have abnormal dopaminergic reactions to reward and abnormal responses in the ventral prefrontal cortex that are consistent with impulsive behavior. Impulsivity in mania is pervasive, encompassing deficits in attention and behavioral inhibition. Impulsivity is increased with severe course of illness (eg, frequent episodes, substance use disorders, and suicide attempts). In mixed states, mania-associated impulsivity combines with depressive symptoms to increase the risk of suicide. Clinical management of impulsivity in mania involves addressing interpersonal distortions inherent in mania; reducing overstimulation; alertness to medical-, trauma-, or substance-related problems; and prompt pharmacologic treatment. Manic episodes must be viewed in the context of the life course of bipolar disorder.

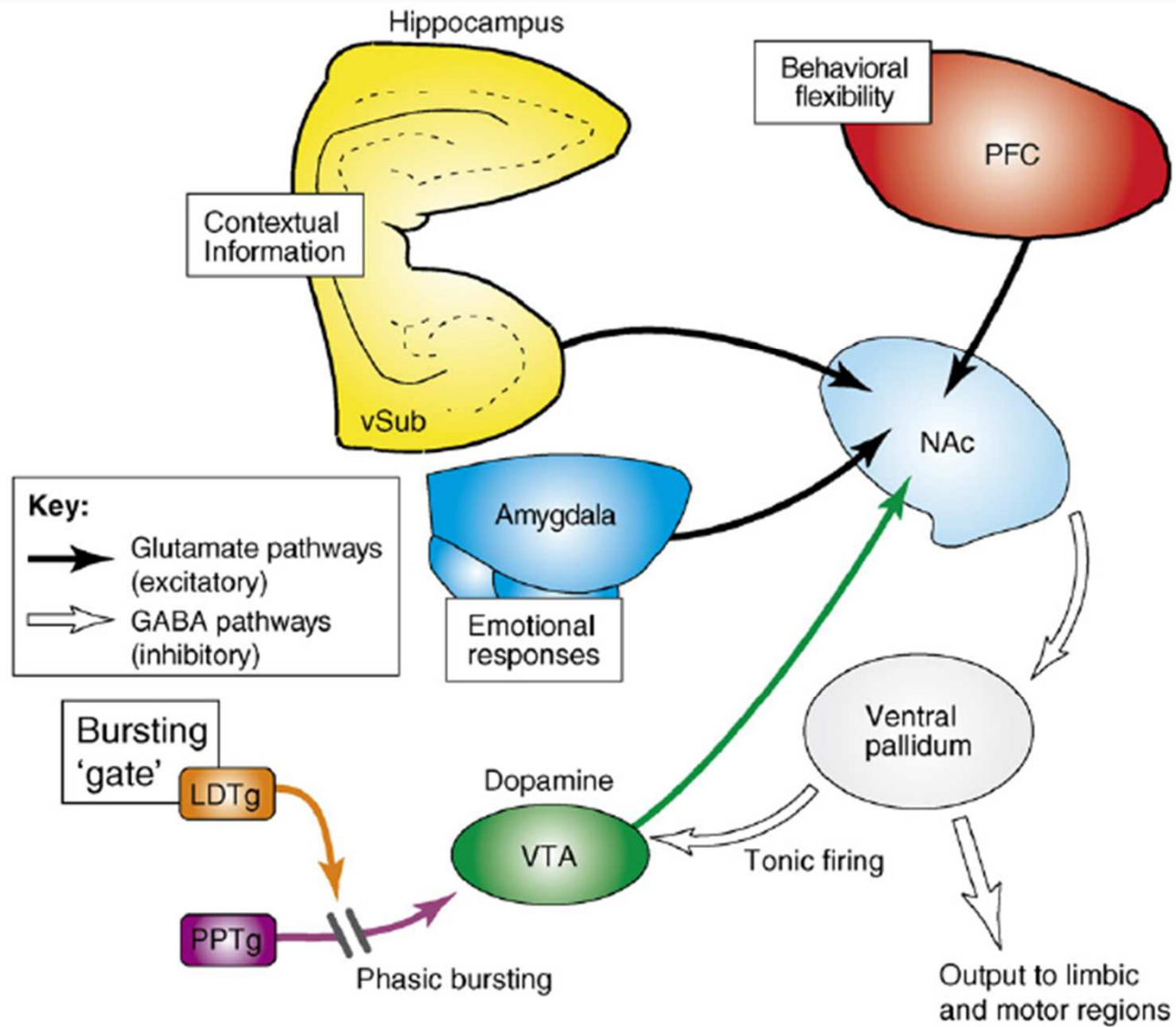
Schlüsselstrukturen des Belohnungssystems



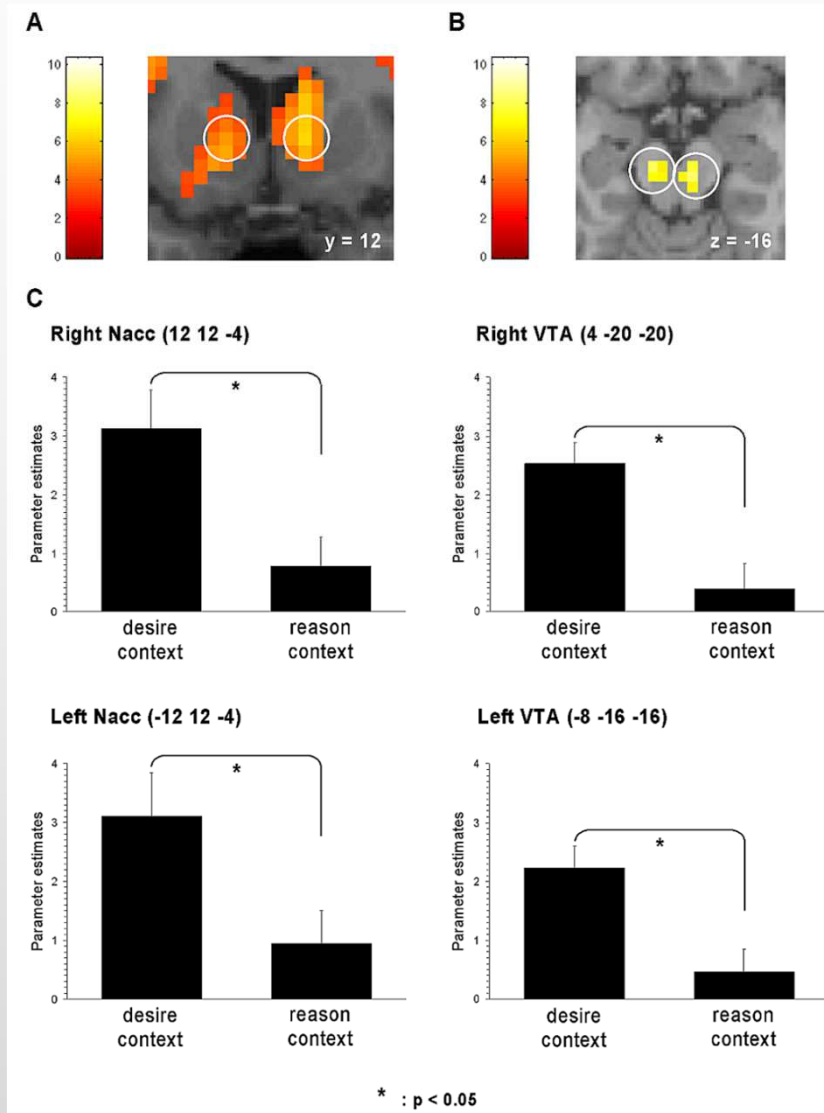
Neurophysiologie der Belohnungsverarbeitung



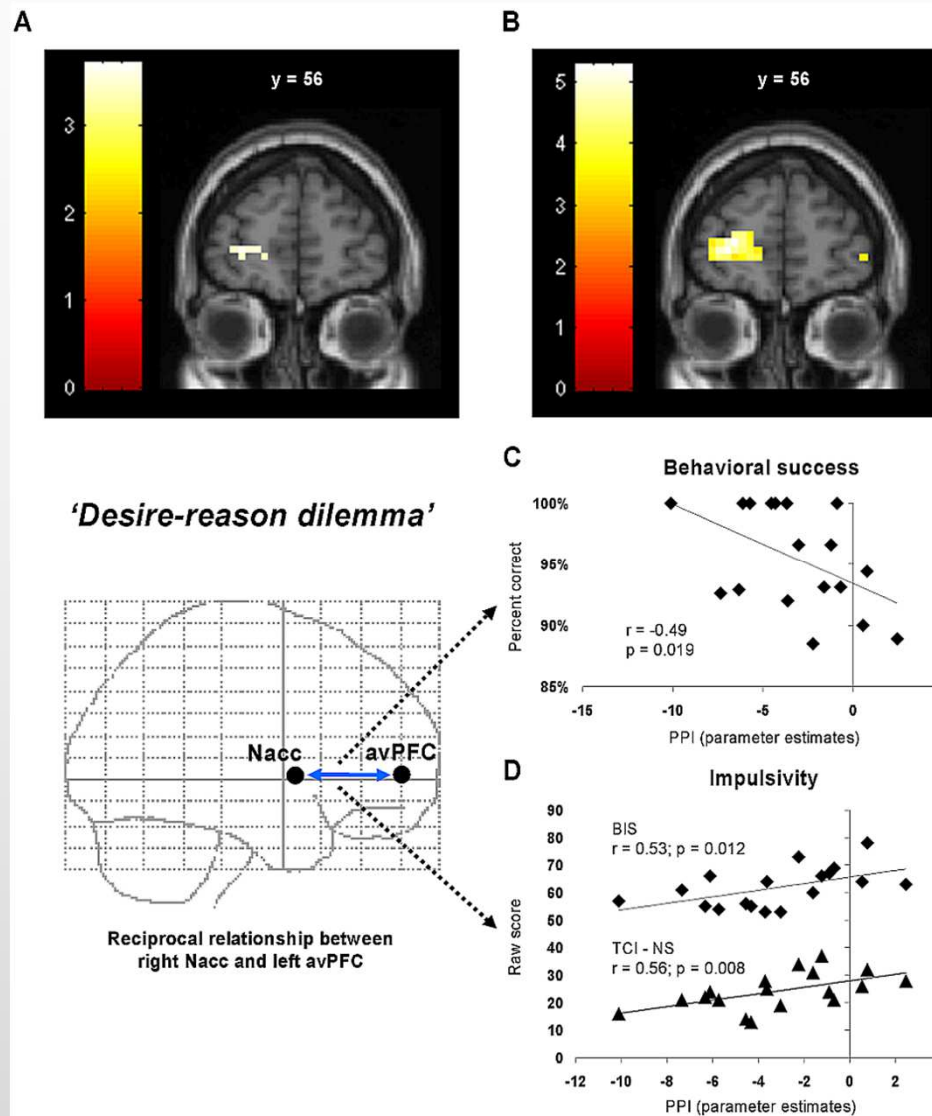
Interaktionen des dopaminergen Systems mit anderen Hirnstrukturen in der Verhaltenssteuerung



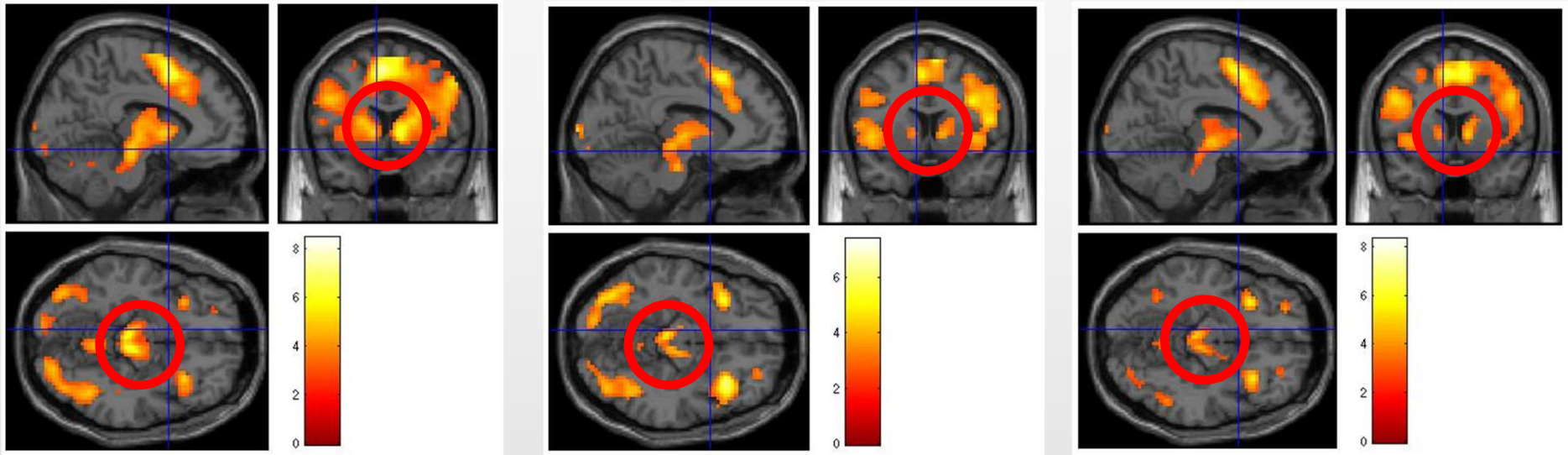
Kontextabhängige Modulation des Belohnungssignals in N. accumbens und VTA



Zielorientiertes Verhalten durch präfrontale Modulation des Belohnungssignals



Belohnungssignale bei unipolarer Depression und bei bipolarer affektiver Störung

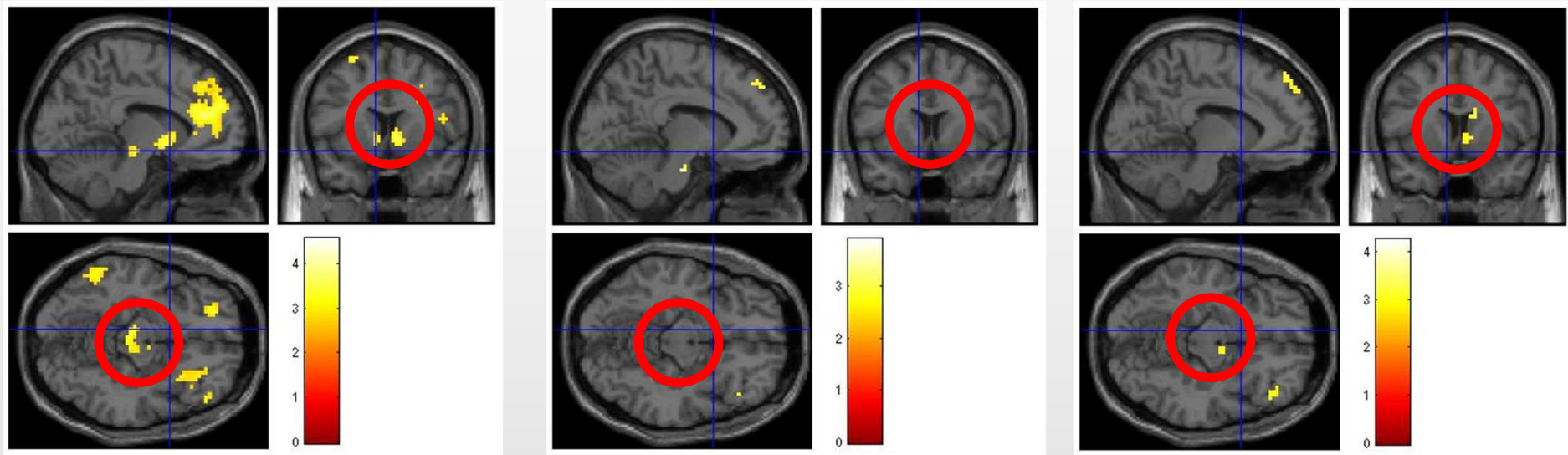


Kontrollen

Unipolare Depression

Bipolare Störung

Defizitäre Suppression von Belohnungssignalen bei Depression und bei bipolarer affektiver Störung

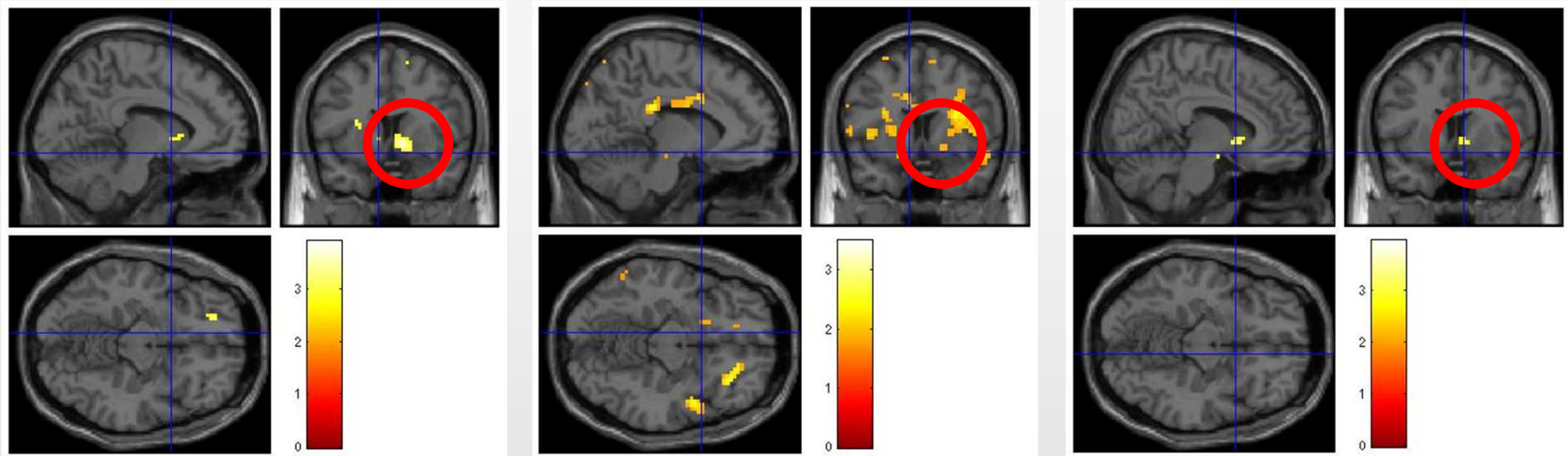


Kontrollen

Unipolare Depression

Bipolare Störung

Defizitäre Suppression von Belohnungssignalen bei Depression und bei bipolarer affektiver Störung

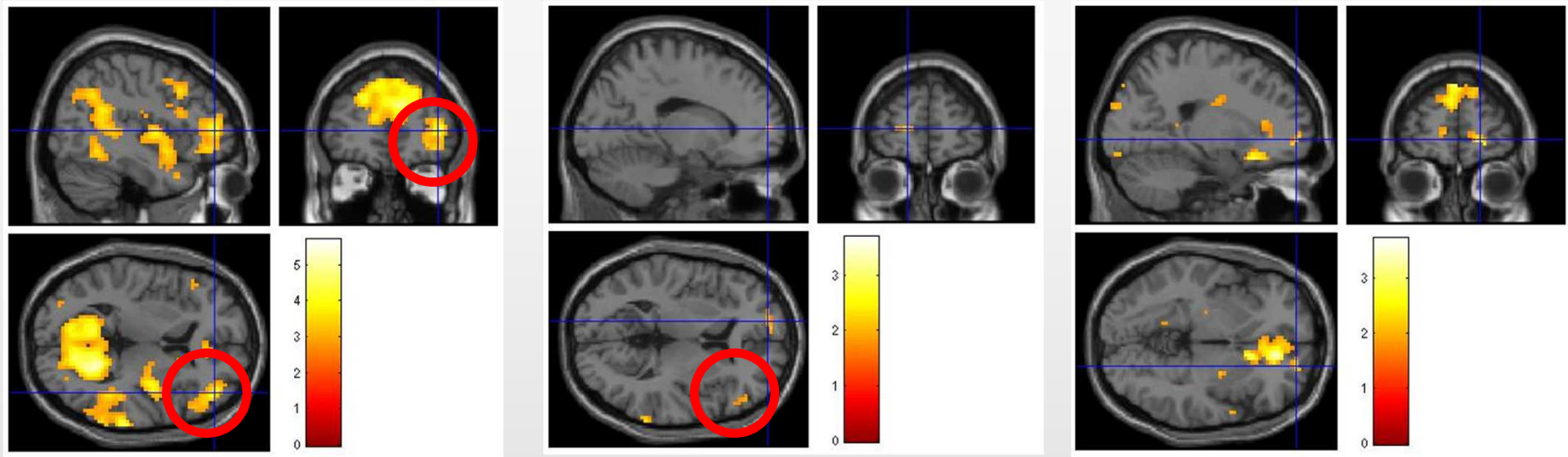


Unipolare < Kontrollen

Bipolare < Kontrollen

Unipolare < Bipolare

Gestörte funktionelle Interaktion zwischen Nucleus accumbens und avPFC bei affektiven Störungen

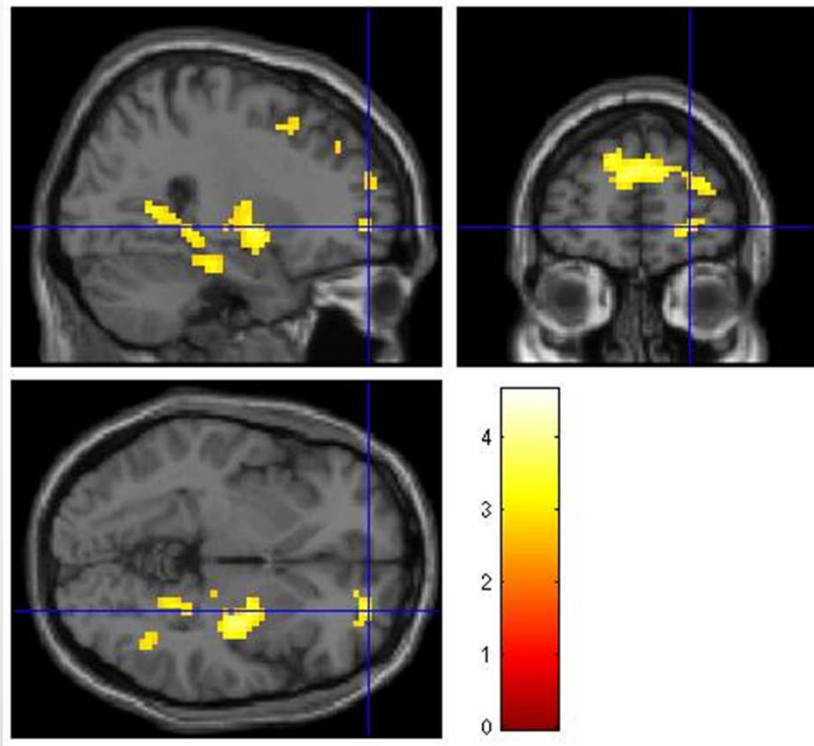


Kontrollen

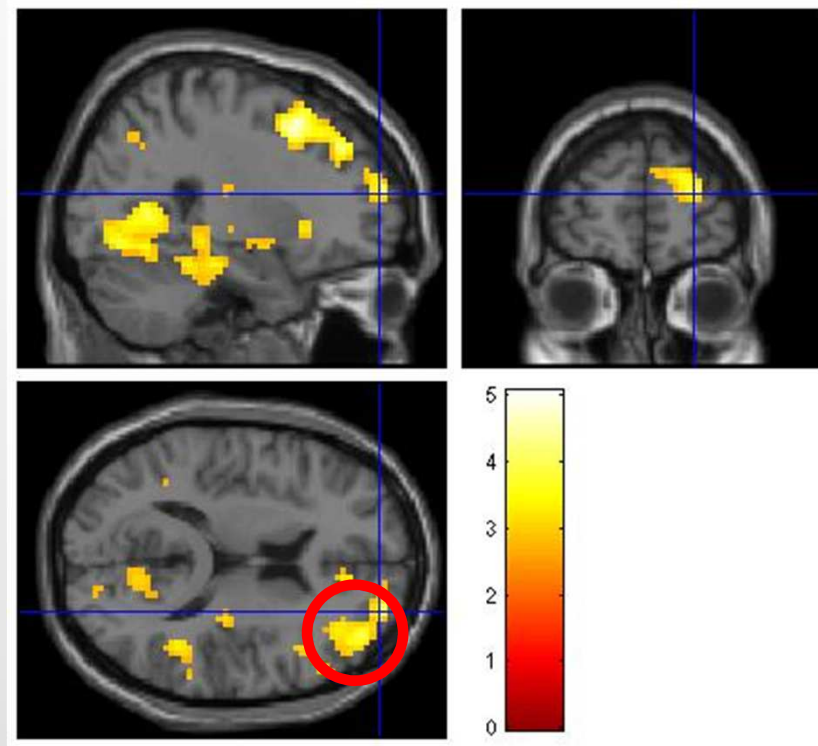
Unipolare Depression
(niederschwellig)

Bipolare Störung
(niederschwellig)

Gestörte funktionelle Interaktion zwischen Nucleus accumbens und avPFC bei affektiven Störungen

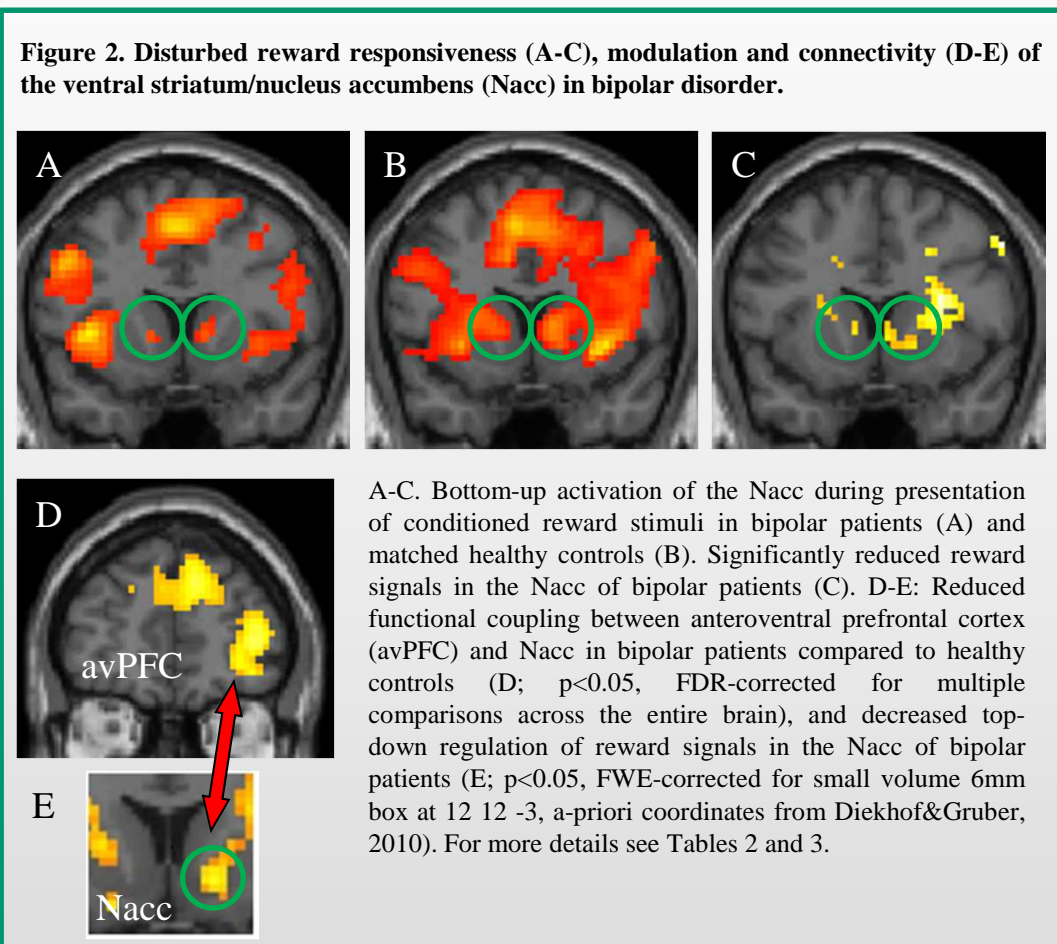


Unipolare < Kontrollen



Bipolare < Kontrollen

Zusammenfassung der neuropathophysiologischen Veränderungen bei Patienten mit bipolarer Störung

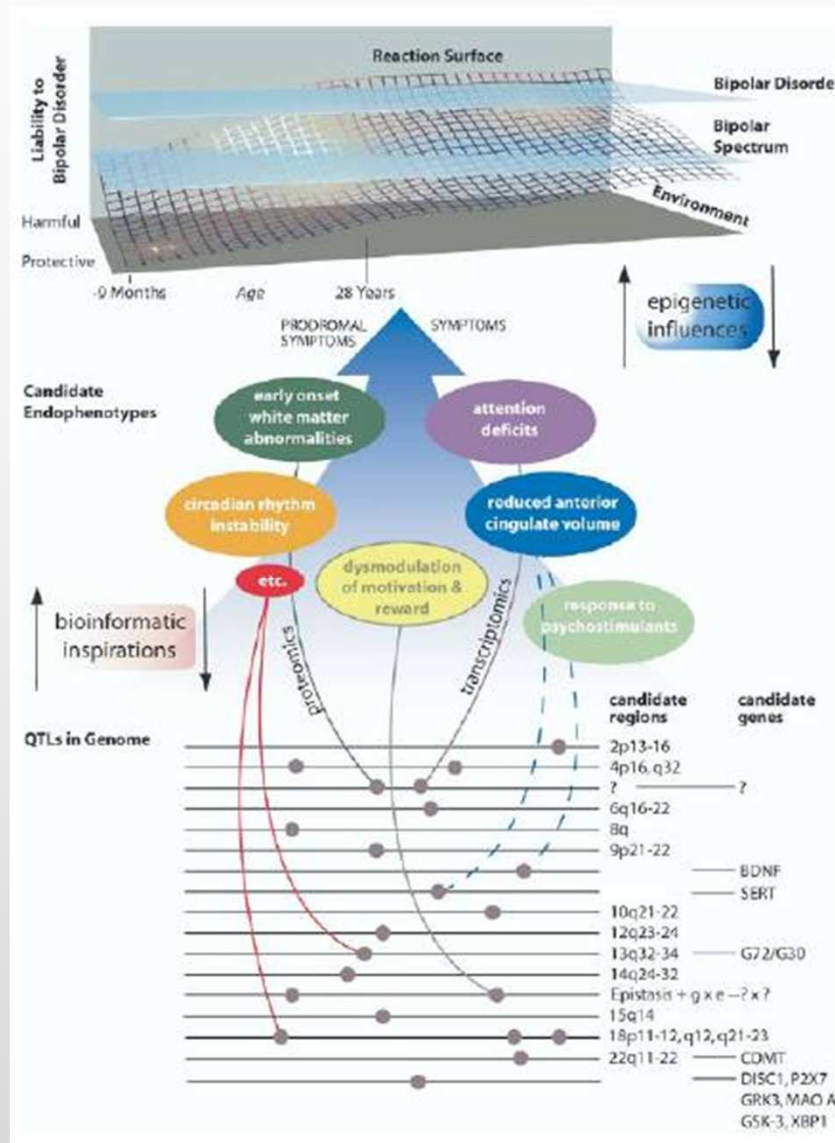


Intermediäre Phänotypen als Schlüssel zu pathogenetisch wirksamen Faktoren

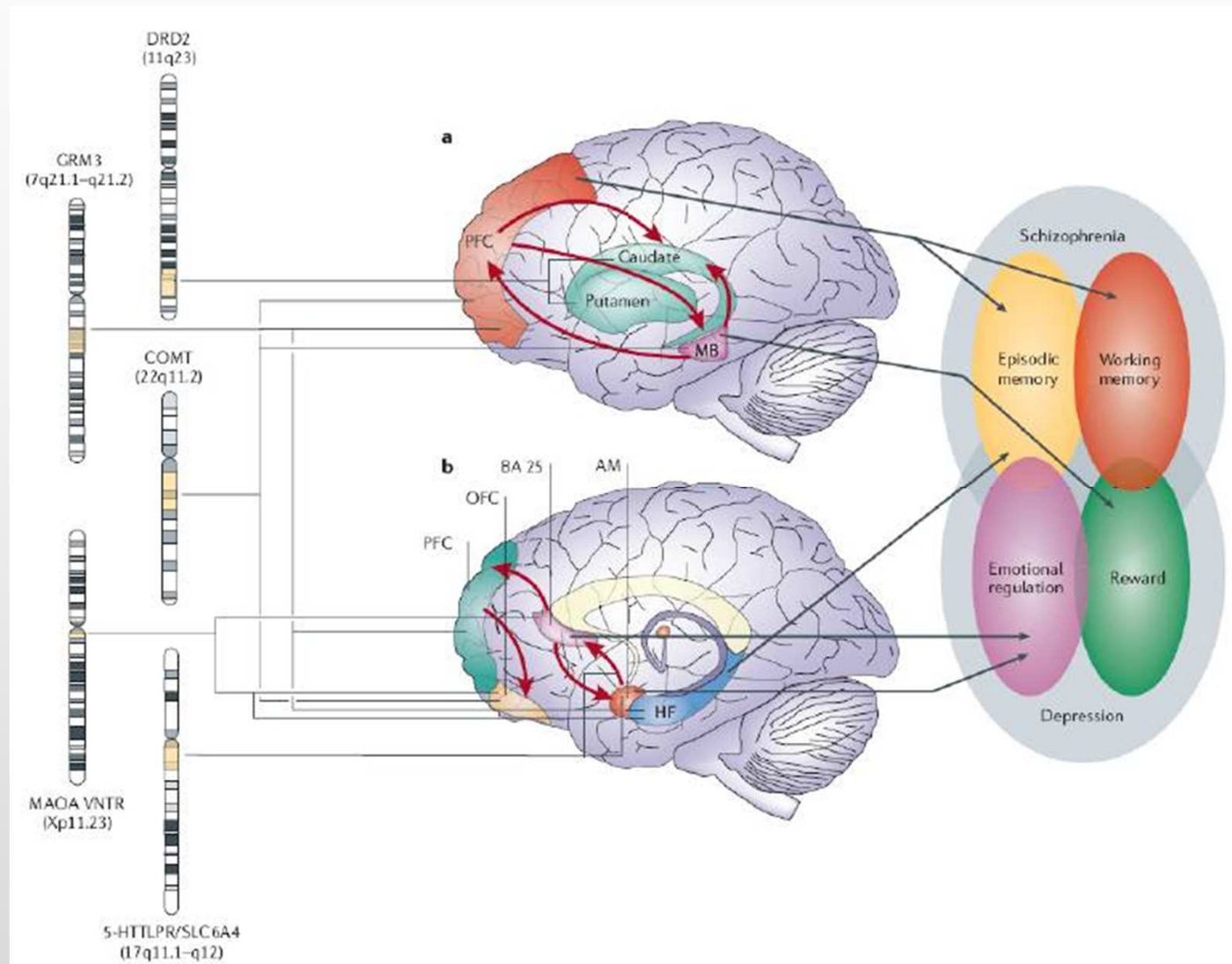
Klinische Phänotypen

Endophänotypen

Genotypen

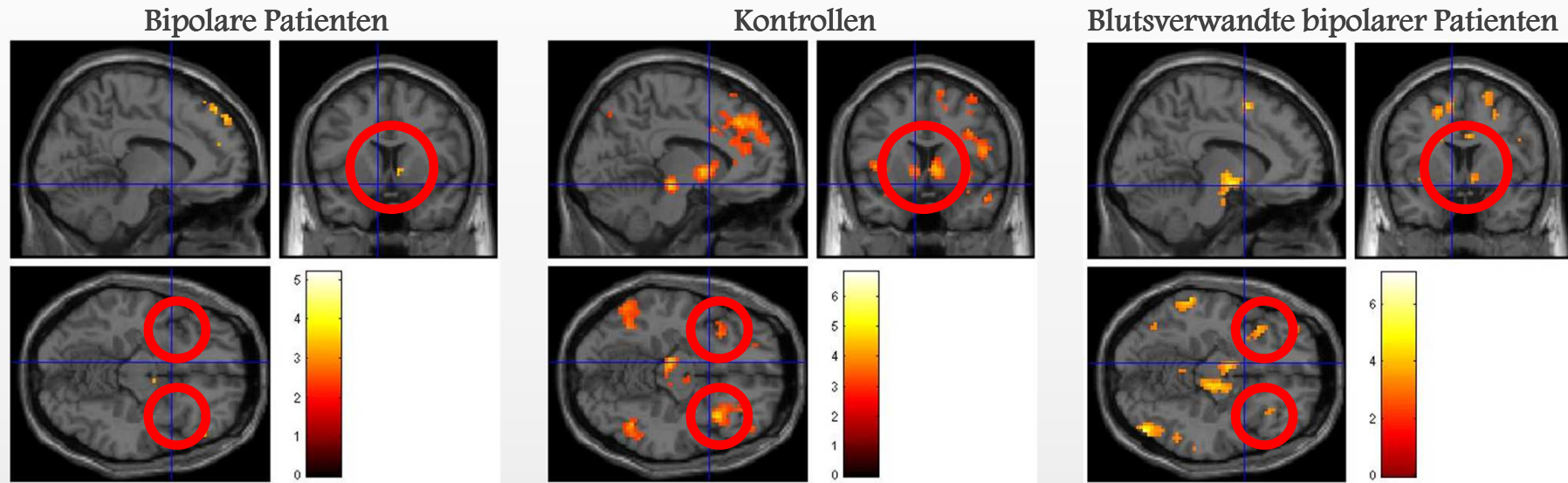


Untersuchung des Einflusses genetischer Faktoren auf neurofunktionelle Mechanismen

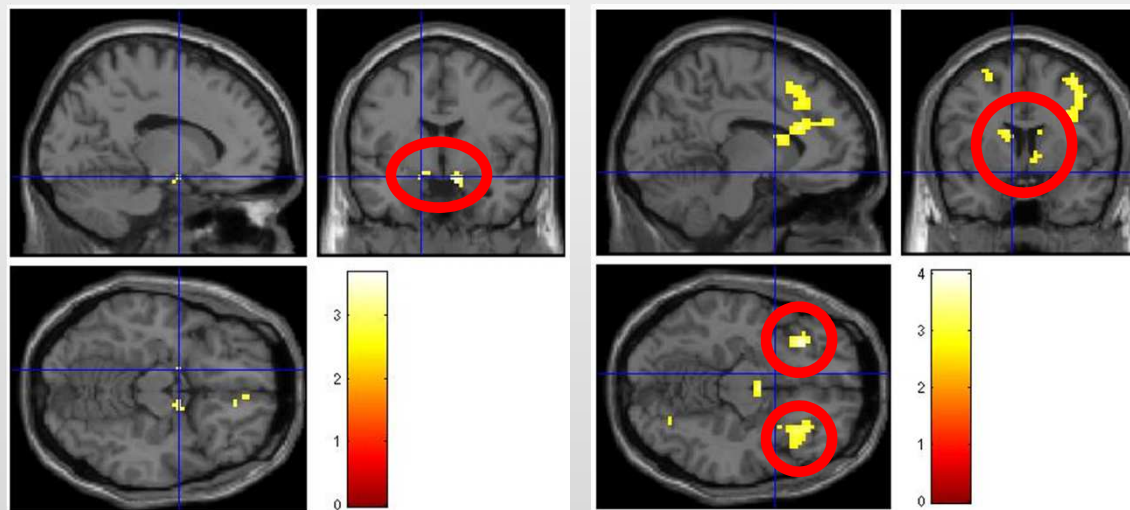


Meyer-Lindenberg &
Weinberger (2006)
Nat Rev Neurosci

Kandidatengene der bipolaren Störung und potentielle Neuroimaging-Endophänotypen



NCAN rs1064395:
Einfluss auf die
Amygdala-Aktivität



MAD1L1 rs11764590:
Reduzierte Effekte in
Minor-Allel-Trägern



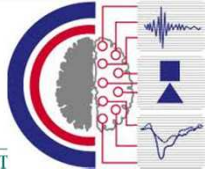
Take-home messages

- Patienten mit affektiven Störungen (Bipolare Störung, auch unipolare Depression) zeigen Veränderungen in verschiedenen motivationalen Mechanismen
- Gering reduziertes Belohnungssignal im N. accumbens
- Reduzierte Suppression des Belohnungssignals im N. accumbens (bei Unterdrückung von Handlungsimpulsen), stärker bei unipolarer Depression
- Reduzierte funktionelle Kopplung zwischen N. accumbens und avPFC
- Teil der Veränderungen auch bei gesunden erstgradigen Verwandten bipolarer Patienten
- Einfluss von Suszeptibilitätsgenen

Danksagung



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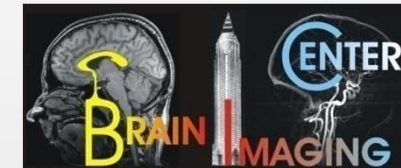
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Herzlichen Dank
für Ihre Aufmerksamkeit!!!

