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Acute anxiety disorder, major depressive disorder, bipolar disorder and schizophrenia are related to different patterns of nigrostriatal and mesolimbic dopamine dysfunction

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Abstract: Dopamine (DA) receptor and transporter dysfunctions play a major role in the pathophysiology of neuropsychiatric diseases including anxiety disorder (AD), major depressive disorder (MDD), bipolar disorder (BD) in the manic (BD_{man}) or depressive (BD_{dep}) state and schizophrenia (SZ). We performed a PUBMED search, which provided a total of 239 *in vivo* imaging studies with either positron emission tomography (PET) or single-proton emission computed tomography (SPECT). In these studies, DA transporter binding, D₁ receptor (R) binding, D₂R binding, DA synthesis and/or DA release in patients with the primary diagnosis of acute AD (n=310), MDD (n=754), BD_{man} (n=15), BD_{dep} (n=49) or SZ (n=1532) were compared to healthy individuals. A retrospective analysis revealed that AD, MDD, BD_{man}, BD_{dep} and SZ differed as to affected brain region(s), affected synaptic constituent(s) and extent as well as direction of dysfunction in terms of either sensitization or desensitization of transporter and/or receptor binding sites. In contrast to AD and SZ, in MDD, BD_{man} and BD_{dep}, neostriatal DA function was normal, whereas MDD, BD_{man} and BD_{dep} were characterized by the increased availability of prefrontal and frontal DA. In contrast to AD, MDD, BD_{man} and BD_{dep}, DA function in SZ was impaired throughout the nigrostriatal and mesolimbocortical system with an increased availability of DA in the striatohalamocortical and a decreased availability in the mesolimbocortical pathway.

Keywords: anxiety; bipolar disorder; depression; mania; schizophrenia.

Introduction

A variety of neurotransmitters have been implied in the pathophysiology of anxiety disorder (AD), major depressive disorder (MDD), bipolar disorder (BD) and schizophrenia (SZ). Among them are serotonin (5-HT; AD, Lowry et al., 2005; MDD, Di Giovanni et al., 2006; SZ, Di Pietro and Seamans, 2007; BD, Deeks and Keeting, 2008), acetylcholine (SZ, Hajos and Rogers, 2010; BD, McEvoy and Allen, 2002; MDD, Mineur and Picciotto, 2010; AD, Graef et al., 2011), glutamate (AD, Carlsson, 2001; SZ, Konradi and Heckers, 2003; BD, Lenox and Wang, 2003; MDD, Mitchell and Baker, 2010) and γ -aminobutyric acid (GABA; SZ, Taylor and Tso, 2014; AD, Nuss, 2015; MDD, Pehrson and Sanchez, 2015; BD, Romeo et al., 2018).

Furthermore, a pivotal role has been ascribed to dysfunctions of the nigrostriatal and mesolimbic dopaminergic pathways (SZ, Seeman and Lee, 1975; MDD, Willner, 1983; AD, Stein et al., 2002; BD, Deeks and Keeting, 2008). In the nigrostriatal system, the neostriatum (STR) receives DAergic afferents from the pars compacta of the substantia nigra (SN) and sends DAergic efferents to the thalamus (THAL), neocortex and back to the SN (Afifi, 1994a). In the mesolimbic system, the ventral striatum (VS) is primarily innervated by DAergic fibers arising from the ventral tegmental area (VTA) and projects to the neocortex and limbic regions including amygdala (AMYG) and hippocampus (HIPPO; Afifi, 1994b).

In recent surveys of all *in vivo* imaging studies, which, so far, had been conducted on DAergic neurotransmission in acute AD, MDD, BD and SZ using either positron emission tomography (PET) or single-proton emission computed tomography (SPECT) (Nikolaus et al., 2010, 2012, 2014a,b, 2016, 2017), we found (1) a significant reduction of DA D₂ receptors (D₂Rs) in the STR of AD patients relative to controls; (2) increases of DA synthesis in the prefrontal cortex (PFC) and frontal cortex (FC) of MDD patients relative to controls; (3) a reduction of DA D₁ receptors (D₁Rs) in the FC of acutely manic BD patients (BD_{man}) relative to controls; (4) a reduction of D₁Rs in the FC of acutely depressed BD patients (BD_{dep}) relative to controls; (5) a reduction of DA transporter (DAT) density in the STR, a reduction of D₁Rs in the STR and reductions of D₂Rs in STR, THAL, FC and parietal cortex (PC) of SZ patients relative to controls,

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as well as (6) an increase of DA synthesis and DA release in the STR of SZ patients relative to controls.

In these analyses, however, AD, MDD, BD_{man}, BD_{dep} and SZ were considered separately, and no comparisons of regional DAT, D₁R, D₂R, DA synthesis and DA release were performed between the individual disturbances. In order to update the pool of studies, we performed a new PUBMED search, providing 38 additional investigations (AD: DAT, $n=5$, D₂R, $n=4$; MDD: DAT, $n=5$, D₂R, $n=5$; DA synthesis, $n=1$; DA release, $n=1$; SZ: D₁R, $n=3$; D₂R, $n=11$; DA synthesis, $n=1$; DA release, $n=3$). For this updated pool, we conducted a novel analysis, comparing (1) regional vesicular monoamine transporter type 2 (VMAT2) binding, DAT binding, D₁R binding, D₂R binding, DA synthesis and DA release separately in AD, MDD, BD_{man}, BD_{dep} and SZ patients relative to healthy controls, and (2) regional VMAT2 binding, DAT binding, D₁R binding, D₂R binding, DA synthesis and DA release between patients suffering from AD, MDD, BD_{dep}, BD_{man} and SZ.

Method

Selection of studies. A PubMed search was performed using the keywords ‘anxiety disorder’, ‘depression’, ‘bipolar disorder’, ‘schizophrenia’, ‘schizoaffective disorder’, ‘schizophreniform disorder’ and ‘psychosis’ in combination with either ‘VMAT2’, ‘DAT’, ‘D₁ receptor’, ‘D₂ receptor’, ‘dopamine synthesis’ or ‘dopamine release’ and either ‘PET’ or ‘SPE(C)T’.

The search provided 27 investigations on acute AD including obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, social AD and generalized AD [310 patients, age: 36 ± 8 years (mean $\pm$ standard deviation), duration of disease: 15 ± 8 years, Yale-Brown Obsessive-Compulsive Scale (Ybocs) score: 26 ± 5 ; Hamilton Anxiety (HAMA) Rating Scale score: 21 ± 6 ; 330 controls, age: 35 ± 8 years], 51 investigations on acute MDD [667 patients, age: 41 ± 9 years, duration of disease: 11 ± 12 years, Hamilton Depression Rating Scale (HDRS) score: 21 ± 5 , Becks Depression Inventory (BDI) score: 21 ± 6 ; 870 controls, age: 40 ± 11 years], four investigations on acute BD_{man} [15 patients, age: 32 ± 12 years, duration of disease: 1 year, Young Mania Rating Scale (YMRS) score: 27 ± 7 ; 44 controls, age: 29 ± 4 years], five investigations on acute BD_{dep} [49 patients, age: 41 ± 0.5 years, duration of disease: not specified (n.s.), HDRS score: 21 ± 1 ; 207 controls, age: 38 ± 2 years] and 145 investigations on acute SZ including schizoaffective and schizophreniform disorder [1532 patients, age: 33 ± 8 years, duration of disease: 7 ± 8 years, Positive and Negative Syndrome Scale (PANSS) score: 73 ± 16 , Brief Psychiatric Rating Scale (BPRS) score:

47 ± 15 ; 1568 controls, age: 32 ± 8 years] published in peer-reviewed journals between 1986 and December 2017.

In the present analysis, all available *in vivo* investigations on AD, MDD, BD_{dep}, BD_{man} and SZ patients in the acute stage of disease were enrolled irrespective of their medication state (Tables 1–4). The inclusion criterion was that patients with the primary diagnosis of AD, MDD, BD_{dep}, BD_{man}, or SZ had to be compared to healthy controls. Moreover, quantitative data of patients and controls had to be communicated in the original publication.

Data were evaluated as previously described (Nikolaus et al., 2010, 2012, 2014a,b, 2016, 2017). Percentual differences of VMAT2, DAT, D₁R and D₂R binding as well as DA synthesis and DA release to the respective control groups were calculated for the following brain regions: STR (nucleus caudate, putamen), VS, globus pallidus (GP), THAL, PFC (Brodmann areas 9–12, 46, 47, and 49), FC (PFC plus Brodmann areas 4 and 6), PC (Brodmann areas 3, 5, 7, 8, 39, and 40), temporal cortex (TC; Brodmann areas 20–22, 38, 41 and 42), occipital cortex (OC; Brodmann areas 17–19), cingulate (CING), HIPPO, parahippocampal gyrus (PHG), AMYG, insula (INS), midbrain/pons (MB), SN, VTA, locus caeruleus (LC) and cerebellum (CER). Left and right radioactivity accumulations were pooled, if given separately in the original publication. If the authors had analyzed more than one area within STR, PFC, FC, PC, TC, OC and CING, the mean values of these data were calculated for AD, MDD, BD_{dep}, BD_{man} and SZ subjects and the respective controls prior to computing percentual differences.

Statistic calculations were performed with IBM SPSS Statistics 22 (IBM SPSS Software Germany, Ehningen, Germany). The Kolmogorov-Smirnov test for normal distribution could not be performed for a number of variables in the individual disorders, as the sum of weighted cases per disorder and brain region fell short of 5. Hence, medians of percentual differences of VMAT2, DAT, D₁R and D₂R binding as well as DA synthesis and DA release in the individual brain regions relative to controls were computed for patients with AD, MDD, BD_{man}, BD_{dep} and SZ. Differences between AD, MDD, BD_{man}, BD_{dep} and SZ patients and the respective controls were assessed with the non-parametric Mann-Whitney *U*-test ($\alpha=0.05$) for independent samples. Furthermore, the individual parameters of synaptic function were compared between disorders (AD vs. MDD, AD vs. BD_{man}, AD vs. BD_{dep}, AD vs. SZ, MDD vs. BD_{man}, MDD vs. BD_{dep}, MDD vs. SZ, BD_{man} vs. SZ or BD_{dep} vs. SZ) with the Mann-Whitney *U*-test ($\alpha=0.05$). No corrections were made for multiple comparisons. As implied by the outcome of our precedent surveys on AD, MDD, BD_{man}, BD_{dep} and SZ (Nikolaus et al., 2010, 2012, 2014a,b, 2016, 2017), significance tests were performed one-sidedly.

Table 1: All *in vivo* investigations of synaptic constituents (VMAT2, DAT, D₁ receptor, D₂ receptor, DA release) on patients with acute anxiety disorder (AD) with either PET or SPECT.

Study	Sub-type	Mean inventory scale score $\pm$ SD	Constituent	Ligand	Comorbidity	Premedication	Smoking	Patients (m/f)	Mean age $\pm$ SD (years)	Controls (m/f)	Mean age $\pm$ SD (years)	Mean duration $\pm$ SD (years)	Medication at the time of scanning	Duration of withdrawal (days)
Broft et al., 2015	Anxiety	BDI: 33 $\pm$ 11 BAI: 27 $\pm$ 12 EDE: 4 $\pm$ 1	D ₂		Anorexia, depression	Sleeping pills, no psychotropics for ≥ 4 weeks; <i>current</i> : n.s.	y/n	0/21	25 $\pm$ 7	0/25	26 $\pm$ 5	11 $\pm$ 8	y	0
Denys et al., 2004	OCD	Ybocs: 26 $\pm$ 7 HDRS: 12 $\pm$ 5	D ₂	[¹²³ I]IBZM	None, MDD, personality disorder	None, SSRIs	y/n	3/7	36 $\pm$ 12	3/7	34 $\pm$ 10	18 $\pm$ 11	n	168
Erro et al., 2012	Anxiety	BDI: 6 $\pm$ 7 HADS: >7 MMSE: 28 $\pm$ 1	DAT	[¹²³ I]FP-CIT	M. Parkinson	None	n.s.	4/5	59 $\pm$ 9	18/7	60 $\pm$ 8	1 $\pm$ 0.3	n.s.	0
Figee et al., 2014	OCD	UPDRSIII: 16 $\pm$ 9 Ybocs: 29 $\pm$ 2 HAMA: 29 $\pm$ 3 HDRS: 27 $\pm$ 2	D ₂	[¹²³ I]IBZM	None, MDD, PD	None, benzodiazepines		7/9	44 $\pm$ 10	9/9	38 $\pm$ 18	26 $\pm$ n.s.	0	1
Hesse et al., 2005	OCD	Ybocs: 25 $\pm$ 9 BDI: 7 $\pm$ 4	DAT	[¹²³ I] β -CIT	None	None, psychotropics	n.s.	8/7	32 $\pm$ 12	7/3	40 $\pm$ 13	16 $\pm$ 9	n	168
Hoexter et al., 2012	PTSD	BDI: 28 $\pm$ 10 BAI: 9 $\pm$ 9	DAT	[^{99m} Tc]TRODAT	None	n.s.	n.s.	4/17	39 $\pm$ 13	4/17	40 $\pm$ 13	n.s.	n.s.	n.s.
Kim et al., 2003	OCD	CAPS: 10 $\pm$ 13 Ybocs: 30 $\pm$ 7 Ybocs _{obs} : 15 $\pm$ 4 Ybocs _{comp} : 15 $\pm$ 3 CGI: 6 $\pm$ 1	DAT	[¹²³ I]IPT	None	None, psychotropics	n.s.	11/5	29 $\pm$ 11	11/8	18–50 y	9 $\pm$ 8	n	28
Lee et al., 2015	GAD	HAMA: 23 $\pm$ 7 HDRS: 11 $\pm$ 4 RLCQ: 17 $\pm$ 10	DAT	[^{99m} Tc]TRODAT	None	Benzodiazepines, non- benzodiazepine GABA _A agonists	n.s.	4/8	37 $\pm$ 13	4/8	37 $\pm$ 13	4 $\pm$ n.s.	y	0
Maron et al., 2010	PD	HAMA: 18 $\pm$ 6 PDSS: 9 $\pm$ 2	DAT	[¹²³ I]nor- β -CIT	n.s.	n.s.	n.s.	0/7	37 $\pm$ 17	0/7	35 $\pm$ 5	5 $\pm$ 5	n.s.	n.s.
Meyer et al., 1999	OCD	n.s.	VMAT2	[¹¹ C]DTBZ	TS, ADHD	$\alpha 2$ antagonists, D _{1/2} /5-HT antagonists, SSRIs, VMAT2 blockers	n.s.	7/1	30 $\pm$ 9	22 (gender n.s.)	34 $\pm$ 8	28 $\pm$ n.s.	y	0
Moresco et al., 2007	OCD	Ybocs: 29 $\pm$ 5 Ybocs _{obs} : 14 $\pm$ 3 Ybocs _{comp} : 15 $\pm$ 3 CGI: 5 $\pm$ 1 NIMH: 11 $\pm$ 1	D ₂	[¹¹ C]raclopride	None	None, benzodiazepines; n.s. <i>current</i> : fluvoxamine for ≥ 2 weeks		6/3	28 $\pm$ 5	8/1	27 $\pm$ 8	16 $\pm$ 6	y/n	0
Moriyama et al., 2011	SAD	UPDRSIII: 35 $\pm$ 16 HY: 3 $\pm$ 1 SE: 82 $\pm$ 16 BSPS: 57 $\pm$ 11	DAT	[^{99m} Tc]TRODAT	M. Parkinson	n.s.	y/n	3/9	53 $\pm$ 13	5/15	51 $\pm$ 11	7 $\pm$ 4	n.s.	n.s.
Olver et al., 2009	OCD	Ybocs: 22 $\pm$ 8 Ybocs _{obs} : 11 $\pm$ 4 Ybocs _{comp} : 11 $\pm$ 4 HAMA: 15 $\pm$ 9 HDRS: 12 $\pm$ 5	D ₁	[¹¹ C]SCH23390	None	None, SSRIs	n	4/3	40 $\pm$ 14	4/3	40 $\pm$ 12	19 $\pm$ n.s.	n	10

Table 1 (continued)

Study	Sub-type	Mean inventory scale score $\pm$ SD	Constituent	Ligand	Comorbidity	Premedication	Smoking	Patients (m/f)	Mean age $\pm$ SD (years)	Controls (m/f)	Mean age $\pm$ SD (years)	Mean duration $\pm$ SD (years)	Medication at the time of scanning	Duration of withdrawal (days)
Perani et al., 2008	OCD	Ybocs: 29 ± 4 Ybocs _{obs} : 14 ± 2 Ybocs _{comp} : 15 ± 3 CGI: 5 ± 1 NIMH: 11 ± 1	D ₂	[¹¹ C]raclopride	None	None, benzodiazepines	n.s.	6/3	31 $\pm$ 7	12/3	21–55 y	19 $\pm$ 9	n	≥ 1
Schneier et al., 2000	SAD	LSAS: n.s.	D ₂	[¹²³ I]IBZM	None	None, psychotropics	n.s.	5/5	33 $\pm$ 10	5/5	33 $\pm$ n.s.	n.s.	n	365
Schneier et al., 2008	OCD	Ybocs: 23 ± 6 LSAS: 24 ± 13 STAI _{state} : 42 ± 11 HDRS: 10 ± 6 TDS: 24 ± 3	D ₂	[¹²³ I]IBZM	None, GAD, PTSD, MDD	None, psychotropics	y/n	6/2	33 $\pm$ 12	4/3	30 $\pm$ 11	n.s.	y/n	n.s.
Same controls	OCD + SAD	Ybocs: 21 ± 6 LSAS: 72 ± 24 STAI _{trait} : 38 ± 10 HDRS: 15 ± 6 TDS: 26 ± 2	D ₂	[¹²³ I]IBZM	None, MDD	None, psychotropics	y/n	6/1	36 $\pm$ 8	4/3	30 $\pm$ 11	n.s.	y/n	n.s.
Schneier et al., 2009	SAD	LSAS: 79 ± 9 TDS: 26 ± 3	DAT	[¹²³ I] β -CIT	None, OCD, GAD, dystymia	n.s.	y/n	12 (gender n.s.)	n.s.	10 (gender n.s.)	n.s.	n.s.	n	252
Partly the same subjects	SAD	LSAS: 79 ± 19	D ₂	[¹¹ C]raclopride	None, OCD, GAD, dystymia	n.s.	y/n	11/4	31 $\pm$ 7	12 (gender n.s.)	n.s.	n.s.	n	252
Partly the same subjects	SAD	LSAS: 79 ± 19	D ₂	[¹¹ C]raclopride	None, OCD, GAD, dystymia	n.s.	y/n	12 (gender n.s.)	n.s.	12 (gender n.s.)	n.s.	n.s.	n	252
Tiihonen et al., 1997	SAD	CGI: 6 ± 2	DAT	[¹²³ I] β -CIT	None, agoraphobia	None	n.s.	3/8	41 $\pm$ 5	3/8	40 $\pm$ 12	20 $\pm$ 12	n	n.a.
Van der Wee et al., 2004	SAD	Ybocs: 23 ± 4 Ybocs _{obs} : 12 ± 2 Ybocs _{comp} : 11 ± 3 LSAS: 74 ± 14 HDRS: 8 ± 4	DAT	[¹¹ C] β -CIT	None	n.s., current: paroxetine	y/n	11/4	32 $\pm$ 9	11/4	32 $\pm$ 10	12 $\pm$ 7	n	1
Van der Wee et al., 2008	SAD	HDRS: 8 ± 2	DAT	[¹¹ C] β -CIT	None	n.s.	y/n	7/5	39 $\pm$ 13	7/5	33 $\pm$ 10	24 $\pm$ 15	n	n.s.
Vulink et al., 2016	OCD	Ybocs: 34 ± 6 BABS: 15 ± 3	D _{2/3}		BBD, social phobia	No psychotropics for ≥ 4 weeks;	y/n	9/3	28 $\pm$ 7	9/3	28 $\pm$ 6	n.s.	n	28

Table 1 (continued)

Study	Sub-type	Mean inventory score $\pm$ SD	Constituent	Ligand	Comorbidity	Premedication	Smoking	Patients (m/f)	Mean age $\pm$ SD (years)	Controls (m/f)	Mean age $\pm$ SD (years)	Mean duration $\pm$ SD (years)	Medication at the time of scanning	Duration of withdrawal (days)
Wong et al., 2008	OCD	Ybocs: n.s. BPRS: n.s. YGTS _{mit} : n.s. YGTS _{pt} : n.s.	DAT	[¹¹ C]WIN35,428	TS	None, psychotropics	n.s.	9/2	32 $\pm$ 8	3/2	25 $\pm$ 4	n.s.	n	168
Partly the same subjects	OCD	Ybocs: n.s. BPRS: n.s. YGTS _{mit} : n.s. YGTS _{pt} : n.s.	D ₂	[¹¹ C]raclopride	TS	None, psychotropics	n.s.	12 (gender n.s.)	34 $\pm$ 9	3 (gender n.s.)	n.s.	n.s.	n	168
Partly the same subjects	OCD	Ybocs: n.s. BPRS: n.s. YGTS _{mit} : n.s. YGTS _{pt} : n.s.	DA release	[¹¹ C]raclopride	TS	None, psychotropics	n.s.	12 (gender n.s.)		6/4	26 $\pm$ 7	n.s.	n	168

Given are the reference (in alphabetical order), the assessed disorder, mean rating scale scores ($\pm$ SD), employed radioligands comorbidities, premedication, cigarette smoking habits, numbers of (male and female) patients and controls, mean age of patients and controls ($\pm$ SD; years), mean duration of disease ($\pm$ SD; years), medication state at the time of the investigation and duration of withdrawal (days). Abbreviations (in alphabetical order): α_2 , Adrenoreceptor of the α_2 receptor subtype; ADHD, attention-deficit hyperactivity disorder; BABS, Brown Assessment of Beliefs Scale; BAI, Beck's Anxiety Inventory; BDD, body dysmorphic disorder; BDI, Beck's Depression Inventory; BSPI, Brief Symptom Inventory; CAPS, Clinician-administered PTSD Scale; CGI, Clinical Global Impression Scale; D_{1/2}, 5-HT₂ antagonist, dopamine D_{1/2} receptor plus serotonin 5-HT₂ receptor antagonist; D_{2/3}, dopamine receptor of the D₂ and D₃ receptor subtype; DAREL, dopamine release; EDE, Eating Disorder Examination; f, female; GABA_A agonist, GABA_A receptor agonist GAD, generalized anxiety disorder; HADS, Hospital Anxiety Depression Scale; HAMA, Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale; HY, Hoehn and Yahr Scale; LSAS, Liebowitz Social Anxiety Scale; M., morbus; m, male; MDD, major depressive disorder; MMSE, Mini-Mental State Examination; NIMH, NIMH Obsessive-Compulsive Rating Scale; n, no; n.a., not applicable; n.s., not specified in the original investigation; OCD, obsessive-compulsive disorder; PD, panic disorder; PDSS, Shears Panic Disorder Severity Scale; PTSD, post-traumatic stress disorder; RLCQ, Recent Life Change Questionnaire; SAD, social anxiety disorder; SERT, serotonin transporter; SE, Schwab and England Scale; STAI_{state}, State Spielberger Anxiety Inventory; SSRI, selective serotonin reuptake inhibitor; TDS, Karolinka Trait Detachment Scale; TS, Tourette syndrome; UPDRSIII, Unified Parkinson Disease Rating Scale (motor); y, yes; y/n, yes as well as no; Ybocs, Yale-Brown Obsessive-Compulsive Score; Ybocs_{obs}, Yale-Brown Obsessive-Compulsive Score – obsessive score; Ybocs_{comp}, Yale-Brown Obsessive-Compulsive Score-Compulsive score.

Table 2: All *in vivo* investigations of synaptic constituents (DAT, D₁ receptor, D₂ synthesis, DA release) on patients with acute major depressive disorder (MDD) with either PET or SPECT.

Study	Mean rating scale score $\pm$ SD	Constituent	Ligand	Comorbidity	Premedication	Smoking	Patients (m/f)	Mean age $\pm$ SD (years)	Controls (m/f)	Mean age $\pm$ SD (years)	Mean duration $\pm$ SD (years)	Medication at the time of scanning	Duration of withdrawal (days)
Agren et al., 1992	n.s.	DASyn	[¹¹ C]DOPA	n.s.	n.s.	n.s.	6 (gender n.s.)	40 $\pm$ 9	8 (gender n.s.)	35 $\pm$ 7	n.s.	n.s.	n.s.
Agren et al., 1993	HDRS: 22 $\pm$ 6	DASyn	[¹¹ C]DOPA	n.s.	TCAs, TeCAs, lithium	n.s.	4/3	37 $\pm$ 6	11/0	31 $\pm$ 6	n.s.	n	23
Agren and Reibring, 1994	n.s.	DASyn	[¹¹ C]DOPA	n.s.	n.s.	n.s.	7 (gender n.s.)	n.s.	11 (gender n.s.)	n.s.	n.s.	n.s.	n.s.
Amsterdam and Newberg, 2007	HDRS: >17	DAT	[^{99m} Tc]TRODAT	n.s.	Psychotropics	n.s.	7/3	39 $\pm$ n.s.	22/24	40 $\pm$ n.s.	n.s.	y	7
Amsterdam et al., 2012	HDRS: n.s.	DAT	[^{99m} Tc]TRODAT	None	Psychotropics	n.s.	24 (gender n.s.)	n.s.	43/41	38 $\pm$ 15	24 $\pm$ 11	n	180
Argyelan et al., 2005	HDRS: 27 $\pm$ 6	DAT	[^{99m} Tc]TRODAT	None	None, SSRIs, SNRIs, antipsychotics	n.s.	6/10	39 $\pm$ 13	12 (gender n.s.)	34 $\pm$ 14	n.s.	n	14
Broft et al., 2015	BDI: 33 $\pm$ 11 BAI: 27 $\pm$ 12 EDE: 4 $\pm$ 1	D ₂	[¹¹ C]raclopride	Anorexia, AD	Sleeping pills, no psycho- tropics for $\geq$ 4 weeks; current: n.s.	y/n	0/21	25 $\pm$ 7	0/25	26 $\pm$ 5	11 $\pm$ 8	y	0
Brunswick et al., 2003	HDRS: 22 $\pm$ 4	DAT	[^{99m} Tc]TRODAT	None	Antidepressants (incl. SSRIs, MAOIs)	n.s.	9/6	40 $\pm$ 12	22/24	40 $\pm$ 11	n.s.	n	7
Busto et al., 2009 <i>Same cohorts</i>	HDRS: 23 $\pm$ 6 BDI: 24 $\pm$ 7 HDRS: 23 $\pm$ 6	D ₂	[¹¹ C]raclopride	None	None	y/n	2/8	36 $\pm$ 13	3/8	28 $\pm$ 4	n.s.	n	n.a.
Camardese et al., 2014	BDI: 24 $\pm$ 7 HDRS: 22 $\pm$ 6 SHPS: 5 $\pm$ 1	DAT	[¹¹ C]raclopride	None	None	y/n	2/8	36 $\pm$ 13	3/8	28 $\pm$ 4	n.s.	n	n.a.
Cannon et al., 2009	MADRS: 22 $\pm$ 5 IDS-C: 27 $\pm$ 7	D ₁	[¹¹ C]NNC-112	None, AD	Antidepressants	n.s.	10/10	48 $\pm$ 10	10/10	44 $\pm$ 13	n.s.	n.s.	n.s.
Chung et al., 2016	BDI: 14 $\pm$ 8 MMSE: 27 $\pm$ 2	DAT	[¹²³ I]FP-CIT	M. Parkinson	Antipsychotics, antidepressants	n	7/11	31 $\pm$ 11	8/11	31 $\pm$ 9	12 $\pm$ 9	n	21
de Kwaasteniet et al., 2014	BDI: 14 $\pm$ 8 UPDRSIII: 21 $\pm$ 9 HDRS: 21 $\pm$ 1 MADRS: 34 $\pm$ 3 MSM: 12 $\pm$ 1	DAT	[¹²³ I]FP-CIT	M. Parkinson	None	n.s.	17/17	67 $\pm$ 9	28/46	67 $\pm$ 9	n.s.	n	n.a.
D'haenen and Bossuyt, 1994	n.s.	D ₂	[¹²³ I]IBZM	None	TCAs, TeCAs, lithium, SNRIs, MAOIs,	n.s.	7/10	52 $\pm$ 3	5/10	55 $\pm$ 2	24 $\pm$ 5	y	0
Dougherty et al., 2006	HDRS: 16 $\pm$ n.s.	D ₁	[¹¹ C]SCH23390	Anger attacks	benzodiazepines, non- benzodiazepine GABA _A agonists, D ₂ agonists, $\alpha_{1/2}/D_{1/5}/HT_{1/2}/H1-4/mACh$ antagonists	n.s.	4/17	41 $\pm$ 12	3/8	41 $\pm$ 8	n.s.	n	7
Ebert et al., 1994	HDRS: 26 $\pm$ 4	D ₂	[¹²³ I]IBZM	None	Antidepressants (incl. SSRIs)	n.s.	4/6	43 $\pm$ 7	6/4	42 $\pm$ 6	n.s.	n	21
Ebert et al., 1996	HDRS: 26 $\pm$ 4	D ₂	[¹²³ I]IBZM	None	TCAs	n.s.	10/0	33 $\pm$ 14	5/0	35 $\pm$ 8	n.s.	y	0
Felicio et al., 2010	BDI: 25 $\pm$ 6	DAT	[^{99m} Tc]TRODAT	M. Parkinson	None	y/n	20 (gender n.s.)	40 $\pm$ 13	10/0	50 $\pm$ 15	n.s.	n	n.a.
Frosini et al., 2015	BDI: 17 $\pm$ 4 MMSE: 28 $\pm$ 1 UPDRSII: 67 $\pm$ 5 UPDRSIII: 7 $\pm$ 3	DAT	[¹²³ I]FP-CIT	M. Parkinson	None, antidepressants Antidepressants	n.s.	5/5 15 (gender n.s.)	63 $\pm$ 9 n.s.	6/4 35 (gender n.s.)	65 $\pm$ 5 n.s.	5 $\pm$ 2 n.s.	y/n n	0 10

Table 2 (continued)

Study	Mean rating scale score $\pm$ SD	Constituent	Ligand	Comorbidity	Premedication	Smoking	Patients (m/f)	Mean age $\pm$ SD (years)	Controls (m/f)	Mean age $\pm$ SD (years)	Mean duration $\pm$ SD (years)	Medication at the time of scanning	Duration of withdrawal (days)
Hirvonen et al., 2008	HDRS: 19 $\pm$ 3 BDI: 24 $\pm$ 7	D ₂	[¹¹ C]raclopride	None	None, SSRIs	y/n	10/15	40 $\pm$ 9	7/12	39 $\pm$ 10	n.s.	n	1825
Klimke et al., 1999	HDRS: 27 $\pm$ 5	D ₂	[¹²³ I]IBZM	n.s.	Antidepressants, benzodiazepines	n.s.	7/8	52 $\pm$ 13	10/7	59 $\pm$ 16	10 $\pm$ n.s.	y/n	0
Laasonen-Balk et al., 1999	HDRS: 16 $\pm$ 7 BDI: 20 $\pm$ 7 MADRS: 21 $\pm$ 6 GAS: 58 $\pm$ 7	DAT	[¹²³ I] β -CIT	None	None	n.s.	5/10	36 $\pm$ 8	8/10	35 $\pm$ 6	n.s.	n	n.a.
Ledermann et al., 2016a	BDI: 17 $\pm$ 9 MADRS: 16 $\pm$ 9 SHPS: 2 $\pm$ 1	D ₂	[¹¹ C]raclopride	Fibromyalgia	SSRIs, TCAs, NSAIDs	n.s.	0/11	45 $\pm$ 10	0/17	43 $\pm$ 14	11 $\pm$ 12	y	0
Ledermann et al., 2017	PDI: 25 $\pm$ 7 BDI: 17 $\pm$ 9 MADRS: 16 $\pm$ 9	DAT	[¹¹ C]raclopride	Fibromyalgia	SSRIs, TCAs, NSAIDs	n.s.	0/11	45 $\pm$ 10	0/17	43 $\pm$ 14	11 $\pm$ 12	y	0
Same cohorts as Ledermann et al., 2016	SHPS: 2 $\pm$ 1 PDI: 25 $\pm$ 7												
Lehto et al., 2006	HDRS: 30 $\pm$ 8	DAT	[¹²³ I]nor- β -CIT	None	None	n.s.	5/24	29 $\pm$ 9	2/16	31 $\pm$ 9	n.s.	n	n.a.
Lehto et al., 2008a	HDRS: 10 $\pm$ 5	D ₂	[¹²³ I]lepeptide	None, dysthymia	Benzodiazepines, antidepressants	n.s.	4/6	53 $\pm$ 7	4/6	52 $\pm$ 7	7 $\pm$ n.s.	n	90
Lehto et al., 2008b	HDRS: 19 $\pm$ 5	DAT	[¹²³ I]nor- β -CIT	None, dysthymia	None	y/n	2/17	27 $\pm$ 5	3/16	31 $\pm$ 9	n.s.	n	n.a.
Majurim et al., 2017	BDI: 15 $\pm$ 9 BES: 31 $\pm$ 5 YFAS: 31 $\pm$ 5 DEBQ _{min} : 50 $\pm$ 8 DEBQ _{tot} : 38 $\pm$ 6 DEBQ _{ref} : 35 $\pm$ 3	DASyn	[¹⁸ F]DOPA	BED, pathological gambling, anxiety	None, SSRIs	y/n	8/14	46 $\pm$ 8	8/9	43 $\pm$ 11	n.s.	y/n	0
Malison et al., 1998	YDI: >17	DAT	[¹²³ I] β -CIT	None, dysthymia, PD, ADHD, substance abuse	None, TCAs, SSRIs, 5-HT _{2A} antagonists, NA/DA reuptake inhibitors	n.s.	7/8	44 $\pm$ 10	7/8	45 $\pm$ 11	n.s.	n	21
Martinot et al., 2001	MADRS: 29 $\pm$ 4 DRRS: 17 $\pm$ 4 DMSloc: 10 $\pm$ 4 DMSaf: 12 $\pm$ 4 TAS: 14 $\pm$ 5	DASyn	[¹⁸ F]DOPA	None	SSRIs	n.s.	3/9	46 $\pm$ 8	4/6	42 $\pm$ 12	n.s.	y/n	0
Meyer et al., 2001	HDRS: 17 $\pm$ n.s.	DAT	[¹¹ C]RTI-32	None	n.s.	y/n	5/4	35 $\pm$ 8	12/11	37 $\pm$ 10	n.s.	n	84
Meyer et al., 2006	HDRS: 20 $\pm$ 3	D ₂	[¹¹ C]raclopride	None	None, antidepressants	n	9/12	25 $\pm$ 10	9/12	34 $\pm$ 11	>2	n	180
Montgomery et al., 2007	HDRS: 17 $\pm$ 4 BDI: 28 $\pm$ 9	D ₂	[¹¹ C]FLB 457	None	Psychotropics	y/n	2/5	44 $\pm$ 9	6/1	36 $\pm$ 11	n.s.	n	120
Neumeister et al., 2001	SIGHsad: 33 $\pm$ 5	DAT	[¹²³ I] β -CIT	None	n.s.	n	1/10	31 $\pm$ 8	1/10	31 $\pm$ 10	n.s.	n.s.	n.s.

Table 2 (continued)

Study	Mean rating scale score $\pm$ SD	Constituent	Ligand	Comorbidity	Premedication	Smoking	Patients (m/f)	Mean age $\pm$ SD (years)	Controls (m/f)	Mean age $\pm$ SD (years)	Mean duration $\pm$ SD (years)	Medication at the time of scanning	Duration of withdrawal (days)
Parsey et al., 2001	HDRS: 21 $\pm$ 15 BPRS: 23 $\pm$ 13	D ₂	[¹²³ I]IBZM	None	Benzodiazepines, neuroleptics, SSRIs	y/n	7/2	36 $\pm$ 12	7/3	30 $\pm$ 10	n.s.	n	3
Same cohorts	HDRS: 21 $\pm$ 15 BPRS: 23 $\pm$ 13	D ₂	[¹²³ I]IBZM	None	Benzodiazepines, neuroleptics, SSRIs	y/n	7/2	36 $\pm$ 12	7/3	30 $\pm$ 10	n.s.	n	3
Remy et al., 2005	BDI: 19 $\pm$ 8	DAT	[¹¹ C]RTI-32	M. Parkinson	Enhancers of DA release, D ₂ agonists, MAOIs	n.s.	5/3	57 $\pm$ 9	9/4	60 $\pm$ 7	3 $\pm$ 2	n	84
Ryding et al., 2006	BSIC: >18	DAT	[¹²³ I]β-CIT	None, self-harm, adjustment disorder, substance abuse	Antidepressants, antipsychotics	n.s.	10/2	39 $\pm$ 14	10/2	39 $\pm$ 14	n.s.	n	180
Saijo et al., 2010	HDRS: 19 $\pm$ 6 GAS: 42 $\pm$ 9	D ₂	[¹¹ C]FLB457	AD, insomnia	SSRIs, benzodiazepines, ECT	n.s.	5/2	43 $\pm$ 11	11/0	41 $\pm$ 11	2 $\pm$ 2	y	0
Sarchiapone et al., 2006	HDRS: 20 $\pm$ 6 MADRS: 22 $\pm$ 2 SHPS: 10 $\pm$ 2	DAT	[¹²³ I]FP-CIT	None, dysthymia	Psychoactive drugs	n.s.	6/5	41 $\pm$ 12	5/5	36 $\pm$ 12	n.s.	n	120
Savitz et al., 2013	MADRS: 25 $\pm$ 7	D ₂	[¹¹ C]raclopride	None	Psychotropics	n	4/8	38 $\pm$ 11	11/13	35 $\pm$ 8	n.s.	n	21
Shah et al., 1997	HDRS: 24 $\pm$ 8 NS: 7 $\pm$ 2	D ₂	[¹²³ I]IBZM	None, BD	None, antidepressants (incl. lithium), benzodiazepines	n.s.	9/6	45 $\pm$ 14	9/6	41 $\pm$ 10	n.s.	y/n	84
Staley et al., 2006	BDI: 28 $\pm$ 7 YDI: 25 $\pm$ 5	DAT	[¹²³ I]β-CIT	n.s.	None, benzodiazepines	y/n	16/16	39 $\pm$ 10	16/16	39 $\pm$ 10	11 $\pm$ n.s.	n.s.	n.s.
Tolmunen et al., 2004	HDRS: 18 $\pm$ 3	DAT	[¹²³ I]nor-β-CIT	n.s.	n.s.	n.s.	0/6	27 $\pm$ 6	10 (gender n.s.)	26 $\pm$ 6	1 $\pm$ 1	n.s.	n.s.
Vinamäki et al., 1998	HDRS: 27	DAT	[¹²³ I]β-CIT	BPD, substance abuse	Benzodiazepines	n.s.	1/0	34	5/0	34 $\pm$ 1	n.s.	n.s.	n.s.
Wing et al., 2015	BDI: 11 $\pm$ 6 UPDRSIII: 2 $\pm$ 1 RBDQ: 4.5 $\pm$ 15 BDI: 11 $\pm$ 6	D ₂	[¹¹ C]DOPA	REM sleep behavior disorder	Antidepressants incl. SSRIs	y/n	8/3	48 $\pm$ 8	10/3	47 $\pm$ 11	40 $\pm$ 9	y	0
Same cohorts	UPDRSIII: 2 $\pm$ 1 RBDQ: 4.5 $\pm$ 1	D ₂	[¹¹ C]raclopride	REM sleep behavior disorder	Antidepressants incl. SSRIs	y/n	8/3	48 $\pm$ 8	10/3	47 $\pm$ 11	40 $\pm$ 9	y	0
Yang et al., 2008	HDRS: 25 $\pm$ 8	DAT	[^{99m} Tc]TRODAT	None	Antidepressants	y/n	3/7	51 $\pm$ 7	3/7	53 $\pm$ 6	3 $\pm$ 7	n	84
Same cohorts	HDRS: 25 $\pm$ 8	D ₂	[¹²³ I]IBZM	None	Antidepressants	y/n	3/7	51 $\pm$ 7	3/7	53 $\pm$ 6	3 $\pm$ 7	n	84
Yen et al., 2016	HDRS: 19 $\pm$ 5	DAT	[^{99m} Tc]TRODAT	Alcohol abuse	None-DAergic medication	y/n	21/0	39 $\pm$ 7	24/0	39 $\pm$ 9	n.s.	n.s.	n.s.

Given are the reference (in alphabetical order), the assessed disorder, mean rating scale scores ($\pm$ SD), employed radioligands comorbidities, premedication, cigarette smoking habits, numbers of (male and female) patients and controls, mean age of patients and controls ($\pm$ SD; years), mean duration of disease ($\pm$ SD; years), medication state at the time of the investigation and duration of withdrawal (days). Abbreviations (in alphabetical order): $\alpha_{1/2}$, $\alpha_{1/2}$, adrenoreceptor; AD, anxiety disorder; ADHD, attention-deficit hyperactivity disorder; BAI, Beck's Anxiety Inventory; BD, bipolar disorder; BDI, Beck Depression Inventory; BED, binge eating disorder; BES, Binge Eating Scale; BHS, Beck Hopelessness Scale; BPD, borderline personality disorder; BPRS, Brief Psychiatric Rating Scale; BSIC, Beck Suicidal Intent Scale; CD, conduct disorder; CGIS, clinical global impression scale; DAT, dopamine transporter; D₁₋₅, dopamine D₁₋₅ receptor; D₂, dopamine release; DASyn, dopamine synthesis; DEBO_{em}, Dutch Eating Behavior Questionnaire emotional; DEBO_{eat}, Dutch Eating Behavior Questionnaire (external scale); DEBO_{eat}, Dutch Eating Behavior Questionnaire (restrained scale); DMSloc, Depressive Mood Scale (loss of control subscale); DMSaf, Depressive Mood Scale (affective flattening subscale);

Table 2 (continued)

Dn.s., depression not specified; DRRS, Depression Retardation Raing Scale; ECT, electroconvulsive therapy; EDE, Eating Disorder Examination; f, female; GABA_A, GABA_A receptor; GAS, Endicott's Global Assessment Scale; H1-4, histamine H1-4 receptor; HAMA, Hamilton Anxiety Scale; HDRS, Hamilton Depression Rating Scale; 5-HT_{1/2}, serotonin 5-HT_{1/2} receptor; 5-HT_{2A}, serotonin 5-HT_{2A} receptor; IDS-C, Inventory of Depressive Symptoms Clinician Rated; M., Morbus; m, male; mACh, muscarinic acetylcholine receptor; MADRS, Montgomery-Asberg Depression Rating Scale; MAOI, monoamine oxidase inhibitor; MDD, major depressive disorder; MMSE, Mini-Mental State Examination; MSM, Maudsley Staging Method; n, no; n.a., not applicable; NA, noradrenaline; n.s., not specified; NS, Newcastle Scale; NSAID, non-steroidal anti-inflammatory drugs; PD, panic disorder; REM, rapid eye movement; RLCQ, Recent Life Change Questionnaire; SAD, seasonal affective disorder; SNRI, 5-serotonin/noradrenaline reuptake inhibitors; SHPS, Snaith-Hamilton Pleasure Scale; SIGHSad, Structured Interview Guide for the Hamilton Depression Rating Scale- Seasonal Affective Disorder Version; SSRI, selective serotonin reuptake inhibitors; TAS, Tyrer Anxiety Scale; TCA, tricyclic antidepressants; UPDRSII, Unified Parkinson Disease Rating Scale (self-evaluation of the activities of daily life), UPDRSIII, Unified Parkinson Disease Rating Scale (motor scale); y, yes; y/n, yes/no; YDI, Yale Depression Inventory; YFAS, Yale Food Addiction Scale.

Results

Comparison between patients and controls

AD

VMAT2 binding in the STR [number of investigations (n)=1] was not different from healthy individuals (data not shown). Likewise, DAT (Figure 1) in STR (n=11) and VS (n=1) was unaltered.

D₁R (Figure 2) in the STR was lowered relative to controls (n=1, -27%, $p < 0.05$). Moreover, D₂R (Figure 3) was reduced in STR (n=11, -21%, $p = 0.005$) and VS (n=5, -16%, $p = 0.047$).

DA release (Figure 5) was elevated in the STR (n=2, +27%, $p = 0.051$). So far, no investigation of DA synthesis has been conducted on AD patients.

MDD

DAT (Figure 1) was diminished in PFC (n=2, -13%, $p = 0.051$), FC (n=2, -13%, $p = 0.051$), CING (n=1, -93%, $p < 0.05$), AMYG (n=1, -46%, $p < 0.05$), SN (n=1, -17%, $p < 0.05$) and LC (n=1, -54%, $p < 0.05$) relative to healthy individuals. Contrarily, DAT binding was unaltered in STR (n=24), VS (n=2), THAL (n=2), PC (n=1), TC (n=1), OC (n=1) and MB (n=2).

D₁R (Figure 2) was reduced in the STR (n=2, -8%, $p = 0.051$), but not different from healthy subjects in VS (n=1), CING (n=1), AMYG (n=1) and INS (n=1).

D₂R (Figure 3) was increased in the CING (n=2, +8%, $p = 0.051$). No decreases of D₂R were detected in STR (n=15), VS (n=4), THAL (n=2), FC (n=1), TC (n=1), HIP (n=1), AMYG (n=1) and CER (n=1) relative to controls.

DA synthesis (Figure 4) was elevated in PFC (n=3, +75%, $p = 0.017$) and FC (n=3, +75%, $p = 0.017$), but not different from controls in the STR (n=5).

DA release (Figure 5) was increased in the VS (n=1, +7%, $p < 0.05$), but unaltered in the STR (n=3). So far, no investigation of VMAT2 binding have been conducted on MDD subjects.

BD_{man}

DAT (Figure 1) was elevated relative to controls in the STR (n=1, +15%, $p < 0.05$).

D₁R (Figure 2) was diminished in the FC (n=1, -25%, $p < 0.05$), but unaltered in the STR (n=1). Also D₂R (Figure 3)

Table 3: All *in vivo* investigations of synaptic constituents (DAT, D₁ receptor, D₂ receptor, DA synthesis) on patients with acute bipolar disorder (BD) with either PET or SPECT.

Study	State	Mean rating scale score $\pm$ SD	Constituent	Ligand	Comorbidity	Premedication	Smoking	Patients (m/f)	Mean age $\pm$ SD (years)	Controls (m/f)	Mean age $\pm$ SD (years)	Mean duration $\pm$ SD (years)	Medication at the time of scanning	Duration of withdrawal (days)
Amsterdam and Newberg, 2007	Dep	HDRS: >17	DAT	[^{99m} Tc]TRODAT	n.s.	Psychotropics	n.s.	2/3	41 $\pm$ n.s.	22/24	40 $\pm$ n.s.	n.s.	n	7
Amsterdam et al., 2012	Dep	HDRS: n.s.	DAT	[^{99m} Tc]TRODAT	None	None, psychotropics	n.s.	15 (n.s.)	n.s.	43/41	38 $\pm$ 14	n.s.	n	180
Brunswick et al., 2003	Dep	HDRS: 22 $\pm$ 4	DAT	[^{99m} Tc]TRODAT	MDD	Antidepressants (incl. SSRIs, MAOIs)	n.s.	9/6	40 $\pm$ 12	22/24	40 $\pm$ 11	n.s.	n	7
Sarchiapone et al., 2006	Dep	HDRS: 20 $\pm$ 6 MADRS: 22 $\pm$ 2 SHPS: 10 $\pm$ 2	DAT	[¹²³ I]FP-CIT	MDD, dysthymia	Psychoactive drugs	n.s.	6/5	41 $\pm$ 12	5/5	36 $\pm$ 12	n.s.	n	120
Suhara et al., 1992	Dep	HDRS: 21 $\pm$ 12	D ₁	[¹¹ C]SCH23390	n.s.	Antidepressants (incl. TCAs, TeCAs, D ₁ /D ₃ antagonists, lithium)	n.s.	3/0	41 $\pm$ 6	21/0	20–72	n.s.	n	15
Same controls	Man	n.s.	D ₁	[¹¹ C]SCH23390	n.s.	n.s.	n.s.	1/0	37	21/0	20–72	n.s.	n	8
Tolmunen et al., 2004	Man	HDRS: 15	DAT	[¹²³ I]nor- β -CIT	n.s.	n.s.	n.s.	0/1	25	10 (n.s.)	26 $\pm$ 6	n.s.	n.s.	n.s.
Yatham et al., 2002a	Man	YMRS: 27 $\pm$ 7	DA _{syn}	[¹⁸ F]DOPA	None	None, benzodiazepines	n.s.	6/7	33 $\pm$ 12	6/7	32 $\pm$ 12	n.s.	n	n.a.
Same cohorts as Yatham et al., 2002b	Man	YMRS: 27 $\pm$ 7	D ₂	[¹¹ C]raclopride	None	None, benzodiazepines	n.s.	6/7	33 $\pm$ 12	6/7	32 $\pm$ 12	n.s.	n	n.a.
Same cohorts as Yatham et al., 2002a	Man	YMRS: 27 $\pm$ 7	D ₂	[¹¹ C]raclopride	None	None, benzodiazepines	n.s.	6/7	33 $\pm$ 12	6/7	32 $\pm$ 12	n.s.	n	n.a.

Given are the reference (in alphabetical order), the state (manic or depressed) at the time of *in vivo* measurement, mean rating scale scores ($\pm$ SD), employed radioligands comorbidities, premedication, cigarette smoking habits, numbers of (male and female) patients and controls ($\pm$ SD; years), mean age of patients and controls ($\pm$ SD; years), mean duration of disease ($\pm$ SD; years), medication state at the time of the investigation and duration of withdrawal (days). Abbreviations (in alphabetical order): D₁ dopamine D₁ receptor; D₂, dopamine D₂ receptor; D_{2/3}, dopamine D_{2/3} receptor; DA_{syn}, dopamine synthesis; dep, depressed; DAT, dopamine transporter; f, female; HDRS, Hamilton Depression Rating Scale; m, male; MADRS, Montgomery-Asberg Depression Rating Scale; man, manic; MAOI, monoamine oxidase inhibitor; n, no; n.s., not specified; SHPS, Snaith-Hamilton Pleasure Scale; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressants; TeCA, tetracyclic antidepressants; YMRS, Young Mania Rating Scale.

Study	Disorder	Mean inventory scale score±SD	Constituent	Ligand	Comorbidity	Premedication	Smoking	Patients (m/f)	Mean age±SD (years)	Controls (m/f)	Mean age±SD (years)	Mean duration±SD (years)	Medication at the time of scanning	Duration of withdrawal (days)
Abi-Dargham et al., 1998	SZ	PANSS _{post} : 19±5	D ₂	[¹²³ I]IBZM	None	None, neuroleptics, benzodiazepine	n.s.	12/3	41±9	12/3	40±11	n.s.	n	169
		PANSS _{neg} : 20±7												
		BPRS: 44±11												
Same patients and controls	SZ	PANSS _{post} : 19±5	DArel	[¹²³ I]IBZM	None	None, neuroleptics, benzodiazepine	n.s.	12/3	41±9	12/3	40±11	n.s.	n	169
		PANSS _{neg} : 20±7												
		BPRS: 44±11												
Abi-Dargham et al., 2000	SZ	PANSS: 67±12	D ₂	[¹²³ I]IBZM	None	None, antipsychotics, benzodiazepine	y/n	11/7	31±8	11/7	31±8	n.s.	n	1
		PANSS _{post} : 19±5												
		PANSS _{neg} : 20±7												
Partly the same patients and controls as Abi-Dargham et al., 2009	SZ, SFD	PANSS: 71±7	D ₁	[¹¹ C]NNC212	None	Antipsychotics, benzodiazepine	y/n	13/3	33±12	11/5	34±10	n.s.	n	1
		PANSS _{post} : 19±7												
		PANSS _{neg} : 18±6												
Partly the same controls as Abi-Dargham et al., 2012	SZ, SFD	PANSS _{gen} : 34±7	D ₁	[¹¹ C]NNC212	None	Antipsychotics	y/n	16 (gender n.s.)	n.s.	16 (gender n.s.)	n.s.	n	21	
		PANSS _{post} : 19±7												
		PANSS _{neg} : 18±6												
Abi-Dargham et al., 2009	SZ	n.s.	D ₂	[¹²³ I]IBZM	n.s.	None	n	2/4	29±6	6/2	28±8	n.s.	n	n.a.
		PANSS _{post} : 18±6												
		PANSS _{neg} : 17±6												
Partly the same patients and controls as Abi-Dargham et al., 2000	SZ	n.s.	DArel	[¹²³ I]IBZM	n.s.	None	n	2/4	29±6	6/2	28±8	n.s.	n	n.a.
		PANSS _{post} : 18±6												
		PANSS _{neg} : 17±6												
Same patients and controls	SZ, SAD	PANSS: 67±22	D ₁	[¹¹ C]NNC212	None	None	y/n	5/7	25±5	12/12	26±5	n.s.	n	n.a.
		PANSS _{post} : 18±6												
		PANSS _{neg} : 17±6												
Partly the same controls as Abi-Dargham et al., 2002	SZ, SAD	PANSS _{gen} : 32±12	D ₁	[¹¹ C]NNC212	None	None	y/n	5/7	25±5	12/12	26±5	n.s.	n	n.a.
		PANSS _{post} : 18±6												
		PANSS _{neg} : 17±6												
Partly the same controls as Abi-Dargham et al., 2002	SZ, SAD	PANSS: 62±13	D ₁	[¹¹ C]NNC212	None	Antipsychotics, benzodiazepine	y/n	11/2	31±10	20/4	30±10	n.s.	n	1
		PANSS _{post} : 16±5												
		PANSS _{neg} : 14±6												
Different collectives; partly the same controls as Abi-Dargham et al., 2002	SZ	PANSS _{gen} : 32±7	D ₂	[¹¹ C]FLB457	None	Previous: none, antipsychotics; current: risperidone or olanzapine for ≥13 days	n.s.	13/1	27±n.s.	13 (gender n.s.)	27±2	n.s.	y	0
		PANSS _{post} : 21±4												
		PANSS _{neg} : 17±5												
Partly the same controls as Abi-Dargham et al., 2002	SZ	CGI: 5±1	DAT	[¹¹ C]PE21	None	None, antipsychotics incl. benzodiazepines	n.s.	6/2	37±10	10/2	33±12	3±4	y/n	0
		PANSS _{post} : 18±5												
		PANSS _{neg} : 19±7												
Partly the same controls as Abi-Dargham et al., 2002	SZ, SFD	PANSS _{gen} : 41±11	D ₂	[¹¹ C]FLB457	n.s.	Previous: n.s., current: perospirone for 2 weeks	n.s.	2/4	35±7	10/0	35±7	n.s.	y	0
		PANSS _{post} : 18±5												
		PANSS _{neg} : 19±7												

Table 4 (continued)

Study	Disorder	Mean inventory scale score $\pm$ SD	Constituent	Ligand	Comorbidity	Premedication	Smoking	Patients (m/f)	Mean age $\pm$ SD (years)	Controls (m/f)	Mean age $\pm$ SD (years)	Mean duration $\pm$ SD (years)	Medication at the time of scanning	Duration of withdrawal (days)
Barnas et al., 2001 <i>Partly the same patients as Küllerle et al., 1996, 1997 and Kasper et al., 1998 and the same controls as Küllerle et al., 1996, 1997, Kasper et al., 1998 and Brücke et al., 1991</i>	SZ	PANSS: 102 $\pm$ 23 CGI: n.s. BAS: n.s.	D ₂	[¹²³ I]IBZM	n.s.	Previous: antipsychotics; current: zolpidem for $\geq$ 4 weeks; co-medication: benzodiazepine, anticholinergic	n.s.	7/5	33 $\pm$ 9	6/2	51 $\pm$ 17	n.s.	n.s.	n.s.
Bertolino et al., 2000 <i>Partly the same patients as Breier et al., 1997</i>	SZ	BPRS: 38 $\pm$ n.s.	DArel	[¹¹ C]raclopride	n.s.	None, antipsychotics	n.s.	6/3	40 $\pm$ 9	5/2	36 $\pm$ 7	16 $\pm$ 11	n	14
Biglani et al., 1999	SZ	BPRS: 46 $\pm$ 11 SAPS: 31 $\pm$ 23 SANS: 34 $\pm$ 17 GAS: 45 $\pm$ 13 AIMS: 2 $\pm$ 4 SA: 3 $\pm$ 4 BAS: 3 $\pm$ 4 n.s.	D ₂	[¹²³ I]epidepride	None	Typical neuroleptics for $\geq$ 3 months	n.s.	11/1	40 $\pm$ 11	11/0	36 $\pm$ 10	n.s.	y	0
Bose et al., 2008 <i>Partly the same patients as McGowan et al., 2004</i>	SZ paranoid	n.s.	DAsyn	[¹⁸ F]DOPA	None	None, typical and atypical neuroleptics	n.s.	18/1	35 $\pm$ 12	22/9	32 $\pm$ 10	7 $\pm$ n.s.	n.s.	n.s.
Breier et al., 1997 <i>Same patients and controls; partly the same patients as Bertolino et al., 2000</i>	SZ	BPRS: 29 $\pm$ 7 BPRS: 29 $\pm$ 7	D ₂ DArel	[¹¹ C]raclopride [¹¹ C]raclopride	None None	None, antipsychotics None, antipsychotics	n.s. n.s.	8/3 8/3	32 $\pm$ 3 32 $\pm$ 3	9/3 9/3	29 $\pm$ 3 29 $\pm$ 3	7 $\pm$ 2 7 $\pm$ 2	n n	1095 1095
Bressan et al., 2003	SZ	PANSS: 65 $\pm$ n.s. PANSS _{pos} : 14 $\pm$ 3 PANSS _{neg} : 18 $\pm$ 3 PANSS _{tot} : 33 $\pm$ 10 CDSS: 6 $\pm$ 6 AIMS: 2 $\pm$ 5 SA: 1 $\pm$ 3 BAS: 3 $\pm$ 4 n.s.	D ₂	[¹²³ I]epidepride	None	Typical and atypical neuroleptics, SNRI, sodium channel blocker, anticholinergics	n.s.	7/1	31 $\pm$ 8	5/1	30 $\pm$ 3	n.s.	y	0
Brücke et al., 1991 <i>Partly the same patients as Küllerle et al., 1996, 1997 and Kasper et al., 1998 and the same controls as Küllerle et al., 1996, 1997, Kasper et al., 1998 and Barnas et al., 2001</i>	SZ, mania	n.s.	D ₂	[¹²³ I]IBZM	None, chronic pain	Typical and atypical neuroleptics	n.s.	12 (gender n.s.)	39 $\pm$ 19 (gender n.s.)	12 (gender n.s.)	53 $\pm$ 16	n.s.	y	0

Table 4 (continued)

Study	Disorder	Mean inventory scale score $\pm$ SD	Constituent	Ligand	Comorbidity	Premedication	Smoking	Patients (m/f)	Mean age $\pm$ SD (years)	Controls (m/f)	Mean age $\pm$ SD (years)	Mean duration $\pm$ SD (years)	Medication at the time of scanning	Duration of withdrawal (days)
Buchsbaum et al., 2006	SAD, SFD, SZ paranoid, undiff.	BPRS: 53 $\pm$ 9 AIMS: 2 $\pm$ n.s. CASH _{neg} : n.s. GAF: 30 $\pm$ 10 n.s.	D ₂	[¹¹ C]fallypride	None, alcohol abuse	None, neuroleptics	y/n	12/3	29 $\pm$ 9	9/6	27 $\pm$ 8	n.s.	n	n.s.
Caravaggio et al., 2015	SZ	n.s.	D _{2/3}	[¹¹ C](+)-PHNO	n.s.	Atypical neuroleptic (olanzapine)	n.s.	3/0	30 $\pm$ 16	6/4	29 $\pm$ 8	n.s.	y	0
Catafau et al., 2009	SZ	n.s.	D ₂	[¹²³ I]IBZM, [¹¹ C] raclopride	n.s.	Current: risperidone, olanzapine or clozapine for $\geq$ 1 month; co-medication: benzodiazepines, SSRIs, anticholinergics, lithium, anticonvulsant sodium channel blockers	n.s.	10/10	36 $\pm$ 10	5/5	26 $\pm$ 6	n.s.	y	0
Catafau et al., 2011	SZ	n.s.	D ₂	[¹²³ I]IBZM	n.s.	Previous: n.s. current: SB-773812 for 16–18 days	n.s.	10/4	33 $\pm$ 7	27/0	26 $\pm$ 5	n.s.	y	0
Same controls		n.s.	D ₂	[¹²³ I]IBZM	n.s.	Previous: n.s. current: SB-773812 or risperidone for 16–18 days	n.s.	12/0	36 $\pm$ 8	27/0	26 $\pm$ 5	n.s.	y	0
Chen et al., 2013	SZ	PANSS: 79 $\pm$ 22 PANSS _{neg} : 22 $\pm$ 6 PANSS _{pos} : 20 $\pm$ 7 PANSS _{gen} : 37 $\pm$ 11 CGI: 5 $\pm$ 1 GAF: 41 $\pm$ 15 PANSS: 71 $\pm$ 11 PAS: 63 $\pm$ 24	DAT	[^{99m} Tc]TRO-DAT	None	None	n.s.	26/21	27 $\pm$ 9	59/53	34 $\pm$ 12	1 $\pm$ 3	y	0
Corripio et al., 2006 Partly the same patients as Perez et al., 2003	SZ	PANSS: 71 $\pm$ 11 PAS: 63 $\pm$ 24	D ₂	[¹²³ I]IBZM	None	None	n.s.	3/8	24 $\pm$ 4	10/8	24 $\pm$ 5	n.s.	n	n.a.
Corripio et al., 2011	SZ	PANSS: 86 $\pm$ 16 PAS: 1 $\pm$ 0	D ₂	[¹²³ I]IBZM	None, substance abuse	None	y/n	18/7	28 $\pm$ 8	10/8	24 $\pm$ 5	1 $\pm$ n.s.	n	n.a.
Dao-Castellana et al., 1997	SAD, SZ disorg., undiff., catatonic	PANSS _{neg} : 21 $\pm$ 12 PANSS _{pos} : 33 $\pm$ 7 PANSS _{gen} : 43 $\pm$ 13	DAsyn	[¹⁸ F]DOPA	None	None, neuroleptics	n.s.	6/02	26 $\pm$ 9	7/0	25 $\pm$ 5	6 $\pm$ 8	n	84
de Haan et al., 2003	SZ paranoid, disorg., undiff.	PANSS: n.s. MADRS: n.s. SA: n.s. BAS: 0 $\pm$ 0	D ₂	[¹²³ I]IBZM	None	Previous: typical and atypical neuroleptics; current: haloperidol, olanzapine for 6 weeks; co-medication: benzodiazepine	n.s.	19/1	19 $\pm$ 6	9 (gender n.s.)	24 $\pm$ n.s.	n.s.	y	0
Demjaha et al., 2013	SZ paranoid	PANSS: 104 $\pm$ 11 PANSS _{pos} : 26 $\pm$ 4 GAF: 48 $\pm$ 4	DAsyn	[¹⁸ F]DOPA	None	Typical and atypical neuroleptics	y/n	5/9	46 $\pm$ 10	5/7	44 $\pm$ 9	16 $\pm$ 9	y	0
Same controls	SZ paranoid	PANSS: 51 $\pm$ 6 PANSS _{pos} : 12 $\pm$ 2 GAF: 68 $\pm$ 5	DAsyn	[¹⁸ F]DOPA	None	Typical and atypical neuroleptics	y/n	6/6	44 $\pm$ 12	5/7	44 $\pm$ 9	16 $\pm$ 9	y	0
Elkashef et al., 2000	SZ n.s.	n.s.	DAsyn	[¹⁸ F]DOPA	None	Typical and atypical neuroleptics	n.s.	15/4	36 $\pm$ 8	8/5	35 $\pm$ 11	17 $\pm$ 8	y/n	0

Table 4 (continued)

Study	Disorder	Mean inventory scale score $\pm$ SD	Constituent	Ligand	Comorbidity	Premedication	Smoking	Patients (m/f)	Mean age $\pm$ SD (years)	Controls (m/f)	Mean age $\pm$ SD (years)	Mean duration $\pm$ SD (years)	Medication at the time of scanning	Duration of withdrawal (days)
Fagerlund et al., 2013 <i>Partly the same patients as Gienhoj et al., 2006 and Norbak-Emig et al., 2016</i>	SZ paranoid, undiff., unspec.	PANSS: 70 $\pm$ 13 PANSS _{pos} : 20 $\pm$ 4 PANSS _{neg} : 20 $\pm$ 5 PANSS _{gen} : 30 $\pm$ 7	D _{2/3}	[¹²³ I] epideptide	Substance abuse	None	n.s.	16/8	27 $\pm$ 6	13/7	28 $\pm$ 5	n.s.	n	n.a.
Farde et al., 1987 Farde et al., 1990 <i>Some patients as Nordström et al., 1992</i>	SZ SZ paranoid, disorg., undiff., hebephrenic	n.s. CPRS: 12 $\pm$ 4	D ₂ D ₂	[¹¹ C]raclopride [¹¹ C]raclopride	n.s. None	None None, benzodiazepines	n.s. n.s.	9/6 10/8	24 $\pm$ 4 24 $\pm$ 3	10/4 10/10	29 $\pm$ 5 28 $\pm$ 5	<1 year >6 months	n n	n.a. 1
Gefvert et al., 1998 <i>Partly same controls as Nordström et al., 1992</i>	SZ, SFD	PANSS: 56 $\pm$ n.s CGI: 4 $\pm$ n.s	D ₁	[¹¹ C]SCH23390	n.s.	Previous: neuroleptics incl. clozapine, benzo diazepines; current: quetiapine for 29 days	n.s.	11/0	34 $\pm$ n.s.	n.s.	n.s.	n.s.	n	1
Gienhoj et al., 2006 <i>Partly the same patients as Fagerlund et al., 2013 and Norbak-Emig et al., 2016</i>	SZ	PANSS: 70 $\pm$ n.s. PANSS _{pos} : 20 $\pm$ n.s. PANSS _{neg} : 18 $\pm$ n.s. PANSS _{gen} : 30 $\pm$ n.s.	D ₂	[¹²³ I] epideptide	None, substance abuse	None, benzodiazepines	n.s.	17/8	27 $\pm$ n.s.	13/7	27 $\pm$ n.s.	n.s.	n	1
Griff-Guerrero et al., 2009	Z, SFD	PANSS: 75 $\pm$ n.s. PANSS _{pos} : 21 $\pm$ 7 PANSS _{neg} : 14 $\pm$ 6 PANSS _{gen} : 40 $\pm$ 5 BPRS: 53 $\pm$ 23	D ₂ /D ₃	[¹¹ C](+)-PHNO	None	None, neuroleptics	y/n	9/4	26 $\pm$ 6	9/4	27 $\pm$ 6	2 $\pm$ n.s.	n	14
Gray et al., 1995 <i>Partly the same patients as Pilowsky et al., 1994</i>	SFD, SZ paranoid, disorg., undiff.		D ₂	[¹²³ I]IBZM	n.s.	None, antipsychotics	n.s.	5/8	29 $\pm$ 5	12 (gender n.s.)	31 $\pm$ 2	1 $\pm$ 1	n	180
Hietala et al., 1994	SFD, SZ paranoid, disorg., undiff., catatonic	BPRS: 51 $\pm$ 19	D ₂	[¹¹ C]raclopride	None	None, neuroleptics, benzodiazepines	n.s.	9/4	25 $\pm$ 7	6/4	27 $\pm$ 7	1 $\pm$ 1	n	1
Hietala et al., 1995	SAD, SZ disorg., catatonic	PANSS: 81 $\pm$ 14	DAsyn	[¹⁸ F]DOPA	n.s.	None, benzodiazepines	n.s.	4/3	26 $\pm$ 7	6/2	27 $\pm$ 7	4 $\pm$ n.s.	n	14
Hietala et al., 1999 <i>Partly the same patients as Hietala et al., 1995</i>	SAD, SZ disorg., catatonic	PANSS: 78 $\pm$ 14	DAsyn	[¹⁸ F]DOPA	n.s.	None, benzodiazepines	n.s.	4/6	30 $\pm$ 9	8/5	30 $\pm$ 9	4 $\pm$ 3	n	14
Howes et al., 2009 <i>Same controls as Valli et al., 2008</i>	n.s.	PANSS: 62 $\pm$ 3 PANSS _{pos} : 17 $\pm$ 7 PANSS _{neg} : 16 $\pm$ 10 PANSS _{gen} : 29 $\pm$ 17 HDRS: 9 $\pm$ 12 HAM-A: 8 $\pm$ 13 CAARMS _{pos} : 50 $\pm$ 41 CAARMS _{neg} : 11 $\pm$ 8 PANSS _{pos} : n.s. PANSS _{neg} : n.s. PANSS _{gen} : n.s.	DAsyn	[¹⁸ F]DOPA	None	n.s.	n.s.	7 (gender n.s.)	36 $\pm$ 15	8/4	24 $\pm$ 5	n.s.	n	56
Hsiao et al., 2003	SZ	PANSS _{pos} : n.s. PANSS _{neg} : n.s. PANSS _{gen} : n.s.	DAT	[^{99m} Tc]TRO-DAT	None	None	n.s.	2/10	26 $\pm$ 8	2/10	30 $\pm$ 9	1 $\pm$ 1	n	n.a.
Joo et al., 2018	SZ	PANSS: 59 $\pm$ 18	D ₂	[¹⁸ F]fallypride	None	Atypical neuroleptics for $\geq$ 4 weeks	n.s.	6/10	37 $\pm$ 11	8/9	32 $\pm$ 10	7 $\pm$ 4	n.s.	n.s.
Karlsson et al., 2002	SZ, SFD	BPRS: 33–60	D ₁	[¹¹ C]SCH23390	None	None	n.s.	8/2	25 $\pm$ 2	8/2	26 $\pm$ 4	n.s.	n	n.a.

Table 4 (continued)

Study	Disorder	Mean inventory scale score $\pm$ SD	Constituent	Ligand	Comorbidity	Premedication	Smoking	Patients (m/f)	Mean age $\pm$ SD (years)	Controls (m/f)	Mean age $\pm$ SD (years)	Mean duration $\pm$ SD (years)	Medication at the time of scanning	Duration of withdrawal (days)
Kasper et al., 1998 <i>Partly the same patients as Küfferle et al., 1996, 1997, and Tauscher et al., 1999 and same controls as Küfferle et al., 1996, 1997, Tauscher et al., 1997, 1999, Barnas et al., 2001 and Brücke et al., 1991</i>	SZ	PANSS: 73 $\pm$ 22 BAS: 0 $\pm$ 0 EPS: 1 $\pm$ 1	D ₂	[¹²³ I]IBZM	None	Typical and atypical neuroleptics, benzodiazepines, anticholinergic	n.s.	5/5	31 $\pm$ 7	6/2	51 $\pm$ 17	n.s.	y	0
Kim et al., 2011	SZ paranoid, undiff., residual	PANSS: 75 $\pm$ 17 PANSS _{pos} : 17 $\pm$ 5 PANSS _{neg} : 19 $\pm$ 5 PANSS _{gen} : 39 $\pm$ 9 SA: 2 $\pm$ 2 BAS: 1 $\pm$ 1	D ₂	[¹¹ C]raclopride	None	Typical and atypical neuroleptics; co-medication: benzodiazepines	n.s.	7/14	35 $\pm$ 10	7/14	35 $\pm$ 10	8 $\pm$ 5	y	0
Kim et al., 2017	SZ	LUNERS: 47 $\pm$ 26 PANSS: 50 $\pm$ 10 PANSS _{pos} : 11 $\pm$ 3 PANSS _{neg} : 13 $\pm$ 4 PANSS _{gen} : 26 $\pm$ 5 PANSS: 94 $\pm$ 18 PANSS _{pos} : 19 $\pm$ 4 PANSS _{neg} : 29 $\pm$ 8 PANSS _{gen} : 46 $\pm$ 9 PANSS: 74 $\pm$ 24 PANSS _{pos} : 13 $\pm$ 6 PANSS _{neg} : 25 $\pm$ 8 PANSS _{gen} : 36 $\pm$ 12 SA: 7 $\pm$ 5 BAS: 2 $\pm$ 2	D ₂	[¹⁸ F]DOPA	n.s.	Atypical neuroleptics	n.s.	17/7	31 $\pm$ 9	8/4	30 $\pm$ 8	9 $\pm$ 9	y	0
Kosaka et al., 2010	SZ		D ₁	[¹¹ C]SCH23390 [¹¹ C]NNC112	n.s.	Antipsychotics incl. sulpiride	n.s.	5/1	47 $\pm$ 8	6/6	43 $\pm$ 9	18 $\pm$ 4	n.s.	n.s.
Küfferle et al., 1996 <i>Partly the same patients as Kasper et al., 1998 and Küfferle et al., 1997 and same controls as Brücke et al., 1991, Tauscher et al., 1997, Küfferle et al., 1997 and Barnas et al., 2001</i>	SZ, SAD, DD, psychotic disorder not otherwise specified		D ₂	[¹²³ I]IBZM	OCD	Typical neuroleptics for 14–80 days	n.s.	11/6	32 $\pm$ 9	6/2	51 $\pm$ 17	n.s.	y	0
Küfferle et al., 1997 <i>Partly the same patients as Küfferle et al., 1996, Kasper et al., 1998, and Tauscher et al., 1999 and same controls as Barnas et al., 2001, Brücke et al., 1991, and Küfferle et al., 1996</i>	SZ, SAD	CGI: 6 $\pm$ 2 SA: 4 $\pm$ 7 BAS: 1 $\pm$ 1	D ₂	[¹²³ I]IBZM	n.s.	Typical and atypical neuroleptics for 14 to 90 days; co-medication: benzodiazepines, anticholinergics	n.s.	12/6	31 $\pm$ 10	6/2	51 $\pm$ 17	n.s.	y	0
Kubota et al., 2017	SZ	PANSS: 78 $\pm$ 23 PANSS _{pos} : 14 $\pm$ 3 PANSS _{neg} : 12 $\pm$ 6 PANSS _{gen} : 52 $\pm$ n.s.	D ₂	[¹¹ C]raclopride	None	None, aripiprazole, benzodiazepines	y/n	4/7	34 $\pm$ 7	8/9	34 $\pm$ 10	3 $\pm$ 4	y/n	0

Table 4 (continued)

Study	Disorder	Mean inventory scale score $\pm$ SD	Constituent	Ligand	Comorbidity	Premedication	Smoking	Patients (m/f)	Mean age $\pm$ SD (years)	Controls (m/f)	Mean age $\pm$ SD (years)	Mean duration $\pm$ SD (years)	Medication at the time of scanning	Duration of withdrawal (days)
<i>Same patients and controls</i>	SZ	PANSS: 78 $\pm$ 23 PANSS _{pos} : 14 $\pm$ 3 PANSS _{neg} : 12 $\pm$ 6 PANSS _{neg} : 52 $\pm$ n.s.	D ₂	[¹¹ C]MMPA	None	None, aripiprazol, benzodiazepines	y/n	4/7	34 $\pm$ 7	8/9	34 $\pm$ 10	3 $\pm$ 4	y/n	0
Kumakura et al., 2007	n.s.	PANSS: 80 $\pm$ 5 PANSS _{pos} : 15 $\pm$ 4 PANSS _{neg} : 24 $\pm$ 40 n.s.	DA syn	[¹⁸ F]DOPA	None	None, neuroleptics	n.s.	8/0	37 $\pm$ 6	15/0	37 $\pm$ 6	n.s.	n	180
Künstler et al., 2000	SZ paranoid	n.s.	D ₂	[¹²³ I]IBZM	n.s.	Typical and atypical neuroleptics; co-medication: benzodiazepine	n.s.	10/13	38 $\pm$ 11	5/7	40 $\pm$ n.s.	Months to years	y	0
Laakso et al., 2000	SZ	PANSS: 73 $\pm$ 23	DAT	[¹¹ C]CFT	None	None	n.s.	6/3	30 $\pm$ 7	6/3	30 $\pm$ 6	2 $\pm$ n.s.	n	n.a.
Laruelle et al., 1996	SZ	PANSS _{pos} : 17 $\pm$ 2 PANSS _{neg} : 15 $\pm$ 2 BPRS: 37 $\pm$ 3	D ₂	[¹²³ I]IBZM	None	None, antipsychotics incl. benzodiazepines	n.s.	14/1	42 $\pm$ 2	14/1	41 $\pm$ 2	14 $\pm$ 2	n	1
<i>Partly same patients and controls as Laruelle and Abi-Dargham 1999, Laruelle et al., 1999, 2000</i>	SZ	PANSS _{pos} : 17 $\pm$ 2 PANSS _{neg} : 15 $\pm$ 2 BPRS: 37 $\pm$ 3	DATel	[¹²³ I]IBZM	None	None, antipsychotics incl. benzodiazepines	n.s.	14/1	42 $\pm$ 2	14/1	41 $\pm$ 2	14 $\pm$ 2	n	1
Laruelle et al., 1999	SZ	PANSS _{pos} : 18 $\pm$ 6 PANSS _{neg} : 17 $\pm$ 7	D ₂	[¹²³ I]IBZM	None	None, antipsychotics incl. benzodiazepines	n.s.	28/6	40 $\pm$ 9	32/4	40 $\pm$ 9	n.s.	n	142
<i>Partly same patients and controls as Laruelle et al., 1996, 2000, Laruelle and Abi-Dargham 1999</i>	SZ	PANSS _{pos} : 18 $\pm$ 6 PANSS _{neg} : 17 $\pm$ 7	DATel	[¹²³ I]IBZM	none	None, antipsychotics incl. benzodiazepines	n.s.	28/6	40 $\pm$ 9	32/4	40 $\pm$ 9	n.s.	n	142
Laruelle and Abi-Dargham 1999	SZ	PANSS _{pos} : 18 $\pm$ 6 PANSS _{neg} : 17 $\pm$ 7	D ₂	[¹²³ I]IBZM	None	None, antipsychotics incl. benzodiazepines	n.s.	28/6	40 $\pm$ 9	32/4	40 $\pm$ 9	n.s.	n	142
<i>Same patients and controls as Laruelle et al., 1996, 1999, 2000</i>	SZ	PANSS _{pos} : 18 $\pm$ 6 PANSS _{neg} : 17 $\pm$ 7	DATel	[¹²³ I]IBZM	None	None, antipsychotics incl. benzodiazepines	n.s.	28/6	40 $\pm$ 9	32/4	40 $\pm$ 9	n.s.	n	142
Laruelle et al., 2000	SZ	PANSS _{pos} : 18 $\pm$ 6 PANSS _{neg} : 17 $\pm$ 7	DAT	[¹²³ I]β-CIT	None	None, antipsychotics incl. benzodiazepines	n.s.	22/2	41 $\pm$ 8	20/2	39 $\pm$ 8	n.s.	n	142
<i>Partly same patients and controls as Laruelle et al., 1999, Laruelle and Abi-Dargham 1999</i>	SAD, SZ paranoid, disorg., undiff.	PANSS: 44 $\pm$ 8 PANSS _{pos} : 23 $\pm$ 4 PANSS _{neg} : 19 $\pm$ 7 MADRS: 23 $\pm$ 10	DAT	[¹²³ I]FP-CIT	n.s.	None	n.s.	9/1	22 $\pm$ 4	7/3	20 $\pm$ 1	3 $\pm$ 1	n	n.a.

Table 4 (continued)

Study	Disorder	Mean inventory scale score $\pm$ SD	Constituent	Ligand	Comorbidity	Premedication	Smoking	Patients (m/f)	Mean age $\pm$ SD (years)	Controls (m/f)	Mean age $\pm$ SD (years)	Mean duration $\pm$ SD (years)	Medication at the time of scanning	Duration of withdrawal (days)
Lehrer et al., 2010	SZ, SAD	BPRS: 52 $\pm$ 12	D ₂	[¹¹ C]flupyrone	n.s.	None, neuroleptics	n.s.	25/8	29 $\pm$ 11	11/7	29 $\pm$ 9	4 $\pm$ 5	n	30
Lindström et al., 1999	SZ, SFD	CGIS: 5 $\pm$ 1	D ₂ Asyn	[¹⁸ F]DOPA	n.s.	None, typical neuroleptics	n.s.	10/2	31 $\pm$ 8	8/2	n.s.	n.s.	n	730
Mamo et al., 2007	SZ, SAD	PANSS: 51 $\pm$ 12 AIMS: 1 $\pm$ 5 SA: 0 $\pm$ 1 BAS: 0 $\pm$ 1 CGI: 3 $\pm$ 1	D ₂	[¹¹ C]raclopride	n.s.	Previous: typical and atypical neuroleptics; current: aripiprazole for $\geq$ 14 days	n.s.	9/3	31 $\pm$ 7	60 (gender n.s.)	n.s.	8 $\pm$ n.s.	y	0
Mane et al., 2011	SZ, SFD, SAD	PANSS: 89 $\pm$ 16 PANSS _{pos} : 26 $\pm$ 6 PANSS _{neg} : 25 $\pm$ 9	DAT	[¹²³ I]FP-CIT	None	None	y/n	10 (gender n.s.)	n.s.	10 (gender n.s.)	n.s.	n.s.	n	n.a.
Partly same patients and controls	SZ, SFD, SAD	PANSS: 56 $\pm$ 16 PANSS _{pos} : 14 $\pm$ 6 PANSS _{neg} : 13 $\pm$ 4 GAF: 66 $\pm$ 16	DAT	[¹²³ I]FP-CIT	None	Atypical neuroleptics	y/n	9/5	27 $\pm$ 6	4/3	30 $\pm$ 5	n.s.	n.s.	n.s.
Martinot et al., 1989	SZ	SAPS: n.s.	D ₂	[⁷⁶ Br]JSP	n.s.	None, neuroleptics	n.s.	12/0	n.s.	12/0	n.s.	n.s.	n.s.	n.s.
Martinot et al., 1991	SZ paranoid, disorg., undiff., catatonic	SAPS: n.s.	D ₂	[⁷⁶ Br]lisuride	n.s.	None, neuroleptics, benzodiazepines	n.s.	12/7	23 $\pm$ 5	14/0	23 $\pm$ 4	2 $\pm$ n.s.	y/n	0
Martinot et al., 1994	SZ disorg., undiff.	SAPS: 19 $\pm$ 14 SANS: 87 $\pm$ 14 MADRS: 12 $\pm$ 3 DRS: 16 $\pm$ 4 PEF: 32 $\pm$ 11 PPS: 17 $\pm$ 7	D ₂	[⁷⁶ Br]lisuride	n.s.	None, neuroleptics	n.s.	7/3	20 $\pm$ 2	10/0	21 $\pm$ 2	n.s.	n	120
Mateos et al., 2005	SZ, SFD	PANSS: 48 $\pm$ 6 PANSS _{pos} : 28 $\pm$ 5 PANSS _{neg} : 25 $\pm$ 6 SA: 1 $\pm$ 1	DAT	[¹²³ I]FP-CIT	None, cannabis abuse	Current: risperidone for 4 weeks	n.s.	14/6	26 $\pm$ 5	6/4	27 $\pm$ 4	0.3 $\pm$ 0.2	n	0
Mateos et al., 2006	SZ, SFD	PANSS: 46 $\pm$ 7 PANSS _{pos} : 26 $\pm$ 7 PANSS _{neg} : 25 $\pm$ 7 SA: 1 $\pm$ 1	DAT	[¹²³ I]FP-CIT	None	Previous: none, current: risperidone for 4 weeks	n.s.	20/10	26 $\pm$ 6	8/7	29 $\pm$ 4	0.4 $\pm$ 0.2	n	0
Mateos et al., 2007	SZ, SFD	PANSS: 41 $\pm$ 8 PANSS _{pos} : 30 $\pm$ 7 PANSS _{neg} : 23 $\pm$ 8 SA: 1 $\pm$ 1	DAT	[¹²³ I]FP-CIT	None, cannabis abuse	None	n.s.	14/6	26 $\pm$ 3	8/7	29 $\pm$ 7	0.3 $\pm$ 0.2	n	n.a.
Partly the same patients and controls as Mateos et al., 2006	SZ, SFD	PANSS: 41 $\pm$ 8 PANSS _{pos} : 30 $\pm$ 7 PANSS _{neg} : 23 $\pm$ 8 SA: 1 $\pm$ 1	DAT	[¹²³ I]FP-CIT	None, cannabis abuse	Current: risperidone for 4 weeks	n.s.	14/6	26 $\pm$ 3	8/7	29 $\pm$ 7	0.3 $\pm$ 0.2	y	0
McGowan et al., 2004	n.s.	AIMS: 0.1 CASH _{total} : 11 CASH _{pos} : 4 CASH _{neg} : 6	D ₂ Asyn	[¹⁸ F]DOPA	None	None, typical and atypical neuroleptics	n.s.	16 (gender n.s.)	40 $\pm$ 11	12 (gender n.s.)	38 $\pm$ 7	n.s.	n.s.	n.s.
Subgroup of the subjects assessed by Bose et al., 2008	SAD, SZ paranoid, disorg	EPS _{part} : 3 $\pm$ 4 EPS _{total} : 0 $\pm$ 1 EPS _{neg} : 1 $\pm$ 4	D ₂	[¹²³ I]IBZM	n.s.	Previous: antipsychotics; current: olanzapine for at least 2 weeks	n.s.	12/8	34 $\pm$ 12	6/4	32 $\pm$ 13	n.s.	y	0

Table 4 (continued)

Study	Disorder	Mean inventory scale score $\pm$ SD	Constituent	Ligand	Comorbidity	Premedication	Smoking	Patients (m/f)	Mean age $\pm$ SD (years)	Controls (m/f)	Mean age $\pm$ SD (years)	Mean duration $\pm$ SD (years)	Medication at the time of scanning	Duration of withdrawal (days)
Meisenzahl et al., 2008	SZ, SAD	PANSS: 106 $\pm$ 18 SANS: 58 $\pm$ 17 BPRS: 64 $\pm$ 10 EPS: n.s. EPS ^{park} : n.s. EPS ^{dysk} : n.s. EPS ^{dyt} : n.s.	D ₂	[¹²³ I]IBZM	None	Previous: none, anti- psychotics; current: typical and atypical neuroleptics for 2 weeks; co-medication: benzodiazepine, non- benzodiazepine GABA _A agonist, anticholinergic Psychotropics incl. antidepressants	n.s.	19/10	32 $\pm$ 12	n.s.	n.s.	n.s.	n	0.5
Mizrahi et al., 2012 <i>Partly the same patients as Suridjan et al., 2013 and Tseng et al., 2017</i>	SZ, SFD	PANSS _{pos} : 19 $\pm$ 4	D ₂	[¹¹ C](+)-PHNO	None, AD, substance abuse		y/n	7/3	24 $\pm$ 5	7/5	26 $\pm$ 4	n.s.	y	0
Nakajima et al., 2015	SZ, SAD	PANSS: 83 $\pm$ 29 PANSS _{pos} : 23 $\pm$ 9 PANSS _{neg} : 20 $\pm$ 8 PANSS _{gen} : 40 $\pm$ 14 BPRS: 55 $\pm$ 19 AIMS: 1 $\pm$ 2 SA: 1 $\pm$ 1 BAS: 0 $\pm$ 0 CIRS-G: 2 $\pm$ 1	D ₂	[¹¹ C]raclopride	None	None, antipsychotics	n.s.	5/5	66 $\pm$ 12	5/5	63 $\pm$ 9	35 $\pm$ 17	n	90
Norbak-Emig et al., 2016 <i>Partly the same patients as Glenthøj et al., 2006 and Fagerlund et al., 2013</i>	SZ paranoid, undiff., unspec.	PANSS: 70 $\pm$ 13 PANSS _{pos} : 20 $\pm$ 4 PANSS _{neg} : 20 $\pm$ 6 PANSS _{gen} : 30 $\pm$ 7	D _{2/3}	[¹²³ I]leptideptide	Substance abuse	None, SSRIs	n.s.	18/7	27 $\pm$ 5	12/7	26 $\pm$ 4	2 $\pm$ 2	n.s.	n.s.
Nordström et al., 1992 <i>Same patients as Farde et al., 1990; partly the same controls as Gefvert et al., 1998</i>	SZ	CPRS: 12 $\pm$ 4	D ₂	[¹¹ C]raclopride	n.s.	None	n.s.	10/8	24 $\pm$ 3	25 (gender n.s.)	n.s.	n.s.	n	n.a.
Nordström et al., 1995a	SZ, SFD	CGI: n.s.	D ₂	[¹¹ C]raclopride	n.s.	Previous: classical neuroleptics; current: clozapine for 2 months to 7 years	n.s.	9/7	36 $\pm$ 11	34 (gender n.s.)	18–50 years	n.s.	y	0
Nordström et al., 1995b <i>Same patients and controls</i>	SFD, SZ undiff.	BPRS: 33 $\pm$ 4	D ₂	[¹¹ C]MSP	None	None, benzodiazepines	n.s.	5/2	28 $\pm$ 6	7/7	28 $\pm$ 7	2 months to >3 years	n	n.s.
Nozaki et al., 2009	SFD, SZ undiff. controls	BPRS: 33 $\pm$ 4	D ₂	[¹¹ C]MSP	None	Current: haloperidol	n.s.	5/2	28 $\pm$ 6	7/7	28 $\pm$ 7	2 months to >3 years	n	n.s.
	SZ, SFD	PANSS: 79 $\pm$ 21 PANSS _{pos} : 23 $\pm$ 7 PANSS _{neg} : 17 $\pm$ 7 PANSS _{gen} : 40 $\pm$ 11	DAsyn	[¹⁸ F]DOPA	None	None, antipsychotics	y/n	10/8	36 $\pm$ 7	10/10	35 $\pm$ 10	n.s.	n	120
Paquet et al., 2004	SZ paranoid, disorg., undiff., residual	PANSS: 50 $\pm$ n.s. PANSS _{pos} : 12 $\pm$ 5 PANSS _{neg} : 13 $\pm$ 4 PANSS _{gen} : 25 $\pm$ 6	D ₂	[¹²³ I]IBZM	None	Haloperidol or olanzapine for $\geq$ 3 months; co-medication: anticholinergics	y/n	30 (gender n.s.)	35 $\pm$ 10 (gender n.s.)	30 (gender n.s.)	33 $\pm$ 9	n.s.	y	0

Table 4 (continued)

Study	Disorder	Mean inventory scale score $\pm$ SD	Constituent	Ligand	Comorbidity	Premedication	Smoking	Patients (m/f)	Mean age $\pm$ SD (years)	Controls (m/f)	Mean age $\pm$ SD (years)	Mean duration $\pm$ SD (years)	Medication at the time of scanning	Duration of withdrawal (days)
Pedro et al., 1994 <i>Same patients and controls as Pilowsky et al., 1994</i>	SFD, SZ paranoid, disorg., undiff.,	BAS: 1 $\pm$ 1 EPS _{par} : 2 $\pm$ 3 EPS _{gen} : 1 $\pm$ 2 EPS _{day} : 0 $\pm$ 0	D ₂	[¹²³ I]IBZM	n.s.	None, antipsychotics	n.s.	6/6	34 $\pm$ 10	9/6	33 $\pm$ n.s.	2 $\pm$ 4	n	180
		BPRS: 56 $\pm$ 10 BPRS _{par} : 22 $\pm$ 7 BPRS _{gen} : 9 $\pm$ 5												
		PANSS: 69 $\pm$ 10 BPRS: 25 $\pm$ 6 PAS: 27 $\pm$ 13 BPRS: 42 $\pm$ 9												
		BPRS: 45 $\pm$ 11 GAS: 31 $\pm$ 10												
		BPRS: 45 $\pm$ 12 GAS: 31 $\pm$ 9												
Pilowsky et al., 1992	SZ	BPRS: 45 $\pm$ 11 GAS: 31 $\pm$ 10	D ₂	[¹²³ I]IBZM	n.s.	Current: clozapine for $\geq$ 4 months Typical neuroleptics	n.s.	11/3	31 $\pm$ 7	12 (gender n.s.) 14 (gender n.s.)	36 $\pm$ 7 n.s.	n.s. 9 $\pm$ 5	y y	0 0
Pilowsky et al., 1993	SZ	BPRS: 45 $\pm$ 12 GAS: 31 $\pm$ 9	D ₂	[¹²³ I]IBZM	None	Typical and atypical neuroleptics	n.s.	12/6	31 $\pm$ 6	12 (gender n.s.)	n.s.	9 $\pm$ 8	y	0
Pilowsky et al., 1994 <i>Partly the same patients and controls as Pedro et al., 1994</i> <i>Partly the same patients as Gray et al., 1995</i>	SFD, SZ paranoid, disorg., undiff., catatonic	BPRS: 60 $\pm$ 10	D ₂	[¹²³ I]IBZM	n.s.	None, antipsychotics	n.s.	11/9	31 $\pm$ 8	11/9 (gender n.s.)	31 $\pm$ 8	3 $\pm$ 4	n	180
Poels et al., 2013	SZ, SAD	PANSS: 64 $\pm$ 15	D ₁	[¹¹ C]SCH23390	None	None, antipsychotics incl. benzodiazepines	n.s.	4/3	28 $\pm$ 11	6/5	31 $\pm$ 10	7 $\pm$ n.s.	n	1
Same patients and controls	SZ, SAD	PANSS: 64 $\pm$ 15	D ₁	[¹¹ C]NMC212	None	None, antipsychotics incl. benzodiazepines	n.s.	4/3	28 $\pm$ 11	6/5	31 $\pm$ 10	7 $\pm$ n.s.	n	1
Pogarell et al., 2012	SZ	PANSS: 76 $\pm$ 18	D ₂	[¹²³ I]IBZM	None	n.s.	n.s.	7/1	25 $\pm$ 6	4/3	24 $\pm$ 3	2 $\pm$ 1	n	7
Same patients and controls	SZ	PANSS: 76 $\pm$ 18	D ₂	[¹²³ I]IBZM	None	n.s.	n.s.	7/1	25 $\pm$ 6	4/3	24 $\pm$ 3	2 $\pm$ 1	n	7
Reith et al., 1994	SZ paranoid, residual undiff. psychosis	PANSS _{par} : 14 $\pm$ 3 PANSS _{gen} : 12 $\pm$ 2 BPRS: 24 $\pm$ 4 n.s.	D _{Asyn}	[¹⁸ F]DOPA	None	None, neuroleptics	n.s.	5/0	38 $\pm$ 4	9/4	36 $\pm$ 13	n.s.	n	1095
Same controls			D _{Asyn}	[¹⁸ F]DOPA	Epilepsy	Neuroleptics, anticonvulsants	n.s.	1/4	39 $\pm$ 5	9/4	36 $\pm$ 13	n.s.	y	0
Ring et al., 1994	Psychosis	PSE: n.s.	D ₂	[¹²³ I]IBZM	Epilepsy	Anticonvulsant sodium channel blockers, anticonvulsant carbonic anhydrase inhibitors, barbiturates	n.s.	5/2	35 $\pm$ n.s.	3/4	41 $\pm$ n.s.	n.s.	y	0
Safont et al., 2011	Psychosis	PANSS: 82 $\pm$ 14 PANSS _{par} : 25 $\pm$ 5 PANSS _{gen} : 15 $\pm$ 7 PANSS _{neg} : 41 $\pm$ 7 n.s.	D ₂	[¹²³ I]IBZM	None, cannabis or nicotine abuse	None	y/n	25/12	28 $\pm$ 7	10/8	24 $\pm$ 5	<1 year	n	n.a.
Schmitt et al., 2002	SAD, SZ paranoid, disorg.		D ₂	[¹²³ I]IBZM	n.s.	Previous: none, neuroleptics; current: risperidone, olanzapine for $\geq$ 1 week; co-medication: TCAs, anticholinergics, benzodiazepines	n.s.	16/17	37 $\pm$ 13	10 (gender n.s.)	n.s.	n.s.	y	0

Table 4 (continued)

Study	Disorder	Mean inventory scale score±SD	Constituent	Ligand	Comorbidity	Premedication	Smoking	Patients (m/f)	Mean age±SD (years)	Controls (m/f)	Mean age±SD (years)	Mean duration±SD (years)	Medication at the time of scanning	Duration of withdrawal (days)
Halvick et al., 2003	SZ paranoid	PANSS: 83±23 PANSS _{pos} : 23±7 PANSS _{neg} : 19±11	D ₂ /D ₃	[¹¹ C]FLB457	None	None, benzodiazepine	n.s.	3/6	36±12	8 (gender n.s.)	n.s.	3±2	y/n	0
		PANSS _{gen} : 40±11												
		PANSS: 80±21 PANSS _{pos} : 22±5 PANSS _{neg} : 20±10 PANSS _{gen} : 38±11 PANSS: 76±21 PANSS _{pos} : 17±9 PANSS _{neg} : 23±10 PANSS _{gen} : 36±4 EPS: 4±3												
Halvick et al., 2006	SFD, SZ paranoid, disorg.		D ₂	[¹¹ C]raclopride	None	None	n.s.	9/9	29±11	13/4	17–50 years	3±2	n	n.a.
Tauscher et al., 1997 <i>Partly the same controls as Tauscher et al., 1999, Küfferle et al., 1996, 1997, Kasper et al., 1998, Barnas et al., 2001 and Brücke et al., 1991</i>	SZ paranoid, disorg.		D ₂	[¹²³ I]IBZM	n.s.	<i>Previous</i> : typical neuroleptics; <i>current</i> : quetiapine for ≥14 days	n.s.	2/0	34±1	6/2	51±17	n.s.	y	0
Tauscher et al., 1999 <i>Partly the same patients as Küfferle et al., 1997 and Kasper et al., 1998 and partly the same controls as Tauscher et al., 1999, Küfferle et al., 1996, 1997, Kasper et al., 1998, Barnas et al., 2001 and Brücke et al., 1991</i>	SAD, SZ paranoid, undiff.	CGI: 7±2 EPS: 2±3 BAS: 2±2	D ₂	[¹²³ I]IBZM	n.s.	<i>Current</i> : haloperidol, olanzapine or clozapine for ≥14 days; co-medication: benzodiazepines, anticholinergics	n.s.	2/4	33±14	6/2	51±17	n.s.	y	0
Thompson et al., 2014 <i>Partly the same controls as Abi- Daugham et al., 2002, 2012</i>	SPD	n.s.	D ₁	[¹¹ C]NINC212	None, substance abuse	None, antipsychotics	y/n	12/6	42±7	14/7	41±6	n.s.	n	21
Ibbo et al., 1997	SZ	BPRS: 18±3 GAF: 65±3	D ₂	[¹²³ I]epidepride	None	Typical neuroleptics	n.s.	11/2	37±3	10/3	33±2	7±3	n	
Tseng et al., 2018 <i>Partly the same patients as Suridjan et al., 2013 and Mirzahi et al., 2012</i>	SZ	PANSS _{pos} : 19±4 PANSS _{neg} : 17±4	D ₁ rel	[¹¹ C](+)-PHNO	None, substance abuse	None	y/n	6/3	24±5	13/12	25±4	n.s.	n	n.a.
Tune et al., 1993 <i>Partly the same patients as Wong et al., 1997 and Tune et al., 1996</i>	SZ paranoid, undiff.	BPRS: 47±n.s. SANS: 38±n.s. PSE: 13±2 MMSE: 28±1 HDRS: 3±1 BPRS: n.s.	D ₂	[¹¹ C]MSP	None	None, neuroleptics	n.s.	17/8	35±7	13/4	39±6	6±2	n	28
Tune et al., 1996 <i>Same patients as Tune et al., 1993</i>	SZ	PANSS _{pos} : 89±18 PANSS _{neg} : 23±6 PANSS _{pos} : 22±7 PANSS _{neg} : 43±7	D ₂	[¹²³ I]epidepride	None	None	n.s.	3/4	32±14	4/3	31±9	1±n.s.	n	n.a.

Table 4 (continued)

Study	Disorder	Mean inventory scale score $\pm$ SD	Constituent	Ligand	Comorbidity	Premedication	Smoking	Patients (m/f)	Mean age $\pm$ SD (years)	Controls (m/f)	Mean age $\pm$ SD (years)	Mean duration $\pm$ SD (years)	Medication at the time of scanning	Duration of withdrawal (days)
Tuppurainen et al., 2006 <i>Same patients and controls</i>	SZ	PANSS: 89 $\pm$ 18 PANSS _{pos} : 23 $\pm$ 6 PANSS _{neg} : 22 $\pm$ 7 PANSS _{gen} : 43 $\pm$ 7	D ₂	[¹²³ I] epidepride	None	None	n.s.	3/4	32 $\pm$ 14	4/3	31 $\pm$ 9	1 $\pm$ n.s.	n	n.a.
Tuppurainen et al., 2003	SZ, SAD	PANSS: 49 $\pm$ 13 MMSE: 29 $\pm$ 1	D ₂	[¹¹ C]raclopride	n.s.	Previous: bn.s. current: risperidone for $\geq$ 6 weeks; co-medication: benzodiazepine, μ -opioid agonist Anticholinergics	n.s.	4 (gender n.s.)	61 $\pm$ 3	12 (gender n.s.)	n.s.	39 $\pm$ 7	n	0
Vallabhajosula et al., 1997 <i>Same patients and controls</i>	SZ	n.s.	D ₂	[¹²³ I]IBZM	n.s.	n.s.	n.s.	2/1	32 $\pm$ 5	2/1	45–48 years	n.s.	n	14
Vall et al., 2008 <i>Same controls as Howes et al., 2009</i>	SZ	n.s.	D ₂	[¹²³ I]IBZM	n.s.	Current: haloperidol for 6 weeks	n.s.	1/1	34 $\pm$ 4	2/1	45–48 years	n.s.	y	0
Vermaleken et al., 2004	SZ paranoid	'acute'; score n.s.	DAsyn	[¹⁸ F]DOPA	n.s.	n.s.	n.s.	1/0	58 $\pm$ n.s.	8/4	24 $\pm$ 5	n.s.	n	2920
Weinstein et al., 2018	SZ	PANSS: 76 $\pm$ 19 SA: 16 $\pm$ 5	D ₂	[¹⁸ F]DMFP	None	Current: amisulpride for $\geq$ 2 weeks; comedication: benzodiazepines, non- benzodiazepine GABA _A agonists, lithium	n.s.	6/3	36 $\pm$ 13	12/0	35 $\pm$ 16	8 $\pm$ n.s.	y	0
Same patients and controls	SZ, SAD, SFD	PANSS: 68 $\pm$ 25 PANSS _{pos} : 17 $\pm$ 7 PANSS _{neg} : 17 $\pm$ 6 PANSS _{gen} : 34 $\pm$ 14	D ₂	[¹¹ C]raclopride	n.s.	None, neuroleptics	y/n	7/3	34 $\pm$ 12	6/3	32 $\pm$ 8	n.s.	n	21
Wong et al., 1986	SZ	PANSS: 68 $\pm$ 25 PANSS _{pos} : 17 $\pm$ 7 PANSS _{neg} : 17 $\pm$ 6 PANSS _{gen} : 34 $\pm$ 14 BPRS: n.s. MMSE: n.s.	DAel	[¹¹ C]raclopride	n.s.	None, neuroleptics	y/n	7/3	34 $\pm$ 12	6/3	32 $\pm$ 8	n.s.	n	21
Wong et al., 1997 <i>Partly the same patients as Tune et al., 1993, 1996</i>	Psychosis	HDRS: 7 $\pm$ 6 MADRS: 10 $\pm$ 10 MAPRS: 5 $\pm$ 5 YMRS: 18 $\pm$ 16 BPRS: 34 $\pm$ 32 PPDP: 52 $\pm$ 28 PSE: 9 $\pm$ 11	D ₂	[¹¹ C]MSP	None	None, neuroleptics	n.s.	13/2	29 $\pm$ 3	9/2	n.s.	5 $\pm$ 5	n	18
Same controls Wulff et al., 2015	SZ paranoid, undiff. SZ paranoid, undiff., disorg., unspec.	PANSS: 81 $\pm$ 15 PANSS _{pos} : 20 $\pm$ 4 PANSS _{neg} : 20 $\pm$ 8 PANSS _{gen} : 41 $\pm$ 8 GAF-f: 42 $\pm$ 12 GAF-s: 40 $\pm$ 9 SWNS: 67 $\pm$ 14	D ₂	[¹¹ C]MSP [¹²³ I]IBZM	None	None, antidepressants	n.s.	3/9 14/14	45 $\pm$ 24 23 $\pm$ 4	19/5 13/13	40 $\pm$ 22 23 $\pm$ 5	n.s. 1 $\pm$ 2	n.s. n	n.s. 30

Table 4 (continued)

Study	Disorder	Mean inventory scale score $\pm$ SD	Constituent	Ligand	Comorbidity	Premedication	Smoking	Patients (m/f)	Mean age $\pm$ SD (years)	Controls (m/f)	Mean age $\pm$ SD (years)	Mean duration $\pm$ SD (years)	Medication at the time of scanning	Duration of withdrawal (days)
Xiberas et al., 2001	SZ	PANSS _{pos} : 17 $\pm$ 5 PANSS _{neg} : 24 $\pm$ 5	D ₂	[¹⁸ F]FLB457	None	Current: typical and atypical neuroleptics for at least 25 days; co-medication: anticholinergics, benzodiazepines	n.s.	16/3	32 $\pm$ 7	6/0	24 $\pm$ 4	n.s.	y	0
Yang et al., 2003	SZ	BPRS: 28 $\pm$ 6 SA: 3 $\pm$ 3	D ₂	[¹²³ I]IBZM	None	None, typical and atypical neuroleptics	n.s.	8/12	27 $\pm$ 10	10/10	36 $\pm$ 9	n.s.	y/n	0
Yang et al., 2004	SZ paranoid, disorg., undiff.	PANSS: 64 $\pm$ 11	DAT	[^{99m} Tc]TRODAT	None	None	n.s.	6/5	25 $\pm$ 10	9/3	33 $\pm$ 13	1 $\pm$ 2	n	n.a.
Same patients and controls	SZ paranoid, disorg., undiff.	PANSS: 64 $\pm$ 11	D ₂	[¹²³ I]IBZM	None	None	n.s.	6/5	25 $\pm$ 10	9/3	33 $\pm$ 13	1 $\pm$ 2	n	n.a.
Yasuno et al., 2004	SZ	BPRS: 29 $\pm$ 9 BPRS _{pos} : 15 $\pm$ 5 BPRS _{neg} : 6 $\pm$ 5	D ₂	[¹¹ C]FLB457	None	None	n.s.	10/0	30 $\pm$ 8	19/0	30 $\pm$ 8	2 $\pm$ n.s.	n	n.a.
Partly the same patients as Suhara et al., 2002														
Yoder et al., 2004	SZ	PANSS _{pos} : n.s. PANSS _{neg} : n.s. PANSS _{gen} : n.s. AIMS: n.s.	DAT	[¹¹ C]β-CFT	None, tardive dyskinesia	None, neuroleptics	n.s.	8/2	41 $\pm$ 11	10 (gender n.s.)	45 $\pm$ 18	n.s.	y/n	0

Given are the reference (in alphabetical order), the subtype of disorder, mean rating scale scores ($\pm$ SD), employed radioligands comorbidities, premедication, cigarette smoking habits, numbers of (male and female) patients and controls, mean age of patients and controls ($\pm$ SD; years), mean duration of disease ($\pm$ SD; years), medication state at the time of the investigation and duration of withdrawal (days). Abbreviations (in alphabetical order): AD, anxiety disorder; AIMS, Abnormal Involuntary Movement Scale; BAS, Barnes Scale for Drug-induced Akathisia; BD, bipolar disorder; BMRS, Blackburn mania rating scale; BPRS, Brief Psychiatric Rating Scale – positive symptoms; BPRS_{neg}, Brief Psychiatric Rating Scale – negative symptoms; CAARMS_{tot}, Comprehensive Assessment of At-Risk – total; CAARMS_{pos}, Comprehensive Assessment of At-Risk – positive symptoms; CASH_{neg}, Andreason's Comprehensive Assessment of Symptoms and History Scale – total score; CASH_{pos}, Andreason's Comprehensive Assessment of Symptoms and History scale – positive symptoms score; CASH_{neg}, Andreason's Comprehensive Assessment of Symptoms and History scale – negative symptoms score; CDSS, Calgary Depression Rating Scale for Schizophrenia; CGI, Clinical Global Impression Scale; CPRS, Comprehensive Psychopathologic Rating Scale; CIRS-G, Cumulative Illness Rating Scale for Geriatrics; DA, dopamine; DAT, dopamine transporter; D₁, dopamine D₁ receptor; D₂, dopamine D₂ receptor; D_{2/3}, dopamine D_{2/3} receptor; DAREL, dopamine release; DAsyn, dopamine synthesis; DD, delusional disorder; DRS, Depressive Retardation rating scale; EPS, Extrapyramidal Symptoms Scale; EPS_{park}, Extrapyramidal Symptoms Scale – parkinsonism; EPS_{dysk}, Extrapyramidal Symptoms Scale – dyskinesia; EPS_{dysk}, Extrapyramidal Symptoms Scale – dystonia; f, female; GABA_A, GABA_A receptor; GAF-f, Global Assessment of Functioning – functioning score; GAF-s, Global Assessment of Functioning – symptom score; GAS, Endicott's Global Assessment Scale; HAMA, Hamilton Anxiety Rating Scale; HDRS, Hamilton Depression Rating Scale; LUNERS, Liverpool University Neuroleptic Side Effects Rating Scale; m, male; MADRS, Montgomery Asberg Depression Rating Scale; MAPRS, Montgomery Asberg Psychopathology Rating Scale; MMSE, Mini Mental State Examination; n, no; n.a., not applicable; n.s., not specified in the original investigation; PANSS_{pos}, Positive and Negative Syndrome Scale; PANSS_{neg}, Positive and Negative Syndrome Scale – general Negative Syndrome Scale; PANSS_{gen}, Positive and Negative Syndrome Scale; PANSS_{gen}, Positive and Negative Syndrome Scale; PAs, Premorbid Adjustment Scale; PEF, Psychomotor Expressiveness Factor; PPdP, PAs-Peyer-dePaulo Affective Symptom Rating Scale; PPS, Psychomotor Poverty Syndrome psychopathology score; PAs, Premorbid Adjustment Scale; PEF, Psychomotor Expressiveness Factor; PPdP, PAs-Peyer-dePaulo Affective Symptom Rating Scale; PPS, Psychomotor Poverty Syndrome; PSE, Present State Examination; SA, Simpson and Angus scale for parkinsonian symptoms; SAD, schizoaffective disorder; SANS, Andreason's Scale for Assessment of Negative Symptoms; SAPS, Andreason's Scale for Assessment of Positive Symptoms; SFD, schizophrenia from disorder; SNRI, selective norepinephrine reuptake inhibitor; SPD, schizotypal personality disorder; SSRI, selective serotonin reuptake inhibitor; SZ, schizophrenia; SWNS, Subjective Well-being Under Neuroleptics Scale (short version); y, yes; y/n, yes/no; YMRS, Young Mania Rating Scale.

DAT

Figure 1: State of *in vivo* findings on DAT binding in anxiety disorder (AD), major depressive disorder (MDD), the manic state of bipolar disorder (BD_{man}), the depressive state of bipolar disorder (BD_{dep}) and schizophrenia (SZ).

Considered were 12 studies on AD (155 patients, age: 38 ± 4 years; 170 controls, age: 39 ± 10 years), 22 studies on MDD (343 patients, age: 41 ± 12 years; 546 controls, age: 40 ± 13 years), one study on BD_{man} (one patient, age: 25 years; 10 controls, age: 26 ± 6 years), four studies on BD_{dep} (46 patients, age: 41 ± 1 years; 150 controls, age: 38 ± 2 years) and 11 studies on SZ (184 patients, age: 31 ± 7 years; 134 controls, age: 33 ± 7 years), in which DAT was assessed in neostriatum (STR), ventral striatum (VS), thalamus (THAL), prefrontal cortex (PFC), frontal cortex (FC), parietal cortex (PC), temporal cortex (TC), occipital cortex (OC), cingulate (CING), hippocampus (HIPP), amygdala (AMYG), midbrain/pons (MB), substantia nigra (SN), locus caeruleus (LC) and cerebellum (CER). The box plots give medians, 25th/75th percentiles (boxes) and 5th/95th percentiles (whiskers) of DAT binding in the investigated brain regions expressed as percentages of control values. The circles represent the percentages of control values in the individual investigations (white circles, percentual difference relative to controls not significant in the original investigation; black circles, percentual difference relative to controls significant in the original investigation with a p of at least 0.05). Asterisks indicate significant differences of the pooled samples of AD, MDD, BD_{dep} , BD_{man} or SZ patients relative to the pooled samples of controls or significant differences between pooled samples of AD, MDD, BD_{dep} , BD_{man} or SZ (Mann-Whitney U -test, one-sided, $\alpha = 0.05$).

and DA synthesis (Figure 4) did not differ between patients and healthy individuals in the STR ($n=1$, each).

No studies of VMAT2 binding and DA release were available on BD_{man} .

 BD_{dep}

DAT (Figure 1) was not different from healthy subjects in the STR ($n=4$).

D_1R (Figure 2) was lowered in the FC ($n=1$, -31% , $p < 0.05$), but unaltered in the STR ($n=1$) relative to healthy controls.

No investigations were available on VMAT2, D_2R , DA synthesis and DA release in BD_{dep} patients.

SZ

DAT (Figure 1) was decreased in the STR compared to healthy individuals ($n=16$, -2% , $p=0.011$).

D_1R (Figure 2) was elevated in VS ($n=5$, $+10\%$, $p=0.002$), PFC ($n=5$, $+21\%$, $p=0.047$), FC ($n=9$, $+14\%$, $p=0.017$), PC ($n=3$, $+13\%$, $p=0.019$) and OC ($n=4$, $+10\%$, $p=0.007$). No difference relative to controls were observed in STR ($n=8$), TC ($n=5$), CING ($n=5$), HIPP ($n=1$), PHG ($n=1$) and AMYG ($n=1$).

D_2R (Figure 3) was decreased in STR ($n=79$, -5% , $p=0.025$), THAL ($n=14$, -8% , $p=0.006$), TC ($n=11$, -15% , $p=0.035$) and MB ($n=1$, -16% , $p < 0.05$). A further reduction was observed in the VS ($n=9$, -7% , $p=0.058$), which

D₁R

Figure 2: State of *in vivo* findings on D₁R binding in anxiety disorder (AD), major depressive disorder (MDD), the manic state of bipolar disorder (BD_{man}), the depressive state of bipolar disorder (BD_{dep}) and schizophrenia (SZ).

Considered were 1 study on AD (seven patients, age: 40 ± 14 years; seven controls, age: 40 ± 12 years), two studies on MDD (28 patients, age: 37 ± 9 years; 14 controls, age: 36 ± 7 years), one study on BD_{man} (1 patient, age: 37 years; 29 controls, age: 20–72 years), one study on BD_{dep} (one patient, age: 37 years; 21 controls, age: 20–72 years) and eight studies on SZ (98 patients, age: 33 ± 9 years; 113 controls, age: 32 ± 6 years), in which D₁R were assessed in neostriatum (STR), ventral striatum (VS), thalamus (THAL), prefrontal cortex (PFC), frontal cortex (FC), parietal cortex (PC), temporal cortex (TC), occipital cortex (OC), cingulate (CING), hippocampus (HIPPPHG), parahippocampal gyrus (PHG), amygdala (AMYG) and insula (INS). The box plots give medians, 25th/75th percentiles (boxes) and 5th/95th percentiles (whiskers) of D₁R binding in the investigated brain regions expressed as percentages of control values. The circles represent the percentages of control values in the individual investigations (white circles, percentual difference relative to controls not significant in the original investigation; black circles, percentual difference relative to controls significant in the original investigation with a *p* of at least 0.05). Asterisks indicate significant differences of the pooled samples of AD, MDD, BD_{dep}, BD_{man} or SZ patients relative to the pooled samples of controls or significant differences between pooled samples of AD, MDD, BD_{dep}, BD_{man} or SZ (Mann-Whitney *U*-test, one-sided, $\alpha = 0.05$).

marginally failed to reach statistical significance. No differences to controls were obtained in GP (*n*=3), PFC (*n*=3), FC (*n*=8), PC (*n*=2), OC (*n*=2), CING (*n*=3), HIPPPHG (*n*=3), AMYG (*n*=2), INS (*n*=2), MB (*n*=1) and SN (*n*=4).

DA synthesis (Figure 4) was increased in STR (*n*=16, +10%, $p < 0.001$), CING (*n*=4, +3%, $p = 0.024$), AMYG (*n*=1, +53%, $p < 0.05$) and MB (*n*=1, +52%, $p < 0.05$). Moreover, an elevation was observed in the TC (*n*=3, +2%, $p = 0.061$), which marginally failed to reach statistical significance. No differences were found in VS (*n*=5), THAL (*n*=1), PFC (*n*=3), FC (*n*=4), PHG (*n*=1), SN (*n*=1), VTA (*n*=1) and CER (*n*=1).

DA release (Figure 5) was elevated in STR (*n*=10, +80%, $p < 0.001$) and VS (*n*=2, +43%, $p = 0.051$).

No alterations were observed in THAL (*n*=1), PFC (*n*=1), FC (*n*=1), PC (*n*=1), TC (*n*=1), CING (*n*=1), PHG (*n*=1), AMYG (*n*=1), INS (*n*=1), SN (*n*=2) and VTA (*n*=1).

So far, no investigation of VMAT2 has been conducted on SZ.

Comparison between disorders

DAT

DAT (Figure 1) was lowered in the STR (−17%, $p = 0.051$) of SZ patients relative to BD_{man}. There were no differences

D_2R

Figure 3: State of *in vivo* findings on D_2R binding in anxiety disorder (AD), major depressive disorder (MDD), the manic state of bipolar disorder (BD_{man}) and schizophrenia (SZ).

Considered were 11 studies on AD (128 patients, age: 33 ± 5 years; 121 controls, age: 31 ± 4 years), 18 studies on MDD (242 patients, age: 42 ± 7 years; 248 controls, age: 41 ± 10 years), one study on BD_{man} (13 patients, age: 33 ± 12 years; 24 controls, age: 32 ± 12 years) and 68 studies on SZ (1068 patients, age: 32 ± 8 years; 1018 controls, age: 32 ± 9 years), in which D_2R were assessed in neostriatum (STR), ventral striatum (VS), globus pallidus (GP), thalamus (THAL), prefrontal cortex (PFC), frontal cortex (FC), parietal cortex (PC), temporal cortex (TC), occipital cortex (OC), cingulate (CING), hippocampus (HIPPI), amygdala (AMYG), insula (INS), midbrain/pons (MB), substantia nigra (SN) and cerebellum (CER). The box plots give medians, 25th/75th percentiles (boxes) and 5th/95th percentiles (whiskers) of D_2R binding in the investigated brain regions expressed as percentages of control values. The circles represent the percentages of control values in the individual investigations (white circles, percentual difference relative to controls not significant in the original investigation; black circles, percentual difference relative to controls significant in the original investigation with a p of at least 0.05). Asterisks indicate significant differences of the pooled samples of AD, MDD, BD_{man} or SZ patients relative to the pooled samples of controls or significant differences between pooled samples of AD, MDD, BD_{man} or SZ (Mann-Whitney U -test, one-sided, $\alpha = 0.05$).

between AD and BD_{man} (STR), AD and BD_{man} (STR), AD and MDD (STR, VS), AD and SZ (STR), BD_{man} and BD_{dep} (STR), BD_{man} and MDD (STR), BD_{dep} and MDD (STR, FC), and BD_{dep} and SZ (STR).

D_1R

Reductions of D_1R (Figure 2) in the STR of AD patients relative to SZ (-32% , $p = 0.06$), and in the FC of BD_{dep} patients relative to SZ (-39% , $p = 0.058$) marginally failed to reach statistical significance. No differences were observed between AD and BD_{man} (STR), AD and MDD (STR), BD_{man} and BD_{dep} (STR, FC), BD_{man} and MDD (STR), BD_{man} and SZ (STR, FC), BD_{dep} and MDD (STR),

BD_{dep} and SZ (STR, FC) and MDD and SZ (STR, VS, CING, AMYG).

D_2R

D_2R (Figure 3) was diminished in the STR of AD compared to MDD patients ($+22\%$, $p = 0.0001$). Moreover, a decrement was observed in the VS (-16% , $p = 0.069$) of AD patients relative to MDD, which, however, marginally failed to reach statistical significance. D_2R was reduced in the STR of SZ patients relative to MDD (-6% , $p = 0.025$), whereas no differences between disorders were found in VS, THAL, FC, TC, CING and AMYG. No differences were observed between AD and SZ (STR, VS), BD_{man} and MDD

DA synthesis

Figure 4: State of *in vivo* findings on DA synthesis in major depressive disorder (MDD), the manic state of bipolar disorder (BD_{man}), and schizophrenia (SZ).

Considered were six studies on MDD (65 patients, age: 43 ± 5 years; 67 controls, age: 40 ± 7 years), one study on BD_{man} (13 patients, age: 33 ± 12 years; 13 controls, age: 32 ± 12 years), and 14 studies on SZ (152 patients, age: 37 ± 8 years; 190 controls, age: 31 ± 10 years), in which DA synthesis was assessed in neostriatum (STR), ventral striatum (VS), thalamus (THAL), prefrontal cortex (PFC), frontal cortex (FC), temporal cortex (TC), cingulate (CING), hippocampus (HIPP), parahippocampal gyrus (PHG), amygdala (AMYG), midbrain/pons (MB), substantia nigra (SN), ventral tegmental area (VTA) and cerebellum (CER). The box plots give medians, 25th/75th percentiles and 5th/95th percentiles of the individual synaptic constituents in the investigated brain regions expressed as percentages of control values. The box plots give medians, 25th/75th percentiles (boxes) and 5th/95th percentiles (whiskers) of DA synthesis in the investigated brain regions expressed as percentages of control values. The circles represent the percentages of control values in the individual investigations (white circles, percentual difference relative to controls not significant in the original investigation; black circles, percentual difference relative to controls significant in the original investigation with a p of at least 0.05). Asterisks indicate significant differences of the pooled samples of MDD, BD_{man} or SZ patients relative to the pooled samples of controls or significant differences between pooled samples of MDD, BD_{man} or SZ (Mann-Whitney U -test, one-sided, $\alpha = 0.05$).

(STR), BD_{man} and SZ (STR). Due to the lack of data, no comparisons were possible between AD and BD_{dep}, BD_{man} and BD_{dep} and BD_{dep} and MDD.

DA synthesis

DA synthesis was decreased in the STR of MDD patients relative to SZ (-8% , $p = 0.015$). In contrast, prefrontal ($+68\%$, $p = 0.002$) and frontal DA synthesis ($+68\%$, $p = 0.016$) were elevated in MDD compared to SZ. No differences were observed between MDD and BD_{man} (STR) and SZ and BD_{man} (STR). Due to the lack of data, no comparisons were possible between AD and MDD, AD and

BD_{man}, AD and BD_{dep}, AD and SZ, BD_{man} and BD_{dep}, BD_{man} and BD_{dep} and SZ.

DA release

DA release was augmented in the STR of SZ patients relative to AD ($+61\%$, $p = 0.043$) and MDD ($+82\%$, $p = 0.009$), whereas no difference was observed between AD and MDD. Likewise, no differences between SZ and AD and SZ and MDD were detected in the VS. Due to the lack of data, no comparisons were possible between AD and BD_{man}, AD and BD_{dep}, BD_{man} and BD_{dep}, BD_{man} and MDD, BD_{dep} and MDD, BD_{man} and SZ, and BD_{dep} and SZ.

DA release

Figure 5: State of *in vivo* findings on DA release in anxiety disorder (AD), major depressive disorder (MDD) and schizophrenia (SZ). Considered were 2 studies on AD [20 patients, age: not specified (n.s.); 22 controls, age: n.s.], three studies on MDD (30 patients, age: 36 ± 0.2 years; 38 controls, age: 29 ± 2 years), and 10 studies on SZ (113 patients, age: 32 ± 6 years; 133 controls, age: 32 ± 6 years), in which DA release was assessed in neostriatum (STR), ventral striatum (VS), thalamus (THAL), prefrontal cortex (PFC), frontal cortex (FC), parietal cortex (PC), temporal cortex (TC), cingulate (CING), parahippocampal gyrus (PHG), amygdala (AMYG), insula (INS), substantia nigra (SN) and ventral tegmental area (VTA). The box plots give medians, 25th/75th percentiles (boxes) and 5th/95th percentiles (whiskers) of DA release in the investigated brain regions expressed as percentages of control values. The circles represent the percentages of control values in the individual investigations (white circles, percentual difference relative to controls not significant in the original investigation; black circles, percentual difference relative to controls significant in the original investigation with a *p* of at least 0.05). Asterisks indicate significant differences of the pooled samples of AD, MDD or SZ patients relative to the pooled samples of controls or significant differences between pooled samples of AD, MDD or SZ (Mann-Whitney *U*-test, one-sided, $\alpha = 0.05$).

Discussion

Role of neurotransmitters in neuropsychiatric disorders

AD

AD patients displayed a reduction of D_1R in the STR, reductions of D_2R in STR and VS and an elevation of DA release in the STR.

In addition, previous analyses of 5-HT and GABA function (including those findings, which had been obtained in merely one investigation) had revealed decreases of SERT in THAL, hypothalamus (HT), AMYG and MB, decreases of 5-HT_{1R} in MB, PFC, FC, TC, CING, HIPPO, PHG, AMYG, INS and fusiform gyrus (FG), a decrease of 5-HT_{2R} in the VS,

an elevation of 5-HT_{2R} in TC, decreases of GABA_AR in STR, FC, TC, OC, CING, AMYG, INS and entorhinal cortex (EC) and an increase of GABA_AR in the PHG (Table 5; Nikolaus et al., 2014b, 2016).

It is known that GABA exerts inhibitory effects on both DA (Grace and Bunney, 1979) and 5-HT neurons (Luparini et al., 2004). Moreover, DA inhibits the release of GABA (Girault et al., 1986) and 5-HT (Ferre et al., 1994) via D_2R action. 5-HT, in turn, stimulates the release of both DA (Ichikawa and Meltzer, 1995, 2000) and GABA (Cozzi and Nichols, 1996) via 5-HT_{1/2R} and 5-HT_{2R}, respectively.

On the basis of these interactions, it may be hypothesized that, in AD, the initial deficit is either the abnormal elevation of DA in the STR or the elevation of GABA throughout the nigrostriatal/mesolimbocortical system. If the abundant release of neostriatal DA occurs first in order, neostriatal DA levels are bound to be elevated

Table 5: *In vivo* findings on DA (VMAT, DAT, D₁R, D₂R, DA synthesis [DAsyn], DA release [DArel]), 5-HT (SERT, 5-HT_{1A}R, 5-HT_{2A}R, 5-HT synthesis [5-HTsyn]) and GABA function (GABA_AR) in anxiety disorder (AD) major depressive disorder (MDD), bipolar disorder in manic (BD_{man}) or depressed condition (BD_{dep}) and schizophrenia (SZ).

[illegible]

Table 5 (continued)

Disorder	Region	VMAT2	DAT	D ₁ R	D ₂ R	DAsyn	DArel	SERT	5-HT _{1A} R	5-HT _{2A} R	5-HTsyn	GABA _A R
BD _{dep}	OC									↓		
	CING											
	HIPP											
	PHG											
	AMYG											
	INS									↓		
	FG									↓		
	EC											
	MB							↑				
	SN											
	VTA											
	LC											
	PAG											
	CER											
	STR		=	=				=				
	VS							↓				
	GP											
	HT											
	THAL							=				
	PFC								↑			
	FC			↓					↑			
	PC								=			
	TC								=			
	OC								=			
	CING							↑				
	HIPP							↓		↑		
	PHG									↑		
	AMYG									↑		
	INS							↑		=		
	FG											
	EC											
	MB							=		=		
	SN							=				
	VTA											
	LC											
	PAG											
SZ	CER											
	STR		↓	=	↓	↑	↑	=		=		=
	VS			↑	=	=	↑	=		=		
	GP				=							
	HT											
	THAL			=	↓	=	=	=		=		=
	PFC			↑	=	=	=		=	=		=
	FC			↑	=	=	=		=	↓		↓
	PC			↑	=	=	=		=	=		=
	TC			=	↓	=	=		↓	↓		↓
	OC			↑	=				↓	↓		=
	CING			=	=	↑	=	=	=	=		=
	HIPP			=	=			=	=	=		=
	PHG			=		=	=		=			=
	AMYG			=	=	↑	=	=	↓	=		=
	INS			=	=		=	=	=			=
	FG											
	EC							=		=		
	MB				↓	↑		=	↓			
	SN				=	=	=	=	=	=		=
	VTA					=	=					

Table 5 (continued)

Disorder	Region	VMAT2	DAT	D ₁ R	D ₂ R	DAsyn	DARel	SERT	5-HT _{1A} R	5-HT _{2A} R	5-HTsyn	GABA _A R
	LC											
	PAG											
	CER					=						

Displayed are significant increases (↑), significant decreases (↓) or no alterations (=) relative to healthy controls as obtained from the present and previous analyses (Nikolaus et al., 2014a,b, 2016) in the following brain regions: neostriatum (STR), ventral striatum (VS), globus pallidus (GP), hypothalamus (HT), thalamus (THAL), prefrontal cortex (PFC), frontal cortex (FC), parietal cortex (PC), temporal cortex (TC), occipital cortex (OC), cingulate (CING), hippocampus (HIP), parahippocampal gyrus (PHG), amygdala (AMYG), insula (INS), fusiform gyrus (FG), entorhinal cortex (EC), midbrain /pons (MB), substantia nigra (SN), ventral tegmental area (VTA), locus caeruleus (LC), periaqueductal gray (PAG), cerebellum (CER).

(as DAT density in this region is normal), leading to the observed desensitization of D₁R and D₂R in STR and VS. DA inhibits the release of GABA and 5-HT via D₂R action (Girault et al., 1986; Ferre et al., 1994). Hence, the desensitization of striatal D₂ heteroreceptors incurs, for one, the elevation of GABA concentrations in the STR as well as in the projection areas of striatohalamocortical GABAergic neurons, which is consistent with the detected desensitization of GABA_AR in STR, FC, TC, OC, CING, AMYG, INS and EC of AD patients. Secondly, also 5-HT levels are likely to be augmented, which is consistent with the observed desensitization of SERT in MB, THAL, HT and AMYG, of 5-HT₁R in MB, PFC, FC, TC, CING, HIP, PHG, AMYG, INS and FG and of 5-HT₂R in the VS.

If, however, the elevation of GABA constitutes the initial deficit, the likely consequence, for one, is the observed desensitization of GABA_AR throughout the nigrostriatal and mesolimbocortical system. Since GABA exerts inhibitory effects on both DA (Grace and Bunney, 1979) and 5-HT neurons (Luparini et al., 2004), the desensitization of GABA_AR in striatal, neocortical and limbic regions, secondly, diminishes the inhibitory GABAergic input to DA and 5-HT neurons leading to an elevation of both DA and 5-HT concentrations throughout the nigrostriatal/mesolimbocortical system (as reflected by the desensitizations of D₁R, D₂R and 5-HT₁R). Likely, an important role may be ascribed to the PHG, which displays an elevation of GABA_AR binding sites, indicative of GABA shortage in this region (see below).

DA and 5-HT concentrations are regulated by autoreceptors of the D₂R and 5-HT₁R subtype, respectively, which are localized at the presynaptic terminal and modulate neurotransmitter synthesis and release via inhibitory feedback loops (for a review see Chiodo et al., 1995). Thus, irrespective to the site of primary neurochemical dysfunction, the desensitizations of inhibitory D₂ autoreceptors in STR and VS and 5-HT₁ autoreceptors in MB, PFC, FC, TC, CING, HIP, PHG, AMYG, INS and

FG reduce feedback inhibition, resulting in a further enhancement of DA efflux in STR/VS and of 5-HT efflux in mesencephalic, neocortical, cingulate and limbic regions.

The desensitization of D₁, D₂, 5-HT₁ and 5-HT₂ heteroreceptors in the respective regions may be conceived to reflect adaptive responses to the increased availability of monoamines. Firstly, the desensitization of D₁ heteroreceptors in the STR can be surmised to lead to a compensatory decline of excitatory input to the nigral, neocortical and limbic target regions of descending and ascending projections. Secondly, the desensitization of D₂ heteroreceptors in STR and VS is likely to reduce also the inhibitory input to the nigral, ventral tegmental, neocortical and limbic target regions of descending and ascending DAergic projections. Thirdly, since 5-HT₁R stimulate the release of DA (Ichikawa and Meltzer, 1995, 2000), the desensitization of 5-HT₁ heteroreceptors in MB, neocortex and limbic system likely induces an adaptive reduction of DA efflux in these regions. As, however, so far, no *in vivo* imaging studies have been conducted on DA synthesis and DA release in MB, neocortex and limbic system, further investigations are required to either confirm or refute this hypothesis. Fourthly, the desensitization of 5-HT₁ heteroreceptors in MB, neocortex and limbic system presumably reduces the inhibitory input to the target regions of descending and ascending 5-HTergic projections.

While excitatory D₁R and inhibitory D₂R both are desensitized in the STR, excitatory 5-HT₂R (in contrast to 5-HT₁R) is unaltered throughout most part of the neocortex with a significant elevation in the TC (Nikolaus et al., 2016). The sensitization of temporal 5-HT₂R may ultimately constitute an adaptive response to the desensitization of 5-HT₂R in the VS, as the latter may be assumed to reduce not only ventrostriatal excitation but also the net excitatory input to the target regions of ascending 5-HTergic fibers. Due to the small number of investigations, the observation of both decreased 5-HT₂R in the VS (n=1)

and increased 5-HT₂R in the TC (n=2), however, must be viewed with caution. Yet, it can not be dismissed that the alterations of excitatory 5-HTergic actions relative to controls may be related to the role of the TC and its limbic connections in self-awareness (for a review see Chavoix and Insausti, 2017) and emotional learning and memory (for a review see Grosso et al., 2015), functions, which are presumably disturbed in acute AD.

Taken together, the condition of acute AD is characterized by an abundance of neo- and ventrostriatal DA, mesencephalic, thalamic/hypothalamic, cingulate, neocortical (PFC, FC, TC), and limbic (HIP, PHG, AMYG, INS, FG) 5-HT and neostriatal, neocortical (FC, TC, OC), cingulate and limbic (AMYG, INS, EC) GABA. Thereby, sensitization and desensitization mechanisms likely result in a net overweight of excitatory DAergic and 5-HTergic neurotransmission. Arguably, the underlying deficit is either an abnormal elevation of neostriatal DA release or the elevation of GABA throughout the nigrostriatal/mesolimbocortical system.

MDD

MDD patients displayed reductions of DAT in PFC, FC, CING, AMYG, SN and LC, a reduction of D₁R in STR, an elevation of D₂R in the CING, an elevation of DA synthesis in PFC and FC and an elevation of DA release in the VS.

Furthermore, a previous analysis had evidenced reductions of SERT in STR, THAL, PFC, MB and AMYG, an elevation of SERT in the INS, a reduction of 5-HT₁R in the MB, an elevation of 5-HT₁R in the PHG, reductions of 5-HT₂R in CING, PFC, FC, OC, INS and FG, an increase of 5-HT₂R in the THAL, reductions of 5-HT synthesis in the CING, but no alterations of GABA_AR in OC and MB (Table 5; Nikolaus et al., 2014b, 2016).

The observed desensitizations of 5-HT₁R and 5-HT₂R in MB, CING, PFC, FC, OC, INS and FG may be interpreted to reflect an increased availability of 5-HT in these regions. 5-HT synthesis is not different from healthy controls in STR, THAL and PFC, but diminished in FC, TC and CING (Nikolaus et al., 2016). As no impairment of GABA_AR function and even a sensitization of CING D₂R has been detected, no effect of D₂R or GABA_AR desensitization on 5-HT levels can be inferred. Rather, the extensive reduction of SERT in MB, STR, THAL, PFC and AMYG implies that SERT hypofunction constitutes the initial deficit in MDD, leading to an abundance of 5-HT throughout the mesolimbocortical system. This is underlined by genetic studies, which show an association between polymorphisms of the SERT gene *SLC6A4* and the risk to develop

depression and suicidality (Ho et al., 2013). In the THAL, the finding of SERT desensitization is opposed to the finding of 5-HT₂R sensitization, which, in contrast, reflects a decreased availability of 5-HT. Thereby, it must be borne in mind that – although pooling of the available studies on thalamic SERT binding has yielded a median reduction – the findings obtained in the individual studies had been widely discrepant, showing increases, decreases or no alteration relative to controls (Nikolaus et al., 2016). As the finding of thalamic 5-HT₂R sensitization was obtained in merely one study, further investigations are needed to determine the exact role of thalamic 5-HT in MDD. So far, the most likely solution of the present contradiction is that thalamic 5-HT₂R sensitization occurs in a subset of patients displaying a sensitization of the thalamic SERT, leading to increased neurotransmitter reuptake into the presynaptic terminal and subsequent 5-HT shortage.

Corresponding to AD, the desensitization of mesencephalic 5-HT₁ autoreceptors reduces feedback inhibition, resulting in an enhancement of 5-HT release and a further augmentation of mesencephalic 5-HT levels. Contary to AD, however, the desensitization of 5-HT₁R is confined to the MB and does not involve frontal, cingulate and limbic regions. Thus, in MDD, there is no adaptive reduction of inhibitory neurotransmission in these areas. Rather, limbic inhibition is enhanced via sensitization of 5-HT₁ heteroreceptors in the PHG, with the sensitization of 5-HT₁ autoreceptors additionally reducing parahippocampal 5-HT efflux. This indicates entirely different routes of cognitive and emotional processing in AD and MDD. Thereby, in either disorder, a relevant role may be played by the PHG, which is relevant for processing contextual associations (for a review see Aminoff et al., 2013), and displays sensitizations of 5-HT₁R in MDD and GABA_AR in AD. A further compensation of 5-HT abundance is achieved in MDD by the desensitization of 5-HT₂R in CING, PFC, FC, OC INS and FG (none of which is present in AD), leading to a decline of excitatory neocortical, cingulate and limbic neurotransmission.

As 5-HT₂R is desensitized in CING, PFC, FC, OC, CING, INS and FG, the consequence ought to be a reduction of DA efflux in these regions. DA synthesis and DA release, however, are increased in PFC/FC and VS, respectively, implying augmented DA concentrations, and, thusly, an increase of DA action in the descending and ascending projections of the mesolimbocortical system. Interestingly, in line with SERT hypofunction in the MB, DAT is desensitized in PFC, FC, CING and AMYG, leading to a further increase of DA availability in prefrontal/frontal, cingulate and limbic regions. Possibly, the enhancement of DA synthesis in PFC/FC and of DA release in the VS, together with

the desensitization of DAT in PFC/FC, CING and AMYG constitute adaptive responses, aiming to maintain (or even enhance) mesolimbocortical DA function. Thereby, the desensitization of DAT in the SN is likely to incur an elevation of nigral DA to some level, which may eventually account for the normality of DA synthesis, DA release, DAT and D₂R function in the STR.

MDD patients display a desensitization of striatal D₁R. As the striatal D₂R density is not different from controls, this can not be interpreted in terms of an adaptive response to an abundance of striatal DA. Rather, due to the higher expression of D₁R relative to D₂R in neocortical tissues (Palacios et al., 1988), the elevation of prefrontal/frontal DA levels is likely to induce a net increase of excitatory action in the descending fibers of the nigrostriatal and mesolimbocortical pathways, which requires compensation by the observed desensitization of striatal D₁R.

D₂R is sensitized in the CING, which reflects DA shortage. Since 5-HT stimulates DA efflux via 5-HT_{1/2}R (Ichikawa and Meltzer, 1995, 2000), an association can be inferred between the desensitization of 5-HT₂R in the CING and the implied reduction of DA. The assumption of DA shortage, however, is not consistent with the normal D₁R binding in the CING, although the latter finding must be viewed with reserve, since it was obtained in merely one investigation. As the CING is relevant for the processing of emotion and social behavior (for a review see Hadland et al., 2003), further investigations are required to elucidate the exact role of cingulate 5-HT and DA function in MDD, and, for that matter, also AD and BD, on which *in vivo* studies of CING D₂R binding are completely lacking.

Taken together, MDD is characterized by an abundance of ventrostriatal and prefrontal/frontal DA and mesencephalic, neostriatal, thalamic, cingulate, prefrontal/frontal, insular and fusiform 5-HT, while striatal DA and mesencephalic GABA levels are normal. Sensitization and desensitization mechanism likely result in a net reduction of excitatory DA and 5-HT action. Arguably, the initial deficit is SERT hypofunction. As, however, findings on GABA_AR function are limited to MB and OC, further investigations are needed to clarify the exact role of GABA_AR in acute MDD.

BD

BD_{man} patients displayed an increase of DAT in the STR and a reduction of D₁R in the FC. In addition, previous analyses had revealed an increase of SERT in the MB as well as decreases of 5-HT₂R in FC, PC, TC, OC, INS and FG (Nikolaus et al., 2016, 2017).

BD_{dep} patients showed a decrease of D₁R in the FC, while precedent analyses had additionally evidenced a decrease of SERT in VS and HIPPP, an increase of SERT in CING and INS, and increases of 5-HT₁R in PFC, FC, HIPPP, PHG and AMYG (Nikolaus et al., 2016, 2017). GABA_AR binding, so far, has neither been assessed in BD_{man} nor in BD_{dep} (Table 5).

In BD_{man}, striatal DA synthesis, D₁R and D₂R are not different from healthy controls. Strikingly, however, frontal D₁R is diminished, which – contrary to AD, but similar to MDD – reflects an increased availability of frontal DA.

So far, studies on 5-HT synthesis and GABA_AR are lacking in BD_{man}. However, the desensitization 5-HT₂R in FC, PC, TC, OC, INS and FG may be interpreted as an adaptive response to the enhanced availability of 5-HT in neocortical and limbic target regions of ascending 5-HTergic fibers. In line with this assumption, the sensitization of MB SERT may be conceived as an adaptation to elevated 5-HT concentrations at the site of origin of ascending 5-HTergic neurons.

Since 5-HT stimulates DA release via 5-HT_{1/2}R (Ichikawa and Meltzer, 1995, 2000), the desensitization of these binding sites in the neocortex can be assumed to (though not effectively) diminish cortical DA concentrations and – together with the desensitization of frontal D₁R – to reduce the (excitatory) DAergic input to the mesolimbic target regions of descending DA neurons (Nikolaus et al., 2017). Interestingly, striatal DAT is augmented in BD_{man}, reflecting an increased availability of DA in this region. Although this finding must be viewed with caution, since it was obtained in merely one investigation, it may not be excluded that the elevation of DAT density constitutes the very mechanism granting normal striatal DA levels and normal D₁R and D₂R binding.

Similar to BD_{man}, striatal D₁R does not differ between BD_{dep} and healthy controls, whereas frontal D₁R is diminished, suggesting increased availability of frontal DA also in BD_{dep}. In BD_{dep}, SERT is decreased in VS and HIPPP, which reflects diminished levels of mesolimbic 5-HT. Interestingly, however, SERT binding is increased in CING and INS (implying high 5-HT), whereas both cingulate and insular 5-HT₁ auto- and heteroreceptor binding are normal. It is striking that, also in MDD, SERT binding is elevated in the INS (in contrast to the AMYG), while insular 5-HT₁ auto- and heteroreceptor binding is unaltered relative to healthy controls (Nikolaus et al., 2016). This, possibly, indicates that the INS (and in BD_{dep} also the CING) contain a higher basal amount of 5-HT than VS, HIPPP and AMYG in BD_{dep} and MDD, which, via increased sensitization of the SERT, is effectively transported back into the presynaptic terminals.

The relative shortage of 5-HT in VS and HIPPO may incur a reduction of 5-HTergic input to the neocortical and limbic target regions of mesolimbic projections, which likely results in the observed sensitization of inhibitory prefrontal/frontal and limbic 5-HT₁ heteroreceptors, ultimately enhancing the inhibitory input to the target regions of prefrontal/frontal and limbic projections. As 5-HT stimulates DA release via 5-HT_{1/2}R action (Ichikawa and Meltzer, 1995, 2000), the sensitization of frontal 5-HT₁R also in BD_{dep} will lead to an augmentation of DA release, entailing the observed desensitization of frontal D₁R. Yet, on the other hand, the sensitization of inhibitory 5-HT₁ autoreceptors in prefrontal/frontal cortex and limbic system increases the inhibitory action of the negative feedback loop, secondarily leading to a further aggravation of 5-HT shortage.

Taken together, both BD_{man} and BD_{dep} are characterized by elevated frontal DA. However, increased mesencephalic, limbic (INS, FG) and frontoparietotemporooccipital 5-HT underlie the condition of BD_{man}, whereas BD_{dep} patients display decreased prefrontal/frontal and mesolimbic 5-HT levels. Notably, different neocortical and limbic regions are involved in BD_{man} and BD_{dep}. The abundance of 5-HT in BD_{man} may be either due to increased 5-HT synthesis (which, so far, has not been assessed *in vivo* imaging studies) or to still insufficient sensitization of SERT. Another cause might be a persistent desensitization of 5-HT₁ autoreceptors, which, however, warrants further investigation in *in vivo* imaging studies. In turn, the shortage of prefrontal and limbic 5-HT in BD_{dep} may be either due to reduced 5-HT synthesis or to a persistent 5-HT₁ autoreceptor sensitization, either of which is still awaiting further *in vivo* assessment.

SZ

SZ patients showed reductions of DAT in the STR, increases of D₁R in VS, PFC, FC, PC and OC, reductions of D₂R in STR, THAL, TC and MB, increases of DA synthesis in STR, CING, AMYG and MB as well as increases of DA release in STR and VS.

Furthermore, previous analyses had yielded reductions of 5-HT₁R in TC, OC, MB and AMYG, reductions of 5-HT₂R in FC, TC and OC as well as reductions of GABA_AR in FC and TC (Table 5; Nikolaus et al., 2014b, 2016).

Given the known association between SZ and variations of the GABA_AR gene (Cherlyn et al., 2010), it may be hypothesized that defects of the GABA_AR gene – and, thus, of GABA_AR dysfunction – constitute the initial deficit in SZ with a decrease of GABA_AR density in FC

and TC lowering the inhibitory input to the target regions of descending corticothalamostriatal projections. The likely consequence would be the abundance of DA and 5-HT as reflected by the the observed augmentation of DA synthesis and release in MB, STR, VS, CING and AMYG as well as by the desensitizations of D₂R in STR, THAL and TC, 5-HT₁R in TC, OC, MB and AMYG and 5-HT₂R in FC, TC and OC.

On the other hand, it may be argued that the initial deficit in SZ, rather, is excess DA synthesis (in STR, MB, CING and AMYG) and DA release (in STR and VS), leading to the increased availability of DA in the striatothalamocortical pathway and the observed desensitization of D₂R in STR, THAL, TC and MB. Thereby, the desensitization of inhibitory D₂ autoreceptors in STR, THAL, TC and MB will reduce the feedback inhibition, ultimately leading to a further enhancement of DA release, while the desensitization of D₂ heteroreceptors will result in the reduction of inhibitory input to the target regions of ascending and descending DAergic fibers.

As D₂R inhibit the release of GABA and 5-HT (Girault et al., 1986; Ferre et al., 1994), a further consequence of D₂R desensitization will be an augmentation of GABA efflux in the neocortical projection areas of ascending GABAergic neurons, which is consistent with the observed desensitization of GABA_AR in FC and TC.

Also 5-HT levels are likely to be increased, which is in agreement with the observed desensitizations of 5-HT₁R in MB, TC, OC and AMYG and of 5-HT₂R in FC, TC and OC. Thereby, for one, the desensitization of 5-HT₁ autoreceptors in MB, TC, OC and AMYG will disinhibit the feedback loop, resulting in a further enhancement of 5-HT efflux in mesencephalic, neocortical and limbic regions. Secondly, the desensitization of 5-HT₁ and 5-HT₂ heteroreceptors will lead to a compensatory reduction of both inhibitory and excitatory action in the target regions of ascending and descending 5-HT neurons. Thirdly, the desensitization of 5-HT_{1/2}R sites in the neocortex, can be assumed to diminish DA concentrations in the neocortex and in the ventrostriatal target region of descending DAergic projections, which is consistent with the detected sensitization of D₁R in VST, PFC, FC, PC and OC.

Strikingly, the sensitization of D₁R in VST, PFC, FC, PC and OC, as opposed to the desensitization of D₂R in STR, THAL, TC and MB, implies regional differences of DA levels in SZ, with an increased availability in the striatothalamocortical and a decreased availability in the mesolimbocortical pathway. Similarly, findings in MDD had evidenced regional differences in 5-HT levels, with an increased availability in MB, CING and neocortex but a decreased availability in the PHG.

Taken together, acute SZ is characterized by an abundance of mesencephalic, neostriatal, thalamic, cingulate, temporal and amygdalar DA, but DA shortage in VS, PFC, FC, PC and OC. Further features are GABA abundance in FC and TC and 5-HT abundance in MB, FC, TC, OC and AMYG. Sensitization and desensitization mechanisms likely result in a net reduction of inhibitory DA action. The initial deficit may be either GABA_AR dysfunction or excess DA synthesis and release.

Appraisal of results

AD, MDD, BD_{man}, BD_{dep} and SZ share the characteristic of imbalanced DA function. Findings, however, show that the individual disorders greatly differ as to the affected brain region(s), the affected synaptic constituent(s) and the direction of dysfunction in terms of either sensitization or desensitization of transporter and receptor binding sites.

The results can be summarized as follows:

1. No desensitization of DAT is evident in AD, whereas, in SZ, DAT desensitization is confined to the STR, and, in MDD, involves the prefrontal/frontal cortex as well as CING, AMYG and SN. In contrast, in BD_{man}, DAT is sensitized in the STR. Comparisons between disorders revealed that, in BD_{man}, striatal DAT binding is increased relative to SZ.
 2. In AD and MDD, D₁R is desensitized in the STR, while, in BD_{man} and BD_{dep}, D₁R is desensitized in the FC. In contrast, in SZ, D₁R is sensitized, with the sensitization involving the VS as well as practically the whole neocortex. Comparison between disorders revealed no differences in D₁R.
 3. In AD, D₂R is desensitized in STR and VS, while, in SZ, D₂R desensitization is more extensive, involving – apart from the STR – also THAL, TC and MB. In contrast, in MDD and BD_{man}, neostriatal D₂R binding is normal. Comparisons of D₂R between disorders revealed that, in AD, striatal D₂R is decreased relative to MDD. Moreover, in MDD, striatal D₂R is increased relative to SZ.
 4. In MDD, DA synthesis is increased in PFC and FC, while, in MDD as well as BD_{man}, neostriatal DA synthesis is normal. In contrast, in SZ, extensive increases of DA synthesis are evident, involving STR, CING, AMYG and MB. Comparisons between disorders revealed that, in MDD, striatal DA synthesis is lower compared to SZ. In contrast, prefrontal and frontal DA synthesis in MDD is higher relative to SZ.
 5. In AD and SZ, DA release is elevated in STR and/or VS. Comparison between disorders revealed that, in AD and MDD, DA release is significantly decreased relative to SZ.
- Precedent analyses (Nikolaus et al., 2014b, 2016, 2017), additionally, have revealed the following features:
6. In AD, SERT is desensitized in THAL, HIPPO and AMYG, while, in MDD, SERT desensitization is even more extensive, involving – apart from THAL and AMYG – also STR, MB and PFC. In BD_{man}, SERT is sensitized in the MB, whereas, in BD_{dep}, SERT is sensitized in CING and INS and desensitized in VS and HIPPO. Interestingly, MDD and BD_{dep} share the feature of SERT sensitization in the INS. No alterations of SERT are evident in SZ. Previous analyses have yielded no significant difference of SERT density between the individual disorders (Nikolaus et al., 2016).
 7. In AD, 5-HT₁R desensitization is observed in MB, PFC, FC, TC, CING, HIPPO, PHG, AMYG, INS and FG. In SZ, 5-HT₁R desensitization is merely present in MB, AMYG, TC and OC. Also in MDD, 5-HT₁R desensitization is limited, occurring solely in the MB, whereas the PHG displays a sensitization of 5-HT₁R. Likewise, 5-HT₁R is sensitized in BD_{dep}, involving PFC, FC, HIPPO, PHG and AMYG. 5-HT₁R is diminished in CING, FC, AMYG and INS of AD compared to MDD patients, and in CING, FC and MB of AD compared to SZ patients. Moreover, 5-HT₁R in the INS of AD subjects is decreased compared to BD_{dep} (Nikolaus et al., 2016).
 8. In AD, 5-HT₂R is desensitized in the VS and sensitized in the TC. In MDD, 5-HT₂R desensitization is evident in CING, PFC, FC, OC, INS and FG. Moreover, a sensitization of 5-HT₂R is observed in the THAL. In BD_{man}, 5-HT₂R desensitization is evident in INS, FG and throughout the whole neocortex. In SZ, 5-HT₂R desensitization does not involve CING and the limbic system, but is confined to the neocortex (FC, TC, OC). 5-HT₂R is increased in the TC of AD compared to MDD patients, and in the FC and TC of AD compared to SZ patients. Furthermore, 5-HT₂R is elevated in the FC of MDD compared to SZ patients (Nikolaus et al., 2016).
 9. In AD, GABA_AR is desensitized in STR, CING, FC, TC, OC, AMYG, INS and EC and sensitized in the PHG. In contrast, in SZ, GABA_AR desensitization is confined to the neocortex (FC, TC), whereas, in MDD, GABA_AR is normal. In AD patients, GABA_AR is lower in the AMYG relative to SZ. Moreover, in MDD, occipital GABA_AR binding is higher relative to both AD and SZ (Nikolaus et al., 2014b).

From this may be inferred that striatal DA synthesis is higher and that prefrontal/frontal DA synthesis is lower in SZ relative to MDD. This underlines our conclusion that, in MDD, DA levels are normal in the STR, but abundant in PFC/FC. This also holds for BD_{man} and BD_{dep} . On the other hand, an increased availability of neostriatal DA can be inferred for SZ (relative to both AD and MDD). Thereby, DA function in SZ is impaired throughout the nigrostriatal and mesolimbocortical system with an increased availability of DA in the striatohalamocortical and a decreased availability in the mesolimbocortical pathway. Striatal DAT binding is higher in BD_{man} than in SZ. This implies that the elevation of DA reuptake may constitute the mechanism, which grants normal neostriatal DA levels as well as normal neostriatal D_1R and D_2R binding in BD_{man} . Moreover, neostriatal D_2R binding is lower in AD relative to MDD and BD_{man} , which indicates different roles of D_2R auto- and heteroreceptor function in the individual disorders.

Mesencephalic 5-HT levels are increased in AD, MDD, BD_{man} and SZ, but normal in BD_{dep} . Furthermore, AD, MDD, BD_{man} and SZ share the feature of elevated neocortical 5-HT, which, however, in BD_{man} is more extensive, involving the whole frontoparietotemporooccipital cortex. In contrast, BD_{dep} is characterized by a decrease of prefrontal/frontal and limbic 5-HT. Strikingly, in MDD, the desensitization of MB 5-HT₁ auto- and heteroreceptors is concurrent with a sensitization of parahippocampal 5-HT_{1R}. This corresponds to the increase of 5-HT_{1R} in limbic regions of BD_{dep} patients. Hence, the same line of events – sensitization of limbic 5-HT₁ heteroreceptors leading to an increase of inhibitory input, and sensitization of limbic 5-HT₁ autoreceptors leading to a decline of 5-HT levels – may be assumed to occur in both disorders. However, in MDD, an interaction of limbic and mesencephalic 5-HT function can be inferred, which is not present in BD_{dep} . Moreover, contrary to AD and SZ, the desensitization of 5-HT_{1R} in MDD is confined to the MB and does not involve neocortical, cingulate and limbic regions. Thus, contrary to AD and SZ, in MDD, there is no adaptive reduction of inhibitory neurotransmission in these areas. It is striking that AD is characterized by the highest temporal 5-HT_{2R} binding and the lowest cingulate and frontal 5-HT_{2R} binding relative to MDD and SZ. Moreover, AD patients display the lowest GABA_A binding in the AMYG relative to SZ, which implies a specific role of excitation in temporal and inhibition in cingulate/limbic and frontocortical regions.

Although the conjecture of region-specific alterations of VMAT2, DAT, D_1R , D_2R , DA synthesis and DA release is intriguing, it must be put into perspective: for one, investigations of several parameters of synaptic function are

scarce in individual diseases with merely one study of VMAT2 in AD (Table 1), one study on D_1R in AD (Table 1), two studies on D_1R in MDD (Table 2), three studies on DA release in MDD (Table 2), one study on D_1R in BD_{man} (Table 3), one study on D_1R in BD_{dep} (Table 3), one study on D_2R in BD_{man} (Table 3) and one study on DA synthesis in BD_{man} (Table 3). Moreover, so far, no study has been conducted on VMAT2 in MDD, BD_{man} , BD_{dep} and SZ, DA synthesis in AD and DA synthesis in BD_{man} and BD_{dep} . In numerous cases, furthermore, the number of available studies per brain region is limited (Figures 1–5). If, in addition, the number of investigated subjects is comparatively small, findings are difficult to interpret as to their portability.

Furthermore, as illustrated by Figures 1–5, the individual findings underlying the obtained differences between AD, MDD, BD_{man} , BD_{dep} and SZ patients and the respective controls were rather inconsistent with reports of no alterations and both significant and non-significant increases as well as decreases of DAT, D_1R , D_2R , DA synthesis and DA release. Thereby, inconsistent findings may be due to varying subtypes of the respective disorders, varying comorbidities, varying disease durations and varying disease severities, which, in addition, have been assessed with a variety of different inventories (Tables 1–4). Additional factors, which may influence the outcome of studies, are differences in methodology: results can not be expected to be entirely consistent, when they were acquired with different imaging tools such as SPECT and the higher-resolving PET, and with quantification methods ranging from the determination of ratios to cerebellar or cortical reference regions over compartmental modeling to statistical parametric mapping of distribution volumes. In addition, the employment of various radioligands for a given binding site may not only bias (semi)quantitative values due to differences in affinities, but also due to the pitfalls inherent to the respective imaging modality such as the lack of exact attenuation correction in SPECT in conjunction with the usage of specific reconstruction algorithms (Catafau et al., 2009; Bullich et al., 2010).

Another important issue is the fact that in the majority of original investigations patients had undergone previous and/or current treatment with anticonvulsants, anxiolytics, antidepressants and neuroleptics, acting – among others – on sodium channels and pre- and postsynaptic DA, 5-HT, noradrenaline and GABA binding sites (Tables 1–4).

Therefore, future *in vivo* imaging studies are required, which address individual parameters of neurotransmitter function in unmedicated or – preferably – medication-naïve patients with the primary (and preferably exclusive)

diagnosis of individual subtypes of AD (obsessive-compulsive disorder, panic disorder, phobia, etc.), MDD (melancholic, atypical, catatonic depression, seasonal affective disorder, etc.), BD (bipolar I, bipolar II, etc.) in either the manic or depressed state or SZ (paranoid, disorganized, catatonic, etc.). This especially pertains to brain regions, which are known to play a major role in the mediation of cognition, emotion and social functioning such as HIPPO (for a review see Eichenbaum, 2017), PHG (for a review see Aminoff et al., 2013), AMYG (for a review see Gothard et al., 2018), CING (for a review see Hadland et al., 2003), TC (for a review see Grosso et al., 2015) and PFC (for a review see Hise and Koenigs, 2018). A variety of these regions displayed interesting disease-specific alterations of transporter and receptor binding in individual disorders, such as the elevation of temporal 5-HT₂R in AD, insular SERT in MDD and BD_{dep}, mesencephalic SERT in BD_{man}, parahippocampal 5-HT₁R in MDD or cingulate D₂R in MDD. Noteworthy are, furthermore, the increase of inhibitory prefrontal/frontal and limbic 5-HT₁R in BD_{man} and excitatory ventrostriatal prefrontal/frontal and parietooccipital D₁R in SZ, which exemplify that entirely different modes of neurotransmitter action – in this case, increased prefrontal/frontal and limbic 5-HTergic inhibition in BD_{man} as opposed to increased mesolimbocortical DAergic excitation in SZ – may underlie the individual pathological conditions.

Besides, there is evidence that neurotransmitters beyond DA, 5-HT and GABA may play a role in the manifestation of AD, MDD, BD and SZ. Among them are acetylcholine (for review see Koukouli and Maskos, 2015), histamine (for a review see Shan et al., 2017), glutamate (for a review see O'Donovan et al., 2017), substance P (for a review see Nikolaus et al., 2013) and endocannabinoids (for a review see Campos et al., 2016). Since, as of yet, the number of available *in vivo* imaging studies on these neurotransmitters is scarce, future efforts must also be directed towards elucidating their contributions to the pathophysiology of AD, MDD, BD and SZ.

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