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WFSBP CONSENSUS PAPER

Biological markers for anxiety disorders, OCD and PTSD – a consensus statement. Part I: Neuroimaging and genetics

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ABSTRACT

Objectives: Biomarkers are defined as anatomical, biochemical or physiological traits that are specific to certain disorders or syndromes. The objective of this paper is to summarise the current knowledge of biomarkers for anxiety disorders, obsessive-compulsive disorder (OCD) and post-traumatic stress disorder (PTSD).

Methods: Findings in biomarker research were reviewed by a task force of international experts in the field, consisting of members of the World Federation of Societies for Biological Psychiatry Task Force on Biological Markers and of the European College of Neuropsychopharmacology Anxiety Disorders Research Network.

Results: The present article (Part I) summarises findings on potential biomarkers in neuroimaging studies, including structural brain morphology, functional magnetic resonance imaging and techniques for measuring metabolic changes, including positron emission tomography and others. Furthermore, this review reports on the clinical and molecular genetic findings of family, twin, linkage, association and genome-wide association studies. Part II of the review focuses on neurochemistry, neurophysiology and neurocognition.

Conclusions: Although at present, none of the putative biomarkers is sufficient and specific as a diagnostic tool, an abundance of high-quality research has accumulated that will improve our understanding of the neurobiological causes of anxiety disorders, OCD and PTSD.

Abbreviations: 5-HT: Serotonin; 5-HTP: Hydroxytryptophan; 5-HTT: Serotonin transporter; 5-HTTLPR: Serotonin-transporter-linked polymorphic region; A-SepAD: Adult Separation Anxiety Disorder; ACC: Anterior cingulate cortex; ADORA2A: Adenosine A_{2A} receptor; ADNR: Anxiety Disorders Research Network; ASIC/ACCN: Acid sensing ion channel; BA: Brodmann area; BDD: Body Dysmorphic Disorder; Beta-CIT: 2β-Carbomethoxy-3β-(4-iodophenyl)tropane; BDNF: Brain-derived neurotrophic factor; BOLD: Blood oxygenation level dependent; C-SepAD: Childhood Separation Anxiety Disorder; CBT: Cognitive-behavioural therapy; CCK: Cholecystokinin; CCK-4: Cholecystokinin tetrapeptide; CLOCK: Circadian locomotor output cycles kaput; CO₂: Carbon dioxide; COMT: Catechol-O-methyltransferase; CRH: Corticotropin-releasing hormone; CRHR1: Corticotropin releasing hormone type 1 receptor; CSF: Cerebrospinal fluid; CYP2D6: Cytochrome P450 2D6; DAT (SLC6A3): Dopamine transporter; DISP1: Dispatched homolog 1 (drosophila); DLGAP1: Discs large (drosophila) homolog-associated protein 1; dlPFC: Dorsolateral prefrontal cortex; DRD2/3/4: Dopamine D2/D3/D4 receptor; DSM: Diagnostic and Statistical Manual of Mental Disorders; DTI: Diffusion tensor imaging; ECNP: European College of Neuropsychopharmacology; ECNP-NI: European College of Neuropsychopharmacology Network Initiative; FDG: Fluorodeoxyglucose; fMRI: Functional magnetic resonance imaging; GABA: Gamma-aminobutyric acid; GABHS: Group A β-hemolytic streptococci; GAD: Generalized Anxiety Disorder; GAD1: Glutamate

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decarboxylase 1; GPC6: Glypican 6; GRIK2: Glutamate receptor, ionotropic, kainate 2; GRIN2B: Glutamate receptor, ionotropic, N-methyl D-aspartate 2B; GWAS: Genome-wide association study; HMPAO: Hexamethylpropylene amine oxime; HPA axis: Hypothalamic-pituitary-adrenal axis; HTR1A/2A/3A/3B/6: Serotonin 1A/2A/3A/3B/6 receptor gene; IL: Interleukin; LOD: Logarithm of the odds; MAO: Monoamine oxidase; MAOA: Monoamine oxidase A; MRS: Magnetic resonance spectroscopy; NAA: N-acetyl aspartate; NET (SLC6A2): Norepinephrine transporter; NPS: Neuropeptide S; NPSR1: Neuropeptide S receptor 1; NR3C1: Nuclear receptor subfamily group C, member 1; OCD: Obsessive–Compulsive Disorder; OCDs: Obsessive–Compulsive and Related Disorders; OFC: Orbitofrontal cortex; OXTR: Oxytocin receptor; PANDAS: Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; PCDH10: Protocadherin 10; PDA: Panic Disorder with or without Agoraphobia; PDE1A: Phosphodiesterase 1A; PEPSI: Proton echo planar spectroscopic imaging; PET: Positron emission tomography; PTPRD: Protein-tyrosine phosphatase, receptor-type, delta; PTSD: Posttraumatic Stress Disorder; rCBF: Regional cerebral blood flow; RGS2: Regulator of G-protein signaling 2; ROIs: Regions of interest; SAD: Social Anxiety Disorder; SAPAP3: SAP90/PSD95-associated protein 3; SLC1A1: Glutamate transporter; SLC6A4 (5-HTT): Serotonin transporter; SLITRK1: SLIT- and NTRK-like family, member 1; SNP: Single nucleotide polymorphism; SNRI: Serotonin norepinephrine reuptake inhibitor; SPECT: Single-photon emission computed tomography; SSRI: Selective serotonin reuptake inhibitor; TBSS: Tract-based spatial statistics; TPH: Tryptophan hydroxylase; TPH2: Tryptophan hydroxylase 2; UTR: Untranslated region; uVNTR: Upstream variable number of tandem repeats; WFSBP: World Federation of Societies for Biological Psychiatry

Introduction

Biological markers for mental disorders have been addressed by the World Federation of Societies for Biological Psychiatry (WFSBP) Task Force on Biological Markers in a series of consensus initiatives on depression (Mossner et al. 2007), schizophrenia (Stober et al. 2009; Thibaut et al. 2015), alcoholism (Hashimoto et al. 2013), attention-deficit/hyperactivity disorder (ADHD; Thome et al. 2012) and dementia (Wiltfang et al. 2005). The present consensus statement of biological markers of anxiety disorders was organised by members of the WFSBP Task Force on Biological Markers and of the Anxiety Disorders Research Network (ADRN) within the European College of Neuropsychopharmacology Network Initiative (ECNP-NI) (Baldwin et al. 2010), an initiative intended to meet the goal of extending current understanding of the causes of mental disorders.

Anxiety disorders are the most prevalent psychiatric disorders (Alonso & Lepine 2007; Gustavsson et al. 2011; Wittchen et al. 2011; Kessler et al. 2012) and are associated with a considerable degree of impairment, high health-care utilisation and an enormous economic burden for society (Alonso et al. 2004). A short description of the anxiety disorders, OCD and post-traumatic stress disorder (PTSD) is given in Table 1.

Panic disorder with or without agoraphobia (PDA), although not the most prevalent anxiety disorder in representative surveys, is the disorder treated most often in clinical settings (Bandelow & Michaelis 2015; Regier et al. 1993), perhaps due to the tendency of many patients to assume they suffer from a serious physical illness. In two-thirds of the cases, PDA is

accompanied by agoraphobia. The majority of studies on the neurobiology of anxiety disorders have been conducted with patients with PDA, perhaps because recruiting patients with this disorder is easy due to a high rate of PDA patients in clinical research settings.

Generalised anxiety disorder (GAD) has high comorbidity with major depression. When looking for neurobiological causes of the disorder, we have to be aware of the possible confounding of neurobiological causes for both disorders.

Patients with *social anxiety disorder (SAD)*, the second most common form of pathological anxiety, tend to hide their problem. As shyness and shame are typical features of social anxiety, it is not surprising that these patients are hesitant to see a physician and talk about their symptoms (Ormel et al. 1991). Therefore, despite the high number of affected individuals, patients with SAD are less often diagnosed and treated in clinical settings.

Specific phobias are the most common anxiety disorders (Wittchen et al. 2011; Bandelow & Michaelis 2015); however, most patients do not seek help for this condition because they can cope with their phobias. As a consequence, there is only sparse literature on the neurobiology of specific phobias.

Separation anxiety disorder (SepAD) has been for a long time considered as a childhood disorder. However, in the last two decades, several authors have reported high prevalence estimates of adult SepAD in the general population and among adult outpatients (Shear et al. 2006; Pini et al. 2014; Silove et al. 2015). Therefore, according to the latest version of the Diagnostic and Statistical Manual of Mental Disorders –

Table 1. Short description of anxiety disorders as defined by DSM-5 (APA 2013).

Panic disorder (PDA)
Panic disorder is characterised by recurrent panic attacks, which are discrete periods of intense fear or discomfort, accompanied by at least four of 13 somatic and psychic symptoms.

Agoraphobia
About two-thirds of all patients with panic disorder suffer from comorbid agoraphobia, which is defined as fear in places or situations (e.g., crowds, public transport) from which escape might be difficult or in which help may not be available in the event of having unexpected panic attacks.

Generalised Anxiety Disorder (GAD)
Patients suffer from excessive anxiety and worry, accompanied by somatic anxiety symptoms as well as from restlessness, irritability, difficulty concentrating, muscle tension, sleep disturbances and being easily fatigued.

Specific Phobia
Specific phobia is characterised by excessive or unreasonable fear of single objects or situations (e.g., flying, heights, animals, seeing blood, etc.).

Social Phobia (Social Anxiety Disorder, SAD)
SAD is characterised by persistent and unreasonable fear of being observed or evaluated negatively by others in social performance or interaction situations (e.g., speaking in public or being exposed to possible scrutiny by others) and is associated with somatic and cognitive anxiety symptoms.

Separation Anxiety Disorder (SepAD)
Experience of excessive distress when separation from home or major attachment figures is anticipated or occurs. Individuals worry about the well-being or potential death of attachment figures, particularly when separated from them, and feel compelled to remain in touch with them. Forms: childhood (C-SepAD) and adult separation disorder (A-SepAD)

Obsessive–Compulsive and Related Disorders (OCDs)
OCD is characterised by recurrent obsessions (concerns involving contamination, harm, or sexual and religious preoccupations) or compulsions (e.g., washing, checking, repeating, ordering, counting, hoarding), or both, that cause impairment in terms of distress, time or interference with functioning. Other OCDs include:

- Body dysmorphic disorder (BDD)
- Hoarding disorder
- Trichotillomania (hair pulling disorder)
- Excoriation (skin-picking) disorder
- OCDs due to another medical condition (e.g., PANDAS/PANS)

Post-Traumatic Stress Disorder (PTSD)
PTSD develops after a terrifying ordeal that involved physical harm or the threat of physical harm and is characterised by recurrent and intrusive distressing recollections of the event, nightmares, dissociative flashback episodes, distress at exposure to cues that resemble the traumatic event, avoidance of stimuli associated with the trauma, estrangement from others, sleep disturbances, irritability, difficulty concentrating, hypervigilance and exaggerated startle response.

5th edition (DSM-5), the disorder can now also be diagnosed in adults (A-SepAD; Anderson et al. 2013).

Obsessive–compulsive disorder (OCD) and *PTSD* have been classified as anxiety disorders in the past, but these disorders have now been removed from this category and are now described in different chapters in the DSM-5 (obsessive–compulsive and related disorders [OCDs] and trauma- and stressor-related disorders, respectively; APA 2013). The OCDs include trichotillomania (hair pulling disorder), excoriation disorder (skin picking disorder), body dysmorphic disorder (BDD) and hoarding disorder (APA 2013).

Illness anxiety disorder is a “new” diagnostic category in the DSM-5 and belongs to the category “Somatic Symptom and Related Disorders”. It is characterised by excessive preoccupation of having a serious medical illness. Because this category was only introduced recently, it was not included in the present article, due to the lack of neurobiological findings.

Mixed anxiety and depression is a category listed only in the International Classification of Diseases, 10th edition (ICD-10) and not in the DSM-5. It is often diagnosed in primary care. Research on its neurobiological background is limited (Möller et al. 2016).

The age of onset of anxiety disorders is usually in the mid-20s. Women are approximately 1.5 to 2 times more likely than men to be diagnosed with an anxiety condition (Bandelow & Michaelis 2015), OCD

(Rasmussen & Eisen 1992) or PTSD (Breslau 2009). The mean age of onset of OCD is reported as 20 years, with bimodal peaks at 12–14 and 20–22 years (Rasmussen & Eisen 1992; Zohar 1999).

The aetiology of anxiety disorders

Anxiety is a normal human emotion with a Gaussian distribution in the population – it becomes a disorder when it disturbs or impairs behaviour or leads to suffering. The switch from “normal” anxiety to an anxiety disorder, OCD or PTSD is thought to be caused by an interplay of psychosocial stressors and neurobiological alterations. These neurobiological dysfunctions have been postulated to have a strong genetic basis, as all these disorders show moderate to high heritability (Table 9), with a higher prevalence of acquiring them during the lifetime.

Several specific phobias have been viewed as relics of natural survival mechanisms rather than pathological conditions. During the evolution of humankind, humans who were afraid of dangerous animals such as spiders or snakes, which represent the content of specific phobias nowadays, survived and had the chance to transmit their fears genetically to their descendants.

Psychosocial stressors that have been associated with the aetiology of anxiety disorders include traumatic experiences during childhood or adolescence,

e.g., separation from parents, parents' marital discord, childhood illness, sexual or physical violence or a family history of mental illness. Although dysfunctional rearing styles have been seen for long as the major cause of anxiety disorders, the evidence supporting a relevant contribution of parental attitudes to their aetiology is weak (Bandelow et al. 2002, 2004). In addition to childhood adversity, traumatic events during adulthood, e.g., divorce or loss of a family member, have been hypothesised as possible causes of anxiety disorders.

Anxiety induced by separation from close attachment figures is normal and adaptive in early childhood. Therefore, it seems plausible that SepAD simply derives from traumatic separation events. However, separation anxiety and actual separation experiences do not seem to be closely related. In a retrospective study investigating childhood separation anxiety in PDA patients and control subjects, the correlation between reported actual separation events and separation anxiety measures was close to zero (Bandelow et al. 2001), meaning that individuals may develop separation anxiety without having a history of distressing separation experiences, perhaps on the basis of a neurobiologically determined vulnerability.

Although the aetiology of PTSD is thought to be based on severe traumatic events, a range of factors, other than the trauma itself, are needed to fully account for the pathogenesis of this disorder. Not everyone experiencing a severe trauma will develop PTSD. The rate depends on the type of trauma and ranges between 9% for being involved in an accident (Butler et al. 1999) and 53% for sexual abuse such as rape (Kessler et al. 1995). Although men are more likely to experience trauma, the likelihood of developing PTSD is higher in women (Breslau 2009). Individuals with PTSD have an increased ratio of other psychiatric disorders prior to the traumatic experience, including pre-existing affective, anxiety or substance abuse disorders (Perkonig et al. 2000). Vulnerability or resilience to traumatic stress appears to be determined by genetic and neurobiological factors.

Biomarkers

Unlike physical illnesses such as hepatitis, diabetes or cancer, there is no laboratory test or imaging method that can be used to diagnose an anxiety disorder, OCD or PTSD. Although drug treatment is well established and highly effective (Baldwin et al. 2014; Bandelow et al. 2008, 2015) and despite much knowledge of the mechanisms of action of these drugs, the

neurobiological backgrounds of these disorders are still not clarified sufficiently.

A disease biomarker refers to "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention" (Biomarkers Definitions Working 2001). Ideally, in the future, it will be possible to diagnose mental disorders aided by objective parameters, e.g., blood or cerebrospinal fluid (CSF) tests, genetic tests, brain imaging methods or their combination. Biomarkers can be used for assessing severity of the disorders and predicting the differential response to a variety of treatment modalities. Identifying biomarkers can thus help to detect the underlying biological basis of anxiety disorders, OCD and PTSD, and on this basis, offer targeted, i.e., indicated preventive interventions and – along the lines of "precision medicine" – to develop individualised therapies that are more effective.

Most studies of the neurobiology of mental disorders are based on comparisons between affected patients and healthy control individuals. Moreover, as we know that certain drugs and psychological therapies can effectively treat mental disorders, we can draw conclusions regarding the aetiological background of the disorders when we are able to identify the underlying mechanisms of action of the treatments. Furthermore, understanding how psychotherapy impacts on neural circuits may help to elucidate the pathomechanisms of anxiety disorders, OCD and PTSD (Brooks & Stein 2015).

The present article (Part I) summarises the findings of potential biomarkers in neuroimaging and genetic studies, while Part II (Bandelow et al. 2016) focuses on neurochemistry, neurophysiology and neurocognition in anxiety disorders, OCD and PTSD.

Neuroimaging

Advanced neuroimaging techniques (Table 2) have provided new insights into the possible alterations in anxiety disorders, OCD and PTSD. Various methods have been used to study whether baseline, pre-treatment characteristics or changes in brain functioning and metabolism correlate with symptom improvement following treatment. As regarding single-photon emission computed tomography (SPECT) and positron emission tomography (PET) studies of neurochemical systems, several research groups have revealed state changes in availability or density of neurotransmitter receptors and transporters in brain of patients with

Table 2. Principles of brain imaging methods.

Abbreviation	Method	Principle
MRI	Magnetic resonance imaging	An image of the brain is formed by signals from hydrogen protons in tissues containing water molecules.
DTI	Diffusion tensor imaging	MRI method, in which diffusion of water molecules can be used to reveal microscopic details about tissue architecture in the brain. The neurons of the white matter in the brain have a fibrous structure analogous to the anisotropy of crystals. By computing fractional anisotropy, the white-matter connectivity of the brain can be assessed.
MRS	Magnetic resonance spectroscopy	In contrast to MRI, which uses signals from hydrogen protons to create two-dimensional images of the brain, MRS uses proton (^1H) or phosphorus (^{31}P) or other signals to determine the concentrations of brain metabolites.
PEPSI	Proton echo-planar spectroscopic imaging	While PEPSI yields spectral resolution that approximates that of conventional MRS, it enables a reduction in encoding time.
fMRI	Functional magnetic resonance tomograph	This method is used to measure how different parts of the brain respond to external stimuli or challenges. Blood oxygenation level dependent (BOLD) fMRI measures the hemodynamic response to transient neural activity based on a change in the oxyhemoglobin/desoxyhemoglobin ratio.
PET	Positron emission tomography	A positron-emitting tracer, a radionuclide, is introduced into the body on a biologically active molecule. Pairs of gamma rays emitted indirectly by the tracer are detected. For example, by using the glucose analogue fluorodeoxyglucose (FDG), the concentrations of the tracer will indicate tissue metabolic activity corresponding to the regional glucose uptake.
SPECT	Single-photon emission computed tomography	A gamma-emitting radionuclide is attached to a specific ligand to create a radioligand, whose properties bind it to certain types of tissues and is injected. SPECT is similar to PET, however, the radioisotope is longer lasting and less expensive than fludeoxyglucose (FDG) used for PET scans.

anxiety disorders (Maron et al. 2012). In the following sections, structural and functional data will be discussed separately for disorders listed in Table 1.

PDA

Structural brain morphology – MRI studies

In an early study Fontaine et al. (1990) observed focal abnormalities in the temporal lobes, including areas of abnormal signal activity and asymmetric atrophy. Sobanski et al. (2010) found reduced temporal and frontal lobe volumes. Smaller amygdala volumes have been found bilaterally in PDA patients in comparison with healthy controls (Massana et al. 2003b). The same authors found also lower left grey matter density of the parahippocampal gyrus in PDA patients (Massana et al. 2003a). A study by Hayano et al. (2009) revealed a decrease of amygdala volume bilaterally in PDA patients vs. healthy controls. In one study, volume reduction in the right posterior-medial orbitofrontal cortex (OFC) region was only found in PDA patients with an absent or a single posterior orbital sulcus (Roppongi et al. 2010). Functional importance of these changes was suggested by the study of Lai (2011) that reported a significant correlation between grey matter volume decrease in the right basal ganglion and the severity of PDA symptomatology. Decreased grey matter volumes in the putamina were also found in PDA patients (Yoo et al. 2005). In contrast to healthy controls, volume reductions in the right dorsal and the rostral anterior cingulate cortex (ACC) were found in

PDA patients (Asami et al. 2008). The same group found gender differences in grey matter volume reductions: volume reduction in the right amygdala and the bilateral insular cortex was significantly greater in the males, while reduction in the right superior temporal gyrus was greater in females (Asami et al. 2009). In another study, an increase in grey matter volume was found in the left insula (Uchida et al. 2008). In a voxel-based morphometry study, increased grey matter volumes were found in the midbrain and rostral pons of the brainstem (Protopopescu et al. 2006). In a magnetic resonance imaging (MRI) investigation of the pituitary gland, significantly smaller volumes were found in PDA patients than in healthy controls (Kartalci et al. 2011).

A diffusion tensor imaging (DTI) study suggested increased white matter connectivity in left anterior and right posterior cingulate regions in PDA as indexed by greater fractional anisotropy (Han et al. 2008).

In a summary of structural MRI studies in patients with PDA, the main areas of interest to investigate possible structural changes include the amygdala, the hippocampal and parahippocampal gyri and the brainstem nuclei (Del Casale et al. 2013). However, as alterations in the volume have been found in so many different brain regions in the studies reported above, it is difficult to draw any reliable conclusions at present. Moreover, it remains uncertain how closely these alterations that manifest as volume reductions or increases are related to symptoms or aetiology of anxiety disorders.

Table 3. Treatment biomarkers in PDA: summary of positive neuroimaging findings.

References	Number of patients	Treatment	Method	Predictor
Lueken et al. (2013)	49	CBT	fMRI	Response to CBT in panic patients was associated with an inhibitory functional coupling between the ACC and the amygdala
Reinecke et al. (2014)	14	CBT	fMRI	Response to brief CBT predicted by increased pre-treatment activation in bilateral insula and left dorsolateral prefrontal cortex during threat processing
Ball et al. (2014)	48	CBT	fMRI	In patients with PDA/GAD: greater BOLD in cortico-limbic circuitry predicted response to CBT
Lueken et al. (2015)	41	CBT	fMRI	Inhibitory ACC-amygdala coupling during fear conditioning was associated with the long variant of the 5-HTTLPR polymorphism in CBT responders only
Hahn et al. (2015)	49	CBT	fMRI	No brain regions predictive of CBT outcome
Lai and Hsu (2011)	15	SNRI	MRI	Subtle increases of grey matter in left infero-frontal cortex, right fusiform gyrus, and right cerebellum after duloxetine treatment
Lai and Wu (2013)	21	SSRI	MRI	Subtle changes of white matter micro-structural integrity after remission
Lai et al. (2013)	21	SSRI	MRI	Increased fractional anisotropy in some regions of right uncinate fasciculus and left fronto-occipital fasciculus after remission
Spindelegger et al. (2009)	12	SSRI	[¹¹ C]WAY-100635 PET	Reduction of the 5-HT(1A) binding potential after SSRI treatment
Kang et al. (2012)	15	SSRI	[¹⁸ F]FDG PET	Treatment responders showed metabolic increases in global neocortical and limbic areas

Changes after treatment. Many studies have investigated changes in imaging responses after treatment with medication and psychotherapy (Table 3). In one study, remission after escitalopram treatment was accompanied by an increase in the grey matter volume in the left superior frontal gyrus, but a reduction in the right precentral gyrus. The changes in total grey matter volume after remission were correlated with changes in clinical scores (Lai & Wu 2013). Another study found increased white matter micro-structural integrity reflected by fractional anisotropy in some regions of the right uncinate fasciculus and the left fronto-occipital fasciculus after escitalopram remission (Lai et al. 2013). Earlier, increases of grey matter volume were shown in the left infero-frontal cortex, the right fusiform gyrus and the right cerebellum areas in remitted depressive patients with comorbid PDA following 6 weeks medication with duloxetine (Lai & Hsu 2011). None of these studies has specifically focussed on predictive influence of brain structural measures on treatment response.

Functional MRI

Usually, in functional MRI (fMRI) studies, presentation of words with threatening contents or photographs displaying fearful or angry faces represents a common paradigm to elicit fear reaction and activation of certain brain regions, especially the amygdala, which is thought to be of relevance for fear reactions (Phelps & LeDoux 2005). After presentation of words with potentially threatening content, PDA patients showed increased activation in the left posterior cingulum and the left medial frontal cortex compared with controls (Maddock et al. 2003) or activation of the right

amygdala and right hippocampus (van den Heuvel et al. 2005). Fear provocation with anxiety-related images was associated with increased activity in the inferior frontal cortex, the hippocampus, the anterior and posterior cingulate and the OFC (Bystritsky et al. 2001). In response to presentation of anxious faces, PDA patients displayed a lower activation of the ACC and the amygdalae, when compared with healthy controls (Pillay et al. 2006). Presentation of happy faces was associated with a bilateral hyperactivation of the ACC but there were no differences in amygdala responsivity compared to healthy controls (Pillay et al. 2007). In an fMRI study a masking paradigm was used and fearful and neutral faces were presented subthreshold, while controls responded to fearful masked faces showing the classic amygdala responsivity, PDA patients were characterised by the absence of that signal (Ottaviani et al. 2012). In another study, PDA patients differed from controls in showing increased activity in the left inferior frontal gyrus in response to panic-related relative to neutral words (Dresler et al. 2012).

PDA patients do not necessarily show an abnormal response to fearful stimuli, unless the stimulus is panic-specific. Therefore, in an fMRI study, the authors determined *a priori* for each patient which stimuli were rated the most fearful. They found greater activation in PDA patients than control subjects in the insular cortices, left inferior frontal gyrus, dorsomedial prefrontal cortex, the left hippocampal formation and left caudatum, when responses to panic or neutral pictures were compared (Engel et al. 2015).

Significant correlations were found between certain genetic polymorphisms of the serotonergic system and a decreased activation of the right prefrontal cortex

Table 4. Studies with PET, SPECT, PEPSI and MRS in PDA.

References	Method	Patient characteristics	Findings
<i>Metabolism</i>			
Nordahl et al. (1990)	[¹⁸ F]FDG PET	PDA patients; performance of auditory discrimination vs. HC	Hippocampal region asymmetry; metabolic decreases in left inferior parietal lobule and anterior cingulate (trend), increase in the metabolic rate of the medial orbital frontal cortex (trend)
Bisaga et al. (1998)	[¹⁸ F]FDG PET	Lactate-sensitive and medication-free PDA patients (<i>n</i> = 6) vs. HC (<i>n</i> = 6)	Increase in left hippocampal and parahippocampal area; decrease in the right inferior parietal and right superior temporal regions
Prasko et al. (2004)	[¹⁸ F]FDG PET	PDA patients before vs. after treatment (CBT: <i>n</i> = 6, antidepressants: <i>n</i> = 6)	Decreases in right hemisphere, superior, middle, medial and inferior frontal gyrus, superior and middle temporal gyrus; increases in left hemisphere in medial and middle frontal gyrus, superior, middle and transverse temporal gyrus
Sim et al. (2010)	[¹⁸ F]FDG PET	PDA patients (<i>n</i> = 5) before and after treatment with paroxetine	Cerebral cortex and limbic brain functions changed after treatment
Kang et al. (2012)	[¹⁸ F]FDG PET	PDA patients (<i>n</i> = 15) in comparison with HC (<i>n</i> = 20); changes in glucose metabolism after 12 weeks of escitalopram treatment	Patients with PDA showed decreased metabolism in both frontal, right temporal, and left posterior cingulate gyri. After 12 weeks of escitalopram, treatment responders showed metabolic increases in global neocortical areas as well as limbic areas whereas nonresponders did not
Dager et al. (1997)	PEPSI	PDA patients (<i>n</i> = 15); HC (<i>n</i> = 10)	Panic patients had a larger and prolonged sodium lactate increase in the insular cortices during lactate-induced panic
Dager et al. (1999)	PEPSI	PDA patients (<i>n</i> = 15); HC (<i>n</i> = 10)	PDA patients had significantly greater global brain lactate increases in response during lactate-induced panic
<i>Cerebral blood flow</i>			
Seo et al. (2014)	Tc-99m-ECD SPECT	PDA patients before and after CBT (<i>n</i> = 14)	After CBT, increased rCBF was detected in the left postcentral gyrus, left precentral gyrus (BA 4), and left inferior frontal gyrus (BA 9 and BA 47), whereas decreased rCBF was detected in the left pons
Boshuisen et al. (2002)	[H ₂ ¹⁵ O] PET	PDA patients (<i>n</i> = 17); HC (<i>n</i> = 21) before and after a pentagastrin challenge	After challenge with CCK antagonist pentagastrin larger activity of the right amygdala
Ponto et al. (2002)	[H ₂ ¹⁵ O] PET	PDA patients (<i>n</i> = 14) and HC (<i>n</i> = 12) after inhalation of 35%/65% CO ₂ /O ₂ mixture	Patients with PDA, especially when symptomatic, exhibited an abnormal pattern in global cerebral blood flow response to provocation
Stewart et al. (1988)	[¹³³ Xe]-SPECT	Patients (<i>n</i> = 10) who did not panic after sodium lactate, HC (<i>n</i> = 5)	Hemispheric CBF after the infusion was increased
De Cristofaro et al. (1993)	[^{99m} Tc]-HMPAO SPECT	Lactate-sensitive PDA patients (<i>n</i> = 7) vs. HC (<i>n</i> = 5)	Right-left asymmetry in inferior frontal cortex; blood flow increase in the left occipital cortex; decrease in the bilateral hippocampus vs. controls
Eren et al. (2003)	[^{99m} Tc]-HMPAO SPECT	PDA patients (<i>n</i> = 22), HC (<i>n</i> = 19)	Bilateral frontal decrease and a right medial and superior frontal increase of regional blood flow
Lee et al. (2006)	[^{99m} Tc]-HMPAO SPECT	PDA patients (<i>n</i> = 22), HC (<i>n</i> = 26)	Decreased rCBF flow in right superior temporal lobe in PDA patients
<i>Serotonin</i>			
Maron et al. (2004a)	[¹²³ I]nor-beta-CIT SPECT	PDA patients (<i>n</i> = 8); HC (<i>n</i> = 8)	Patients with current panic symptoms had significantly lower 5-HTT binding in the midbrain raphe, the temporal lobes, and the thalamus as compared with healthy controls. In contrast, remitted patients with PDA had normal 5-HTT binding properties in the midbrain and in the temporal regions, but still a significantly lower thalamic 5-HTT binding
Maron et al. (2011)	[¹¹ C]MADAM PET	PDA patients (<i>n</i> = 11); HC (<i>n</i> = 22)	Male patients showed a higher 5-HTT binding potentials in the brainstem raphe, temporal gyri, anterior cingulate, insular, orbitofrontal, prefrontal and frontal cortices, but lower 5-HTT availability in the hippocampus. In contrast, female patients showed no differences in 5-HTT availability in any studied brain region as compared with female controls

(continued)

Table 4. Continued

References	Method	Patient characteristics	Findings
Neumeister et al. (2004)	[¹⁸ F] FCWAY (PET)	Unmedicated PDA patients (<i>n</i> = 16); HC (<i>n</i> = 15)	Reduced serotonin type 5-HT _{1A} receptor binding
Nash et al. (2008)	[¹¹ C]WAY-100635 PET	Symptomatic untreated PDA patients (<i>n</i> = 9), patients recovered on paroxetine medication (<i>n</i> = 7) and healthy volunteers (<i>n</i> = 19)	PDA is associated with reduced 5-HT _{1A} receptor availability. Fully recovered patients after treatment with the SSRI paroxetine showed normalised density of postsynaptic receptors, but remaining reduction in the density of 5-HT _{1A} receptors in the raphe and in the hippocampus
<i>GABA</i>			
Goddard et al. (2001)	[¹⁸ H] MRS	PDA patients (<i>n</i> = 14); HC (<i>n</i> = 14)	Patients with panic disorder had a 22% reduction in total occipital cortex GABA concentration (GABA plus homocarnosine)
Goddard et al. (2004)	[¹⁸ H] MRS	PDA patients (<i>n</i> = 10); HC (<i>n</i> = 9)	Panic disorder patients had a deficient GABA neuronal response (blunted reduction of occipital cortex GABA level) to acute benzodiazepine administration
Ham et al. (2007)	[¹⁸ H] MRS	PDA patients (<i>n</i> = 22); HC (<i>n</i> = 25)	Significantly decreased GABA concentrations in the ACC
Hasler et al. (2008)	[¹¹ C] flumazenil SPECT	Subjects with PDA (<i>n</i> = 15) who were naive to benzodiazepine drug exposure and HC (<i>n</i> = 18)	Benzodiazepine – γ -aminobutyric acid type A receptor binding in PDA
Malizia et al. (1998)	[¹¹ C] flumazenil SPECT	Patients with PDA (<i>n</i> = 7) who had been off medication for at least 6 months and who had never abused alcohol with HC (<i>n</i> = 8)	Global reduction in benzodiazepine site binding throughout the brain in patients with PDA compared with controls
Cameron et al. (2007)	[¹¹ C] flumazenil SPECT	PDA patients (<i>n</i> = 11); HC (<i>n</i> = 21)	Decreased binding in the insular cortices bilaterally correlated significantly with disorder severity and comorbid depression
Bremner et al. (2000b)	[¹²³ I]-iomazenil SPECT	PDA patients (<i>n</i> = 13); HC (<i>n</i> = 16)	Decrease in left hippocampal and precuneus benzodiazepine receptor binding
Kaschka et al. (1995)	[¹²³ I]-iomazenil SPECT	Patients with PDA and depression (<i>n</i> = 9); dysthymic patients (<i>n</i> = 9)	Lower iomazenil binding in both lower lateral temporal lobes, in the left medial inferior temporal lobe and in both orbitofrontal lobes than in dysthymic patients
Kuikka et al. (1995)	[¹²³ I]-iomazenil SPECT	Unmedicated PDA patients (<i>n</i> = 17); HC (<i>n</i> = 17)	Abnormal regional benzodiazepine receptor uptake in the PFC
Brandt et al. (1998)	[¹²³ I]-iomazenil SPECT	PDA patients (<i>n</i> = 12); HC (<i>n</i> = 9)	Increased benzodiazepine receptor density in the PFC
<i>Neurokinins</i>			
Fujimura et al. (2009)	[¹⁸ F]SPA-RQ PET	PDA patients (<i>n</i> = 14); HC (<i>n</i> = 14)	Neurokinin NK ₁ receptor binding in was significantly decreased

HC, Healthy controls; rCBF, Regional blood flow; MADAM, 5-HTT radioligand; [¹⁸F] FCWAY, 5HT_{1A} receptor binding tracer; [¹¹C]WAY-100635, 5-HT_{1A} tracer; Tc-99m-ECD, Technetium-99m-ethyl cysteinate dimer; 5-HTT, serotonin transporter; FDG, fluorodeoxyglucose; HMPAO, hexamethylpropyleneamine oxime

and increased activity of both amygdalae after presentation of faces with emotional expressions (Domschke et al. 2006). The finding of higher activation, which contradicts the findings of Pillay et al. (2006) who found lower activation may be explained by an interaction with a genetic polymorphism.

Changes after treatment. An fMRI study with a large sample of patients with PDA failed to find any brain regions predictive of cognitive behavioural therapy (CBT) outcome (Hahn et al. 2015). However, in an earlier study, Lueken et al. (2013) observed that treatment response to CBT was associated with an inhibitory functional coupling (negative connectivity) between the ACC and the amygdala, whereas responders and non-responders were characterised by distinct neuronal activation at baseline. Their later study in the same sample demonstrated that greater inhibitory ACC-amygdala

coupling during fear conditioning was associated with the long variant of the serotonin-transporter-linked polymorphic region (5-HTTLPR) polymorphism in CBT responders only. This points towards potential intermediate connectivity phenotype modulating response to exposure-based CBT (Lueken et al. 2015). Better response to brief CBT was predicted by increased pre-treatment activation in bilateral insula and left dorsolateral prefrontal cortex (PFC) during threat processing in a study by Reinecke et al. (2014). In addition, greater activation in cortico-limbic circuitry, including superior frontal gyri, anterior insula, superior temporal, supramarginal and hippocampus, predicted better CBT response in mixed sample of patients with PDA and GAD (Ball et al. 2014). Remission following escitalopram treatment was associated with changes in regional homogeneity, a measure of regional connectivity, in temporo-parietal regions in a fMRI study, which, however, did not

Table 5. Treatment biomarkers in GAD: summary of positive fMRI findings.

References	Number of patients	Treatment	Method	Predictor
Hoehn-Saric et al. (2004)	6	SSRI	fMRI	Reduced activation in PFC, the striatum, insula and paralimbic regions after treatment with citalopram
Whalen et al. (2008)	15	SNRI	fMRI	Treatment response was predicted by greater pre-treatment reactivity to fearful faces in rACC and lesser reactivity in the amygdala
Nitschke et al. (2009)	15	SNRI	fMRI	Higher levels of pre-treatment ACC activity in anticipation of both aversive and neutral pictures were associated with greater reductions in symptoms

specifically explore predictive measures of treatment response (Lai & Wu 2013) (Table 3).

PET, SPECT, PEPSI and MRS

Studies with PET, SPECT, proton echo-planar spectroscopic imaging (PEPSI) and MRS in PDA patients are listed in Table 4. These methods can measure metabolic and neurotransmitter receptor changes. PET studies found differences between PDA patients and controls before and after selective serotonin reuptake inhibitor (SSRI) treatment. PEPSI is a technique capable of simultaneously measuring metabolites from multiple brain regions. With this method, lactate changes during lactate-induced panic were measured. Cerebral blood flow was measured with $[H_2^{15}O]$ PET and $[^{133}Xe]$ - and $[^{99m}Tc]$ -hexamethylpropyleneamine oxime (HMPAO)-SPECT. With these methods, some differences in cerebral blood flow were found between PDA patients and controls. γ -Aminobutyric acid (GABA) function was investigated with MRS and $[^{11}C]$ -flumazenil or $[^{123}I]$ -iomazenil SPECT. In patients with PDA, reductions in benzodiazepine binding or GABA concentrations in certain regions of the brain were found. Serotonin (5-HT) function was assessed in a number of studies. Alterations in serotonin transporter (5-HTT) binding were found with the 5-HTT-specific methods $[^{123}I]$ -nor-2 β -carbomethoxy-3 β -(4-iodophenyl)tropane ($[^{123}I]$ -nor-beta-CIT) SPECT and $[^{11}C]$ -MADAM PET. Reduced 5-HT_{1A} receptor binding and availability was shown with $[^{11}C]$ -WAY-100635 PET that normalised in some brain regions – particularly OFC – after recovery on treatment with SSRIs. $[^{18}F]$ -Substance P antagonist-receptor quantifier ($[^{18}F]$ -SPA-RQ) was used to measure neurokinin 1 (NK₁) (substance P-preferring) receptor binding. SPA-RQ is a nonpeptide antagonist selective for human NK₁ receptors and is competitively displaced *in vitro* by substance P.

GAD

Structural brain morphology – MRI studies

In GAD patients, increased grey matter volumes in amygdala as well as increased grey matter volumes in

the dorsomedial PFC have been found (Hilbert et al. 2015). A decrease of hippocampal volumes has also been noted (Abdallah et al. 2013). Interestingly, studies in adolescents suffering from GAD have shown an increase in superior temporal gyrus and a decrease in medial and superior frontal gyri in adolescents with GAD (Strawn et al. 2013). Moreover, a predominance of grey matter volume changes on the right cerebellar hemisphere has been noted (Hilbert et al. 2015).

fMRI

Similarly to what has been described for studies in PDA patients, reactivity to anxiety provoking stimuli has been tested in GAD patients. In response to angry faces, GAD patients presented increased responses in the lateral PFC (Blair et al. 2008) or the medial PFC and ACC (Paulesu et al. 2010). In contrast, hypo-activation of PFC to (only in female patients) (Palm et al. 2011) or reduced dorsal ACC activity (Blair et al. 2012) was observed in response to fearful, sad, angry and happy facial expressions. In one study, patients presented higher amygdala activation than healthy controls in response to neutral, but not angry faces (Holzel et al. 2013). In a study by Greenberg et al. (2013), patients showed a deficient ventromedial PFC recruitment during fear inhibition. After fear induction in a gambling task, patients demonstrated decreased activity in the amygdala and increased activity in the bed nucleus of the stria terminalis when compared to controls (Yassa et al. 2012).

In a number of studies, changes after serotonin nor-epinephrine reuptake inhibitor (SNRI) treatment were observed (Table 5).

In a systematic review of fMRI studies in GAD, it was reported that the studies differed largely in methodology, making it difficult to identify a common finding (Mochcovitch et al. 2014). However, despite conflicting techniques and results, the majority of studies showed PFC and ACC hypofunction and deficient top-down control system during emotion regulation tasks.

PET and SPECT

In a PET study, GAD patients showed lower absolute metabolic rates in basal ganglia and white matter.

Relative metabolism was increased in the left inferior gyrus, Brodmann Area (BA) 17, in the occipital lobe, right posterior temporal lobe and the right precentral frontal gyrus (Wu et al. 1991).

Dopamine (DAT) and serotonin transporters (5-HTT) were investigated in PET studies. DAT availability in the striatum was significantly lower in the GAD patients than in the healthy controls, while 5-HTT availability did not differ between the groups (Lee et al. 2015). In another study, brain 5-HTT availability was not changed in GAD (Maron et al. 2004a, 2004b).

Significant decreases in frontocortical GABA_A receptors were found in PET studies with GAD patients (Nikolaus et al. 2010).

Some studies measure changes after treatment. In small samples, greater levels of pre-treatment ACC activity and lesser reactivity in the amygdala in anticipation of facial presentation were associated with better reductions in anxiety and worry symptoms after 8 weeks treatment with venlafaxine. This suggests that ACC-amygdala responsivity could prove useful as a predictor of antidepressant treatment response in GAD (Whalen et al. 2008; Nitschke et al. 2009). fMRI-guided repetitive transcranial magnetic stimulation (rTMS) was used to treat GAD. First, a symptom provocation fMRI experiment was used to determine the most active location in the PFC of the patients. Then, rTMS was stereotactically directed to the previously determined prefrontal location. Two of six subjects showed a response (Bystritsky et al. 2008, 2009).

SAD

Structural brain morphology – MRI studies

Changes of cortical thickness (both increase and decrease) of the insula and the ACC were found in SAD patients (Fisler et al. 2013). Irle et al. (2010) have found significantly reduced amygdala and hippocampal volume in comparison to healthy subjects. Further, on the right side, hippocampal volume was significantly related to more severe SAD symptoms.

fMRI

In SAD studies, patients are often exposed to angry or contemptuous human facial photographic stimuli in order to elicit social fear responses. Freitas-Ferrari et al. (2010) have summarised the available fMRI studies in a comprehensive review and found significant and consistent evidence of altered brain functioning in SAD, with a predominance of limbic structures, especially the amygdala, hippocampus and insula.

Some articles have been published after this review. SAD patients showed decreased positive connections within the frontal lobe and decreased negative connections between the frontal and occipital lobes when compared with healthy controls (Ding et al. 2011). In a study of the connectivity of the amygdala, a decreased influence from inferior temporal gyrus to amygdala was found in SAD, while bidirectional influences between amygdala and visual cortices were increased compared with healthy controls (Liao et al. 2010). These results suggest that an amygdala dysfunction in SAD is characterised both by a decreased regulatory influence of OFC and increased communication with the visual cortex, according to the authors. A reduction of prefrontal control over amygdala activation was also found in another study (Sladky et al. 2015). During a social situation task, patients showed significant decreased activation in the left cerebellum, left precuneus and bilateral posterior cingulate cortex (Nakao et al. 2011). In an alternation learning task, the highest correlations between degree of activation and the anxiety scores as assessed by the Liebowitz Social Anxiety Scale were obtained in the left temporal region and in the OFC (Gross-Isseroff et al. 2010). In contrast to healthy controls, habituation to social stimuli was found in the amygdalae, orbital frontal cortex and pulvinar thalamus (Sladky et al. 2012). According to the authors, this result, which is somehow counterintuitive, is compatible with the assumption that increased effort is needed within modulatory networks in prefrontal brain areas of SAD patients to exert sufficient top-down control over hyperactivation in the amygdala when confronted with unknown and potentially threatening stimuli.

Changes after treatment. Some fMRI studies measured changes after CBT treatment in patients suffering from SAD. These are summarised in Table 4.

PET, SPECT and MRS

Cerebral blood flow. In an early SPECT study, regional cerebral blood flow (rCBF) in patients with SAD was not different from healthy controls (Stein & Leslie 1996). In a PET study measuring rCBF in patients with SAD exposed to a tailored phobic situation when they had to perform in front of a panel of experts, deactivations were found in the right lingual gyrus and in the right medial frontal gyrus; no significant hyperactivations were found during exposure. According to the authors, deactivation of these regions may reflect a strategy of visual avoidance employed by patients to

Table 6. Treatment biomarkers in SAD: summary of positive neuroimaging findings.

References	Number of patients	Treatment	Method	Predictor
Doehrmann et al. (2013)	39	CBT	fMRI	Pre-treatment cortical hyperactivity to social threat signals can predict CBT success
Klumpp et al. (2013)	14	CBT	fMRI	CBT response was predicted by pre-treatment activity in prefrontal regions and the amygdala
Klumpp et al. (2014)	21	CBT	fMRI	Greater BOLD in amygdala-pregenual ACC
Mansson et al. (2015)	26	Internet-CBT	fMRI	BOLD response patterns in the fear-expressing dorsal ACC-amygdala regions were highly predictive of long-term treatment outcome
Furmark et al. (2002)	18	CBT; citalopram	[H ₂ ¹⁵ O] PET	Sites of action of citalopram and CBT were amygdala, hippocampus and neighbouring areas
Furmark et al. (2005)	36	Citalopram; NK ₁ antagonist	[H ₂ ¹⁵ O] PET	Administration of both NK ₁ -antagonist and citalopram improved SAD and attenuated neural activity in medial temporal lobe network
Faria et al. (2014)	72	SSRI	[H ₂ ¹⁵ O] PET	Amygdala-frontal co-activation patterns differentiate effective from ineffective anxiolytic treatments
Van der Linden et al. (2000)	15	SSRI	Tc-99m HMPAO SPECT	SSRI treatment led to significantly reduced activity in the left temporal cortex; the left mid frontal cortex; and the left cingulum
Evans et al. (2009)	12	Tiagabine	[¹⁸ F] FDG PET	Following treatment with tiagabine glucose uptake in the PFC was increased
Kilts et al. (2006)	12	Nefazodone	[H ₂ ¹⁵ O] PET	Decrease of rCBF in right amygdala and hippocampus; after treatment, increase in left middle occipital, and on both sides in lingual gyri and hippocampi

dampen their phobic experience (Van Ameringen et al. 2004).

In a study with [H₂¹⁵O] PET, during public versus private speaking, subjective anxiety increased more in patients with SAD than in a healthy control group. Increased anxiety was accompanied by enhanced regional blood flow in the amygdaloid complex in the social phobics relative to the comparison subjects (Tillfors et al. 2001). In another study by this research group, individuals speaking alone before they were speaking in front of an audience were compared with those who did the reverse. Anticipation of a public speaking challenge was accompanied by enhanced cerebral blood flow in the right dorsolateral PFC, left inferior temporal cortex and in the left amygdaloid-hippocampal region. Brain blood flow was lower in the left temporal pole and bilaterally in the cerebellum in the anticipation group (Tillfors et al. 2002). In a study with [¹⁸F]fludeoxyglucose ([¹⁸F]FDG) PET, individuals with SAD demonstrated less pre-treatment regional cerebral metabolic rate of glucose uptake (rCMRglu) within the ACC and ventral medial PFC at baseline compared with the healthy controls.

In a PET study with SAD patients who underwent a public speaking-challenge at baseline and after placebo treatment, salivary cortisol increase after placebo treatment was positively associated with hypothalamic rCBF in a midbrain cluster encompassing the hypothalamus with its statistical maximum in the mammillary bodies, while negative covariations were observed in the medial PFC as well as in the motor and pre-motor

cortices. These results suggest that stress-induced cortisol excretion in SAD may be inhibited by activity in the medial PFC and enhanced by activity in the hypothalamus (Ahs et al. 2006). In a PET study with the [¹¹C]5-hydroxytryptophan ([¹¹C]5-HTP), serotonin synthesis was examined in SAD patients (Frick et al. 2015). The authors demonstrated increased [¹¹C]5-HTP influx rates in the amygdala, raphe nuclei region, caudate nucleus, putamen, hippocampus and ACC of patients with SAD compared with healthy controls, supporting an enhanced serotonin synthesis rate (Frick et al. 2015).

Studies showing changes after treatment are summarised in Table 6.

Dopamine. Based on the high rate of social phobia in Parkinson's disease (Riedel et al. 2010), which is characterised by reduced dopaminergic and noradrenergic functioning, abnormal dopamine functioning had been hypothesised for SAD. In a case-control study using SPECT technology, Tiihonen et al. (1997) reported lower striatal density of the DAT in SAD patients compared with control subjects. This finding was replicated in another SPECT study of DAT binding (Warwick et al. 2012). Conversely, van der Wee et al. (2008) reported a significantly higher binding potential for the DAT in the striatum of psychotropic medication-naïve patients with SAD compared with healthy controls.

Several studies investigated dopamine receptor radiotracers. One by Schneier et al. (2000) using the dopamine D₂ and D₃ receptor tracer [¹²³I]-

iodobenzamide demonstrated lower D₂ receptor binding in the striatum of patients with SAD than in healthy controls, but in a follow-up study (Schneier et al. (2009) with [¹¹C]-raclopride binding, the authors could not find any significant difference in dopamine D₂ receptor (*DRD2*) availability nor in DAT binding between SAD and control groups.

A more recent study using high-resolution PET and the high-affinity *DRD2* antagonist radioligand [¹¹C]FLB 457 before and after CBT showed a negative correlation between symptom change after CBT and D₂ receptor binding, thus indicating a role for the dopamine system in cortical and limbic brain regions in the pathophysiology of SAD (Cervenka et al. 2012).

Serotonin. In a study using [¹¹C]WAY-100635 PET, reduced 5-HT_{1A} binding in the amygdala and mesio-frontal areas was demonstrated in a SAD sample (Lanzenberger et al. 2007). Brain 5-HTT availability was increased in thalamus, but not in midbrain in patients with SAD in a study using [¹²³I]-beta-phenyl-tropane SPECT (van der Wee et al. 2008).

Another PET study showed that dysregulation of cortisol levels might increase the vulnerability for SAD, by altering limbic serotonergic 5-HT_{1A} receptors. Indeed, SAD patients displayed significantly lower baseline cortisol plasma levels compared with normal controls and strong negative correlations between cortisol levels and 5-HT_{1A} binding in amygdala, hippocampus and retrosplenial cortex, were observed (Lanzenberger et al. 2010).

Some studies looked at changes after treatment with SSRIs, which belong to the standard drugs used to treat SAD. Interestingly, Pantazatos et al. (2014) reported that before treatment SAD patients show reduced functional connectivity in left hippocampus-left temporal pole, and this brain index discriminates SAD from both PDA patients and healthy controls. Moreover, increased following the 8 weeks treatment with paroxetine increased functional connectivity and restored to levels comparable to the ones of healthy volunteers. This study suggests promise for emerging functional connectivity-based biomarkers for SAD diagnosis and pharmacological treatment effects.

Effect of successful treatment was also observed in another study including a large sample of SAD patients and a placebo group. Here, responders to SSRIs were characterised by treatment-induced co-activations of the rCBF between the left amygdala and the dorsolateral PFC as well as the rostral ACC. This represents an interesting finding on the way to identify useful neuro-markers, differentiating between successful and

unsuccessful anxiolytic treatments (Faria et al. 2014). An earlier study with a small sample of patients with SAD has reported that non-responders to SSRI medication had higher rCBF at baseline in the anterior and lateral part of the left temporal cortex and the lateral part of the left mid-frontal regions as compared with responders (Van der Linden et al. 2000). In addition, the magnitude of treatment response to the GABA reuptake inhibitor tiagabine was inversely correlated with pre-treatment rCMRglu within the ventromedial PFC in patients with generalised SAD (Evans et al. 2009). After escitalopram therapy, DAT binding was increased in patients with SAD, which may be due effect of serotonergic modulation by SSRI on the dopamine system (Warwick et al. 2012).

Oxytocin. The neurohormone oxytocin has emerged as an important regulator of anxiety and of stress-coping circuitries. Oxytocin is synthesised in magnocellular neurons located within the supraoptic, paraventricular and accessory nuclei of the hypothalamus. Anxiogenic and stressful stimuli activate the oxytocin system. Oxytocin acts as a modulator of anxiety-related behaviours and hypothalamic-pituitary-adrenal (HPA) axis activity (Neumann & Slattery 2015). Besides its effects on sexual reproduction and childbirth, it plays a role in social bonding.

In an fMRI study, oxytocin attenuated the heightened amygdala reactivity to fearful faces in individuals with SAD (Labuschagne et al. 2010). In fMRI studies with SAD patients, oxytocin enhanced functional connectivity of the amygdala with the rostral ACC/medial PFC (Dodhia et al. 2014; Gorke et al. 2015).

MRS

In an MRS study, a method for measuring whole-brain fluoxetine concentrations was tested (Miner et al. 1995). Another study measured choline, creatine, N-acetylaspartate and myo-inositol and found no change of these compounds after clonazepam treatment (Tupler et al. 1997). Phan et al. (2005) found glutamate (relative to creatine) levels were significantly higher in SAD patients than in healthy controls in the ACC, but not in the occipital cortex. Pollack et al. (2008) found significantly higher whole brain levels of glutamate and glutamine but no significant differences in GABA concentrations.

Specific phobias

In a systematic review of 38 studies involving two used structural MRI, 24 used fMRI, 11 used PET and

Table 7. Treatment biomarkers in OCD: summary of positive neuroimaging findings.

References	Number of patients	Treatment	Method	Predictor
Hoexter et al. (2013)	15	CBT	MRI	Improvement after CBT was correlated significantly with larger pre-treatment grey matter volumes within the right medial PFC
Hoexter et al. (2013)	14	SSRI	MRI	Improvement under fluoxetine treatment was associated with smaller pre-treatment grey matter volume in the middle-lateral OFC
Banks et al. (2015)	15	Surgery	MRI	Features of ACC structure and connectivity predict clinical response to dorsal anterior cingulotomy for refractory OCD
Shin et al. (2014)	25	SSRI	fMRI	BOLD in right ventral frontal cortex
Sanematsu et al. (2010)	17	SSRI	fMRI	BOLD in left superior temporal gyrus
Wen et al. (2013)	30	SSRI	SPECT	Global change in rCBF
Ho Pian et al. (2005)	15	SSRI	99mTc-HMPAO SPECT	Decreased thalamic blood flow in OCD patients responding to fluvoxamine
Rauch et al. (2002)	9	SSRI	PET	Higher rCBF in PCC and lower in OFC predicted better treatment response

one used SPECT, results converged to a greater activation in the insula, ACC, amygdala and prefrontal and OFC of patients exposed to phobia-related situations compared to healthy controls, thus supporting hypotheses of hyperactivation of a neuroanatomic structural network involved in specific phobia (Linares et al. 2012). A recent study examined grey and white matter changes with voxel-based morphometry in subjects with snake or dental phobia and healthy controls. Results showed that patients with dental phobia differed from individuals with snake phobia and healthy controls had significantly increased grey matter volumes in areas including the right subgenual ACC, left insula, left orbitofrontal and left prefrontal cortices (Hilbert et al. 2015).

OCD

At different levels of investigation, brain imaging studies have converged in showing that abnormalities within orbitofrontal-basal ganglia neural circuits represent a core feature of OCD pathology (Saxena & Rauch 2000). These brain networks are thought to be pivotal in mediating the disorder, the associated cognitive impairment and its clinical manifestations. To account for additional neuropsychological and neuroimaging findings, a quantitative meta-analysis of functional MRI studies has been performed providing experimental evidence to extend the anatomical model and include areas of the frontal and the parietal cortex (Menzies et al. 2008).

Structural brain morphology – MRI studies

Structural brain abnormalities are frequently found in OCD patients at the group level, compared with controls. In OCD, structural changes are widespread

throughout the whole brain, but are seen especially in the dorsolateral prefrontal striatal cortices and temporo-parieto-occipital areas. However, meta-analysis of structural studies revealed reduced grey matter density in parietal and frontal areas (superior frontal gyrus, supramarginal gyrus [BA 40], dorsolateral PFC [BA 9] and anterior PFC [BA 10]), and increased grey matter in the lateral part of the OFC (BA 47) and in the putamen to be associated with OCD (Rotge et al. 2010).

Similarly, altered morphology in terms of increased surface area of the tail and head of the caudate and thalamus and increased thickness in the lateral OFC, left medial temporal cortex and right posterior cingulate were shown not only in patients with OCD but also (to a less degree) in their unaffected first-degree relatives (Shaw et al. 2015). The results were compatible with theoretical models of OCD behaviour, involving increased functional activation of sub-cortical nuclei coupled with reduced cortical inhibition (Fineberg & Sahakian 2010), and suggested these anatomical changes may represent a useful vulnerability marker for the investigation of genes linked to the disorder.

Although many studies reveal structural brain abnormalities mainly in the fronto-striato-thalamic circuit (especially in globus pallidus and medial frontal cortex), Tan et al. (2013) showed that alterations are not limited to fronto-striatal circuits but might extend to temporal and parietal areas (in line with results from functional MRI meta-analyses by Menzies et al. 2008). Thus it is possible that other regions, e.g., parietal lobe, may also play a role in OCD (Valente et al. 2005), which might contribute to neuropsychological signature and symptomatology of OCD patients. In fact, this was confirmed by a more recent asystematic review of voxel-based morphometry studies, where consistent evidence was found for volume reductions in the

dorsolateral prefronto-striatal “executive” circuit, which includes the dorsomedial, dorsolateral, ventrolateral and frontopolar prefrontal cortices and of reciprocally connected regions, the temporo-parieto-occipital associative areas as a possible sign for altered anatomical connectivity in fronto-subcortical circuitry. Moreover, increased volumes of the capsula interna and reduced frontal and parietal white matter volumes were reported in this study (Piras et al. 2015).

Interestingly, a direct comparison between OCD and PDA or PTSD showed that decreased bilateral grey matter volumes in dorsomedial and anterior cingulate gyri were shared across disorders. However, increased grey matter in the anterior putamen was a unique feature of OCD; in sharp contrast, the same brain region showed abnormally low volumes in PDA and PTSD as compared to healthy volunteers (Radua et al. 2010). A multicentre study showed smaller medial frontal grey matter volume in OCD patients in BA 6/8/9, extending to the anterior cingulate BA 24/32, and inferior frontal gyrus/insula (BA 13/47). OCD patients additionally showed a relative preservation of putamen and OFC with aging (de Wit et al. 2014).

In a review of DTI studies in OCD, the cingulate bundle, the corpus callosum and the anterior limb of the internal capsule are most commonly affected by decreased white matter integrity in adult OCD patients, although findings in the literature are generally inconsistent, possibly due to differences in sample characteristics or method of analysis (Koch et al. 2014).

Changes after treatment. Hoexter et al. (2013) found a significant correlation between improvement of OCD symptoms under fluoxetine treatment and smaller pre-treatment grey matter volume in the middle-lateral OFC compared to patients who did not exhibit an improvement in symptom severity under fluoxetine, while improvement of OCD after CBT was correlated significantly with larger pre-treatment grey matter volumes within the right medial PFC (Table 7).

Data are also available from OCD patients undergoing brain surgery for refractory OCD. Banks et al. (2015) revealed features of ACC structure and connectivity that predict clinical response to dorsal anterior cingulotomy. They suggested that the variability seen in individual responses to a highly consistent, stereotyped procedure might be due to neuroanatomical variation in the patients.

Functional imaging research

Symptom provocation. A common assay to investigate the neural underpinnings of OCD is represented

by symptom provocation experimental paradigms in which patients are exposed to individually tailored stimuli designed to induce an anxious or symptomatic state. One of the seminal studies, using PET, found increased glucose consumption in the right caudate, left ACC and bilateral OFC during symptom provocation (Rauch et al. 1994). The involvement of these and other brain regions was confirmed by a following study in which symptom provocation was used in conjunction with fMRI (Breiter et al. 1996). More recently, a novel experimental paradigm was designed to achieve live tailored provocation either by placing provoking stimuli (i.e., “contaminated” gloves) in patient’s hands during fMRI scanning or by having real-time video exposure to the experimenter disorganising and littering patient’s home. In this study, effective symptom provocation was associated in OCD patients with deactivation of the caudate and pre-frontal circuits and hyperactivation of the subthalamic nucleus and putamen (Banca et al. 2015). Dimensionality of OCD, i.e., the fact that patients have thoughts and compulsions related to different domains (i.e., symmetry, forbidden thoughts, cleaning, hoarding) has been investigated by Mataix-Cols et al. (2004) using symptom provocation, highlighting that different neural circuits might be implicated in the manifestation of different OCD symptom dimensions.

Resting state. Departing from traditional localisation approaches, it is postulated that psychiatric disorders are underpinned by alterations within distributed brain networks for which resting state investigation represents a valuable tool. Resting state studies might have a key relevance in the OCD framework where basal ganglia-thalamo-cortical connectivity features are likely to play a pivotal role. A seminal paper demonstrated that by sampling the signal from different areas of the basal ganglia and addressing functional connectivity with the rest of the brain, OCD patients showed an imbalance of connectivity of fronto-striatal loops (Harrison et al. 2009). Namely, reduced functional connectivity was identified along the dorsal axis linking the caudate to the lateral PFC and increased connectivity was identified along the ventral axis between the nucleus accumbens and the anterior PFC. By adopting a data-driven approach, instead of seed based analysis, clusters of decreased global connectivity in the left lateral PFC were found in OCD patients. Within regions of interest (ROIs) located in subcortical structures, increased global connectivity in the dorsal striatum and anterior thalamus was found, which was reduced in patients on medication (Anticevic et al. 2014). Results have been extended further by showing that

pathophysiological changes within fronto-striatal circuits are common across OCD symptom dimensions. However, it is possible to identify unique functional connectivity “fingerprints” related to symptom dimensions: *viz* aggression symptoms were related to altered functional connectivity between the ventral striatum, amygdala and ventromedial frontal cortex; sexual/religious symptoms involving ventral striatum-insula connectivity; and hoarding modulated the strength of functional connectivity between both ventral and dorsal striatal regions and distributed frontal areas (Harrison et al. 2013). Teasing apart the potential confounding effect of medication, Posner and colleagues (Posner et al. 2014) found that un-medicated OCD patients showed hypo-connectivity along the ventral/limbic circuit possibly pointing to this network as candidate vulnerability marker to test the effect of pharmacological or behavioural treatment. The degree of functional connectivity of relevant brain areas seems to have a clinical relevance for OCD. For example, higher symptom severity was linked to greater hypo-connectivity of the right superior OFC (Meunier et al. 2012). In fact, excessive fronto-striatal connectivity between the nucleus accumbens and the PFC was normalised after deep brain stimulation treatment, and the degree of connectivity normalisation significantly correlated with OCD symptoms improvement (Figeet et al. 2013).

Changes after treatment. Different studies evaluating the impact of SSRI and using different imaging modalities and methods of analysis consistently have shown that lower pre-treatment glucose metabolic rate with the OFC is associated with better response to SSRI in OCD patients (Swedo et al. 1992; Saxena et al. 1999; Rauch et al. 2002). However, this does not directly transfer to behavioural therapy where better response is associated with higher cerebral metabolic rate in the left OFC (Brody et al., 1998). In a longitudinal study, hemodynamic response of the ACC and right OFC to obsession-inducing images was reduced after CBT (Morgievet et al. 2014) and associated with reduced symptom severity. In a longitudinal study, resting state data of OCD patients were acquired before and after SSRI treatment. As effect of time and chronic medication with SSRIs is correlated with changes in connectivity degree in right ventral frontal cortex (Shin et al. 2014) as well as activation in the right cerebellum and in the left superior temporal gyrus (Sanematsu et al. 2010) (Table 7).

PET and SPECT

In vivo quantification of specific neurochemicals in various brain regions by means of proton magnetic

resonance spectroscopy (MRS) in OCD has received limited research attention to date, and findings should be regarded as preliminary (Brennan et al. 2013). Several factors might limit the results, for example, small sample sizes, varying severity, illness duration and treatment as well as suboptimal technical methodologies (i.e., low magnetic field, single voxel assay). Further technological advances and the possibility of coupling several imaging techniques might hold important findings in the future.

Serotonin. In respect to the role of the 5-HTT in the neurobiology of OCD, SPECT and PET studies have shown inconsistent results, apparently because of different tracer properties, but also due to the variability in patient characteristics (gender, 5-HTTLPR genotype, smoking, age at onset, etc.). So, no difference in 5-HTT density was observed between unmedicated OCD patients of both genders and healthy controls, however reduced 5-HTT availability in various brain regions was found by several other studies, and higher mid-brain-pons [¹²³I]-beta-CIT binding in one report (for review, see Maron et al. 2012).

5-HT_{2A} receptors. One PET study using a low selectivity tracer [¹⁸F]altanserin showed significantly higher 5-HT_{2A} receptor distribution in the caudate nuclei in untreated OCD patients as compared with age- and gender-matched healthy volunteers. 5-HT_{2A} receptor binding did not correlate significantly with the severity of OCD and appeared to be not different from the findings in healthy controls after treatment with SSRIs (Adams et al. 2005). Other PET studies used a selective radioligand [¹¹C]MDL 100907. One showed a significant reduction of cortical 5-HT_{2A} receptor availability in drug-naïve patients, which correlated negatively with clinical severity (Perani et al. 2008). However, Simpson et al. (2011) failed to detect group differences in [¹¹C]MDL 100907 binding potential in any region of interest and demonstrated no correlation between regional 5-HT_{2A} availability and OCD severity, indicating that OCD is not characterised by major changes in 5-HT_{2A} availability in the cortical or limbic brain regions.

5-HT synthesis capacity rates. A PET method estimating brain regional 5-HT synthesis was previously validated in both healthy and clinical populations by using the tracer α -[¹¹C]methyl-I-tryptophan (¹¹C-AMT; Diksic & Young 2001). Berney et al. (2011) had recently reported that medication-free patients exhibited significantly greater [¹¹C]-AMT K* trapping in the right hippocampus and in the left temporal gyrus relative to age- and sex-matched controls. Furthermore, these differences were more robust in male patients, who also had

higher [^{11}C]-AMT K^* values in the caudate nucleus. In addition, there were significant and positive correlations between OCD symptom severity and 5-HT synthesis rate in the caudate and the temporal lobe of the patients, suggesting that increased 5-HT neurotransmission could be a contributing factor to the pathophysiology and symptom profile of OCD.

Changes after treatment with serotonergic drugs.

A seminal paper hinting at the tight reciprocal influence of cortical and basal ganglia brain areas demonstrated that clomipramine, a tricyclic antidepressant with serotonin reuptake inhibiting properties, led to a decreased metabolic rate in the OFC and caudate nucleus and an increase in the right anterior putamen (Benkelfat et al. 1990). In a study using 5-HTT imaging with [^{123}I]beta-CIT SPECT before and after 1 year of citalopram treatment of OCD, it was shown that higher occupancy of 5-HTT by citalopram was associated with better clinical response (Stengler-Wenzke et al. 2006). Responders to SSRIs treatment showed greater glucose consumption normalisation in the anterior lateral OFC and caudate nucleus compared with non-responders (Saxena et al. 1999); in addition, activity in the lateral OFC (BA 11 and BA 47) predicted subsequent reduction in OCD symptom severity associated with treatment with SSRIs (Saxena et al. 1999; Rauch et al. 2002) (Table 7).

Across PET and SPECT studies, the head of the caudate was found to be associated with greater glucose metabolism and reduced cerebral blood flow in OCD patients, versus controls (Whiteside et al. 2004). A large study in OCD has suggested that baseline increased rCBF in forebrain regions and decreased perfusion in posterior brain regions can potentially predict treatment response to SSRI monotherapy or combined medication with quetiapine (Wen et al. 2013). Furthermore, higher whole brain perfusion as well as higher rCBF values in the cerebellum were associated with drug response (Ho Pian et al. 2005). In contrast, no pattern of baseline activation distinguishing responders from non-responders to subsequent SSRI pharmacotherapy was detected in another other SPECT perfusion study, which included SAD, OCD and PTSD samples (Carey et al. 2004).

A study comparing response to CBT and the SSRI fluoxetine had complicated results; correlations between normalised left OFC metabolism and treatment response revealed that higher normalised metabolism in this region was associated with greater improvement in the CBT-treated group, but worse outcome in the SSRI group (Brody et al. 1998).

No significant differences in pre-treatment rCBF were observed in a SPECT study between responders and non-responders to behaviour therapy, however, the post-treatment rCBF values in the left medial PFC and bilateral middle frontal gyri were significantly lower in the responders than in the non-responders (Yamanishi et al. 2009).

Paediatric OCD

Even though the interpretation of imaging data in paediatric OCD is more difficult than in adult patients, in light of the extensive structural and functional maturation occurring at cortical and subcortical level during the developmental period, several studies have been conducted in the field.

A report reviewing 28 neuroimaging studies using various techniques and including a total of 462 paediatric OCD patients documented a dysfunction of the prefrontal-striatal-thalamic circuit, with the involvement of other basal ganglia structures (putamen and globus pallidus) and the thalamus. In contrast, adult studies reported mainly involvement of the caudate nucleus and OFC (Huysen et al. 2009). More recently, a literature review and preliminary meta-analysis of neuroimaging studies in paediatric OCD found altered functional activation in the same brain regions of affective and cognitive cortico-striatal-thalamic circuits as for adult OCD patients, despite some variations in the direction of activation difference (Brem et al. 2012). Studies that have been published after this latter MRI review have shown different abnormalities in specific brain regions of paediatric OCD. In particular, a DTI study found that patients with childhood OCD exhibited significantly greater fractional anisotropy compared with matched controls in left dorsal cingulum bundle, splenium of the corpus callosum, right corticospinal tract and left inferior fronto-occipital fasciculus (Gruner et al. 2012).

A Canadian study found that OCD children and adolescents had higher levels of right prefrontal white matter choline and N-acetylaspartate (NAA), with levels of NAA, creatine and myo-inositol being positively and significantly correlated with severity of symptoms (Weber et al. 2014). In the same year, another American study showed compromised white matter integrity and reduced myelination in some brain regions of children with OCD, particularly the corpus callosum and fibre tracts that connect the frontal lobes to widespread cortical and subcortical targets (Rosso et al. 2014). More recently, a Spanish study did not confirm the hypothesis of differences in glutamate plus glutamine concentrations in the ACC between

children and adolescents with OCD and healthy controls; however, the authors found differences in the glutamine concentration in OCD patients depending on the duration of illness (Ortiz et al. 2015).

OCRDs

As compared with the relatively large pool of OCD imaging studies, relatively few imaging studies exist for the other OCRDs.

Trichotillomania. For trichotillomania, early studies using ROIs approaches provided mixed results, such as reduced cerebellar volumes (Chamberlain et al. 2009). In a whole brain analysis, trichotillomania was associated with increased grey matter density in the striatum, amygdalo-hippocampal formation and cortical regions, including frontal and cingulate cortex (Chamberlain et al. 2008). Another study found excess cortical thickness in right frontal and other regions in patients with trichotillomania and their clinically unaffected first degree relatives versus controls (Odlag et al. 2014). However, reduced thickness of the right para-hippocampal gyrus in trichotillomania cases as compared with controls was identified in a separate trichotillomania study (Roos et al. 2015). No differences in white matter tracts between trichotillomania patients and controls were identified using tract-based spatial statistics (TBSS; Roos et al. 2013); while a separate non-TBSS study identified reduced fractional anisotropy (suggestive of disorganised tracts) in regions close to the anterior cingulate, pre-supplementary motor area and temporal cortices (Chamberlain et al. 2010). Remarkably, in an independent study, similar white matter findings were found in people with *skin picking disorder* versus controls (Grant et al. 2013).

Hoarding. Most hoarding-related imaging research has examined hoarding within the context of other disorders – notably OCD, dementia and brain damage – rather than as a discrete entity (Mataix-Cols et al. 2011). In one fMRI study using an inhibitory control task, aberrant brain activation differed between hoarding disorder and OCD, when a region of interest approach was used (Tolin et al. 2014).

BDD. There have been a handful of structural imaging studies to date (for a detailed review of imaging findings in BDD, see Rossell et al. 2015). For example, one study found reduced OFC and thalamus volumes in patients with BDD versus controls (Atmaca et al. 2010); while another reported reductions in amygdala, dorsal

anterior cingulate and other regions in patients (Buchanan et al. 2014). Widespread white matter abnormalities have been identified in BDD, perhaps most consistently in the inferior longitudinal fasciculus, which connects temporal and occipital lobes, likely involved in the processing of body image (Rossell et al. 2015).

Paediatric autoimmune neuropsychiatric syndrome (PANS, formerly known as paediatric autoimmune neuropsychiatric disorders associated with streptococci, PANDAS)

It has been hypothesised that one OCD subtype is associated with autoimmune disorders triggered by streptococcal infections (e.g., rheumatic fever and Sydenham's chorea) (Miguel et al. 2005). Children who develop acute OCD after a group A β -hemolytic streptococcal (GABHS) infection were first described by Swedo (2002), who coined the formerly used acronym PANDAS. Since many children get GABHS infections without developing PANDAS, a genetic vulnerability or susceptibility has been proposed.

Volumetric MRI studies found larger caudate, putamen and pallidus in PANDAS patients (Giedd et al. 2000). MRI and functional imaging studies in Sydenham's chorea have localised acute changes to the basal ganglia (Singer & Loiselle 2003). In an MRI study evaluating the size of the basal ganglia in patients with Sydenham's chorea and healthy controls, children with Sydenham's chorea had a 10% increase in size of the caudate and a 7% increase in size of both putamen and globus pallidus (Giedd et al. 1995). Similar volumetric analyses in children with PANDAS showed that the average size of the caudate, putamen and globus pallidus, but not thalamus or total cerebrum, was significantly greater in the affected group than in healthy controls (Giedd et al. 2000).

Viewed collectively, the above imaging studies indicate potentially important differences in neurobiological abnormalities in OCRDs as compared with OCD itself. Conclusions are tempered by the relatively limited quantity of imaging research available for these other conditions.

PTSD

Structural brain morphology – MRI studies

MRI studies (Bremner et al. 1995, 1997; Gurvits et al. 1996; Stein et al. 1997; Woon et al. 2010) and a meta-analysis (Karl et al. 2006) consistently showed that PTSD is associated with reduced hippocampal volumes meta-analysis, with the exception of one study (Bonne et al. 2001). In addition, significant reduction in grey

Table 8. Treatment biomarkers in PTSD: summary of positive neuroimaging findings.

References	Number of patients	Treatment	Method	Predictor
Levy-Gigi et al. (2013)	39	CBT	MRI	Response to CBT is predicted by greater right hippocampal grey matter volume
Dickie et al. (2013)	30	CBT	MRI	Symptom improvement was correlated with and predicted by cortical thickness in the right subgenual ACC
Bryant et al. (2008a)	13	CBT	MRI	Response to CBT is predicted by larger rostral ACC
van Rooij et al. (2015)	41	CBT	fMRI	Responders showed increased pre-treatment activation of the left inferior parietal lobe during contextual cue processing compared with CBT-nonresponders
Bryant et al. (2008b)	14	CBT	fMRI	Poor improvement after CBT was associated with greater bilateral amygdalae and ventral ACC activation in response to masked fearful faces
Zhu et al. (2015)	21	SSRI	fMRI	After treatment, significantly increased amplitude of low-frequency fluctuation (ALFF) values were observed in the left OFC, while decreased ALFF values were found in the precuneus
Seedat et al. (2004)		SSRI	[^{99m} Tc]-HMPAO-SPECT	Treatment with citalopram resulted in significant deactivation in the left medial temporal cortex irrespective of clinical response
Lindauer et al. (2008)		Psychotherapy	[^{99m} Tc]-HMPAO-SPECT	Response correlated positively with activation in the left superior temporal gyrus, and superior/middle frontal gyrus

matter volume was observed in the left anterior cingulate gyrus, left insula and right parahippocampal gyrus in PTSD patients (Meng et al. 2014). Grey matter reduction in medial PFC, left hippocampus, left middle temporal gyrus and right superior frontal gyrus were also reported (Li et al. 2014). The decreased volume of the inferior temporal cortex was found to be inversely related to self-reported anxiety level in PTSD patients (Kroes et al. 2011). Findings of reduced hippocampal and medial OFC volumes were independently shown by Levy-Gigi et al. (2013), in this study no difference was found for amygdala volumes. However, an investigation of a larger sample of nearly a hundred PTSD patients were characterised by decreased amygdala volumes (Morey et al. 2012). Volume reduction was not associated with the PTSD chronicity, trauma load and severity of depressive symptoms.

According to a recent review of studies investigating white matter volume in PTSD, volume reductions were reported more often than increases in these populations, however, these findings require further replication as the heterogeneity of the exact locations indicated only a weak overlap across published studies (Daniels et al. 2013). In the same review, when addressing DTI studies differences were found consistently in the cingulum and the superior longitudinal fasciculus, however the directions of the difference (i.e., increases in fractional or decreases anisotropy) were equally found.

Changes after treatment. Changes in the hippocampus and the amygdala were seen in PTSD patients responding to CBT (Table 8).

Functional imaging research

In a meta-analysis of fMRI studies in PTSD, SAD and specific phobia, greater activity than matched comparison subjects in the amygdala and insula were found in all three disorders but to a less degree in PTSD than in the other two disorders. By contrast, only patients with PTSD showed hypo-activation in the dorsal and rostral ACC and the ventromedial prefrontal cortex-structures linked to the experience and regulation of emotion (Etkin & Wager 2007).

Changes after treatment. Three studies evaluated changes of brain activation following psychological therapy (Bryant et al. 2008a, 2008b; van Rooij et al. 2015). One study investigated the effect of pharmacological medication with SSRI on low-frequency fluctuation showing increases in the left OFC and decreases in the precuneus (Zhu et al. 2015) (Table 8).

PET and SPECT

Brain 5-HTT availability was reduced in the amygdalae in a sample of PTSD patients (Murrough et al. 2011b). Although no difference in regional 5-HT_{1A} receptor binding was reported in a previous PET study in PTSD (Bonne et al. 2005), another PET study has demonstrated up-regulation of brainstem and forebrain 5-HT_{1A} receptors (Sullivan et al. 2013). The recently developed 5-HT_{1B}-receptor selective radiotracer [¹¹C]P943 appears promising in examining these receptors in PTSD. To date, however, there is only one published study that used this tracer showing that early

Table 9. Heritability of anxiety disorders, OCD and PTSD.

Disorder	Heritability estimates
Panic disorder	48% (Hettema et al. 2001)
Agoraphobia	67% (Kendler et al. 1999)
GAD	32–38% (Scherrer et al. 2000; Dellava et al. 2011)
SAD	39–56% (Kendler et al. 1999; Mosing et al. 2009; Isomura et al. 2015)
Specific phobia	25–59% (Kendler et al. 1999; Van Houtem et al. 2013); in children: 60% (Bolton et al. 2006)
SepAD	43–73% (Bolton et al. 2006; Scaini et al. 2012)
OCRDs	
OCD	27–47%; for adults while for early onset paediatric OCD: 45–65% (Van Grootheest et al. 2005)
Hoarding	51–71% (Mathews et al. 2007; Monzani et al. 2014)
Trichotillomania	32–78% (Novak et al. 2009; Monzani et al. 2014)
Skin Picking	40–44% (Monzani et al. 2012)
PTSD	13–70% (True et al. 1993; Koenen et al. 2002; Sartor et al. 2012)

trauma exposure is associated with reduced functioning of the 5-HT_{1B} receptor in the human brain (Murrough et al. 2011a).

A reduction in benzodiazepine binding in the brain localised to the mPFC was found in a PET study (Bremner et al. 2000a).

Changes after treatment. In a SPECT study, treatment with citalopram resulted in significant deactivation in the left medial temporal cortex unrelated to clinical response (Seedat et al. 2004). In another SPECT study, treatment effects of brief “eclectic” psychotherapy correlated positively with activation in the left superior temporal gyrus, and superior/middle frontal gyrus (Lindauer et al. 2008) (Table 8).

Genetic markers

Albeit indicative, family studies have the drawback of being unable to disentangle genetics from environmental factors, as common traits may be due not only to genetic influences but also be transmitted via shared environmental factors and model learning. Twin studies can more precisely separate genetics, shared environmental and other influences. It is assumed that most twins – monozygotic and dizygotic – share the same environment (or if some twins of a sample have not been brought up in the same family, the different environmental factors are equally distributed in monozygotic and dizygotic twins) and that unique environmental factors can be accounted for in twins in an easier way than in non-twin brothers and sisters. Thus, when a difference in concordance rates is detected, this is more likely due to genetic factors. Heritability is calculated from the difference in concordance rates for a specific disorder in monozygotic and dizygotic twins. Heritability estimates for anxiety disorders, OCD and PTSD are listed in Table 9.

Molecular genetic studies, mainly including linkage and association studies, are performed to

identify risk loci and risk genes, respectively, contributing to the heritability of disorders. Given the complex genetic and polygenic nature of anxiety disorders, OCD and PTSD, a multitude of common genetic variants is expected in this context, with each variant increasing the genetic disease risk by approximately 1–2%.

Linkage studies

Linkage studies analyse the co-inheritance of particular genetic markers with the disease of interest in families with several affected individuals. If a marker significantly co-segregates with the disease, it can be hypothesised that the region surrounding this marker (“locus”) contains genes that confer risk to the disease. Evidence for linkage is most commonly expressed as a logarithm of the odds (LOD) score, which is based on the number of estimates of recombination frequency. A LOD score greater than three is considered to have a significant odd in favour of genetic linkage and a LOD score less than three but greater than 1.9 is recognised as “suggestive” (Lander & Schork 1994). The advantage of linkage studies is the hypothesis-free model which does not take into consideration *a priori* hypothesis. However, detection sensitivity is rather low, particularly for complex genetic disorders such as anxiety disorders, OCD and PTSD where each individual gene is likely to have a small effect. Linkage studies in anxiety disorders have previously revealed several potential risk loci on chromosomes 1p, 4q, 7p, 9q, 11p, 15q and 20p for PDA, and on chromosomes 3q, 14p and 16q for agoraphobia, specific phobias and SAD, respectively (Smoller et al. 2008; Domschke & Deckert 2012).

Association studies

Association studies investigate the allelic frequency of a particular polymorphism in an *a priori* defined candidate gene in a patient sample as compared with a

Table 10. Genetic treatment biomarkers in anxiety disorders.

Study	Number of patients	Treatment	Genotype	Results
<i>PDA</i>				
Perna et al. (2005)	<i>n</i> = 92	SSRI (12 weeks)	<i>SLC6A4</i> 5-HTTLPR LL	Significant association between antidepressant treatment response and allelic variation within the promoter of the 5-HTT gene in female subjects
Yevtushenko et al. (2010)	<i>n</i> = 102	SSRIs (6 weeks)	<i>HTR1A</i> -1019 GG	Significant association between antidepressant treatment response and 5-HT1A-1019 GG genotype
Lonsdorf et al. (2010)	<i>n</i> = 69	CBT (10 weeks)	<i>COMT</i> rs4680 (Val158Met)	Significant association between CBT response and genotype
Reif et al. (2014)	<i>n</i> = 283	CBT (10 weeks)	<i>MAOA</i> -uVNTR	Carriers of the long <i>MAOA</i> VNTR alleles showed significantly worse outcome after CBT
<i>GAD</i>				
Narasimhan et al. (2011)	<i>n</i> = 155	SNRI (18 months)	<i>BDNF</i> rs6265 (Val66Met)	No association between rs6265 and antidepressant treatment response
Narasimhan et al. (2012)	<i>n</i> = 112	SNRI (18 months)	<i>COMT</i> rs4680 (Val158Met)	No significant association between antidepressant treatment response and rs4680
Cooper et al. (2013)	<i>n</i> = 112	SNRI (24 weeks)	Pituitary adenylate cyclase-activating peptide rs2856966 A	No significant association between A118G and antidepressant treatment response
Lohoff et al. (2013b)	<i>n</i> = 112	SNRI (24 weeks)	<i>SLC6A4</i> 5-HTTLPR LL	Significant association between antidepressant treatment response and genotype
Lohoff et al. (2013a)	<i>n</i> = 156	SNRI (24 weeks)	<i>HTR2A</i> rs7997012 G	Significant association between antidepressant treatment response and genotype
Perlis et al. (2013)	<i>n</i> = 164	SNRI (6–12 weeks)	<i>CRHR1</i> ; <i>DRD3</i> ; nuclear receptor subfamily group C1; phosphodiesterase 1A (<i>PDE1A</i>)	Variants in <i>CRHR1</i> , <i>DRD3</i> , nuclear receptor subfamily group C, member 1 (<i>NR3C1</i>) and <i>PDE1A</i> were associated with response to duloxetine
<i>SAD</i>				
Stein et al. (2006)	<i>n</i> = 32	SSRI (12 weeks)	<i>SLC6A4</i> 5-HTTLPR LL	Significant association between SSRI treatment response and <i>SLC6A4</i> 5-HTTLPR genotype
Stein et al. (2013)	<i>n</i> = 346	SSRI (10 weeks)	<i>RGS2</i>	Significant association between SSRI treatment response in two of four investigated <i>RGS2</i> SNPs
Andersson et al. (2013)	<i>n</i> = 314	CBT	<i>SLC6A4</i> , <i>COMT</i> and <i>TPH2</i>	No significant association between CBT response and genotypes
<i>OCD</i>				
Brandl et al. (2014)	<i>n</i> = 184	Various antidepressants (>10 weeks)	<i>CYP2D6</i>	Significantly more failed medication trials in <i>CYP2D6</i> non-extensive compared with extensive metabolizers
Qin et al. (2015)	<i>n</i> = 804	SSRIs	<i>DISP1</i> ; <i>GRIN2B</i> ; <i>PCDH10</i> ; <i>GPC6</i>	GWAS comparing responders and non-responders to SSRI treatment
<i>PTSD</i>				
Mushtaq et al. (2012)	<i>n</i> = 330	SSRI (12 weeks)	<i>SLC6A4</i> 5-HTTLPR LL	Relative to the SS and SL 5HTTLPR genotypes, the LL genotype is associated with greater responsiveness of PTSD to sertraline

sample of healthy controls. If the allelic distribution of this polymorphism differs significantly between patients and controls, the marker allele or another tagged polymorphism (with high linkage disequilibrium to the tested polymorphism), which has higher frequency in the patient sample compared to controls, may be associated with disease status. The advantage of association studies is their higher sensitivity to detect genetic variations with small overall effects; however, association studies are relatively prone to

high false-positive results, requiring replication in independent samples. A wealth of association studies in anxiety disorders has provided evidence for several potentially relevant risk genes (Domschke & Deckert 2012; Howe et al. 2015; Gottschalk & Domschke 2016). The candidates investigated in this hypothesis-guided study approach have mainly been derived from animal models of anxiety, challenge studies and/or psychopharmacological principles in anxiety disorders as reflected by the following chapters on e.g.,

neurochemistry, the HPA-axis, neurophysiological findings or sensitivity to carbon dioxide (CO₂) or cholecystokinin tetrapeptide (CCK-4).

Genome-wide association studies

It is important to note that many association findings in anxiety disorders described above have not been replicated and explain only a small fraction of the expected heritability, leaving the majority as the missing heritability in anxiety disorders. Recently, the approach of genome-wide association studies (GWAS) has been proposed to provide a powerful advantage to overcome the major limitations of candidate gene studies. GWAS allow us to genotype hundreds of thousands of polymorphisms across the whole genome, in a hypothesis-free manner, and expected to provide novel information regarding the involvement of genetic variation(s) in the phenotype or process of interest.

Gene–environment interaction

Despite the focus of the present review on biomarkers of anxiety disorders, OCD and PTSD, genetic factors cannot be considered without regard to environmental risk factors. This is because of the complex interaction between the genetic aetiology of anxiety disorders, OCD and PTSD and environmental influences such as abuse, loss/separation experiences in childhood or recent stressful life events (Klauke et al. 2010). Thus, gene–environment interaction studies are crucial in order to define the combined action of genetic markers and environmental factors, which will be most informative in the context of mental disorders. For instance, the serotonin transporter (*SLC6A4*) and neuropeptide S receptor 1 (*NPSR1*) risk variants have been shown to confer increased anxiety sensitivity in healthy subjects only in the context of a high load of early/recent life traumata (e.g., Klauke et al. 2011, 2012a). Moreover, early aversive life experiences might increase the vulnerability to anxiety in the presence of homozygosity of the catechol-O-methyltransferase (*COMT*) Val158Met Met allele or the low-activity monoamine oxidase A (*MAOA*) upstream variable number of tandem repeats (uVNTR) alleles as shown in healthy volunteers characterised for anxiety sensitivity (Baumann et al. 2013).

Pharmacogenetics

A substantial number of patients do not typically respond to standard treatments. There is a belief that

responsiveness to or tolerability of treatment may be influenced by inherited factors. Pharmacogenetics may significantly contribute to a better prediction of drug response and side effect tolerance by personalising the choice of the best pharmacological agent for a particular patient, taking into account genetic information that has an influence on drug metabolism, drug transport and drug mechanism. Furthermore, several studies have investigated the association between genotypes and response to psychotherapy. These “therapygenetic” studies have multiplied in the past decade due to the improved technology for detecting gene variants (Pickar & Rubinow 2001; Serretti et al. 2005). However, the best strategy to detect the key markers involved has not been clearly identified, since both candidate gene studies and GWAS provided results that fell short of these expectations (Fabbri et al. 2013).

To date, the majority of candidate gene studies involved in antidepressant response have been conducted in patients with depression; those have mainly investigated metabolism-related genes that encode for receptors and transporters in addition to proteins involved in second-messenger systems. The most promising results in the pharmacokinetic field have been reported for variations of genes encoding for the cytochrome P450 2D6 (*CYP2D6*) and P-glycoprotein, although comparative evidence between different drugs is present only for the *CYP2D6* gene variants (Porcelli et al. 2011). A complicating factor in relation to drug actions in the brain is that the number of potential pharmacodynamic targets appears to be quite large. The most important of a long list currently appear to be genes encoding *COMT*, *MAOA*, *SLC6A4*, tryptophan hydroxylase (*TPH*), the norepinephrine transporter (*NET/SLC6A2*) or *DAT (SLC6A3)*, monoamine receptors (*HTR1A*, *HTR2A*, *HTR6*, *HTR3A*, *HTR3B* and β_1 adrenoceptor), dopamine (DA) receptors, G-protein β_3 subunit, corticotropin-releasing hormone receptor I (*CRHR1*), glucocorticoid receptor, angiotensin-converting enzyme, circadian locomotor output cycles kaput (*CLOCK*), nitric oxide synthase, interleukin (IL)-1 β and brain-derived neurotrophic factor (*BDNF*; Kato & Serretti 2010).

Epigenetics

Epigenetics is the “branch of biology which studies the causal interactions between genes and their products, which brings the phenotype into being” (Waddington 1942). Epigenetic processes can change the final outcome of a locus or chromosomal region without changing the underlying DNA sequence (Goldberg et al. 2007), or in other words, “switch genes on and off”. For instance, DNA methylation of the cytosine

pyrimidine ring in CpG dinucleotides has been shown to be of major functional significance by mainly “silencing” gene transcription (cf. Jaenisch & Bird 2003). Other epigenetic mechanisms crucially governing gene function comprise for example histone acetylation or microRNAs. Thus, besides risk genes not yet identified in candidate gene studies, epigenetic processes might constitute one missing link in the so-called “missing” or “hidden” heritability.

However, even if it will be possible to identify epigenetic processes, which modulate gene expression in anxiety disorders, this does not imply that the influence of genetic factors is less than what it is currently estimated (i.e., from the moderate to high heritability scores for anxiety disorders). On the contrary, when a twin study is conducted, the probands already have the disorder. When a heritability of, for example, 50% is found in a twin study, and epigenetic processes triggered by environmental factors play a role, this can only mean that the heritability was even higher than 50% before the modulation of gene expression took place and epigenetic processes have attenuated the influence of heritability.

PDA

Association studies

Serotonin system. Within the serotonin system, compelling evidence has accumulated for *MAOA* to be associated with PDA: a polymorphism in *MAOA* promoter region (*MAOA-uVNTR*) has been found to impact on gene expression; high-expression alleles have been reported to increase the risk for PDA, particularly in female patients (Deckert et al. 1999; Reif et al. 2012). This excess of high activity *MAOA-uVNTR* alleles in female patients with PDA was not modified by the *SLC6A4* promoter polymorphism (Sand et al. 2000a). No association of the *MAOA-uVNTR* could be identified with personality traits linked to anxiety (e.g., neuroticism, harm avoidance) (Sabol et al. 1998; Eley et al. 2003; Yu et al. 2005). Moreover, *HTR1A*, *HTR2A* and the tryptophan hydroxylase 2 (*TPH2*) genes have been suggested to contribute to the pathogenesis of PDA (e.g., Rothe et al. 2004; Maron et al. 2005, 2007), while the role of *SLC6A4* in PDA is controversial (Deckert et al. 1997; Schumacher & Deckert 2010). An epistatic analysis of interactions between the functional serotonin receptor 1A (*HTR1A*) polymorphism, the *NET* variants as well as polymorphisms in the *MAOA* gene and the *COMT* gene (see below) has been performed by Freitag et al. (2006). A nominally significant interaction exists between the *HTR1A* and the *COMT* polymorphism

(Freitag et al. 2006), indicating the importance of serotonergic and catecholaminergic interaction.

Dopamine/Norepinephrine. The most consistently replicated vulnerability gene of the dopaminergic/noradrenergic system is the gene encoding *COMT*: A functional single nucleotide polymorphism (SNP) within *COMT*, rs4680 G/A, which leads to an amino acid change from valine (Val) to methionine (Met) at position 158 (Val158Met) is the focus of psychiatric research since the Val allele is associated with an increase in *COMT* enzymatic activity, which in turn results in a decrease of cortical dopamine levels (Chen et al. 2004). This functional Val158Met polymorphism has been found to be associated with the disease in females only and potentially in an ethnic-specific manner (Hamilton et al. 2002; Domschke et al. 2004, 2007). A recent meta-analysis, investigating the association between *COMT* Val158Met and anxiety-related traits, demonstrated that Val-homozygote white males had higher neuroticism, while Val-homozygote Asian males had higher harm avoidance trait (Lee & Prescott 2014). One of the few gene–gene interaction studies in PDA discerned a potentially epistatic effect of *COMT* and *HTR1A* (see above; Freitag et al. 2006). Lee et al. (2005) investigated three polymorphisms in the promoter region and the 5′ untranslated region (UTR) of *NET* for association with PDA in a German population of 115 patients and 115 control individuals and observed significant association of two polymorphisms (rs2397771 and rs2242446) in a subgroup of patients with PDA without agoraphobia. In a case–control study consisting of 449 PDA patients and 279 controls, Buttenshon et al. (2011) found seven SNPs (rs2242446, rs11076111, rs747107, rs1532701, rs933555, rs16955584 and rs36021) located within the 5′ end of *NET* to be significantly associated with the disorder. However, in another German population of 87 individuals with PDA compared with 89 control individuals, no significant association of six *NET* gene variants with PDA was observed (Sand et al. 2002). In addition, Esler et al. (2006) could not detect loss of function mutations in *NET* coding regions in PDA patients. Nevertheless, they detected hypermethylation of CpG islands in the *NET* gene promoter region, with potential silencer property in altering gene expression (Esler et al. 2006). Chromatin immunoprecipitation demonstrated binding of the inhibitory transcription factor, MeCP2, to the promoter region in PDA patients (Esler et al. 2006).

Moreover, in a family-based study including 622 individuals in 70 families, no significant association or linkage between dopamine D4 receptor (*DRD4*) or *DAT* polymorphisms and PDA was observed in multiplex

families (Hamilton et al. 2000). Yet, the authors could show LOD scores of ~ 1.1 and 1.05 for *DAT* and *DRD4* exon 1 loci, respectively, thus providing some weak support for a role for these polymorphisms in PDA (Hamilton et al. 2000).

GABA. Despite its obvious function in the therapy of anxiety disorders, a role of the GABA system has not been convincingly supported on a genetic level (Pham et al. 2009). Although significant linkage has been reported for a region on chromosome 15q near the GABA A receptor and suggestive evidence for loci on 2p, 2q and 9p with PDA in a study comprising 120 multiplex panic disorder pedigrees with a total of 1,591 individuals (Fyer et al. 2006), there is only sparse and not robustly replicated evidence for genes encoding the glutamate decarboxylase (GAD), GABA receptor, GABA transporter and the peripheral benzodiazepine receptor in PDA (Sand et al. 2000b; Domschke & Zwanzger 2008). A recent study, however, reported genetic evidence for the involvement of the GABA A receptor subunit $\beta 3$ and GABA A receptor subunit $\alpha 5$ genes in the susceptibility to PD (Hodges et al. 2014).

Acid-sensing ion channel (ACCN). CO₂ hypersensitivity has been associated with PDA (see Chapter "CO₂ hypersensitivity", Part II, Bandelow et al. 2016). An interesting potential PDA risk gene emerging from studies of the respiratory system is the acid-sensing ion channel (ASIC) 2 gene (*ACCN2*) coding for ASIC 1a, which is essential for CO₂-mediated fear behaviour and has been found to be associated with PDA (Smoller et al. 2014).

Neuropeptide S. Particularly compelling evidence has accumulated for the neuropeptide S (NPS) system in anxiety and arousal in rodent models of anxiety (for review, see Pape 2010), which is mirrored by several studies reporting association of functional *NPSR1* gene variation with PDA and several related dimensional phenotypes such as anxiety sensitivity or physiological arousal (Domschke et al. 2011); for review see Gottschalk and Domschke, 2016).

HPA-axis. The A allele of the *CRHR1* G/A variant (rs17689918) has been identified to be significantly associated with PDA in female patients as well as increased anxiety sensitivity scores and anxious apprehension prior to a behavioural avoidance task (Weber et al. 2015).

Other systems. In line with the CCK-4 acting as a potent inductor of panic attacks, association has been

reported for the cholecystokinin (CCK) gene and the CCK receptor 1 and 2 (*CCKAR* and *CCKBR*) genes with PDA (Kennedy et al. 1999; Hosing et al. 2004; Koefoed et al. 2010) (for review see Zwanzger et al. 2012).

It is known that patients with PDA are sensitive to caffeine-containing drinks. The adenosine receptor is targeted by caffeine and has been implicated in anxiety also on a genetic level with converging evidence for a variant in the adenosine A_{2A} receptor gene (*ADORA2A*) to be associated with PDA (Deckert et al. 1998; Hamilton et al. 2004).

GWAS. Only few GWAS have been conducted so far in PDA in relatively small samples compared with schizophrenia or bipolar disorder, with the most compelling evidence from a German study for a role of the transmembrane protein 132 gene (Erhardt et al. 2011) and some meta-analytic support for the bradykinin receptor B2 and NPY receptor Y5 gene loci in Japanese patients with PDA (Otowa et al. 2012).

A meta-analysis of GWAS of patients with different anxiety disorders (GAD, PDA, SAD and specific phobias) identified the following markers showing the strongest association: rs1709393 located in an uncharacterised non-coding RNA locus on chromosomal band 3q12.3 and rs1067327 within *CAMKMT* encoding the calmodulin-lysine N-methyltransferase on chromosomal band 2p21 (Otowa et al. 2016).

Epigenetics

The first studies of DNA methylation in anxiety disorders have revealed significant hypomethylation of the *MAOA* and glutamate decarboxylase 1 (*GAD1*) genes in PDA (Domschke et al. 2012b, 2013). Recent reports of genetic variation in microRNAs to be associated with PDA point to a potential role of this particular epigenetic mechanism in the pathogenesis of anxiety disorders (Muinos-Gimeno et al. 2011; Hommers et al. 2015a).

Gene–environment interaction

In patients with PDA, separation life events were reported to interact with *SLC6A4* and *HTR1A* gene variants (Choe et al. 2013). On an epigenetic level, promoter methylation of the *MAOA* and *GAD1* genes has been found to negatively correlate with the experience of adverse life events in the past 12 months in PDA patients as well as in healthy controls suggesting DNA methylation as a functional

joint between genetic and environmental factors (Domschke et al. 2012b, 2013).

Imaging/intermediate phenotype genetics

As reviewed above, altered structural and functional neural activation patterns have been identified in the context of anxiety disorders. These imaging markers of anxiety disorders have been suggested to be driven by genetic factors and thus to constitute valid intermediate phenotypes of anxiety disorders (for review, see Domschke & Dannlowski, 2010).

In PDA and related traits, the *NPSR1* gene has been investigated most comprehensively by means of an imaging genetic approach: While healthy probands carrying the *NPSR1* T risk allele showed increased amygdala activation in response to fearful faces (Dannlowski et al. 2011), in patients with PDA the *NPSR1* T risk allele conferred decreased activation of the dorsolateral prefrontal, lateral orbitofrontal and ACC during fear-relevant face processing (Domschke et al. 2011). *NPSR1* T allele carriers have also been found to display lower glutamate/glutamine-to-creatine ratios in the ACC during CCK-4-induced panic challenge paradigms in an MRS study (Ruland et al. 2015). The notion of a disrupted cortico-limbic interaction emerging from these and related findings in healthy probands (e.g., Beste et al. 2013; Tupak et al. 2013; Guhn et al. 2015; Neufang et al. 2015) has been shown to possibly arise from a dysfunctional maturation of cortico-limbic connectivity in adolescence (Domschke et al. 2015a). Functional neuroimaging furthermore revealed reduced activation of prefrontal areas in a differential conditioning task, indicating disturbances of fear generalisation, and increased activity of the amygdala in female PDA patients carrying the *CRHR1* risk allele A during a safety-learning paradigm (Weber et al. 2015). Several further imaging genetic studies in PDA have provided evidence for genetic as well as epigenetic variation in e.g., the *COMT*, *HTR1A* and *ACCN2* genes to confer a distorted cortico-limbic interaction particularly during emotional processing with an overactive limbic system and a decreased inhibitory function of cortical regions (Domschke et al. 2006, 2008; Smoller et al. 2014; for a comprehensive review see Domschke & Dannlowski 2010).

Besides neural network markers, other anxiety-related intermediate phenotypes have been discerned to be linked to genetic risk factors in healthy probands, such as anxiety sensitivity (e.g., Stein et al. 1999), behavioural inhibition (Smoller et al. 2005), responsivity to panicogenic challenge tests with CO₂ or CCK-4 (see above; Maron et al. 2008; Schruers et al. 2011), the

acoustic startle response (Montag et al. 2008; Klauke et al. 2012b; Gajewska et al. 2013; Domschke et al. 2012a, 2015b), peripheral sympathetic activity (Domschke et al. 2009) or anxiety response to caffeine (Alsene et al. 2003; Childs et al. 2008).

Pharmacogenetics

Two available studies in PDA have demonstrated that better response to antidepressant (SSRI) treatment is predicted by the *5-HTTLPR* L-allele and the *HTR1A* -1019C allele, respectively (Perna et al. 2005; Yevtushenko et al. 2010). The *COMT* 158Val allele was associated with greater symptom relief during exposure-based CBT (Lonsdorf et al. 2010), while carriers of the long *MAOA-uVNTR* alleles showed significantly worse outcome after CBT (Reif et al. 2014).

Positive findings for genetic treatment biomarkers in anxiety disorders are summarised in Table 6.

GAD

Association studies

MAOA and *SLC6A4* have been found to be potentially implicated in the pathogenesis of GAD (Tadic et al. 2003; You et al. 2005), while association of GAD with *HTR1A* gene variation was partly mediated by comorbidity with depression (Molina et al. 2011). A recent study reported the Met allele of the functional *BDNF* Val66Met polymorphism to be associated with GAD risk along with an increase in serum BDNF levels (Moreira et al. 2015).

Pharmacogenetics

An intensive search for genetic predictors of treatment response has also been conducted in GAD, where a few genes, including the ones coding for the pituitary adenylate cyclase-activating peptide, *SLC6A4*, *HTR2A*, *CRHR1*, the dopamine D3 receptor (*DRD3*), the nuclear receptor subfamily group C, member 1 (*NR3C1*) and the phosphodiesterase 1A (*PDE1A*), were found as potential markers predicting response to either venlafaxine or duloxetine medication (Table 6).

SAD

Association studies

Norepinephrine. Gelernter et al. (2004) detected significant linkage for SAD on chromosome 16. Since the gene encoding NET, *SLC6A2*, maps to this broad region, it has been hypothesised that this gene may

be a possible candidate for influencing social phobia risk (Gelernter et al. 2004).

Dopamine. A significant impact of several polymorphisms in *DRD2*, *DRD3* and *DRD4* in addition to *DAT* (*SLC6A3*) on SAD was excluded in a sample of 17 multiplex social phobia families (Kennedy et al. 2001).

Epigenetics

Patients with SAD showed significantly decreased oxytocin receptor (*OXTR*) gene methylation as compared with healthy controls (Ziegler et al. 2015). Hypomethylation of this CpG site was further found to be associated with higher scores on SAD severity scales, and an increased saliva cortisol response during the Trier Social Stress Test in healthy controls (Ziegler et al. 2015).

Gene–environment interaction

While high social support was shown to constitute a protective factor against SAD *per se*, low social support was reported to increase SAD risk in individuals with the long and more active *5-HTTLPR* *L*-allele (Reinelt et al. 2014).

Imaging (epi-)genetics

The less active and short *S* allele of the *5-HTTLPR* polymorphism was found to be associated with symptom severity and amygdala excitability in SAD patients during social anxiety provocation in relation to general affective ratings using [$H_2^{15}O$]PET (Furmark et al. 2004).

In another [$H_2^{15}O$]PET study, placebo response was associated with reduced stress-related activity in the amygdala only in SAD patients who were homozygous for the long *L* allele of the *5-HTTLPR* or the *G* allele of the *TPH2* *G-703T* polymorphism, but not in carriers of the *S* or *T* alleles (Furmark et al. 2008). In a similar study, patients with SAD as well as controls showed increased activation in the left amygdala in response to angry faces when compared with neutral ones. The response was more pronounced in carriers of the *5-HTTLPR* short *S* allele and/or *TPH2* *T* allele (Furmark et al. 2009). In an imaging epigenetics approach, increased amygdala response during social phobia-related word processing has been identified in patients with SAD (Ziegler et al. 2015).

Pharmacogenetics

Reduction in social anxiety symptoms during SSRI treatment was significantly associated with *5-HTTLPR*

genotype in a very small sample (Stein et al. 2006). However, none of three gene candidates (*5-HTT*, *COMT* and *TPH2*), predicted response to CBT in another, larger study (Andersson et al. 2013). Recently, the most powerful study ($n = 346$ patients) with SAD has found that two of four SNPs within the regulator of G-protein signalling 2 gene (*RGS2*) predicted remission to sertraline treatment, suggesting that this gene could be a biomarker of the likelihood of substantially benefiting from SSRI medication among patients with SAD (Stein et al. 2013) (Table 6).

Specific phobia

Association studies

The long and more active *MAOA* *uVNTR* alleles have been found to be associated with anxiety disorders of the phobic spectrum (Samochowiec et al. 2004). In Han Chinese patients with specific phobias, association with a *BDNF* gene variation has been reported (Xie et al. 2011).

Intermediate phenotype genetics

In a study with patients suffering from blood-injury phobia, homozygosity for the *ADORA2A* 1976T allele as compared to the presence of at least one 1976C allele, resulted in a significantly increased respiratory rate and a trend towards elevated measures of blood pressure and respiratory minute volume. These results suggest that blood-injury phobia might be modulated by the *ADORA2A* 1976C/T polymorphism for which a link with sympathetic psychophysiological indicators of anxiety-related arousal was found (Hohoff et al. 2009). None of the sympathetic measures was influenced by *COMT* or *NET* polymorphisms.

SepAD

A common genetically determined neurophysiological vulnerability underlying childhood onset SepAD (C-SepAD) and adult PDA has been suggested based on Donald Klein's longstanding separation anxiety–PDA hypothesis (Bandelow et al. 2001; Preter & Klein 2008). Evidence supports this hypothesis suggesting a shared genetic liability between SepAD and PDA (Roberson-Nay et al. 2010). Furthermore, in a multivariate Norwegian twin sample, Battaglia et al. (2009) demonstrated that shared genetic determinants appear to be the major underlying cause of the developmental continuity of C-SepAD into adult panic disorder and the association of both disorders with heightened sensitivity to CO_2 . This may be the primary underlying cause

of both disorders' association with heightened sensitivity to CO₂ and the developmental continuity of C-SepAD and adult PDA, as well as A-SepAD.

Association studies

Dopamine. Higher scores on attachment anxiety and possibly a combination of avoidance and attachment anxiety have been found to be associated with the presence of one or two copies of the *DRD2* A1 allele (Lawford et al. 2006).

Oxytocin. As expected, given the evolutionary conservation of the small nonapeptide oxytocin, mutation analysis of its gene has shown no consistent disturbance in A-SepAD (Costa et al. 2009a). A positive genetic association with A-SepAD has been found for the SNP, rs53576, within the *OXTR* gene. Specifically, the GG genotype has been linked to high levels of separation anxiety and insecure attachment in patients with major depression (Costa et al. 2009a). The *OXTR* rs53576 variant was furthermore found to moderate the influence of attachment and bonding styles during childhood on dimensional social anxiety in healthy probands (Notzon et al. 2016). Although the genetic function of the rs53576 SNP is not known, a recent study suggests that it may impact hypothalamic-limbic structure and function (Tost et al. 2010), while its location within the third intron might impact epigenetic regulation of *OXTR* expression.

Neurosteroids. A variation in the 18kDa translocator protein gene has been reported to possibly be involved in A-SepAD (Costa et al. 2009b, 2012).

OCD

Evidence from five genetic linkage analyses and over 100 genetic candidate gene association studies supports several candidate regions and genes in OCD, with the most consistent reports in the glutamatergic and serotonergic systems (Pauls et al. 2014).

Linkage studies

Childhood OCD. Even though childhood OCD is considered a highly familial disorder (do Rosario-Campos et al. 2005), there are few genetic studies in the OCD paediatric/adolescent population. A recent genome-wide linkage analysis identified five areas of interest on chromosomes 1p36, 2p14, 5q13, 6p25 and 10p13, with the strongest result on chromosome 1p36.33-p36.32 (Mathews et al. 2012). Furthermore,

chromosome 15q14 has previously been linked to familial OCD in another genome-wide linkage analysis, supporting preceding findings that this region may contain one or more OCD susceptibility loci (Ross et al. 2011).

Association studies

Serotonergic system. Genes related to the serotonergic neurotransmitter system have been examined extensively in the genetic risk of developing OCD given the role of serotonin in the proposed neuro-circuitry, and the significance of SSRIs as the first-line pharmacological treatment of OCD. A recent meta-analysis of OCD genetic association studies showed significant results for a serotonin transporter promoter (*SLC6A4*) polymorphism (*HTTLPR*) and the serotonin 2A receptor (*HTR2A*) rs6311 marker (Taylor 2013). Also, in an early onset paediatric study, the *HTTLPR* La allele conferred as risk allele (Walitza et al. 2014). However, two recent GWAS of OCD did not detect any significant markers related to this system (Stewart et al. 2013; Mattheisen et al. 2015).

Glutamatergic system. Evidence has implicated abnormalities in the glutamatergic system as part of the aetiology of OCD, with the most robust genetic results being from genes that are involved in this system. A meta-analysis by Taylor (2013) reported a non-significant trend in a glutamatergic system gene, the neuronal glutamate transporter gene (*SLC1A1*). Furthermore, although the first published GWAS of OCD by the International OCD Foundation Genetics Collaborative group did not detect genome-wide significant association between any tested markers and OCD diagnosis (Stewart et al. 2013), interesting trends were observed in several glutamatergic system genes including the discs large (drosophila) homologue-associated protein 1 (*DLGAP1*) and glutamate receptor, ionotropic, kainate 2 (*GRIK2*) genes. Another recent but more in-depth meta-analysis examining nine SNPs across the 3' region of the *SLC1A1* gene and OCD illness by Stewart et al. (2007) revealed a consistent nominally significant finding in one of the SNPs, rs301443, with another SNP showing modest association when controlled for gender (rs12682897). The second GWAS conducted by the OCD Collaborative Genetics Association also did not report any genome-wide significant results (Mattheisen et al. 2015) but detected a trend in the top-hit marker on chromosome 9 near the protein-tyrosine phosphatase, receptor-type, delta (*PTPRD*) gene, which promotes glutamatergic synaptic differentiation.

Dopamine. Interest in the dopaminergic system came from the treatment of OCD using antipsychotics as augmenting agents alongside SSRIs (Fineberg et al. 2013). Although Taylor (2013) in his recent meta-analysis of OCD genetic association studies showed nominal significant finding for the *COMT* rs4680 marker (OR = 1.200, 95% CI 1.001–1.438, $P = 0.010$), and non-significant trends for two additional dopaminergic system genes, the *DAT1* and *DRD3*, no further replication genetic studies support dopamine's genetic link to OCD.

Other systems. Genes involved in the *GABAergic* system have been investigated with inconsistent and non-replicated results (Taylor 2013). Similar lack of further support was reported for the *BDNF* gene including the most studied Val66Met (rs6265) variant (Zai et al. 2015b) and genes related to neuroplasticity (Taylor 2013).

Epigenetics

Epigenetics refers to the heritable changes in gene expression without changes to the underlying DNA sequence – a change in phenotype without a change in genotype. To date, there are no published epigenetic studies in OCD.

Imaging genetics

In a recent systematic review of imaging genetics of OCD, the use of anatomical or physiological imaging technologies as phenotypes to evaluate genetic variations (Grunblatt et al. 2014), the most promising results came from the serotonergic (*SLC6A4*, *HTR2A*), glutamatergic (*SLC1A1*, *SAP90/PSD95-associated protein 3* [*SAPAP3*]), and dopaminergic (*COMT*) systems. More specifically, genetic variations of the serotonergic system have been linked to anatomical changes in the OFC and the raphe nuclei; glutamatergic system to the OFC, ACC and the thalamus and dopamine-related variants to the putamen. However, these results are based on limited findings, and further replication and exploration is needed.

Pharmacogenetics

Several pharmacogenetic studies are listed in Table 10. No definitive results support a single genetic variation or gene that determines SSRI response in OCD; however, several SNPs across candidate genes within the cytochrome P450, glutamatergic and serotonergic systems appear interesting (Zai et al. 2015a). These markers include *CYP2D6*, *SLC6A4*, serotonin

1D β receptor, *HTR2A*, *SLC1A1* and the glutamate receptor, ionotropic, N-methyl D-aspartate 2B (*GRIN2B*).

However, the most intriguing pharmacogenetic findings involving both pharmacokinetic and pharmacodynamic lines of evidence have emerged from studies in OCD and have been reviewed in more details in very comprehensive review by Zai et al. (2014). As the authors summarised, only two cytochrome P450 liver enzyme genes, *CYP2D6* and *CYP2C19*, have been studied in relation to the SSRI response in OCD. This showed that non-responders appear to be more common among non-extensive metabolizers according to genetic status of *CYP2D6*, suggesting that genes regulating metabolism of drugs may play an important role in treatment response (Brandl et al. 2014). Regarding the pharmacodynamic studies in OCD, available data are still inconsistent, preliminary or not yet replicated in independent and well-powered samples. Among various candidates, a number of genes related to the serotonin, glutamate and dopamine systems, in addition to neurotrophic factors have been identified as promising genetic predictors of treatment response to antidepressants in OCD (Zai et al. 2014). Furthermore, OCD remains the only anxiety disorder, where the GWAS approach was applied to detect novel biomarkers of treatment response. Many new loci were identified as top hits in the recent GWAS of SSRI response in OCD patients including *GRIN2B*, glypican 6 (*GPC6*), dispatched homologue 1 (*Drosophila*) (*DISP1*), ankyrin repeat and fibronectin type III domain containing 1, arrestin domain containing 4 (T-cell lymphoma invasion and metastasis 1, protocadherin 10 (*PCDH10*) and *LOCT30101*) (Qin et al. 2015). However, a great deal of further research (Zai et al. 2014) is required to clarify their functional status and their potential role in the treatment response.

Genetics of other OCDs

Although knowledge is limited, there appear to be genetic differences between OCD and the other OCDs. The heritability scores for OCDs are shown in Table 9.

Very few studies have examined genetic factors in these disorders. Markers within *COMT* (Lochner et al. 2005b), neurotrophic tyrosine kinase receptor type 3 (Alonso et al. 2008), and *SLC6A4* (Hasler et al. 2006) have been examined in OCD patients with hoarding phenotype. Four candidates, *SAPAP3* (Bienvenu et al. 2009; Zuchner et al. 2009; Boardman et al. 2011), *HTR2A* (Hemmings et al. 2006), the SLIT- and NTRK-like family, member 1 gene (*SLITRK1*) (Zuchner et al. 2006), and genetic variations within the monoaminergic

system (Lochner et al. 2005a) have been investigated in OCD patients with grooming disorders including *trichotillomania*. Inconsistent findings were detected for *SAPAP3* and significant results for *HTR2A* and *SLITRK1* require replications. Only one genetic study (Phillips et al. 2015) has examined OCD candidate genes in BDD and antidepressant response, which was negative. No additional published studies to date have examined the genetic influence of antidepressant response in these conditions (Zai et al. 2015a). There are no published epigenetic or imaging genetic studies in either of these disorders to date.

In summary, these genetic findings, including imaging genetics and pharmacogenetics, in OCD are exciting but too premature to be used as biomarkers given the relatively small sample sizes and difficulty in replicating results. Even fewer studies have examined the genetics of other OCDs.

PTSD

Association studies

Association studies for PTSD have been summarised by Domschke (2012) and Koenen et al. (2013). These studies showed that various neurotransmitter systems may confer susceptibility to PTSD, including the serotonin system (*SLC6A4* promoter region polymorphism, *5-HTTLPR*), *HTR2A*, the HPA axis (the FK506 binding protein 5 gene, which is coding for a protein influencing glucocorticoid receptor sensitivity, *CRHR1*), the dopaminergic system (*COMT*, *DRD2* and *DAT1*), the endocannabinoid system (the cannabinoid receptor 1 gene) and the GABA system (GABA receptor subunit α_2 gene). Recent studies also showed an involvement of the adrenergic system, in particular the NET, in the genetics of PTSD (Pietrzak et al. 2013, 2015).

A study by Smith et al. (2011) addressed DNA methylation as a possible mediator of persistent changes in gene function following chronic stress. Global methylation was increased in subjects with PTSD. Together, these results suggest that psychosocial stress may alter global and gene-specific DNA methylation patterns potentially associated with peripheral immune dysregulation.

GWAS

In veterans with and without combat-related PTSD, a genome-wide SNP on chromosome 4p15, rs717947, was found to be associated with PTSD severity in a small sample. In a replication study with larger samples, this SNP rs717947 was significantly associated with PTSD diagnosis in females, but not in males. The

rs717947 was also found to be a methylation quantitative trait locus in the replication study (Almli et al. 2015). Another GWAS meta-analysis identified the phosphoribosyl transferase domain containing 1 gene as a genome-wide significant locus for PTSD (Nievergelt et al. 2015).

Epigenetics

Since PTSD is thought to emerge from the interactions between traumatic events and a genetic vulnerability (Auxemery 2012), epigenetic processes may crucially mediate these interactions. Most epigenetic studies have examined the methylation status of cytosine residues of genomic DNA. Overall, epigenetic regulation in PTSD has been supported by genes involved in: stress responses (e.g., the HPA axis), neurotransmitter systems, immune responses or repetitive genomic elements (Uddin et al. 2010, 2011), partly in a sexually dimorphic fashion (Uddin et al. 2013). Only few studies have conducted an epigenome-wide approach or used epigenome-wide markers (Rampp et al. 2014; Zannas et al. 2015).

Discussion

Neuroimaging

Over the past 30 years, brain-imaging methods have increasingly been applied in anxiety research. The widespread use of neuroimaging techniques has produced an increasingly diverse picture of the involvement of different brain structures and neurotransmitter systems in processing of fear. For example, some studies have emphasised the disruption of the inhibition of the amygdala by the prefrontal cortex in particular anxiety disorders, e.g., in SAD (Kasper et al. 2014). However, despite a plethora of high-quality publications in the field, imaging research has not yet succeeded in reliably identifying neuroanatomical, functional or metabolic alterations, which have been unequivocally associated with certain anxiety disorders. Several inconsistencies in the reported findings may be due to heterogeneity in diagnoses, paradigms, study designs, image acquisition methods or analysis, in addition to many various confounding factors. Some of the reported discrepancies in the results may have been due to artefacts. In particular, the issue of multiple testing in studies that examined ROIs may represent a substantial source of error. Given that numerous different ROIs can be compared statistically, the risk of false-positive (by chance alone) results is relatively high; however, voxel-based morphometry enables a whole-brain analysis without restricting the analysis to

specific brain regions and correction for multiple testing is usually applied in order to reduce the rate of false positive findings. Nonetheless, the choice of ROIs may be guided by expectation bias, e.g., as there is a widespread opinion that the amygdala is an important centre in anxiety control systems, and thus, some studies may have chosen the amygdala *a priori* as a ROI and have disregarded other regions that might also show associations with anxiety disorders. Moreover, due to the difficulty of recruiting large samples for imaging studies, risk of publication bias when smaller studies that reported null findings have not been published may be high.

The main challenge that we face is that we do not even know what we are searching for: Is an exaggerated anxiety response in a brain imaging procedure caused by an increased firing rate of nerve cells in a small brain nucleus? Is a decrease in ability to attenuate a physiological arousal reaction caused by the dysfunction of the brain network or a bundle of nerve cells, e.g., serotonergic neurons? When a certain brain region has been activated in an anxiety paradigm, does this represent a nucleus showing an anxiety response, or a bundle of nerve cells that passes through this region? Is anxiety caused by a fluctuation in serotonin levels at the synapses (too much or too little), during the wrong interval of time and/or at the wrong receptor location?

However, researchers should not be discouraged to continue their search of biomarkers in anxiety disorders. Clearly, brain-imaging methods, perhaps with more sophisticated and refined imaging techniques, will be the mainstay of neurobiology research in the next several decades.

Genetic research

In recent years, genetic research has completely changed the view on the aetiology of anxiety disorders, OCD and PTSD. Until the 1960s, the prevailing theories assumed that childhood adversities, rearing styles or unfavourable parental attitudes were responsible for the development of pathological anxiety. It was previously assumed that parental styles, e.g., rigid toilet-training practises, lead to internalised conflicts and predispose an individual to developing OCD, and severe trauma has been viewed as the sole reason for the development of PTSD. However, heritability estimates for anxiety disorders, OCD and PTSD vary between 25 and 75%, with an average of approximately 50%, thus leaving the remaining 50% for a complex interaction of environmental factors, such as dysfunctional rearing styles, childhood and adulthood

adversities and possible organic stressors like birth complications, substance abuse and many others.

However, although genetic factors play a major role in anxiety disorders in addition to OCD and PTSD, genetic research has not unequivocally succeeded in identifying genes reliably associated with one of these disorders. In linkage studies, LOD scores of over three, which mean that a linkage is being considered as significant, have not yet been found for any chromosomal regions with candidate genes in anxiety disorders, OCD or PTSD, underlining the complex genetic background of these disorders entailing multiple gene polymorphisms.

Since 2005, the approach of GWAS has provided a powerful tool and advantage to overcome the major limitations of candidate gene studies. GWAS allow us to genotype hundreds of thousands of polymorphisms across the whole genome with high reproducibility and low cost. In order to obtain reliable results with this method, very large sample sizes are needed, requiring international cooperation of genetic researchers to collect blood/saliva samples from as many patients as possible. However, when analysing a large number of SNPs, a high false positive rate can be expected. Using the conventional α level of 0.05 for 500,000 SNPs would result in approximately 25,000 false positive results. The traditional Bonferroni correction for multiple comparisons would be far too conservative. A newly developed method, joint analysis could result in increased power to detect genetic association (Skol et al. 2006). Moreover, we will have to keep in mind that psychiatric disorders are polygenic which does not make the problem less complex.

The currently known risk genes are of no diagnostic or predictive value, as the field is far from having identified the entirety of all genetic and epigenetic risk interactions. Future studies in larger samples, targeting genomic variations in a more comprehensive way (e.g., exome sequencing; see Goldman & Domschke 2014), including the use of advanced technologies, and additional subtle factors of gene regulation (e.g., copy number variations and various epigenetic mechanisms such as small non-coding RNAs (Hommers et al. 2015b; Ono et al. 2015), will aid in further unravelling of the genetic underpinnings of anxiety disorders, OCD and PTSD. Further progress in the field of anxiety disorders, OCD and PTSD genetics will aim to robustly establish valid biomarkers of disease risk, allowing for indicated and thus more effective preventive interventions.

In addition to the prediction of disease risk, genetic/epigenetic markers have been suggested to aid in the prediction of individual treatment response since there

is a considerable rate of non-response to initial pharmacological or psychological therapies. One goal of genetic research is the development of individualised treatment strategies. The first pharmacogenetic studies in the field of anxiety disorders, OCD and PTSD point to a potential role of the *SLC6A4*, *HTR1A*, *HTR2A*, *MAOA*, *COMT* and *CRHR1* gene variants in mediating interindividual differences in response to pharmacotherapy or CBT in PDA, SAD and/or GAD, respectively.

With further advances in genetic research, genetic information may provide guidance for innovative treatment options and individualised, i.e., personalised treatment (“precision medicine”) of anxiety disorders, OCD and PTSD, thereby decreasing the duration of patient suffering, reducing the number of ineffective medication trials, reducing health-care costs and improving patients’ quality of life.

Despite manifold methodological shortcomings, the neuroimaging and genetics fields are two of the most promising areas of neurobiological research.

Declaration of interest

Dr. Bandelow has been on the speakers’ and/or advisory board for Glaxo, Janssen, Lundbeck, Meiji-Seika, Otsuka, Pfizer and Servier.

Prof. Baldwin has attended advisory boards for Grunenthal, Eli Lilly, Lundbeck, Pfizer and Servier. His university has received grants from Lundbeck and Pfizer to support research into anxiety disorders.

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Dr. Jarema has been on the speakers’ and/or advisory board for Angelini, Janssen, Lilly, Lundbeck and Servier.

Dr. Wichniak has been on the speakers’ and/or advisory board for Angelini, Janssen, Lundbeck and Servier.

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