Functional neuroanatomy in panic disorder: Status quo of the research

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Abstract

AIM
To provide an overview of the current research in the functional neuroanatomy of panic disorder.

METHODS
Panic disorder (PD) is a frequent psychiatric disease. Gorman et al (1989; 2000) proposed a comprehensive neuroanatomical model of PD, which suggested that fear- and anxiety-related responses are mediated by a so-called "fear network" which is centered in the amygdala and includes the hippocampus, thalamus, hypothalamus, periaqueductal gray region, locus coeruleus and other brainstem sites. We performed a systematic search by the electronic database PubMed. Thereby, the main focus was laid on recent neurofunctional, neurostructural, and neurochemical studies (from the period between January 2012 and April 2016). Within this frame, special attention was given to the emerging field of imaging genetics.

RESULTS
We noted that many neuroimaging studies have reinforced the role of the "fear network" regions in the pathophysiology of panic disorder. However, recent functional studies suggest abnormal activation mainly in an extended fear network comprising brainstem, anterior and midcingulate cortex (ACC and MCC), insula, and lateral as well as medial parts of the prefrontal cortex. Interestingly, differences in the amygdala activation were not as consistently reported as one would predict from the hypothesis of Gorman et al (2000). Indeed, amygdala hyperactivation seems to strongly depend on stimuli and experimental paradigms, sample heterogeneity and size, as well as on limitations of neuroimaging techniques. Advanced neurochemical studies have substantiated the
major role of serotonergic, noradrenergic and glutamatergic neurotransmission in the pathophysiology of PD. However, alterations of GABAergic function in PD are still a matter of debate and also their specificity remains questionable. A promising new research approach is “imaging genetics”. Imaging genetic studies are designed to evaluate the impact of genetic variations (polymorphisms) on cerebral function in regions critical for PD. Most recently, imaging genetic studies have not only confirmed the importance of serotonergic and noradrenergic transmission in the etiology of PD but also indicated the significance of neuropeptide S receptor, CRH receptor, human TransMEMbrane protein (TMEM123D), and amiloride-sensitive cation channel 2 (ACC2) genes.

CONCLUSION
In light of these findings it is conceivable that in the near future this research will lead to the development of clinically useful tools like predictive biomarkers or novel treatment options.

Key words: Panic disorder; Anterior cingulate cortex; Amygdala; Insula; Functional magnetic resonance imaging; Diffusion tensor imaging; Voxel-based morphometry; Imaging genetics; Serotonin; Noradrenaline

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Core tip: This systematic review is focused on the most current research in the functional neuroanatomy of panic disorder. Recent neurofunctional studies suggest that the “fear network”, as proposed by Gorman et al., may need to be amended by additional regions (ACC, insula). Most recently, imaging genetic studies have not only confirmed the importance of serotonergic and noradrenergic transmission in the etiology of panic disorder (PD) but also indicated the significance of neuropeptide S receptor and corticotropin releasing hormone receptor gene variants. Imaging genetics studies are of major importance for the refining of the neuroanatomical model, because genetic risk variants may significantly influence fear network activity in PD.

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INTRODUCTION
Panic disorder (PD) is a considerably common psychiatric disease. According to epidemiological studies, six-month prevalence rates have been estimated roughly 1%[1] while lifetime prevalence amounts to 2%-5%[2,3]. PD is characterized by the occurrence of recurrent panic attacks, which are not explained by another psychiatric or medical condition. According to the Diagnostic and Statistical Manual of Mental Disorders (5th edition) panic attacks are sudden episodes of intense fear or discomfort that may be accompanied by palpitations, accelerated heart rate, sweating, trembling, chest pain, nausea or abdominal distress, dizziness, paresthesias, derealization, depersonalization, fear of “going crazy” or even fear of dying[4,5]. Besides panic attacks, many patients with PD suffer from anticipatory anxiety and maladaptive changes in cognition and behavior resulting in phobic avoidance[6]. PD therefore is often accompanied by agoraphobia and other mental disorders[4].

With regard to the pathogenesis of PD, several cognitive, behavioral and neurobiological theories have been developed[7-9]. Gorman et al.[10] introduced a neuroanatomical model that was aimed at integrating the different views of PD as either a biological or a psychological disease. The authors suggested experiments to test their theories. Later, they provided a revised version of their model[11]. Since its inception, this neuroanatomical model has stimulated and greatly influenced research in PD - primarily in the field of neuroimaging studies.

According to Gorman et al.[10] three components of PD: (1) acute panic attacks, (2) anticipatory anxiety; and (3) phobic avoidance are located in three specific sites of the CNS: The brainstem, limbic system, and prefrontal cortex. These three neural systems were suggested to be structurally and functionally closely connected, reflecting manifold interactions of the three mentioned clinical features. Hence, according to Gorman et al.[10] different treatments for PD and agoraphobia not only affect different symptoms of the illness but also different parts of the brain. Thus, according to the authors, antipanic drugs like tricyclic antidepressants (TCAs) or monoamine oxidase inhibitors (MAOIs) block brainstem-provoked panic attacks; benzodiazepines and relaxation training reduce anticipatory anxiety via the limbic system, and desensitization and cognitive therapies relieve phobic avoidance by influencing functions of the prefrontal cortex. In our opinion it is notable that both psychopharmacological and psychotherapeutic treatments are put on the same level by being conceptualized to act directly on specific neural networks. Therefore the neuroanatomical model proposed by Gorman et al.[10] successfully integrates biological and psychological facets of PD.

In the revised version of their hypothesis, Gorman et al.[11] suggest that the behavioral symptoms of PD are mediated by a “fear network” in the brain, which is centered in the amygdala and includes the hippocampus, thalamus, hypothalamus, the periaqueductal gray (PAG) region, locus coeruleus (LC), and other brainstem sites. This theory states that patients with PD have a decreased threshold for the activation of the fear network. Excessive activity in this network leads to autonomic and neuroendocrine activation through...
projections from the amygdala to the brainstem and hypothalamus, resulting in typical PD symptoms. The lateral nucleus of the amygdala receives afferents from cortical regions involved in processing and evaluating sensory information. According to Gorman et al.\(^\text{[11]}\) abnormal functioning in these cortical areas could potentially result in the misinterpretation of sensory information (bodily cues), leading to an inappropriate activation of the fear network via misguided excitatory input to the amygdala. The authors propose that activation of the fear network as a result of cognitive misinterpretations could lead to the release of certain neurotransmitters that can cause autonomic behavioral responses related to PD. These responses include an increase in respiratory rate, increases in blood pressure, heart rate, defensive behaviors and postural freezing. Thus, processes at the biological level can directly lead to behavioral symptoms\(^\text{[15]}\). With regards to drug therapy in PD, Gorman et al.\(^\text{[11]}\) not only stated that antidepressants exhibit their antipanic effects via the brainstem, as proposed in their original model\(^\text{[10]}\), but also that therapy with SSRIIs might act directly on the limbic system (in particular on the central and lateral nuclei of the amygdala; please see section “The role of serotonin”)\(^\text{[11]}\). In light of the above, it is intriguing that recent antidepressant medications seem to be able to enhance neuroplasticity mechanisms and adult neurogenesis in the hippocampus and even in the prefrontal cortex\(^\text{[12]}\). Therefore, due to its unique characteristics, the novel antidepressant agomelatine might also be effective in PD. Preliminary studies have provided encouraging results regarding effectiveness and tolerability of this substance, although it has to be noted that agomelatine is not yet approved for the treatment of PD.\(^\text{[13,14]}\)

One of the most important techniques of the neuroanatomical approach to PD is to perform neuroimaging studies on the brain regions that are supposedly active during panic attacks. Today, there are numerous neurofunctional, neurostructural, and neurochemical studies that have demonstrated the significant role of certain structures in the fear network\(^\text{[15-18]}\).

A promising new research method is “imaging genetics”. In this approach genetic information and functional magnetic resonance imaging (fMRI) data are combined in the same subject to define neuromechanisms linked to genetic variation\(^\text{[19]}\). Imaging genetics studies are of major importance for the adjustment and refining of the neuroanatomical model, because genetic risk variants may partly drive fear network activity in PD\(^\text{[15]}\). The aim of this review is to provide a comprehensive overview of the most significant findings in the field of the functional and structural neuroanatomy of PD. Because of the wide range of this topic, we will focus on recent studies. With regards to prior studies (published before January 2012), we refer to previously published review articles, e.g.\(^\text{[15-18]}\). However, a complete and exhaustive presentation of all relevant studies is infeasible and certainly beyond the scope of this work.

**MATERIALS AND METHODS**

We searched the electronic database PubMed for neurostructural, neurofunctional, and neurochemical studies on PD that were published in the period between January 2012 and April 2016. The search was conducted using the following search terminology: “(Panic disorder) and [functional magnetic resonance imaging (fMRI) or diffusion tensor imaging (DTI) or positron emission tomography (PET) or single-photon emission computed tomography (SPECT) or magnetic resonance spectroscopy (MRS) or near-infrared spectroscopy (NIRS) or imaging genetics or serotonin or norepinephrine or noradrenaline or locus coeruleus or dopamine or hypothalamic-pituitary-adrenal (HPA) axis or insula)”. The total number of publications found by the PubMed research was 457 (fMRI: 94; DTI: 2; PET: 5; SPECT: 5; MRS: 11; NIRS: 2; imaging genetics: 21; serotonin: 137; norepinephrine: 19; noradrenaline: 28; locus coeruleus: 3; dopamine: 8; HPA axis: 23; insula: 99). The total number of publications after screening for topic was reduced to 281 (fMRI: 88; DTI: 2; PET: 3; SPECT: 1; MRS: 8; NIRS: 1; imaging genetics: 17; serotonin: 106; norepinephrine: 11; noradrenaline: 4; locus coeruleus: 2; dopamine: 2; HPA axis: 16; insula: 20). The remaining 281 studies were screened for duplicates and finally evaluated for eligibility. Subsequently, a secondary search was conducted that involved a broad review of potential neuroimaging studies by carefully perusing through the citation lists of the retrieved articles. Thereafter, a final screening of the retrieved articles was performed to ensure that the focus of the articles was within the scope of the present review. The literature search was conducted both jointly and independently by the authors (TS, GW). Finally, 76 studies published between January 2012 and April 2016 were included in this review.

**RESULTS**

**Functional neuroimaging studies**

**Resting state studies:** Only a few studies investigated neural functional connectivity pattern using resting state functional magnetic resonance imaging (rs-fMRI) in patients with PD. In one of these studies, Pannekoek et al.\(^\text{[20]}\) examined differences in the resting-state functional connectivity (RSFC) of the amygdala, dorsal anterior cingulate cortex (dACC) as well as posterior cingulate cortex (PCC) among 11 patients with PD and 11 healthy controls. They mainly found an increased RSFC between the amygdala and the bilateral precuneus as well as altered RSFC between dACC and frontal, parietal and occipital areas. Lai et al.\(^\text{[21-23]}\) reported abnormalities in 30 first-episode medication-naïve patients with PD compared to 21 matched controls using different rs-fMRI parameters. They observed right-lateralized altered local
fractional amplitude of low frequency fluctuations (fALFF) signal in the occipital cortex, putamen and thalamus in PD patients\(^{[21]}\). ALFF represents the strength or intensity of low frequency oscillations in the BOLD (i.e., blood-oxygen-level dependent) signal. The fractional ALFF represents the ratio of the amplitude in a low frequency band to the amplitude in the total frequency band. The authors also observed abnormal regional homogeneity in the occipital cortex of PD patients compared to controls\(^{[22]}\) and decreased inter-hemispheric functional coordination (based on the voxel-mirrored homotopic connectivity) in PD patients in the PCC and precuneus.

Shin et al\(^{[24]}\) combined rs-fMRI and magnetic resonance spectroscopy (MRS) techniques to investigate the functional connectivity of the perigenual ACC in 11 patients with PD and whether or not it is mediated by the local gamma-aminobutyric acid (GABA) concentration. Patients showed increased RSFC between ACC and precuneus. This functional connectivity negatively was correlated with the GABA concentration of the ACC.

**Provocation studies:** As extensively described in a recent review by Dresler et al\(^{[15]}\), the most consistent differences between patients with PD and healthy controls yielded by provocation studies were found in the cingular, insular, frontal and brainstem areas. An electronic search of PD provocation studies between 2012 and 2016 returned only one additional investigation. Goossens et al\(^{[25]}\) studied the effects of hypercapnia on the brainstem BOLD signal in 15 patients with PD using fMRI. Three brainstem regions were defined as regions of interest (ROI) due to their putative involvement in panic and chemosensitivity: The PAG, the raphe nuclei and the LC. The authors demonstrated increased brainstem activation, i.e., located in the rostral raphe ROI in response to hypercapnia compared to 12 healthy controls and 15 healthy divers. However, a limitation of this study is a rather low voxel resolution, which limits the ability to differentiate between closely situated brainstem nuclei. Nevertheless, this study provides further support for the significant role of specific brainstem nuclei in triggering panic attacks.

**Motor, sensory and cognitive tasks**

Investigating auditory habituation by means of fMRI, Pfleiderer et al\(^{[26]}\) reported an increased activity of superior temporal and frontopolar cortex in 20 PD patients during the third block of auditory stimulation when compared to 20 healthy controls, as well as a positive correlation of these regions with anxiety measures.

Using fMRI, Wintermann et al\(^{[27]}\) studied a sample of 13 patients with PD both with and without agoraphobia, and 13 healthy controls while olfactorily stimulating their senses with stress-related sweat odors as well as artificial odors and non-fearful non-body odors. Although PD patients did not differ from HC regarding their olfactory identification ability, patients showed an increased activation in the superior temporal gyrus, the supramarginal gyrus, and the cingulate cortex for sweat odor caused by ergometric exercise. Presenting sweat odor from the anxiety condition, PD patients showed an increased activation in the inferior frontal gyrus (IFG), which was positively correlated with the severity of the psychopathology. By means of a pH-sensitive MRI strategy Magnotta et al\(^{[28]}\) investigated brain pH in 13 PD patients, which has been suggested to play a critical role in PD. Greater activity-evoked (visual flashing checkerboard) T1 rho changes, indicating pH changes in the visual cortex and ACC in patients compared to 13 HC, were detected.

**Emotional processing**

In order to understand the neurobiological underpinnings of PD, functional neuroimaging studies have often investigated the neurobiological bases of anxiety using paradigms focusing on activation correlates of stimuli with direct diagnostic relevance to PD. For example, panic-related pictures are presented to people suffering from PD to study the neural underpinnings of threat processing in this group\(^{[29]}\).

In the present review, studies will be presented divided in paragraphs for the modality of stimulation (i.e., pictorial stimuli, word stimuli, conditioned stimuli).

**Emotional processing - pictorial stimuli**

By means of fMRI, Gorka et al\(^{[30]}\) investigated insular response to unpredictable aversiveness using negative or neutral images selected from the International Affective Picture System in 13 PD patients with comorbid major depressive disorder (MDD). Patients with PD exhibited greater bilateral insula activation to unpredictable aversiveness compared with 19 healthy controls and 9 control patients with MDD only. This study highlights the specific role of the insula in the pathophysiology of anxiety disorders. Wittman et al\(^{[31]}\) investigated the neural correlates of the anticipation of agoraphobic situations in 72 PD patients with agoraphobia using agoraphobia-specific and neutral pictures presented with and without anticipatory stimulus. Stronger activations were observed in the bilateral ventral striatum and left insula in patients compared to 72 controls during the anticipation of agoraphobia-specific pictures.

Engel et al\(^{[22]}\) used pictures showing characteristic panic/agoraphobia situations to investigate activation differences in 19 PD patients in the predefined ROIs, i.e., prefrontal, cingulate, and insular cortex, and the amygdalo-hippocampal complex. Greater activation in PD patients than in 21 controls was detected in the insula, left IFG, dorsomedial prefrontal cortex (DMPFC), the left hippocampal formation, and left caudatum, when panic-related and neutral scenes were compared.

In a very recent fMRI study, Feldker et al\(^{[32]}\) presented panic-related and neutral visual scenes to
26 PD patients to study the neural underpinnings of threat processing. Similarly to the results found by Engel et al[22], patients showed hyperactivation in an extended fear network comprising the brainstem, insula, thalamus, ACC, mcingulate cortex and DMPFC for disorder-related vs neutral scenes, compared to 26 healthy controls. No significant amygdala differences between groups could be found. Subjective levels of anxiety significantly correlated with brainstem activation in PD patients.

Interestingly, Liebscher et al[33] very recently showed that successful cognitive-behavioral therapy (CBT) led to the patients receiving antidepressants and a wait-list control group.

Four recent studies investigated the neural activation in patients with PD during processing of emotionally neutral and disorder-specific faces. Ottaviani et al[34] studied amygdala response to masked fearful faces as well as to faces containing low range of spatial frequencies (LSF) in PD in 13 PD patients. In contrast to 15 healthy controls, patients failed to show bilateral amygdala activation to fearful masked faces vs neutral faces. LSF faces did not elicit an amygdala response in patients or controls. Demenescu et al[35] examined amygdala fMRI activation and its connectivity with the medial prefrontal cortex during emotional face perception in 14 patients with PD and 17 patients with social phobia. Patients with PD, but not those with social phobia showed hypoactivation in the amygdala and lingual gyrus during perception of angry, fearful, happy and neutral faces, compared to 16 healthy participants. The authors also found a positive correlation between degree of anxiety symptoms and functional connectivity of the amygdala to dACC and to DMPFC during perception of fearful faces.

Petrowski et al[36] investigated the neural activation of emotionally neutral faces and places in 15 PD patients with agoraphobia. Patients showed decreased neural activation in the occipital cortex and the cerebellum, and increased activation in the precuneus compared with 15 healthy controls.

Poletti et al[37] applied in their fMRI study a face-matching paradigm to 18 outpatients with PD to study the neural correlates of implicit emotional processing of fearful or angry affective facial expressions. The authors performed a correlational analysis and showed a positive relationship between anxiety sensitivity and fMRI activation during emotional processing in the a-priori defined ROIs, i.e., the DMPFC, ACC and insula, but not in the amygdala.

**Emotional processing - conditioned stimuli**

In an fMRI study with 20 PD patients, Dresler et al[38] applied an emotional Stroop task with panic-related and neutral words. On the behavioral level, PD patients showed a significant emotional Stroop effect (panic-related compared to neutral words), which, on the neural level, was accompanied by increased BOLD signal in the left IFG compared to 23 healthy controls.

van Tol et al[39] used fMRI to examine neural activation during the performance of an emotional word encoding and recognition paradigm in 51 patients with MDD, 59 patients with comorbid MDD and anxiety, and 56 patients with PD and/or social anxiety disorder without comorbid MDD. Both groups of patients, *i.e.*, with MDD and PD showed a common hyporesponse in the right hippocampus during positive word encoding compared with 49 control subjects. During negative encoding, altered insular, amygdala and ACC activation was observed in depressed patients only. During positive word recognition, only PD patients showed increased IFG activation.

**Emotional processing - word stimuli**

Only two recently published studies (from 2012 till 2016) used word stimuli to investigate altered functional activation in PD patients.

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**Emotional processing - conditioned stimuli**

In an fMRI study by Tuescher et al[40], 8 PD patients, 8 posttraumatic stress disorder patients and 8 healthy controls learned to associate specific neutral stimuli with either a safe or threat context indicating the possibility of an electrical shock. In comparison to the other two groups, PD patients demonstrated significantly less activation in response to the “threat” condition and increased activation in response to the “safe” condition in the subgenual cingulate cortex, ventral striatum, amygdala, and in the PAG.

Lueken et al[41] investigated neural activation patterns in 60 patients with PD and agoraphobia during a fear conditioning task. Differential conditioning was associated with enhanced activation of the bilateral IFG, whereas simple conditioning and safety signal processing were related to increased midbrain activation in patients with PD and agoraphobia vs 60 healthy controls. Anxiety sensitivity was positively associated with the magnitude of midbrain activation.

In a randomized, controlled, multicenter clinical trial Kircher et al[42] investigated the effects of cognitive behavioral therapy (CBT) and brain activation during fear conditioning in 42 medication-free patients with PD and agoraphobia. After CBT, patients revealed reduced activation for the conditioned response (CS’ > CS) in the left IFG compared to control subjects, which was correlated with reduction in agoraphobic symptoms. Patients also demonstrated increased functional connectivity between the IFG and amygdala, insula, as well as ACC after CBT.

**Emotional processing - internal triggers of fear**

The hypothesis of an increased attentional focus in PD towards bodily symptoms and their neural correlates was tested in a study by Pfleiderer et al[43] in a group at risk for PD, *i.e.*, 24 healthy female students with high...
levels of anxiety sensitivity. In contrast to 24 females with normal levels of anxiety sensitivity, the highly anxiety-sensitive group reported higher arousal scores and higher activation during interoception (attention on the heartbeats) in a network of cortical, i.e., frontal, motor regions and subcortical brain regions, i.e., claustrum, thalamus, amygdala, parahippocampus that overlaps with known fear circuitry structures.

**Brief summary:** Even if not always consistent, functional studies suggest abnormal activation mainly in an extended fear network comprising brainstem, insula, anterior and midcingulate cortex and lateral as well as medial parts of the prefrontal cortex. Interestingly, differences in amygdala activation were not as consistently reported as one would predict from the hypothesis of Gorman et al\(^{[51]}\).

**Structural neuroimaging studies**

Previous structural neuroimaging data in PD using a manual tracing of ROI as well as using an automated voxel-based morphometry (VBM) technique showed changes in total and in gray matter (GM) volume in limbic structures, e.g., in the amygdala, hippocampus, in frontal, cingulate and temporal cortical areas, in the basal ganglia, and in the brainstem structures, such as midbrain and rostral pons (comprehensive review of structural findings in PD until 2012 by e.g.\(^{[15,44]}\)). Regarding the latter finding, Fujiwara et al\(^{[45]}\) also showed increased midbrain volume in 38 PD patients compared to the control group of 38 matched healthy subjects.

With regard to subcortical structures, Kartalci et al\(^{[46]}\) reported that 27 patients with PD had significantly smaller pituitary volumes compared to 27 healthy subjects. In particular, patients with agoraphobia had a significantly smaller pituitary volume than patients without agoraphobia. In addition, Terlevic et al\(^{[47]}\) observed decreased hypothalamic volumes in 12 patients with generalized anxiety disorder, but not in those with PD (11 patients) compared to 21 healthy controls.

A cortical area often studied in PD and known for its reciprocal connections with the amygdala is the orbitofrontal cortex (OFC). Atmaca et al\(^{[48]}\) detected significantly smaller left OFC volumes in 20 PD patients compared to 20 healthy controls. Lai et al\(^{[49]}\) showed in 30 first-episode, drug-naive and late-onset PD patients lower GM volumes in left OFC, as well as in the left IFG, left superior temporal gyrus and in the right insula compared to 21 healthy controls. Na et al\(^{[50]}\) showed decreased GM volume in the left medial OFC in only 12 patients with both PD and agoraphobia compared to 22 healthy control subjects, but not in the 10 patients with PD and without agoraphobia nor in in the total sample.

Considering the white matter (WM) abnormalities in PD, the first study to investigate the WM integrity by applying the DTI technique revealed higher structural integrity in terms of greater fractional anisotropy (FA) values in the cingulum bundle\(^{[51]}\). In a recent study with 30 first-episode, medication-naive and late-onset PD patients, Lai et al\(^{[52]}\) showed reduced integrity in WM tracts of the right inferior fronto-occipital fasciculus (IFOF), left body of corpus callosum and left superior longitudinal fasciculus (SLF) when compared to 21 controls. Kim et al\(^{[53]}\) reported no significant difference in WM integrity between 26 PD patients and 26 healthy controls. However, the authors showed increased right-lateralized FA in posterior thalamic radiation, posterior and superior corona radiata, SLF, and sagittal stratum in catechol-O-methyltransferase (COMT) AA/AG genotype group compared to GG genotype in PD.

Kim et al\(^{[54]}\) reported decreased FA in frontal WM and the genu of the corpus callosum in 36 short-term medicated patients with PD compared to 27 healthy controls.

Furthermore, increased structural integrity in the internal capsule, corpus callosum, superior and posterior corona radiata, thalamic radiations, sagittal stratum, and SLF were detected in 12 PD patients with a suicide attempt compared to 24 PD patients without suicidal attempt\(^{[55]}\). However, due the lack of a healthy control group, this result is difficult to interpret.

Very recently, Lai et al\(^{[56]}\) compared 53 medication-naive patients with 1\(^{st}\)-episode PD, 53 medication-naive patients with 1\(^{st}\)-episode MDD and 54 healthy controls with regard to the WM integrity. The PD group had lower integrity in bilateral superior longitudinal fasciculi and left IFOF when compared to controls, whereas MDD patients revealed reductions in the WM integrity when compared to controls in the bilateral superior longitudinal fasciculi, inferior longitudinal fasciculi, inferior fronto-occipital fasciculi, and corpus callosum. The MDD group had lower WM integrity than the PD group in the left anterior thalamic radiation, left uncinate fasciculus, left IFOF, and bilateral corpus callosum.

Using VBM, Konishi et al\(^{[57]}\) demonstrated in 40 PD patients significant volumetric reductions in widespread WM regions including fronto-limbic, thalamo-cortical and cerebellar pathways compared to 40 healthy controls.

One structural imaging study investigated cortical gyrification in PD and detected significant reduction in gyrification in 23 patients with PD in the lateral brain, extending from the fronto-parietal to the temporal areas compared with 33 healthy individuals\(^{[58]}\).

Schwartz et al\(^{[59]}\) demonstrated a significant relationship between behavioral inhibition and hippocampal structure. Behavioral inhibition in childhood predicted reduced hippocampal volumes in adolescents who were offspring of parents with PD or PD with comorbid major depression, suggesting a role of the hippocampus in anxiety disorder. Trzesniak et al\(^{[60]}\) was one of the first to use proton magnetic resonance spectroscopy imaging \(^{[1]}\)H-MRSI to examine possible neurochemical abnormalities in the hippocampus in PD. Compared with 18
controls, twenty-five PD patients demonstrated significantly lower NAA/Cr in the left hippocampus.

Interestingly, Shinoura et al. [61] reported in a case report study that damages to the dorsal part of the ACC led to repeated panic attacks, indicating that this structure might play an important pathophysiologic role in PD.

**Brief summary of structural findings:** Previous and recent neurostructural findings indicate the presences of structural neuroanatomical alterations in PD in multiple cortical, subcortical and brainstem areas. Studies on WM also revealed significant abnormalities in the structural connectivity between these regions.

**Neurochemical alterations in PD**

**The role of serotonin:** It is well established that PD responds to drugs that increase serotonergic function, such as certain TCAs, inhibitors of monoamine oxidase (classical MAOIs), selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors SNRIs [62]. The SSRIs are now generally accepted as the first-line pharmacological treatment for PD [63]. Therefore, there is clear evidence for an important role of serotonin in the pathophysiology of PD that has led to extensive research – predominantly in neuroimaging and animal studies. According to Gorman et al. [64] the anxiolytic effect of SSRIs is mediated by at least three mechanisms: (1) inhibitory serotonergic projections from the raphe nuclei downregulate the activity of noradrenergic neurons in the LC [65]. The authors concluded that SSRIs, by increasing serotonergic activity in the brain, have a secondary effect of decreasing noradrenergic activity. This would lead to an amelioration of the somatic symptoms of panic attacks; (2) the projection of the dorsal raphe (DRN) neurons to the PAG is thought to modify defense/escape behaviors. As derived from animal studies, stimulation of the DRN markedly increases serotonin release in the dorsal PAG region, resulting in diminished activity in this brain area [66] associated with reduced defense/escape responses, *i.e.*, reduced propensity for panic-like reactions; and (3) as a third point, Gorman et al. [64] state that long-term treatment with an SSRI may reduce hypothalamic release of corticotropin-releasing factor CRF [66], CRF, which leads to adrenal cortical production of cortisol, is also a neurotransmitter in the CNS and has been shown to increase fear in preclinical models [67]. CRF enhances activity of the LC, when administered directly into the brain [68]. Furthermore, as stated by Gorman et al. [64] SSRIs seem to have an effect on the central nucleus of the amygdala itself. Serotonergic neurons originating in the dorsal and medial raphe nuclei project directly to the amygdala via the medial forebrain bundle [69]. Moreover, serotonergic neurons modulate sensory input at the lateral nucleus of the amygdala, inhibiting excitatory inputs from glutamatergic thalamic and cortical pathways [70]. According to Gorman et al. [64] this might be one of the major mechanisms for the anxiolytic action of the SSRIs.

Neumeister et al. [71] used PET to study serotonin type 1A (5-HT1A) receptor binding in 16 patients with PD and 15 matched healthy controls. PD patients showed lower values in the anterior and posterior cingulate cortex (PCC) as well as in the raphe nuclei. For the first time, this study provided in vivo evidence for the involvement of serotonin type 1A receptors in the pathophysiology of PD. Nash et al. [72] performed a 5-HT1A receptor binding study in PD patients at different stages of therapy. Nine drug-naive patients with PD, 7 patients who had recovered on SSRI medication and 19 healthy volunteers underwent a single PET scan. In untreated patients, both presynaptic and postsynaptic 5-HT1A receptor binding was reduced predominantly in the raphe nuclei, OFC, temporal cortex and amygdala. In recovered patients, presynaptic binding was also reduced, but there was no significant reduction in postsynaptic binding. Maron et al. [73] investigated the binding of the serotonin transporter (SERT) in patients with PD by SPECT. The authors reported a significant decrease in SERT binding in the midbrain, in the temporal lobes and in the thalamus in 8 acute PD patients, but not in 8 remitted patients in comparison to matched controls. Regional SERT binding was negatively correlated with the severity of panic symptoms. In a further SERT binding study of PD, Maron et al. [74] reported increased binding potential of the serotonin transporter in the raphe nuclei and several cortical areas. These findings were observed in male patients, but not in females. The authors concluded that distinctive functioning of the serotonin system in male and female PD patients might underlie the gender-dependent expression of the disease.

Given the fact that several neurochemical studies revealed altered 5-HT function in the raphe nuclei, it is noteworthy that structural abnormalities of this area have also been very recently reported. Šilhán et al. [75] detected reduced brainstem raphe echogenicity in 26 patients with PD by transcranial sonography (TCS). TCS of the raphe nuclei indicated the diagnosis of PD with a sensitivity of 64% and a specificity of 73%. These findings are suggestive of structural disintegration of the brainstem raphe in PD, an anatomical region, that has also been assumed to be a biological focus in the pathogenesis of depression [76].

Deakin et al. [77] proposed a hypothesis suggesting that different subpopulations of serotonergic neurons in the dorsal and median raphe nuclei through topographically organized projections to different brain regions are involved in the pathophysiology of anxiety and affective disorders. These different subpopulations of serotonergic neurons included: (1) serotonergic neurons within the DNR may reduce hypothalamic release of corticotropin-releasing factor CRF [66]; CRF, which leads to adrenal cortical production of cortisol, is also a neurotransmitter in the CNS and has been shown to increase fear in preclinical models [67]. CRF enhances activity of the LC, when administered directly into the brain [68]. Furthermore, as stated by Gorman et al. [64] SSRIs seem to have an effect on the central nucleus of the amygdala itself. Serotonergic neurons originating in the dorsal and medial raphe nuclei project directly to the amygdala via the medial forebrain bundle [69]. Moreover, serotonergic neurons modulate sensory input at the lateral nucleus of the amygdala, inhibiting excitatory inputs from glutamatergic thalamic and cortical pathways [70]. According to Gorman et al. [64] this might be one of the major mechanisms for the anxiolytic action of the SSRIs.
median raphe nucleus that increase stress resilience and moderate antidepressant-like effects. This concept partly overlaps with the model developed by Gorman et al. The Deakin/Graeff hypothesis still is a cornerstone that stimulates most recent research in PD.

Spiacci et al. investigated whether or not the enhancement of 5-HT-mediated neurotransmission within the dorsal PAG affects panic-like defensive reactions in rats submitted to a hypoxia challenge. Intra-dorsal-PAG injection of serotonin, a 5-HT1A receptor agonist or a 5-HT2A agonist reduced the number of upward jumps during hypoxia, interpreted as escape attempts. These effects were similar to those caused by chronic, but not acute, intraperitoneal administration of the antidepressant fluoxetine, or acute systemic administration of the benzodiazepine receptor agonist alprazolam. These observations confirm that the dorsal PAG is a key region involved in panic-like defensive behaviors. In a subsequent study, the authors demonstrated that serotonergic neurons of the lateral wings of the DRN (one of the five subnuclei of the DRN) are primarily involved in the mediation of PD-associated responses.

While the function of the DRN in the regulation of panic-like defense behaviors is well understood, the median raphe nucleus has received less attention. Generally, evidence derived from animal studies points to a relevant role of this raphe nucleus in the regulation of anxiety, but not of panic. This can be achieved through the serotonergic pathway that rises from the MRN to the dorsal hippocampus. Alternatively, the DRN seems to participate in both anxiety and panic. Interestingly, the regulation of anxiety by the dorsal and median raphe serotonergic pathway is carried out through different target structures - the amygdala, dorsal PAG and ventral hippocampus in the case of the DRN, and the dorsal hippocampus in the case of the median raphe nucleus. Because these structures have different functional profiles, it is conceivable that different aspects of anxiety are underpinned by each of them. In this regard, Gray et al. have argued that the amygdala may underpin the neurovegetative arousal and affective components of anxiety, whereas the dorsal hippocampus may regulate cognitive manifestations, such as worry. This suggestion is supported by the reported interaction between the dorsal hippocampus and the prefrontal cortex underpinning fear learning and memory. According to a recent study by Ohmura et al., the ventral (anterior part in humans) hippocampus may be involved in inappropriate retrieval of fear memory in PD. By microinjection of a 5-HT7 receptor antagonist into a rat’s ventral hippocampus, the expression of freezing behavior - an index of fear memory retrieval - was significantly suppressed. The authors argue that the 5-HT7 receptor might be a target of drug development for the treatment of PD.

Brief summary: A major role of serotonin in the pathophysiology of PD has been deduced from the therapeutic effects of serotonergic drugs. In accordance with this hypothesis, studies on 5-HT1AR and SERT binding have revealed altered and mostly reduced serotonergic activity in the raphe nuclei, orbitofrontal cortex, temporal lobes, ACC and PCC, amygdala, and hypothalamus in patients with PD. In the course of therapy with SSRIs, postsynaptic alterations seem to decline, while the presynaptic changes persist. In addition to these functional alterations structural abnormalities, e.g., disintegration of the raphe nuclei in the brainstem have also been described. Serotonin is synthesized primarily in the dorsal and median raphe nuclei. There is evidence from preclinical studies, that efferent inputs of dorsal raphe neurons may moderate panic-like defensive behaviors by controlling the activity of the dorsal PAG.

Alterations of the noradrenergic system

Much research into the neurochemistry of PD has explored the function of the monoamine transmitter noradrenaline. The noradrenergic system plays an important role by regulating the attentional alerting system that prepares and sustains alertness to process high priority signals. Noradrenergic transmission is closely linked to the serotonergic system and to the HPA axis, and therefore mediates between central arousal and the peripheral physical reactions. According to Gorman et al., the response to sensory input for the conditioned stimuli is carried out by amygdalar projections. Efferents of the central nucleus of the amygdala are directed to the LC, resulting in an increase in noradrenaline release and contributing to increases in blood pressure, heart rate, and the behavioral fear response. Recent studies in anxiety disorders and particularly in PD revealed higher baseline noradrenaline secretion and increased reactivity to challenges of the noradrenergic system. It has furthermore been suggested that the noradrenergically mediated attentional alerting system is particularly active in states of anxiety. The assumption of an important role of noradrenergic transmission in the pathophysiology of PD has recently been confirmed by genetic studies that revealed an association between PD and variation in genes modulating the noradrenergic system, such as the COMT, the monoamine oxidase A (MAOA) and the norepinephrine transporter (NET) genes.

Brief summary: The noradrenergic system plays an important role by regulating the attentional alerting system, which exhibits increased activity during states of anxiety. Noradrenergic transmission is closely linked to the serotonergic system and to the HPA axis, and therefore mediates between central arousal and peripheral physical reactions. Neurochemical studies have revealed higher baseline noradrenaline secretion and increased reactivity to challenges of the noradrenergic system in patients suffering from PD. Recently, genetic studies have demonstrated that there is an association between PD and variations in...
COMT, MAOA, and NET genes, thus underlining the high importance of noradrenergic transmission in the pathophysiology of PD.

The role of GABAergic neurotransmission

Benzodiazepines are among the most potent and powerful anxiolytic agents. These drugs act through an enhancement of gamma-aminobutyric acidergic (GABAergic) inhibition targeting the GABA receptor. This fact, along with the results of several neurochemical studies, point towards a major role of the GABA system in the pathophysiology of PD. Thus, anticipatory anxiety and panic attacks might be triggered by a decreased GABAergic inhibition in distinct brain regions. In this light, decreased GABA receptor binding or reduced GABA activity (MRS studies) has been reported mostly in frontal, limbic, temporal and respectively insular regions. However, results are inconsistent, as some authors observed reciprocal effects like increased GABA receptor binding in patients with PD (cf. comprehensive review articles by, e.g. . In a recent study, Long et al. investigated GABA levels in different cerebral regions by MRS. Eleven PD patients, including five with PD family history, six without PD family history and eight healthy controls participated in the study. The authors observed decreased GABA activity in the ACC/medial prefrontal cortex in PD patients, which tended to be more pronounced in patients with PD family history.

However, some methodological limitations of the abovementioned studies have to be taken in account. Firstly, spectroscopic studies still lack a sufficient image and spectral resolution as well as discriminatory power of ROIs. Secondly, it has not yet been proven that the results are specific for PD. In our opinion it would be advisable to include psychiatrist comparison groups. Schür et al. pointed out that the inhibitory GABA system is thought to be involved in the etiology of several psychiatric disorders. The authors therefore performed a meta-analysis including a total of 40 MRS studies in seven different psychiatric disorders (n = 1.591). Brain GABA levels were lower in autism spectrum disorders and in depressed - but not in remitted - patients compared with healthy controls. No significant differences in GABA levels were found in PD (n = 81). In conclusion, alterations of GABAergic function in PD are still a matter of debate and also their specificity remains questionable.

Brief summary: The results of several neurochemical studies point towards an involvement of the GABAergic system in the etiology of PD. Decreased GABAergic inhibition was reported in limbic, frontal, temporal, and respectively insular regions. Unfortunately, the findings regarding the GABAergic system are partly inconsistent and may not be specific for PD.

Alterations of glutamatergic neurotransmission

There is some evidence derived from animal studies that an excitatory-inhibitory imbalance might play a role in the pathophysiology of PD. Glutamate is the main excitatory neurotransmitter in the mammalian cortex while GABA is the main inhibitory neurotransmitter. Glutamate is the metabolic precursor of GABA, which can be recycled through the tricarboxylic acid cycle to synthesize glutamate. As has already been stressed in the previous section, some studies point towards decreased activity of the inhibitory GABA system in patients with PD, although results of the available studies are inconclusive. Glutamate deploys its excitatory action via binding with N-methyl-D-aspartate and alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptors, which are predominantly located in the cortical and limbic structures. According to animal studies, glutamatergic neurotransmission in the lateral nucleus of the amygdala (LA) is involved in fear-conditioning and extinction. Until now, only a few studies have investigated the possible role of glutamate in PD.

Zwanzger et al. studied the effects of cholecystokinin-tetrapeptide (CCK-4)-induced panic on brain glutamate plus glutatione (Glx) levels in eighteen healthy subjects by MRS. The authors reported an increase of Glx/creatinine levels in the bilateral ACC peaking at 2-10 min after administration of a challenging task. Moreover, HPA axis stimulation was monitored while a significant increase in plasma cortisol was observed throughout the challenge. Maddock et al. investigated changes in glutamate plus glutatione in twenty-one PD patients (thirteen remitted, eight symptomatic) and twelve healthy control subjects. MRS was used to measure Glx changes in the visual cortex induced by visual stimulation. PD patients had smaller Glx responses than healthy control subjects, regardless of whether they were acutely ill or remitted. The authors conclude that their results contradict the assumption of a general upregulation of brain metabolic responses in PD.

Preclinical data have suggested that GABA and glutamate neurotransmission are modulated by the neuropeptide S (NPS) system. NPS receptors are widely distributed in the central nervous system with highest expressions in the cortex, thalamus, hypothalamus and the amygdala. Polymorphisms of the NPS receptor gene might genetically drive altered fear circuit function and therefore increase the risk of PD in humans. Ruland et al. performed a study of CCK-4-induced panic on brain Glx levels and enrolled thirty-five healthy volunteers with functional neuropeptide S receptor gene (NPSR1) rs324981 A/T variants. MRS during the challenge revealed significantly lower increases of Glx/Cre levels in T risk allele carriers as compared to AA homozygotes in bilateral ACC. These results of a blunted and possibly maladaptive ACC glutamatergic reactivity in T allele carriers are in accordance with the assumption that the NPS system conceivably plays an important role in the pathophysiology of PD.

**Brief summary:** Glutamate is the main excitatory
neurotransmitter in the mammalian cortex. Preclinical studies have suggested that an excitatory-inhibitory imbalance of the glutamatergic and GABAergic systems might play a role in the etiology of PD. Glutamatergic neurotransmission in the amygdala is thought to be involved in fear-conditioning and extinction. The results of animal studies have further suggested that glutamatergic and GABAergic transmissions are modulated by the NPS system. NPS receptors are widely distributed in the central nervous system with highest expressions in the cortex, thalamus, hypothalamus and the amygdala. In a recent imaging genetic study, blunted glutamatergic ACC response due to CCK-4-induced panic was reported in NPSR1 risk allele carriers.

**Imaging genetics**

During the past decade, studies on the genetic basis of PD have focused on genes related to classical neurotransmitters, mainly monoamines. More recently, other groups of molecules have been identified, including genes involved in neurodevelopment and synaptic plasticity. More than twenty different genes were reported to confer susceptibility to - or modulate the pathological mechanisms of - PD\[108\]. Identified genes belong to different biological pathways and implicate inter alia the serotonergic, noradrenergic, neuropeptidergic (e.g., NPS) or glucocorticoid system. Imaging genetic studies, as specified below, are designed to evaluate the impact of genetic variations (polymorphisms) on cerebral function in regions critical for PD. Most of the imaging genetic studies used functional magnetic resonance imaging. Some other studies assessed structural connectivity and structural alterations by DTI and VBM.

**Genetic variations of serotonin receptor 1A, SERT, and MAOA**

Evidence from preclinical and clinical research, including genetic studies, pharmacological trials and neuroimaging, reveals a substantial impact of the serotonin system and particularly the serotonin receptor 1A (5-HT1AR) on the neurobiology of PD\[109,110\]. Yu et al\[111\] performed an imaging genetic study by investigating the impact of 5-HT1AR polymorphism on WM connectivity within the cingulum bundle in PD. For this purpose, 32 patients were examined by DTI. The patients were divided into a CC genotype group and a non CC genotype group (GG/CG genotype group) with regard to the 5-HT1AR rs6295 polymorphism. Tractography revealed significantly increased FA values in the left cingulum bundle in the 5-HT1AR CC genotype group compared to the GG/CG genotype. The extent of this alteration was positively correlated with the severity of symptoms that was assessed by several rating scales. Another target of research is the serotonin transporter (SERT) gene, which is also hypothesized to be involved in the pathophysiology of PD due to its identified polymorphisms\[112\]. According to Bijlsma et al\[113\] disturbance of SERT functioning leads to fear learning deficits. In a preclinical study, the authors reported disrupted fear acquisition and a concomitant increase in contextual conditioned startle fear in SERT knockout rats. Kang et al\[114\] demonstrated that SERT polymorphisms can predict health-related quality of life assessments in patients with PD. They used the 36-Item Short Form Health Survey (SF-36), which is a set of generic and coherent quality of life measures. The sample consisted of 179 patients with PD and 110 healthy controls. Patients with PD showed lowered quality of life in all sub-domains of the SF-36 compared to healthy controls. SERT polymorphisms independently and additively accounted for 2.2% of variation (6.7% of inherited variance). Despite its conceivable significant role in the pathophysiology of PD, no imaging genetic study on the SERT polymorphisms in PD has yet been carried out. Reif et al\[115\] investigated the impact of a promoter polymorphism in the monoamine oxidase A gene (MAOA-uVNTR) on CBT response and brain activity in fear conditioning in a large controlled multicenter study on 369 patients with PD and agoraphobia. This promoter polymorphism is associated with PD and agoraphobia\[116\] and also has been demonstrated to influence gene expression and monoamine levels\[117\]. Carriers of the risk allele (causing higher activity of MAOA) had significantly worse clinical outcome. This was accompanied by elevated heart rate and increased fear during an anxiety exposition task. Moreover, risk allele carriers did not habituate due to repetitive exposure. FMRI with a classical fear conditioning paradigm revealed that the protective allele is associated with increased activation of the ACC upon presentation of the CS+ during acquisition of fear. After treatment, further differentiation between high- and low-risk subjects was observed in the inferior parietal lobes, implying differential brain activation patterns upon CBT. This complex multicenter study has demonstrated that a genetic risk factor for PD and agoraphobia may be associated with poor response to CBT and specific underlying neural mechanisms. The authors emphasize that, in the future, genetic information might help to develop individualized treatment methods.

**Brief summary:** According to recent studies, SERT polymorphisms are associated with fear learning deficits and lowered quality of life measures in healthy subjects. Imaging genetic studies in PD have demonstrated that there is a significant impact of genetic variations on severity of symptoms (5-HT1AR) and response to CBT (MAOA). DTI revealed higher structural integrity within the left cingulum in patients carrying the 5-HT1AR risk allele. In an fMRI study, PD patients with a MAOA risk allele (causing higher activity of MAOA) exhibited a blunted anterior cingulate response during a classical fear conditioning paradigm. After cognitive behavioral treatment, differential brain activation patterns, primarily in the inferior parietal lobes, were described in high- and low-risk subjects.
Genetic variations of COMT and NET
With regard to the noradrenergic system, the COMT and NET gene polymorphisms are hypothesized to be involved in the pathophysiology of PD. Kim et al. (2017) studied the effects of the COMT gene polymorphism on WM connectivity in PD by DTI. Twenty-six patients with PD and 26 matched healthy controls were enrolled and underwent genotype analysis for COMT rs4680. No differences in WM connectivity were found between patients and healthy control subjects. However, comparison of COMT AA/AG genotype and GG genotype groups in PD patients revealed increased FA in posterior thalamic radiation, posterior and superior corona radiata, superior longitudinal fasciculus (SLF), and sagittal stratum, all located in the right hemisphere. Symptom severity scores in the COMT AA/AG genotype group were positively correlated with the FA in WM tracts. Inoue et al. (2018) investigated possible associations of COMT, human TransMEMbrane protein 132D (TMEM132D), and GABA receptor alpha 6 subunit (GABRA6) genotypes in PD patients and healthy controls. The polymorphisms rs4680 in COMT and rs3219151 in GABRA6 showed positive associations with PD. In a second step, the authors examined neurophysiological correlates of emotional function in the following areas: ACC and frontal cortex. In PD patients, fMRI responses in the bilateral ACC were stronger in carriers of the AA genotype vs AC + CC genotype in TMEM132D, and stronger in CT + TT genotype vs CC genotype in GABRA6. A response observed in the medial OFC was stronger in carriers of the CT + TT genotype in GABRA6. These results suggest that TMEM132D, GABRA6, and COMT variants may increase vulnerability to panic. Other genetic variants that have attracted growing interest are the polymorphism of the NET gene. The NET is responsible for the reuptake of norepinephrine. Silverstein et al. (2019) studied different variants located within the NET gene with regard to possible associations with PD. The case-control sample consisted of 449 patients with PD and 279 matched controls. Genotyping revealed 29 single nucleotide polymorphisms. Seven polymorphisms were significantly associated with PD, and the NET gene showed overall evidence for association with the disease. These results indicate that NET gene polymorphisms could be involved in the pathophysiology of PD.

Brief summary: Specific polymorphisms of COMT and NET genes have been demonstrated to be associated with a diagnosis of PD. COMT risk allele carriers suffering from PD seem to exhibit increased symptom severity, accompanied by disturbed WM connectivity in wide-spread areas of the right hemisphere (e.g., posterior thalamic radiation, posterior and superior corona radiata, SLF, and sagittal stratum).

Polymorphism of neuropeptide S receptor 1 gene
As already mentioned in the paragraph “alterations of glutamatergic neurotransmission”, NPS is thought to modulate GABAergic and glutamatergic neurotransmission and therefore might be involved in the pathophysiology of PD by affecting fear circuit function. Domschke et al. (2019) applied a multilevel approach to explore the role of a NPS receptor (NPSR1) gene variant (A/T) in the etiology of PD. The T allele leads to a 10-fold increase in NPSR expression and NPS efficacy. Domschke et al. (2019) reported that the T allele was associated with PD in female patients. The T risk allele was also related to elevated anxiety sensitivity, increased heart rate and higher symptom reports during a behavioral avoidance test. During an emotional activation task, T allele carriers showed decreased activity in the dorsolateral prefrontal, lateral orbitofrontal and anterior cingulate cortices. Dannowski et al. (2021) studied the effects of the T risk allele on amygdala and PFC function by means of fMRI. Seventy-nine healthy subjects were enrolled and genotyped for (NPSR1) gene variants. The authors reported increased amygdala and PFC responses to anxiety related emotional stimuli in risk allele carriers. Guhn et al. (2022) measured neural correlates of cognitive emotion regulation in 66 volunteers genotyped for the NPSR1 A/T variant (AA homozygotes vs T allele carriers) by means of an emotional n-back task presented during functional near-infrared spectroscopy scanning. T allele carriers showed a signal increase to negative pictures in the dorsolateral and medial prefrontal cortex (DLPFC and mPFC). The authors considered this activation to be part of an adaptive mechanism to compensate for presumably increased subcortical activity driven by an overactive NPS system. Neufang et al. (2023) investigated the impact of NPSR1 gene variations in 47 healthy subjects on cerebral activation patterns during a task probing alerting functions (Attention Network Task) using fMRI. In the alerting condition, homozygote TT allele carriers showed higher activation in the right PFC and the LC as compared to the AA/AT group. In a recent study, Domschke et al. (2024) explored the influence of NPSR1 genotypes on fronto-limbic connectivity within the developing brain. Sixty healthy subjects (8-21 years) were examined by fMRI during presentation of a go/no-go task. In A allele carriers, connectivity between the right DLPFC and the right amygdala was higher in older (≥ 14 years) than in younger (< 14 years) subjects. TT homozygotes (≥ 14 years) showed a reduction of fronto-limbic connectivity between the DLPFC and both the amygdala and the insula. These results suggest a risk-increasing effect of the NPSR1T allele for possible anxiety-related traits via impaired top-down control of limbic structures during adolescence.

Brief summary: The T risk allele of the NPSR1 gene is associated with PD in female patients. This genetic variation is also related to elevated anxiety sensitivity. Moreover, fMRI studies revealed decreased activity in the dorsolateral prefrontal, lateral orbitofrontal and anterior cingulate cortices. Healthy subjects carrying
the risk allele exhibit increased amygdala and PFC responses to anxiety related emotional stimuli. During a probe of alerting function, higher activations in the right PFC and the LC region have been observed in healthy risk allele carriers. The results of a very recent study suggest that the NPSR1T allele might be responsible for impaired top-down control of limbic structures during adolescence, therefore increasing the risk for possible anxiety-related traits.

**Polymorphisms of corticotropin releasing hormone receptor 1 gene**

Another neuropeptide that has attracted attention is the neurotransmitter corticotropin-releasing hormone (CRH), also known as corticotropin-releasing factor (CRF) or corticoliberin. CRH plays a central role in the regulation of the HPA axis. The CRH receptor 1 (CRHR1) triggers the release of the stress response regulating hormone cortisol. Preclinical and clinical studies have indicated that CRHR1 is a possible candidate gene for mood and anxiety disorders\[^79,125,126\]. Weber et al\[^127\] studied different variants located within the CRHR1 gene with regard to possible associations with PD. Genotyping in 531 matched case/control pairs (PD patients and healthy control subjects) revealed 9 single nucleotide polymorphisms (SNPs). Four SNPs were associated with PD. One risk allele (the minor allele of rs17689918) was found to significantly increase risk for PD in females. Subsequently, fMRI was used in 48 PD patients. The risk allele carriers showed aberrant fear conditioning predominantly in the bilateral prefrontal cortex and altered safety signal processing in the amygdala, suggesting existing fear sensitization and sustained fear. Furthermore, in this multilevel study, Weber et al\[^127\] performed an expression analysis of CRHR1 gene. For this purpose, postmortem tissue of 76 deceased individuals obtained from the MRC Sudden Death Brain and Tissue Bank, Edinburgh, United Kingdom, was analyzed. In CRHR1 risk allele carriers, the authors found decreased CRHR1 mRNA expression in forebrains and amygdalae. These results indicate that CRHR1 polymorphisms may play a significant role in the pathophysiology of PD and elucidate the mechanisms by which genetic variation in CRHR1 is linked to this disorder. Aberrant fear conditioning due to CRHR1 variation was demonstrated in PD as well as in healthy subjects. MRI scans in PD patients revealed that risk allele carriers exhibited aberrant fear conditioning with blunted activations in the bilateral prefrontal cortex. Moreover, during processing of safety cues, patients of this group showed elevated responses in the amygdalae compared to patients without the risk allele. Behavioral and neurofunctional findings of this study indicated an increased fear sensitization and sustained fear in this group. Postmortem analyses in risk allele carriers revealed decreased CRHR1 mRNA expression in the PFC and amygdala.

**Polymorphisms of human TransMEMbrane protein TMEM123D and amiloride-sensitive cation channel 2 genes**

The human TransMEMbrane protein TMEM123D is expressed in neurons and colocalized with actin filaments that putatively function as a cell-surface marker for oligodendrocyte differentiation\[^130\]. Recent case-control genome-wide association studies have linked variants of the TMEM123D gene with PD, anxiety comorbidity with depression, and anxiety symptom severity in healthy and diseased subjects\[^131,132\]. Haaker et al\[^133\] investigated an independent sample of 315 healthy normal subjects (99 female) of Caucasian descent, of which 132 (22 female) underwent structural MRI assessment. Carriers of a specific risk allele (rs11060369 A homozygotes) showed higher GM volumetric estimates in the left amygdala. Moreover, participants of this group had higher ratings for trait anxiety, behavioral inhibition, and negative affect. Variants of the TMEM123D gene therefore may play an important role in the etiology of PD.

Animal studies have shown that carbon dioxide-mediated fear behavior depends on chemosensing of acidosis in the amygdala through the acid-sensing ion channel\[^134\]. In humans, the amygdala also acts as a chemosensor that detects hypercarbia and acidosis via the amiloride-sensitive cation channel 2 (ACCN2)\[^135\]. Patients with PD exhibit a hypersensitivity to inhaled carbon dioxide, possibly reflecting a lowered threshold for sensing signals of suffocation\[^136\]. Smoller et al\[^135\] examined whether genetic variation of ACCN2 is associated with PD, as well as with amygdala structure and function. The authors conducted a case-control analysis (n = 414 PD cases and 846 healthy control subjects) of ACCN2 SNPs. Two SNPs at the ACCN2 locus showed evidence of association with PD (rs685012; rs10875995). The association appeared to be stronger when PD cases with early-onset (age ≤ 20 years) and with prominent respiratory symptoms were compared with controls. One of the detected PD risk alleles (rs10875995) was associated with increased amygdala volume and heightened task-evoked amygdala reactivity to fearful and angry faces as assessed by fMRI. These results suggest that altered chemosensing of acidosis in the amygdala triggered by ACCN2 gene
specific fear-evoking stimuli are more difficult to develop
strongly involved in salience and significance detection
However, in our view, it is notable that the amygdala is
paradigms, sample heterogeneity and size, as well
seems to strongly depend on stimuli and experimental
it is too weak to be detected with common thresholds,
not as characteristic of PD as proposed earlier, whether
unclear whether aberrant amygdala activation is simply
exception, rather than the rule”. At present, it remains
that “in PD, amygdala hyperactivity appears to be the
the pathophysiology of PD, it seems surprising that
amygdala hyperactivation only reached marginal signifi-
cance. In the same tenor, Etkin et al[11] stated that,
given the role of the amygdala proposed for
studies suggest abnormal activation mainly in an
distributed fear network comprising brainstem, anterior
and midcingulate cortex, insula, and lateral as well
as medial parts of the prefrontal cortex. Interestingly,
differences in the amygdala activation were not as
consistently reported as one would predict from the
hypothesis of Gorman[11]. Feldker et al[29] stated that,
given the role of the amygdala proposed for
the pathophysiology of PD, it seems surprising that
amygdala hyperactivation only reached marginal signifi-
cance. In the same tenor, Etkin et al[138] concluded that
“in PD, amygdala hyperactivity appears to be the
exception, rather than the rule”. At present, it remains
unclear whether aberrant amygdala activation is simply
not as characteristic of PD as proposed earlier, whether
it is too weak to be detected with common thresholds,
or whether specific methodological limitations make it
difficult to detect. Indeed, amygdala hyperactivation
seems to strongly depend on stimuli and experimental
paradigms, sample heterogeneity and size, as well
as on limitations of neuroimaging techniques[16,139,140].
However, in our view, it is notable that the amygdala is
strongly involved in salience and significance detection
in the information stream[141]. Since paradigms with
specific fear-evoking stimuli are more difficult to develop
for PD patients in contrast to patients with specific
phobias, we can speculate that the often observed lack
of amygdala hyperactivation in PD might be based on
such methodological issues, e.g., using appropriate
stimuli and experimental paradigms.

In summary, the alterations of neural activation
in patients with PD as reported in past and present
studies are somewhat inconsistent. Interestingly, two
very recent studies using clear panic-related pictorial
stimuli and relatively large sample sizes have put strong
emphasis on a specific role of the insula and dACC
in the pathophysiology of PD[29,32]. There is growing
evidence that the insula, the dACC as well as subcortical
structures, such as the amygdala, play a crucial role in
salience processing across multiple sensory and cognitive
domains by integrating external sensory information with
internal emotional and bodily state signals[142]. The latter
can be paraphrased with the term interoception, which
refers to conscious awareness, emotional processes
and behavior related to physiological information aris-
ing from the body. This includes processing of proprio-
ceptive and visceroceptive processes such as heart rate,
respiration, and blood pressure. Abnormal interoception
has been suggested to play a key role in the etiology
and maintenance of anxiety disorders[143] in terms of
oversensitive perception of somatic sensations and
subsequent catastrophizing interpretations. There is
evidence to assume that ascending inputs providing
information about interoceptive and visceroceptive
signals related to the current bodily state converge in the
insula and anterior cingulate cortices[144]. In close cooperation with the amygdala,
insular activity seems to represent a specific subjective
emotion state and the emotive value of external
stimuli in terms of salience[145]. Thus, this observation
may explain differences between studies on PD patients
regarding the amygdala or insula activation, which might
be attributed to different subjective emotive values of
presented stimuli. Another source of variability that
induces potentially different insula/amygdala activation
in patients with PD, as well as in control subjects, is
the subject-specific state of physiological arousal.
Thus, simultaneous acquisition of physiological signals,
e.g., heart or respiratory rate in the MR scanner, may
potentially explain some part of activation variance in
these brain structures.

In addition, the ACC is another brain structure con-
sidered to be a key node within the salience network[142]
and which has often been observed to show abnormal
functioning in PD. It is involved in automatic attentional
control as well as in response selection and conflict
monitoring[146], thus enabling rapid access to the motor
system.

Moreover, the salience network recruits the ventral
fronto-parietal network, mainly consisting of the
tempo-parietal junction and inferior frontal gyrus
(IFG)[147], which is typically activated by infrequent or
unexpected behaviorally relevant (salient) events. This
recruits additional executive resources to ensure focused
attention on task-relevant goals, e.g., to cope with panic-
relevant stimuli[149]. This may explain the often observed abnormal activation of the IFG in patients with PD.

In summary, besides the brainstem/midbrain, amygdala and prefrontal cortex, further brain areas such as the insula and the ACC are emerging from recent imaging studies in PD and seem to be of greater importance than originally proposed.

Interestingly, recent studies applying the DTI to investigate the WM connectivity in PD reported abnormal WM integrity in the cingulum bundle as well as in the major fiber tracts, which connect frontal with temporal, parietal and occipital brain regions: The inferior and superior longitudinal fasciculi[149]. This finding is in accordance with the observation of abnormal functional activation in regions of the salience network and of the ventral fronto-parietal network. However, to date only few studies have investigated the integrity of specific WM tracts in patients with PD. Therefore, more studies are required to elucidate the abnormal structural connectivity in PD.

**Structural neuroimaging studies**

With regard to structural brain imaging studies of GM, volumetric and morphometric changes in limbic structures in frontal and temporal cortical areas, in the basal ganglia, in the pituitary gland and hypothalamus as well as in the midbrain/brainstem structures were reported in recent studies. Similar findings have been described in prior neurostructural studies in PD[15,44,150,152]. The relatively large heterogeneity between studies makes it difficult to relate abnormal GM structure in a specific brain region or a network to PD. The reasons for this inconsistency are manifold. Many of the reviewed studies had the disadvantages of relatively small sample sizes and of comorbid depression or other psychiatric disorders among patients, which may also have an impact on the GM volume estimation.

**Neurochemical studies**

A major role of serotonin in the pathophysiology of PD has been deduced from the therapeutic effects of serotonergic drugs[62,63]. In accordance with this hypothesis, studies on 5-HT1AR and SERT binding have revealed altered and mostly reduced serotonergic activity in the raphe nuclei, orbitofrontal cortex, temporal lobes, ACC and PCC, amygdala, and hypothalamus in patients with PD[71-74]. In the course of therapy with SSRIs postsynaptic alterations seem to decline, while the presynaptic changes persist[75]. In addition to these functional alterations structural abnormalities, e.g., disintegration of the raphe nuclei in the brainstem, have also been described[75]. Ascending serotonergic projections to cortical and subcortical brain regions have their origin mainly in the dorsal and median raphe nuclei. There is evidence from current animal studies, that efferent inputs of dorsal raphe neurons may moderate panic-like defensive behaviors by controlling the activity of the dorsal PAG[78,79], thus confirming the earlier hypotheses of Deakin and Graeff[77] as well as of Gorman et al[11] on this point. Very recently, serotonergic transmission has been proposed as a possible new drug target for PD, as suggested by the results of a preclinical study, which demonstrated that a 5-HT7 receptor antagonist reduced fear memory retrieval[83].

The noradrenergic system is centrally involved in the regulation of the attentional alerting system[84], which exhibits increased activity during states of anxiety[89,90]. Noradrenergic transmission is closely linked to the serotonergic system and to the HPA axis, and therefore mediates between central arousal and peripheral physical reactions[111]. Neurochemical studies have revealed higher baseline noradrenaline secretion and increased reactivity to challenges of the noradrenergic system in patients suffering from PD[56,58]. Recently, genetic studies have demonstrated that there is an association between PD and variations in COMT[91], MAOA[92], and NET[93,95] genes, thus underlining the important role of noradrenergic transmission in the pathophysiology of PD.

Benzodiazepines are among the most potent and powerful anxiolytic agents[96]. These drugs act through an enhancement of gamma-aminobutyric acidergic (GABAergic) inhibition, targeting the GABA receptor[97]. This fact, along with the results of several neurochemical studies points towards an involvement of the GABA system in the pathophysiology of PD. Decreased GABAergic inhibition was reported in limbic, frontal, temporal, and respectively insular regions[98,99]. Unfortunately, the findings regarding the GABAergic system are partly inconsistent and may not be specific for PD[100].

Glutamate is the main excitatory neurotransmitter in the mammalian cortex. It is the metabolic precursor of GABA, which can be recycled through the tricarboxylic acid cycle to synthesize glutamate[102]. Preclinical studies have suggested that an excitatory-inhibitory imbalance of the glutamatergic and GABAergic systems might play a role in the etiology of PD[101]. Glutamatergic neurotransmission in the lateral nucleus of the amygdala is thought to be involved in fear-conditioning and extinction[104]. The results of animal studies have further suggested that glutamatergic and GABAergic transmissions are modulated by the NPS system. NPS receptors are widely distributed in the central nervous system with highest expressions in the cortex, thalamus, hypothalamus and the amygdala[100]. In a recent imaging genetic study, blunted glutamatergic ACC response due to CCK-4-induced panic was reported in NPSR1 risk allele carriers[107]. The results of additional imaging genetic studies on genetic NPSR1 variations will be presented below.

**Imaging genetics**

During the past decade, studies on the genetic basis of PD focused on genes related to classical neurotransmitters, mainly monoamines. More recently, other
groups of molecules have been identified, including genes involved in neurodevelopment and synaptic plasticity. More than twenty different genes were reported to confer susceptibility to - or modulate the pathological mechanisms of - PD[108]. Identified genes belong to different biological pathways and implicate inter alia the serotonergic, noradrenergic, neuropeptidergic (e.g., NPS) or glucocorticoid system. Imaging genetic studies, as specified below, are designed to evaluate the impact of genetic variations (polymorphisms) on cerebral function in regions critical for PD. Most of the imaging genetic studies used functional magnetic resonance imaging. Some other studies assessed structural connectivity and structural alterations by DTI and VBM.

**Serotonergic system:** According to recent genetic studies, SERT polymorphisms are associated with fear learning deficits[113] and lowered quality of life measures[114] in healthy subjects. Imaging genetic studies in PD have demonstrated that there is a significant impact of genetic variations on severity of symptoms (5-HTR1A)[111] and response to CBT (MAOA)[115]. DTI revealed increased structural integrity within the left cingulum in patients carrying the 5-HTR1A risk allele[111]. In an fMRI study, PD patients with an MAOA risk allele (causing higher activity of MAOA) exhibited a blunted anterior cingulate response during a classical fear conditioning paradigm. After CBT treatment, differential brain activation patterns, primarily in the inferior parietal lobes, were described in high- and low-risk subjects[115].

**Noradrenergic system:** Specific polymorphisms of COMT[91] and NE[92-96] genes have been demonstrated to be associated with a diagnosis of PD. COMT risk allele carriers suffering from PD seem to exhibit increased symptom severity accompanied by disturbed WM connectivity in wide-spread areas of the right hemisphere[93].

**Neuropeptidergic system:** The T risk allele of the NPSR1 gene is associated with PD in female patients. This genetic variation is also related to elevated anxiety sensitivity. Moreover, fMRI scans revealed decreased activity in the DLPC, lateral OFC and ACC[110]. Healthy subjects carrying the risk allele exhibit increased amygdala and PFC responses to anxiety related emotional stimuli[21]. During a probe of alerting function, higher activations in the right PFC and the LC have been observed in healthy risk allele carriers[123]. Results of a very recent study suggest that the NPSR1 T allele might be responsible for impaired top-down control of limbic structures during adolescence, therefore increasing the risk for possible anxiety-related traits[124].

**CRH:** Another neuropeptide that has attracted attention is the neurotransmitter CRH. CRH plays a central role in the regulation of the HPA axis. Preclinical and clinical studies have indicated that CRHR1 is a possible candidate gene for PD[125,126]. In a multi-level study by Weber et al[127], one allele was found to increase risk for PD in females. Aberrant fear conditioning due to CRHR1 variation was demonstrated in PD as well as in healthy subjects. MRI scans in PD patients revealed that risk allele carriers exhibited aberrant fear conditioning with blunted activations in the bilateral prefrontal cortex. Moreover, during processing of safety cues, patients of this group showed elevated responses in the amygdala compared to patients without the risk allele. Behavioral and neurofunctional findings of this study indicated an increased fear sensitization and sustained fear in this group. Postmortem analyses in risk allele carriers (brain tissue was obtained from a Tissue Bank) revealed decreased CRHR1 mRNA expression in the PFC and amygdala[127].

**Human TransMEMbrane protein (TMEM123D):** TMEM123D is expressed in neurons and colocalized with actin filaments that putatively function as a cell-surface marker for oligodendrocyte differentiation[130]. Recent association studies have linked variants of the TMEM123D gene with PD[131,132]. Morphometric analyses in healthy volunteers revealed that carriers of a specific risk allele show increased GM volume in the left amygdala. Moreover, these subjects had higher ratings for trait anxiety, behavioral inhibition, and negative affect[133]. Thus, the results of population genetic studies were confirmed by imaging genetic studies.

**Amiloride-sensitive cation channel 2:** Patients with PD exhibit increased sensitivity to inhaled carbon dioxide[136]. The amygdala acts as a chemosensor that detects hypercarbia and acidosis via the ACCN2[135]. In a recent multi-level study by Smolier et al[135] it was demonstrated that genetic variation of ACCN2 is associated with PD as well as with amygdala structure and function. Two polymorphisms of the ACCN2 gene showed association with PD. One of the detected PD risk alleles was associated with increased amygdala volume and elevated amygdala reactivity to fearful and angry faces. These results suggest that genetic variation of ACCN2 may be involved in the pathophysiology of PD.

As stated above, the intention of imaging genetic studies is to evaluate the impact of genetic variation (polymorphisms) on cerebral function in regions critical for PD. Given the fact that PD is a multifaceted disease with various pathogenic pathways, the etiological effects of specific polymorphisms shall not be overestimated or generalized. Nevertheless, genetic imaging will help to understand the multitude and the interplay of pathogenic factors in PD. Moreover, future neuroimaging studies will become more sophisticated by including genetically defined patient and control samples. Regardless of the undeniable advantages of imaging genetics, some limitations of the studies presented above have to be mentioned: (1) results of studies in healthy subjects may not or only to some extent be transferable to patients suffering from PD; (2) given the wide variety of genes involved in the pathophysiology of PD, it is still
difficult to define homogenous samples and to control for interfering factors; (3) general methodological limitations of neuroimaging studies (e.g., related to paradigms and assessment techniques; please see above) cannot be avoided; (4) identified genes often fail to find replication in larger cohort sets or in different populations; and (5) epigenetic factors and non-coding genomic elements may also play a role in the pathophysiology of PD. Nevertheless, great progress has been made in the field of genetics of psychiatric disorders and by now there is a considerable amount of notable findings. In this light, it is conceivable that in the near future this research will lead to the development of clinically useful tools such as predictive biomarkers or novel treatment options.

Limitations and future directions
This review discusses the recently published neuro-functional, neurostructural and neurochemical alterations in PD.

However, the premise that PD is a single phenotype, might not be accurate. Studies on abnormal brain structure in PD revealed a relatively large heterogeneity of significant findings, which makes it difficult to relate specific regions or tracts with aberrant gray or WM to PD. Additionally, the application of functional MRI did not reduce the heterogeneity of reported findings, even if the brain’s salience network, mainly composed of the amygdala, insula and ACC becomes increasingly important for the understanding of panic attacks.

On the other hand, the new era of imaging genetics provided first insights into the potential etiological heterogeneity of PD. Imaging genetic studies have not only confirmed the importance of serotonergic and noradrenergic transmission in the etiology of PD, but also indicated the significance of neuropeptide S receptor and CRH receptor gene variants. These new insights reveal possible targets for the development of drugs for personalized anxiolytic treatment. Furthermore, appropriate imaging genetics studies may lead to a better understanding of non-response to psychotherapy, e.g., due to the variability of top-down control that the prefrontal/anterior cingulate cortex exerts on the amygdala/hippocampus, as well as on the brainstem in PD. In the future the imaging genetics approach will be of major importance for the further development of the neuroanatomical model, because genetic risk variants may significantly influence fear network activity in PD. Therefore, imaging genetic consortia are necessary to accumulate a sufficient number of functional and structural brain scans, which may allow researchers to detect genome-wide significant loci affecting brain function and structure in PD.

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COMMENTS
Background
Panic disorder (PD) is a frequent psychiatric disease. Gorman et al (2000) proposed a comprehensive neuroanatomical model of PD, which suggests that fear- and anxiety-related responses are mediated by a so-called “fear network” which is centered in the amygdala and includes the hippocampus, thalamus, hypothalamus, periaqueductal gray region, locus coeruleus and other brainstem sites. It was further assumed that the serotonergic system plays a pivotal role in the etiology of PD.

Research frontiers
The main focus of this systematic review was laid on recent neurofunctional, neurostructural, and neurochemical studies. Within this frame, special attention was given to the emerging field of imaging genetics.

Innovations and breakthroughs
Recent functional imaging studies revealed abnormal activation not only in the “fear network” proposed by Gorman et al (2000), but also in additional brain regions such as anterior and midcingulate cortex, insula, and prefrontal cortex. Thus, the so-called “salience” network of the brain becomes increasingly important for the understanding of PD. Advanced neurochemical studies have substantiated the major role not only of serotonergic, but also of noradrenergic and glutamatergic neurotransmission in the pathophysiology of PD. In addition, imaging genetic studies have confirmed the importance of serotonergic and noradrenergic transmission in the etiology of PD and, moreover, have indicated the significance of neuropeptide S receptor and CRH receptor gene variants.

Applications
Genetic imaging studies have revealed that genetic risk variants may significantly affect fear network activity in PD. Thus, the inhomogeneity of neuroimaging findings, as reported in this review, could be partly due to such influences. In future studies these effects will have to be considered carefully. Other practical applications of the genetic imaging approach could be the development of clinically useful tools such as predictive biomarkers or drugs for personalized anxiolytic treatment.

Terminology
All terms that may not be familiar to the majority of the readers are explained at the beginning of each major section.

Peer-review
This is, in summary, an interesting review manuscript aimed to provide a detailed and comprehensive overview of the current research in the functional neuroanatomy of panic disorder. The authors mainly focused on recent neurofunctional, neurostructural, and neurochemical studies about the specified topic. They concluded that it is conceivable that new research advances may lead in the near future to the development of clinically useful tools like predictive biomarkers or novel treatment options.
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