The Neurobiology of Panic: A Chronic Stress Disorder

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Abstract

Panic disorder is an often chronic and impairing human anxiety syndrome, which frequently results in serious psychiatric and medical comorbidities. Although, to date, there have been many advances in the diagnosis and treatment of panic disorder, its pathophysiology still remains to be elucidated. In this review, recent evidence for a neurobiological basis of panic disorder is reviewed with particular attention to risk factors such as genetic vulnerability, chronic stress, and temperament. In addition, neuroimaging data are reviewed which provides support for the concept of panic disorder as a fear network disorder. The potential impact of the National Institute of Mental Health Research Domain Criteria constructs of acute and chronic threats responses and their implications for the neurobiology of panic disorder are also discussed.

Keywords

panic disorder, pathophysiology, acute fear, chronic stress, genetics, anxious temperament, brain imaging, functional neuroanatomy, Research Domain Criteria

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Introduction

Panic disorder (PD), a dramatic anxiety syndrome characterized by recurrent episodes of acute fear, is a common psychiatric condition with a 12-month prevalence of 1–2% and lifetime prevalence of 4% or greater.1–3 Its phenomenology is complex, encompassing aspects of acute fear (spontaneous and cued panics), chronic anxiety (anticipatory fear), interoceptive sensation sensitivity, and, in 30–50% of cases, agoraphobia.4 Its course is often chronic,5 complicated by serious psychiatric co-morbidities (particularly with major depressive disorder (MDD), other anxiety disorders and substance abuse),6–8 and associated with increased suicidality.9 Beyond the personal distress and impairments accompanying PD, there are indirect costs to society, in general, including overutilization of health care resources and lost work productivity.10,11 PD has also been linked to adverse physical health outcomes including higher rates of cardiovascular12,13 and respiratory disease.14 Thus, PD is a significant public health concern, presenting frequently to primary care and psychiatric care settings.

Despite considerable advances in the epidemiology, diagnosis, and treatment of PD, its underlying pathophysiology still requires clarification. A neurobiological basis for PD is strongly suggested by a range of clinical features, such as heritability (estimated at 43%),15 presence of nocturnal panics (in 1/4 patients), symptoms of autonomic overactivity, behavioral sensitivity to a variety of pharmacologic challenge agents (e.g., caffeine, lactate, CO₂, cholecystokinin-4 (CCK-4), yohimbine, and m-chlorophenylpiperazine), and robust response to pharmacotherapies that enhance brain serotonin (5-HT), norepinephrine (NE), and γ-aminobutyric (GABA) neurotransmission. However, improvements in the accuracy of our neurobiological models of panic are expected to lead to refinements in diagnosis, and more strategic and personalized therapies.

In this paper, the recent literature bearing on major risk factors for PD, such as genetics, temperament, and...
chronic stress, and their neurobiological effects is briefly reviewed. Then, the implications of the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) research framework for the diagnosis of PD are discussed, and its potential to further our understanding of PD neurobiology. Finally, the rapidly evolving literature supporting a functional neuroanatomical model of PD is reviewed, including findings from preclinical neuroscience, cognitive neuroscience, and imaging science. The review is not intended to be exhaustive but, rather, emphasizes replicated findings, meta-analyses, and promising novel leads.

**Risk Factors for PD**

**Genetic Vulnerability to PD**

While almost half of the variance regarding the etiology of panic is attributable to genetic factors, thus far, there have been few replicated linkage or association/candidate gene findings. However, linkage analyses have implicated a number of chromosomal regions in PD (including 13q, 14q, 4q31-q34, 22q, and 9q31) (reviewed in the studies by Maron et al. and Smoller). In contrast, many association studies surveying genes related to panic-salient neurochemical systems, such as 5-HT, NE, GABA, corticotrophin release factor, CCK, and neuropeptide Y, have been negative or, if positive, not replicated. One exception is a variant of the gene coding for the monoamine degradative enzyme, catechol-O-methyltransferase (COMT). The COMT Val158Met polymorphism, previously implicated in prefrontal dopamine (DA) neurotransmission and working memory function, also confers susceptibility to PD, a result which has been independently replicated and which remained positive in a meta-analysis. A follow-up functional neuroimaging study (paradigm of functional magnetic resonance imaging (fMRI) activation to emotional/facial stimuli) suggested that DA function may be impaired in fear circuit structures implicated in PD. In this latter study, for patients with the COMT val risk allele, orbital frontal, ventromedial prefrontal cortex (PFC), and right amygdala activation to emotional stimuli were greater. 5-HT metabolism polymorphisms (e.g., the short allele of the 5-HT transporter promoter gene (5-HTTLPR)), much studied across stress-related disorders, have been associated with panic diagnosis (e.g., the LL genotype of the 5-HTTLPR gene, and longer alleles of the monoamine oxidase-A enzyme (MAO-A) gene promoter region). However, these findings have not been replicated in larger genome-wide association studies (GWAS) (see later). One group has suggested that 5-HTTLPR variants (such as the s-allele) may be more related to severity of panic symptoms rather than the categorical diagnosis of PD.

In a recent candidate gene meta-analytic study of 23 common variants of 20 candidate genes (including genes involved in the 5-HT, NE, DA, and neuropeptide systems), COMT rs4680 and TMEM132D rs7370927 (a transmembrane protein whose function is unclear) were significantly associated with panic diagnosis, with strengthening of the association when early age of onset and panic with prominent respiratory features were taken into account. Considering common anxiety disorders (generalized anxiety disorder, GAD, PD, and phobic disorders) as having common neurobiological vulnerabilities toward threat, a meta-analysis of GWAS studies of these conditions (the largest of its kind, involving 18,000 unrelated subjects) implicated several novel candidate genes in shared risk for anxiety: rs1709393 (a novel non-coding RNA locus) and CAMKMT (coding for the enzyme, calmodulin-lysine N-methyltransferase, involved in calcium signaling). Another novel risk gene for PD was identified in the orexin system (G1246A, a polymorphism in the orexin 2 receptor gene), a neuropeptide system known to be involved in arousal and sleep regulation and recently implicated in animal and human models of PD. In addition, a recent study (comparing n = 414 PD patients and 846 healthy controls), parsing the genetic basis of CO2 sensitivity in PD, found an association to several single nucleotide polymorphisms (SNPs) on the amiloride-sensitive cation channel 2 (ACCN2) gene. This gene is the human equivalent of an animal acid-sensing ion channel (ASIC1a) gene expressed in the amygdala. The association was stronger when early age of onset and panic with prominent respiratory features were taken into account. The investigation further found that one of the SNPs (rs10875995) was associated with increased amygdala volume and reactivity to face stimuli in PD patients. Other factors influencing the genome, including epigenetic changes, may well be relevant to the pathophysiology of PD. In this regard, MAO-A gene hypomethylation has been observed in women with PD, which normalized with effective cognitive behavioral therapy (CBT) treatment. Furthermore, in a pilot study, negative life events in PD have been linked to GAD1 gene hypomethylation (the GABA transporter t gene), consistent with the well-known impact of life events on triggering panic illness episodes. An epigenome-wide association study (EWAS) conducted in 48 PD patients and matched controls, and performing array analyses on peripheral leukocytes, just reported evidence of modest DNA hypomethylation at various CpG sites (40 sites with most showing hypomethylation). While larger scale studies are needed to confirm the above findings, this is an exciting frontier in PD research, as environmental factors are clearly implicated in its pathogenesis. Other fruitful strategies for future genetic research include gene × environment interaction studies.
focusing on dimensions of psychopathology. For example, in one recent study with 782 healthy adults (531/782 were female), a significant interactive effect was found between levels of childhood adversity and homozygosity on the low-activity COMT met allele. These factors together explained increases in reported anxiety sensitivity, a well-known cognitive risk factor for PD. Moderating and protective factors can usefully be studied in this manner, as demonstrated in a recent study of self-efficacy, childhood trauma, and 5-HTTLPR gene variation in 678 adults. In subjects with 5-HTTLPR/rs25531 LALA genotypes, high levels of self-efficacy moderated the effect of early childhood adverse events on trait anxiety. In a large twin cohort (n = 346 twin pairs), genetic factors accounted for sensitivity to respiratory and anxious effects of 35% CO2 inhalation, a well-replicated characteristic of clinical PD. In addition, other investigators observed a moderating effect of 5-HTTLPR genotype on sensitivity to CO2 in healthy human subjects (n = 96), with L/L allele status conferring particular sensitivity to the effects of 17.5% CO2 inhalation. These kinds of intermediate phenotypes are likely to add power and interpretability to future genetic studies of panic.

**Temperament and PD Risk**

Studies attempting to link PD to premorbid temperament have focused on a variety of constructs including behavioral inhibition (BI), neuroticism (N), trait anxiety, and harm avoidance (HA). Perhaps the best studied of these risk factors is BI. BI, essentially a neophobic tendency, is a weak childhood predictor of later conversion to clinical anxiety disorder. Children of PD- and major depression (MDD)-affected parents have been observed to have a twofold risk of having especially elevated BI. In addition, in a case–control study design (n = 268 anxiety patients, n = 542 MDD patients, and n = 541 healthy subjects), investigators reported an association between elevated BI in patients and several SNPs of the GAD2 gene (encoding the neuronal GABA synthetic enzyme GAD67). Furthermore, in one volumetric MRI study, high BI in childhood predicted low hippocampal volumes in teens of PD parents, consistent with the negative impact of chronic stress on the brain development of these teens. A somewhat related infant phenotype, high reactivity, especially in males, two decades later predicted exaggerated amygdala activation to emotional stimuli (fMRI paradigm), a potentially useful trait for follow-up genetic studies. In a large population-based anxiety sample (n = 9270), other investigators linked several SNPs of the GAD1 gene (encoding glutamic acid decarboxylase 65 (GAD65), a GABA synthetic enzyme found in axon terminals) with N, a risk factor for both anxiety disorders and MDD. Other personality traits have also been implicated in PD. For example, anxiety proneness trait in college students (n = 16) vs. comparison subjects (n = 16) with normative anxiety predicted exaggerated bilateral amygdala and insula responses to emotional (face) stimuli, suggesting an important intermediate phenotype for anxiety disorders. Comparing PD patients (n = 60), first-degree family members (n = 37), and matched healthy controls (n = 37), substantially higher trait anxiety levels were observed in the PD group. Interestingly, in a systematic review of 13 studies (10 in MDD and 3 in PD), high HA and low self-directedness were associated with both mood and anxiety symptoms across all studies; longitudinal studies-suggested effects were not state dependent. In a large case–control genetic study (n = 470 PD patients and n = 458 healthy subjects), males with PD were noted to be more likely to have the met/met allele of COMTVal158Met if they had low levels of the trait of openness to experience.

Overall, temperament has been implicated to some degree in the pathogenesis of PD by different study designs. It is conceivable that temperament styles, such as HA, could reflect prodromal phases of adult anxiety syndromes. However, the survey data mentioned do not support that view. Ongoing measurement of anxiety traits in imaging genetics study designs is likely to be an important feature of future RDoC-oriented investigations of panic, since diagnostic category findings, by themselves, have been hard to replicate.

**Chronic Stress: A Risk Factor for PD?**

Acute stressful life events have been strongly associated with the onset of clinical episodes of PD. In addition, childhood emotional maltreatment may upregulate adult fear network activity, predisposing to adult anxiety disorders. However, less is known about chronic stress as a risk factor for panic or the effects of chronic stress on the course of PD. Data from a recent longitudinal (3 year) study of MDD and PD patients (n = 677) found that chronic enduring stressors led to a worse illness course and poorer MDD and PD treatment responses. Moreover, in one survey of primary care patients with chronic pain (n = 250), almost half had at least one comorbid anxiety disorder, consistent with the concept that chronic physiological stress could confer risk of PD.

Recent animal studies have documented various neurobiological effects of chronic stress on brain function, with potential implications for human PD. For instance, in one mouse study, chronic restraint and unpredictable stress impaired tonic inhibitory GABA receptor currents in lateral amygdala projection neurons, thereby disinhibiting central nucleus of the amygdala neuronal activity. This change, if longstanding, would
be expected to increase the prevalence of future anxiety and fear behaviors.\textsuperscript{53} In another mouse study, chronic stress led to increased glutamatergic activity/excitability of basolateral amygdala neurons and anxiety behaviors.\textsuperscript{54} Applying a chronic partial restraint stress to rats, other investigators observed that intact insular cortex function was critical to the development of stress-induced visceral hypersensitivity (induced by colonic distention).\textsuperscript{55} This animal model is reminiscent of aspects of human PD, which is also characterized by sensation sensitivity and abnormalities in insular cortex functioning. Another investigation examined the effects of chronic immobilization stress on somato-sensory cortical activation to CO\textsubscript{2} exposure.\textsuperscript{56} Chronic stress blunted cortical responses in this paradigm. In addition, studying neonatal isolation in rats, a model of childhood separation anxiety (a potential risk factor for human PD), other investigators observed that in stressed animals, dorsal periaqueductal gray matter (DPAG) electrical stimulation produced marked panic-like responses.\textsuperscript{57} Other preclinical studies have addressed the issue of genetic variation and stress vulnerability. For example, one mouse genetic model study examined stress sensitivity and variation in GABA synthetic enzymes. GAD 65 \textemdash \textasciitilde mice were noted to be vulnerable to fear, anxiety, and stress, while +/\textasciitilde mice demonstrated stress resilience.\textsuperscript{58} Abnormalities in neurotrophin (NT) secretion (e.g., brain-derived neurotrophic factor (BDNF)) have been implicated in the onset of some stress-related conditions, such as PD.\textsuperscript{59} One group, investigating the NT-3/TrkC system, observed that mice overexpressing TrkC were more sensitive to the effects of chronic stress.\textsuperscript{60} In addition, a novel primate (marmoset) genetic model evaluated the relationship between 5-HTT polymorphisms, and responses to acute threat and acute SSRI exposure.\textsuperscript{61} The low-expressing haplotype (AC/C/G) was associated with high anxiety responses to an intruder and SSRI challenge. These phenotypic features are resemble characteristics seen in humans with anxiety conditions, such as PD. Human studies of susceptibility to future life stressors are also underway. One example of this work is a longitudinal study with a 1\textendash 4 year follow-up period of young adults (n = 340). In this protocol, baseline amygdala hyper-reactivity to emotional stimuli (detected by fMRI) predicted later emergence of affective and anxiety symptoms in response to stressors.\textsuperscript{62} Thus, chronic stress via neuroplasticity changes in the extended amygdala and other fear network structures can predispose to the development of chronic anxiety. In addition, with stress-vulnerable animal genotypes and human endophenotypes being identified, it is conceivable that individual PD clinical presentations result from a unique combination of genetic, temperamental, neurophysiological, and environmental factors.

**RDoC and PD Neurobiology**

**Introduction**

The NIMH RDoC project is intended to move psychiatric diagnosis towards a more dimensional and neurocircuitry-based framework.\textsuperscript{63} This transdiagnostic approach aims to examine the neural underpinnings of common bio-behavioral dimensions in order to hasten translational and personalized medicine successes in psychiatry.\textsuperscript{64} Within the RDoC framework, systems/domains relevant to PD include the negative valence domain (within which the constructs of acute threat (fear), potential threat (anxiety), and sustained threat (chronic stress) are pertinent). A second domain of potential relevance is arousal/modulatory systems.\textsuperscript{65} The implications of RDoC for PD as a diagnostic entity are potentially great. As we have seen from the current literature, there are common genetic and neurobiological factors that span the traditional DSM-V anxiety disorder categories. Moreover, at the phenomenological level, sub-syndromal panic (e.g., patients with recurrent panic who do not meet full PD criteria) is common and has been associated with more serious psychopathology than previously appreciated.\textsuperscript{66,67} In contrast, isolated panic attacks, known to be very common (up to 20\% of the general population in some surveys), are not associated with significant lifetime psychopathology. Thus, the concept of studying the biological basis of dimensions of anxiety psychopathology across wide range of affective and anxiety conditions, such as panic attack frequency, has face validity and may well lead to more personalized treatment.\textsuperscript{68} Moreover, anxiety traits in healthy populations also offer another window on risk factors for morbid anxiety. Also, mammalian neurophysiological mechanisms, subserving fear conditioning, contextual conditioning, extinction learning and failure, and pertinent to understanding normal and abnormal human anxiety, are likely to be active in varying degrees across anxiety disorders and involve elements of the fear circuit (for more detail see section “The functional neuroanatomy of panic”).\textsuperscript{69,70}

**PD: A Disorder of Negative Valence Systems?**

Animal studies of fear have been critical to our understanding of fear processing and responding in humans. One influential animal model of acute fear responding has been Fanselow’s threat imminence model.\textsuperscript{71} In this scheme, defensive reactivity dynamics (to external or internal threats) in animals are divided into categories of pre-encounter defense, post-encounter defense and circa strike defense. In pre-encounter defense, the animal is scanning the environment for potential threats. Once a threat is detected, post-encounter responses are activated such as motor freezing (mediated via
ventral PAG), fear-related bradycardia, and potentiation of the startle reflex (mediated via central nucleus of the amygdala). In animals, these responses are designed to prevent detection. In the circa-strike scenario (e.g., imminent attack from a predator), active fight or flight responses are triggered (mediated via dorsal PAG). Cross-species preservation of threat response processes and circuitries involved may be advantageous for ongoing RDoC inquiries aiming to analyzing the key behaviors and neural systems underpinning clinical PD. Studies of genetic influences on human acute threat circuitry and responses have been limited. However, physiologic threat responses (heart rate, skin conductance, respiratory rate, and startle or potentiated startle) appear to be moderately heritable (estimates ranging from 30 to 50%). Genetic studies of PD risk alleles (e.g., RGS2 rs10801153) examining the impact of these on PD pathophysiology, as well as their effect on anxiety trait and a behavioral avoidance task (BAT), found convergent positive results with these two analytic approaches.

Functioning imaging work in human subjects has provided some support for the translational relevance of the imminence threat model. In one study of healthy subjects using an fMRI activation paradigm with a virtual predator, activation of forebrain structures (ventral prefrontal and ACC) occurred with post-encounter threat responses, with progressive engagement of structures further down the neural axis (hypothalamus, and PAG) with increasing threat imminence. Another group, evaluating an emotion (anxiety) provocation task in healthy subjects (n = 55) during fMRI scanning, observed that amygdala and midbrain areas were activated briefly by transient threat stimuli, while ventro-basal forebrain structures (including the bed nucleus of the stria terminalis (BNST)) and anterior insula demonstrated sustained activity as task continued. Lower levels of anxiety were associated with increased sustained activity in ventromedial PFC. The latter study supported the notion that, in humans, acute threat and chronic threat circuitries are separable. Transdiagnostic anxiety patient studies of responses to face stimuli (disorder-related threat stimuli) have observed amygdala activation across disorders. In the study of Feldker et al., broader activation of frontal, para-limbic (thalamus and insula), and brainstem regions were also noted. Moreover, subclinical levels of anxiety and depression in healthy subject sample also moderated amygdala responding to emotional words (both negative and positive words).

Transdiagnostic studies of behavioral and physiological aspects of defensive reactivity have also been informative. Using an imagery-based fear elicitation paradigm in patients (specific phobia, social phobia, PD, OCD, GAD, and posttraumatic stress disorder (PTSD)) and healthy controls, patients were generally found to have exaggerated startle responses to clinically relevant imagery. Interestingly, reactivity varied across the spectrum of diagnoses, with more discrete disorders (e.g., specific phobia) exhibiting the strongest fear-potentiated startle (FPS), while more complex, anxiety-based disorders (PTSD and GAD) tended to have blunted FPS. The startle effect was inversely correlated with subjective distress. Chronic stress/dysphoria has been postulated to impair defensive responding in the above paradigm and may also negatively impact reward processing. However, in one study comparing PD with and without MDD, MDD patients and controls on indices of threat and reward processing enhanced threat sensitivity (measured by startle response to threat anticipation) was specific to PD diagnosis, while diminished reward sensitivity (ascertained by frontal EEG asymmetry during anticipation of reward) was more typical of MDD.

Aspects of the threat imminence model and its diagnostic and treatment significance were examined in several large PD with agoraphobia (AG) samples (N = 369 and N = 124 patients) participating in ongoing CBT treatment studies. RDoC principles informed the evaluation processes which, beyond traditional diagnostic and severity measures, included other levels of assessment such as behavioral, physiological (heart rate, skin conductance, and startle), and genetic outcomes. An important design component was the inclusion of a BAT test during which patients entered a small enclosed chamber for 10 minutes. At pre-treatment baseline, a gradation of defensive responding up to full panic attacks was observed in PD/AG patients. Consistent with the threat imminence model, startle responses were suppressed just prior to escape from the test chamber. Thus, panic attacks can be conceptualized as examples of circa strike defensive responses, while anticipatory fear can be viewed as an example of post-encounter defense (freezing-like responses). In addition, in this study, 5-HT system genetic markers were linked to acute threat responses, while hypothalamic–pituitary–adrenal (HPA) axis genetic markers modulated anxious apprehension or post-encounter/freezing behaviors.

The Functional Neuroanatomy of Panic

Introduction

In several landmark papers, Gorman et al. proposed a neuroanatomic network to account for the pathogenesis of PD. Key structures in this fear network (thought to be characterized by excessive neural activity) included the amygdala (a central component), the hippocampus and hypothalamus, thalamus, brainstem structures (e.g., the locus ceruleus (LC), PAG, parabrachial nucleus), and
cortical structures (PFC). In this scheme, brainstem structures mediated acute fear expression (panic), while chronic anticipatory anxiety was mediated via limbic structures and phobic avoidance was processed via the PFC. The “neuroanatomical hypothesis,” moreover, helped resolve how diverse antipanic treatment modalities (e.g., CBT and pharmacotherapy) could work, with CBT postulated to influence prefrontal cortical function and pharmacotherapies (e.g., benzodiazepines and antidepressants) to modulate brainstem functioning. Other neuroanatomical models have elaborated on this framework, emphasizing the roles of the LC/NE system, 5-HT system, and HPA axis, and their interactions within the network,86,87 and the restraint role of the 5-HT system on hypothalamic and brainstem PAG activity.88,89

In addition, a false suffocation alarm theory of panic, involving sensitive carotid and brainstem chemoreceptors, was also proposed to account for the respiratory presentation of PD and the behavioral sensitivity to lactate, CO2, and pH fluctuations.90 Subsequent empirical work in animals and PD patients has generally supported the importance of the structures outlined by Gorman’s network (evidence summarized later). More recent work, with significance for PD, has implicated the insula cortex in interoceptive cue processing,91 the medial PFC in learned extinction processes,92 and the BNST in contextual fear and sustained threat monitoring.93,94 While neuroanatomical models of panic have identified the amygdala as a central node in the panic network, recent work in amygdala-damaged patients demonstrated that CO2-evoked chemical panics still occur in these patients.95 Thus, the amygdala is not essential for the expression of some types of panic.

**Sensory Systems and PD**

The thalamus, an important sensory integration node, has been found to be hyperactive across a range of anxiety disorders in activation functional imaging studies.96 Moreover, a deep brain stimulation (DBS)/movement disorder patient, after DBS probe placement in the thalamic area, had treatment-emergent panic.97 Also, disorder-relevant visual threats that activated an extended fear network (event-related fMRI paradigm) in PD patients (n = 26) vs. healthy controls (n = 26) included structures such as the brainstem, thalamus, insula, ACC, mid-cingulate cortex, and dorso-medial PFC.98 Surprisingly, the amygdala response did not differ between groups. Notably, subjective anxiety intensity also correlated with the magnitude of brainstem activation. Building on psychophysiological data suggesting poor sensory inhibition (to internal and external stimuli) in PD, other investigators used an fMRI paradigm to study auditory sensory processing in PD (n = 20) and controls (n = 20).99 In this paradigm, PD patients exhibited a dishabituation pattern with exaggerated responses to tones in the anterior insula, left parietal inferior, and right secondary auditory cortex. These changes correlated with anxiety severity. Other work, using activation fMRI methods, has observed aberrant processing of olfactory stimuli in PD with patients (n = 13) exhibiting a frontocortical activation pattern, compared to controls (n = 13), who tended to activate more typical olfaction processing areas (amygdala and hippocampus).100 Thus, there is emerging evidence of difficulties with sensory processing in several modalities in PD that could bias patients toward threat sensitivity and fearful responding. Moreover, a recent systematic review of evoked potential studies in PD (seven studies included) linked PD diagnosis to impairments in attention, information processing, and responsiveness to new stimuli.101

**Fear Processing Structures and PD**

As proposed by Gorman’s original neuroanatomical hypothesis, limbic cortex structures, such as the amygdala, have been strongly implicated in fear processing and response coordination in PD. In addition, the insula cortex and dorsal anterior cingulate cortex (dACC) have also increasingly been implicated in fear processing in PD and related disorders. In this subsection, we review structural, functional, neurochemical, and treatment imaging studies that support a role for each of these structures in the pathophysiology of PD.

**Amygdala.** A number of studies have reported structural differences in the amygdala in PD (generally gray matter volume reductions detected with volume-based morphometry (VBM) techniques). These findings have been extensively reviewed elsewhere.102-104 Effects seemed to be greater in the right amygdala, which may be of significance given that emotional processing has previously been associated with right hemispheric structures.105 Gray matter reductions may confer premorbid risk or, alternatively, could be a consequence of chronic stress. In addition, amygdala subregional shape variations may be of relevance to amygdala functioning in PD.106 A recent volumetric MRI study, comparing concordant and discordant monozygotic twins for lifetime anxiety and depressive disorders, observed bilateral gray matter volume reductions in fusiform gyrus and amygdala in affected twins, suggesting a shared inherited neurobiological substrate for illness risk.107

Functional imaging studies have tended to find amygdala hyperactivity in PD in response to a variety of provocative stimuli (provocative challenges, emotional face presentations, and threat stimuli).108 This result is not unique to panic but rather appears to be a shared feature across anxiety spectrum disorders.109 Several case reports of spontaneous panics occurring in the MRI...
scans documented within-panic activation of the right amygdala, insula, and PFC. In one H2O15 PET blood flow study of PD patients vs. healthy subjects awaiting a pentagastrin challenge, anticipatory anxiety in PD patients was actually associated with hypoactivity of the right amygdala, while challenge led to hyperactivation of the ACC, midbrain areas, superior temporal lobe, and para-hippocampal gyrus. Freezing responses such as anticipatory fear may therefore be associated with reduced amygdala activity. Other conditions under which the amygdala might be hypoactive in PD include illness chronicity and chronic stress.

Insula. The importance of the insula cortex in processing interoceptive stimuli in anxiety states has been highlighted by more recent research. For example, VBM studies have identified abnormal gray matter volume reductions in the right insula in PD. Activation fMRI studies in PD, using different stimulus paradigms, have tended to demonstrate insula cortex overactivity to threat. For instance, in 18 PD patients, investigators demonstrated a positive correlation between anxiety sensitivity and brain activation during emotional processing of facial expressions. Active processing regions in this study included the PFC, ACC, and insula. Panic-relevant pictures activated both insula cortices (among other structures) prominently in PD patients (n = 21) compared to matched controls. Another activation study, examining a mixed group of anxiety patients (GAD = 15, SAD = 14, PD = 15) and 15 controls performing a facial emotion matching task, documented a common response (right amygdala activation) across disorders to negative affective stimuli. However, in this protocol, PD patients were unique in exhibiting greater posterior insula activation across all face types. A PET neurochemical imaging study observed abnormal bilateral insula cortex reductions in GABA/BZD receptor binding in PD, consistent with the concept of decreased intra-insula inhibitory tone. Finally, a study documented the potential significance of bilateral insula activation to an emotion regulation task, with greater baseline activation predicting better response to brief CBT therapy.

Dorsal ACC. The ACC, a limbic system structure, functions as an error detection system in the brain and has also been implicated in emotion regulation and emotional decision-making. The dACC, together with dorso-medial PFC (dmPFC), is important for conscious threat appraisal and tends to be activated across anxiety conditions during active worrying/catastrophizing. Case report findings have linked damage to the right dACC and onset of PD. In a recent meta-analysis of 24 studies of VBM studies done across DSM-5 anxiety disorders including PD, decreased gray matter volume in the right ACC and left inferior frontal gyrus were important transdiagnostic findings. In one fMRI activation study, healthy subjects receiving anxiety provocation with a CCK-4 bolus had marked activation of the rostral ACC. In this protocol, the activation effect was blocked by acute administration of the benzodiazepine anxiolytic, alprazolam. Thus, during acute stress conditions, the ACC is highly activated and also appears to be an important target of anxiolytic treatment. One neurochemical (MRS-GABA) imaging study detected low GABA levels in an ACC/mPFC voxel. This finding was especially pronounced in family history positive PD patients. Reduced GABA inhibitory tone in the ACC in PD therefore could predispose to excessive threat detection. Several small MRI resting state functional connectivity (fcMRI) studies in PD have reported abnormalities involving the ACC. In one study, disturbed resting state limbic network connectivity in PD was observed with increased connectivity between right amygdala and bilateral precuneus areas. Also, salience network connectivity between the dACC and frontal, parietal, and occipital areas was altered in PD. However, no default mode network (DMN) differences were noted. A second study detected increased connectivity between ACC and precuneus areas (medial nodes of the DMN) in PD, which correlated negatively with ACC GABA concentrations. The latter findings could reflect altered somato-sensory processing in PD. Regarding treatment imaging work, in a recent meta-analysis of candidate predictors of CBT treatment responsivity across anxiety disorder, ACC activation emerged as very promising biomarker.

Fear Regulating Structures and PD

The PFC, and especially mPFC, has been increasingly implicated in several psychobiological processes related to fear modulation. These include inhibition of fear responses, threat/safety cue discrimination, extinction learning, and threat appraisal and biases. Faulty “top-down” regulation of fear-generating/processing structures appears to be involved across the spectrum of anxiety conditions, and particularly so with more complex disorders chronic anxiety syndromes, such as GAD and PTSD. Also, the hippocampus has important roles in contextual fear conditioning and extinction and regulation of contextual fear memories. In this subsection, we briefly review recent preclinical, structural/functional imaging, neurochemical imaging, and treatment imaging findings in PD pertinent to these fear regulatory structures.

Prefrontal Cortex. A meta-analysis of VBM MRI studies across anxiety disorders found that left inferior frontal gyrus gray matter reductions to be a shared characteristic of anxiety syndromes. Moreover, frontal-limbic gyrus...
white matter reductions were recently reported in a PD patient vs. healthy subject study (n = 40 in each group). Moreover, in a human treatment imaging study, in a preclinical treatment study, chronic imipramine administration improved rat hippocampal neurogenesis. In addition, in a human treatment imaging study, pharmacotherapy improved rat hippocampal neurogenesis.

BRAINSTEM STRUCTURES AND PD

Preclinical studies have strongly implicated brainstem nuclei as key structures for fear expression. Earlier theories of PD such as the LC-NE hyperactivity theory, the suffocation alarm hypothesis, and 5-HT restraint hypothesis presupposed brainstem dysfunction as a key element in the generation of spontaneous and cued panic attacks. However, there have been relatively few imaging studies of this area in PD, partly due to technical/resolution issues. In a previously mentioned activation fMRI study of PD patients, subjective levels of anxiety correlated with the magnitude of brainstem activation detected. Another fMRI protocol, comparing PD patients to healthy subjects and divers, reported an exaggerated brainstem activation response to hypercapnia (7% CO2) in PD, consistent with the predictions of the suffocation alarm hypothesis. Also, a PET neurochemical imaging study observed abnormally elevated 5-HT transporter binding in males with PD in the ACC and midbrain, partially consistent with the 5-HT restraint theory of panic. In addition, other PET neurochemical studies observed abnormal reductions in 5-HT1A receptor binding in PD patients in the midbrain (presynaptic receptors) and in postsynaptic cortical target areas.

DISCUSSION/CONCLUSIONS

Since the 1990s, “the decade of brain,” there have been important shifts with respect to our concepts concerning the neurobiology of PD. Earlier conceptions viewed PD as due to perturbations in isolated neurochemical systems (e.g., NE system or HPA axis), or, alternatively, as a learned disorder (cognitive/behavioral model). In recent decades, with the increasingly powerful methods of analysis of molecular genetics, preclinical neuroscience, cognitive neuroscience, and imaging science, a complex picture of PD as a fear network disorder has emerged, with biological similarities to other anxiety syndromes and some unique differences.

Replicated genetic risk factors for PD in the neurochemical systems most implicated in the disorder have been difficult to achieve, perhaps due to the polygenic nature of PD, with the exception of several COMT polymorphisms. Thus, DA dysregulation in several fear network structures could contribute to the pathophysiology of PD. Genetic risk markers in the 5-HT system have not been reproducible, though the 5-HT system has been strongly implicated in PD treatment and modulation of fear network activity. Epigenetic findings are beginning to
emerge with implications for treatment outcomes and the role of life events in PD. Temperament factors remain relevant in studies of panic risk, as they map to imaging findings (e.g., low hippocampal volumes or exaggerated amygdala reactivity), which may predict later anxiety symptomatology. Chronic stress is emerging as a potential risk factor for PD. Moreover, chronic stress as a consequence of ongoing PD could lead to chronic inflammation and physical disorders such as cardiovascular disease. Recent neuroimaging data have generally supported and extended early functional neuroanatomical models of PD. While the amygdala has occupied a central place in fear circuit models of panic, important new findings suggest that it is not necessary for some types of panic. In the last five years, panic and anxiety biological studies have had a more transdiagnostic emphasis and have also begun to directly address RDoC constructs. For example, studies of PD patients, examining their defensive dynamics, have distinguished their acute threat responses (with physiological and genetic correlates) and found them to be distinct from anticipatory anxiety (chronic threat responses), consistent with animal model predictions.

Promising future directions for PD genetics and imaging genetics studies include further examination of genes underpinning special types of panic, such as CO2-evoked panic. Arousal regulation genes (e.g., in the orexin, adenosine, and neuropeptide S systems) are promising ongoing research targets, as are genes involved in DA regulation. PD neuroimaging research directions are likely to involve imaging genetics consortia projects, since several limitations with the current neuroimaging data base in PD and anxiety disorders have been the small scale of individual studies and disparate study methodologies. Imaging “connectomics” studies with DTI and fcMRI methods will likely be more prevalent, with the drive to better understand the interactions between fear circuit structures and cross-talk with other brain networks involved in cognitive control and reward processes. PD imaging studies of fear circuitry nodes of recent interest, such as the BNST, (implicated in chronic sustained threat) are also likely to be fruitful.

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