PET and SPECT Studies in Anxiety Disorders

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Contents

Abstract

Neuroimaging studies using PET and SPECT to evaluate neurofunctional differences between patients with anxiety- and stress-related disorders and healthy controls were reviewed. At rest, patients with social anxiety disorder display increased serotonin synthesis rate and upregulated serotonin transporter expression, whereas

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R. A. J. O. Dierckx et al. (eds.), *PET and SPECT in Psychiatry*,
https://doi.org/10.1007/978-3-030-57231-0_10

studies targeting dopamine have yielded mixed results. Posttraumatic stress disorder is associated with a compromised benzodiazepine receptor function. In panic disorder, both benzodiazepine receptors and serotonergic (5-hydroxytryptamine 1A ($5HT_{1A}$)) receptors are downregulated. Across the anxiety disorders, there is downregulation of both benzodiazepine and $5HT_{1A}$ receptors. Symptom provocation studies, where regional cerebral blood flow is measured, support that activity in the brain's fear circuit is altered with increased reactivity in the amygdala, the midbrain, and possibly also the insular cortex, whereas activity in emotion-regulating areas in the prefrontal cortex such as the subgenual anterior cingulate cortex and the orbitofrontal cortex is compromised in the symptomatic state, predominantly in phobic disorders. Some studies demonstrate a coupling between individual differences in neurotransmission and fear network activity. Treatment studies suggest that reductions of neural activity in the amygdala may be a final common pathway for successful therapeutic interventions, thereby linking neurotransmission to plasticity in the core fear network of the brain.

10.1 Anxiety, Genes, and Environment

Anxiety involves a subjective experience of fear and apprehension associated with physiological reactions and avoidance or escape behavior. When the intensity or the frequency of anxiety reactions compromises quality of life, an anxiety disorder is diagnosed. Anxiety problems are prevalent and costly and induce significant suffering. Epidemiological studies show that the lifetime prevalence of any anxiety disorder is almost 30% with roughly twice as many women than men being affected (Kessler et al. 1994, 2005, 2012). Anxiety may come out of the blue like in panic disorder (PD), result from memory activation as in posttraumatic stress disorder (PTSD), be elicited by environmental triggers like in social anxiety disorder (SAD) and specific phobia (SP), or be determined by internal worry cues as in generalized anxiety disorder (GAD). These, together with obsessive-compulsive disorder (OCD), were the principal diagnostic categories for the anxiety disorders in the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*) (American Psychiatric Association 1994). The current version of DSM, i.e., *DSM-5*, differs from *DSM-IV* in many respects. For example, OCD falls under "obsessive-compulsive and related disorders" and is diagnosed separately from the anxiety syndromes now including the new entity of "hoarding disorder." Also, PTSD has its own category called "trauma and stressor-related disorders" including acute stress and adjustment disorders. Beside these differences, anxiety disorders in *DSM-5* now include separation anxiety disorder and selective mutism, both previously classified in the section "Disorders Usually First Diagnosed in Infancy, Childhood, or Adolescence." In this chapter, we will focus on DSM-5 anxiety- and stress-related disorders including SP, SAD, GAD, PD, and PTSD. In all these disorders, anticipation of feared events or situations causes negative affect and eventually leads to their avoidance.

10.1.1 Anxiety Etiology

Recent etiological theories of anxiety capitalize both on inborn and acquired mechanisms but to a different extent. Anxiety disorders tend to cluster in families (Tillfors et al. 2001a), most likely reflecting common genetic and not environmental factors (Hettema et al. 2001). There are two independent genetic factors in anxiety disorders: the first associated predominantly with PD, GAD, and agoraphobia, while the second mainly influences specific phobias (Hettema et al. 2005). Genetic factors account for a moderate proportion of around 30–40% of the variance in the anxiety disorders. Thus, environmental factors also contribute to fear and anxiety; particularly unique rather than commonly shared environmental factors influence anxiety development rendering gene-environmental interactions pivotal.

Fear conditioning, a plausible candidate mechanism both for the acquisition of anxiety and for mediating gene-environmental interactions, is moderately heritable in the range of 35–45% (Hettema et al. 2003). In addition, there is tentative evidence that fear conditioning to stimuli like snakes and spiders that often trigger fear has a higher heritability than conditioning to neutral stimuli like circles and triangles (Hettema et al. 2003). In early research, some candidate genes for fear conditioning have been identified in humans (Garpenstrand et al. 2001; Lonsdorf et al. 2009), and certain moderately heritable personality traits may also act as vulnerability factors for the development of anxiety. Although previous twin studies were suggestive of a moderate heritability for anxiety disorders (Hettema et al. 2003), genome-wide association studies have struggled to identify genes significantly associated with these disorders (Sharma et al. 2016). On the other hand, anxiety disorders are considered stress-related. Evidence from animal studies suggests a strong role for stress on the epigenetic control of the hypothalamic–pituitary–adrenal (HPA) axis and stress-related brain responses. Neuroepigenetics may explain individual variations in the likelihood of environmental disturbances and consequently anxiety-related disorders (Bartlett et al. 2017).

10.2 Anxiety and Brain Imaging

Initial brain imaging studies of mental disorders that used tools like PET and SPECT focused on schizophrenia and depression and were performed in the resting state. In the second wave of imaging studies, i.e., activation studies, cognitive and emotional tasks were used to activate certain brain areas in order to isolate and localize the task-related processes. Symptom provocation studies were carried out in an attempt to define dysfunctional regions related to anxiety. Most of the second-wave studies utilized tracers like [^{18}F]fluorodeoxyglucose (FDG) and [^{15}O]oxygen to determine glucose metabolism and regional cerebral blood flow (rCBF). In the anxiety disorders, a number of provocation studies have been published in specific phobia and SAD (Ahs et al. 2009, Åhs et al. 2017; Carlsson et al. 2004; Fredrikson et al. 1993, 1995; Rauch et al. 1995, 1996; Tillfors et al. 2001b, 2002; Van Ameringen et al. 2004; Veltman et al. 2004; Wik et al. 1996, 1997) as well as in PTSD (Barkay et al. 2012; Bremner et al. 1999a, b; Britton et al. 2005; Fischer et al. 1966; Liberzon

et al. 1999; Nardo et al. 2011; Pissiota et al. 2002; Shin et al. 1997, 1999, 2004; Zubieta et al. 1999). There are at least 24 published studies from the early 1990s to 2019 that have used PET or SPECT tracers to determine activity in brain areas responsive to symptomatic challenge in the situationally elicited anxiety disorders, SP, SAD, and PTSD and that also have described activations in the three-dimensional Montreal Neurological Institute (MNI) or Talairach and Tournoux (1988) space. Several additional studies use emotional probes other than symptom provocation such as aversive facial and affective pictures to elicit affective and/or perceptual processes (Bergman et al. 2014; Fusar-Poli et al. 2009; Sergerie et al. 2008; Sabatinelli et al. 2011). Also, other challenges like anticipation of anxiety-inducing pentagastrin administration have been studied using PET (Boshuisen et al. 2002). There are additional studies that have used pharmacological and physiological perturbations to induce anxiety in healthy individuals and patients like the cholecystokinin tetrapeptide (CCK4) (Eser et al. 2009; Schunck et al. 2006) and carbon dioxide (CO_2) challenge (Ponto et al. 2002).

Studies have been mixed with respect to activation patterns. Because physiological alterations besides their anxiety-inducing properties also have peripheral effects, the CNS alterations are less straightforward to interpret as compared to studies that have used psychological procedures to induce anxiety. Some studies have also imaged behavioral and pharmacological treatment effects (cf. Fredrikson et al. 1995; Furmark et al. 2002; Peres et al. 2007; Lindauer et al. 2008; Sakai et al. 2006). Also, in the area of imaging genetics, candidate genes for anxiety and learning have been related to brain function using neuroimaging tools (cf. Bergman et al. 2014; Winterer et al. 2005; Bigos and Weinberger 2010).

10.2.1 Anxiety, Symptom Provocation, and the Fear Network

We have previously performed a meta-analysis of increased and decreased brain activity as a function of symptom provocation in specific and social phobia on the one hand and PTSD on the other (Fredrikson and Faria 2013). Both phobias and PTSD are characterized by the fact that environmental factors elicit anxiety. Thus, symptom provocation can be accomplished through psychological means rendering them comparable in terms of anxiety induction methods.

Both in phobias and in PTSD, rCBF in the amygdala and the midbrain increases reliably across studies. Also, the insular cortex tends to be activated, while hippocampus activity is not increased, neither in phobia nor in PTSD, perhaps reflecting the noncognitive nature of situationally elicited fear and anxiety (Ray and Zald 2012). In other words, cues may activate an amygdala-localized memory trace (Agren et al. 2012) while not taxing context-dependent memory representation in the hippocampus. In the phobic disorders, as a function of fear, activity in the anterior cingulate cortex (ACC) increases but decreases in the orbitofrontal cortex, whereas in PTSD, this pattern is not observed. Like in rodents, the human fear network is likely to encompass the amygdala, the insula, the hippocampus, the anterior cingulate cortex, the orbitofrontal prefrontal cortex, and the periaqueductal gray of

the midbrain (Shin and Liberzon 2010). A consistent finding is that the amygdala, the insular cortex, and the midbrain seem involved in generating emotional distress and that areas in the prefrontal cortex, to a certain extent, seem to inhibit negative affect possibly by regulating the amygdala. The anterior cingulate cortex covaries both with the inhibition and expression of anxiety (see also Etkin et al. (2011)). The orbitofrontal and the ventromedial prefrontal cortices and the subgenual part of the ACC have all been attributed anxiety-reducing properties. For phobias, the orbitofrontal cortex may be central because symptom provocation results in reduced orbitofrontal cortex activity coupled with enhanced amygdala activation and symptomatic treatment with cognitive behavioral therapy (CBT) increases orbitofrontal activity (cf. Peres et al. 2007) while amygdala reductions are observed at the same time (cf. Furmark et al. 2002). We suggest that part of the experience of losing emotional control during phobic anxiety is also related to reduced activity in the orbitofrontal cortex.

The third wave of brain imaging studies using symptom provocation designs is today almost exclusively performed using functional magnetic resonance imaging (fMRI) rather than PET and SPECT. They are beyond the scope of this chapter but have been reviewed elsewhere (e.g., Bandelow et al. 2016; Brühl et al., 2014; Etkin and Wager 2007; Goossen et al., 2019; Hughes and Shin 2011). It should be noted that increased activity in the fear circuit is not restricted to conditions of symptom provocation but occurs also in response to nontraumatic but distressing cues in PTSD (Gold et al. 2011) and in the resting state in patients with PD (Sakai et al. 2005), perhaps reflecting a disorder-related vulnerability factor or a scar resulting from repeated anxiety activation. Longitudinal research is needed to determine this. Collectively, it can be concluded that parts of the fear circuit in patients with situationally elicited anxiety disorders are hyperactive. This may be a mechanism accounting for increased autonomic and endocrine drive present in anxiety-disordered patients (Ahs et al. 2006), as well as behavioral manifestations of anxiety (Laukka et al. 2011).

10.2.2 Anxiety and Neurotransmission

Brain imaging studies in anxiety disorders have also characterized neurochemistry in the resting state. An advantage of PET and SPECT is the virtually unlimited potential for using organic compounds like ^{18}F, ^{15}O, ^{13}N, and ^{11}C serving as radioisotopes enabling determination of brain perfusion, metabolism, and neurochemistry. The whole-brain coverage is excellent; the meaning of the signal is well understood, making baseline measurements possible and allowing for comparisons of differences between individuals at rest. An additional focus of this paper is to perform a comprehensive review of differences in brain neurochemistry between patients with anxiety- and stress-related disorders and healthy controls as revealed by PET and SPECT imaging. We searched PubMed and crossed each disorder with each imaging technique like "positron emission tomography OR PET OR single-photon emission computed tomography OR SPECT AND generalized anxiety disorder OR

social anxiety disorder OR (specific OR simple) phobia OR posttraumatic stress disorder" to retrieve references. We also extracted studies by using the reference list of resulting publications. From 1994 to 2019, several have used PET or SPECT tracers to determine dopamine and serotonin neurotransmission with ligands probing, for example, dopamine-D_2 and $5HT_{1A}$ receptors as well as dopamine and serotonin reuptake transporters. Also, activity in the neurokinin 1/substance P (NK1/SP) system and benzodiazepine (BZD) receptors has been imaged. With one exception, all neurochemical studies have been performed in the resting state. Table 10.1 details the main findings for GAD (n = 3 studies), SP (n = 1), SAD (n = 12), PD (n = 15), and PTSD (n = 10).

Most studies have been performed in PD, and data suggest that BZD receptors are downregulated even though conflicting evidence exists. Also, $5HT_{1A}$ receptors are downregulated in PD. Data for the serotonin transporter in PD are inconclusive since one study report enhanced and another attenuated reuptake of serotonin. One study reported similar dopamine transporter availability in the striatum of patients with PD and healthy controls.

Social anxiety disorder is the second most investigated condition. A reduced D_2 receptor binding potential was initially suggested, but one study failed to demonstrate differences between striatal regions of patients and controls. Also with respect to dopamine reuptake mechanisms in SAD, data are inconclusive because one study reported higher, one lower, and one similar uptake activity in SAD patients when compared to controls. These were mainly SPECT studies, but by using relatively more specific and sensitive PET methodology, we recently demonstrated elevated dopamine transporter availability in SAD correlating with symptom severity in the amygdala, hippocampus, and putamen (Hjorth et al. 2019). A more consistent pattern emerges for serotonin since three studies indicate increased availability of serotonin transporters in thalamic and striatal regions. This appears true also for the ventral striatum/nucleus accumbens, and interestingly, there is evidence of higher co-expression of serotonin and dopamine transporters in fear- and reward-related brain regions in SAD (Hjorth et al. 2019). Two studies also report increased serotonin synthesis capacity in SAD in limbic and basal ganglia regions. Increased synthesis could, in turn, result from downregulation of inhibitory raphe $5HT_{1A}$ autoreceptors as reported by Lanzenberger et al. (2007). Taken together, these findings may indicate an overactive presynaptic serotonin system in socially anxious individuals.

In PTSD, BZD receptors appear downregulated even though there is conflicting evidence with studies not showing differences between patients and controls. For GAD, there are still too few studies to draw any general conclusions, but suggestive evidence of downregulated BZD receptors exists. Studies are lacking also for specific phobia, but there are indications that alterations in the NK1/SP system activity may characterize one or several anxiety disorders including specific phobia. There are only a few studies investigating NK1/substance P system activity. One study in PTSD reported widespread decreased binding of an NK1 receptor ligand at rest, while another one noted increased NK1 binding in the amygdala in patients. Co-expression of NK1 receptors and serotonin transporters was suggested to be

Table 10.1 Neurochemical alterations in the anxiety disorders based on PET and SPECT studies

First author (year)	Neurofunction	Patients/controls	Imaging/ligand	Main results
Neurochemical alterations in GAD, as compared to controls, based on PET and SPECT studies				
Tiihonen et al. (1997a, b)	GABA/BZD	GAD (10♀) HC (10♀)	SPECT: [^{123}I] NNC-13-8241	↓ TP (L)
Maron et al. (2004a, b)	SERT	GAD (7) HC (7)	SPECT: [^{123}I] nor- β-CIT	= Midbrain 5HTT – Corr with symptom severity in pts
Lee et al. (2015)	DAT/SERT	GAD (12) HC (12)	SPECT: [^{99m}Tc] TRODAT-1 [^{123}I]ADAM	↓ DAT striatum (GAD)
Neurochemical alterations in SP, as compared to controls, based on PET and SPECT studies				
Michelgård et al. (2007)	NK1/SP	SP (16) HC (0)	PET: [^{11}C] GR205171	↓ Amygdala uptake during anxiety provocation – Corr with symptom severity
Neurochemical alterations in SAD, as compared to controls, based on PET and SPECT studies				
Tiihonen et al. (1997a, b)	DAT	SAD (11) HC (28)	SPECT: [^{123}I] β-CIT	↓ Striatum 0 – Corr
Schneier et al. (2000)	D_2	SAD (10) HC (10)	SPECT:[^{123}I] iodobenzamide	↓ Striatum – Corr (trend) with LSAS
Lanzenberger et al. (2007)	$5HT_{1A}$	SAD (12) HC (18)	PET: [^{11}C] WAY-100635	↓ Amygdala, ACC, insula, raphe 0 – Corr
Schneier et al. (2008)	D_2	SAD + OCD (7) OCD (8) HC (8)	SPECT: [^{123}I] - IBZM	↓ Striatum (SAD) – Corr KSP detachment
van der Wee et al. (2008)	SERT/DAT	SAD (12) HC (12)	SPECT: ^{123}I-β-(4-iodophenyl)-tropane	↑ SERT thalamus ↑ DAT striatum 0 – Corr
Schneier et al. (2009)[a]	DAT/D_2	SAD (17) HC (13)	SPECT: [^{123}I] β-CIT PET: [^{11}C] raclopride	= DAT, D_2 (baseline and after challenge) 0 – Corr
Moriyama et al. (2011)	DAT	Parkinson + SAD (11) Parkinson (21)	SPECT: TRODAT-1	+ Corr with symptom severity in the putamen and N Caud
Frick et al. (2015a, b)	5HT synthesis	SAD (18) HC (17)	PET: [^{11}C]5-HTP	↑ Amygdala, raphe nuclei, caudate nucleus, putamen, hippocampus, and ACC + Corr with symptom severity in the amygdala

(continued)

Table 10.1 (continued)

First author (year)	Neurofunction	Patients/controls	Imaging/ligand	Main results
	SERT	SAD (26) HC (17)	PET: [^{11}C] DASB	↑ Raphe nuclei, caudate nucleus, putamen, thalamus, and insula – Corr with symptom severity in dorsal ACC
Frick et al. (2015b)	NK1	SAD (17) HC (17)	PET: [^{11}C] GR205171	↑ amygdala 0 – Corr
Furmark et al. (2016)	5HT synthesis	SAD (18) HC (6)	PET: [^{11}C]5-HTP	↑ Hippocampus, globus pallidum, and putamen 0 – Corr
Plavén Sigray et al. (2017)	D_2	SAD (12) HC (16)	PET: [^{11}C] FLB457	↑ OFC ↑ dlPFC + Corr with symptom severity in OFC
Hjorth et al. (2019)	DAT	SAD (27) HC (43)	PET: [^{11}C]PE2I	+ Corr with symptom severity in the amygdala, hippocampus, putamen ↑ Amygdala, hippocampus, striatum (trend)
	SERT		PET: [^{11}C] DASB	↑ Nucleus accumbens ↑ Amygdala, hippocampus, striatum, thalamus, insula (trend) 0 – Corr
	SERTxDAT co-expression			↑ Amygdala, striatum, thalamus ↓ Dorsomedial thalamus 0 – Corr
Neurochemical alterations in PD, as compared to controls, based on PET and SPECT studies				
Schlegel et al. (1994)	GABA/BZD	PD (10) Epileptic pts. (10)	SPECT: [^{123}I] iomazenil	↓ FC, occipital, TP
Kaschka et al. (1995)	GABA/BZD	PD + depression (9) Dysthymic (9)	SPECT: [^{123}I] iomazenil	↓ Inferior TP, inferior FC, (rCBF-related) ↓ Medial inferior TP ↓ left TP (not rCBF-related)

Table 10.1 (continued)

First author (year)	Neurofunction	Patients/controls	Imaging/ligand	Main results
Kuikka et al. (1995)	GABA/BZD	PD (17) HC (17)	SPECT: [^{123}I] iomazenil	↑ R > L-ratio in pts. ↑ TP
Brandt et al. (1998)	GABA/BZD	PD (12) most on meds HC (9)	SPECT: [^{123}I] iomazenil	↑ Supraorbital cortex (R) ↑ Temporal cortex (R) - Trend correlation with STAI in HC 0 – Corr in pts
Malizia et al. (1998)	GABA/BZD	PD (7) HC (8)	PET: [^{11}C] flumazenil	↓ Globally most pronounced in OFC + insula (R)
Bremner et al. (2000a, b)	GABA/BZD	PD (13) HC (16)	SPECT: [^{123}I] iomazenil	↓ Hipp, precuneus ↓ PFC in panic attackers – Corr symptom severity in PFC
Maron et al. (2004a, b)	SERT	PD (8) PD remission (8) HC (8)	SPECT: [^{123}I] nor- β-CIT	↓ midbrain, TP, thalamus – Corr with symptom severity Clinical improvement = normalization, except in the thalamus
Neumeister et al. (2004)	$5HT_{1A}$	PD (16) with comorbid Agoraphobia (6) HC (15)	PET: [^{18}F] FC WAY	↓ ACC, PCC, raphe
Sullivan et al. (2005)	$5HT_{1A}$	MDD + PD (7) MDD (21) HC (0) MDD with vs. without comorbid PD	PET: [^{11}C] WAY-100635	↓ TP, ACC, PHG, hipp in comorbid PD – Corr anxiety
Cameron et al. (2007)	GABA/BZD	PD (11) HC (21)	PET: [^{11}C] flumazenil	↓ Insula (R + L) 0 - corr
Hasler et al. (2008)	GABA/BZD	PD (15) HC (18)	PET: [^{11}C] flumazenil	↓ PFC, frontal, temporal, parietal ↑ Hipp – Corr with symptom severity in hipp + Corr with symptom severity in dPFC

(continued)

Table 10.1 (continued)

First author (year)	Neurofunction	Patients/controls	Imaging/ligand	Main results
Nash et al. (2008)	$5HT_{1A}$	PD (9) PD remission (7) HC (9)	PET: [^{11}C] WAY-100635	↓ Raphe, OFC, TP, amygdala 0 – Corr
Fujimura et al. (2009)	SERT	PD (14) HC (14)	PET: [^{18}F] SPA-RQ	↓ In widespread areas including the amygdala
Maron et al. (2010)	DAT	PD (7) PD remission (7) HC (7)	SPECT: [^{123}I] nor- β-CIT	↓ Striatum ↑ Striatum current vs. remitted – Corr DAT with symptom severity
Maron et al. (2011)	SERT	PD ♂ (5) PD ♀ (6) HC ♂ (12) HC ♀ (12)	PET: [^{11}C] MADAM	♂ ↑ Raphe, cortex (in 13 out of 20 studied regions ↓ Hipp ♀ = 0 - corr
Neurochemical alterations in PTSD, as compared to controls, based on PET and SPECT studies				
Bremner et al. (2000a, b)	GABA/BZD	PTSD (13) HC (13)	SPECT: [^{123}I] iomazenil	↓ PFC (BA 9) + Corr with symptom severity
Fujita et al. (2004)	GABA/BZD	PTSD (19) HC (19)	SPECT: [^{123}I] iomazenil	= – Corr with childhood trauma Scores in pts
Bonne et al. (2005)	$5HT_{1A}$	PTSD (12) HC (11)	PET: [^{18}F] FC WAY	=
Liberzon et al. (2007)	μ-Opioid receptors	PTSD (16) Trauma exposed HC (14) HC (15)	PET: [^{11}C] carfentanil	Trauma exposed: ↓ Ext amygdala, NAcc, dFC, insula ↑ OFC PTSD: ↓ ACC 0 – Corr
Czermak et al. (2008)	Nicotinic acetylcholine receptors (β_2 subunit)	PTSD (10 HC (10)	SPECT: [^{123}I] 5-1A-85,380	↑ MTP + Corr with reexperience
Geuze et al. (2008)	GABA/BZD	PTSD (9) Trauma-exposed HC (11)	SPECT: [^{11}C] flumazenil	↓ Cortex, hipp, thalamus
Fujimura et al. (2009)	NK1/SP	PTSD (14) HC (14)	PET: [^{18}F]-SPA-RQ	↓ In widespread areas
Murrough et al. (2011)	SERT	PTSD (15) HC (15)	PET: [^{11}C] AFM	↓ Amygdala – Corr symptom severity
Frick et al. (2016a, b)	SP/NK1	PTSD (16) HC (16)	PET: [^{11}C] GR205171	↑ Amygdala 0 – Corr

Table 10.1 (continued)

First author (year)	Neurofunction	Patients/controls	Imaging/ligand	Main results
	SERT		PET: [^{11}C] DASB	↑ Precentral gyrus, posterior cingulate cortex – Corr with symptom severity in the amygdala
	SP × SERT co-expression			↓ Putamen, thalamus, insula, and lateral orbitofrontal gyrus – Corr with symptom severity
Reuveni et al. (2018)	BZD	PTSD (12) HC (15)	PET: [^{11}C] flumazenil	↑ Caudal ACC and precuneus + Corr symptom severity and BZD binding in the mid-insular and anterior insular cortices

[a]i.v. D—amphetamine to induce dopamine release

lower in PTSD patients and correlated with symptom severity in several brain regions (Frick et al. 2016a, b). In specific phobia, one study report reduced NK1 receptor availability during an anxious state. Individual differences in subjective fear during symptom provocation were related to uptake with highly fearful individuals having a lowered uptake in the amygdala, indicating a reduction in NK1 receptor availability and hence suggestive of enhanced endogenous substance P release (Michelgård et al. 2007). Similar to PTSD, patients with SAD, as compared to healthy subjects, have increased NK1 receptor availability in the amygdala (Frick et al. 2015a, b). Moreover, pharmacological blockade of the NK1 receptor resulted in anxiety reductions of a similar magnitude as those achieved through citalopram treatment, and both treatments attenuated amygdala reactivity to symptomatic challenge in patients with SAD (Furmark et al. 2005), suggestive of a mechanistic role for the NK1/substance P system in anxiety. Increased NK1 availability in the amygdala has also been demonstrated to be associated with anxious traits and introversion in healthy individuals (Hoppe et al. 2018).

Across studies, the most consistent result is that BZD receptor binding is reduced in limbic and frontal areas in patients with panic disorder with a similar pattern for PTSD and possibly GAD. Also, monoaminergic neurotransmission seems altered both in SAD and PD consistent with reduced $5HT_{1A}$ receptor availability. There is insufficient data to evaluate specific phobia with respect to integrating and segregating neurotransmission patterns.

Reductions in BZD receptor activity occur most frequently in limbic and frontal areas both for PD and PTSD. Monoaminergic alterations, both in serotonergic and dopaminergic neurotransmissions, are often localized in the limbic system.

Reflecting tracer binding properties, monoaminergic alterations are located also in the striatum and the midbrain raphe, areas rich in dopamine and serotonin, respectively. The altered neurotransmission dynamics in the limbic and frontal parts of the brain concur with studies determining rCBF and FDG in the resting state (Molina et al. 2010; Kim et al. 2007; Bonne et al. 2003; Mirzaei et al. 2001; Semple et al. 1993, 2000), which also are characterized by an altered perfusion and metabolism in the limbic and frontal areas (see Table 10.2 for a summary of studies). There has been little work on resting-state PET and SPECT in recent years, presumably due to the fact that resting-state fMRI has emerged as a substantial field in neuroimaging.

Table 10.2 Alterations in glucose metabolism or regional cerebral blood at rest in anxiety disorders based on PET and SPECT studies

First author, year	Neurofunction	Patients/ controls	Imaging/ ligand	Main results
Semple et al. (1993)	rCBF	PTSD (6) (comorbid cocaine-abuse) HC (7)	PET: $[^{15}O]H_2O$	↑ trend for OFC
Semple et al. (2000)	rCBF	PTSD (−) (comorbid cocaine-abuse) HC (−)	PET: $[^{15}O]$ butanol	↓ FC
Mirzaei et al. (2001)	rCBF	PTSD (8) HC (8)	SPECT: $[^{99m}Tc]$ HMPAO	Ratio only – More left lateralized and heterogeneous in pts
Bonne et al. (2003)	rCBF	PTSD (11) HC (11) Trauma-exposed HC (17)	SPECT: $[^{99m}Tc]$ HMPAO	↑ CBL (L + R), BA4, 6, 22, 19, 37 Vs trauma-exposed HC ↑ CBL (L + R), 20, 21, 40, 3, 4 (HC) Vs trauma-exposed HC + Corr symptomatology in CBL and visual cortex
Kim et al. (2007)	rCBF	PTSD (19) HC (19)	SPECT: $[^{99m}Tc]$ HMPAO	↓ thalamus (R) + corr symptom severity ↑ superior parietal (R) + corr symptom severity
Bisaga et al. (1998)	Glucose	PD♀ (6) HC♀ (6)	PET: $[^{18}F]$FDG	↑ Hipp, parahipp ↓ Inferior parietal, superior temporal
Evans et al. (2009)	Glucose	SAD (15) HC (10)	PET: $[^{18}F]$FDG	↓ ACC vmPFC ↑ vmPFC after tiagabine 3–6 mg GABA reuptake inhibitor
Molina et al. (2010)	Glucose	PTSD (15) HC (6)	PET: $[^{18}F]$FDG	↓ Acc, precuneus (BA 7), insula, hipp, FC, PDF, visual cortex, verbal areas ↑ Fusiform, temporal, occipital, precuneus (BA 31), CBL

Table 10.2 (continued)

First author, year	Neurofunction	Patients/ controls	Imaging/ ligand	Main results
Kim et al. (2012)	Glucose/rCBF	PTSD♀ (12 SPECT & PET) HC♀ (10 SPECT; 15 PET)	SPECT: $[^{15}O]H_2O$ PET: $[^{18}F]FDG$	rCBF: ↓ hippocampus, basal ganglia Glucose: ↓ hippocampus, superior temporal, precentral gyri
Ramage (2016)	Glucose	PTSD danger traumas (19) PTSD non-danger traumas (26) HC soldiers (26) HC civilians (24)	PET: $[^{18}F]FDG$	↑ Amygdala (PTSD with danger traumas compared to HC) ↑ Precuneus (PTSD non-danger traumas compared to danger traumas PTSD) ↑ Precuneus, dACC ↓ l amygdala (PTSD with danger traumas) ↑ Precuneus ↓r amygdala (PTSD non-danger traumas)
Zandieh et al. (2016)	Glucose	PTSD (9) HC (10)	PET: $[^{18}F]FDG$	↓ Occipital lobe in 6 of the 9 PTSD, temporal lobe in 1 of the 9 PTSD, caudate nucleus in 5 of the 9 PTSD ↓ posterior cingulate cortex, parietal and frontal lobes in 2 of the 9 PTSD
Baeken et al. (2018)	Glucose	MDD with GAD (22) MDD without GAD (15) HC (15)	PET: $[^{18}F]FDG$	↑ Parahippocampus (MDD in comparison with HC) ↓ frontotemporal and parietal cortices (MDD in comparison with HC) ↑ dmFC (MDD patients without GAD)

10.2.3 Anxiety Treatment and Brain Function

For certain disorders and some neural functions, there are also treatment studies. For example, Spindelegger et al. (2009) treated patients with PD comorbid with SAD with selective serotonin reuptake inhibitors (SSRIs) for 12 weeks and reported a decrease in $5HT_{1A}$ availability. Because the binding in patients initially is lower than in controls, the causative role of $5HT_{1A}$ receptors in determining anxiety symptomatology remains uncertain. It is not clear if there is cross talk between the monoaminergic systems or if the ligands fail to selectively mirror only one system. For example, Warwick et al. (2012) reported an increased dopamine transporter (DAT) binding in the caudate and putamen after 12 weeks of escitalopram treatment in patients with SAD suggesting serotonergic influences on dopamine signaling. Thus, the interpretation of alterations in neurotransmission in anxiety disorders is probably not unidimensional and restricted to one brain function but multidimensional and related to multiple mechanisms.

10.3 Multiple Mechanisms Mediating Anxiety

Altered neurotransmission could represent a primary vulnerability factor or a secondary scar resulting from repeated anxiety experiences which in turn could modulate the activity of the fear network in the brain (Shin and Liberzon 2010). For example, Hariri and co-workers reported a negative correlation between $5HT_{1A}$ receptor density and BOLD reactivity to emotional pictures in normal healthy volunteers. Fisher et al. (2006) and Kienast et al. (2008) demonstrated positive relations between serotonin and dopamine functions and amygdala BOLD reactivity to negative stimuli. Also, after pharmacologic treatment, reduced serotonin synthesis rate correlated with attenuated stress-related activity in the amygdala in patients with SAD (Frick et al. 2016a, b). This is in line with a modulating role for the monoaminergic system with respect to fear network activity. Also data in patients with specific animal phobia support that the NK1/SP system in the brain modulates activity in the amygdala. Ahs et al. (2009) reported a positive correlation between anxiety ratings and increased amygdala rCBF, while Michelgård et al. (2007) observed a corresponding negative correlation between anxiety ratings and NK1 receptor availability suggesting a potential coupling between fear circuit network activity reflected in rCBF and neurotransmission in the NK1/SP system. Neurochemical modulation of the central nervous system activity is further supported by imaging genetic studies linking monoaminergic polymorphisms to emotionally determined amygdala reactivity (Domschke and Dannlowski 2010; Munafò et al. 2008) and to modulation of intrinsic couplings within the fear network (Pezawas et al. 2005). One implication of the hypothesis that the monoaminergic and other neurotransmission systems modulate fear circuit activity is that all treatments targeting specific neurochemical systems should influence symptomatology through activity in the fear network. A couple of studies from our and other laboratories are consistent with this notion because reductions in anxiety achieved through administration of SSRI and NK1 receptor antagonism both attenuated amygdala reactivity in SAD (Furmark et al. 2002, 2005; Faria et al. 2012; Phan et al. 2013). In addition, in PTSD, prefrontal activity was enhanced by SSRI (Fernandez et al. 2001) with similar findings reported by Fani et al. (2011). Attenuation of amygdala reactivity may be a final common pathway for anxiety reductions irrespective of treatment modality. Effective CBT in SAD and specific phobia reduce amygdala reactivity (Furmark et al. 2002; Lipka et al. 2014). Also, responders but not nonresponders, to placebo administration in a randomized controlled trial evaluating pharmacological anxiolytics for SAD, had reduced amygdala reactivity (Furmark et al. 2008; Faria et al. 2012).

A parsimonious working hypothesis is that both psychological and pharmacological interventions work through altering fear network activity either by bottom-up mechanisms reducing amygdala and insula activity directly or through prefrontal top-down control of fear-initiating areas (Faria et al. 2014). The hypothesis that neurotransmission is tightly coupled to fear network activity also implies that effective CBT is mediated by alterations in the neurochemistry of the brain, as supported by initial evidence (Cervenka et al. 2012).

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