Panic and the Brainstem: Clues from Neuroimaging Studies

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Abstract
One of the most influential theories has conceived unexpected panic attack (PA) as a primal defensive reaction to threat within the internal milieu of the body. This theory is based on findings suggesting the involvement of dysfunctional respiratory regulation and/or abnormally sensitive central neural network of carbon dioxide (CO_2)/hydrogen ion (H^+) chemoreception in PA. Thus, unexpected PA may be related to phylogenetically older brain structures, including the brainstem areas, which process basic functions related to the organism's internal milieu. The brainstem represents a crucial area for the regulation of homeostatic functions, including chemoreception and cardio-respiratory control. In addition, the midbrain dorsal periaqueductal gray may be involved in the unconditioned defense reactions to proximal threats, including internal physical stimuli. Our aim was to specifically consider the potential involvement of the brainstem in panic disorder (PD) by a comprehensive review of the available neuroimaging studies. Available data are limited and potentially affected by several limitations. However, preliminary evidence of a role of the brainstem in PD can be found and, secondly, the brainstem serotonergic system seems to be involved in panic modulation with indications of altered both serotonergic receptors and 5-HT transporter bindings. In conclusion, our review suggests that the brainstem may be involved in psychopathology of PD and supports the relevant role of subcortical serotonergic system in panic pathogenesis.
Key-words: anxiety disorders, brain imaging, brainstem, panic disorder, provocation studies, serotonergic receptors.

Introduction

Despite two decades of scientific research, the pathophysiology of panic disorder (PD) is still not well understood. Several clinical, psychophysiological, provocation (i.e. aimed to induce panic attacks (PAs) in laboratory settings) and neuroimaging studies led to biological, cognitive and behavioral theories, involving distinct neuroanatomical areas [1-5]. This heterogeneity might be the expression of the complexity of PD that results from the interplay of unexpected PAs, anticipatory anxiety and phobic avoidance [6]. These clinical phenomena may reflect the involvement of multiple brain pathways making difficult the interpretation of findings from imaging studies. In addition, it is unclear to what extent the available animal models of defensive responses to threats may reliable represent the human unexpected PAs and/or the behavioral modifications resulting from the recurrence of PAs [7-9]. Given these limitations, one of the most influential theories, i.e. Donald Klein's "Suffocation False Alarm Theory", has conceived unexpected PA as a primal defensive reaction to threat within the internal milieu of the body, distinct from the fear response [2]. This theory was based on the compelling findings suggesting the involvement of an abnormal respiratory regulation and/or an abnormally sensitive central neural network of carbon dioxide (CO_2)/hydrogen ion (H^+) chemoreception in PAs [2, 3, 10-13]. In addition, most studies showed no or inconsistent cortisol response in laboratory-induced PAs [12, 14, 15], even though some abnormalities in the hypothalamic-pituitary-adrenal (HPA) axis have been found in subjects with PD [15, 16] and future work is needed to clarify this controversial issue. According to Donald Klein's view, unexpected PAs may be related to the activation of phylogenetically primitive brain structures, including the brainstem areas, which process basic functions related to organism's internal milieu, while anticipatory anxiety/phobic avoidance may be related to higher brain systems [17]. On the other hand, Gorman and coworkers have proposed strong similarities between human PAs and conditioned fear responses in animals, conceiving both PAs and related phenomena as the results of a dysfunctional "fear network" centered on the amygdala and the limbic system [4]. Recently, Dresler and coworkers revisited and discussed the "fear network" model of PD on the basis of an extensive review of neuroimaging studies, showing that a crucial role of the amygdala/limbic system in PD has not unequivocally been supported and suggesting a relevant role of other brain areas, such as the brainstem or the insula [18].

The brainstem and its connections are a crucial area for the regulation of a number of homeostatic functions, including chemoreception and cardio-respiratory control, which have been implicated in panic mechanisms. The respiratory control network consists of a long column of cells in the lateral brainstem that extends from the caudal medulla, along the ventrolateral medulla, to the dorsolateral pons, as well as to the nucleus of the solitary tract (NTS) [19-21]. The frequency and amplitude of the descending respiratory drive arises from the respiratory oscillator network, which is primarily associated with the pre-Bötzinger complex in the ventrolateral medulla and is modulated by several peripheral and central afferent signals. They include inputs from the central chemoreceptor region on the ventral surface of the brainstem and from several other brainstem regions, such as the NTS, retrotrapezoid nucleus, raphe nuclei and locus coeruleus [22-25]. The brainstem neurons in the rostrolateral and ventrolateral medulla control heart rate and sympathetic tone and both respiratory and cardiovascular control networks in brainstem work together to coordinate breathing and

sympathetic outflow, mediated by afferent inputs and interactions at the level of the pattern generators [23, 25, 26]. In addition, the midbrain dorsal periaqueductal gray (dPAG) may play a role in the unconditioned defense reaction to proximal threats, including internal physical stimuli [27, 28]. Finally, these brainstem areas are widely modulated by neurotransmitters involved in panic, such as serotonin and acetylcholine [29-32].

The aim of the present study is to assess the involvement of the brainstem in PD by a comprehensive review of the available neuroimaging studies.

Methods

A comprehensive literature search was performed to identify neuroimaging studies on PD. PubMed and Google Scholar databases were used. The search terms included “computer tomography” (CT), “functional/magnetic resonance imaging (f/MRI), “positron emission tomography” (PET), “single photon emission computer tomography” (SPECT), “near-infrared spectroscopy“ (NIRS), “magnetic resonance spectroscopy” (MRS), “imaging genetics” and “panic disorder”. All studies were analyzed applying the following inclusion criteria: English-language articles; published from 1984 to December 2012; human studies; diagnosis of PD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-III [33], DSM-III-R [34] or DSM-IV/ DSM-IV-TR [35, 36]; brainstem structures investigated. After selection, articles were divided according to the study design: provocation studies, resting-state studies, emotional processing studies, receptor binding studies, structural studies, treatment studies. After this subdivision, for each article the general features of the study, the imaging technique used, the presence of control group(s) and results were reported. Further information (e.g., sample characteristics, axis I comorbidity and treatments) was added when relevant.

Results

The electronic search identified 344 articles. Among these, 326 were excluded and 18 studies were selected.

Provocation studies

In a PET study the effects of sodium lactate infusion on regional cerebral blood flow (rCBF) were investigated in a sample of patients with PD and in normal controls using radiolabeled water ($H_2{}^{15}O$-PET). Half of the clinical sample experienced a lactate-induced PA that was associated with a bilateral blood flow increase in the temporal pole, insular cortex, claustrum, lateral putamen, midbrain and in or near the left cerebellar vermis. Non-panicking patients and control subjects did not show this rCBF modification. During lactate infusion, all subjects experienced a significant increase in number of anxiety symptoms, heart rate, arterial PH and a significant reduction in hematocrit. However, panicking patients showed a greater increase in number of anxiety symptoms and systolic blood pressure, and a significantly greater reduction in the partial pressure of arterial CO_2 (PCO_2) suggesting an exaggerated subjective, autonomic, and respiratory response to lactate infusion [37]. Even though this study suggested that sodium lactate was able to activate brainstem during the panic provocation challenge, caution is needed when interpreting these results. It is well known that studies relying on relative changes in rCBF, such as oxygen-15 PET and fMRI blood oxygen level-dependent (BOLD), are particularly vulnerable to breath-by-breath and/or condition-related changes in the PCO_2 which acts as a potent vasodilatator [38, 39]. Moreover, the presence of an anxiety disorder as well as changes in state anxiety are often associated with respiratory

alterations that affect arterial PCO_2, thus producing significant changes in CBF that are independent of task-related neural activation [40, 41]. For these reasons, although in the study of Reinman and coworkers [37] some cardio-respiratory measures (e.g heart rate, blood pressure, arterial PH and PCO_2, and hematocrit) were taken into account, it cannot be excluded that their finding might have been influenced by PCO_2 modifications related to hyperventilation and/or state anxiety.

In another $H_2{}^{15}O$-PET study, Boshuisen and coworkers [42] investigated rCBF in patients with PD and normal controls when anticipating a pentagastrin challenge and afterwards, when the pentagastrin had subsided (resting condition). Almost all patients with PD (16 out of 17) had a PA during the pentagastrin challenge compared to only two of the control subjects. In the anticipatory phase, during the scan, patients experienced on average four panic-related symptoms and two patients had a PA. In the resting condition, none of the subjects reported a PA. In the anticipatory phase, compared to healthy controls, patients displayed increased blood flow in the parahippocampal gyrus, the left hippocampus, the right temporal lobe, the orbitofrontal cortex, the anterior cingulate gyrus, the hypothalamus, the thalamus and the midbrain (probably in the PAG) and decreased blood flow in the precentral gyrus, the inferior frontal gyrus, the right amygdala and the anterior insula. In the resting condition only the precentral gyrus, the inferior frontal gyrus, and the anterior insula were deactivated in patients, while the parahippocampal gyrus, the anterior cingulate gyrus and the midbrain showed increased activity. The pattern of rCBF increase/decrease observed before and after the pentagastrin challenge was similar, although different in intensity [42].

Kent and coworkers [43] used $H_2{}^{15}O$-PET to obtain brain images of five untreated subjects with PD and five healthy comparison subjects before and during an anxiogenic challenge with intravenous doxapram, which is a respiratory stimulant. There were significant differences between the groups neither in global (weighted average) subcortical (midbrain, hippocampus, amygdala, thalamus and striatum) or cortical (prefrontal cortex: anterior cingulate, medial, dorsolateral, orbitofrontal and subgenual) blood flow in response to placebo or doxapram injections nor when the regions of interest were analyzed individually. In another study six patients with PD and seven normal control subjects underwent PET with ^{18}F-fluorodeoxyglucose (FDG) imaging after a single-blinded administration of either doxapram or a placebo saline solution. In response to doxapram, patients decreased their prefrontal activity and increased cingulate gyrus, amygdala and brainstem activity to a greater extent than controls [44]. The small size of the samples and potential confounding factors related to the respiratory stimulant activity of doxapram might have affected the results of these last two studies.

Goossens and coworkers compared 12 patients with PD, 11 healthy controls, and 12 expert divers in a fMRI experiment with hypercapnic gas mixture (7% CO_2, 93% O2). They reported increased focal brainstem activation in response to hypercapnia, that is the most validated panic provocation procedure, in patients with PD compared to controls, while divers displayed a decreased response [45]. This is the first study showing that the behavioural response to CO_2 that characterizes patients with PD is likely due to increased neural sensitivity to CO2 at brainstem level. However when interpreting these findings some limitations should be taken into consideration. First, the combination used of hyperoxia (~93% fraction of inspired O_2 (FIO_2)) with hypercapnia (~7% fraction of inspired CO_2 ($FICO_2$)) is likely to dampen the bold response [46]. Second, due to the lack of measures of respiration physiology during the scans (e.g. airway pressure, airway flow, and tidal volume), the impact of these sources of variance on the BOLD

fMRI signal cannot be adequately considered. Third, BOLD fMRI imaging brainstem is particularly vulnerable to physiological noise, thus artifacts and variance may be related to physical displacement with each cardiac and respiratory cycle [47, 48]. In addition, image susceptibility differences within the brainstem region can cause signal loss and/or distort the images. Finally, hypercapnic reflex increase during ventilation can cause signal artifacts due to task-related variation in the intrathoracic pressure [49].

In summary, although the evidence of an increased focal brainstem activation in response to hypercapnia by Goossens and coworkers [45] is promising, provocation studies are not enough consistent to draw definitive conclusions on the role of brainstem, also considering the limitations that might affect this kind of studies.

Resting state studies

To date only one resting state study investigated the involvement of the brainstem in PD. Sakai and coworkers assessed cerebral glucose metabolism in patients with PD using FDG-PET. Patients exhibited significantly higher levels of glucose uptake in the bilateral amygdala, hippocampus, thalamus, and in the midbrain, caudal pons, medulla, and cerebellum than healthy controls [50]. Unfortunately, patients showed high state anxiety before scanning that might have influenced the results and the lack of cardio-respiratory measurements does not allow to make appropriate inferences on the brainstem related findings. Thus it is not possible to conclude whether the observed pattern was linked to panic attacks, to anticipatory anxiety or to other cardio-respiratory factors [38, 40, 51].

Emotional processing studies

Chechko and coworkers investigated emotional perception as a trait marker using fMRI in patients with remitted PD as compared to healthy controls. They used a face–word interference test [52], in which a word superimposed on a face could be either congruent (e.g., word ‘‘fear’’ on a fearful face) or incongruent (e.g., word ‘‘fear’’ on a happy face). Patients displayed larger interference effect than the healthy controls. Indeed they needed more time than controls to indicate the valence of the facial stimulus when the word was incongruent with the face. Patients displayed higher dorsal anterior cingulate cortex (ACC) activation for the contrast ‘incongruent vs. congruent’, when the preceding trial was congruent. When the preceding trial was incongruent, patients showed decreased activation in the ACC and the medial prefrontal cortex (mPFC) along with increased activation of the limbic system (including the amygdala), the midbrain, and the pons [53].

In a fMRI study by Tuescher and coworkers [54] participants (patients with PD, patients with post traumatic stress disorder and a control group) learned to associate specific neutral stimuli with either a safe or threatening context indicating the possibility of an electrical shock. In comparison to the other two groups, patients with PD displayed decreased activation in the threat condition and increased activity in the safe condition in the subgenual cingulate, ventral striatum and extended amygdala, as well as in the dorsal midbrain/mesial PAG.

In summary, PD patients tend to have abnormal brainstem activation in response to emotional stimuli when compared with healthy controls.

Receptor binding studies

Bremner and coworkers [55] did not found significant differences in benzodiazepine receptor binding in the pons or in the midbrain between patients with PD and healthy controls using SPECT [^{123}I] iomazenil. In a PET study using the selective serotonin type-1A receptors (5-HT_{1A}R) radioligand (^{18}F)trans-4-fluoro-N-2-[4-(2-methoxyphenyl)piperazin-1-yl)ethyl]-N-(2-pyridyl) cyclohexanecarboxamide (FCWAY), Neumeister and coworkers [56] showed in patients with PD a marked reduction of cerebral 5-HT_{1A}R binding in the anterior and posterior cingulate cortices, and the midbrain raphe, an area where 5-HT_{1A}R stimulation regulates serotonin synthesis and release. The subgroups analysis (PD vs. PD with secondary major depressive episode and drug-naive vs. previously medication exposure) showed that the reduction of cerebral 5-HT_{1A}R binding was explained neither by previous exposure to psychotropic drugs nor by comorbid depression [56]. Nash and coworkers [57] replicated the study by Neumeister and coworkers [56] measuring 5-HT_{1A}R binding with the radiotracer (Carbonyl-^{11}C)WAY-100635. This allowed a better *in vivo* quantification in patients with PD not only in the untreated state but also after recovery from treatment with selective serotonin reuptake inhibitors (SSRIs). In comparison with controls, both presynaptic and postsynaptic 5-HT_{1A}R binding was reduced in untreated patients with the most significant reduction being in the raphe nucleus, in the orbitofrontal cortex, in the temporal cortex and in the amygdala. In recovered patients presynaptic binding was also reduced while postsynaptic binding was unchanged [57]. In a SPECT study, using a radio ligand that specifically labels the serotonin transporter [5-HTT), [^{123}I] nor-beta-CIT, Maron and coworkers [58] showed that patients with current PD had a significant decrease in 5-HTT binding in the midbrain, in the temporal lobes and in the thalamus in comparison to the controls. The binding of 5-HTT in patients with PD in remission was similar to that found in the control group in the midbrain and in the temporal lobes, but they was lower in the thalamus. Regional 5-HTT binding significantly and negatively correlated with the severity of panic symptoms. Notably, the clinical and control samples included mainly female subjects (7 female and 1 male for each group). To further elucidate the role of 5-HT in PD and to overcome the gender bias of this SPECT study, the same group conducted a subsequent PET study using a highly selective and specific tracer, (N-methyl-^{11}C)N,N-dimethyl-2-(20-amino-40 methylphenyl-thio) benzylamine [(^{11}C)MADAM] in a new sample of eleven medication-free PD patients of both genders. Male patients had a higher 5-HTT binding potential in the brainstem compared with male controls whereas no significant differences were observed between female patients and controls [59]. Other neuroimaging studies have demonstrated lower brain 5-HTT availability in depressed [60] and healthy [61] females, as well as lower brain 5-HT synthesis rate [62], but higher 5-HT_{1A}R binding potential [61] in females than in males. However, no sex differences in brain 5-HTT availability were detected in a large sample of healthy subjects [63]. Moreover, small sample size may have influenced the negative finding in female patients. In summary, with the exception of Maron and coworkers [58], receptor binding studies showed reduced density of 5-HT_{1A}R and 5-HTT in the midbrain of patients with PD.

Structural studies

Protopepescu and coworkers [64] found an increased gray matter volume in the midbrain and in the rostral pons of the brainstem in patients with PD using voxel-based morphometry (VBM), an operator-independent technique allowing the detection of brain gray matter concentration (an estimate of tissue density) or volume (an estimate of absolute volume). VBM is used to characterize the whole brain rather than a priori determined brain regions between different

groups of subjects. Uchida and coworkers confirmed this finding in an independent VBM study [65]. Fujiwara and coworkers [66] found that relative midbrain volume was larger in the PD group than in the healthy control group. Moreover the relative volume of the dorsal midbrain was larger in the PD group, while the volume of the ventral midbrain was not. They also found a significant positive correlation between relative dorsal midbrain volume and total Panic Disorder Severity Scale (PDSS) score, and a significant negative correlation between relative dorsal midbrain volume and Global Assessment of Functioning (GAF) score in the PD group. These results suggested that the dorsal midbrain is associated with PD pathophysiology and that the midbrain volume increase may reflect clinical severity.

In summary, patients with PD show increased brainstem volume.

Treatment studies

In a study performed to investigate regional brain glucose metabolic changes associated with successful completion of cognitive–behavioral therapy (CBT) in patients with PD, decreased glucose utilization was detected in the pons. A significant correlation was observed between the percent change in glucose utilization of the midbrain around the PAG and the frequency of PAs during the previous 4 weeks [67]. Using a structural MRI, Lai and Wu found a modest increase in the volume of the brainstem after a 6 weeks treatment with duloxetine in a group of first episode drug-naïve patients with major depressive disorder (MDD) and PD. The volumetric increase was correlated with improvement of clinical symptoms [68]. These results seem to challenge the finding of greater brainstem volume in patients with PD compared to controls showed in other studies [64-66]. However, some reasons may explain this discrepancy. A deficit of the dorsal raphe nuclei in the ventral midbrain of patients with MDD was found [69] and the subjects with PD in the sample of Lai and Wu [68] had co-morbid MDD. Thus, increased brainstem volume might be the result of an antidepressant effect of duloxetine. Accordingly, Fujiwara and coworkers [64] found that in the PD group the relative volume of the dorsal midbrain was larger than in the healthy controls, while the volume of the ventral midbrain (encompassing dorsal raphe nuclei) was not [68].

In summary, effective treatments for PD could be associated with modification of the brainstem volume and the metabolism.

Discussion

The role of the brainstem in psychiatric disorders has been investigated to a lesser extent compared to other brain structures. Although the prefrontal cortex and the amygdala are more fascinating since they deal directly with thinking, decision making and emotions, the brainstem contains systems that are essential for life [70]. These systems are so crucial for survival that the evolution has built alarm systems, located in the caudal areas of the brainstem, to take care of basic physiologic functions. Moreover in the rostral part, the midbrain, the PAG has been linked to acute fear reaction in several models [71]. Thus the brainstem may play a central role in PD [72]. The present review was conducted to assess evidences of an involvement of the brainstem in PD and data from the literature, although limited and often not focused, support this idea. The assessment of published studies on this topic deserves some preliminary observations. First, data are scanty since only a few studies had adequate field of view and resolution to discern differences between patients with PD and controls. Imaging studies of the brainstem are difficult to perform and interpret even when the most meticulous and advanced methods are applied [73]. Several authors warned on respiratory confounds/artifacts related to neuroimaging studies [38, 45, 74] and some have

published cautionary papers specifically related to imaging in anxiety and PD [40, 41]. Cardio-respiratory movements are a significant confounding factor in the interpretation of fMRI studies [51, 74, 75]. Studies reliant on relative changes in regional cerebral blood flow (rCBF), such as oxygen-15 PET and BOLD fMRI, are particularly vulnerable to breath-by-breath and/or condition related changes in the PCO_2 [38, 39]. Second, PD involves a number of heterogeneous clinical phenomena making very difficult to associate neuroimaging findings with a specific phenomenon related to panic, such as PAs, anticipatory anxiety or phobic avoidance. Finally, it is unlikely that neuroimaging studies may be able to capture unexpected PAs, the core phenomena of PD, and several confounding factors may affect the results of neuroimaging studies performed during laboratory-induced PAs, as discussed above.

Given these limitations, two main findings emerged from this review. First, data support a role of the brainstem in PD, with the intriguing hypothesis that the volume of this area could be larger in patients with PD [64] [65, 66], as suggested also in a recent review focused on structural neuroimaging in PD [76]. The increased volume reported and the activation of brainstem during hypercapnic stimulation [45] are in line with our idea of deranged homeostatic alarm system non fully overlapping with amygdala centered fear alarm system [3]. This idea is also supported by a recent study that showed CO_2 inhalation-induced PAs in humans with bilateral amygdala damage. Although in 2 out of the 3 subjects examined in the study the amygdala lesions were incomplete, these findings suggest that behavioral responses to internal threats related to homeostatic functions may involve different areas than those involved in defensive responses to external threats (such as the amygdala) [77]. A significant cardio-respiratory instability, undetected in the subjects' perception, was present in the hour preceding the onset of naturally occurring PAs in patients with PD [78]. This finding is in line with the idea that signals from the organism's internal milieu may be involved in the occurrence of unexpected PAs. These signals are processed below the conscious awareness by phylogenetically older areas, including the brainstem [17]. To date, it remains unclear whether the abnormalities of brainstem in PD are the expression of a primary hypersensitivity of brain structures that modulate basic physiologic functions or the expression of an adaptation of the same areas to abnormal functions of peripheral somatic systems [79-82].

Second, the brainstem serotonergic system seems to be involved in panic modulation with evidence of both altered serotonergic receptors and 5-HT transporter bindings [56-58]. This is in line with studies that linked serotonin to pathophysiology of PD. Serotonergic system in the brainstem is linked to cardiac, respiratory and balance systems [83-87] and the same are involved in PD [88-90]. Manipulation of the serotonergic system affects the behavioral response to CO_2 inhalation in patients with PD: experimentally lowered or increased availability of serotonin respectively increases or decreases panic response to CO_2 [91] [92]. Drugs with serotonergic profile seem to be more efficacious in reducing both the CO_2-induced and the clinical PAs than drugs with noradrenergic profile [93, 94]. Finally, data from neuroimaging are also in line with the hypothesis of a central role of PAG in PD [71, 72, 95] and once again serotonergic systems seem to be involved [96, 97].

Overall, our review supports the need to take into consideration the brainstem as an important area in the pathophysiology of PD. We were surprised of the limited brain imaging literature on the brainstem in PD, since in the last decades a possible role of this structure in the brain network underlying panic has been repeatedly suggested [1, 3, 98]. Further studies are needed and we can make some suggestions to improve the quality of the information on the role of brain structures in PD. Studies focusing on PAs occurring before the development of secondary

phenomena like anticipatory anxiety and agoraphobia, might help to disentangle the role of structures like the brainstem in PAs. Studies on high-risk populations, for example children of patients with PD, might help to find trait abnormalities possibly related to genetic vulnerability. The use of provocation challenges, such as hypercapnic inhalation test, in high risk population could help to find out brain structures initiating PAs without the influence of anticipatory anxiety. Finally, to deepen the understanding of the pathogenesis of PD, it might be useful to measure also psychophysiological aspects, such as cardiorespiratory physiology, and hormonal patterns, in relation to stress reactivity.

Conclusion

In conclusion, the available data support an involvement of the brainstem in panic disorder and the role of the subcortical serotonergic system in panic pathogenesis. Future studies with imaging techniques should include careful assessments of brainstem areas in order to give a neuroanatomical foundation to emerging theories on panic etiopathogenesis.

Conflict of interest

The author(s) declare that they have no competing interests.

Abbreviation

[^{11}C]MADAM = [N-methyl-^{11}C]N,N-dimethyl-2-(20-amino-40 methylphenyl-thio)benzylamine
[^{18}F]-FCWAY = [^{18}F]trans-4-fluoro-N-2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl]-N-(2-pyridyl)cyclohexanecarboxamide
^{11}C = Carbon-11
^{123}I = Iodine-123
^{18}F = Fluorine-18
5-HT_{1A}R = Selective Serotonin Type-1A Receptors
5-HTT = Serotonin Transporter
ACC = Anterior Cingulate Cortex
CBT = Cognitive–Behavioral Therapy
CO_2 = Carbon Dioxide
CT = Computer Tomography
dPAG = dorsal Periaqueductal Gray
DSM = Diagnostic and Statistical Manual of Mental Disorders
f/MRI = functional/Magnetic Resonance Imaging
FDG = ^{18}F-fluorodeoxyglucose
FDG-PET = ^{18}F-fluorodeoxyglucose-Positron Emission Tomography
$FICO_2$ = Fraction of Inspired Carbone Dioxide
FIO_2 = Fraction of Inspired Oxygen
GAF = Global Assessment of Functioning
H^+ = Hydrogen ion
$H_2{}^{15}O$-PET = Oxygen-15 labeled water-Positron Emission Tomography
MDD = Major Depressive Disorder
mPFC = medial Prefrontal Cortex
MRS = Magnetic Resonance Spectroscopy
NIRS = Near-Infrared Spectroscopy
NTS = Nucleus of Solitary Tract
O_2 = Oxygen

PA = Panic Attack
PAG = Periaqueductal Gray
PCO_2 = Partial Pressure of Arterial CO_2
PD = Panic Disorder
PDSS = Panic Disorder Severity Scale
PET = Positron Emission Tomography
rCBF = regional Cerebral Blood Flow
SPECT = Single Photon Emission Computer Tomography
SSRIs = Selective Serotonin Reuptake Inhibitors
VBM = Voxel-Based Morphometry

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