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Neuroimaging findings related to panic disorder: A brief review

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Keywords
panic disorder, neuroimaging, fMRI, PET, EEG, fNIRS, anxiety

Abstract
Panic disorder (PD) is defined by recurrent unanticipated panic attacks and anxiety of losing control, which negatively affects the patients' quality of life. Various neuroimaging techniques allow to assess brain structure or function and therefore represent important tools to understand the mechanisms related to PD pathology. Current studies have highlighted neural differences between PD patients and healthy controls using MRI, PET, SPECT, or EEG. However, there is an urgent need to discuss findings from various investigations simultaneously in order to obtain a multidimensional understanding of PD pathology, which further allows identifying possible target regions for more effective treatment or prevention strategies. Therefore, the present work briefly reviewed PD related neuroimaging studies published between 2012 and 2021. Relevant articles were searched using a combination of keywords relevant to various neuroimaging techniques (e.g., MRI, MRS, PET, EEG, fNIRS) and to PD (e.g., panic, anxiety, panic disorder). Studies involving patients with comorbid conditions other than agoraphobia and participants aged under 18 were excluded. A total of 20 studies fulfilling inclusion criteria were considered in this review. Most of the reviewed studies point to structural and functional neural changes in regions of the proposed fear network mostly including the hippocampi, thalamic nuclei, amygdala, anterior cingulate corti, insulae and other frontal lobe regions. Such neural changes in PD are thought to result in a hypersensitive fear network affecting normal emotional processing. Finally, studies showed that different treatments can partly reverse these changes, which significantly improves the quality of life in PD patients.

Anahtar kelimeler
panik bozukluk, nörogörüntüleme, fMRI, PET, EEG, fNIRS, anksiyete

Öz
Panik bozuklukla ilişkili nörogörüntüleme bulguları: Kısa bir derleme
Panik bozukluk (PB), hastaların yaşam kalitesini olumsuz etkileyen, beklenmedik ve tekrarlayan panik ataklar ve kontrolü kaybetme kaygısıyla tanımlanmaktadır. Nörogörüntüleme teknikleri, beyinde panik bozuklukla ilişkili yapısal ve fonksiyonel değişimlerin altını çizerek PB ile ilgili mekanizmaların anlaşılmasında önemli araçlar haline gelmiştir. Güncel araştırmalar PB hastaları ve sağlıklı kontroller arasındaki önemli nöral farklılıkları MRI, PET, SPECT ve EEG gibi yöntemlerle aydınlatmaktadır. Ancak PB patolojisini çok boyutlu olarak anlayabilmek için gerçekleştirilen araştırmalardan elde edilen sonuçların tartışılmasına ihtiyaç vardır. Olası hedef bölgelerin tanımlanması ileride daha etkili tedavi ve müdahale stratejilerinin geliştirilmesine olanak verecektir. Bu makalede PB ile ilişkili nörogörüntüleme bulguları derlenmiştir. Alanyazın taramasına 2012 ve 2021 yılları arasında yayınlanmış ve 18 yaşından büyük katılımcıların yer aldığı PB ile ilişkili nörogörüntüleme çalışmalarının bulguları dahil edilmiştir. Araştırma PubMed, Web of Science ve PsycINFO'da nörogörüntüleme teknikleri için anahtar kelimeler (örn., fMRI, PET, EEG, fNIRS) ve "panik", "anksiyete" ve "panik bozukluk" gibi PB ile ilişkili anahtar kelimelerin taranmasıyla gerçekleşmiştir. Komorbid durumları olan hastaları içeren (örn., depresyon ve panik bozukluk tanısı olan), 18 yaşından küçük ergen ve çocuklarla yapılmış, 2012 yılından öncesine ait çalışmalar araştırmaya dahil edilmemiştir. Derlemede toplamda içleme kriterlerini karşılayan 20 çalışmaya yer verilmiştir. Birçok çalışma, hipokampal ve talamik bölgeler, frontal, oksipital, temporal lop, amigdala, anterior singulat korteks ve insula ile ilişkili bölgelere işaret ettiği gibi, PB hastalarında 'korku ağı modeli' olarak sunulması önerilen beyin bölgelerinde anlamlı yapısal ve fonksiyonel değişikliklere işaret eden çalışmalar da bulunmaktadır. Sonuç olarak çalışmalardan elde edilen bulgular, çeşitli tedavilerin, hastaların yaşam kalitesini anlamlı ölçüde yükseltecek şekilde PB'den etkilenen bölgelerde faydalı olduğunu göstermiştir.

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Anxiety is defined as worrying about circumstances in which the result may be uncertain. Our fear and anxiety responses however can be wide and disperse (Hyde et al., 2019). While the fear response to real threatening events is normal and necessary for survival, extreme fear responses may be the symptom of a possible form of anxiety disorder. According to DSM 5, panic disorder (PD) is one of the most common anxiety disorders and is reported to have a 1-year prevalence of approximately 2-3% among adolescents and adults in the USA and European countries, with females being affected twice as often as males (American Psychiatric Association [APA], 2013).

PD is defined by distinct periods of extreme, uncontrollable fear accompanied by cardiorespiratory, autonomic, and gastrointestinal symptoms. PD can be accompanied by cognitive and behavioral symptoms as well, which commonly includes the responsiveness to threat-related environmental signals and the avoidance of certain phobic objects, circumstances, or actions (Harber et al., 2019). In PD, individuals suffer repeated panic attacks, of which at least some are not triggered or anticipated. Such panic attacks can be very exhausting and therefore significantly decrease the patients' quality of life.

While many studies shed light on the behavioral characteristics of PD, neurophysiological measures allow to investigate the underlying pathophysiology and therefore have gained more and more importance for the comprehensive understanding of PD (Lai, 2018). Consequently, there is an increase in studies utilizing various complementing neuroimaging techniques in PD. While radiopharmaceutical investigations and studies on regional cerebral blood flow (CBF) help to identify brain regions with altered ligand binding and aberrant regional CBF compared to control subjects, noninvasive magnetic resonance imaging (MRI) techniques further allow to investigate functional activity and structural brain changes related to PD.

One of the major contributions to the field of PD research were made by Gorman et al. (2000), by proposing a neuroanatomical hypothesis of PD. They suggested that the neural mechanisms for the generation and regulation of the fear response are extremely sensitive in patients with PD. Brain regions involved in those processes are mainly the amygdala, hippocampi, thalamic nuclei, hypothalami, periaqueductal gray region, locus coeruleus and other brainstem regions. Hence, these regions together constitute the so-called fear network. Gorman et al. (2000) argued that panic attacks may occur due to the inability of the frontal lobes to regulate the overactivation of the limbic areas in the fear response. Therefore, a probable treatment of PD would ideally target regions of the fear network. Gorman et al. (2000) also argued that cognitive behavioral therapy (CBT) may intervenes at the cortical level, while medication normalizes brainstem activity and decreases the activity of the amygdala in patients with PD. However, the possibility for different target regions of distinct forms of treatment still remains a matter of debate (Lai, 2019).

With the improvement of advanced imaging techniques over the years, more studies utilized those measures to investigate the neural substrates related to PD. Carvalho et al. (2010) reviewed functional MRI (fMRI) studies on PD at the current time and stressed the significant roles of the prefrontal cortex (PFC), the anterior cingulate cortex (ACC), the hippocampus, the amygdala and the brainstem in the pathology of PD, which further confirmed the proposed fear network model by Gorman et al. (2000). A very recent review conducted by Lai (2019) also supports the fear network model for PD and they argue that the ACC, the insula, and parts of the parietal lobes should be added to the traditional fear neatwork.

Despite the large effort to decipher the underlying mechanism of PD development, displayed by the numerous works utilizing different neurophysiological measures, researchers are still puzzled to define biomarkers for PD, identify possible neural risk factors for PD and understanding its neuropathology. Building up on the previously mentioned important works that suggest structural and functional changes in structures of the fear network to be major contributors to PD pathology, the present study aimed to review current PD studies of various neuroimaging methodologies. The rational to include studies of different modalities stems from the major goal to provide a complementary and multidimensional perspective on the underlying neural bases of PD development, its manifestation and possible treatment effects on the brain. While structural measures provide knowledge on neural integrity, volume and thickness of brain structures, functional and metabolic measures allow to assess differences in brain activation, CBF, and the distribution of metabolites. On the other hand, electrophysiological measures contribute to the additional understanding of temporal patterns of brain function related to cognition in PD. Therefore, the simultaneous evaluation of various methodologies (MRI, fMRI, MRS, DTI, PET, SPECT, EEG, fNIRS) is thought to be advantageous over a single modalities perspective in order to fully understand the neural bases for the alterations in the individuals' emotions, thoughts, behaviors, and physiological reactions in PD.

Therefore, the current review may not only contribute to basic science but may also be useful for physicians, psychiatrists, and therapist for the identification of the most promising target regions for the most ideal treatment and therapy approaches, as well as to build preventive programs to increase subjects' resilience and mental defense strategies with the ultimate goal to preserve the PD patients' quality of life.

METHODS

Various neuroimaging studies on PD published between 2012-2021 were reviewed in this study. The

search and inclusion criteria for articles were as follows; the search was limited to articles that included PD patients aged over 18 years without any comorbid conditions (e.g., patients with depression and PD) except for agoraphobia. Since ‘‘pure’’ PD (without agoraphobia) appears to be rare (Goodwin et al., 2005) and PD commonly presents with comorbid agoraphobia (which relates to the fear about being in places or situations from which escape might be embarrassing or difficult and in which help might not be available in the case it is needed), it was inevitable to include studies with PD and agoraphobia (PDA) subjects. The neuroimaging and measurement techniques included in this review were functional Magnetic Resonance Imaging (fMRI), Diffusion Tensor Imaging (DTI), Magnetic Resonance Spectroscopy (MRS), Single-Photon Emission Computed Tomography (SPECT), Positron Emission Tomography (PET), functional Near-Infrared Spectroscopy (fNIRS), and Electroencephalography (EEG). PubMed, Google Scholar, Web of Science and PsycINFO were used as databases for the relevant literature; search was performed using following keywords in different combinations (AND/OR): “panic disorder”, “anxiety”, “agoraphobia”, “MRI”, “fMRI", “MRS”, “DTI”, “PET”, “SPECT”, “fNIRS", “EEG”, “neuroimaging”. The number of identified articles was: 134. All studies were reviewed with respect to the objective of the current work and their scientific quality and eligibility. Articles with titles in accordance with this review’s goals were selected and further evaluated based on their abstracts and full texts. After this step, the final selection of articles was made and resulted in the inclusion of 20 articles in the present work.

MRI Derived Measures

Functional and volumetric MRI Findings in PD

Over the past decade, there was an increasing interest in the usage of non-invasive brain imaging techniques to provide novel information on the neurophysiology related to PD (Grambal et al., 2015). Within the many kinds of neuroimaging modalities, MRI is one of the most convenient and popular methods to investigate the physiology of nervous tissue due to its excellent spatial resolution (Lai, 2018). While structural MRI allows to study the anatomy of the brain, fMRI enables to infer brain activity based on the blood oxygen level-dependent (BOLD) signal at different brain areas (Weiskopf et. al, 2004). Both, measures of structural and functional MRI, have been related to behavior and cognition processes in PD.

Dresler et al. (2012) used an emotional Stroop task, where subjects have to name the color of neutral or panic-related words, to study the differences in the reaction time (RT) and BOLD activity in response to disorder-specific words in PD patients and healthy controls (HCs). Based on the longer RTs towards the panic-related words in PD patients compared to HCs, they suggest that PD patients may have an attentional bias towards panic-related words. During the task the PD patients further had greater BOLD activity in the left inferior frontal gyrus (IFG) and left PFC in comparison to HC, which had the authors speculating that the aberrant frontal activity may relate to altered emotional processing and an attentional bias towards panic-related stimuli (Dresler et al., 2012). Beyond such attentional bias to aversive stimuli, Engel et al. (2015) investigated the effects of personal significance of such aversive stimuli by measuring activation patterns in response to visually presented panic-specific and non-specific aversive pictures in PD patients with agoraphobia (PDA) and HC subjects. Therefore, 120 pictures showing characteristic panic/agoraphobia situations (e.g., high places, crowds, narrow places, wide places, public transport facilities) were rated by the subjects and 20 pictures with highest Self-Assessment Manikin ratings were selected for each subject. Additionally, 20 aversive but not panic-specific images and 80 neutral pictures were selected from the International Affective Picture System matching the preselected panic-specific pictures’ content (e.g., humans displayed or not), complexity and luminosity. While PDA patients and HCs showed similar activation patterns in response to non-specific fear-inducing pictures at frontal, temporal, and brainstem areas, PDA patients showed significantly higher activation in the insular cortices, left hippocampal formation, left caudate, dorsomedial prefrontal cortex (dmPFC) and left IFG in response to panic-specific pictures. These activation pattern suggest a complex representation and processing of personally relevant panic-specific stimuli in comparison to non-specific aversive stimuli superimposed on emotional fear processing.

Using newly developed panic disorder-related vs. neutral visual scenes, Feldker et al. (2016) showed increased activation in an extended fear network including the brainstem, insula, thalamus, ACC, midcingulate cortex (MCC), and dmPFC in PD patients compared to HCs. Furthermore, they were the first to demonstrate a direct relation between affective processing, the increased activation in brainstem regions responsible for the regulation of the homeostatic alarm system and the degree of subjective anxiety in PD patients evoked by panic disorder-related visual scenes. The authors believe that changes in the interoceptive awareness and elaborated emotion-specific processing may cause disorder-related visual processing in PD (Feldker et al., 2016).

Instead of using visual stimulation during fMRI, Burkhardt et al. (2019) used an imagery design to investigate correlates of altered threat-related processing in individuals with PD by applying disorder-related script-driven imagery. Therefore, 17 PD patients and 17 HCs were exposed to disorder-related (e.g., stan-

ding on a crowded platform, entering a narrow elevator) and neutral narrative scripts (e.g., watching TV at home, reading a newspaper). During the imagination of disorder-related vs. neutral narrative scripts, PD patients showed significantly increased activity in the right amygdala and brainstem, in addition to decreased activity mostly in the rostral ACC as well as the medial and ventral PFC in comparison to the HCs. Since the amygdala plays a significant role in the vigilance of detecting and processing emotion-based stimuli in normal and pathological forms of anxiety, this abnormal amygdala activity has been associated with hypervigilance towards threat (Burkhardt et al., 2019).

Taking the significant role of the amygdala in the fear response and the development of PD into account, Asami et al. (2018a) were interested in the structural differences of amygdala volumes between PD patients and control groups. They showed that PD patients compared to HCs had smaller volumes in the right lateral and basal sub-nuclei of the amygdala, which are thought to be responsible for the processing of sensory input related to anxiety and fear. In another study, Asami et al. (2018b) scanned the whole brain and found decreased cortical thickness in the left rostral middle frontal cortex (MFC) of PD patients in contrast to HCs. This structural abnormality was not only related to PD symptoms severity but also corresponded to lower social functioning (Asami et al., 2018b). In addition to the before mentioned structural changes in the amygdala and the MFC, Asami et al. (2018c) further reported reduced gray matter volumes in the anterior, medio-dorsal, and pulvinar nuclei of the thalamus in female PD patients, possibly due to excessive activation of the amygdala paralleled by emotional dysfunction and abnormalities in fear-related cognition in PD. A much earlier study on volumetric brain changes related to PD was conducted by Lai and Wu (2013a). They were interested in measuring the therapeutic effects of 6-week escitalopram treatment to assess the "state-dependent" and "trait-like" brain changes after remission, showing that gray matter volumes in drug-naïve, first episode PD patient increased at the left superior frontal gyrus (SFG) (state-dependent) and decreased at the right precentral gyrus (trait-like) with treatment, which also correlated with the improvement of clinical symptoms.

Besides the studies of differential BOLD activation during aversive visual stimulation, comparable differences have been replicated for the auditory domain as well. Since one of the major symptoms of PD is the fear of future panic attacks, the anticipation of threat in PD was studied in the auditory domain by Brinkmann et al. (2017). In their study, they investigated the pattern and duration of phasic and sustained activation in the amygdala and the bed nucleus of the stria terminalis (BNST) for unpredictable threat anticipation by presenting cued aversive (human screams) and neutral (water) sounds from the International Affective Digitized Sounds database. While the amygdala is important for immediate regulation of response to fear (stress response), the BNST by large facilitates the activation of the hypothalamic–pituitary–adrenal (HPA) axis. As a result, PD patients had greater phasic activation in the amygdala, ACC, insula, and PFC, which lasted around one second during the anticipation period of the aversive sounds. PD patients also had greater sustained activation in BNST and PFC during the entire anticipation period compared to the HC group. These findings point to distinct temporal activation patterns in brain structures relevant for the regulation of the fear response, which may be responsible for chronically increased levels of anxiety associated with PD pathology. Held-Poschardt et al. (2017) also investigated neural responses related to anticipation in PD, but this time the anticipation towards reward and loss was tested with the help of a monetary incentive delay (MID) task, where participants are given cues regarding monetary gain or loss during an anticipation phase. Compared to HCs, PD patients had increased activation in the ventral striatum when anticipating a potential loss, while the activity in the ventral striatum was decreased during the anticipation of potential gain. The findings suggested a generally higher sensitivity to negative events in PD.

DTI Findings in PD

Diffusion Tensor Imaging (DTI) is a non-invasive advanced MRI technique that is used to measure the restricted diffusion of water molecules in a compartment in order to reconstruct neural fiber tracts, which in turn allows to speculate about aberrations in white matter (WM) microstructure (Basser et al., 1994). Typical DTI derived measures that relate to neural integrity and healthy membrane functioning are the fractional anisotropy (FA) and mean diffusivity (MD). Kim et al. (2014) showed that PD subjects in comparison to HCs had decreased FA values in frontal lobe regions including the corpus callosum (CC), which points to WM damage in structures of the fear network. These changes correlated with the clinical severity of PD symptoms and underline the frontal lobe dysfunction in PD. Similarly, Lai and Wu (2013b) compared characteristics of WM tracts in first-episode PD patients and HCs and showed that patients had altered WM integrity in the right inferior fronto-occipital fasciculus (IFOF), left body of CC and left superior longitudinal fasciculus (SLF) in comparison to HCs. They noted that changes in the SLF might be related to disinhibition of fear and panic reactions and decreased FA values in the IFOF might lead to disintegration of sensory stimuli. Additionally, alterations in the CC might explain an unbalanced involvement of the affected fear network structures in either brain hemisphere (Lai and Wu, 2013b). Beyond that, Kim et al. (2014) also showed that the patients' FA values of the CC correlated with disease severity even in a very early stage of the disease.

To summarize, the here reviewed DTI studies suggest structural WM changes in large scale neural tracts connecting major brain structures related to emotional control. Associated with such changes are the disinhibition of the fear responses, which further supports the proposed fear network model of PD.

MRS Findings in PD

Magnetic resonance spectroscopy (MRS) is another non-invasive neuroimaging technique that allows to detect the concentrations of different metabolites like N-acetyl-l-aspartate (NAA), choline (CHO), creatine (CRE) and GABA at various brain regions (Long et al., 2013). Long et al. (2013) used GABA-edited MRS to investigate levels of GABA in PD patients with and without a family history of PD psychopathology and HCs. GABA deficits were detected in the ACC and mPFC in patients with PD but not in HCs, which could be due to dysfunctional GABA synthesis or dysfunctional enzymes that are present in glutamate-glutamine cycling in PD patients. Such findings are complementary to the allosteric effects of benzodiazepines on GABA receptors during acute treatment of anxiety disorders to reduce amygdala activity. However, for the long-term treatment of PD alternatives to benzodiazepines, such as selective serotonin reuptake inhibitors (SSRIs), are preferred. Furthermore, the reported GABA deficit was even greater in patients with a family history, pointing to the significant role of biological factors in PD pathophysiology. Maddock et al. (2013) also studied neurometabolic abnormalities in PD and showed that after visual stimulation with a checkerboard stimulus, the PD patients had greater increase in brain lactate levels but smaller change in glutamate plus glutamine (glx) levels in the visual cortex compared to healthy subjects. The increase in brain lactate was suggested to be a result of abnormal metabolic responses and pH dysregulation in PD patients and might explain their higher vulnerability to panic attacks. In accordance with the postulated model of an acid-sensitive fear circuit in PD (Esquivel et al., 2010), such activity dependent elevated lactate levels may contribute to the trait vulnerability in PD. Interestingly, no differences were found between remitted and symptomatic PD patients regarding their lactate levels, so that high lactate levels were present even during the improvement phase of PD symptoms.

Shin et al. (2013) combined resting-state fMRI and MRS techniques to investigate GABA levels in several regions of interest (ROI) in the perigenual area of the ACC and measured the functional connectivity (FC) between the ACC and the precuneus in PD. Compared to the HCs, the PD patients had greater FC between the ACC and the precuneus during the resting state, which was seemingly influenced by lower GABA concentration in the ACC. Both, the ACC and the precuneus are central elements of the default mode network (DMN), which plays an important role in the generation of internal thoughts. Hence, higher FC between these brain areas may be associated with the PD patients' extreme focus on and misinterpretation of internal bodily responses (Shin et al., 2013).

Other Neuroimaging Techniques

PET and SPECT Findings in PD

Positron Emission Tomography (PET) and single photon emission computed tomography (SPECT) are widely used invasive imaging techniques (Baeken et al., 2017) that allow to study brain metabolism and perfusion based on the application of radiopharmaceuticals and radioactive tracers respectively. While PET allows to detect changes in the metabolisms of an organ that can precede anatomical changes, SPECT allows to assess the blood flow by tracing the radioactive agents within the bloodstream. These techniques have become indispensable tools for various clinical (diagnosis, prognosis, tumor detection, treatment/therapy evaluation) and research settings (Asl et al., 2017).

Kang et al. (2012) used PET to investigate the effects of 12 weeks of escitalopram treatment on brain metabolism in PD patients. For this, they measured the baseline glucose metabolism in 15 individuals with PD and 20 HCs before treatment and compared these values with the second scan after 12 weeks. At the pretreatment stage, they found reduced metabolism in the frontal, right temporal and left posterior cingulate gyri in individuals with PD as compared to HCs. Posttreatment findings suggested metabolic increases in various neocortical areas as well as in limbic areas for treatment responders. Reduced metabolism in the before mentioned regions may point to aberrant neocortical function in PD, while escitalopram treatment may act on the neocortex, the amygdala, and parahippocampal gyrus (Kang et al., 2014).

Seo et al. (2014) on the other hand investigated the effect of CBT on neural correlates of PD using SPECT. They report that the regional cerebral blood flow (rCBF) in patients with PD increased at the left IFG and left pre- and postcentral gyri, while the rCBF decreased at the left pons after CBT treatment. Changes in the levels of rCBF in the left IFG were associated with fear reactivity, autonomic responses, emotional behavior, and perception of motivational stimuli, which points to the significance of CBT facilitating cognitive restructuring. Interestingly, they could not detect any rCBF changes in major regions of the traditional fear network. This may point to PD relevant metabolic aberrations in brain regions beyond structures that have been described using functional and structural MRI measures. This once more stresses the importance of using a variety of complementing imaging techniques to investigate the pathology in PD.

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Functional Near-Infrared Spectroscopy (fNIRS) Findings in PD

Functional near-infrared spectroscopy (fNIRS) is another noninvasive optical imaging technique that allows to record hemodynamic activity (Ghonchi, 2020). It contrasts the differences of deoxygenated (HbR) and oxygenated hemoglobin (HbO) related to brain activity through a set of spatially distributed optodes (emitters and detectors) placed on the scalp. Some advantages of fNIRS compared to fMRI are its tolerance to motion artifacts, higher temporal resolution, and easier long-term monitoring due to its portability (Li et al., 2020). Therefore, fNIRS has been used to study the neural correlates of various cognitive processes in both healthy and patient populations (Ferreri et al., 2014).

Deppermann et al. (2014) for example described hypofrontality during the Verbal Fluency Task (VFT) in individuals with PD in comparison to HCs, where subjects had to either name as many nouns as possible beginning with a certain letter (phonological part), name as many nouns as possible belonging to a certain category (semantical part) or to name the weekdays (control part) in a certain amount of time. To test the effects of repetitive transcranial magnetic stimulation in addition to psychoeducation on prefrontal hypoactivation, they used intermittent theta burst stimulation (iTBS) in PD patients randomly assigned to sham and verum groups. Although solely the verum group really received 15 iTBS-sessions above the left dlPFC, increased activation in the left IFG during the second parallel VFT/fNIRS recordings were present only in the sham group. The authors try to explain this contradictory finding by possible task-related psychophysiological arousal. Overall, their findings support that PD is characterized by prefrontal hypoactivation during cognitive performance.

EEG Findings in PD

Electroencephalography (EEG) is a common method to measure changes in the brains ongoing and event-related neural electrical activity (Li et al., 2020). The importance of EEG to explore abnormal parameters in psychiatric disorders was reported in various studies (Carvalho et al., 2013).

The EEG signal can be evaluated by rather simple parameters in clinical settings or inspected by more sophisticated means using the quantitative electroencephalography (qEEG) approach. This approach allows to dissect the EEG signal into various qualities such as its amplitude, latency, signal complexity, oscillations, and specific frequency bands. While for some studies analyzing the signals from single electrodes may be of interest, EEG also offers the possibility for network connectivity analysis. Furthermore, event-related measures of the EEG signal allow to infer cognitive processes from specified components of the averaged brain potentials. Therefore, qEEG is an interesting candidate for the complementary usage with other diagnostic evaluations for precise diagnosis, disease severity assessment and treatment evaluation (Popa et al., 2020).

One of the described components of the event related potentials (ERPs) is the so-called mismatch negativity (MMN) reflecting the preattentive sensitivity to unexpected stimulus changes. To test to what extend the MMN may mirror increased body arousal and reduced cognitive resources directed to non-fear-related stimuli in PD, Rentzsch et al. (2019) recorded ERPs from 35 PD patients and 42 HCs in response to an auditory oddball paradigm. The subjects listened to 1.800 tones (80 dB) composed of standard (80%) and deviant (10%) tones in terms of their "frequency" and "duration". They observed significantly lower "duration" MMN amplitudes in PD patients vs. HCs, which may support the notion of reduced preattentive sensitivity to non-fear-related stimuli in the PD group.

On the other hand, Silva et al. (2017) used the coherence function to examine the communication among brain structures during a visual oddball paradigm. To investigate frontoparietal gamma coherence (GC) and the effects of anxiety on working memory, they recorded the EEG of 9 PD patients and 10 HC before and after the demonstration of a fear-inducing computer simulation. Their electrophysiological variable of interest was the Gamma band (30 and 80 Hz) because of its strong relationship with cognitive processes such as attention, working memory and sensorimotor integration. They suggest that the recorded greater GC in HCs vs. PD at frontal and parietal areas (P3-Pz, F4-F8 and Fp2-F4) during the simulation possibly points to the participation of these areas in the expected behavior. On the other hand, the computer simulation produced increased GC at F3-P3 in PD patients, which could be associated with "noise" causing disturbed communication between these areas, which in turn may relate to the PD typical symptoms.

CONCLUSION

Due to the severe impact of PD related cognitive and behavioral symptoms on the patients' life quality, it is important to understand the underlying brain mechanisms associated with those symptoms to develop effective strategies for prevention and adequate treatment. To define the neuropathological basis of PD, different brain imaging techniques provide complementary information on the structural, functional, and metabolic changes associated with PD (Grambal et al., 2015). A brief review of such studies published between 2012-2021 was presented. The findings of the reviewed studies were demonstrated in Table 1.

As explained by the APA (2013) in DSM-5, one of the most prominent characteristics of PD is the anticipation of further panic attacks and the exaggerated fear associated with this expectation. The increased antici-

Table 1. Summary of the Reviewed Studies

Author (Date)	Participants	Method	Findings
Asami et al. (2018a)	PD (n = 38) HC (n = 38)	MRI	↓volume in right lateral and basal nuclei of amygdala in PD
Asami et al. (2018b)	PD (n = 38) HC (n = 38)	MRI	↓ left rostral MFC thickness in PD
Asami et al. (2018c)	PD (n = 25) HC (n = 25) all female	MRI	↓gray matter volume and shape deformations in anterior, medio-dorsal and pulvinar nucleus of thalamus in PD
Lai and Wu (2013a)	PD (n = 21) HC (n = 21)	MRI	↑ gray matter volume in left SFG after antidepressant treatment
Brinkmann et al. (2017)	PD (n = 17) HC (n = 19)	fMRI	↑ phasic activation in insula, ACC, amygdala, PFC; ↑ sustained activation in PFC, bed nucleus
Dresler et al. (2012)	PD (n = 20) HC (n = 23)	fMRI	↑ BOLD in left IFG
Held- Poschardt et al. (2017)	PD w/wo agoraphobia (n = 10), HC (n = 10)	fMRI	↓ BOLD in ventral striatum during reward anticipation, ↑ BOLD in ventral striatum during loss anticipation
Feldker et al. (2016)	PD (n = 26) vs. HC (n = 26)	fMRI	↑ activation in extended fear network (insula, brainstem, thalamus, MCC, ACC, dmPFC)
Engel et al. (2015)	PD with agoraphobia (n = 19), HC (n = 21)	fMRI	↑ activity in left ant. insula and right IFG to panic-related stimuli in PDA vs. HC; comparable BOLD in PDA and HC towards unspecific aversive pictures
Burkhardt et al. (2019)	PD (n = 17) HC (n = 17)	fMRI	↑ BOLD in right amygdala to disorder-related vs. neutral scripts and ↓BOLD in bilateral vlPFC, right vmPFC, left dmPFC and right dlPFC in PD
Shin et al. (2013)	PD w/wo agoraphobia (n = 11), HC (n = 11)	fMRI & MRS	Greater FC between ACC & precuneus modulated by lower GABA in ACC
Kim et al. (2014)	PD (n = 36) HC (n = 27)	DTI	↓ FA in WM around frontal lobe regions incl. corpus callosum
Lai and Wu (2013b)	PD (n = 30) HC (n = 21)	DTI	↓ white matter integrity in right IFOF, left body of corpus callosum and left SLF
Long et al. (2013)	PD w/wo PD family history (FH) (n = 5/6), HC (n = 8)	MRS	GABA deficits in ACC and medial PFC; greater GABA deficit in PD with family history
Maddock et al. (2013)	Remitted (n = 13) & symptomatic (n = 8) PD, HC (n = 12)	MRS	↑lactate & ↓glx levels in visual cortex after visual stimulation in all PD
Kang et al. (2012)	PD (n = 15) HC (n = 20)	PET Pre/post escitalopram	Before: lower [18F]FDG uptake in various regions in PD After: increased [18F]FDG uptake in various regions in most PD
Seo et al. (2014)	PD (n = 14)	SPECT before/after CBT	↑regional CBF in left IFG, left postcentral and precentral gyrus & ↓ regional CBF in the left pons after CBT.
Deppermann et al. (2014)	PD w/wo agoraphobia (n = 44), HC (n = 23);	FNIRS, VFT sham vs verum iTBS	Baseline hypofrontality in PD during phonological and partly during semantical task. ↑ signal in left IFG during phonological task after pseudo iTBS only in sham PD
Rentzsch et al. (2019)	PD (n = 35) HC (n = 42)	EEG	↓duration mismatch negativity amplitudes in PD vs. HC
Silva et al. (2017)	PD (n = 9) HC (n = 10)	EEG	↑GC in PD at F7-F3, F4-P4 may produce prejudicial "noise" ↓GC at P3-Pz, F4-F8 and Fp2-F4 in PD

Remarks: PD = panic disorder patients, HC = healthy controls, ↓ = reduced or decreased; ↑ = greater or increased, GC = gamma coherence, iTBS = intermittent theta burst stimulation, CBT = cognitive behavioral therapy, w/wo = with or without

pation of threat in PD was indirectly presented by the here reviewed fMRI studies reporting increased phasic (amygdala, ACC, insula) and sustained (BNST) activity to aversive sounds (Brinkmann et al., 2017). Interestingly, in another study the anticipation of potential monetary loss caused increased activation in the ventral striatum, while the anticipation of reward resulted in decreased activation of the bilateral ventral striatum in PD (Held-Poschardt et al., 2017). Such sustained hyperactivity patters in regions of the proposed fear network (Gorman et al., 2000) may further relate to the increased sensitivity and attentional bias towards aversive stimuli in PD (Dresler et al., 2012). While increased amygdala activity was demonstrated by various fMRI studies using aversive stimulation (Brinkmann et al., 2017) and imagery scripts (Burkhardt et al., 2019), volumetric studies identified decreased amygdala volume in addition to reduced MFC volume (Asami et al., 2018a). While the frontal lobe regions such as the PFC would usually control excessive

amygdala, hypothalamus and hippocampal activity, the hypoactive PFC in PD patients fails to control such sensitivity. Hypofrontality has been demonstrated not only during fMRI but also during fNIRS, where PD patients showed significant hypofrontality in the dlPFC (Deppermann et al., 2014). The prefrontal hypoactivity pattern may be related to insufficient top-down regulation resulting in impaired emotional regulation, which may contribute to the pathophysiology of panic disorders in general (Wang et al., 2018). Hypofrontality and increased activity in the amygdala and other regions of the fear network were further associated with GABA deficits in the ACC and medial PFC in PD patients with even greater deficits in individuals with a family history of PD, which further supports the view on genetic influences on PD vulnerability (Long et al., 2013). Interestingly, in a multimodal imaging study by Shin et al. (2013), GABA changes were associated with increased FC within nodes of the default mode network, which may cause an increased internal focus on bodily sensations and therefore may further elaborate fear perception in the patients. Beyond the findings of elaborated activity in the regions related to the fear response, other studies suggest distinct activation pattern produced by personally significant (trauma-specific) and non-specific aversive stimuli in patients with PD. While the hyperactive amygdala together with PFC hypoactivity may contribute to an overall sensitivity and attentional bias, the additional activation of memory related brain structures through trauma-specific cues resulted in activation of the left IFG, insular cortices, left hippocampal formation, left caudate, and dmPFC regions (Engel et al., 2015). Consequently, that the aberrant activity in PD is not restricted to the fear network was demonstrated in a PET study by Kang et al. (2012), where they showed slower metabolism for several brain areas, including the right SFG, right medial frontal gyrus, right middle temporal gyrus, left cingulate gyrus, right caudate body, and left middle frontal gyrus in individuals with PD vs. HCs. Noticeably, a SPECT study could not find any change in the levels of rCBF in the fear network, but instead showed that CBT treatment was related to increased rCBF in the left IFG, left postcentral gyrus, and left precentral gyrus, as well as to decreased rCBF in the left pons in PD patients. Nevertheless, they associated their findings to aberrant fear reactivity and autonomic responses reported for PD (Seo et al., 2014). While the fMRI, PET and fNIRS studies allow to follow aberrant activations, DTI enables the understanding of related structural changes. The here reviewed DTI works point to changes within major WM tracts that not only connect the hemispheres and cortical lobes, but especially the regions of the fear network. Decrease FA values for the CC, SLF, IFOF and ILF were therefore associated with disinhibition of the fear response in PD (Kim et al., 2014). Finally, while some EEG measures were associated with reduced preattentive sensitivity to nonfear-related stimuli in individuals with PD (Rentzsch et al., 2019), the greater GC at frontal and parietal electrode pairs in PD patients was suggested to create “noise” that may infer with the proper communication between these areas, which in turn may relate to the PD typical symptoms (Silva et al., 2017).

In conclusion, various neuroimaging findings support the fear network model and confirmed clear metabolic, structural, and functional differences between PD patients and HCs. Each technique pointed out distinctive neuropathological findings related to PD, however studies combining different neuroimaging techniques are scarce (Shin et al., 2013). Hence, more studies combining the strengths of different imaging methods are needed. Furthermore, there are not enough studies contrasting specifically PD patients with and without agoraphobia. Most studies included these two diagnoses together as one patient group due to its common comorbidity, but there could be nuances in their related pathologies. Future studies may further pay attention to include more homogenous groups according to participants’ age and conduct longitudinal designs to follow changing neural mechanisms with age and treatment more adequately. That would also allow to closely follow aberrant neural function and anatomical changes associated with different phases of the disease severity, such as first-episode, moderate, and severe PD.

DECLARATIONS

Conflict of Interest The authors declare that they have no conflict of interest.

Data Availability Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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