Degree project

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The Impact of Selective Serotonin Reuptake Inhibitors on Amygdala Activation in Patients with Panic Disorder

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Abstract

Panic disorder (PD) is a debilitating anxiety disorder that often reduces the quality of life and some of its symptoms are physical distress and fear. PD is often comorbid with other anxiety disorders and depressive disorders and also cardiovascular and respiratory illnesses. Pharmacotherapy and psychotherapy are the two most common treatment options for people with PD. A standard type of pharmacotherapy is selective serotonin reuptake inhibitors (SSRI) which in short work by increasing the level of serotonin in the brain and has been shown to be efficacious and safe. A vital brain structure that is closely linked to PD is the amygdala, and some of its functions are learning, emotional processing, and memory. There seems to be a functional and structural abnormality in the amygdala for people with PD compared to healthy individuals, for example, a smaller volume of gray matter and increased activity. The aim of the thesis is to conduct a systematic review on the effect of SSRIs on the functional alterations of the amygdala in patients suffering from PD. The present systematic review will try to answer the question: If SSRIs affect amygdala activation for PD patients compared to healthy individuals who are currently not undergoing any kind of pharmacotherapy. The results showed opposite findings; one study did not detect activation changes in the amygdala for PD patients using SSRIs, one detected higher activity in the right amygdala, whereas the other two showed a decrease in the left amygdala (one study did not specify left, bilateral, or right). More research regarding amygdala activation in PD patients using SSRIs is needed due to the small scale of studies currently available.

Keywords: panic disorder, selective serotonin reuptake inhibitors, amygdala, amygdala activation, serotonin

The Impact of Selective Serotonin Reuptake Inhibitors on Amygdala Activation in Patients with Panic Disorder

There are several types of anxiety disorders, and they all share characteristics of anxiety, inordinate fear, and related behavioral disturbances (American Psychiatric Association, 2013). A common type of anxiety disorder is panic disorder (PD), which, according to Pfleiderer et al. (2007) has a global lifetime prevalence of 1-3%. Furthermore, the ubiquitousness of PD is elevated among individuals who have other anxiety disorders, especially agoraphobia (fear and/or avoiding situations or places that might make you feel trapped or helpless, e.g., using public transportation; American Psychiatric Association, 2013). PD can be a debilitating disorder that often impacts the quality of life in ways such as work, family, social life, and interpersonal relationships (Kim et al., 2021). There are a few ways to combat PD, and one of the most common ones is the administration of selective serotonin reuptake inhibitors (SSRIs), as it has been shown to be very efficacious for both the acute phase treatment and long-term treatment (Batelaan et al., 2011). In people suffering from PD, there seem to be functional and structural differences in the amygdala—a brain structure involved in such functions as emotional processing, learning, and memory (Asami et al., 2018; Martin et al., 2009; Roy-Byrne et al., 2006). However, the neural pathways involved in regulating panic responses, including the effect of SSRIs on the activation of the amygdala are still poorly understood (Shekhar et al., 2006). A greater understanding of this could potentially help optimize treating patients with PD (and other disorders).

Panic Disorder

PD is typically defined by recurring and unanticipated episodes of strong fear and physical distress. Comparing PD with another common anxiety disorder—generalized anxiety disorder (GAD)—, the median age of onset is relatively similar (for PD, around 25 years of age, and for GAD, around 30 years of age; Penninx et al., 2021). Additionally, fear is a common symptom in both disorders, but PD is more of an urgent character, especially in the domain of physical symptoms. According to DSM-5 (American Psychiatric Association, 2013), at least four symptoms (out of 13) must occur to be diagnosed with PD, and these symptoms are palpitations, pounding heart, or accelerated heart rate, sweating, trembling or shaking, sensations of shortness of breath or smothering, feelings of choking, chest pain or discomfort, nausea or abdominal distress, feeling dizzy, unsteady, light-headed, or faint, chills or heat sensations, paresthesias (numbness or tingling sensations), derealization (feelings of unreality) or depersonalization (being detached from oneself), fear of losing control or “going crazy”, and fear of dying (American Psychiatric Association, 2013).

The most common medical comorbidities for PD patients are major depressive disorder (MDD), other anxiety disorders (e.g., GAD, agoraphobia, etc.), irritable bowel syndrome, cardiovascular illnesses, and respiratory illnesses (Meuret et al., 2017; Tilli et al., 2012).

Individuals with PD are often burdened with impaired quality of life, for example in their relationships, in their work/school environment, and in the general social aspect (Kim et al., 2021). Examples of this can be an absence from work/school which could lead to unemployment or dropping out of school. Absence from doctor appointments and impairments may also be seen in older adults regarding caregiving duties or volunteer activities (American Psychiatric Association, 2013). PD might be additionally associated with suicidal ideation and attempts (Cougle et al., 2009).

Treatment of Panic Disorder

The two most common ways to treat PD patients are psychotherapy (treatment based on personal interaction with a therapist) and pharmacotherapy (treatment with the use of medication). The most used form of psychotherapy is cognitive behavior therapy (CBT), which focuses on changing maladaptive emotional responses by altering the patient's behaviors or thoughts. It appears to be both effective and efficacious in the treatment of PD (Kaczkurkin & Foa, 2015). According to Quagliato et al. (2018), it is important to treat PD early because the longer PD patients stay untreated, the greater the risk of no response to pharmacotherapy.

Three main types of medication are typically used for pharmacotherapy; benzodiazepines, selective norepinephrine reuptake inhibitors (SNRI), and SSRIs (Jakubovski et al., 2018; Quagliato et al., 2018). Treating PD patients with benzodiazepines exhibits a fast onset of action but can cause tolerance, withdrawal symptoms, and dependence. SNRIs are similar to SSRIs in terms of efficacy and acceptability and are a first-line pharmacological option for treating patients with PD (Du et al., 2021). The mechanism of action for venlafaxine (a common type of SNRI) can be briefly explained as it inhibits the reuptake, and consequently the availability, of noradrenaline, dopamine, and serotonin in the prefrontal cortex (Katzman & Jacobs, 2007).

SSRIs are the most prescribed type of antidepressant in many countries, including the United States, and are efficacious for depressive and anxiety disorders (Preskorn et al., 2004). There are many different SSRIs available, such as citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, vilazodone, and vortioxetine, and they differ in what dosage is recommended for treatment, ranging between 0.5 mg/day to 300 mg/day (Jakubovski et al., 2018). Although the mechanism of action for SSRIs is not yet fully understood (Edinoff et al., 2021), Nutt (1999) demonstrates that SSRIs work differently depending on which disorders these are used to treat. Generally, SSRIs work by increasing the synaptic availability of serotonin (5-hydroxytryptamine, 5-HT) due to blocking the

transportation of the neurotransmitter back into neurons (Nutt, 1999; Quagliato et al., 2018). According to Ziffra (2021), SSRIs have a robust base of evidence regarding the relative safety and efficacy for the treatment of PD. Further, Jakubovski et al. (2018) propose that higher doses of SSRIs, depending on what type of SSRI, between 50 mg to 300 mg/day, are related to a greater treatment benefit at the expense of reduced tolerability. SSRIs have a slower onset of action compared to benzodiazepines and have the potential to aggravate anxiety and panic early in the treatment course (Nutt, 1999; Quagliato et al., 2018)

Structural and Functional Brain Changes in Panic Disorder

Both structural and functional differences (specifically in the limbic, frontal, and brainstem regions) have been found in individuals suffering from PD, as compared to healthy individuals, using magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), and quantitative electroencephalography (qEEG; Asami et al., 2018; Kang et al., 2012; Martin et al., 2009; Roy-Byrne et al., 2006). Structural differences are for example a smaller gray matter volume in the temporal lobes in PD patients compared to healthy individuals (Wu et al., 2018). Additionally, Wu et al. (2018) state that there are lower gray matter volumes in several other brain regions, such as the bilateral dorsomedial prefrontal cortex (involved in emotion regulation network and emotional appraisal), left dorsolateral prefrontal cortex (involved in behavioral inhibition; Shackman et al., 2009), right insula (cognitive interpretations of body arousal and emotional awareness), and right superior orbital frontal cortex (emotion regulation).

Regarding functional changes, PD patients have been shown to have reduced metabolism in the left inferior parietal lobe and right superior temporal lobe (which are both important for the perception of emotions in facial stimuli), and a reduced overall bilateral cerebral blood flow compared to healthy control subjects (Lee et al., 2006; Martin et al., 2009; Pfleiderer et al., 2007). Further, using PET neuroimaging, Kang et al. (2012) demonstrated a lower rate of metabolism in the right medial frontal gyrus, right superior frontal gyrus, and left middle frontal gyrus, which are all involved in emotion regulation. It also showed a lower rate of metabolism in the right caudate, which functions are, for example, reward processing and motivational salience. The right middle temporal gyrus (recognition of known faces) and left cingulate gyrus (emotion processing) did also show a decrease in metabolism. There are also observations of increased activity in certain brain areas, according to Sakai et al. (2005), PD patients exhibited higher levels of glucose uptake in the brainstem (caudal pons and medulla oblongata), cerebellum, and midbrain, the role of which in anxiety disorders is not apparent (although, it could be related to increased arousal). Additionally, the hippocampus, which main function is the consolidation of declarative memories, and the thalamus, which seems to play an important role in regulating the activity

in the amygdala in PD patients, also have a higher level of glucose uptake (Asami et al., 2018).

As both gray matter is reduced and a lowered metabolism rate is found in parts of the brain where emotional regulation is involved, these findings suggest that panic disorder has a direct diminished impact on emotional regulation capability.

Structural and Functional Changes in the Amygdala in Panic Disorder

The amygdala is a limbic structure consisting of several subnuclei that are all involved in different functions and are often categorized into five major groups (RajMohan & Mohandas, 2007): The basolateral nuclei (stimulate fear response), the cortical-like nuclei (processing of pheromonal information; Kemppainen et al., 2002), the centromedial nuclei, other amygdaloid nuclei, and the extended amygdala. The extended amygdala consists of centromedial amygdala, sublenticular substantia innominata and bed nucleus of the stria terminalis (Kemppainen et al., 2002). The different parts of the amygdala have anatomic connections to different brain regions, such as the amygdalo-cortical connections, which show connections to the insular, temporal, frontal, occipital cortices, medial prefrontal cortex, and orbitofrontal cortex (Meisner et al., 2022). Additionally, Meisner et al. (2022) have provided evidence for the existence of a connection between the brain stem and hypothalamic structures, which promote coordinated autonomic, endocrine, and behavioral responses linked to biological drives such as motivational, social, and reproductive behaviors. According to RajMohan and Mohandas (2007), the amygdala contains two distinct output pathways. The first, known as the dorsal route, utilizes the stria terminalis to project towards the septal area and hypothalamus. The second, the ventral route, employs the ventral amygdalofugal pathway to terminate in the septal area, hypothalamus, and the medial dorsal thalamic nucleus.

The input of 5-HT to the amygdala seems to affect the activation in response to stimuli of emotional quality, for example, a neutral tone that is paired with aversive stimuli, such as an electrical shock (Bienvenu et al., 2012; Bocchio et al., 2016). The amygdala is an important brain region for emotional response, as it is a salience and arousal “detector” of emotions, and it seems to be both structurally and functionally different in PD patients compared to healthy individuals (Asami et al., 2018; Janak & Tye, 2015; Martin et al., 2009; Roy-Byrne et al., 2006).

According to Asami et al. (2018), by the utilization of MRI, there appears to be a reduced volume of gray matter in the right amygdala in PD patients compared to healthy individuals. More specifically, the subregions of the amygdala, such as the right lateral and right basal nuclei showed smaller volumes. Yoon et al. (2016) conducted a systematic review and detected a trend toward a smaller right amygdala for PD patients compared to healthy individuals (albeit, it did not reach statistical significance). Additionally, Yoon et al. (2016)

demonstrated an inward deformation of the centromedial and laterobasal parts of the right amygdala in PD patients. Sobanski et al. (2010) conducted a quantitative volumetric and voxel-based morphometric MRI study and demonstrated a contradicting result, as no structural abnormalities were found for PD patients.

By using fMRI, patients with PD who are currently on SSRI medication have been shown to have increased activity during an auditory habituation paradigm, specifically in the right amygdala (Pfleiderer et al., 2007). Burkhardt et al. (2019) conducted a pilot study where PD patients and healthy individuals used mental imagery of disorder-specific situations while undergoing an fMRI scan. It showed that PD patients had elevated right amygdala activation compared to healthy individuals. A clinical EEG study that utilized laboratory-induced panic symptoms for PD patients who were currently on SSRI showed a significant increase in the right amygdala activation. Sakai et al. (2005) demonstrated that PD patients who are not on medication for PD have higher activity in the bilateral amygdala. During resting state, pictorial stimuli, and spontaneous panic attack studies, Dresler et al. (2013) found elevated activity in the right amygdala. Kim and Yoon (2018) reviewed recent resting-state fMRI studies for PD patients and found an increase in activation in the right amygdala. Sobanski and Wagner (2017) showed that differences in the amygdala activation for PD patients were not as consistently salient as expected and it seems like amygdala hyperactivation is greatly dependent on experimental paradigms, stimuli, limitations of neuroimaging techniques, and sample size- and heterogeneity.

The results from the structural findings are somewhat surprising because a higher arousal/fear responsivity is thought to be correlated with an increased volume of gray matter in the amygdala, as it has been shown that stress induces neuroplastic changes in the amygdala (Zhang et al., 2018). The functional findings are contrasting compared to the structural ones, although they are more in line with what might be expected as it demonstrated higher amygdala activation.

The Present Thesis

The aim of this thesis is to conduct a systematic review on the effect of SSRIs on the functional alterations of the amygdala in patients suffering from PD. The present systematic review will try to answer the question: If, and to what degree, do SSRIs affect either the left, right, or bilateral amygdala activation for PD patients (diagnosed according to DSM-5) compared to healthy individuals who are not under any pharmacotherapy. This is achieved by gathering data through original studies which used functional neuroimaging techniques such as fMRI, PET, SPECT, and qEEG.

Methods

Search Strategy

Three electronic databases were used to search for relevant articles: MEDLINE EBSCO, Scopus, and Web of Science. The keywords used were: “selective serotonin reuptake inhibitors”, “antidepressant”, “panic disorder”, “amygdala”, and two abbreviations (“PD” and “SSRIs”). The final search was conducted on May 5th, 2023, and used the search string “*("selective serotonin reuptake inhibitor*" OR SSRI* OR antidepressant*) AND ("panic disorder" OR "panic attack" OR PD) AND amygdala*” with no restriction for the publication date. The search gave in total 198 hits: MEDLINE EBSCO (n = 33), Scopus (n = 85), Web of Science (n = 80).

In order to obtain the relevant studies for this systematic review, 57 duplicates were removed by the use of the reference software Zotero. The remaining 141 articles were then screened by scrutinizing the title and abstract, and 108 articles were excluded. The remaining 33 articles were then carefully assessed by reading the studies more thoroughly, i.e., methods, results, and discussion. Following this, 29 studies were excluded due to six reasons: Did not study PD (n = 16), not a human sample (n = 4), did not have a control group (n = 2), not written in English (n = 1), participants did not use SSRI (n = 3), and did not study the activation of the amygdala (n = 3). Four studies were finally included in this review. The PRISMA flow diagram depicts the search and screening process (see Figure 1).

Inclusion and Exclusion Criteria

The present systematic review includes original research articles published in peer-reviewed journals. Participants included are PD patients over 18 years old undergoing pharmacotherapy treatment, specifically SSRIs such as citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, vilazodone, or vortioxetine (dosage between 0.5 mg/day to 300 mg/day). There needed to be a control group, which in this case are healthy control participants who are not currently undergoing any pharmacotherapy treatment. A second inclusion criterion is the use of fMRI, SPECT, PET, and qEEG. Additionally, the included studies are written in the English language and published before May 5th, 2023.

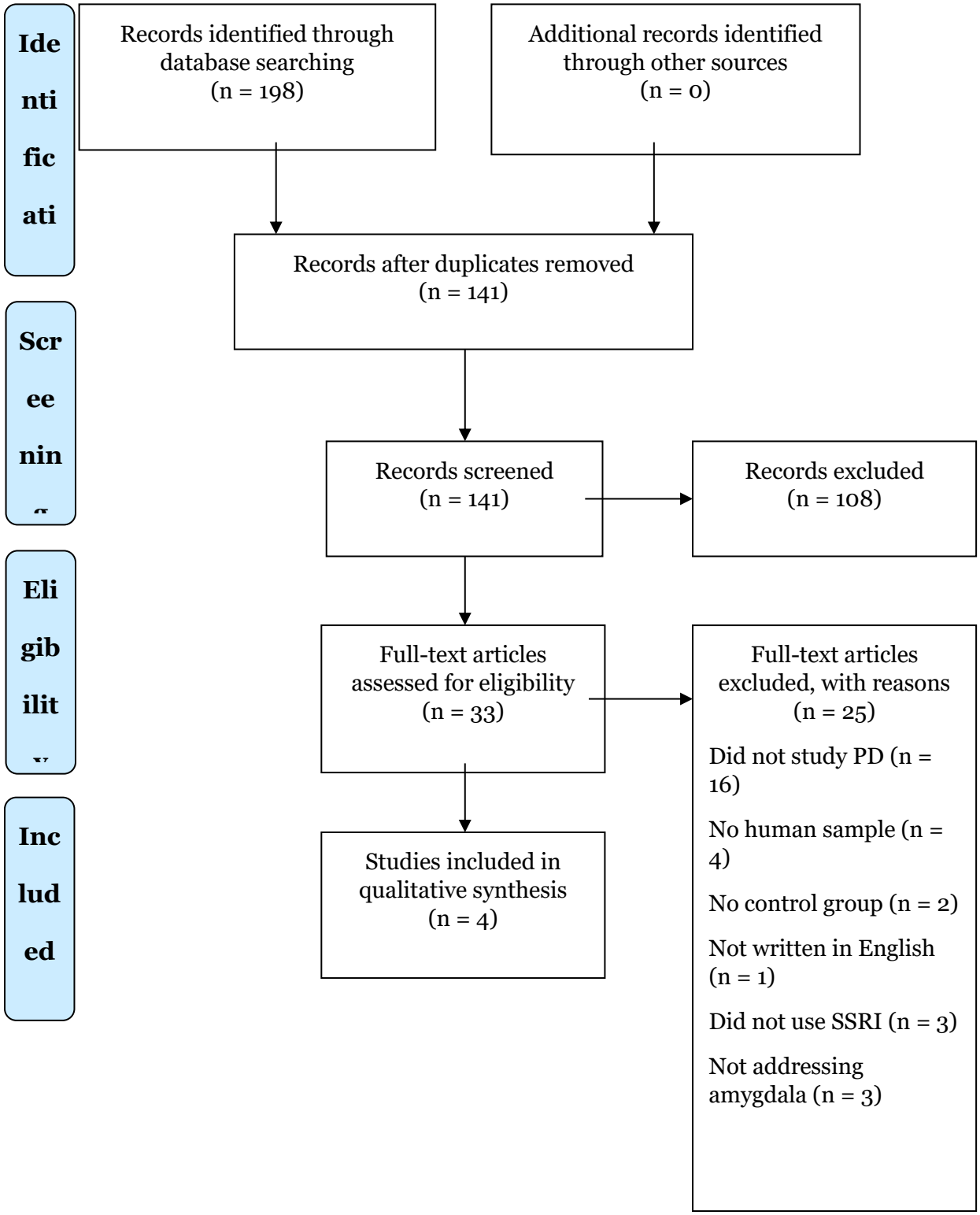
Structural neuroimaging methods such as MRI and diffusion tensor imaging studies have been excluded due to the present review focusing on functional alterations. Additional studies that have been excluded are review articles, meta-analyses, and book chapters.

Data Extraction

The data extracted from the four included original studies are authors and years, clinical sample (sample size, gender distribution, mean age) what type of pharmacotherapy was administered (SSRI), the dosage, the brain imaging technique used (fMRI and PET), and findings regarding amygdala activation.

Figure 1

PRISMA 2009 Flow Diagram



Note. Standard flow diagram used to document the literature search process (Moher et al., 2009)

Results

Study Characteristics

Table 1 shows the demographic aspect of the participants, what type of antidepressant was used, what kind of neuroimaging technique was used to scan the participants, and finally the main findings of the four studies. One study was conducted in Germany (Liebscher et al., 2016), one in South Korea (Kang et al., 2012), one in The United Kingdom (Nash et al., 2008), and one in The Netherlands (Van Tol et al., 2012). All studies were published between the years 2008 (Nash et al., 2008) and 2016 (Liebscher et al., 2016) and the sample size varied between 26 (Nash et al., 2008) and 62 subjects (Van Tol et al., 2012), and the female ratio was between no females (Nash et al., 2008) and 63 % (Liebscher et al., 2016; one study did not report the female to male ratio; Van Tol et al., 2012). The mean age for the subjects ranged from 35,05 (Liebscher et al., 2016) to 43,35 (Nash et al., 2008) (one study did not report the mean age; Van Tol et al., 2012).

Table 1

Methodological overview of the included articles

Authors & Years	Clinical Sample for PDP	Clinical Sample for HC	Pharmacotherapy	Study design
Kang et al. (2012)	15 subjects F = 8 Mdn = 42,3	20 subjects F = 7 Mdn = 40,7	SSRI (escitalopram) Dosage: M = 5,2 mg Length = 12 weeks	Between-individual
Liebscher et al. (2016)	28 subjects F = 18 Mdn = 36	29 subjects F = 18 Mdn = 34,09	SSRIs or SNRIs Dosage NI Length: 7,57 weeks	Between-individual
Nash et al. (2008)	7 subjects F = 0 Mdn = 45,4	19 subjects F = 0 Mdn = 41,3	SSRIs (paroxetine or sertraline) Dosage: M = 40 mg Length: 57,6 weeks	Between-individual
Van Tol et al. (2012)	13 subjects F = NI Mdn = NI	49 subjects F = NI Mdn = NI	SSRI Dosage = NI Length = NI	Between-individual

Note. NI = no information, Mdn = median, M = mean, F = female, PDP = panic disorder patient, HC = healthy control

fMRI Studies

Table 2 presents the behavioral and neuroimaging findings of the included studies. Liebscher et al. (2016) investigated the difference between therapist-guided CBT, non-guided CBT, pharmacological treatment (SSRI/SNRI), and HC for neural activation patterns. There were in total 29 PD patients in the therapist-guided CBT group (F = 18), 22 PD patients in the non-guided CBT group (F = 16), 28 participants in the pharmacological treatment group (F = 18), and 29 participants in the HC group (F = 18). All participants were administered the Westphal-Paradigm during the fMRI scan, which is agoraphobia-specific stimuli (e.g., pictures of public places, bridges, using public transport, etc.). Liebscher et al. (2016) hypothesized that there would be an increased amygdala activation prior to therapy in PD patients compared to HC and that there would be reduced disorder-specific symptoms in the CBT group would be reflected in a greater decrease in amygdala activation compared to the SSRI/SNRI and the HC. The results showed that in the pharmacological group, there was a reduction of activity in the left amygdala.

Van Tol et al. (2012) examined patients diagnosed with MDD, social anxiety disorder (SAD), GAD, and PD activation in certain brain structures, including the amygdala. Forty-nine HC (F = 30) and 56 SAD and/or PD patients, 13 of them were PD patients (F = NI) with no comorbidities (not analyzed separately), participated in an emotional word encoding and recognition paradigm during an fMRI scan. During the encoding, the participants classified 40 positive, neutral, and negative words which were presented randomized along with 40 baseline trials in 20 blocks of eight words. After 10 minutes, the participants performed a word-recognition task, which consisted of the old words in the encoding phase, and 120 new words which were intended to distract the participants. The participants answered either that they had seen the word before or probably seen the word before or have not seen it before. Van Tol et al. (2012) did not find any changes in the amygdala for SAD and/or PD patients.

PET Studies

Kang et al. (2012) tested the changes in glucose metabolism in PD patients compared to HC using a type of SSRI called escitalopram using PET as the scanning tool. Fifteen right-handed PD patients (F = 7) were compared to 20 right-handed HC (F = 8), and all were using escitalopram (mean dosage 5.2mg/day) for 12 consecutive weeks. There appears to be a significantly enhanced FDG uptake in several brain regions, including the right amygdala (See Table 2) for PD patients. Kang et al. (2012) hypothesized that the limbic system and neocortical areas are associated with SSRIs treatment response in PD patients. The results showed that following 12 weeks of pharmacotherapy treatment with the SSRI escitalopram, the right amygdala exhibited an increased FDG uptake.

Nash et al. (2008) examined the 5-HT receptor binding in PD patients, before and after SSRI treatment. Nine PD patients were unmedicated, seven PD patients were medicated with paroxetine or sertraline (mean dosage 40mg/day), and 19 HC were scanned by the usage of PET. Nash et al. (2008) hypothesized that PD patients would have reductions in 5-HT1A receptor binding in regions of the brain that are associated with anxiety and that pharmacotherapy treatment (specifically SSRI) would not affect 5-HT1A receptor availability. The results showed that both presynaptic and postsynaptic 5-HT receptor binding in the amygdala was lowered in untreated and medicated PD patients compared to HC.

Table 2

Behavioral and neuroimaging results of the included articles

Authors & Years	Brain Imaging Technique	Behavioral measure/scale	Neuroimaging tasks	Neuroimaging analysis method	Findings
Kang et al. (2012)	PET	HAM-A, BDI, PDSS	Resting state	Whole brain	Right amygdala activation increased compared to HC
Liebscher et al. (2016)	fMRI	HAM-A, BDI, PAS-panic, ASI	WP	Whole brain	Reduction in left amygdala activation compared to HC
Nash et al. (2008)	PET	HAM-A, HAM-D, BDI	WP	ROI (amygdala, raphe, global postsynaptic regions, hippocampus, anterior medial temporal cortex, anterior lateral temporal cortex, parahippocampal gyrus, superior temporal gyrus, medial inferior temporal gyrus, fusiform gyrus, posterior temporal cortex, insula, anterior cingulate gyrus, posterior cingulate gyrus, parietal lobe, occipital lobe, orbitofrontal cortex, gyrus frontomedialis, gyrus precentralis, gyrus frontoinferior, gyrus frontomedius, gyrus frontosuperior)	Both presynaptic and postsynaptic 5-HT receptor binding in the amygdala was lowered in untreated and medicated PD patients compared to HC
Van Tol et al. (2012)	fMRI	BAI, MADRS, IDS, FQ	Emotional word encoding and recognition paradigm	ROI (amygdala, hippocampus, medial prefrontal cortex, inferior frontal gyrus, anterior cingulate cortex, insula)	Did not detect activation changes in the amygdala

Note. BAI = Beck Anxiety Inventory, MADRS = Montgomery-Åsberg Depression Rating Scale, IDS = Inventory of Depressive Symptomatology, FQ = Fear Questionnaire, HAM-D = Hamilton Rating Scale for Depression, PDSS = Panic Disorder Severity Scale, WP = Westphal-Paradigm, BDI = Beck Depression Inventory, PAS-panic = Panic and Agoraphobia Scale subscale panic attacks, ASI = Anxiety Sensitivity Index, HAM-A = Hamilton Rating Scale for Anxiety, ROI = Region of inter

Discussion

The aim of this thesis was to review the effect of SSRIs on the functional alterations of the amygdala in patients suffering from PD. The present systematic review investigated whether SSRIs affect the right-, left, or bilateral amygdala activation of PD patients compared to HC. The included four studies demonstrated results that seem to be at odds with each other. Van Tol et al. (2012) did not detect activation changes in the amygdala for PD patients using SSRIs, whereas Liebscher et al. (2016) exhibited a reduction in the left amygdala. Kang et al. (2012) discovered an increased activation in the right amygdala, and Nash et al. (2008) found a reduced pre- and postsynaptic 5-HT receptor binding in the amygdala (unspecified if right, left, or bilateral).

Comparing the two included PET studies, Kang et al. (2012) tested the changes in glucose metabolism and used escitalopram, while Nash et al. (2008) examined the 5-HT receptor binding and used paroxetine or sertraline on males only. Comparing the two fMRI studies, Liebscher et al. (2016) investigated the difference between CBT, non-guided CBT, SSRI/SNRI (no information regarding what type of SSRIs or SNRIs were administered, and HC groups with the aim to detect neural activation patterns. The study used the Westphal-Paradigm. Van Tol et al. (2012) investigated PD patients who are currently undergoing SSRI treatment (no information regarding what type) activation in brain areas such as the amygdala. The study used a recognition paradigm during an fMRI scan.

As no data appears to exist regarding this exact inquiry this systematic review investigates, it is difficult to embed the findings in regard to other results, albeit studies have been made on other disorders and different study designs have been utilized. Other disorders are for example MDD, as Godlewska et al. (2012) found that MDD patients who underwent escitalopram treatment did not have an increased amygdala activation compared to HC. Likewise, Young et al. (2020) studied MDD patients currently undergoing SSRI treatment but on the contrary found increased activity in the amygdala in response to positive stimuli, and a decrease in activity when presented with negative stimuli. A meta-analysis demonstrated consistently a higher amygdala activation in PTSD, SAD, and specific phobia patients, who did not undergo any pharmacotherapy (Etkin & Wager, 2007). Another study design other than comparing PD patients to HC is comparing pre-treatment vs post-treatment; as Gorka et al. (2019) showed that SSRI treatment diminished amygdala activation in patients with anxiety/and or depression disorders (GAD, PD, PTSD, SAD, MDD) post-treatment.

Prior studies show differences in the two hemispheres in amygdala activation, as the right amygdala is involved in automatic processing (physiological reaction) whereas the left

amygdala is involved in the cognitive process of emotional information, such as assessment of arousal (Adolphs, 2010; Dyck et al., 2011). When a panic attack occurs in PD patients, it is most likely linked to a physiological reaction, and an example of this is Pfleiderer et al. (2007), who found a significant increase in the right amygdala during an episode of a panic attack. Following this, it is surprising, to only see one (Kang et al., 2012) of the four included articles that found an increased right amygdala activation, as PD often presents itself as a physiological reaction. Kang et al. (2012) did not use a neuroimaging task (only resting state), which is in line with already existing evidence (Kim & Yoon, 2018) for enhanced right amygdala activation. Liebscher et al. (2016) and Nash et al. (2008) used a symptom provocation (Westphal-Paradigm) neuroimaging method and both found a reduction in activity in the left amygdala, albeit Nash et al. (2008) did not specify left-, right or bilateral amygdala. These results contradict previous studies where the left amygdala showed greater activation in neuroimaging tasks where the patients are expecting the presentation of certain stimuli, e.g., the Westphal-Paradigm (Dyck et al., 2011). Van Tol et al. (2012) did not find activation changes in the left amygdala (nor right), which can be viewed as surprising due to using a task paradigm where the left amygdala might play a significant part as it was more cognitive and intentional control of mood and emotions.

All of these studies except for Kang et al. (2012) did not detect increased amygdala activity, which does not align with already existing evidence (e.g., Burkhardt et al., 2019; Dresler et al., 2013; Pfleiderer et al., 2007; Sakai et al., 2005). A possible factor contributing to the results shown by Nash et al. (2008) and Liebscher et al. (2016) is the usage of SSRIs, as it has been shown to normalize amygdala hyperactivity in both depression- and anxiety disorders (Godlewska et al., 2012; Gorka et al., 2019; Young et al., 2020). An explanation for the results of Van Tol et al. (2012) could be due to not isolating PD patients and the neuroimaging task used (which is not specifically designed for PD patients, compared to e.g., the Westphal-Paradigm).

Limitations and Suggestions for Future Research

There are several limitations to the present systematic review. Firstly, it only includes four studies, and one of them (Nash et al., 2008) has under 30 participants and was only males. A second possible limitation is this systematic review did not account for gender differences. Another limitation is the low variation of SSRIs (only paroxetine, sertraline, and escitalopram) administered to PD patients, and the dosage is only documented in one study; Liebscher et al. (2016). Moreover, all included studies had a relatively short duration of pharmacotherapy. Van Tol et al. (2012) did not isolate PD patients when presenting their results as that experiment group included both SAD and/or PD patients. A major limitation of this review is the varied methodology, as only two studies use the same neuroimaging task

(Liebscher et al., 2016; Nash et al., 2008), although they differed in other methodological aspects (brain imaging technique, behavioral measure, and neuroimaging analysis). Lastly, only two (Kang et al., 2012; Liebscher et al., 2016) out of four studies were published in the last decade, which shows that more studies are needed for a greater overall understanding of this topic.

Even though substantial research has been conducted on PD, SSRI, and the amygdala, it lacks the integration of these three areas. The ideal future research on this topic would preferably demonstrate a clear isolation between different depression- and anxiety disorders when measuring amygdala activation. Additionally, a greater variation of SSRI types, dosage, and length of pharmacotherapy. Another significant improvement future research could benefit from is a more consistent approach to the methodology as the variety is too great at the moment, which can skew the results and/or make it less valid.

Ethical and Societal Aspects

All included studies in this review except for Kang et al. (2012) were evaluated and approved by ethics boards, and all participants in all of the included studies signed informed consent before participating in the study.

A greater understanding of SSRIs' effect on the functional alterations of the amygdala in PD patients may aid society by helping PD patients (and hopefully other mental disorders) get an efficacious and safe pharmacotherapy treatment during their illnesses. Additionally, a greater treatment for PD patients could reduce the economic cost of being, for example, absent from work, school, or not contributing in general to society.

Final Conclusions

There are not a significant number of studies regarding this topic and the data gathered by the included studies indicate that there is no real consensus. More studies are needed for a greater dataset, but also a bigger variety of different types of SSRIs, different dosages, and different study designs could lead to a greater understanding of the effects of SSRIs on amygdala activation in PD patients.

Word count: 5,093

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