

# Amygdala and emotionality in Parkinson's disease: An integrative review of the neuropsychological evidence

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## Abstract

Parkinson's disease (PD) is often accompanied by significant changes in emotionality, such as apathy, anhedonia, anxiety and depression. The present review summarizes the empirical evidence, including amygdala changes and psychological changes in emotionality in people suffering from PD. Seventeen empirical full-text articles including research on both amygdala and emotionality in PD were reviewed. The changes in amygdala volumes as well as changes in binding potentials, functional connectivity, regional homogeneity and regional cerebral blood flow were found to have various impacts on emotionality in people with PD. The integration of the results showed that some effects of amygdala changes on emotionality were lateralized. Some of the reviewed studies indicated that the volume loss in the left amygdala was found to be related to increased anxiety, whereas bilateral volume loss in amygdala was linked to increased depressivity. The reviewed results also support a hypothesis of bradylimbic affective disturbance in patients with PD. The disturbed activation of amygdala accompanying the evaluation of negative facial expressions implies that the evaluation of the content of affective stimuli in terms of their affective meanings is disturbed in PD patients. Impaired evaluation of affective attributes given by amygdala-based translational deficits is likely to be related to problems in translating the results of cognitive appraisal into somatomotor, arousal and other changes. This mechanism is suggested to be responsible for apathy as well as for other changes in emotionality accompanying PD.

## Abbreviations:

PD - Parkinson's disease

## INTRODUCTION

Parkinson's disease (PD) is suggested to be a very suitable prolific model for studying the neurobiology of normal human emotional behavior as well as psychiatric disorders (Garlovsky *et al.* 2016). Therefore, an in-depth understanding of the brain mechanism underlying Parkinson's disease is a recent, very important challenge for many fields of neurosciences and neuropsychology. It is well-documented that the PD is accompanied by significant changes in emotionality, such as anhedonia, i.e. a lowered ability to experience pleasure (Loas *et al.* 2012), apathy (Bogart 2011), anxiety and depression (Garlovsky *et al.* 2016). Despite the detrimental impact of these emotional changes on the quality of emotional life of people suffering from PD, there is a lack of reviews focusing on the role of amygdala in relation to nonmotor symptoms. Therefore, the present review aims to summarize the empirical evidence, including amygdala changes and psychological changes, in the emotionality of people with PD.

The amygdala is an almond-shaped structure on the medial temporal lobe located adjacent and anterior to the hippocampus (Phelps 2006). The amygdala is a key neural structure responsible for human emotions (LeDoux 2000) due to its role in the detection and processing of emotional stimuli (Němcová *et al.* 2015; Phelps 2006). This structure is part of the limbic-based circuitry involved in the generation and modulation of normal fear responses (Bowers *et al.* 2006; LeDoux 2000). This circuitry is responsible for initiating behavioral, autonomic and neuroendocrine processes essential for appropriate reactions to threats and danger. Furthermore, given the role of amygdala in the encoding and storage of hippocampal-dependent emotional memories (Phelps 2006), this structure also influences the retrieval of emotional life events. The amygdala can also modulate the recognition of facial expressions because of its functional involvement in episodic memory for emotional stimuli. Functional abnormalities in the amygdala are related to depression, anxiety and posttraumatic stress disorder (Grambal *et al.* 2015; LeDoux, 2000; Zach *et al.* 2016).

Changes in the amygdala are well-documented in PD patients. Volumetric changes, a reduction in amygdala dopamine-agonist binding, an increased occurrence of Lewy body pathology and increased pre-synaptic axonal pathology all accompany PD (Bowers *et al.* 2006). Bowers *et al.* (2006) proposed a bradylimbic affective disturbance in patients with PD, hypothesizing that evaluation of affective attributes, such as valence or arousal, is disturbed in PD because of changes in the amygdala and other parts of limbic-based circuitry. The muted reactivity to aversive stimuli that is present in PD patients is suggested to be related to a deficit in translat-

ing the results of cognitive appraisal into somatomotor (Vastik *et al.* 2016), arousal and other changes associated with an aversive motivational state. In other words, cognitive appraisal is not necessarily disturbed, but the outputs of this appraisal are suggested to be insufficient to induce a particular motivational state. The authors proposed that this mechanism may be responsible for the apathy frequently observed in PD patients (Bogart 2011). However, it is also possible that impaired evaluation of affective attributes, resulting from an amygdala-based translational defect, may play an important role also in other changes in emotionality in PD.

There are many insistent questions relating to changes in human amygdala in patients suffering from PD. In the following text, we proceed through the current findings concerning the amygdala in PD and show what changes in the amygdala have been found to be related to changes in emotionality in PD patients. The aim of the present review is to expand our understanding of the neurobiological basis of emotional processing in PD.

## METHODS

### Search strategy

A systematic literature search was completed in February 2018. Manuscripts published between 2000 and 2018 were accessed via the Web of Science and PubMed electronic databases. Peer-reviewed literature providing empirical evidence was retrieved using a standard search strategy based on the key words: Parkinson AND amygdala. Meeting abstracts, reviews and editorial materials were excluded in this phase. After the exclusion, a total of 351 full-text articles were identified, and the titles and abstracts were scanned for relevance.

### Selection of the studies

Only patients diagnosed with idiopathic Parkinson's disease were included. Articles that did not directly report empirical research of amygdala in PD in relation to emotionality, i.e. anhedonia, depression, anxiety or emotional processing, were excluded. At the same time, empirical research based on animal models, case-studies and *post-mortem* cases of PD were excluded. Only articles written in English were included in the review. Two authors (RT and MK) reviewed the methodological quality of the included studies according to the selected criteria. The results were re-reviewed by a third author (TN), who made the final decision.

## RESULTS

In total, 17 empirical full-text articles were selected (Table 1). The outcomes were classified into 5 categories: depression, anxiety, apathy, disgust and fear, and emotion recognition, according to the domain of emotionality that the articles focused on. These categories were not created on a pre-determined conceptual

**Tab. 1.** Review of studies focusing on amygdala and emotionality in PD patients

Publication	PD sample(s)	Key findings
Tessitore <i>et al.</i> 2002	10 PD patients	The imaging data revealed a robust bilateral amygdala response in healthy controls that was absent in PD patients during the hypodopaminergic state.
Remy <i>et al.</i> 2005	20 PD patients	Depression and anxiety in PD might be associated with a specific loss of dopamine and noradrenaline innervation in the limbic system.
Yoshimura <i>et al.</i> 2005	9 PD patients	No neuronal activity was found in the amygdala when responding to fearful expressions in PD patients in comparison with healthy subjects.
Delaveau <i>et al.</i> 2009	14 PD patients	Similar right-amygdala activity was seen in both healthy subjects and PD patients in the placebo session. After levodopa administration, this activity was reduced in both groups.
Ibarretxe-Bilbao <i>et al.</i> 2009	24 early PD patients	Significant gray matter loss in the right amygdala and bilaterally in the orbitofrontal cortex was found in PD patients.
Lawrence <i>et al.</i> 2011	20 PD patients	Apathy was associated with a blunted response to money in the ventromedial prefrontal cortex, amygdala, striatum and midbrain.
Baggio <i>et al.</i> 2012	39 PD patients	Emotion recognition of sadness was positively correlated with gray matter volume in the right orbitofrontal cortex, amygdala and postcentral gyrus in PD patients.
Surdhar <i>et al.</i> 2012	33 non-demented depressed PD patients	Depressed PD patients showed smaller amygdala volumes compared to healthy controls. Amygdala atrophy was suggested to be present in PD with depression.
Sheng <i>et al.</i> 2014	41 PD patients	Compared with the non-depressed patients, those with depressive symptoms exhibited significantly increased regional activity in the left middle frontal gyrus and right inferior frontal gyrus, and decreased regional activity in the left amygdala and bilateral lingual gyrus.
Hu <i>et al.</i> 2015	20 depressed PD patients, 40 non-depressed PD patients	Compared to healthy controls, the depressed PD group showed increased left amygdala functional connectivity with the bilateral mediodorsal thalamus, but decreased left amygdala functional connectivity with the left putamen, left inferior frontal gyrus and the right cerebellum, as well as decreased right amygdala functional connectivity with the left inferior orbitofrontal gyrus, the left gyrus rectus and the right putamen.
Huang <i>et al.</i> 2015	19 depressed PD patients, 19 non-depressed PD patients	Left amygdala activity was increased in the PD group compared with the healthy control group, and it correlated with depression. Functional connectivity between the right amygdala and fronto-parietal areas was found to be decreased in the depressed PD patients compared with non-depressed PD patients.
Schienle <i>et al.</i> 2015	17 non-depressed and non-demented PD patients	Healthy control participants showed amygdala activation during experimental fear induction, whereas no supra-threshold activation was detected in PD patients. No differences were found between PD patients and healthy controls during disgust induction.
van Mierlo <i>et al.</i> 2015	67 PD patients	Depression correlated negatively with bilateral hippocampus and right amygdala volume and positively with the volume of the anterior cingulate cortex.
Kim <i>et al.</i> 2016	35 depressed PD patients, 43 non-depressed PD patients	Regional cerebral blood flow decreases in the amygdala, anterior cingulate cortex, hippocampus and parahippocampal gyrus in depressed PD patients.
Vriend <i>et al.</i> 2016	110 early PD patients	A reduction in left amygdala volume was associated with anxiety in PD patients.
Chagas <i>et al.</i> 2017	15 PD patients with current Major Depressive Disorder, 10 PD patients with previous MDD but without current MDD, 18 PD patients with no current or lifetime MDD	Current and lifetime Major Depressive Disorder (MDD) had a negative impact on the neurodegenerative process of PD, with decreased volume and reduction of cortical thickness in temporal and frontal areas, anterior cingulate cortex, amygdala and cerebellar white matter.
Li <i>et al.</i> 2017	366 early PD patients	Right amygdala grey matter density showed negative correlation with autonomic dysfunction and positive correlation with cognitive performance in PD patients. No significant interrelations were found with anxiety scores.

framework but were allowed to emerge from the data in the course of the review procedure. Few studies included results falling into more than one category. The main results within each category are presented in the following sections.

### Depression

Gray matter volume loss within the limbic circuit has been found to be related to the severity of depressive symptoms in PD patients (van Mierlo *et al.* 2015). More specifically, self-reported rating of depressive symptoms correlated negatively with the volumes of bilateral hippocampus and amygdala and positively with the volume of the anterior cingulate cortex. Reduced amygdala volumes relative to healthy controls were also found in PD patients with depression in the study of Surdhar *et al.* (2012). Interestingly, in the study of Huang *et al.* (2015) volumetric changes were not significantly different in the depressed PD patients compared to healthy control and non-depressed PD patients.

When evaluating the role of a previous Major Depressive Disorder, PD patients with a previous Major Depressive Disorder had smaller bilateral amygdala than PD patients without a previous or current Major Depressive Disorder. The volumes of the right amygdala were smaller in the group with current (and not previous) Major Depressive Disorder compared to PD patients without a previous or current Major Depressive Disorder.

Regional cerebral blood flow was compared in depressed and non-depressed PD patients (measured by self-reported ratings) in the study of Kim *et al.* (2016). Regional cerebral blood flow was found to be decreased in the amygdala and other regions in depressed PD patients compared to non-depressed PD patients.

Differences in amygdala functional connectivity between PD patients and healthy subjects were found in two reviewed studies (Huang *et al.* 2015; Hu *et al.* 2015). Furthermore, depressed PD patients showed increased left amygdala functional connectivity with the bilateral mediodorsal thalamus and increased right amygdala functional connectivity with the left superior temporal gyrus and the calcarine gyrus in comparison to non-depressed PD patients (Hu *et al.* 2015). In contrast, depressed PD patients showed decreased connectivity between the right amygdala and the right middle occipital gyrus, right middle frontal gyrus and the left inferior parietal lobule when compared with non-depressed PD patients in the study of Huang *et al.* (2015).

Remy *et al.* (2005) examined the role of both dopamine and noradrenaline transporter binding in depression. PD patients were divided into a depressed group, i.e. with previous episodes of major depression based on DSM-IV criteria, and a non-depressed group without such episodes. Patients without previous episodes of major depression showed significantly higher bind-

ing potential in the right amygdala than patients with previous episodes of major depression.

Differences between depressed and non-depressed PD patients were also found in the study of Sheng *et al.* (2014), which focused on regional homogeneity during spontaneous neural activity. Depressed PD patients showed decreased regional homogeneity in the left amygdala and bilateral lingual gyrus and increased regional homogeneity in the left middle frontal gyrus and right inferior frontal gyrus. These results indicate that decreased regional homogeneity in amygdala reflects the local destruction of synchronization of spontaneous low-frequency blood oxygen level-dependent fluctuations in the region and consequently also functional deficits of amygdala in PD patients.

### Anxiety

The study of Vriend *et al.* (2016) showed that symptoms of anxiety in PD patients had a negative correlation with the volume of the left amygdala. The authors suggested that PD pathology is responsible for the observed volume loss of the left amygdala and the concomitant development of anxiety symptoms.

Furthermore, Remy *et al.* (2005) measured anxiety by standardized psychometric instrument in PD patients. The anxiety score was negatively correlated with the binding potential in the left ventral striatum, left caudate, left locus coeruleus, left inferior thalamic region and bilaterally in the amygdala and medial thalamus. The authors suggested that the loss of noradrenaline and dopamine in the amygdala is likely to play a role in generating affective symptoms in PD. Interestingly, the study of Li *et al.* (2017) found amygdala degeneration to be related only to cognition and autonomous dysfunction, but not to anxiety in patients in the early stages of PD.

### Apathy

The role of apathy in alterations in the neural circuitry underpinning the cognitive and emotional components of goal-directed behavior was examined in the study of Lawrence *et al.* (2011). PD patients participated in an experimental task involving monetary reward cues. Psychometrically measured apathy was associated with a diminished response to money in several brain regions: the left amygdala, ventromedial prefrontal cortex, striatum and midbrain, all of which have been previously shown to be integral to the representation of reward value and goal-directed behavior. In other words, higher apathy was related to decreased activity in these brain regions during the reward-value experimental task in PD patients.

### Disgust and fear

In the fMRI study of Schienle *et al.* (2015), PD patients were exposed to 10 disgust-eliciting (e.g. dirty toilets, maggots), 10 fear-eliciting (attacks by humans and animals) and 10 neutral pictures (e.g. nature scenes, geometric figures) with the instruction to simply expe-

rience the elicited emotions. The group contrasting for the disgust-inducing condition revealed no significant differences in the activation of amygdala. In the fear-inducing condition, the healthy control participants showed the expected amygdala activation, whereas no supra-threshold activation was detected in the PD patients. In contrast, the PD patients showed activation of the middle temporal gyrus during the fear-inducing condition. The authors, however, concluded that this fMRI investigation found no indication of diminished disgust and fear experience in patients suffering from moderate PD symptoms.

In the same study, proneness to dispositional disgust was measured using a standardized psychometric instrument, with no differences found between PD patients and healthy controls.

#### Emotion recognition

Yoshimura *et al.* (2005) randomly presented PD patients with fearful, surprised and neutral facial expressions in their study. The visual event-related potentials elicited in response to fearful facial expressions were generated within the amygdala and visual temporal cortex in healthy controls, whereas the equivalent current dipoles were located only in the parietal somatosensory cortex in PD patients. These results indicate dysfunction of the amygdala during emotion recognition in patients with PD.

A reduced amygdala response during the perceptual processing of angry and fearful faces was observed also by Tessitore *et al.* (2002). Abnormal amygdala responses in patients with PD were present both in drug-off and drug-on conditions, i.e. 12 hours after their last dopaminergic drug dose the night before as well as 1–2 hours after the first dose of the day.

In the study of Baggio *et al.* (2012) impaired recognition of sadness was associated with gray matter loss in two areas of the right side in the amygdalae and orbito-frontal cortex when examining amygdala atrophy. More specifically, patients with decreased recognition of sadness showed gray matter loss in the medial area and a smaller, more lateral loss, in the dorsal part of the right postcentral gyrus and in the medial right amygdala. In contrast, amygdala gray matter volume did not correlate with the quality of emotion recognition in the study of Ibarretxe-Bilbao *et al.* (2009).

The effect of dopaminergic medication on amygdala activation during an emotional facial matching task was evaluated in the study of Delaveau *et al.* (2009). Under placebo conditions, amygdala was activated, whereas this activation was disrupted after levodopa administration both in PD patients and healthy subjects. This study showed a detrimental levodopa overdose effect for normal activation of the amygdala.

## DISCUSSION

The present study integrates various bodies of research, including changes in amygdala and emotionality in patients with PD. Basically, two research streams may be distinguished: research focusing on volumetric changes relating to atrophy of brain structures in PD and research focusing on differences in activation of amygdala under various conditions. Aside from observed changes in amygdala volumes, changes in binding potentials, functional connectivity, regional homogeneity and regional cerebral blood flow have also been shown to have an impact on various realms of emotionality in people with PD.

Interestingly, some effects of amygdala changes on emotionality in PD were lateralized. When searching for the lateralized functions of amygdala in healthy subjects, the left amygdala is considered to be more involved in detailed emotional information processing and detecting stimulus arousal, while the right amygdala is suggested to be more important for rapid and automatic stimulus detection (Vriend *et al.* 2016). In PD patients, bilateral volume loss was found to be related to the increased depressivity (van Mierlo *et al.* 2015), but in contrast, volume loss only in the left amygdala was found to be related to the increased anxiety (Vriend *et al.* 2016). We may speculate about a possible lateralized effect of volume loss in amygdala in developing anxiety and depressivity in PD patients. Future research should explore how volume loss in the left and right amygdala participates in the development of anxiety and depression in PD patients and whether atrophy in the left and right amygdala may also be responsible for the disturbed evaluation of subjective experience in terms of valence or arousal.

Some reviewed results indicated that the activation of amygdala is disturbed in PD patients when evaluating negative affective stimuli. The study of Yoshimura *et al.* (2005) showed insufficient activation of the amygdala during recognition of fearful facial expressions, but not during evaluation of surprised and neutral facial expressions in comparison to healthy subjects. These results support the hypothesis of bradylimbic affective disturbance in patients with PD (Bowers *et al.* 2006). The evaluation of affective stimuli in terms of their affective meaning may be disturbed in PD patients because of insufficient activation of the amygdala during emotion recognition. This deficit in activation of amygdala was also found during recognition of fear, i.e. during evaluation of negative affective stimuli. This finding is in line with the hypothesis of Bowers *et al.* (2006) suggesting muted reactivity of amygdala to aversive stimuli. The reduced amygdala response during the perceptual processing of negative affective stimuli, i.e. angry and fearful faces, was also found in the study of Tessitore *et al.* (2002).

In contrast, incongruent results were found in research focusing on the role of amygdala volume loss

in emotion recognition in PD patients. Baggio *et al.* (2012) reported the impaired recognition of sadness in association with gray matter loss in the right amygdala. However, amygdala gray matter volume did not correlate with the quality of emotion recognition in the study of Ibarretxe-Bilbao *et al.* (2009). Future research is needed in this field.

The role of dopaminergic medication on amygdala activation is a big question in research focusing on changes in emotionality in PD. Some studies have indicated that dopaminergic medication disrupted the functions of amygdala both in PD patients and healthy subjects (Delaveau *et al.* 2009). A detrimental dopaminergic overdose effect for the normal activation of amygdala should be taken into account when interpreting results, including the impact of amygdala changes on emotionality in patients suffering from PD.

This review has some limitations to be addressed. First, our search was limited to Web of Science and PubMed databases and included only articles written in English. Second, we only discussed the role of amygdala on emotional processes, whereas other neuroanatomic systems are likely to be involved as well. Another limitation is that we did not take into account the genetic phenotypes of PD and the possible differences between the phenotypes of PD patients (see e.g. Fiala *et al.* 2010)

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