Neurobiological correlates of emotional processing in Parkinson's disease

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Review article

Neurobiological correlates of emotional processing in Parkinson's disease: A systematic review of experimental studies

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ABSTRACT

Deficits in emotional processing in patients with Parkinson's disease (PD) have received increasing interest over the past decades. In this systematic review, we present the results of 18 behavioral studies that have examined the neurobiological base of emotional processing in PD. Multiple aspects of emotional processing have been studied, using a variety of research methods. Deficits in PD are mainly related to autonomic and perceptive processing of intense emotional stimuli, which is accompanied by structural and functional neurobiological abnormalities in predominantly ventral regions of affective neurocircuitry. These structures are more strongly dependent on dopaminergic neurotransmission than the dorsal structures of affective neurocircuitry, which are more related to the cognitive and regulatory aspects of emotion and appear to remain largely intact in PD patients. Considering the importance of active dopaminergic neurotransmission, PD can serve as a prolific model for studying the neurobiological correlates of normal human emotional behavior as well as psychiatric disorders such as anxiety, depression, and apathy. Moreover, the fact that PD patients are able to cognitively regulate or modulate their emotional responses despite reduced dopamine supplies, can have important implications for the treatment of affective disorders not only in PD patients but in the general population likewise.

1. Introduction

Non-motor manifestations in Parkinson's disease (PD) have been the focus of a growing number of scientific studies over the past decades. Apart from the characteristic motor symptoms such as tremor, hypokinesia, rigidity, and postural instability, PD patients frequently suffer from psychopathological syndromes, including affective disorders, cognitive deterioration, sleep disturbances and hallucinations [1]. Moreover, several studies have shown that these non-motor symptoms affect the quality of life of PD patients to a greater extent than the motor symptoms and have a negative impact on the prognosis of the disease [2–5].

Even in the absence of clinical disturbances in mood and motivation, patients with PD encounter difficulties in generating and experiencing emotions. For instance, they often have difficulties in interpreting emotions in facial expressions [6–9], which may affect interaction with other people. Considering the disease-related neurological damage to the dopaminergic systems, which are thought to be critical in the processing of emotions [10], the possibility of a more extended emotional deficit in PD patients was raised. Experimental studies on this topic find rather mixed results. Several studies reported altered emotional functioning in PD patients ([11]; [12,13].), whereas other studies do not [14,15]. Moreover, some studies report modality-specific deficits instead of a general dysfunction of emotional processing in PD patients [11,13,16], which suggests the possible involvement of multiple neural substrates.

The present review aims to expand our understanding of the neurobiological base of emotional processing in PD by providing a systematic overview of experimental studies that have incorporated both behavioral and neurobiological correlates (e.g., brain activity, structural volume, sympathetic arousal).

2. Methods

2.1. Search strategy

A systematic literature search was conducted in PubMed and PsycINFO, which was extended with searches of references listed in the reviewed papers. The entire timescale was used, which comprised all literature between 1965 and March 2017 (included). There were no

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Box 1
Search strategy.

Search terms	
PubMed	Parkinson*(title/abstract) OR Parkinson's disease (MeSH) AND (emotion* OR facial* OR arousal OR prosody OR subjective*) AND Humans (MeSH) NOT "review"(filter)
PsycINFO	Parkinson*[title/abstract] AND (emotion* OR facial* OR arousal OR prosody OR subjective*)

language restrictions. Animal studies were excluded. Our search resulted in a total of 4022 articles (without duplicates). For an overview of the Medical Subject Headings and free text words that were used in the search strategy, see Box 1.

2.2. Selection of studies

Papers were selected according to the following inclusion criteria: i) patients were diagnosed with idiopathic Parkinson's disease ii) emotional processing, measured in a behavioral task was the main outcome iii) the study included a neurobiological measure of emotional processing, iv) data analyses incorporated both the behavioral and neurobiological measurements of emotional processing. Papers dealing with the emotional effects of deep brain stimulation (DBS) or ablative brain surgery (e.g., pallidotomy, thalamotomy) were excluded from the present review. We only included papers from completed studies, hence papers reporting on interim analyses were excluded.

The abstracts from all 4022 articles were screened by two authors (AM and AW) based on the above-mentioned criteria. Full copies were screened from articles that could not be classified by abstract or title alone. All potential relevant articles were read in full and screened by two authors (AM and AW). In case of discrepancies between the two authors, consensus was reached after discussion, or by consulting a third author (AL) who made the final decision.

For the selection process the authors followed the guidelines from the PRISMA statement (Preferred Reporting of Systematic reviews and Meta-analyses; [17]). Fig. 1 illustrates the PRISMA Flow Diagram, which summarizes each step in the selection process (see Appendix A for the PRISMA checklist). From the 4022 papers, 3974 could be excluded after reading the title and abstract alone. Further screening for eligibility resulted in 17 studies that were included for extensive review. One additional study was included after checking the reference lists of the included papers.

2.3. Quality assessment

At present, there is no 'gold standard' available for assessing the quality of non-randomized quasi-experimental research. We therefore combined items from two checklists [18,19] that have been systematically reviewed [20]. We selected the items that specifically rated descriptive, statistical and internal validity, leaving out those items that were not relevant for our study (e.g., items on specific pharmaceutical issues). We then expanded our selection with four additional items from the STROBE statement, concerning study design, statistical interpretation of data, and power calculation [21]. Items were scored as either good (2), moderate (1), or inadequate/undefined (0), which enabled us to compare the quality of included studies mutually, despite the fact that we combined items from different checklists. The full checklist is included as supplementary material (Appendix B).

Two authors (AM and AW) reviewed the methodological quality of the included studies according to the selected items. In case of disagreement, consensus was reached after discussion, or by consulting a third author (AL) who made the final decision.

3. Results

3.1. Study characteristics

The literature search resulted in 18 articles that were included for further review. All studies investigated emotional processing in patients with Parkinson's disease (PD) at a neurobiological level. Table 1 illustrates the characteristics and outcomes of the included studies. All studies were cross-sectional. They varied widely in experimental paradigms with multiple aspects of emotional processing being researched. A total of 11 studies investigated facial emotion recognition, 3 studies measured physiological arousal, 2 studies looked at emotional prosody recognition, and 2 studies used a multimodal audio-visual approach. Seven studies measured neurobiological correlates of emotional processing by using electro-encephalogram (EEG) and measuring the event-related potentials (ERP) or spectral modifications (1 study), 6 used blood-oxygen-level dependent functional magnetic resonance imaging (BOLD-fMRI), 2 used structural magnetic resonance imaging (MRI), 2 used positron emission tomography (PET), and 1 used single photon emission CT (SPECT).

3.2. Methodological quality

Table 2 shows that the methodological quality varied among the included studies and remained fairly stable over time. The mean quality score was 26,1 (range 11–32) out of 36, with the majority of scores lying above 20. Studies with a lower quality score poorly described their sample, design and outcomes and their subject groups were not adequately matched in terms of age, sex and education. Sample sizes ranged from 9 to 39 and none of the studies included a formal sample size calculation. Moreover, 8 studies did not report any indicators for strength of evidence and 14 studies lacked adequate adjustment for important confounding factors such as dopaminergic or psychiatric medication, disease severity, or presence of psychiatric disorders. However, the majority of the studies clearly specified their aim, sample characteristics, experimental design and outcomes, and provided extensive and clear interpretations of the reported findings. Given the limited number of included studies we decided not to exclude studies on the basis of an arbitrary cut-off on the quality score.

In the next section, the main results for each modality of emotional processing will be discussed. Per modality results are further subdivided by research method and are presented chronologically.

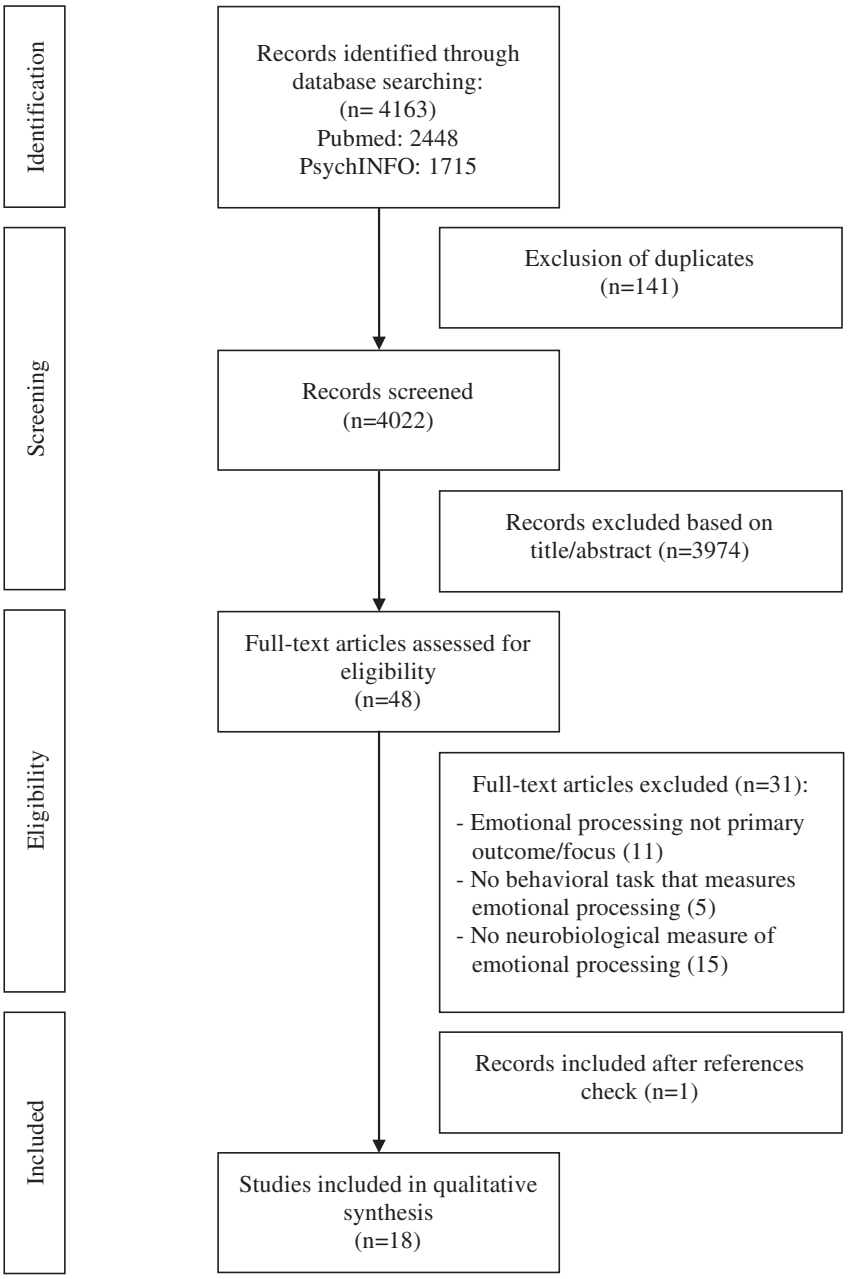

Fig. 1. PRISMA Flow Diagram of search strategy.

3.3. Facial emotion recognition (FER)

3.3.1. Functional imaging (fMRI)

Tessitore et al. [22] conducted a blocked fMRI-experiment in which 9 early PD patients under dopamine replacement therapy (DRT) and 9 matched healthy controls had to match angry and fearful facial expressions. Despite equal task performances, the robust bilateral amygdala response found in healthy subjects was absent in PD patients who were temporarily depleted from DRT. After dopamine repletion, the amygdala response was partially restored, yet remained diminished compared to the healthy subjects, which indicates that reduced dopamine availability in the amygdala is associated with functional processing deficits for emotional facial expressions.

Lotze et al. [23] reported that in their sample of 9 early to advanced PD patients, assessed during their *off* state, patients showed more errors than 9 age-matched healthy controls in an emotion recognition task (i.e., emotional vs. neutral gestures, faces included. In addition, PD patients showed decreased functional activity for observing emotional gestures in the left ventrolateral prefrontal cortex (VLPFC) and right superior temporal sulcus (STS). Additional PET scanning quantified less striatal dopamine transporter availability (DAT) in PD patients compared to healthy controls, with a specific association between reduced DAT in the left putamen and more severe motor impairment as well as more recognition errors in PD patients. Moreover, left putaminal DAT appeared to be positively correlated with left VLPFC activity, which indicates how disturbed dopaminergic neurotransmission can affect functional activity in this area during emotional gesture recognition. However, these patients were not re-assessed during their *on* state, hence the influence of levodopa treatment remains unknown here.

Delaveau et al. [24] further investigated the role of dopaminergic modulation in FER in a sample of 14 non-depressed PD patients, treated with levodopa, and 13 non-matched healthy controls. In non-depressed PD patients, the dopaminergic mesolimbic pathway appears to be relatively intact. Hence, DRT as treatment for motor symptoms may overdose these intact limbic regions and consequently disrupt normal amygdala functioning, as shown previously in healthy subjects [25].

Table 1
Characteristics of studies on neurobiological correlates of emotional processing in Parkinson's disease. Chronologically ordered.

Authors	Sample	Disease duration; H & Y	Levodopa	Psychiatric drugs	Anxiety a/o depression	Cognition	Emotional stimuli	Experimental paradigm	Behavioral outcome	Neurobiological measurement	Results
Facial emotion recognition											
Tessitore et al. [22]	9 PD; 9 HC	ND; Stage 1, 2	Yes	Yes	No	No	Static faces; A, F	Ekman 60 faces test; blocked design (2 Emo/ 3 non-Emo); pseudo-randomized	Matching; RT	BOLD fMRI: Whole brain; ROI (amygdala)	FER: PD (*on & off*) = HC; RT: PD (*on & off*) = HC; fMRI: No bilateral amygdala response in PD (dopa *off*); partially restored in dopa *on*; overall PD < HC
Yoshimura et al. [28]	9 PD; 10 HC	ND; Stage 2, 3	Yes	ND	Yes	No	Static faces; F, Sa, Neu	4–6 sessions: each 150 photos of FE performed by actors; randomized	Discrimination; RT	EEG: ERP; ECD; SSB/DT	FER: PD = HC; RT: PD = HC; EEG: FER (F) parietal cortex activity in PD vs. amygdala and temporal cortex activity in HC
Delaveau et al. [24]	14 PD; 13 HC	11 ± 4.4; *on*: 2 ± 0.9 *off*: 3 ± 0.8	Yes	Yes	Yes	Yes	Static faces; A, F	KDEF; blocked design (7 Emo/7 non-Emo); pseudo-randomized	Matching	BOLD fMRI: Whole brain; ROI (amygdala)	FER: PD = HC; fMRI: PD & HC: Decreased R amygdala activity in dopa *on* vs. placebo
Ibarretxe-Bilbao et al. [30]	24 PD; 24 HC	3 ± 1.6; 1.7 ± 0.4	Yes	No	Yes	Yes	Static faces; A, F, Sa, D, H, S	Ekman 60 faces test; 10 pictures per emotion	Categorization	Structural MRI: VBM ROI (amygdala, OFC)	FER: PD < HC for all emotions (not H) VBM: PD < HC R amygdala and bilateral OFC; PD: OFC GM volume and FER accuracy (+)
Lotze et al. [23]	9 PD; 9 HC	13 ± 4.8; Stage 1–4	Yes (*off* PET/fMRI)	ND	Yes	Yes	Dynamic Emo and non-Emo gestures (face and upper body)	30 video clips: Emo vs. non-Emo gestures; pseudo-randomized	Categorization; Valence (Likert)	BOLD fMRI: Whole brain PET: DAT (ROI putamen)	Valence: PD = HC; Accuracy: PD < HC; fMRI: PD < HC L VLPFC and R STS; PET: PD < HC DAT L putamen; Accuracy and striatal DAT (−); L VLPFC activity and striatal DAT (+)
Delaveau et al. [26]	14 PD; 13 HC	11 ± 4.4; *on*: 2 ± 0.9 *off*: 3 ± 0.8	Yes	Yes	Yes	Yes	Static faces; A, F	KDEF; blocked design (7 Emo/7 non-Emo); pseudo-randomized	Matching	BOLD fMRI: Mask DMN	FER: PD = HC; fMRI: PD < HC posterior DMN (placebo); largely restored in dopa *on*
Baggio et al. [31]	39 PD; 23 HC	6 ± 3.8; 1.8 ± 0.5	Yes	ND	Yes	Yes	Static faces; A, F, Sa, D, H, S	Ekman 60 faces test; 10 pictures per emotion	Categorization	Structural MRI: VBM; DTI (WM integrity: FA)	FER: PD < HC (Neg); VBM: PD < HC R OFC, R amygdala, R PCG, SC, ACC; FA: PD < HC R IFOF; PD: GM volume and A, D, S (+); PD: FA IFOF, CC, ILF and S (+)
Nakajima et al. [32]	11 PD; HC: ND	6 (no SD); 2 (no SD)	Yes	ND	Yes	Yes	Static faces: A, Sa, H, Neu	Morphed faces; 96 images	Matching	SPECT: 3D–SSP	FER: PD < HC (A, H); SPECT: hypoperfusion in occipital lobe in PD; FER (H) and CBF R occipital lobe (−)
Wieser et al. [29]	18 PD; 17 HC	5 ± 4.0; Stage 1–3	Yes	No	Yes	Yes	Static faces; A, F, Sa, D, H, Neu	KDEF: recognition task (36 faces); passive viewing (2 × 212 faces)	Categorization; Valence (Likert); Arousal (Likert)	EEG: ERP (P100, N170, EPN, LPP)	FER: PD = HC; Valence/Arousal: PD = HC; EEG: PD < HC early vs. intact late processing
Robert et al. [33]	36 PD	12 ± 4.0; ND	Yes	Yes	Yes	Yes	Static faces; A, F, Sa, D, H, Neu	Ekman 60 faces test; randomized	Categorization	^{18}FDG PET (resting state)	FER and Apathy scores (−) Apathy and metabolism: L PCC (+); FER and metabolism: precuneus, IOG (+); PCC, SFG, both bilaterally (−)
Wabnegger et al. [27]	17 PD 22 HC	6 ± 3.6; Stage 2, 3	No	No	Yes	Yes	Static faces; A, F, Sa, D, Neu	KDEF; blocked design (50 faces, 10 per emo); pseudo-	Intensity rating (Likert); Categorization	BOLD fMRI: Whole brain; ROI (amygdala,	Intensity: PD = HC except for S (PD > HC); Accuracy: PD = HC; fMRI: PD < HC (S) R putamen, R

(continued on next page)

Table 1 *(continued)*

Authors	Sample	Disease duration; H & Y	Levodopa	Psychiatric drugs	Anxiety a/o depression	Cognition	Emotional stimuli	Experimental paradigm	Behavioral outcome	Neurobiological measurement	Results
								randomized		insula, OFC, IFG, SSC I + II, IPC)	IFG; PD > HC (A, S) R SSC-II, (D, S) L SSC-II, (D) R IPL, (F) L IPL; SSC-II and F intensity, D (+); IPL and A intensity (+)
Physiological arousal											
Wieser et al. [35]	14 PD; 14 HC	7 ± 4.3; Stage 1–3	Yes	ND	Yes	No	Static pictures Neg Pos Neu	IAPS (702 pictures); RVSP paradigm (high vs. low arousal)	Valence (Likert); Arousal (Likert)	EEG: ERP (EPN)	Valence: PD = HC; Arousal (Neg): PD < HC; EEG: PD = HC early processing
Dietz et al. [36]	17 PD; 16 HC	7 ± 4.3; Stage 2, 3	Yes	Yes	Yes	No	Static pictures Neg Pos Neu	IAPS (72 pictures); 2 series of 72 pictures with inter-trial fixation	Valence (Likert); Arousal (Likert)	EEG: ERP (P100, N150, P250, EPN, LPP)	Valence: PD = HC; Arousal (Neg): PD < HC; EEG: PD = HC early vs. PD < HC late processing; LPP and apathy (−)
Schienle et al. [39]	17 PD 22 HC	6 ± 3.6; Stage 2, 3	No	No	Yes	Yes	Static pictures D, F, Neu	QADS; blocked design (10 disgust/10 fear, 10 neu); pseudo-randomized	Intensity rating (Likert)	BOLD fMRI: Whole brain; ROI (amygdala, insula, DLPFC, VLPFC, BG)	Intensity: PD = HC; fMRI: PD = HC (D); PD < HC (F) R pallidum
Emotional prosody recognition											
Schroder et al. [40]	14 PD; 14 HC	5 ± 5·5; Stage 1, 2	Yes	ND	Yes	Yes	Name; Sa, H, Neu	400 words: target (Name) vs. non-target stimuli; pseudo-randomized	Passive/Active listening: Categorization; RT	EEG: ERP (MMN; P3b)	Accuracy: PD < HC (Sa, H) RT: PD = HC EEG passive: PD < HC early processing (S); EEG active: PD < HC P3b (H)
Garrido-Vásquez et al. [41]	10 LPD; 12 RPD; 22 HC;	LPD 6 ± 4.6; Stage 1–3; RPD 6 ± 3.6; Stage 1–4	Yes	ND	Yes	Yes	Sentences/ pseudo speech; A, D, F, H, Neu	160 Emo/160 non-Emo sentences (50% pseudo speech); pseudo-randomized	Categorization	EEG: ERP (P200)	Accuracy: LPD = RPD = HC EEG: LPD < RPD < HC early processing (A, D, H)
Multimodal approach											
Yuvaraj et al. [42]	20PD; 30HC	6 ± 3.5; Stage 1–3	Yes	ND	Yes	Yes	Audio-visual clips F, Sa, D, A, S, H; Static pictures Neu	IAPS (108 pictures); IADS (47 sounds); 30 video clips; Blocked design with rating intervals.	Categorization; Valence (Likert); Arousal (Likert)	EEG frequency bands (α, β, δ, γ, θ); inter-hemispheric coherence	Accuracy: PD = HC Valence/Arousal: PD = HC EEG: PD < HC decreased inter-hemispheric connectivity (Neg emo; all but δ)
Yuvaraj et al. [43]	20PD; 30 HC	6 ± 3.5; Stage 1–3	Yes	ND	Yes	Yes	Audio-visual clips F, Sa, D, A, S, H; Static pictures Neu	IAPS (108 pictures); IADS (47 sounds); 30 video clips; Blocked design with rating intervals.	Categorization; Valence (Likert); Arousal (Likert)	EEG frequency bands (α, β, δ, θ); inter- and intra-hemispheric	Accuracy: PD = HC Valence/Arousal: PD = HC EEG: PD < HC overall decreased electrical activity; RH > LH activity (emo): PD < HC; Ant = Post activity (emo): PD < HC (α)

Legend: -, negative correlation; +, positive correlation; 18FDG PET, 18fluorodeoxyglucose positron emission tomography; 3D–SSP, three-dimensional stereotactic surface projection; A, anger; ACC, anterior cingulate cortex; Ant, anterior; BG, basal ganglia; BOLD fMRI, blood oxygenation level-dependent functional magnetic resonance imaging; CBF, cerebral blood flow; CC, corpus callosum; D, disgust; DAT, dopamine transporter availability; DLPFC, dorsolateral prefrontal cortex; DMN, default mode network; Dopa, dopaminergic drugs; DTI, diffusion tensor imaging; ECD, equivalent current dipole; EEG, electroencephalography; Emo, emotional; EPN, early posterior negativity; ERP, event-related potential; F, fear; FA, fractional anisotropy; FE, facial expression; FER, facial emotion recognition; GM, grey matter; H, happiness; HC, healthy controls; H & Y, Hoehn & Yahr; IADS, International Affective Digitized Sounds; IAPS, International Affective Picture system; IFG, inferior frontal gyrus; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; IOG, inferior occipital gyrus; IPC, inferior parietal cortex; IPL, inferior parietal lobule; KDEF, Karolinska Directed Emotional Faces set; L, left; LH, left hemisphere; Likert, Likert scale; LPD, PD subgroup with left-sided motor symptoms; LPP, late positive potential; MMN, mismatch negativity; MRI, magnetic resonance imaging; ND, no data; Neg, negative; Neu, neutral; Non-Emo, non-emotional; OFC, orbitofrontal cortex; *off*, off dopa condition; *on*, on dopa condition; PCC, posterior cingulate cortex; PCG, post central gyrus; PD, Parkinson's disease; PET, positron emission tomography; Pos, positive; Post, posterior; QADS, questionnaire for the assessment of disgust sensitivity; R, right; RH, right hemisphere; RPD, PD subgroup with right-sided motor symptoms; ROI, region of interest; RT, reaction time; RVSP, rapid serial visual presentation paradigm; S, surprise; Sa, sadness; SC, subgenual cortex; SD, standard deviation; SFG, superior frontal gyrus; SPECT, single photon emission CT; SSB/DT, scalp-skull-brain/dipole tracing; SSC-I, primary somatosensory cortex; SSC-II, secondary somatosensory cortex; STS, superior temporal sulcus; VBM, voxel-based morphometry; VLPFC, ventrolateral prefrontal cortex; WM, white matter.

Table 2
Checklist methodological quality of included quasi-experimental studies.

Items	Author/Year																	
	Tessitore et al. [22]	Yoshimura et al. [28]	Schroder et al. [40]	Wieser et al. [35]	Delaveau et al. [24]	Ibarretxe-B. et al. [30]	Lotze et al. [23]	Delaveau et al. [26]	Baggio et al. [31]0	Nakajima et al. [32]	Wieser et al. [29]	Dietz et al. [36]	Garrido-V. et al. [41]	Yuvaraj et al. [42]	Yuvaraj et al. [43]	Robert et al. [33]	Wabnegger et al. [27]	Schienle et al. [39]
Reporting																		
Hypothesis/aim/objective clearly described[1]	2	2	2	2	2	2	2	2	2	1	2	2	2	1	2	2	2	2
Main outcomes clearly described in Introduction/Methods[1]	2	2	2	2	2	2	1	2	2	1	2	2	2	1	2	2	2	2
Subject characteristics clearly described[1]	1	0	2	2	1	2	1	1	2	0	2	2	2	2	2	1	2	2
Description study design[3]	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	1
Description/explanation for drop-outs[2]	2	2	2	2	2	2	2	2	2	0	2	2	2	2	2	2	2	2
Main findings clearly described (not statistically)[1]	2	1	2	2	2	2	1	2	2	0	2	2	2	1	1	1	2	2
Statistical methods clearly described (confounding incl.) [2]	2	1	1	1	2	2	1	1	2	1	2	2	2	1	1	2	2	2
Actual probability values reported for main outcomes[1]	0	0	1	1	2	2	1	1	2	2	2	1	1	2	2	1	2	2
Comparability																		
Comparison (control) group included[2]	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	0	2	2
Adequate group matching[2]	2	0	2	2	0	2	1	0	1	0	1	0	2	1	1	NA	1	1
Presentation and analyses of data																		
Appropriate statistical tests[1]	2	2	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2
Adequate adjustment for confounding[1]	1	0	0	0	1	2	0	1	2	0	1	2	0	0	1	2	1	1
All comparisons involve the same number of subjects[2]	1	2	2	1	1	1	1	1	0	0	1	1	1	1	1	1	1	1
Descriptive	2	1	2	2	2	2	2	2	2	1	2	2	2	2	2	2	2	2

(continued on next page)

Table 2 *(continued)*

Items	Author/Year																
	Tessitore et al. [22]	Yoshimura et al. [28]	Schroder et al. [40]	Wieser et al. [35]	Delaveau et al. [24]	Ibarretxe-B. et al. [30]	Lotze et al. [23]	Delaveau et al. [26]	Baggio et al. [31]0	Nakajima et al. [32]	Wieser et al. [29]	Dietz et al. [36]	Garrido-V. et al. [41]	Yuvaraj et al. [42]	Yuvaraj et al. [43]	Robert et al. [33]	Wabnegger et al. [27]	Schienle et al. [39]
measures identified[2]																		
Unplanned sub analyses explained[1]	1	2	2	2	2	2	2	2	2	0	2	2	2	2	2	2	2	2
Interpretation																		
Appropriate interpretation of findings[3]	2	1	1	2	2	2	1	2	2	1	2	2	2	1	2	2	1	1
Assessment of strength of evidence [3]	0	0	0	1	0	1	0	0	1	1	2	0	1	1	1	0	1	1
Power calculation																		
Appropriate sample size determination[3]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total quality score	26	20	27	28	27	32	22	25	30	11	31	28	29	24	28	24	29	28

Scoring: 0 = inadequate/undefined, 1 = moderate, 2 = good, NA = not applicable. 1 [18], 2 [19], 3 [21]

Delaveau et al. [24] reported that PD patients showed similar right amygdala activation as the controls during a FER task when administered under placebo. However, amygdala activation was indeed abnormal in both groups after administration of levodopa.

In the same population, Delaveau et al. [26] investigated the effect of levodopa on default mode network (DMN) deactivation during the same FER task. Whereas the control group showed the classical deactivation of cortical areas (e.g., medial prefrontal cortex and posterior cingulate cortex), PD patients under placebo did not. However, after levodopa administration, DMN deactivation improved significantly, which again indicates that dopamine levels can modulate brain activation in regions that are essential for perceptual emotional processing.

In a recent fMRI study by Wabnegger et al. [27], 17 mild to moderate PD patients who were depleted from dopaminergic medication prior to testing, showed comparable affective ratings as 22 matched healthy controls when presented with negative (i.e., disgust, anger, fear, sadness) and neutral facial expressions. Region-of-interest analyses revealed increased reactivity in somatosensory regions (all emotions) versus decreased reactivity in the putamen and inferior frontal gyrus (sadness) in PD patients versus controls. The authors speculate about a possible compensatory mechanism that enables intact FER despite striatal deficits. The specific role of dopamine was not further investigated in this study as patients were only assessed in their *off*-state.

3.3.2. Event-related potentials (ERP)

Yoshimura et al. [28] studied FER by measuring ERPs in a sample of 9 mild to moderate PD patients under DRT and 10 non-matched healthy controls. Although PD patients performed the task equally well as healthy controls, the ERP results showed that PD patients appeared to use different neural substrates for recognizing emotions in fearful facial expressions. More specifically, 7 out of 10 healthy subjects showed an increase in initial negative response (N1) of which the equivalent current dipoles were concentrated in the amygdala. In PD patients, on the other hand, N1 was centered bilaterally in the angular gyrus and supramarginal gyrus, and notably there was no neuronal activity in the amygdala. One could however question whether localization of generators with a dipole fit is suitable to identify activity in subcortical structures.

In a more recent ERP study by Wieser et al. [29], emotional recognition accuracy and affective ratings of facial expressions were again not impaired in a sample of 18 mild to moderate PD patients under DRT. The authors did, however, find indirect evidence for diminished early visual discrimination of emotional facial expressions in PD, as reflected by the lack of increased early posterior activity in occipital regions that was present in 17 matched healthy controls. Yet, late cortical evaluative processing seemed to be intact, as PD patients showed no deficits in late components of the ERPs (i.e., late positive potentials) localized in parietal regions. The authors point to possible compensatory effects by appealing to other cortical regions, such as somatosensory and prefrontal areas, in order to successfully discriminate emotional facial expressions. They further hypothesize that the disturbed early perceptual processing of emotional facial expressions may be due to dopaminergic dysfunction in striato-thalamo-cortical circuits, which may evolve into a broader emotional deficit in more advanced stages of the disease.

3.3.3. Structural imaging (MRI)

Ibarretxe-Bilbao et al. [30] found that 24 early PD patients under DRT scored significantly lower than 24 matched healthy controls in recognizing facial expressions for all basic emotions except happiness (i.e., fear, anger, sadness, surprise and disgust). In addition, voxel-based morphometry (VBM) region of interest analyses of grey matter (GM) volume revealed that PD patients showed significant GM volume loss in the right amygdala and bilateral OFC compared to healthy subjects. Interestingly, after correcting for total GM volume, a strong positive correlation between total FER performance in patients and OFC volume

became apparent.

In a more recent structural imaging study by Baggio et al. [31], 39 early PD patients under DRT performed significantly worse than 23 age-matched healthy controls in recognizing negative facial expressions (i.e., fear, anger, disgust, sadness). VBM analyses further showed positive correlations between recognition accuracy and GM volume in the right OFC, amygdala, and dorsal postcentral gyrus for sadness; in the right fusiform gyrus, ventral striatum, and subgenual cortex for anger; and in the dorsal anterior cingulate cortex (ACC) for disgust identification. In addition, diffusion tensor imaging (DTI) data revealed a positive correlation between sadness identification and white matter density in the right frontal lobe, of which the latter was significantly reduced in PD patients.

3.3.4. Single photon emission CT (SPECT)

Nakajima et al. [32] used SPECT in order to investigate brain perfusion in structures related to FER deficits in early to advanced PD. A sample of 11 PD patients under DRT performed worse than healthy subjects (sample size not reported) in recognizing angry and happy faces. The authors reported reduced cerebral blood flow in the occipital lobe in PD patients compared to healthy controls. However, results of this study were difficult to interpret due to incomplete description of subject characteristics, statistical methods, and their main findings (see Table 2).

3.3.5. ^{18}Fluorodeoxyglucose positron emission topography (^{18}FDG PET)

Robert et al. [33] investigated the relation between severity of apathy and FER impairment in a sample of 36 early PD patients under DRT. Apathy scores appeared to be negatively correlated to overall FER performance, irrespective of emotional category. Furthermore, ^{18}FDG PET measurements showed that severity of apathy was positively correlated with increased activity in the left posterior cingulate gyrus (PCG), whereas FER impairment was correlated with low metabolic activity in the bilateral posterior cingulate cortex and the superior frontal gyrus. Conjunction analysis revealed the involvement of the right premotor cortex, right OFC, left middle frontal gyrus, and left PCG in both networks, supporting the association between apathy and FER impairment. However, as these results are based on correlation analyses only, they will need to be verified by group comparisons between PD patients with and without apathy (Kathy [34]).

3.4. Physiological arousal

3.4.1. ERP

Wieser et al. [35] measured physiological arousal in response to a wide range of emotional and neutral pictures in 14 mild to moderate PD patients under DRT and 14 matched healthy controls. Patient subjective ratings revealed a blunted emotional response for highly arousing negative pictures. In contrast, ERP data showed that the early perceptual stages of emotional information processing did not differ between PD patients and healthy controls, as reflected by similar early posterior parietal-occipital negativity. The results indicate that PD patients can adequately receive input regarding visual emotional stimuli, but experience highly arousing stimuli at the behavioral level as less intense than healthy controls.

In a more recent ERP study, Dietz et al. [36] found similar results in a sample of 17 mild to moderate PD patients under DRT. Patients again appeared to be less sensitive to highly arousing negative pictures (i.e., lower arousal ratings) compared to 16 significantly older healthy controls. Moreover, although emotionally arousing pictures usually elicit an increase in amplitude in late positive potentials (LPPs) [37,38], in PD this modulation was only present in response to positive pictures (compared to neutral) and not for negative pictures. Interestingly, higher levels of apathy appeared to be associated with reduced centro-parietal LPP modulation in response to negative pictures. This finding implies that emotional dysfunction may only be apparent in the presence of a certain degree of apathy. Early occipital and frontal components of emotional processing were not impaired in PD patients, a finding that is in line with the results from Wieser et al. [35].

3.4.2. fMRI

Schienle et al. [39] performed a blocked fMRI-experiment in which 17 mild to moderate PD patients, who had stopped their anti-parkinsonian medication prior to testing, and 22 matched healthy controls were presented with pictures depicting negative (i.e., disgust and fear) and neutral scenes. The groups did not differ in their self-reports for disgust proneness and trait anxiety and showed similar affective ratings. Although the authors searched for amygdala abnormalities as the underlying mechanism for reduced reactivity to negative stimuli in PD, this hypothesis could not be verified by their results. They only found a group difference for the right pallidum, which showed higher activity for fearful stimuli in healthy controls. This finding was allocated to disease-related grey matter volume reductions in the basal ganglia, rather than to emotional processing deficits.

3.5. Emotional prosody recognition

3.5.1. ERP

Schroder et al., [40] investigated the concept of emotional prosody (i.e., recognizing the emotional content of spoken language) in 14 mild PD patients under DRT and 14 matched healthy controls. They measured early and late ERP components of vocal emotion processing during an oddball experiment in which subjects had to categorize the emotional prosody of each target word (i.e., happy, sad, neutral). PD patients made more errors than healthy controls in recognizing sadly spoken words in a vocal emotional processing experiment. In addition, early ERP components showed disturbed preattentive processing of sad words, whereas late ERP components showed reduced reactivity in response to happy words. The authors point to striatal dopamine deficiency as a possible explanation for the impaired early preattentive processing of emotional prosody.

A more recent ERP study by Garrido-Vásquez et al. [41] elaborated on this hypothesis by focusing on a possible functional lateralization of the striatum in processing affective vocal stimuli. The PD sample consisted of 10 PD patients with predominantly left-sided (LPD) and 12 PD patients with predominantly right-sighted (RPD) motor symptoms (all mild to moderate and under DRT), and 22 matched healthy controls. Contrary to Schroder et al., [40], PD patients performed equally well compared to healthy controls in categorizing different vocal emotions, although sad sounds were not included here. Data from early ERP components showed deviated ERP patterns (i.e., no P200 reduction) in LPD patients for almost all emotional categories. RPD patients and healthy controls showed no such deficit, which suggests that especially right striatal neurodegeneration might affect emotional prosody recognition.

3.6. Multimodal approach

3.6.1. Electro-encephalogram (EEG)

Yuvaraj et al. [42,43] performed an EEG power analysis in different frequency bands in 20 mild to moderate PD patients under DRT and 30 matched healthy controls who were presented audio-visual emotionally arousing stimuli. Subjective ratings of the valence and intensity of emotional stimuli did not differ between groups, nor was there a difference in recognition performance. EEG results revealed that both groups showed greater right than left hemisphere activity during emotional processing, yet patients showed an overall reduction of EEG power across all 6 basic emotions compared to healthy controls [42]. In addition, PD patients showed reduced interhemispheric functional connectivity for negative emotions [43].

4. Discussion

In this paper we systematically reviewed the evidence base of changes in emotional processing and its neurobiological correlates in patients with Parkinson's disease (PD). The included studies have investigated multiple aspects of emotional processing in PD such as facial emotion recognition, physiological arousal, and emotional prosody. In the majority of studies, PD patients showed no behavioral deficits in the ability to accurately recognize and respond to emotional stimuli [22,24,26–29,39,41–43]. However, some studies did find impairments [23,30,31,35,40], and these overall inconsistencies are probably related to the large differences in sample characteristics and study designs, as well as on the specific aspect or phase of emotional processing that was measured.

Measurements of both structural and functional correlates of emotional processing have provided direct and indirect evidence for the involvement of a number of brain structures, including the orbitofrontal cortices, amygdala, anterior cingulate cortices, and the basal ganglia ([22,24]; Ibarretxte-Bilbao et al., 2009; [23,26,27,31,39]). Moreover, studies that used a dopaminergic intervention highlighted the importance of disrupted dopamine neurotransmission in emotional processing PD [22,24,26]. In addition, ERP recordings showed that certain cortical processing stages were impaired in PD during emotional processing, whereas others were still intact [29,35,36,40,41] or may even have switched to alternative brain regions [28]. Which processing stages are affected was largely dependent on the experimental paradigm. Emotional processing deficits were not restricted to either positive or negative emotions, which again strongly depended on the type of stimuli or emotion investigated. It seems safe though to conclude that in general, emotional processing deficits in PD are related to highly arousing stimuli, rather than neutral or low arousing stimuli, independent of the valence of the emotion (positive or negative).

In the next section, the contribution of specific brain structures, mechanisms, and pathways in emotional processing will be described in more detail. In the final section, multiple neuropathological changes related to emotional dysfunction in PD will be incorporated into a theoretical framework on emotional processing in general.

4.1. Amygdala

All studies that investigated the involvement of the amygdala in emotional processing in PD found both structural and functional abnormalities, except for one study [39]. Amygdala volume appeared to be significantly reduced in PD patients [30,31] and functional activity was disturbed in case of decreased dopaminergic input associated with degenerated parts of the nigrostriatal and mesolimbic dopaminergic pathways [22,24]. Amygdala activity in response to emotional stimuli is known to be highly dependent on dopaminergic projections [10] and dopamine repletion can restore these deficiencies and subsequently improve perceptual emotion processing [22]. In case of a novel or threatening stimulus, dopamine is released into the basolateral part of the amygdala, which in turn leads to suppression of prefrontal cortex inhibition [44]. In PD, reduced dopamine projections to the prefrontal cortex prevent the amygdala from being disinhibited and subsequently may decrease its activity in response to intense emotional stimuli [45]. In addition, amygdala projections to structures that mediate physiological levels of arousal, such as the locus coeruleus in the brainstem and the hypothalamus, may be reduced likewise, just as the eventual response to the emotional stimulus [35,36].

4.2. Orbitofrontal cortices

Grey matter (GM) volume of the orbitofrontal cortex (OFC) appeared to be significantly reduced in PD patients, and was shown to be strongly correlated with worse facial emotion recognition [30,31]. These findings are in line with results from both lesion and neuroimaging studies in healthy subjects showing that orbitofrontal cortices were heavily involved in the processing of intense emotional stimuli [46–50]. Moreover, emotion recognition difficulties in PD patients may arise from reduced dopaminergic input from structures that have close interconnections with orbital prefrontal regions, such as the ventromedial caudate nucleus and substantia nigra pars reticulata (SNpr) [51]. As the disease progresses and the dopamine supply to orbital prefrontal regions further declines, PD patients may experience more severe abnormalities in emotional behavior, being particularly problematic for their social environment [52].

4.3. Anterior cingulate circuit

Reduced ventral anterior cingulate cortex (vACC) and subgenual cortex GM volume was related to impaired recognition of negative emotions in PD [31]. Furthermore, reduced striatal dopamine transporter availability (DAT) in the ventral striatum was associated with decreased ventrolateral PFC (VLPFC) activity and impaired emotion recognition in PD patients [23]. Together, these regions operate as an ‘anterior cingulate circuit' in which the ventral regions in particular are heavily involved in the generation of emotional reactions, whereas the dorsal parts control active labeling of emotions and top-down cognitive regulation of the affective state [49,53–55]. Functioning of this circuit is mainly dependent on dopaminergic input and output from the vACC and vLPFC to the ventral striatum [51,56]. The ventral striatum, in turn, innervates the SNpr, ventral pallidum (VP), medial subthalamic nucleus (STN), and the internal section of the globus pallidus (GPi) [51]. Structures within this circuit have close connections to other parts of the limbic system, such as the amygdala, nucleus accumbens, hypothalamus, insula, hippocampus, and OFC [57]. Neuropathological deficits within this circuit, such as reduced dopaminergic neurotransmission or decreased GM volume, both of which are seen in PD, evidently lead to remarkable impairments in emotional functioning. Moreover, the use of DRT in PD has been linked to.

4.4. A neurobiological model for emotional processing deficits in PD

The confrontation with an emotional stimulus encompasses different processes that together generate an appropriate behavioral response. According to Phillips et al. [49], three main processes can be distinguished: 1) identification and appraisal of the emotional relevance of the stimulus; 2) production of a specific affective state and behavior (i.e., physiological arousal and emotional feelings); 3) top-down regulation of the affective state and emotional behavior (Figure 2). In addition, Ochsner and colleagues (2007) proposed an interaction between bottom-up emotional subcortical appraisal systems and top-down cortical cognitive control processes that eventually results in the production of an emotional response that is appropriate in terms of significance and context.

Although a number of studies included in this review provide clear evidence for impaired autonomic emotional response generation, the more active identification and conscious labeling of emotions at the behavioral level is not necessarily disturbed likewise. The neurobiological models on emotional processing as described above may provide an explanation for this discrepancy [49,54,55], as they link the different aspects of emotional processing to the involvement of two separate neural systems: a ventral and dorsal system. Here, specific parts of a predominantly ventral system are critical for perceiving emotions and generation of an appropriate behavioral emotional response. These regions include the amygdala, ventral striatum, ventral ACC, OFC, and VLPFC, as well as regions that receive input from the aforementioned structures, such as the hypothalamus and locus coeruleus. On the other hand, the more dorsal regions, including the dorsolateral PFC, dorsomedial PFC, dorsal ACC, and hippocampus, are more involved in top-down regulation of the emotional appraisal and affective state, which requires several cognitive processes. Hence, whenever early autonomic

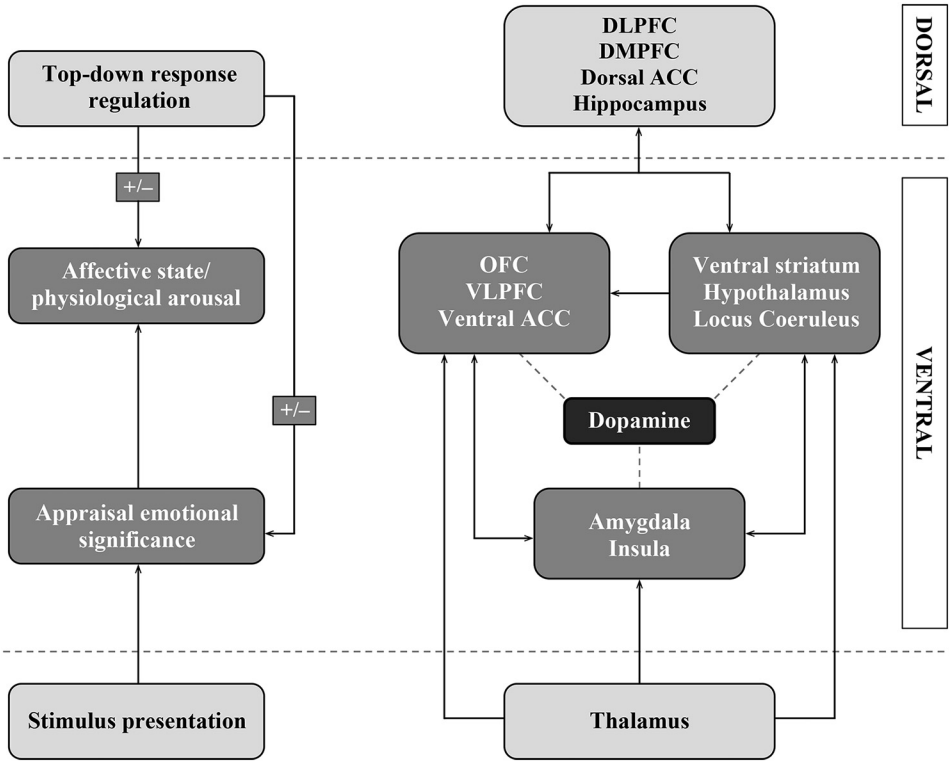

Fig. 2. Schematic representation of emotional processing and its neurobiological base.
We adjusted the schematic model that was initialized by Phillips and colleagues and included dopamine as the key element in two important emotional processes: accurate appraisal of the emotional significance of a stimulus and the production of an affective state and autonomic response. These processes are driven by predominantly ventral neural systems that strongly depend on sufficient dopamine supply. Top-down response regulation is controlled by a predominantly dorsal system. Both systems have reciprocal connections and therefore operate as a neuronal emotional circuit responsible for appropriate human emotional behavior.
Legend: DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; ACC, anterior cingulate cortex; OFC, orbitofrontal cortex; VLPFC, ventrolateral prefrontal cortex.

aspects of emotional processing are compromised, involvement of dorsal regions may serve as a compensatory top-down cognitive control mechanism in order to modulate our emotional responses. In our recent fMRI study on emotional processing in PD, we found evidence for increased activity in the dorsomedial PFC compared to healthy controls, despite disturbed striatal functioning. This potential compensatory increase in frontal activation may have restored emotional processing at the behavioral level, as these patients showed similar intensity ratings of emotional stimuli as controls [58]. The presence of compensatory neural mechanisms may impact upon current treatment strategies of affective disorders in PD. For instance, patients may benefit from the intact or even compensatory influence of prefrontal areas when therapeutic strategies are applied that rely on cognitive control to modulate disturbed processing of emotions.

In addition, several studies included in this review highlighted the critical role of dopamine in perceptual emotional processing. In fact, significant evidence was found for dopaminergic modulation of brain activity, predominantly in the ventral structures of affective neurocircuitry. As such, the progressive degeneration of nigrostriatal, mesocortical and mesolimbic dopaminergic pathways in PD can affect emotional functionality of those structures remarkably, while other, more dorsal, regions remain relatively spared. Therefore, when incorporating findings from studies reviewed here into existing neurobiological models, we believe that dopamine may operate as a critical component of emotional processing in PD (Figure 2).

Nevertheless, although there seems to be consensus on the involvement of a ventral and dorsal system in emotional processing, an open mind must be kept regarding the different theories on the exact disposition of the different neuronal structures within these systems. Morishita et al. [59] for instance, consider the amygdala and hippocampus as modulatory components in the circuit, rather than being part of the ventral or dorsal systems, respectively [49,55]. Another unresolved issue concerns the role of the ventral PFC, the OFC in particular, in emotional processing. Apart from being involved in emotion recognition and the generation of an effective response [49], the OFC is also thought to be important for outcome-based learning and emotion regulation strategies [54,55], although the latter view seems to be more related to reward learning and decision-making rather than perceptual emotional processing. Finally, as some of the reviewed studies point to possible compensatory effects by appealing to other cortical regions, even outside the proposed network for emotional processing, specific pathways and functional interactions between brain structures as well as the involvement of different neurotransmitters needs more clarification.

4.5. Conclusions and future perspectives

We reviewed studies on emotional processing in relation to its neurobiological correlates in Parkinson's disease (PD). These studies varied widely in methodology and clinical profiles, but presented clear evidence that several structural and functional correlates of emotional processing are disturbed in PD. The involvement of either ventral or dorsal neural systems of affective neurocircuitry may explain why certain aspects of emotional functioning are impaired in PD, whereas other aspects are not. Disturbance of dopamine neurotransmission, as we see in PD, can induce neurobiological abnormalities within this emotional circuit, particularly in the ventral regions.

Future studies on emotional processing in PD should consider several aspects. Optimal study designs require larger sample sizes, careful group matching, and accurate correction for confounding factors such as psychiatric medication, mood symptoms (i.e., depression, anxiety, apathy), and cognitive deterioration as they can have a substantial influence on a subjects' emotional response. Furthermore, considering the critical role of dopamine, dopaminergic replacement therapy is possibly the most determining factor for emotional processing in PD. Ideally, future studies should include both patient and control groups that are *on* and *off* dopaminergic medication in order to accurately define and control for the role of dopamine. Related to this, the stage and severity of the disease should be taken into account when interpreting study results. Medicated PD patients who are in more advanced stages of the disease, do not necessarily show more impairments in emotional processing than early PD patients who do not receive dopaminergic replacement therapy [8]. On the other hand, providing DRT in early stages of PD may overdose intact limbic regions resulting in impaired

emotional processing [24]. In addition, the use of DRT (especially dopamine-agonists) has been associated with neuropsychiatric complications such as impulse control disorders in PD [60]. As such, it is very important to check for the possible influence of DRT on emotional processing and to take its role into consideration when interpreting findings.

We further suggest the use of standardized experimental paradigms on emotional processing, which makes it easier to correctly explain any inconsistencies across studies regarding behavioral results. Moreover, many neuroimaging designs seem to focus on specific brain areas such as the amygdala and OFC, which rules out the possibility to explore disturbances or even compensatory mechanisms elsewhere in the brain. Future EEG studies should consider the use of appropriate localization methods in order to draw informative conclusions on neural correlates of emotional processing. Together, these recommendations may increase reliability of findings and subsequently improve the quality of a study dramatically, especially since the latter here varied widely among studies.

This review has some limitations. First our search was limited to Pubmed and PsycINFO, as we anticipated that due to the nature of the topic, studies would be published in journals with a Pubmed or PsycINFO listing. Also, we excluded studies in patients who received ablative surgery or deep brain stimulation. Although these studies may provide important information on affective deficits in PD, this may be more specific to changes associated with the intervention. Another limitation is that we only discussed the role of dopamine, whereas other neurotransmitter systems are likely to be involved as well [61]. However, literature on the involvement of neurotransmitters other than dopamine in emotional processing in PD is very scarce. Fourthly, our quality assessment of the included quasi-experimental studies was based on a structured assessment that has not been validated. We do not expect that this led to a less critical appraisal of the studies since the list was more extensive than other available checklists. Finally, because the studies included in this review varied widely in their methodology and study samples, it remains very difficult to directly compare and to interpret any inconsistencies in results and general conclusions should therefore be drawn with caution. Nevertheless, we attempted to provide an overall view of the current evidence base in order to expand our understanding of this complicated field of research.

In conclusion, this review reported important evidence for abnormal emotional processing in patients with PD, despite the relatively intact ability to accurately recognize and respond to emotional stimuli. Deficits in PD are mainly related to autonomic and perceptive processing of intense emotional stimuli, which is accompanied by structural and functional neurobiological abnormalities in predominantly ventral regions of affective neurocircuitry. Regions within the dorsal system on the other hand that are more responsible for the cognitive and regulatory aspects of emotion, seem to remain largely intact in PD patients. Considering the fact that the ventral structures within this neuronal emotional circuit are strongly dependent on active dopaminergic neurotransmission, Parkinson's disease can serve as a prolific model for studying the neurobiological correlates of normal human emotional behavior. Moreover, the fact that PD patients are able to cognitively regulate or modulate their emotional responses despite reduced dopamine supplies, can have important implications for the treatment of affective disorders not only in this specific population but in the general population likewise.

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K. Dujardin: critical review of manuscript.

Leentjens: supervised conception and organization of the review, assisted in extraction process, critical review of manuscript.

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