From the Department of Neurology,

University Hospital of Saarland, Homburg/Saar

Director: Prof. Dr. Klaus Fassbender

Title of Dissertation

Demographic and clinical factors associated with impaired facial emotion recognition in Parkinson's disease.

Dissertation to obtain the academic degree of Doctor of Medicine

of the medical school of University of Saarland

2017

presented from: Stefania Kalampokini

born on 10.11.1984 in Larissa (Greece)

Contents

Abstract

Objective: Parkinson's disease is a progressive neurodegenerative disorder characterized by the presence of motor symptoms and a variety of non-motor symptoms. The ability to recognize facial emotion expressions, a skill of great importance for non-verbal communication and social interaction, has been reported to be impaired in Parkinson's disease, yet, previous studies showed inconsistent findings. The orbitofrontal cortex, the anterior cingulate, the amygdala, the basal ganglia, temporoparietal areas and visual processing areas seem to constitute crucial neural substrates of the ability to recognize facial emotions. The aim of this study was to further investigate facial emotion recognition in Parkinson's disease patients and its' association with demographic and clinical parameters (including motor and non-motor symptoms). As facial emotion recognition and olfaction, a known non-motor symptom of the disease, could share common neural substrates, we tested whether there is an association of facial emotion recognition and olfaction.

Patients and methods: Thirty-four non-demented Parkinson's disease patients and 24 frequency age- and sex-matched healthy controls underwent clinical neurological and neuropsychological assessment including the Beck Depression Inventory, the Apathy Evaluation Scale, the Rapid Eye Movement sleep Behavior Disorder Screening Questionnaire, the Parkinson neuropsychometric dementia assessment instrument and the cognitive estimation test, standardized olfactory testing with Sniffin' sticks and the Ekman 60 Faces Emotion Recognition Test. The groups did not differ with respect to mini mental state examination score and education.

Results: Parkinson's disease patients had a significantly lower score on the total facial emotion recognition task in comparison with healthy controls (F=8.030, p=0.006), even after controlling for the potential confounding factors depression and apathy. The Parkinson's disease group had a specific impairment in the recognition of surprise (F=7.885, p=0.007). The recognition of anger approached statistical significance (p=0.07). The emotion more accurately recognized by both groups was happiness while fear was less accurate recognized also by both groups. The most common misattributions of emotions in both groups were: happiness as surprise,

sadness as fear, fear as surprise, disgust as anger and surprise as fear. Increasing chronological age (β=-0.294, *p*=0.001, CI 95% -0.462, -0.126) and age at disease onset (β=-0.194, *p*=0.012, CI 95% -0.342, -0.046) were associated with worse performance on the facial emotion recognition task in Parkinson's disease patients. Worse olfactory function along with Parkinson's disease diagnosis predicted worse facial emotion recognition performance within all study participants. Facial emotion recognition was not associated with patients' characteristics like gender and education or disease characteristics like disease disability, motor impairment, disease duration, disease severity, disease most affected body side, type of Parkinson's disease, hypomimia, freezing of gait, postural instability, orthostatic dysregulation and Rapid Eye Movement sleep behavior disorder. In addition, facial emotion recognition was not also predicted by global cognitive performance, executive functions like performance on the cognitive estimation task, depression or apathy.

Conclusion: Facial emotion recognition and especially the recognition of surprise are significantly impaired in Parkinson's patients compared with age- and sex-matched healthy control individuals. The association of facial emotion recognition with age (chronological age and age at disease onset) and olfactory function is endorsed by common structures that undergo neurodegeneration in Parkinson's disease. Impaired facial emotion recognition in Parkinson's disease may rely on anatomical connections of the basal ganglia, which appear to play a role in recognizing emotions from facial cues, as part of a distributed network of cortical and subcortical structures or may reflect a dysfunction of the cortical-basal ganglia-thalamic-cortical functional loops. The relevance of facial emotion recognition in social interaction stresses the clinical relevance and the need for further investigation in this field. Future studies should also determine whether impaired facial emotion recognition is already present in premotor stages of Parkinson's disease. It seems necessary to integrate tasks accessing facial emotion recognition in clinical practice in order to evaluate this non-motor aspect of the disease that can affect patients' social behavior in order to appreciate the full extent of deficits of patients and to provide an adequate treatment in Parkinson's disease.

Keywords: Parkinson's disease, facial emotion recognition, non-motor symptoms, olfaction, age

Zusammenfassung

Demographische und klinische Faktoren assoziiert mit gestörter Gesichtsemotionserkennung in M. Parkinson

Einleitung: Morbus Parkinson ist eine progressive neurodegenerative Erkrankung, die durch das Vorliegen von motorischen und nicht-motorischen Symptomen gekennzeichnet wird. Die Fähigkeit Emotionen in Gesichtern zu erkennen, eine Fertigkeit von großer Bedeutung für die non-verbale Kommunikation und soziale Interaktion scheint beim Morbus Parkinson gestört zu sein, vorherige Studien haben diesbezüglich allerdings widersprüchliche Ergebnisse gezeigt. Der orbitofrontale Kortex, der anterioriore cinguläre Kortex, die Amygdala, die Basalganglien, temporoparietale und visuell verarbeitende Areale stellen die neuronalen Substraten der Emotionserkennung in Gesichtern dar. Das Ziel der Studie war die Emotionserkennung in Gesichtern in Patienten mit Morbus Parkinson weiter zu erforschen und mögliche Assoziationen mit demographischen und klinischen Faktoren (motorischen und nicht motorischen Symptomen) zu evaluieren. Da die Emotionserkennung und der Geruchssinn, ein bekanntes nicht-motorisches Merkmal der Krankheit, in denselben neuronalen Substraten angesiedelt sind, haben wir auch untersucht, ob eine Assoziation zwischen Emotionserkennung und Geruchssinn besteht.

Matherial und Methodik: Vierunddreißig Patienten mit Morbus Parkinson und 24 gematchte gesunde Personen wurden klinisch, neurologisch und neuropsychologisch mit Hilfe des Beck Depression Inventars, der Apathie Evaluation Skala, dem Rapid Eye Movement-Schlaf-Verhaltensstörung Fragebogen, dem Parkinson neuropsychometric dementia assessment Test, dem Test zum kognitiven Schätzen, eines standarisierten Geruchtstest Sniffin' sticks und des Ekman 60 Faces Tests zur Emotionserkennung untersucht. Es gab keine Abweichungen zwischen den beiden Gruppen bezüglich des mini-mental Status und Ausbildungsstatus.

Ergebnisse: Patienten mit Morbus Parkinson hatten eine signifikant niedrigere Leistung im Emotionserkennungtest ($F=8.030$, $p=0.006$) im Vergleich zu den gesunden Personen, auch nach Berücksichtigung der potentiellen Störfaktoren

Depression und Apathie. Die Parkinson Patienten wiesen eine gestörte Emotionserkennung der Emotion Überraschung auf (F=7.885, p=0.007). Die Erkennung der Emotion Wut näherte sich der statistische Signifikanz an (p=0.07). Die Emotion, die am häufigsten richtig erkannt wurde, war Freude, während Furcht von beiden Gruppen am schlechtesten erkannt wurde. Die in beiden Gruppen am häufigsten vorkommende Fehlzuschreibung von Emotionen waren: Freude als Überraschung, Traurigkeit als Furcht, Furcht als Überraschung, Ekel als Wut und Überraschung als Furcht. Zunehmendes Alter (β=-0.294, *p*=0.001, CI 95% -0.462, -0.126) und Alter des Patienten bei Beginn der Erkrankung (β=-0.194, *p*=0.012, CI 95% -0.342, -0.046) waren mit einer schlechteren Leistung der Emotionserkennung bei Parkinson Patienten assoziiert. Verminderter Geruchssinn einhergehend mit der Diagnose eines Morbus Parkinson konnten eine schlechtere Leistung zwischen allen Studie Teilnehmern voraussagen. Die Emotionserkennung war nicht assoziiert mit Eigenschaften der Patienten wie Geschlecht und Ausbildung oder mit Eigenschaften der Erkrankung wie krankheitsbedingte Behinderung, motorische Einschränkungen, Dauer der Erkrankung, der am stärksten betroffenen Körperseite, Parkinson Typ, Hypomimie, Freezing beim Gehen, posturale Instabilität, orthostatische Dysregulation und Rapid Eye Movement-Schlaf-Verhaltensstörung. Ferner konnte die Emotionserkennung mit der globalen kognitiven Leistung, exekutiven Funktionen wie kognitives Schätzen, Depression oder Apathie nicht assoziiert werden.

Schlussfolgerungen: Emotionserkennung in Gesichtern und besonders die Erkennung der Emotion Überraschung sind bei den Parkinson Patienten signifikant gestört im Vergleich zu alters- und geschlechts- gematchten gesunden Personen. Der Zusammenhang der Emotionserkennung und des Alters und Alters des Beginns der Erkrankung sowie der Emotionserkennung und des Geruchssinns ist durch gemeinsame Strukturen, die eine Neurodegeneration in der Parkinson Krankheit durchmachen, zu erklären. Die gestörte Emotionserkennung beim Morbus Parkinson könnte von anatomischen Verbindungen der Basalganglien abhängen, die vermutlich eine Rolle bei der Emotionserkennung von Gesichtermerkmalen spielen, als Teil von einem verbreiteten Netzwerk von kortikalen und subkortikalen Strukturen. Des Weiteren könnte sie eine Funktionsstörung der kortiko-Basalganglien-thalamische-

kortikalen funktionellen Schleifen widerspiegeln. Die Bedeutung der Erkennung von Emotionen in Gesichtern bei den sozialen Interaktionen betont die klinische Bedeutung dieser Funktion und den Bedarf an weiterer Forschung in diesem Bereich. Zukünftige Studien könnten untersuchen, ob eine gestörte Emotionserkennung sogar in den prämotorischen Stadien der Erkrankung vorhanden ist. Es ist notwendig, dass Emotionserkennungsaufgaben im klinischen Alltag integriert werden, um diesen nicht-motorischen Aspekt der Erkrankung, der das soziale Verhalten des Patienten beeinflussen kann, evaluieren zu können und eine adäquate Behandlung der Patienten mit Morbus Parkinson leisten zu können.

Schlüsselwörter: Morbus Parkinson, Emotionserkennung, nicht-motorische Symptome, Geruchssinn, Alter

Demographic and clinical factors associated with impaired facial emotion recognition in Parkinson's disease

1. Introduction

1.1 Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the presence of motor symptoms including bradykinesia, rigidity, resting tremor and postural instability. Other typical motor features are hypomimia (masked face or reduced facial expression), shuffling gait and micrographia. PD is also characterized by a variety of non-motor symptoms including autonomic dysfunction (like orthostatic hypotension, bladder disturbances, constipation, sweating and sexual dysfunction), sleep disorders (like sleep fragmentation, insomnia, excessive daytime sleepiness, rapid eye movement sleep behaviour disorder and restless legs or periodic limb movements), sensory disorders (like olfactory disturbance and pain), neuropsychiatric disorders (including depression, anxiety, apathy, memory, language and executive function impairments as well as dementia) (Chaudhuri et al., 2006; Wolters et al., 2014). PD is a widespread disease with an age-dependent incidence of about 10-20 in 100.000 with a significant higher rate for men as for women. The average age of onset in PD is at about 60 years, although there are cases with early onset of the disease before 40 years (Wolters et al., 2014).

PD was initially classified as a disease of the basal ganglia. The pathological hallmark of PD is the loss of dopaminergic neurones in the substantia nigra (Hughes et al., 1992), resulting in the depletion of dopamine in the striatum (caudate and putamen) of the basal ganglia. However the disease is now recognized as a rather diffuse degeneration of the nervous system (Wolters et al., 2014) involving not only dopaminergic neurons in the pars compacta of the substantia nigra but also other neurons in the central and peripheral nervous system (including the autonomous and the enteric nervous system) (Klingelhoefer and Reichmann, 2015). PD is a synucleopathy, like dementia with Lewy bodies and multiple system atrophy, characterized by the presence of spindle- or thread-like Lewy neuritis in the cells, and of globular Lewy bodies in neuronal perikarya (body of neuron containing the

nucleus). Lewy neurites and Lewy bodies contain an aggregated form of the normally presynaptic protein a-synuclein and other components such as phosphorylated neurofilaments (component of neuronal cytoskeleton) and ubiquitin (heat shock protein required for the breakdown of abnormal proteins). As a consequence, loss of neurons is observed over time. Besides dopaminergic neurons, cholinergic, serotonergic and noradrenergic neurons are also affected in PD (Braak et al., 2003*a*; Wolters et al., 2014). Braak and colleges proposed that the disease results from an anatomically ascending degenerative process, starting in the brainstem (or even the enteric nervous system), with the earliest stage being the involvement of the motor part of the vagal nerve and the olfactory bulb (stages 1 and 2), spreading next to nuclei in the brainstem including the substantia nigra (pars compacta) (stages 3 and 4) and affecting the neocortex in the last stages of the disease (stages 5 and 6). (Braak et al., 2003*a*) The involvement of these areas could explain the non-motor symptoms of the disease.

Particularly, in stages 1 and 2 the lesions are confined to the dorsal IX/X motor nucleus and/or the intermediate reticular zone. The caudal raphe nuclei (belonging to the midbrain reticular formation), the gigantocellular reticular nucleus and the coeruleus-subcoeruleus complex (nuclei complex in brainstem related with rapid eye movement (REM) sleep behaviour disorders (García-Lorenzo et al., 2013) are affected especially in stage 2. Olfactory structures, beginning from olfactory bulb and the olfactory nucleus, are also early in the pathological course of the disease affected. In stage 3 the pathology extents to the pars compacta of the substantia nigra. Other mesencephalic predilection sites, such as the pedunculopontine tegmental nucleus (component of the reticular activating system implicated in locomotion, cognitive functions and REM sleep (Mena-Segovia et al., 2004) and the magnocellular nuclei of the basal forebrain (including the basal nucleus of Meynert) start developing PD pathology. In stage 4 the amygdala, the (ventral) claustrum, specific subnuclei of the thalamus are also affected. The pathological changes extend to other olfactory structures like the olfactory tubercle, the periamygdaloid and entorhinal cortex. In this stage the cortical involvement is only confined to the anteromedial temporal mesocortex. The last stages 5 and 6 are characterized from severe involvement of cortical areas, including insular areas, the anterior cingulate

cortex, prefrontal areas and finally the premotor and primary motor areas as well as sensory associating and primary sensory areas (Braak et al., 2003*a*). The motor symptoms of the disease appear, when the loss of dopaminergic neurons in the substantia nigra has surpassed the clinical threshold and this might be expected in stages 4 and/or 5 (Braak et al., 2003*a*; Wolters et al., 2014]. In the last stages (stage 5 and 6) the damage in important limbic structures (amygdala, hippocampal formation, anteromedial temporal mesocortex) as well as extended neocortical territories can be associated with the increasing cognitive dysfunction. It must be however noted, that the severity of the pathology varies slightly from one person to another (Braak et al., 2003*a*).

The exact cause of the disease remains unknown. Braak et al. hypothesized that PD might originate outside the nervous system, caused by an unidentified pathogen, passing the mucosal barrier of the gastrointestinal tract and secondarily reaching the central nervous system via retrograde axonal transport (via postganglionic enteric neurons entering the central nervous system along unmyelinated praeganglionic fibers generated from the visceromotor projection cells of the vagus nerve). By retrograde axonal and transneuronal transport such a causative pathogen could reach especially vulnerable subcortical nuclei and in this way gain access to the cerebral cortex (Braak et al., 2003*b*). The same study group proposed the dual-hit hypothesis with pathogenic access to the brain through the stomach and nose (Hawkes et al., 2007).

As Braak's model does not explain the synchronicity of many of PD symptoms, Braak and his colleges suggested the cortico-basal ganglia-cortical circuit (Braak and Del Tredici, 2008). Indeed, a wide range of experimental evidence supports the concept of cortical-basal ganglia-thalamic-cortical closed loops, in which the basal ganglia participate in various functional loops (Alexander et al., 1986; Parent and Hazrati, 1995; Mc Haffie et al., 2005). The cortico-basal ganglia parallel circuits´ model consists of motor, associative and limbic loops (Fig. 1) (Obeso et al., 2009; Juri et al., 2010). Each loop has its origin in different cortical areas serving specific functions (Romanelli et al., 2005), but interaction has also been shown to exist between the circuits (Joel and Weiner, 1997; Obeso et al., 2000). The motor striatum (dorsolateral

putamen and dorsolateral region of the caudate) is innervated by the primary and supplementary motor cortex. The associative striatum (consisting of the largest part of the nucleus caudatus and of the putamen) receives input from associative areas of the cortex, mainly from the prefrontal cortex. The limbic striatum (nucleus accumbens and the ventral parts of the putamen and nucleus caudatus (Robbins and Evritt, 1996)) receives input from limbic structures: the hippocampus, the amygdala, orbitofrontal, infralimbic and prelimbic cortices. This arrangement forms the neuronal basis for the influence of the basal ganglia on sensomotor, cognitive and executive behavioural and emotional-motivational functions.

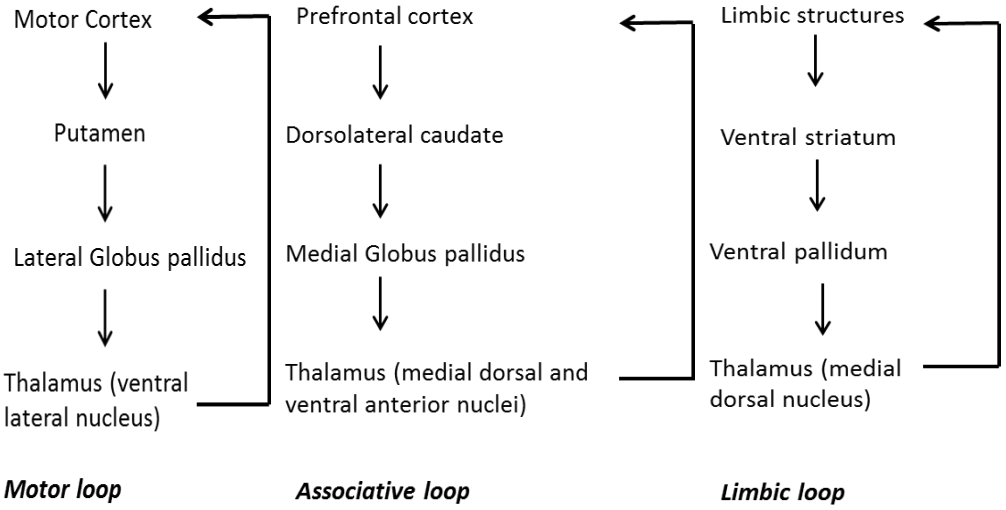

Fig. 1 The cortico-basal ganglia loops

In the current "general" view of the basal ganglia, the striatum and subthalamic nucleus are the two main accesses from the cortex (Juri et al., 2010) and the globus pallidus internus is the efferent point via the thalamus to the cortex. In addition, via thalamus a phylogenetically older system of projection ascending from brainstem structures like the superior coliculus and pedunculopontine nucleus provides the basal ganglia with relative unprocessed external (visual, auditory, somatosensory, etc.) and internal (viscerosensory, homeostatic, etc.) information. The output of the basal ganglia has an ascending and a descending component. The extensive ascending component reaches via medial and ventral thalamic nuclei, to the

premotor and prefrontal areas cortical areas in the frontal lobe, thus closing the so-called basal ganglia-thalamocortical circuits. The descending component consists of basal ganglia projections directed to mesencephalic structures that, in turn, give rise to fibers that descend further to motor output structures in the lower brainstem and spinal cord, as well as to fibers that ascend to forebrain structures. These projections form the neuronal basis for the influence of the basal ganglia on posture and balance as well as on muscle tone (Braak and Del Tredici, 2008; Groenewegen et al., 2014; McHaffie et al., 2005). Across this wide array of motor and behavioural functions in which the basal ganglia are involved, the mechanism by which the basal ganglia contribute to these functions is though selecting appropriate responses in a particular context and, at the same time, though suppressing inadequate responses (”response selection”) (Wolters et al., 2014). Thus, the basal ganglia can be considerated as a subcortical ”control desk”, responsible for choosing the best action modus among different action patterns (Diederich and Parent, 2012).

1.2 Non-motor symptoms of Parkinson’s disease

Olfactory dysfunction in Parkinson’s disease

The olfactory dysfunction in PD includes impairment of odor detection (the threshold or the perception of odors at low concentrations), identification (the ability to name an odor) and discrimination (distinction of different smells) (Doty et al., 1988; Mesholam et al., 1998). Olfaction is impaired in 70-90% of patients with (sporadic) PD and occurs early in the course of the disease (Doty et al., 1988). Hyposmia has even been shown to exist in potential premotor stages of PD, i.e. REM sleep behavior disorder (Stiasny-Kolster et al., 2005). Prospective studies have indeed established hyposmia as a pre-motor sign of PD that can precede the onset of the motor symptoms by as long as 5 years (Ponsen et al., 2004; Ross et al. 2008). This olfactory dysfunction seems to be unrelated to gender, disease duration and severity, dopaminergic therapy (Doty et al., 1988; Hawkes et al., 1997) as well as cognition (Doty et al., 1989). Most PD patients are unaware of their olfactory deficit until testing (Doty, 2007). Degeneration of anatomical areas involved in olfaction is responsible for the olfactory dysfunction in PD. Such neuropathologic changes are

found in the olfactory bulb and the anterior olfactory nucleus in the early disease stages while changes in the olfactory cortex (perirhinal cortex) and in limbic structures like amygdala are found in more advanced stages (Braak et al., 2003; Benarroch, 2010).

REM sleep behavior disorder in Parkinson's disease

REM sleep behavior disorder (RBD) is a parasomnia characterized by the lack of motor inhibition during REM sleep, leading to loss of the normal skeletal muscle REM-related atonia thus enabling patients to physically enact their dreams, which can often be vivid or unpleasant and can lead to a vigorous, potential harmful (dream-enacting) behavior (Wolters et al., 2014). Vocalisations (talking, shouting, vocal threats) and abnormal movements (arm or leg jerks, falling out of bed, violent movements) are commonly reported by bed partners. Surprisingly, there can be restoration of normal motor activity, with disappearance of parkinsonian features during RBD. RBD is a potential marker of neurodegenerative disease particularly PD and Lewy body dementia (Cochen De Cock, 2013). RBD is present in up to 60% of patients with PD and it can appear before, at the same time or after the onset of PD. RBD can precede the development of the motor signs of Parkinson's disease even 15 years before (Cochen De Cock, 2013) and longitudinal data suggest that RBD pronounces the onset of motor symptoms in up to 40% of patients (Chaudhuri et al., 2006) The sublaterodorsal nucleus, the precoeruleus complex and the magnocellular reticular formation in the brainstem have been implicated in the pathophysiology of RBD (Chauduri et al., 2006; Boeve et al., 2007; Postuma et al., 2012).

Dysautonomia in Parkinson's disease

Dysautonomia in PD includes orthostatic hypotension, constipation and urogenical dysfunction (Poewe, 2008). Orthostatic hypotension and urogenical dysfunction are rather late features in PD (unlike Multiple System Atrophy) (Poewe, 2008). The pathophysiology of autonomic disorders in PD involves degeneration and dysfunction of the medullary nuclei as well as of the peripheral nervous system (myenteric plexus) (Chauduri et al., 2006; Poewe, 2008).

Cognitive impairment, depression and apathy in Parkinson's disease

The prevalence of cognitive deficits in PD ranges from 19-36% of patients (Goldmann and Postuma, 2014). Cognitive impairment in PD is typically a dysexecutive syndrome, with impairment of attention and ability to plan, problem-solving and regulating goal-directed behavior (Emre, 2003). Language deficits are also described in PD, such as impaired verbal fluency and naming difficulty (Muzerengi et al., 2007), as well as visuospatial deficits and to an extend impairment of learning and memory (Dubois and Pillon, 1997). Minor cognitive deficits may be present at the early stages of the disease while a dysexecutive syndrome is frequent as the disease progresses. However, executive function impairments are commonly noted even in PD patients, who do not have dementia (Zgaljardic et al., 2003). Regarding the pathology of cognitive impairment in PD, the presence of cortical and subcortical Lewy bodies, amyloid deposition (Alzheimer-type pathological changes) as well as pathology in monoaminergic and cholinergic nuclei (that project to the cortex) is implicated (Aarsland et al., 2005; Emre et al., 2007).

Depression is common in PD patients: a clinically significant depression is present in approximately 30–50% of PD patients (Poewe and Seppi, 2001; Lemke, 2008; Barone, 2011). The prevalence rates in studies vary from 2.7% to 55.6% for major depression, 13% to 34.5% for minor depression and 2.2% to 31.3% for dysrhythmia (Grover et al., 2015). Mechanisms underlying depression are related to disturbances of noradrenalin, serotonin and dopamin transmissions in limbic and cortical structures. The noradrenalin locus coeruleus and serotonin raphe neurons degenerate over the course of PD, which leads to decreases in serotonin and noradrenalin levels in regions innervated by these structures (Ossowska and Lorenc-Koci, 2013).

Apathy, which is described as flattening of affect, decreased motivation or lack of initiative, is a common finding in patients with PD. Patients show reduced interest and participation in the main activities of daily living and a trend towards early withdrawal from initiated activities. Apathy in PD patients has a prevalence that varies from 16.5% to 42%, depending on the assessment tools and the patients´ characteristics (Dujardin et al., 2007). Apathy symptoms could be due to neuronal degeneration in areas that mediate goal-directed behavior (Brown and Pluck, 2000)

such as frontal-subcortical areas or reward centres such as dopamine projections between the ventral tegmentum and nucleus accumbers (Chaudhuri et al., 2006) or again mesolimbic dopaminergic denervation and thus dysfunction of the limbic system (Dujardin and Lopes, 2014).

1.3 Facial emotion recognition in Parkinson's disease

Among the spectrum of non-motor, in particular neuropsychological symptoms in PD, the ability of patients to recognize emotions in others' facial expressions, a skill of great importance for non-verbal communication and social interaction, is gaining growing interest. Facial emotion recognition (FER) is described in several studies to be impaired in PD patients. The studies focused on some or all six basic emotions i.e happiness, fear, anger, sadness, disgust and surprise.

1.3.1 Previous studies of facial emotion recognition in Parkinson's disease

A number of studies assessed facial emotion recognition in PD patients with inconsistent findings. The first study, which suggested that emotional processing of facial stimuli is selectively impaired in PD patients, was the study of Blonder et al. (Blonder et al., 1989). In this study, patients showed impairment of emotional processing of facial stimuli compared to healthy controls but there was no differences found between patients with right hemiparkinsonism and those with left hemiparkinsonism in the pattern of deficits exhibited. Beatty et al. (Beatty et al., 1989), who compared two groups of PD and of chronic progressive multiple sclerosis patients with two groups of neurologically normal controls respectively, found that (both) PD (and multiple sclerosis) patients were less accurate in judging emotional expressions conveyed by the photographs depicting fundamental affective states and were equally impaired in judging each of the seven emotional states (happy, sad, angry, afraid, disgusted, surprised or neutral). Moreover, they showed no particular tendency to confuse faces expressing emotions of opposite polarity (e.g happy and sad). Borod et al. (Borod et al., 1990) examined emotional processing (perception and expression) using a both facial and vocal channel, in various neurological and psychiatric group of patients (schizophrenic, depressive, right-brain damaged, PD)

and normal control right-handed adults. Regarding perception of facial stimuli, PD patients were significantly less accurate than normal controls. PD patients identified more accurately positive faces (than neutral and negative ones), whereas normal controls identified more accurately neutral faces. Negative emotions were identified with the least accuracy in both the PD and normal control group. Jacobs et al. (Jacobs et al., 1995), using perceptual and imagery tasks, found that PD patients were impaired on two tasks of facial affect perception: the emotional facial characteristics, at which the patient answers questions on an exhibited face, and the affect discrimination task of the Florida Affect Battery-revised test, at which subjects were asked whether two faces displayed the same or a different emotion. On the emotional facial characteristics test, fear and sadness showed the greatest differences between the two groups with less accuracy in the PD group among the emotions tested (happiness, sadness, anger, and fear). However, on an affect matching task, at which subjects were required to match a target emotional face with one of five face alternatives that displayed the same or a similar facial emotion, there was no difference found between the PD patients and normal control subjects. Breitenstein et al. (Breitenstein et al., 1998), using both facial and auditory stimuli, comparing patients with focal cortical lesions and PD patients with two matched control groups, revealed significant differences in recognizing facial expressions between PD patients with bilateral symptoms compared to healthy controls. With respect to single emotions, a differential deficit pattern was only observed for the affective prosody subtests and not for the facial expressions subtests.

Moreover, the study by Kan et al. (Kan et al., 2002) showed a significant impairment in the recognition of fear and disgust in PD patients from moving (videotaped) facial stimuli (but not from prosodic or written verbal stimuli). Yip et. al (Yip et. al, 2003) showed an impairment in the recognition of all emotions in patients with bilateral motor symptoms compared to healthy controls, with the recognition of fear and sadness being more impaired, while the right-sided PD patients showed an impairment in the recognition of all emotions except happiness, especially in the recognition of sadness and disgust. Sprengelmeyer et al. (Sprengelmeyer et al., 2003), who examined the issue in unmedicated (early stage) PD patients and medicated (with more advanced disease), showed that unmedicated PD patients

performed significantly worse than controls in recognizing fear, sadness, anger and disgust, while the medicated PD patients performed significantly below controls in recognizing fear and anger. Notably, the unmedicated group showed a consistently worse performance in recognition of disgust compared with the medicated group. Dujardin et al. (Dujardin et al., 2004*a*) reported an impairment of anger, disgust and sadness in early unmedicated PD patients independent of the intensity of emotional facial expressions exhibited, although the same authors showed no impairment in the facial emotion recognition in 12 PD patients in the pre-operative phase of deep brain stimulation in another study (Dujardin et al., 2004*b*).

Furthermore, Suzuki et al. (Suzuki et al., 2006) showed a selective deficit in the recognition of disgust in early PD patients with a refined method using morphed visual stimuli, which was not present when using the conventional method of assessing FER. A french study from Lachenal-Chevallet et al. (Lachenal-Chevallet et al., 2006) showed a deficit for fear and disgust recognition in a small sample of participants. Lawrence et al. (Lawrence et al., 2007) showed impairment in the recognition of anger in a group of PD patients transiently withdrawn from dopamine replacement therapy. Arriati et al. (Arriati et al., 2008) using a facial emotion and emotional prosody recognition battery showed a deficit in recognizing fear and sadness from facial stimuli in PD patients. Clark et al. (Clark et al., 2008) showed impairment in the recognition of anger and surprise in PD. Moreover, the recognition of anger was shown to be impaired in patients with right hemisphere pathology (left body side onset of motor symptoms) and surprise by those with left hemisphere pathology (right body side of onset). At the same study male PD patients exhibited deficits in the recognition of fear (Clark et al., 2008). The results were replicated in a study of the same authors (Clark et al., 2010), which included a sub-sample of the original cohort and primarily showed that PD patients have subtle differences in scanning behaviors during viewing tasks of emotion categorization compared with healthy control subjects, which are driven by different perceptual processes and cognitive strategies. PD patients obtained lower scores compared to healthy controls in all emotions except happiness in the study of Ibarretxe-Bilbao et al. (Ibarretxe-Bilbao et al., 2009), which used high resolution structural magnetic resonance images (MRI) to test whether there are any structural changes that could

explain the impairment of recognition of facial emotions and decision-making in early PD. Assogna et al. (Assogna et al., 2010) using high- and low-intensity stimuli, comprising of digitized pictures of three-dimensional models of faces depicting facial expressions of evoked or felt emotions, showed that PD patients recognized fewer low- and high-intensity facial expressions of disgust than healthy controls. Paulmann and Pell (Paulmann and Pell, 2010) found a significant difference between two small groups of PD and healthy participants in identifying emotions from dynamic facial stimuli, although not from static ones. Herrera et al. (Herrera et al., 2011) showed an emotion recognition deficit in PD patients in absence of other cognitive deficits that could explain it. Narme et al. (Narme et al., 2011) in a study assessing facial emotion recognition and facial configural processing (processing of the spatial relations between facial features) as well, showed a deficit of the PD group in recognizing anger and fear compared to the control group. A study from the same author (Narme et al., 2013), which investigated emotional and cognitive social processes in relation to behavioral disorders, showed also impaired facial emotion recognition of fear and sadness in PD. Baggio et al. (Baggio et al., 2012) in a neuroimaging study showed a significant worse performance of the PD group compared to the healthy control group.

Buxton et al. (Buxton et al., 2013), who investigated the issue using subtle expressions of emotion, showed that although PD patients identified emotional expressions on phototypical test (Ekman and Friesen, 1976) as accurately as the control group, as the facial expressions of emotion became more subtle, the PD group was significantly less accurate at identifying disgust in the moderate level, sadness at the most difficult level and happiness at both levels of subtlety. Saenz et al. (Saenz et al., 2013), showed a significantly impaired recognition of fear and sadness from facial stimuli (hybrid faces derived from one female face) in the PD group. Hipp et al. (Hipp et al., 2014), found that patients with early PD performed worse on almost all lower order vision test (including contrast sensitivity and color discrimination) and on the recognition of higher vision performance i.e recognition of sadness compared to healthy controls. Alonso-Recio et al. (Alonso-Recio et al., 2014a) using facial expression (including all basic emotions except of surprise) and facial identity characteristics (age and gender) discrimination and identification tasks

found significant differences only in the facial expression identification task between PD and healthy controls. Marneweck et al. (Marneweck et al., 2014a) found impairments in discriminating emotional expressions of graded intensity from neutral expressions and four of the basic emotions (anger, disgust, happiness and sadness) in PD patients. An overview of the results of the most important studies accessing FER in PD patients can be seen in Table 1.

On the contrary, twelve studies (Caekebeke et al., 1991; Dewick et al., 1991; Madeley et al., 1995; Adolphs et al., 1998; Tessitore et al., 2002; Pell and Leonard, 2005; Biseul et al., 2005; Yoshimura et al., 2005; Cohen et al., 2010; Pèron et al., 2010; Ventura et al., 2012; Wieser et al. 2012) failed to identify any facial emotion recognition impairment between PD patients and the healthy group of participants. Caekebeke et al. (Caekebeke et al., 1991), who examined the issue using cartoons showing faces that depicted an emotional state in a PD group withdrawn from the Parkinson replacement treatment the night before the assessment and a control group of subjects found no significant difference between the two groups. Dewick et al. (Dewick et al., 1991) showed no significant difference between groups either for the total score or for the three individual expressions (happy, angry, and sad). Madeley et al. (Madeley et al., 1995), using as stimuli the photographs taken from a small sample of participants themselves (PD and healthy controls), found that the two groups did not differ in their ability to recognize facial expressions or in the pattern of misidentification errors. Adolphs et al. (Adolphs et al., 1998) found an intact recognition of emotions in a quantitative task (rating of emotions). Tessitore et al. (Tessitore et al., 2002) using functional magnetic resonance imaging studied the response of patients during a hypodopaminergic state (i.e ≥12 hr after their last dose of dopaminergic treatment) and again during a dopamine-replete state to fearful and angry facial stimuli, found that although the mean accuracy score was lower during the drug-off state compared with both the drug-on state and normal control subjects, this difference did not reach statistical significance. Furthermore, Yoshimura et al. (Yoshimura et al., 2005) in a study using visual event-related potentials in response to the viewing of fearful facial expressions in a small sample of patients and controls, found no difference in the task performance. Pell and Leonard

(Pell and Leonard, 2005), using discrimination, identification and rating tasks of five basic emotions (fear excluded) failed to show a significant difference in the performance of PD and controls. Furthermore, Cohen et al. (Cohen et al., 2010) showed no deficit of PD patients in encoding facial emotion and object information, although PD patients performed significantly slower than controls in a test requiring high cognitive load, especially working memory (N-back task). Ventura et al. (Ventura et al., 2012) found no difference in both correct responses and reaction time among PD and healthy control groups on identification and discrimination facial tasks. Wieser et al. (Wieser et al., 2012), showed reduced early visual emotion discrimination in PD patients based on visual event-related potentials, although PD patients showed no impairment in emotion recognition (measured by affective ratings).

A recent meta-analysis conducted by Gray and Tickle-Degnen (Gray and Tickle-Degnen, 2010) examined the influence of six potential moderators (stimulus modality, task type, emotion displayed, medication status, depression status, executive function and visuospatial ability) on emotion recognition from facial and prosodic stimuli in PD. Regarding stimulus modality, the meta-analysis showed a deficit in emotion recognition in PD from both faces and voices, showing a greater deficit (effect size) for the recognition of emotion from prosody. Concerning task type, the meta-analysis showed deficits in both discrimination (deciding which of two photographs matches an expression or deciding whether two pictures pictured the same emotion) and identification (using labeling of an emotion) tasks, while discrimination tasks yielded a significantly greater deficit. The smaller deficits were found in rating tasks (i.e rating the extent of the emotion of a face showed) and can be attributed, according to the writers, to the very small number of studies using this kind of tasks and it is unlikely that they exhibit real deficits. Regarding specific emotion recognition deficit, PD patients were more impaired in recognizing negative emotions (anger, disgust, fear and sadness) than positive emotions (happiness, surprise). Concerning medication status, although there was a greater impairment (larger effect size) found among patients in hypodopaminergic state at the time of the testing, this finding was not significant. Moreover, the meta-analysis showed

that the emotion recognition deficit in PD exists independent of patients´ depression status. Regarding visuospatial ability, the results suggested that the facial emotion recognition deficit in PD exists beyond a deficit in face processing, while concerning the executive functions the results were less clear showing a difference favoring the control group.

Study	*Test used*	*Emotions tested*	*Participants*	*FER deficits PD*	*Remarks*
Yip et al., 2003	Matsumoto and Ekman (Identification and discrimination task)	all (six basic emotions)	64 PD (56 bilateral PD, 8 right-sided) 64 HC	• bilateral PD: total score, fear, sadness • Right-sided PD: total, all except happiness	
Sprengelmeyer et al., 2003	Ekman 60 Faces Test and Emotion Hexagon	all	20 medicated PD 6 unmedicated PD 40 HC	• PD vs HC: total • unmedicated vs medicated PD: disgust (worse the unmedicated)	Computer manipulated pictures in the Emotion Hexagon task
Dujardin et al., 2004	Hess and Blairy Series (from Matsumoto and Ekman)	anger, disgust, sadness	18 PD 18 HC	total score	PD have not yet received treatment
Suzuki et al., 2006	Matsumoto and Ekman	all	14 PD 39 HC	total score and disgust ONLY in the refined method	• MMSE 24-30 • Conventional and refined method of FER test used • Early PD patients
Lawrence et al., 2007	Ekman 60 Faces Test	all	17 PD 21 HC	anger	PD off-medication
Ariatti et al., 2008	Facial emotion recognition battery (faces from Ekman and Friesen)	all except surprise	27 PD 68 HC	In the Facial affect naming and Facial affect matching subtests: total score, fear, sadness	MMSE≥23
Clark et al., 2008	cropped Photos from Ekman and Friesen	all	20 PD 23 HC	total score, anger, surprise	
Ibarretxe-Bilbao et al., 2009	Ekman 60 Faces Test	all	24 PD 24 HC	total score	• Early PD • Primary neuroimaging study
Assogna et al., 2010	Penn Emotion Recognition Test	all except surprise	70 PD 70 HC	disgust	MMSE>24
Herrera et al., 2011	Mc Brain Face Stimulus Set	all	40 PD 19 HC	total score	MMSE>25
Narme et al., 2011	Photos from Ekman and Friesen Series	happiness, fear, disgust, anger	10 PD 10 HC	total score, anger (in the upright task)	Upright, upside-down, configural task
Baggio et al., 2012	Ekman 60 Faces Test	all	39 PD 23 HC	total score, fear, anger, sadness, disgust	Primary neuroimaging study
Buxton et al., 2013	Ekman and Friesen	all	30 PD 30 HC	• no difference at the easy level • Significant differences for specific emotions at moderate and difficult level	Easy (prototypical), moderate and difficult level of task
Saenz et al., 2013	Adapted from pictures of facial Affects	fear, happiness, sadness	24 PD 24 HC	• fear, sadness • no significant difference between low and high levels of intensity in PD	• Stimuli with increasing level of intensity by 10% • PD duration<4 years
Hipp et al., 2014	Ekman 60 Faces Test	all	28 PD 25 HC	sadness	• Early PD patients (≤3 years disease duration) • MMSE 25-30 (PD sign. diff. with HC)
Alonco-Recio et al., 2014a	80 cropped photos from FACES Database (Ebner, Riediger, & Linderberger, 2010) (Identification and discrimination task)	all except for surprise	53 PD 53 HC	total score	

Table 1. Overview of the most important studies accessing FER in PD patients

1.3.2 Neuroanatomy linked with facial emotion recognition

Several brain structures have been reported to be involved in the identification of facial expressions. A lot of information to this issue is provided from lesional studies. Blonder et al. (Blonder et al., 1989) suggested bilateral involvement in emotional processing at the subcortical level and Jacobs et al. (Jacobs et al., 1995) proposed that the basal ganglia, together with the right hemisphere, are part of a neural network serving emotional facial tasks (perceiving emotional faces, emotional facial imagery). A lateralization of the recognition of negative facial emotions involving discrete visual and somatosensory cortical areas in the right hemisphere has been reported (Adolphs et al., 1996) in patients with focal cortical lesions.

Neuroimaging studies have also examined the issue of neural substrates of facial emotion recognition. Spengelmeyer et al. (Spengelmeyer et al., 1998) showed enhanced activity by fMRI in healthy volunteers in the right putamen and the left insula cortex in response to disgusted facial expressions, whereas enhanced activity in the posterior part of the right gyrus cinguli and the medial temporal gyrus of the left hemisphere was observed during processing of angry faces. Fearful expressions activated the right fusiform gyrus and the left dorsolateral frontal cortex. For all three emotions investigated, activation of the inferior part of the left frontal cortex (Broadmann area 47) was found in common. Phillips et al. (Phillips et al., 1998) showed that fearfull stimuli activated the amygdala while facial expressions of disgust activated the anterior insula and the caudate-putamen. A recent meta-analysis of fMRI studies of Fusar-Poli et al. found that processing of emotional faces was associated with increased activation in a number of visual areas (fusiform gyrus, inferior and middle occipital occipital gyri, lingual gyrus), limbic areas (amygdala and parahippocampal gyrus, posterior cingulate), temporal areas (middle/superior temporal gyrus), temporoparietal areas (parietal lobule, middle temporal gyrus, insula), prefrontal areas (medial frontal gyrus), subcortical areas (putamen) and the cerebellum (declive). Regarding processing of different emotions, happy, fearful and sad faces activated the amygdala, with greater amygdala sensitivity for fearful faces, while disgusted and angry faces activated the insula with greater insular sensitivity for disgusted faces. Furthermore there was a thalamic activation shown in response

to disgusted faces, indicating that the insular-thalamic pathway may represent a core role in recognizing of disgust, probably as part of a neural network. On the other hand, neural response in the visual cortex and cerebellum was observed in all emotions. It is possible, that the visual areas are involved in early perceptual processing of facial stimuli, which may be independent of emotional valence (Adolphs, 2002*b*). The medial frontal cortex, which participates in the conscious experience of emotion, inhibition of excessive emotion or decision-making by observing one's own emotional state, seems to be activated by fearful faces, whereas happy faces activated the anterior cingulate cortex, which is involved in the response to an emotive visual stimulus. Finally, the cerebellum showed no differentiation in brain activation across emotions. The cerebellum is connected with the reticular system, cortical association areas and limbic structures such as the amygdala, the hippocampus and the septal nuclei (Baillieux et al., 2008; Fusal-Poli et al., 2009), providing an explanation for the activation pattern found in the metaanalysis.

Two neuroimaging studies have also examined the issue of neural substrates of FER in PD. In the study of Ibarretxe-Bilbao et al. (Ibarretxe-Bilbao et al., 2009), PD patients, who obtained lower scores in the recognition of all emotions except happiness, had significant volume loss in the right amygdala and bilateral orbitofrontal cortex in comparison with healthy controls. Gray matter volume of the bilateral orbitofrontal cortex was also found to correlate positively with overall emotion recognition in PD patients in this study. Baggio et al. (Baggio et al., 2012) using based morphometry analysis, revealed areas of positive correlation between individual emotion recognition and gray matter volume in PD patients: in the right orbitofrontal cortex, amygdala and postcentral gyrus and sadness identification; in the right occipital fusiform gyrus, ventral striatum and subgenual cortex and anger identification, and in the anterior cingulate cortex and disgust identification. White matter analysis in the same study, revealed significant positive correlations between the frontal portion of the right inferior fronto-occipital fasciculus and the identification of sadness.

Summarizing, a large number of different structures participate in recognizing emotions in faces including the orbitofrontal cortex, the anterior cingulate cortex, the amygdala, the basal ganglia, the right parietal cortex and visual processing areas like the occcipito-temporal cortex (Adolphs, 2002*a*; Adolphs, 2002*b*). Adolphs mentioned that these structures participate in multiple processes and at various points in time, thus making it difficult to assign this complex function to a single structure (Adolphs, 2002*b)*. Moreover, possible neural substrates, responsible for the facial recognition involve the basal ganglia limbic loop, in which the ventral striatum receives projections from the orbitofrontal cortex, anterior cingulate, entorhinal cortex, amygdala and hippocampus and in turn projects to the ventral pallidum and the latter to the thalamus and amygdala (Alexander and Crutcher, 1990; Alexander et al., 1990; Clark et al., 2008).

Particularly relevant for PD, regarding specific emotions, are the associations between anger and dopaminergic striatal system, in particular the ventral striatum (Calder et al., 2004; Lawrence et al., 2007), disgust and the basal ganglia and insula (Phillips et al., 1997; Sprengelmeyer et al., 1998; Calder et al., 2000; Suzuki et al., 2006), fear and the amygdala (Adolphs et al., 1994; Adolphs et al., 1999; Calder et al., 1996; Vytal and Hamann, 2010; Tessitore et al., 2002; Sato et al., 2002; Yoshimura et al., 2005; Kawamura et al., 2009) and happiness and the ventral striatum and putamen (Phan et al., 2002), as all these areas are affected from PD pathology (Braak et al., 2003).

1.4 Aim of the study

As mentioned above, the results of studies assessing facial emotion recognition in PD patients are inconsistent. The aim of the study was to further investigate whether facial emotion recognition is (significantly) impaired in PD patients compared with healthy controls and whether there is a specific emotion recognition deficit regarding the six basic emotions (happiness, anger, sadness, fear, disgust and surprise). Furthermore, possible associations of facial emotion recognition with demographic (such as age, sex, handedness, education, Parkinson medication) and clinical parameters i.e motor (disease duration, age of onset,

severity of motor impairment, type of PD, more affected side, hypomimia, freezing of gait, postural instability) and non-motor symptoms (presence of REM sleep behavior disorder, autonomic dysfunction) were examined. Among the most prominent non-motor features of PD is olfactory impairment, which as mentioned occurs in at least 90% of patients and often appears in the pre-motor stage of the disease (Doty, 2012). Facial emotion recognition and olfaction share common neuroanatomical substrates such as the amygdala and the orbitofrontal cortex (Doty, 2012; Soudry et al., 2011). Furthermore, the perception of facial expressions may integrate cues from sensory modalities other than vision, including olfaction (Leleu, 2015). Thus, particular interest was taken in examining whether poorer performance in facial emotion recognition is associated with impaired olfaction, as this relationship in PD has not yet been directly investigated. As FER requires the integrity of cognitive functions such as visuospatial abilities, attention, language and executive functions (Assogna et al., 2010) and may as well be influenced by mood disorders (Leppanen, 2006, Martinez-Corral et al., 2010), the association of FER in PD with cognitive status, depression and apathy measures was also examined.

2. Patients and Methods

2.1 Participants

Thirty-four patients with PD (18 men, 16 women) and 24 age- and sex-matched healthy controls (HC) (14 men, 10 women) were enrolled in this study. The study was approved by the ethic committee of the medical council of Saarland and all the participants gave their informed written consent to participate (Votum number 98/14). The diagnosis was made according to the United Kingdom PD Society Brain Bank Criteria (Hughes et al., 1992). PD patients were recruited from the department of neurology of the university hospital of Saarland, Germany. HC were recruited from the community (usually spouses of the patients). The groups did not differ with respect to age, sex, mini mental state examination score (U=362, p=0.437>0.05) and education (U=402, p=0.924>0.05). The groups differed in the depression score (BDI) with PD patients having a higher depression score (U=231, p=0.005<0.05).

Exclusion criteria for all subjects were: history of other neurological or psychiatric illness (other than PD in the PD group), history of structural brain lesion (e.g. history of stroke, encephalitis, severe head injury or head surgery), dementia (defined as Mini mental status score <27), delirium, acute confusion state or (dopamine-induced) psychosis or hallucinations, use of CNS-active medications (e.g. treatment with neuroleptics), except for use of dopaminergic, antidepressants and anxiolytics in the PD group, severe depression (Beck Depression score>17), history of drug or alcohol addiction, history of eye disease resulting in uncorrected abnormal vision, history of olfactory deficits resulting in a decrease of odor (e.g. acute upper respiratory tract infection, nose surgery, chronic sinusitis, chronic exposure to substances like pesticides, metallic dusts, industrial solvents or thinners, cleaning products). An additional exclusion criterion in the HC group was a family history of PD or other neurodegenerative diseases. All participants were native German speakers. One control subject had a light diabetic polyneuropathy. Another control subject had a possible seasonal allergic rhinitis (not at the time of the testing). Moreover one PD patient had a nose surgery with probable reduced odor after surgery; the results concerning olfactory function testing were also calculated when these two subjects were excluded.

The PD group had the following demographic characteristics: a mean age of 68.3 years (± 8.2) with a range of 53-80 years, a median education of 13 years with a range of 9-20 years. The median Mini–Mental State Examination (MMSE) was 29 with a range of 27-30 and the Beck Depression Inventory (BDI) score was 8 with a range of 0-17. Thirty one patients were right-handed (91.2%) and 3 (8.8%) were left-handed. Regarding the disease characteristics the median age at onset of PD (defined as onset of symptoms) was 60 with a range of 35-75 years; the median disease duration was 9 with a range of 2-20 years. Sixteen patients (47.1%) had an akinetic-rigid, 13 (38.2%) an equivalent and 5 (14.7%) a tremor-dominant PD type. The predominant side of motor symptoms was in 20 patients (58.8%) the right side and in 14 (41.2%) the left side. The mean Unified Parkinson's Disease Rating Scale (UPDRS) total score was 38.8 (±13) with a range of 15-67 and the mean UPDRS III score was 20.7 (± 6.7) with a range of 6-36. The modified Hoehn and Yahr (H&Y)

score, as measure of disease disability, had a median (=mean) of 2.5 and a range of 1-4. The modified Schwab und england activities of daily living scale was in 9 patients (26.5%) 100%, in 10 patients (29.4%) 90%, in 7 patients (20.6%) 80%, in 6 patients (17.6%) 70%, in one patient (2.9%) 60% and in another one (2.9%) 50%. Sixteen patients (47.1%) reported orthostatic dysregulation i.e one or more of the following symptoms: orthostatic hypotonia, urinary bladder disorder (urinary urgency), obstipation. All patients were taking medication for treatment of PD with a median daily L-Dopa equivalent dosis (LEDD) of 577 with a range of 100-2417.5 mg, calculated as suggested by Tomlinson et al. (Tomlinson et al., 2010) (median daily dosis of L-dopa 275 mg, range 0-1050.8 mg). The patients received most frequently L-Dopa and benzerazide combinations or L-Dopa, Carbidopa und entacapone combinations, dopamine agonists (most commonly pramipexole, rotigotine and ropinirole), inhibitors of monoamine oxidase like rasagiline and amantadine. Less commonly taken were anticholinergica like trihexyphenidyl (3 patients) and bornaprine (1 patient), antidepressants or anxolytics like mirtazapine (3 patients) and citalopram (2 patients) as well as hypnotic agents like oxazepam (1 patient) and zopiclone (2 patients). All patients were tested during ”on” state i.e while being administered their anti-parkinsonian medications. Regarding smoking habits one patient (2.9%) was smoker, 21 patients (61.8%) non-smokers and 12 (35.3%) ex-smokers. The mean pack-year number was 5.24 (±10.7) with a range of 0-49 years.

The HC group had a mean age of 69.5 (±8) years with a range of 53-83 years and a median education of 13 years with a range of 9-19 years. The median MMSE score was 29 with a range of 27-30 and the median BDI score 4 with a range of 1-11. Twenty two (91.7%) healthy participants were right-handed and 2 HC (8.3%) left-handed. Regarding smoke habits one HC (4.2%) was smoker, 13 (54.2%) were non-smokers and 10 (41.7%) were ex-smokers. The mean pack-year number were 8.33 (± 15.8) with a range of 0-64 pack-years.

The demographic characteristics and clinical characteristics of the two groups are shown in Table 1.

Table 1. Demographic characteristics of the participants groups

Variable	*PD group* (n=34)	*HC group* (n=24)	*p*
Age (years)	68.3 (±8.2)	69.5 (±8)	NS
Sex	M/F=18/16	M/F=14/10	NS
Education (years)	13 (9-20)	13 (9-19)	NS
Handedness	31 (91.2%) R	22 (91.7 %) R	
	3 (8.8%) L	2 (8.3%) L	
Age of PD onset**	60 (35-75)	-	
Disease duration (years)	9 (2-20)	-	
MMSE score (/30)	29 (27-30)	29 (27-30)	NS
BDI score (/63)	8 (0-17)	4 (1-11)	*p*=0.005*
PD type		-	
akinetic-rigid	16 (47.1%)		
equivalent	13 (38.2%)		
tremor-dominant	5 (14.7%)		
H&Y score	2.5 (1-4)	-	
H&Y 1	1 (2.9%)		
H&Y 1.5	2 (5.9%)		
H&Y 2	6 (17.6%)		
H&Y 2.5	14 (41.2%)		
H&Y 3	10 (29.4%)		
H&Y 4	1 (2.9%)		
UPDRS total	38.8 (±13)	-	
UPDRS III	20.7 (± 6.7)	-	
Side of predominance		-	
R	20 (58.8%)		
L	14 (41.2%)		
Autonomic		-	
dysregulation***	24 (70.6%)		
Yes	10 (29.4%)		
No			
RBDSQ	5 (1-13)	2.5 (0-7)	*p*<0.001*
L-dopa equivalent daily dose (LEDD, mg)****	577 (100-2417.5)	-	

The values are described as Mean (±SD) or Median (Range) or as percentage of total, NS=non-significant, *statistical significant at 0.05 level, **defined as onset of symptoms, ***orthostatic hypotonia and/or urinary bladder disorder and/or obstipation, ****calculated as suggested by Tomlinson et al. (Tomlinson et al., 2010) Abbreviations: PD=Parkinson's disease, HC=healthy control, M/F: Male/Female Ratio, MMSE=Mini–Mental State Examination, BDI=Beck Depression Inventory, H&Y=Hoehn and Yahr, UPDRS=Unified Parkinson's Disease Rating Scale, RBDSQ=REM Sleep Behavior Disorder Screening Questionnaire, LEDD=L-dopa equivalent daily dose, R=right, L=left

2.2 Methods

All participants (PD and HC) underwent an extensive neuropsychological assessment. The tests were administrated in a single session or in two sessions separated by a few hours and the test procedure lasted 1.5 hours or 2 hours altogether including an intermission. Patients with PD were also asked to report the time of their most recent drug intake, as they had to be in an ‘’on’’ state during the testing. After taking a medical, social and family history (regarding neurodegenerative diseases), all participants were neurologically examined. PD patients were clinical evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS) and H & Y score.

Unified Parkinson's disease rating scale (UPDRS) (Fahn et al., 1987) and Hoehn and Yahr score (see Appendix)

The UPDRS is the most commonly used scale in clinical studies of Parkinson's disease and is used to follow the longitudinal course of Parkinson's disease. It is evaluated by interview and clinical observation and consists of the following six sections:

- Part I: evaluation of mentation, reasoning, behavior, and mood
- Part II: self-evaluation of the activities of daily life including speech, handwriting, dressing, eating, hygiene, falling, turning in bed and walking
- Part III: clinician-scored motor evaluation
- Part IV: complications of therapy i.e. dyskinesias and fluctuations
- Part V: Hoehn and Yahr staging of severity of Parkinson's disease
- Part VI: Schwab and England Activities of Daily Living scale

A higher score indicates a greater severity of symptoms or signs. The patients were also classified in the Hoehn and Yahr stages, which is a five-stages-scale measuring the severity and progression of the disease and in the stages of the Modified Schwab and England Activities of Daily Living Scale, which is a self-rated assessment of overall everyday functional independence rated on an 11-point scale (see Appendix).

Mini Mental State Examination (MMSE) (max. score 30) (Folstein et al., 1975)

The test includes questions to assess general cognitive function including orientation to time and place (from broadest to most narrow), immediate recall (repeating three terms), attention and calculation (spelling a word backwards or subtracting seven from one hundred), (delayed) recall of the three terms named at the beginning of the test, language (naming a watch and a pencil), repetition (of a phrase), ability to follow simple commands (from easy to most complex including drawing figure with interlocking pentagons shown). Higher scores indicate better cognitive function.

Parkinson neuropsychometric dementia assessment (PANDA) instrument (max. score 30) (Kalbe et al., 2008)

The PANDA is a short test for the diagnostic assessment of cognitive impairment that was specifically developed for PD patients. The PANDA consists of a cognitive test part and a brief mood questionnaire, asking the patients how they were feeling lately. The test consists of the following 5 subtests covering a variety of domains such as verbal learning, verbal fluency, working memory and attention as well as visuospatial ability.

Word pair associate learning task with immediate (subtest 1) and delayed recall (subtest 5): In these two subtests, which examine the ability of verbal learning and memory, the participant had to learn four pairs of common, semantically unrelated words (banana–suit, paper–frog, storm–ball and feather–scarf). These pairs were repeated three times in the immediate recall condition, each time followed by naming of one of these words and asking for the second word of the pair (e.g. banana–?) without revealing the participant the right answers in case of mistakes. The order of the words in the recall condition was different in each trial. The maximal raw score was 12 for the immediate recall.

Alternating verbal fluency (subtest 2): This subtest includes cognitive domains like semantic memory (word retrieval), executive functions especially cognitive flexibility, attention and working memory, and speed of processing. The participants were asked to give as many examples of two semantic categories (e.g. the category animals and the category furniture) as possible within 1 min and to switch between

categories after each item. The number of correct words and switching errors were registered. There was no maximal raw score in this subtest.

Visuospatial task or spatial visual thinking or spatial (mental) imagery (subtest 3): In this spatial imagery task (mental mirrors) three half-masked squares with dot patterns (diagonal folded) were shown and the subject had to find the pattern which emerges when removing the mask i.e. when the square was unfolded. The maximal raw score was 3.

Working memory and attention task (subtest 4): In this task rows of numbers were read to the participants in a random order (e.g. „7–2–8–6“), and the subject had to repeat the numbers in a systematic order („2–6–7–8“). The number of items in the largest row correctly repeated was analyzed. The maximal raw score was 6.

In the delayed recall condition (subtest 5) approximately 6–8 min after the immediate recall the four word pairs had to be completed in the same way (after naming the one of the words and asking for the second word of the pair). The number of correctly recalled words was registered. The maximal row score was 4 for the delayed recall condition.

These raw scores were converted into the final subscores based on a table, which depends on age (≤59 years old or >60 years old), which in turn were added together to give the final score (maximal 30).

Test zum kognitiven Schätzen (TKS) (max. score 16) (Brand et al., 2002)

In this 16-item test, which involves many complex cognitive functions including activation and retrieval of specific semantic memories, working memory, planning and mental control, self-monitoring and self-correction, the participants were asked to estimate possible answers to questions in each of four categories: size, weight, quantity and time (4 questions in each category). Pictures of the objects were showed in the first three categories. All items required numerical responses. Participants were told that there was no exact answer for most questions so they had to make a reasonable guess what the answer would be. The estimation questions were asked out loud and participants gave their answers verbally. The participants could answer the questions using their preferred unit of measurement but the responses were converted to the same unit of measurement when scoring

the answers. Individuals were given as much time as necessary to make estimations. The answer had to be within a given range. Every answer below this range was noted as underestimated and every answer over this range was noted as overestimated. The maximal score was 16.

Beck Depression Inventory (BDI) (max. score 63) (Beck et al., 1996)

The BDI is a 21-question multiple-choice self-report inventory for measuring the severity of depression. The BDI-II version was used. It is composed of items relating to symptoms of depression such as hopelessness and irritability, feelings of guilt or of being punished, as well as physical symptoms such as fatigue, lack of appetite, weight loss, and lack of interest in sex. Higher scores indicate increasing depressive mood.

Facial Emotion Recognition Test (Ekman 60 Faces Test) from Ekman and Friesen series (max. score 60) (Ekman & Friesen, 1976)

In this test the subjects had initially to describe situations or circumstances in which people would experience the six basic emotions (happiness, anger, sadness, fear, disgust and surprise) in order to be sure that the participant had understand the meaning of these emotion words sufficiently. An example of a set of six expressions posed by a man was used for practice, to introduce the test.

Black and white photographs of the faces of 10 people (6 female, 4 male) were selected from the Ekman and Friesen (1976) series. For each face, the poses corresponded each of the six emotions (happiness, anger, sadness, fear, disgust and surprise), giving a total of 60 photographs. These photographs were viewed on a personal computer (PC) monitor, presented individually for 5 seconds each, followed by a blank screen. The participants were also given labels with the six emotions written. The participants were then asked to indicate which of the six emotions was depicted in each photograph by verbally referring to the emotion labels or pointing to one of the six emotion labels. The participants could take as long as they needed to decide on the emotion. In the case of a wrong answer, this one was noted,

without revealing the right answer to the participant. An overall score of the expressions correctly recognized was calculated.

Sniffin' Sticks odor identification test (max. score 16) (Hummel et al., 1997)

The Sniffin' Sticks test battery (Burghart, Wedel, Germany) is an olfactory test battery comprising of reusable felt-tip pens (''sticks''), which contain odorants from everyday life (mostly fruits and spices) dissolved in propylene glycol and which the subject has to sniff/smell. The pens were administered birhinally in front of the nose in a quiet, well-ventilated room to avoid any background smell interfering with the test odors. The participant should not have eaten at least fifteen minutes before the test. The participant was asked, before the beginning of the test, to evaluate his/her own smelling ability as normal, reduced or increased.

Odor identification ability was measured by presenting 16 odorants in suprathreshold intensity and asking individuals to choose from a multiple (4)-forced choice format with verbal descriptions. Each stick was held 2 cm in front of the nostrils for 3 to 4 seconds, with an interval of 20 to 30 seconds between each stick. The participants had no time limit to decide on the choice responded to each smell. Olfactory scores were defined as the number of correct responses (0–16).

*REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ) (max. score 13) (*Stiasny-Kolster et al., 2007)

The 10-item self-rated RBDSQ consists of questions regarding abnormal behavior during sleep phase with rapid eye movement (REM) sleep and covers the clinical features of rapid eye movement sleep behavior disorder (RBD). The questions ask about vivid dreams with aggressive or action-packed content, awareness of the moving of the arms and legs in sleep ("fights"), speaking, shouting or laughing while sleeping, doing gestures and complex movements that are useless during sleep (e.g. to wave or to salute) and falling off the bed as a consequence of this behavior.

Apathy Evaluation Scale (AES) (score 18-72) (Marin et al., 1991)

The AES-S, a self-rated scale, was administered to all subjects. The scale consists of 18 items and is aimed to provide global measures of apathy based on questions on interests, motivation, socialization, and how the individuals spend their time. The participant has to choose one answer between choices of a scale like "not at all", "slightly", "somewhat" or "a lot". Each item has a positive or negative meaning on the evaluation and concerns cognition, behavior, and emotion. The AES includes items evaluating cognitive evidence of apathy, for example, lack of interests, lack of curiosity and decrease in the importance attributed to goals or values (e.g health, finances or the welfare of others) as well as emotional evidence of apathy, for example shallow affect and emotional indifference. High AES scores indicate more apathy. In the original validation study of the apathy evaluation scale the mean (± standard deviation) score for healthy controls was 28 (±6) (Marin et al. 1991).

Statistical analysis

Analyses were carried out using the SPSS Version 17.0. Group differences in demographic, clinical and neuropsychological characteristics were analyzed with the independent two-sample Student's t-test for normally distributed continuous variables, the Mann-Whitney U test for non-normally distributed variables and the chi-squared test for categorical variables. To test for differences regarding the performance in the FER task between the two groups, an ANCOVA analysis was conducted using as dependent variable the performance in the FER task and as independent the variables sex, age and group. The analysis was repeated to control for two possible (additional) confounding factors (BDI and Apathy scores), which had a significant difference between the two groups. A sensitivity analysis in the FER task was also conducted, excluding the subjects with specific characteristics. In addition, linear regression analysis was used to explore for possible associations of FER with demographic, clinical or neuropsychological characteristics. Statistical significant threshold for all analyses was set at $p<0.05$.

3. Results

Performance on neuropsychological tasks

Performance on PANDA test

Thirty patients (88.2%) had a normal performance (equal or more than 18 points) and only two patients (5.9%) had a marginal score of 14, indicating according to the classification given by the test a probable dementia. Twenty-two HC (91.7%) had a normal performance and one (4.2%) a marginal performance of 14 points. Data from two patients and one healthy participant were missing on this test. There was no statistically significant difference in the performance on this test between the two groups (U=285, p=0.155). Regarding the subtests of the PANDA test, the groups showed no statistically significant difference. The scores of the two groups in the PANDA test and its' subtests can be seen in Table 2. As verbal learning was defined the difference between the numbers of words recalled after the third trial of word pairs and the number of words recalled after the first trial (in subtest 1).

Performance on TKS

Twenty one patients (61.8%) had a normal performance (score ≥11), 12 patients (35.3%) a slight impaired one (score 8-10) and one patient (2.9%) impaired (score ≤7). Seventeen HC subjects (70.8%) had a normal performance and 7 (29.2%) a slight impaired one. The two groups did not differ significantly on the cognitive estimation task (U=345.5, p=0.319). The scores of the two groups in the TKS can be seen in Table 2.

Apathy evaluation scale

The median score of the PD group on the apathy evaluation scale was 31.5 with a range of 18-29. The median score of the HC group was 24.50 with a range of 18-37. The two groups differed statistically significant, with the PD group exhibiting a higher apathy score (U=281, p=0.045).

Table 2. Performance on PANDA and cognitive estimation task

	PD group	*HC group*	*Test stats, p value*
PANDA total (/30)	24 (14-27)	25 (14-30)	U=285, *p*=0.155
Immediate recall (/12)	8 (2-12)	8 (1-12)	U=356, *p*=0.843
Verbal learning (recall 3-recall 1)	1 (-1-3)	1 (-1-3)	U=358, *p*=0.859
Alternating verbal fluency	12 (7-19)	13 (9-20)	U=299, *p*=0.235
Switching errors	0 (0-2)	0 (0-3)	U=307, *p*=0.106
Visuospatial task (/3)	2 (1-3)	2 (1-3)	U=303, *p*=0.223
Working memory and attention task (/6)	5 (4-6)	5 (4-6)	U=318, *p*=0.357
Delayed recall (/4)	2 (0-4)	2 (0-4)	U=331, *p*=0.514
TKS total (/16)	11 (6-15)	12 (8-15)	U=345.5, p=0.319
size (/4)	3 (1-4)	3 (1-4)	
weight (/4)	3 (1-4)	2.5 (1-4)	
quantity (/4)	3 (1-4)	3 (1-4)	
time (/4)	3 (0-4)	4 (1-4)	

Test stats=test statistic of the Mann-Whitney test. (/max) =max. test score, when available shown in parenthesis. The performances are presented as Medians with Range.
TKS=cognitive estimation task. *statistical significant at 0.05 level

Performance on odor identification test

The mean score of the PD group in the Sniffin' Sticks test was 7.91 (± 2.98) correct responses (out of 16), while the mean score of the HC group was 11.42 (±2.13) correct responses. There was, as expected, a statistically significant difference in the scores of the two groups with the PD group having a significant lower score than the HC group (t=4.940, $p<0.001$). The same results were found when, the two participants, one HC who had a possible seasonal allergic rhinitis and a PD patient who had a nose surgery with probable reduced odor after the surgery, were excluded from the analysis (t=4.976, $p<0.001$).

Performance on Facial Emotion Recognition task

The mean total performance of the PD group in the emotion recognition task was 46.91 (±4.5). The HC group had a total mean performance of 49.63 (±4.4). In order to investigate, if there was a significant difference on the performances of the two groups in the FER task, an ANCOVA analysis was conducted using as dependent variable the performance in the FER task and as independent the variables sex, age and group. As shown in one-way ANCOVA, PD patients had on average a statistically significant lower score on the total FER task in comparison with HC ($F=8.030$, $p=0.006$).

Concerning specific emotions, the PD group showed particularly an impairment in the recognition of surprise with a statistically significant lower score compared to HC ($F=7.885$, $p=0.007$). The difference in the identification of anger was close to statistical significance ($p=0.07$). As the two groups showed a statistically significant difference in BDI and Apathy score, the analysis was repeated to control for these two possible (additional) confounding factors (BDI and Apathy scores). The findings on FER task remained significant even after controlling for depression and apathy ($F'=6.684$, $p=0.013$ for the total FER score and $F'=10.186$, $p=0.002$ for the recognition of surprise). In addition, after excluding three subjects (2 PD patients, one HC) having a marginal score of 14 points in PANDA test (despite having a MMSE score of >27 points and no clinical signs of dementia), the results did not change ($F=6.671$, $p=0.013$ for the FER total score and $F=10.407$, $p=0.002$ for the recognition of surprise). The scores of the two groups regarding the total and specific emotion recognition are shown in Table 3.

Table 3. FER performance of the PD and HC group

	PD group (N=34) Mean (±SD)	*HC group (N=24) Mean (±SD)*	*F*	*p*	*F'*	*p'*
FER total	46.91 (± 4.5)	49.63 (±4.4)	8.030	*0.006**	6.684	*0.013**
happiness	9.76 (±0.43)	9.92 (±0.28)	2.786	*0.101*	3.954	*0.052*
anger	8 (±1.74)	8.67 (± 1.24)	3.320	*0.074*	2.211	*0.143*
sadness	7.85 (±1.6)	8.13 (± 1.6)	0.919	*0.342*	1.016	*0.318*
fear	4.5 (±2.12)	4.96 (±2.33)	1.027	*0.315*	0.516	*0.476*
disgust	8.68 (± 1.25)	8.79 (1.29)	0.160	*0.691*	0.022	*0.882*
surprise	8.12 (±1.7)	9.17 (±1.09)	7.885	*0.007**	10.186	*0.002**

ANCOVA for multiple factors controlling for age and sex; repeated after entering the factors BDI-score and apathy as covariates in the analysis (F', p') * Statistical significance at 0.05 level

The accuracy for recognition of specific emotions (percentage of correct answers) in the PD and HC group respectively was as following (shown in Fig. 2): happiness 97.65% and 99.17%, anger 80% and 86.67%, sadness 78.53% and 81.25%, fear 45% and 49.58%, disgust 86.76% and 87.92% and surprise 81.18% and 91.67%. Thus, the emotion more accurately recognized by both groups was happiness while fear was less accurate recognized also by both groups.

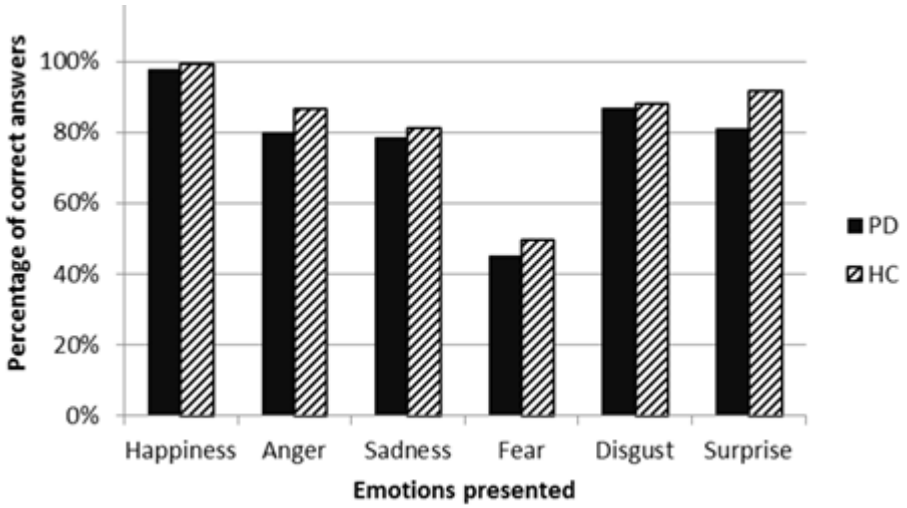

Fig. 2. Accuracy of FER of specific emotions in the two groups

In the PD group the most common misattribution of happiness was as surprise (75% of the wrong answers regarding this emotion), of anger as surprise 36.76%, of sadness as fear (47.95%), of fear as surprise (39.46%), of disgust as anger (53.33%) and surprise as fear (50%). In the HC group happiness was most common misinterpreted as surprise (100% of the wrong answers), anger as disgust (40.63%), sadness as fear (53.33%), fear as surprise (42.98%), disgust as anger 48.28% and surprise as fear (65%). Thus, the most common misattributions of emotions in both groups were: happiness as surprise, sadness as fear, fear as surprise, disgust as anger and surprise as fear.

In PD patients, possible associations between FER and potential predictors were assessed using linear regression analysis. FER was associated with chronological age (β=-0.294, *p*=0.001, CI 95% -0.462, -0.126) and age of onset of the disease (β=-0.194, *p*=0.012, CI 95% -0.342, -0.046). With increasing age PD patients showed a worse total recognition of facial emotions and specifically the increase of the patients' age by one year reduced on average the total FER score by 0.294. As seen in Fig. 3, the effect of age on FER performance was more pronounced in the PD patients compared to controls. In a regression analysis within all subjects, adding age to group classification (PD or control) as predictor factors leaded to a 15% increase in the total variance of FER explained by the model (adjusted R^2 = 0.205, *p*= 0.002) compared to the analysis using as predictor factor the disease status alone. Similarly, with increasing age of onset of the disease, patients had a worse performance on the FER task and specifically the increase of the age of onset of the disease by one year reduced the total FER score on average by 0.194.

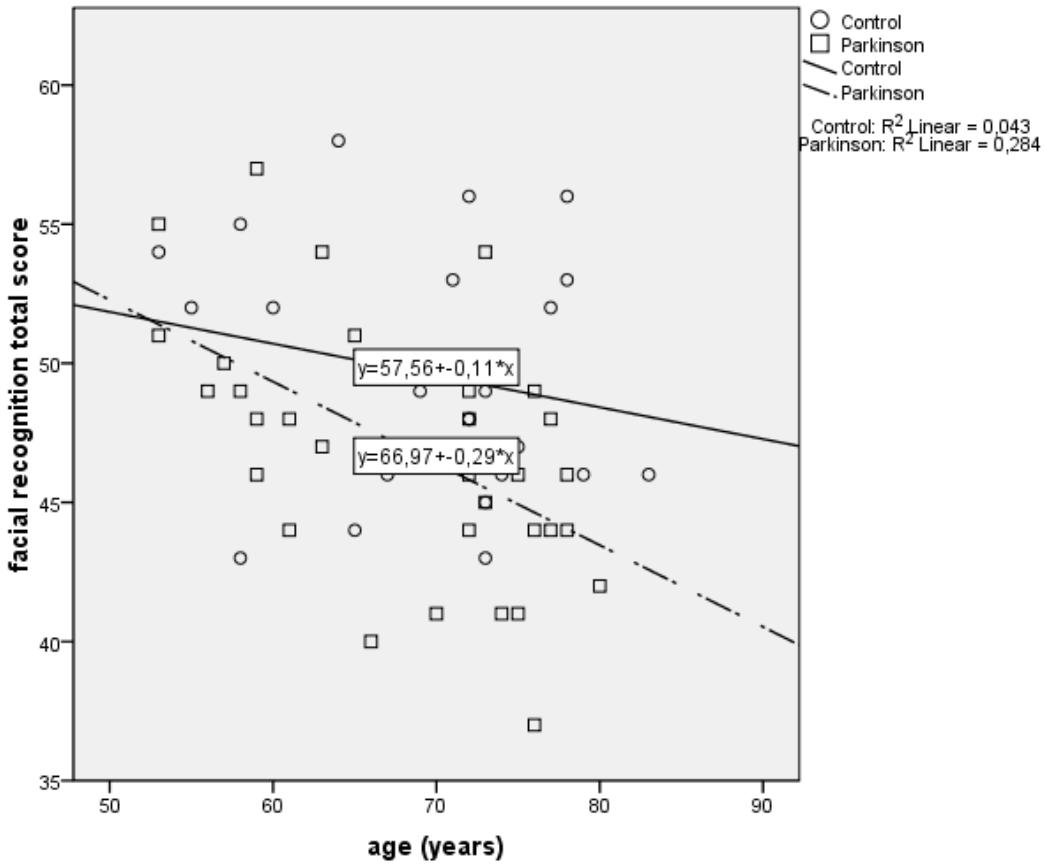

Fig 3. Effect of age on FER-performance in PD and HC

On the other hand, FER was not associated with patients' characteristics like gender, education and handedness. FER was also not predicted by disease characteristics like disease disability measured by UPDRS total score, motor impairment measured by UPDRS III, disease duration, disease severity measured by H & Y score, disease most affected body side, type of PD, hypomimia as quantified by UPDRS item III, (vertical) restriction of ocular movements (clinically assessed), freezing of gait, postural instability, orthostatic dysregulation and REM sleep behavior disorder.

Regarding facial emotion recognition and olfaction, there was a slight positive association (β=0.45) found, which was close to statistical significance (p=0.087, CI 95% -0.069, 0.969). Furthermore, when olfactory function was entered next to group classification as predictor factor into a regression analysis model within all participants, the prediction of FER performance was considerably improved (adjusted R^2= 0.135, p= 0.025 versus adjusted R^2=0.069, p=0.026 in the model using as predictor factor the group classification alone).

In addition FER was not also predicted by cognitive performance (MMSE, performance on PANDA), executive functions measured by PANDA subtests like immediate and delayed recall, visuospatial ability and working memory or performance on the cognitive estimation task. Verbal fluency, showing a slight positive association with FER, only approached statistical significance (β=0.524, *p*=0.08, CI 95% -0.071, 1.119) but did not reached it. There was also no relationship found between FER and BDI or Apathy.

When examining for possible outliers in the FER task, there were two patients, who obtained scores more than 2 SD below the control mean of facial emotion recognition. These patients were not distinguished by any specific factor, such as age, education, duration or severity of PD, cognitive performance, depression or apathy, and dosage or type of medication.

4. Discussion

In the present study, a deficit in facial emotion recognition in PD patients compared with sex- and age-matched healthy controls was shown, consistent with previous studies, which showed a recognition deficit in all or some of the so-called basic emotions in PD (Sprengelmeyer et al., 2003; Yip et al., 2003; Dujardin et al., 2004; Suzuki et al., 2006; Lawrence et al., 2007; Ariatti et al., 2008; Clark et al., 2008; Ibarretxe-Bilbao et al., 2009; Assogna et al., 2010; Herrera et al., 2011; Baggio et al., 2012; Narme et al., 2013; Buxton et al., 2013; Saenz et al., 2013; Hipp et al., 2014). This FER impairment of the PD group in the present study remained significant after controlling for depression and apathy scores, which were found to have a statistically significant difference between the two groups.

Impaired facial emotion recognition in PD may rely on anatomical connections of the basal ganglia, which seem to play an important role in recognizing emotions from facial cues, as part of a distributed network of cortical and subcortical structures (Adolphs, 2002*a*). Both dorsal and ventral structures of the basal ganglia, which degenerate in PD, have functional connections with the amygdala (Sprengelmeyer et al., 1998; Adolphs, 2002*a*), a limbic structure traditionally linked to facial emotion recognition. The amygdala has been shown to be affected in PD in pathological and

neuroimaging studies (Harding et al., 2002; Braak et al., 2003*a*; Yoshimura et al., 2005; Baggio et al., 2012). There are also topographic connections between the basal ganglia and the prefrontal cortex, including the orbitofrontal cortex, areas that have been shown to be related with the facial emotion recognition (Sprengelmeyer et al., 1998; Adolphs, 2002*a*; Ibarretxe-Bilbao et al., 2009). The orbitofrontal cortex is the limbic portion of the frontal association cortex (Porrino et al., 1981) and is also associated with medial temporal limbic structures, which are considered to be critical for the processing of internal states such as affect and motivation (Miller and Cohen, 2001). Thus, the basal ganglia contribute to emotion recognition from faces (Adolphs, 2002*b*; Cheung et al., 2006) possibly both directly and indirectly through their connections with brain areas important for emotional processing, including the orbitofrontal cortex and the amygdala (Adolphs, 2002*b*; Péron et al., 2012).

The facial emotion recognition deficit in PD, expressing possibly a general emotional information processing deficit, may reflect a dysfunction of the cortical-basal ganglia-thalamic-cortical functional loops. The dopamine depletion that occurs in PD can lead to dysfunction of the limbic loop linking areas of the basal ganglia (most importantly the ventral striatum) to the orbitofrontal cortex (Lawrence et al., 2007; Péron et al., 2012), which could explain a FER deficit. Indeed, parts of the limbic loop (posterior parts of the ventral putamen) have been shown to be affected in PD patients in more advanced stages of the disease in neuroimaging studies (Morrish et al., 1996). As many studies showing a FER deficit included only patients early in the disease course (Sprengelmeyer et al., 2003; Dujardin et al., 2004; Suzuki et al. 2006), it can be assumed that these loops can be affected quite early in the course of the disease.

Most of the areas, which are considered to be involved in facial emotion recognition, namely the nigrostriatal system, the amygdala, the insular cortex and almost all cortex areas in later stages of the disease are known to be affected as a result of the PD-related pathology (Braak et al., 2003*a*). In this context should also be noted that brain pathology in PD affects according to a predictable ascending topographical sequence limbic areas, which constitute key neural substrates for the facial emotion recognition function, early in the disease course (Braak et al., 2003*a*). Thus, it might

be of interest for future studies to assess FER as a possible pre-motor sign of the disease.

Diederich et al. (Diederich and Parent, 2012) proposed that FER impairment in PD patients could be due to impairment of ancient (archaic) neural networks involving the basal ganglia. They proposed that the dysfunction of two types of archaic neural networks could be involved in PD: those involving sensory pathways i.e the olfactory system and the subconscious visual retino-tectal system and those concerning motility i.e gait automatisation and REM sleep disorder. The retinotectal visual system (RTVS) is an ancient subconscious visual pathway that extents from the retina to the superior colliculus via thalamus (pulvinar nuclei), connected by a closed loop to the basal ganglia (the substantia nigra pars reticulate), which is mainly responsible for gaze automatism and subconscious, rapid track appreciation of a face (De Gelder et al., 2005). The RTVS is of great importance to the so-called ´´blindsight vision´´ or vision without conscious appreciation (Goodale and Milner, 1992; Crick and Coch, 1995; Morris et al., 1999) and could thus play a role in the recognition of emotions of faces.

A less direct explanation of the facial emotion deficits in PD is that of the ´´reverse stimulation´´ (Goldman and Sripada, 2005). In everyday social interactions, the recognition of emotions involves a ´´facial feedback´´, in which the perceiver mimics, in a way, the emotion expressed in the partner´s face (Dimberg et al., 2000; Adolphs 2002*a*). This muscular activity helps the perceiver to experience to some extent and to categorize this emotion (Stel and van Knippenberg, 2008). Therefore, the deficits in facial emotion recognition in PD patients can be partially attributed to their decreased ability to mimic displayed emotions (Smith et al., 1996). However, in our study FER was not associated with the degree of hypomimia in PD patients. Interesting is to investigate closer, whether the loss of ability to recognize an emotion is associated with the inability to experience that emotion, a phenomenon called empathy (Assogna et al., 2008).

Regarding specific emotion impairment, a specific deficit for the emotion of surprise in PD patients was found in the present study. A significant difference ($p<0.01$) in

recognizing surprise was also found in the study of Clark et al. (Clark et al., 2008), and was replicated in the study of the same authors (Clark et al., 2010), which included a sub-sample of the original cohort, observed in the patients with right side of motor onset (driven by left hemisphere pathology). In the neuroimaging study of Ibarretxe-Bilbao et al. (Ibarretxe-Bilbao et al., 2009), PD patients showed also a statistically significant lower score in the recognition of surprise. In the study of Baggio et al. (Baggio et al., 2012), which primarily explored the neural substrates of FER in PD patients using fMRI, an impairment in the recognition of surprise only approached statistical significance (p=0.07). Compared to the group of the present study, the PD group in the studies of Clark et al. (Clark et al., 2008), Baggio et al. (Baggio et al., 2012) and Ibarretxe-Bilbao et al. (Ibarretxe-Bilbao et al., 2009) was on average younger and had a slightly lower disease severity (measured by Hoehn and Yahr score) and shorter disease duration while other demographic characteristics like MMSE and education were comparable. In the study of Buxton et al. (Buxton et al., 2013) the PD group only approached significance for poorer accuracy at recognizing surprise (p=0.06) at the moderate level of difficulty of the FER task, while there was no significant difference found at the easy level of the task. At this point should be noted, that a lot of studies did not test for surprise (Dewick et al., 1991; Jacobs et al., 1995; Madeley et al., 1995; Breitenstein et al., 1998; Tessitore et al., 2002; Dujardin et al., 2004*a*; Ariatti et al., 2008; Assogna et al., 2010; Cohen et al., 2010; Narme et al., 2011; Wieser et al., 2012; Saenz et al., 2013).

Concerning the neural substrates of the recognition of surprise, there are a few data on this issue, which are mostly collected by the assessment of the five other basic emotions. Bilateral damage to the amygdala has been shown to be related with a deficit in the recognition of fear and surprise (after bilateral amygdala damage in the studies of Adolphs et al. (Adolphs et al., 1994; Adolphs et al., 1995) and after partial bilateral amygdalotomy in the studies of Young et al. (Young et al., 1995; Young et al. 1996)). Posamentier and Abdi (Posamentier and Abdi, 2003) commented that the expression of surprise has strong resemblances with the emotion of fear including wide open eyes and mouth. Indeed, in our study the most commonly misattribution of surprise in both PD patients and healthy participants was as fear. Furthermore,

Posamentier and Abdi suggested that as the emotional states are dynamic, the emotion of surprise can be defined as a "transitory emotion", that can quickly turn into fear (negative emotion) or happiness (positive emotion), depending on the nature of the stimuli (Posamentier and Abdi, 2003). A neuroimaging study in normal subjects (Kim et al., 2003) showed inverse fMRI activation patterns in amygdala and medial prefrontal cortex, depending upon whether the subjects interpreted surprised facial expressions positively or negatively. More negative interpretations of surprised faces were associated with greater activation in the right ventral amygdala, while more positive interpretations with greater activation in the ventral medial prefrontal cortex (Kim et al., 2003). These areas are known to be affected from PD related pathology (Braak et al., 2003*a*), providing a reasonable explanation of this specific emotion impairment in PD patients. However, whether these activation patters are disturbed in PD remains to be elucidated. Moreover, PD patients may exhibit difficulties in resolving visual perceptional ambiguity (Diaz-Santos et al., 2015), possibly contributing to impaired surprise recognition in the PD group, which, as mentioned, can be an ambiguous stimulus. The recognition of surprise is also shown to be impaired in Huntington´s disease (Sprengelmeyer et al., 1996), a disease affecting the basal ganglia and in individuals with Korsakoff´s syndrome (Montage et al., 2006), which is characterized by frontolimbic pathology. The general and specific neural circuitry underlying recognition of rather positive emotions (like happiness and surprise) is, generally, far less well understood than for many negative emotions (Kringelbach and Berridge, 2010) and could be the aim of future studies.

Anger was worse recognized in the PD group compared to the healthy control group, but this difference was only close to statistical significance (p=0.06). Notably, the recognition of anger has been shown to be impaired in PD patients in some previous studies (Sprengelmeyer et al., 2003; Lawrence et al., 2007; Clark et al., 2008). The impairment in recognizing anger has been linked to dysfunction of ventral striatum (Calder et al., 2004), providing a possible explanation for this finding in PD patients.

The emotion most accurately recognized by both groups in the present study was happiness while fear was least accurately recognized. Across studies happiness was the emotion most accurately recognized and fear the one least accurately recognized

by both PD and healthy participants (Adolphs et al., 1998; Kan et al., 2002; Sprengelmeyer et al., 2003; Ariatti et al., 2008; Suzuki et al., 2008; Clark et al., 2008; Ibarretxe-Bilbao et al., 2009; Narme et al., 2013; Buxton et al., 2013; Saenz et al., 2013; Hipp et al., 2014). Facial expressions of fear are, indeed, even among the healthy population the most difficult to recognize (Russell, 1994; Biehl et al., 1997; Ruffman et al., 2008). The most common misattributions of emotions in both our groups were: happiness as surprise, sadness as fear, fear as surprise, disgust as anger and surprise as fear. The only emotion, which the two groups misinterpreted differently, was anger: the PD group as surprise while the HC group as disgust.

Facial emotion recognition impairment was found in our study to be associated with chronological age and age of onset of PD. Older PD patients tended to recognize worse facial emotions. A significant correlation of the total FER score with age of PD patients was also found in the study of Adolphs et al. (Adolphs et al., 1998), in the study of Baggio et al. (Baggio et al., 2012) (r=-0.35, p=0.028) and in the study of Mart´ınez-Corral et al. (Mart´ınez-Corral et al., 2010) (r=-0.312, p=0.033). This finding is consistent with the observations that recognition of emotion, especially of negative emotions like anger, sadness and fear and to a less extent of happiness and surprise, is less accurate in older healthy adults compared to young adults (Ruffman et al., 2008). This can be attributed to the age-related changes found in areas associated with facial emotion recognition like the frontal and temporal regions (Bartzokis et al., 2001; Raz et al., 2005), the orbitofrontal cortex (Convit et al., 2001; Tisserand et al., 2002) and the amygdala (Mu et al., 1999; Allen et al., 2005). PD neuropathological changes, which according to Braak et al. (Braak et al., 2003*a*) affect these areas, in combination with age-related changes could explain the observed association of facial emotion recognition with chronological age. From another point of view, the decline in general cognitive resources, observed with increasing age, such as slowed processing speed or decreased working memory capacity (Philips and Henry, 2005), could partially explain a worsening in the performance in FER with increasing age. Although it is difficult to isolate the effect of age at disease-onset from the effect of chronological age, PD patients with a higher age at disease onset also had a worse performance in the FER task in our

study. It has been suggested that early-onset and late-onset subtypes of PD may demonstrate different phenotypes, since young-onset patients are more likely to carry genetic mutations responsible for their clinical phenotype even in the absence of positive family history, whereas late-onset patients are more likely to represent cases with more multifactorial etiology in which neuroprotective mechanisms have been exhausted and the harmful effects of yet unknown exogenous factors have summed up or are superimposed on natural aging processes leading to the manifestation of the disease (Pagano et al., 2016). A strict classification of symptoms to different subtypes according to age of disease onset has not yet been possible, although the severity of motor and non-motor features seem to increase with age of onset (Pagano et al., 2016). Later age of onset is also considered a risk factor for cognitive decline in PD (Hobson and Meara, 2004).

We found that olfactory function along with PD diagnosis predicted worse facial emotion recognition performance within all study participants. Our finding is of special interest as, to the best of our knowledge, an association of olfaction with FER has not been previously reported in PD. As facial emotion recognition and olfaction share common neuroanatomical substrates, the association between them is plausible. Indeed, the cortical nuclei of the amygdala, a structure traditionally involved in FER, are closely linked to the olfactory bulb and have a well-known involvement in olfactory function (Harding et al., 2002). Furthermore, the orbitofrontal cortex, an important neural substrate of FER, receives projections from the primary olfactory cortex (piriform cortex) (Doty, 2012; Soudry et al., 2011). The orbitofrontal cortex and insular cortex, which have been linked to perception of facial expression of adverse stimuli, in particular that of disgust (Phillips et al., 1997; Rolls, 2015), are considered to be involved in a higher level processing of olfactory and gustatory stimuli. Functional brain imaging studies (Levy et al., 1997) showed activation of these same areas in response to olfactory stimuli, in some studies dependent on valence (pleasantness or unpleasantness) of stimuli (Fulbright et al., 1998; Zald & Pardo, 1997). At a behavioral-cognitive level, emotional cues carried by odors may be a potent factor in regulating the perception of facial emotion. Olfactory stimuli could possibly pre-activate visual representations of emotional

expressions through intersensory integration processes (Leleu et al., 2015). Another explanation could be that the odors involve the motor system by activation of mirror neurons (Gallese & Goldman, 1998). Odors could provoke facial microreaktions, which may facilitate the recognition of facial expressions (Leleu et al., 2015). Olfactory information may also participate in recognition of emotion, for example by facilitating a classification in olfaction-related emotional categories (e.g. pleasant vs. unpleasant) (Leleu et al., 2015). Thus, the perception of facial expressions is not a purely visual process but also integrates cues from other sensory modalities, including olfaction.

All the above mentioned areas, namely the amygdala, the orbitofrontal and insular cortex, involved in both FER and olfaction are affected from PD-related pathology (Braak et al., 2003*a*; Harding et al., 2002). The functional connections of these areas imply that dysfunction of one area, as a result of degeneration, can lead to dysfunction of the other. From another point of view, according to the hypothesis proposed by Diederich & Parent (Diederich and Parent, 2012) both sensory deficits, FER and olfactory function, could result from an impairment of phylogenetically ancient neural networks in PD involving sensory pathways i.e the olfactory system and the subconscious visual retino-tectal system, which is mainly responsible for gaze automatism and subconscious, rapid track appreciation of a face.

The facial emotion recognition impairment was not associated with any demographical characteristic of the patients like gender or education in the present study consistent with other previous studies (Adolphs et al., 1998; Clark et al., 2008; Buxton et al., 2013; Saenz et al., 2013). It was also not associated with handedness, although most participants were right-handed and conclusions should be drawn carefully on this matter. FER was also not associated with disease characteristics like disease disability measured by UPDRS total score and severity of motor impairment measured by UPDRS III in accordance with other studies (Dujardin et al., 2004*a;* Ariatti et al., 2008; Saenz et al., 2013). On the other hand, in the study of Buxton et al. (Buxton et al., 2013) the UPDRS III score was significantly negatively associated with the overall performance in the FER task. Lawrence et al. (Lawrence et al., 2007) showed also a significant negative correlation between the degree of motor

impairment and recognition of sadness. In these two studies (Lawrence et al., 2007; Buxton et al., 2013) the patients were slightly more severely affected compared to the PD patients of the present study. Moreover, Pell and Leonard (Pell and Leonard, 2005) found a marginally significant negative correlation between the degree of motor symptoms and the recognition of disgust. Sprengelmeyer et al. (Sprengelmeyer et al., 2003) reported opposite results with more apparent facial emotion recognition impairment in patients with less severe motor impairment. FER was not associated with disease duration like in many previous studies (Clark et al., 2008; Assogna et al., 2010; Baggio et al., 2012; Buxton et al., 2013) or disease severity measured by H & Y score also in accordance with other studies (Clark et al., 2008; Baggio et al., 2012; Buxton et al., 2013). Across studies, the level of emotion recognition deficit does not appear to be related to the level of motor disability. However, it should be noted that the patients included in the studies exhibited mild to moderate bilateral disease, and other conclusions may have been drawn if most severely affected patients were included (Gray and Tickle-Degnen, 2010). No association was also found with type of PD (akinetic-rigid, equivalent or tremor-dominant) or the disease most affected body side in the present study. Regarding the association between the emotion recognition deficit of PD patients and the predominant side of motor symptoms, Yip et. al (Yip et. al, 2003) showed an impairment in the recognition of all emotions in patients with bilateral motor symptoms, with the recognition of fear and sadness being more impaired, while the right-sided PD patients showed an impairment in the recognition of all emotions, especially in the recognition of sadness and disgust except happiness. Furthermore, Ariatti et al. (Ariatti et al., 2008) found that right-side PD patients were impaired in recognition of fear whereas left-side patients in the recognition of sadness. Clark et al. (Clark et al., 2008) showed that PD patients with left side of onset of symptoms (driven from right-side pathology) show impairment in the facial recognition of anger while those with right side onset (driven from left-side pathology) of surprise. Thus, although the right hemisphere is traditionally thought to be more active than the left in processing of emotions (Adolphs et al., 1996), a clear lateralization in recognizing of facial emotions has not been proved. While it might be considered, that hypokinesia and especially hypomimia (the ability to show emotions with facial

expressions) in PD patients could be associated with impaired ability to recognize the facial emotions of others (Assogna et al., 2010), this was not the case in our study in which FER was not associated with the degree of hypomimia. FER was also not associated with freezing of gait, postural instability, orthostatic dysregulation and REM sleep behavior disorder. A possible association with these clinical parameters, to the best of our knowledge, was not examined before.

Facial emotion recognition was also not associated with the dopaminergic medication in the present study like in other studies (Baggio et al., 2012; Hipp et al., 2014), and in the meta-analysis of Gray and Tickle-Degner (Gray and Tickle-Degner, 2010). Dopamine transmission plays an important role in the modulation of emotional responses. Tessitore et al. (Tessitore et al., 2002) demonstrated in a study using functional MRI in healthy subjects and PD patients that the activation of amygdala in response to fearful emotional stimuli was absent in PD patients during the hypodopaminergic state (i.e., > or =12 hours after their last dose of dopaminergic treatment). Dopamine repletion partially restored this response in PD patients. Accordingly, Sprengelmeyer at al. (Sprengelmeyer at al., 2003) showed that the recognition of disgust was more impaired in unmedicated (drug-naive) compared to medicated PD patients. In another functional study the acute treatment with D2 receptor antagonists reduced the amygdala activity in fMRI in healthy subjects in response to affective pictures (Takahashi et al., 2005). Furthermore, Lawrence et al. (Lawrence et al., 2002) showed that acute dopaminergic blockade in healthy volunteers resulted in a transient disruption of the recognition of facial expressions of anger, while leaving intact the recognition of other facial expressions. The same authors (Lawrence et al., 2007) showed an impaired recognition of facial expressions of anger in a group of PD patients transiently withdrawn from dopamine replacement therapy. Assogna et al. (Assogna et al., 2010) showed a positive correlation of LEDD (daily l-dopa dosis) with only the recognition of fear. On the other hand, Hipp et al. (Hipp et al., 2014) and Baggio et al. (Baggio et al., 2012), showed no correlation of FER with the levodopa medication. Gray and Tickle-Degner (Gray and Tickle-Degner, 2010) in their meta-analysis, although they did find that the emotion recognition impairment (effect size) was greater in patients in a

hypodopaminergic state, consistent with the assumed role of dopamine in emotion regulation and recognition, the difference in the impairment in facial emotion recognition between medicated patients and patients at hypodopaminergic state at the time of testing was not significant. Based on these results, is thus plausible to hypothesize that an impaired FER is unlikely to be explained by a sole dopamine deficiency.

The identification of emotions can be seen as a complex cognitive process, demanding the integrity of many cognitive domains such as visual attention, visuospatial perception, working memory and language (Assogna et al., 2008). The FER performance was, however, not associated with the cognitive performance of patients or executive functions like immediate and delayed recall, verbal fluency and working memory (as covered by the PANDA test) in the present study. Furthermore, after excluding the three subjects (2 patients, one healthy control) having a marginal score of ≤14 points in PANDA test, indicating a probable dementia according to the classification given by the test, the results did not change. It has to be noted that these participants had a MMSE score of >27 points and lacked any clinical signs of dementia while their score (14 points) in PANDA test was very close to the test limit. Moreover, our study was the first to show the lack of association between FER and performance on the cognitive estimation test, which is generally considered to be a measure of executive function, demanding retrieval of semantic memories, working memory and self-monitoring. The results regarding an association of FER with cognitive and executive functions were quite inconsistent in a small number of previous studies, which used heterogeneous methods of assessment and focused on different aspects of executive functions. Adolphs et al. (Adolphs et al., 1998) and Kan et al. (Kan et al., 2002) did not found any correlation of facial emotion recognition with MMSE score (in patients with MMSE score greater or equal to 23). Accordingly, Lawrence et al. (Lawrence et al., 2007) and Pell and Leonard (Pell and Leonard, 2005) failed to show any correlation between facial expression recognition and cognitive scores. Moreover, Ariatti et al. (Ariatti et al., 2008) found no correlation with tasks exploring frontal dysfunction (Frontal Assessment Battery and modified Card Sorting Test). Saenz et al. (Saenz et al., 2013) did not find a significant correlation of FER

performance with attention and executive function tests (digit and spatial span tests, the similarities and picture completion subtests of the Wechsler Adult Intelligence Scale WAIS III, the Stroop test) as well as language (verbal fluency) tests. Alonso-Recio et al. (Alonso-Recio et al., 2014 *b, c*) showed also no correlation of FER with working memory or selective attention of PD patients. On the other hand, Assogna et al. (Assogna et al., 2010) found a positive correlation of total emotion recognition score with MMSE score, with immediate and delayed words recall, phonological verbal fluency and stroop interference time scores. Moreover, Dujardin et al. (Dujardin et al., 2004*a*) reported a relationship between the facial emotion recognition and the overall executive score (including tests of verbal fluency and working memory i.e. stroop test, letter and number sequencing task, crossed tapping test). Hipp et al. (Hipp et al., 2014) showed that lower scores in Frontal Assessment Battery, representing executive dysfunction, correlated with a worse recognition of anger in patients with early PD. It must be noted, that the tests evaluating executive functions in our study permitted only a general comparison on this issue and were less specific than these used in other studies, since they have been used to capture relevant cognitive impairment in PD. As the participants in our study and in most studies, were selected to be cognitively intact, it might well be that associations with cognitive parameters would have arisen, if patients with more pronounced cognitive deficits were included. The lack of an association between facial emotional processing ability and other specific cognitive domains in cognitively intact patients points to the fact that impairment of emotional recognition is a distinct non-motor feature of PD.

FER was also not associated with visuospatial ability in our study. The results of the studies, which used various tests assessing the visuospatial ability, are again not consistent. Yip et al. (Yip et al., 2003) showed that visual organization ability (measured by the Hooper Visual Organisation Test) positively predicted the ability to identify emotions from visual stimuli in patients with bilateral PD while visual attention (measured by the Ballons Test) did not. Saenz et al. (Saenz et al., 2013) found a significant correlation between the scores of FER and Brixton Spatial Anticipation Test (a test of visuospatial ability) but not with a test evaluating visual neglect (Bells test). Marneweck et al. (Marneweck et al., 2014*b*) suggested that the

impaired ability to perceive visual form (measured by a test using variable modulations of a perfect circle) is likely to contribute to the impaired ability to perceive facial expressions of emotions in PD. On the other hand, in the study of Adolphs et al. (Adolphs et al., 1998) and Clark et al. (Clark et al., 2008) FER in PD patients had no correlation with the Benton facial recognition test, one of the most commonly used test among studies, in which the participant is asked to discriminate between faces of unfamiliar people with neutral expressions. Kan et al. (Kan et al., 2002) showed again no correlation of FER from both static and moving facial stimuli with visuospatial function (using Rey-Osterrieth Complex Figure and Facial Identity discrimination test). Dujardin et al. (Dujardin et al., 2004) showed also no correlation between FER and visuospatial perception. Thus, most studies found no significant group differences regarding visuospatial ability, suggesting that the facial emotion recognition deficit in PD exists beyond a general deficit in face processing (Gray and Tickle-Degnen, 2010).

The facial emotion recognition in the present study, like in many previous studies, was not associated with the depression score of the PD patients. The present study, as most studies, excluded severe depressed PD patients. Most studies (Adolphs, 1998; Dujardin et. al., 2004*a*; Pell and Leonard, 2005; Ariatti et al., 2008; Buxton et al., 2013; Saenz et al., 2013) using Beck Depression Inventory or Hamilton Depression Inventory, reported no correlation between depression scores and facial emotion recognition in PD patients. Furthermore, Lawrence et al. (Lawrence et al., 2007), using the Beck Depression Inventory in a group of patients withdrawn from dopamine replacement therapy, reported also no significant correlation. However, in the study by Clark et al. (Clark et al., 2008) and Baggio et al. (Baggio et al., 2012) depression score was negatively correlated with FER. In the study of Kan et al. (Kan et al., 2002) was found a positive correlation between depression score (measured by the Zung Self-Rating Depression Scale) and the face recognition of fear while no correlation was found regarding the total score or the other facial emotions. The Meta-analysis of Gray and Tickle-Degner (Gray and Tickle-Degner, 2010) confirmed that the emotion recognition deficit in PD exists independent of depression. Thus, although affective states may influence sensitivity to and selective attention towards facial emotional expressions (Bourke et al., 2010) and emotion recognition

impairment for all basic emotions except sadness has been shown in the depression literature (Dalili et al., 2015), this does not seem to be the case in PD.

In addition, FER was not associated with apathy in our patients, consistent with the study of Saenz et al. (Saenz et al., 2013) which examined this issue. On the other hand, Robert et al. (Robert et al., 2013) found a significant negative correlation between apathy scores and performances on the FER task and Mart´ınez-Corral et al. (Mart´ınez-Corral et al., 2010) showed that non-demented, non-depressed PD patients with apathy scored significantly worse in the FER than PD patients without apathy and healthy controls.

It is a fact, that the various previous studies on facial emotion recognition in PD showed inconsistent results. This inconsistency can be attributed to variations in methodology across studies. Across studies there has been heterogeneity in the methods of assessment of facial emotion recognition, in patient samples, in age, cognitive status, disease severity and duration, or medication and the number of participants recruited were relative small (Gray and Tickle-Degnen, 2010; Leppanen, 2006). Concerning the methods used to assess facial emotion recognition, the most commonly used task was the Pictures of Facial Affect by Ekman & Friesen (Ekman & Friesen, 1976) as in the present study. Other common stimuli tests were the Japanese and Caucasian Facial Expressions of Emotion series (Matsumoto & Ekman, 1988) used in six comparisons and a subtest of the Florida Affect Battery (Bowers et al., 1991) used in five comparisons. The time of presentation of the visual stimuli varied also, even among the studies using the same test, ranging between three to ten seconds or was unspecified. In the present study, the time was chosen to be five seconds, in order to be sufficient for the patients to give an answer regarding the emotion depicted. Another factor that can have contributed to the inconsistency of the results of studies has been the variation across studies regarding task that was used and task difficulty. Most of the studies used identification tests (using labeling of emotions), while a lot of studies discrimination tests (for example deciding which of two photographs matches a named emotion or deciding whether two pictures expressed the same emotion) and a small number of studies used rating tasks (i.e. rating the extent of the depicted emotion) (Gray & Tickle-Denger, 2010). Concerning

task difficulty, the studies from Clark et al. (Clark et al., 2008) and Suzuki et al. (Suzuki et al., 2006) have controlled for task difficulty, while previous studies did not consider this factor. Dujardin et al. (Dujardin et al., 2004*a*) showed that the PD group was less accurate in recognizing visual stimuli of sadness, anger and disgust compared to the healthy controls, regardless of the level of reduced intensity of the stimuli. Saenz et al. (Saenz et al., 2013), who used hybrid faces created by software allowing variation of the emotion intensity depicted, found no significant difference between the recognition of low and high levels of intensity of stimuli in the PD group. On the contrary, Suzuki et al. (Suzuki et al., 2006) found a selective impairment in the recognition of disgust, only on the difficult task level. Buxton et al. (Buxton et al., 2013), using subtle expressions of emotion, showed that although PD patients identified emotional expressions on Ekman and Friesen phototypical test as accurately as the control group, as the facial expressions of emotion became more subtle, the PD group was significantly less accurate at identifying disgust in the moderate level, sadness at the most difficult level and happiness at both levels of subtlety. The emotions commonly tested across studies were anger, disgust, fear, happiness, sadness, surprise or a combination thereof. Not all studies tested for all the basic emotions. Another important limit of methods used for evaluating facial emotion recognition was the absence of other clues (such as verbal tone, gestures, body posture) of everyday life context, which can help the subjects in recognizing emotions (Assogna et al., 2008; Paulmann and Pell, 2010). Indeed, PD patients in the study of Kan at al. (Kan et al., 2002) performed better with video recordings than with photographs when asked to recognize sadness, anger, and disgust.

The majority of studies included patients who were receiving dopamine replacement therapy (L-Dopa or dopamine agonists) and few selected patients who were not on treatment. Even among the studies using participants on dopamine replacement therapy, there could have been a fluctuation of the levels of the drugs, depending on the time of the latest intake of the medication in relation to the time of testing (Gray and Tickle-Denger, 2010). Indeed, many of the studies did not mention whether patients were at their ”on” state during assessment. Four studies (Breitenstein et al., 2001; Dujardin et al., 2004; Lawrence et al., 2007; Sprengelmeyer et al., 2003)

included patients, who were not receiving medication, either because they were early in the course of the disease or because they were withdrawn from dopamine replacement treatment for the purposes of the study. In our study, all patients received their regular medication for the treatment of PD and were on their ”on” state.

Moreover, studies have varied in the extent to which PD patients have been matched with healthy control subjects on individual characteristics. For example, some studies have included among the PD groups individuals with significantly higher scores in the self-reported depression questionnaires than controls. As depression has been linked with deficits in the identification of emotions of faces (Feinberg et al., 1986), it is possible that these differences could have an influence on the results of the studies. Regarding depression, most of the studies have recruited participants, who did not have a psychiatric history, but only a few administrated a questionnaire of depression symptoms to the PD and control group, like in the present study (using the BDI). The majority of the studies matched the participants on age, gender and education, while a few studies matched only on age and education or age and gender alone. Regarding cognitive functioning, the majority of the studies excluded demented patients. One study (Beatty et al., 1989) (did not screen for dementia and) included patients with significantly lower score on the Mini-Mental State Exam than controls. In our study, the participants were age- and sex- matched and did not differ with respect to mini mental state examination score and education. The two groups in the present study differed in the depression score, which however did not influence the study results, as these were controlled for depression.

One limitation of the study was the size of our sample which did not allow for rigorous regression analyses of many predictor factors simultaneously. Another limitation was the utilization of the subtests of the PANDA test to assess executive and visuospatial functions of the participants and not of more specific tests, to avoid increasing patients’ fatigability by already extensive neuropsychological testing.

The present study contributes to the efforts made to better characterize this increasingly recognized neuropsychiatric feature in PD and to understand closer the pathophysiology underlying the non-motor features of PD. Thus, the relevance of this study extents to the understanding of the pathophysiology disease, which is not yet clarified. Furthermore, the associations of facial emotion recognition with age and age of onset of PD shown in the present study, stress the importance of testing for this neuropsychiatric symptom in older groups of patients in the clinical praxis. The association of facial emotion recognition with olfaction shown in the present study, in particular, has not been reported before. This association is endorsed from common structures that undergo neurogeneration in PD and as olfaction is a well-known pre-motor sign of the disease, it might be of interest for future studies to assess FER as a possible pre-motor sign of the disease with eventually contribution to the early-diagnosis of the disease.

The degree of emotion recognition deficit appears to be correlated with other interpersonal difficulties, such as feeling of frustration in social interactions and this of social isolation (Clark et al., 2008). It is likely that reduced emotion recognition ability contributes to social stress and this can lead to acceleration of the progression of age-related diseases (Hawkley and Cacioppo, 2004). Recognizing accurately the emotional states of others is an essential component of successful social interactions and effective communication in interpersonal relationships (Blair, 2003). This highlights the importance of future research in this field. Therefore, it seems necessary to integrate tasks accessing facial emotion recognition in the clinical praxis in order to evaluate this non-motor aspect of the disease that can affect patients' social behavior in order to appreciate the full extent of deficits of PD patients. Only with this holistic view of the patients and their deficits will be possible to provide an adequate treatment in PD.

References

1. Aarsland D, Zaccai J, Brayne C (2005) A systematic review of prevalence studies of dementia in Parkinson's disease. Mov Disord 20:1255-63.
2. Adolphs R, Tranel D, Damasio H, Damasio A (1994) Impaired recognition of emotion in facial expressions following bilateral damage to the human amygdala. Nature 372:669-72.
3. Adolphs R, Tranel D, Damasio H, Damasio AR (1995) Fear and the human amygdala. J Neurosci 15:5879-91.
4. Adolphs R, Damasio H, Tranel D, Damasio AR (1996) Cortical systems for the recognition of emotion in facial expressions. J Neurosci 16:7678-87.
5. Adolphs R, Schul R, Tranel D (1998) Intact recognition of facial emotion in Parkinson's disease. Neuropsychology 12:253-8.
6. Adolphs R, Russell JA, Tranel D (1999) A role for the human amygdala in recognizing emotional arousal from unpleasant stimuli. Psychological Science 10: 167–171.
7. Adolphs R (2002*a*) Recognizing emotion from facial expressions: psychological and neurological mechanisms. Behav. Cogn. Neurosci. Rev 1: 21–62.
8. Adolphs R (2002*b*) Neural systems for recognizing emotion. Curr Opin Neurobiol 12:169–77.
9. Alexander GE, DeLong MR, Strick PL (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu. Rev. Neurosci 9: 357–381
10. Alexander GE, Crutcher MD (1990) Functional architecture of basal ganglia circuits: neural substrates of parallel processing. Trends Neurosci 13:266-71.
11. Alexander GE, Crutcher MD, DeLong MR (1990) Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. Prog Brain Res 85:119-46.

12. Allen JS, Bruss J, Brown CK, Damasio H (2005) Normal neuroanatomical variation due to age: the major lobes and a parcellation of the temporal region. Neurobiol Aging 26:1245-60

13. Alonso-Recio L, Martín P, Rubio S, Serrano JM (2014*a*) Discrimination and categorization of emotional facial expressions and faces in Parkinson's disease. J Neuropsychol 8:269-88.

14. Alonso-Recio L, Serrano JM, Martín P (2014*b*) Selective attention and facial expression recognition in patients with Parkinson's disease. Arch Clin Neuropsychol 29:374-84.

15. Alonso-Recio L, Martín-Plasencia P, Loeches-Alonso Á, Serrano-Rodríguez JM (2014*c*) Working memory and facial expression recognition in patients with Parkinson's disease. J Int Neuropsychol Soc 20:496-505.

16. Anderson AK, Christoff K, Stappen I, Panitz D, Ghahremani DG, Glover G, Gabrieli JD, Sobel N. (2003) Dissociated neural representations of intensity and valence in human olfaction. Nat Neurosci 6:196-202.

17. Ariatti A, Benuzzi F, Nichelli P (2008) Recognition of emotions from visual and prosodic cues in Parkinson's disease. Neurol Sci 29:219-27.

18. Assogna F, Pontieri FE, Caltagirone C, Spalletta G (2008) The recognition of facial emotion expressions in Parkinson's disease. Eur Neuropsychopharmacol 18:835-48.

19. Assogna F, Pontieri FE, Cravello L, Peppe A, Pierantozzi M, Stefani A, Stanzione P, Pellicano C, Caltagirone C, Spalletta G (2010) Intensity-dependent facial emotion recognition and cognitive functions in Parkinson's disease. J Int Neuropsychol Soc 16:867-76.

20. Baggio HC, Segura B, Ibarretxe-Bilbao N, Valldeoriola F, Marti MJ, Compta Y, Tolosa E, Junqué C (2012) Structural correlates of facial emotion recognition deficits in Parkinson's disease patients. Neuropsychologia 50:2121-8.

21. Baillieux H, De Smet HJ, Paquier PF, De Deyn PP, Mariën P (2008) Cerebellar neurocognition: insight into the bottom of the rain. Clin Neurol Neurosurg 110: 763-73.

22. Barone P (2011) Treatment of depressive symptoms in Parkinson's disease. Eur J Neurol 18: 11–15.
23. Bartzokis G, Beckson M, Lu PH, Nuechterlein KH, Edwards N, Mintz J (2001) Age-related changes in frontal and temporal lobe volumes in men: a magnetic resonance imaging study. Arch Gen Psychiatry 58:461-5.
24. Beatty WW, Goodkin DE, Weir WS, Staton DR, Monson N, Beatty P (1989) Affective judgment by patients with parkinson's disease or chronic progressive multiple sclerosis. Bulletin of the Psychonomic Society 27:361-364.
25. Beck AT, Steer RA and Brown GK (1996) Manual for the Beck Depression Inventory-II. Psychological Corporation, San Antonio TX.
26. Benarroch EE (2010) Olfactory system. Functional organization and involvement in neurodegenerative disease. Neurology 75:1104–8.
27. Biehl M, Matsumoto D, Ekman P, Meant V, Heider K, Kudoh T, Ton V (1997) Matsumoto and Ekman's Japanese and Caucasian Facial Expressions of Emotion (JACFEE): reliability data and cross-national differences. J Nonverbal Behav 21:3-21.
28. Biseul I, Sauleau P, Haegelen C, Trebon P, Drapier D, Raoul S, Drapier S, Lallement F, Rivier I, Lajat Y, Verin M (2005) Fear recognition is impaired by subthalamic nucleus stimulation in Parkinson's disease. Neuropsychologia 43:1054-9.
29. Blair RJ (2003) Facial expressions, their communicatory functions and neuro-cognitive substrates. Philos Trans R Soc Lond B Biol Sci 358: 561-72.
30. Blonder LX, Gur RE, Gur RC (1989) The effects of right and left hemiparkinsonism on prosody. Brain Lang 36:193-207.
31. Boeve BF, Silber MH, Saper CB, Ferman TJ, Dickson DW, Parisi JE, Benarroch EE, Ahlskog JE, Smith GE, Caselli RC, Tippman-Peikert M, Olson EJ, Lin SC, Young T, Wszolek Z, Schenck CH, Mahowald MW, Castillo PR, Del Tredici K, Braak H (2007) Pathophysiology of REM sleep behaviour disorder and relevance to neurodegenerative disease. Brain 130:2770-88.

32. Borod JC, Welkowitz J, Alpert M, Brozgold A, Martin C, Peselow E, Diller L (1990) Parameters of emotional processing in neuropsychiatric disorders: conceptual issues and a battery of tests. J Commun Disord 23:247-271
33. Bourke C, Douglas K, Porter R (2010) Processing of facial emotion expression in major depression: a review. Aust N Z J Psychiatry 44:681-96.
34. Bowers D, Blonder LX, Heilman KM (1991) The Florida Affect Battery-Manual. FL: University of Florida, Center for Neuropsychological Studies, Gainesville.
35. Braak H, Del Tredici K, Rüb U, de Vos RA, Jansen Steur EN, Braak E. (2003a). Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 24: 197-211.
36. Braak H, Rüb U, Gai WP, Del Tredici K (2003b). Idiopathic Parkinson's disease: possible routes by which vulnerable neuronal types may be subject to neuroinvasion by an unknown pathogen. J Neural Transm 110:517-36.
37. Braak H, Del Tredici K (2008) Cortico-basal ganglia-cortical circuitry in Parkinson's disease reconsidered. Exp Neurol 212:226-9.
38. Brand M, Kalbe E, Kessler J (2002) Test zum kognitiven Schätzen. Hogrefe, Göttingen
39. Breitenstein C, Daum I, Ackermann H (1998) Emotional processing following cortical and subcortical brain damage: contribution of the fronto-striatal circuitry. Behavioural Neurology 11:29-42.
40. Brown RG, Pluck G (2000). Negative symptoms: the 'pathology' of motivation and goal-directed behaviour. Trends Neurosci 23: 412–17.
41. Buxton SL, MacDonald L, Tippett LJ (2013) Impaired recognition of prosody and subtle emotional facial expressions in Parkinson's disease. Behav Neurosci 127:193-203.
42. Calder AJ, Young AW, Rowland D, Perrett DI, Hodges JR, Etcoff NL (1996) Facial emotion recognition after bilateral amygdala damage: differentially severe impairment of fear. Cogn. Neuropsychol 13,699–745.
43. Calder AJ, Keane J, Manes F, Antoun N, Young AW (2000) Impaired recognition and experience of disgust following brain injury. Nat Neurosci 3:1077-8.

44. Calder AJ, Keane J, Lawrence AD, Manes F (2004) Impaired recognition of anger following damage to the ventral striatum. Brain 127:1958-69.
45. Caekebeke JFV, Jennekens-Schinkel A, Van der Linden ME, Buruma OJS, Roos RAC (1991) The interpretation of dysprosody in pat ients with Parkinson's disease. Journal of Neurology, Neurosurgery, and Psychiatry 54:145-148.
46. Chaudhuri KR, Healy DG, Schapira AH (2006) Non-motor symptoms of Parkinson's disease: diagnosis and management. Lancet Neurol 5: 235-45.
47. Cheung CC, Lee TM, Yip JT, King KE, Li LS (2006) The differential effects of thalamus and basal ganglia on facial emotion recognition. Brain Cogn 61:262-8.
48. Clark US, Neargarder S, Cronin-Golomb A (2008) Specific impairments in the recognition of emotional facial expressions in Parkinson's disease. Neuropsychologia 46:2300-9.
49. Clark US, Neargarder S, Cronin-Golomb A (2010) Visual exploration of emotional facial expressions in Parkinson's disease. Neuropsychologia 48:1901-13.
50. Cochen De Cock V (2013) Recent data on rapid eye movement sleep behavior disorder in patients with Parkinson disease: analysis of behaviors, movements, and periodic limb movements. Sleep Med 14:749-53.
51. Cohen H, Gagné MH, Hess U, Pourcher E (2010) Emotion and object processing in Parkinson's disease. Brain Cogn 72:457-63.
52. Convit A, Wolf OT, de Leon MJ, Patalinjug M, Kandil E, Caraos C, Scherer A, Saint Louis LA, Cancro R (2001) Volumetric analysis of the pre-frontal regions: findings in aging and schizophrenia. Psychiatry Res 107:61-73.
53. Crick F, Koch C (1995) Are we aware of neural activity in primary visual cortex? Nature 375:121–3.
54. Dalili MN, Penton-Voak IS, Harmer CJ, Munafò MR (2015) Meta-analysis of emotion recognition deficits in major depressive disorder. Psychol Med 45:1135-44.

55. De Gelder B, Morris JS, Dolan RJ (2005) Unconscious fear influences emotional awareness of faces and voices. Proc Natl Acad Sci USA 102:18682-7.
56. Dewick HC, Hanley JR, Davies AD, Playfer J, Turnbull C (1991) Perception and memory for faces in Parkinson's disease. Neuropsychologia 29:785-802.
57. Diaz-Santos, M., Cao, B., Yazdanbakhsh, A., Norton, D. J., Neargarder, S., & Cronin-Golomb, A. (2015). Perceptual, cognitive, and personality rigidity in Parkinson's disease. Neuropsychologia 69: 183-193.
58. Diederich NJ, Parent A (2012) Parkinson's disease: acquired frailty of archaic neural networks? J Neurol Sci 314:143-51.
59. Dimberg U, Thunberg M, Elmehed K (2000) Unconscious facial reactions to emotional facial expressions. Psychol Sci 11:86-9.
60. Doty RL, Deems DA, Stellar S (1988) Olfactory dysfunction in parkinsonism: a general deficit unrelated to neurologic signs, disease stage, or disease duration. Neurology 38:1237–44.
61. Doty RL, Riklan M, Deems DA, Reynolds C, Stellar S (1989) The olfactory and cognitive deficits of Parkinson's disease: evidence for independence. Ann Neurol 25:166–71.
62. Doty RL (2007) Olfaction in Parkinson's Disease. Parkinsonism Relat Disord. 13:225-8.
63. Doty RL (2012). Olfaction in Parkinson's disease and related disorders. Neurobiol Dis, 46, 527-52.
64. Dubois B, Pillon B (1997) Cognitive deficits in Parkinson's disease. J Neurol 244:2-8.
65. Dujardin K, Blairy S, Defebvre L, Duhem S, Noël Y, Hess U, Destée A (2004a) Deficits in decoding emotional facial expressions in Parkinson's disease. Neuropsychologia 42:239-50.
66. Dujardin K, Blairy S, Defebvre L, Krystkowiak P, Hess U, Blond S, Destée A (2004b) Subthalamic nucleus stimulation induces deficits in decoding emotional facial expressions in Parkinson's disease. J Neurol Neurosurg Psychiatry 75:202-8.

67. Dujardin K, Sockeel P, Devos D, Delliaux M, Krystkowiak P, Destée A, Defebvre L (2007) Characteristics of apathy in Parkinson's disease. Mov Disord 22:778-84.
68. Dujardin K, Lopes R (2014) Apathy and impaired recognition of emotion: are they related in Parkinson's disease? J Neurol Neurosurg Psychiatry 85:1061.
69. Ekman P & Friesen WV (1976) Pictures of facial affect. CA: Consulting Psychologists, Palo Alto.
70. Emre M (2003) Dementia associated with Parkinson's disease. Lancet Neurol. 2:229-37.
71. Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C, Mizuno Y, Broe GA, Cummings J, Dickson DW, Gauthier S, Goldman J, Goetz C, Korczyn A, Lees A, Levy R, Litvan I, McKeith I, Olanow W, Poewe W, Quinn N, Sampaio C, Tolosa E, Dubois B (2007) Clinical diagnostic criteria for dementia associated with Parkinson's disease. Mov Disord 22:1689-707.
72. Fahn S, Elton RL and the members of the UPDRS Development Committee (1987) The Unified Parkinson’s disease rating scale. In S. Fahn, C. D. Marsden, D. B. Calne, M. Goldstein (Eds) Recent developments in Parkinson’s disease. NJ: Macmillan Healthcare, Florham Park.
73. Feinberg TE, Rifkin A, Schaffer C, Walker E (1986) Facial discrimination and emotional recognition in schizophrenia and affective disorders. Arch Gen Psychiatry 43:276-9.
74. Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 12:189-98.
75. Fulbright RK, Skudlarski P, Lacadie CM, Warrenburg S, Bowers AA, Gore JC, Wexler BE. (1998) Functional MR imaging of regional brain responses to pleasant and unpleasant odors. AJNR Am J Neuroradiol 19:1721-6.
76. Fusar-Poli P, Placentino A, Carletti F, Landi P, Allen P, Surguladze S, Benedetti F, Abbamonte M, Gasparotti R, Barale F, Perez J, McGuire P, Politi P (2009) Functional atlas of emotional faces processing: a voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. J Psychiatry Neurosci 34:418-32.

77. Gallese V, Goldman A. (1998) Mirror neurons and the simulation theory of mind-reading. Trends Cogn Sci 2: 493-501

78. García-Lorenzo D, Longo-Dos Santos C, Ewenczyk C, Leu-Semenescu S, Gallea C, Quattrocchi G, Lehericy S. (2013). The coeruleus/subcoeruleus complex in rapid eye movement sleep behaviour disorders in Parkinson's disease. Brain 136: 2120-9.

79. Goldman AI, Sripada CS (2005) Simulationist models of face-based emotion recognition. Cognition 94:193-213.

80. Goldman JG, Postuma R (2014) Premotor and nonmotor features of Parkinson's disease. Curr Opin Neurol 27:434-41.

81. Goodale MA, Milner AD (1992) Separate visual pathways for perception and action. TINS 15:20–5.

82. Gray HM, Tickle-Degnen L (2010) A meta-analysis of performance on emotion recognition tasks in Parkinson's disease. Neuropsychology 24:176-91.

83. Groenewegen HJ (2014). Basal Ganglia. In B. C. Wolters E (Ed.), Parkinson Disease and other movement disorders. Motor behavioural disorders and behavioural motor disorders (pp. 45-46). VU University Press, Amsterdam/The Netherlands.

84. Grover S, Somaiya M, Kumar S, Avasthi A (2015) Psychiatric aspects of Parkinson's disease. J Neurosci Rural Pract. 6:65-76.

85. Harding AJ, Stimson E, Henderson JM, Halliday GM (2002) Clinical correlates of selective pathology in the amygdala of patients with Parkinson's disease. Brain 125:2431-45.

86. Hawkes CH, Shephard BC, Daniel SE (1997) Olfactory dysfunction in Parkinson’s disease. J Neurol Neurosurg Psychiatry 62:436−46.

87. Hawkes CH, Del Tredici K, Braak H (2007) Parkinson's disease: a dual-hit hypothesis. Neuropathol Appl Neurobiol 33:599-614.

88. Hawkley LC, Cacioppo JT (2004) Stress and the aging immune system. Brain Behav Immun 18:114-9.

89. Herrera E, Cuetos F, Rodríguez-Ferreiro J (2011) Emotion recognition impairment in Parkinson's disease patients without dementia. J Neurol Sci 310:237-40.
90. Hipp G, Diederich NJ, Pieria V, Vaillant M (2014) Primary vision and facial emotion recognition in early Parkinson's disease. J Neurol Sci 338:178-82.
91. Hobson P, Meara J (2004) Risk and incidence of dementia in a cohort of older subjects with Parkinson's disease in the United Kingdom. Mov Disord 19:1043–1049.
92. Hughes AJ, Daniel SE, Kilford L, Lees AJ (1992) Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinic-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 55:181-4.
93. Hummel T, Sekinger B, Wolf SR, Pauli E, Kobal G (1997) 'Sniffin' sticks': olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. Chem Senses 22:39-52.
94. Ibarretxe-Bilbao N, Junque C, Tolosa E, Marti MJ, Valldeoriola F, Bargallo N, Zarei M (2009) Neuroanatomical correlates of impaired decision-making and facial emotion recognition in early Parkinson's disease. Eur J Neurosci 30:1162-71.
95. Jacobs DH, Shuren J, Bowers D, Heilman KM (1995) Emotional facial imagery, perception, and expression in Parkinson's disease. Neurology 45:1696-702.
96. Joel D, Weiner I (1997) The connections of the primate subthalamic nucleus: indirect pathways and the open-interconnected scheme of basal ganglia-thalamocortical circuitry. Brain Res Brain Res Rev 23: 62–78.
97. Juri C, Rodriguez-Oroz M, Obeso JA (2010) The pathophysiological basis of sensory disturbances in Parkinson's disease. J Neurol Sci 289:60-5.
98. Kalbe E, Calabrese P, Kohn N, Hilker R, Riedel O, Wittchen HU, Dodel R, Otto J, Ebersbach G, Kessler J (2008) Screening for cognitive deficits in Parkinson's disease with the Parkinson neuropsychometric dementia assessment (PANDA) instrument. Parkinsonism Relat Disord 14:93-101.

99. Kan Y, Kawamura M, Hasegawa Y, Mochizuki S, Nakamura K (2002) Recognition of emotion from facial, prosodic and written verbal stimuli in Parkinson's disease. Cortex 38:623-30.

100. Kawamura M, Kobayakawa M (2009) Emotional impairment in Parkinson's disease. Parkinsonism Relat Disord 15: 47–52.

101. Kim, H., Somerville, L.H, Johnstone, T., Alexander, A.L., & Whalen, P.J. (2003) Inverse amygdala and medial prefrontal cortex responses to surprised faces. Neuroreport 14, 2317-22.

102. Klingelhoefer L, Reichmann, H (2015). Pathogenesis of Parkinson disease--the gut-brain axis and environmental factors. Nat Rev Neurol 11: 625-636.

103. Kringelbach ML, Berridge KC (2010) The functional neuroanatomy of pleasure and happiness. Discov Med 9:579-87.

104. Lachenal-Chevallet K, Bediou B, Bouvard M, Thobois S, Broussolle E, Vighetto A, Krolak-Salmon P (2006) Emotional facial expression recognition impairment in Parkinson disease. Psychol Neuropsychiatr Vieil. 4:61-7. [Abstract-Article in French].

105. Lawrence AD, Calder AJ, McGowan SW, Grasby PM (2002) Selective disruption of the recognition of facial expressions of anger. Neuroreport 13:881-4.

106. Lawrence AD, Goerendt IK, Brooks DJ (2007) Impaired recognition of facial expressions of anger in Parkinson's disease patients acutely withdrawn from dopamine replacement therapy. Neuropsychologia 45:65-74.

107. Leleu A, Demily C, Franck N, Durand K, Schaal B, Baudouin JY (2015) The Odor Context Facilitates the Perception of Low-Intensity Facial Expressions of Emotion. PLoS One 21:e0138656.

108. Lemke MR (2008) Depressive symptoms in Parkinson's disease. Eur J Neurol 15: 21–25.

109. Leppanen JM (2006) Emotional information processing in mood disorders: a review of behavioral and neuroimaging findings. Current Opinion in Psychiatry 19: 34–39.

110. Levy LM, Henkin RI, Hutter A, Lin CS, Martins D, Schellinger D. (1997) Functional MRI of human olfaction. J Comput Assist Tomogr 21(6):849-56.

111. Madeley P, Ellis AW, Mindham RH (1995) Facial expressions and Parkinson's disease. Behav Neurol 8:115-9.

112. Marin RS, Biedrzycki RC, Firinciogullari S (1991) Reliability and validity of the Apathy Evaluation Scale. Psychiatry Res 38:143-62

113. Marneweck M, Palermo R, Hammond G (2014*a*) Discrimination and recognition of facial expressions of emotion and their links with voluntary control of facial musculature in Parkinson's disease. Neuropsychology 28:917-28.

114. Marneweck M, Hammond G (2014*b*) Discriminating facial expressions of emotion and its link with perceiving visual form in Parkinson's disease. J Neurol Sci 346:149-55.

115. Martínez-Corral M, Pagonabarraga J, Llebaria G, Pascual-Sedano B, García-Sánchez C, Gironell A, Kulisevsky J (2010) Facial emotion recognition impairment in patients with Parkinson's disease and isolated apathy. Parkinsons Dis 2010: 930627.

116. Matsumoto D, Ekman P (1988) Japanese and Caucasian Facial Expressions of Emotion (JACFEE) and Neutral Faces (JACNeuf). Department of Psychiatry, University of California, San Francisco.

117. McHaffie JG, Stanford TR, Stein BE, Coizet V, Redgrave P (2005) Subcortical loops through the basal ganglia. Trends Neurosci 28:401-7.

118. Mena-Segovia J, Bolam JP, Magill PJ (2004) Pedunculopontine nucleus and basal ganglia: distant relatives or part of the same family? TRENDS in Neurosciences 27:585-8.

119. Mesholam RI, Moberg PJ, Mahr RN, Doty RL (1998) Olfaction in neurodegenerative disease: a meta-analysis of olfactory functioning in Alzheimer's and Parkinson's diseases. Arch Neurol 55:84-90.

120. Miller EK, Cohen JD (2001) An integrative theory of prefrontal cortex function. Annu. Rev. Neurosci. 24: 167–202.

121. Montagne B, Kessels RP, Wester AJ, de Haan EH (2006) Processing of emotional facial expressions in Korsakoff's syndrome. Cortex 42:705-10.

122. Morley JF, Duda JE (2011) Neuropsychological correlates of olfactory dysfunction in Parkinson's disease. J Neurol Sci 310:228-30.

123. Morris JS, Ohman A, Dolan RJ (1999) A subcortical pathway to the right amygdala mediating “unseen” fear. Proc Natl Acad Sci 96:1680–5.

124. Morrish PK, Sawle GV, Brooks DJ (1996) Regional changes in [18F]dopa metabolism in the striatum in Parkinson's disease. Brain 119:2097-103.

125. Mu Q, Xie J, Wen Z, Weng Y, Shuyun Z (1999) A quantitative MR study of the hippocampal formation, the amygdala, and the temporal horn of the lateral ventricle in healthy subjects 40 to 90 years of age. AJNR Am J Neuroradiol 20: 207-11.

126. Muzerengi S, Contrafatto D, Chaudhuri KR (2007) Non-motor symptoms: identification and management. Parkinsonism Relat Disord 13:450-6.

127. Narme P, Bonnet AM, Dubois B, Chaby L (2011) Understanding facial emotion perception in Parkinson's disease: the role of configural processing. Neuropsychologia 49:3295-302.

128. Narme P, Mouras H, Roussel M, Duru C, Krystkowiak P, Godefroy O (2013) Emotional and cognitive social processes are impaired in Parkinson's disease and are related to behavioral disorders. Neuropsychology 27:182-92.

129. Obeso JA, Rodriguez-Oroz MC, Rodriguez M, Lanciego JL, Artieda J, Gonzalo N, Olanow CW (2000) Pathophysiology of the basal ganglia in Parkinson's disease. Trends Neurosci 23:8–19.

130. Obeso JA, Marin C, Rodriguez-Oroz C, Blesa J, Benitez-Temino B, Mena-Segovia J, Rodríguez M, Olanow CW (2008) The basal ganglia in Parkinson's disease: current concepts and unexplained observations. Ann Neurol 64:30–46.

131. Ossowska K, Lorenc-Koci E (2013) Depression in Parkinson's disease. Pharmacol Rep 65:1545-57.

132. Pagano G, Ferrara N, Brooks DJ, Pavese N (2016) Age at onset and Parkinson disease phenotype. Neurology 86:1400-7.

133. Parent A, Hazrati LN (1995) Functional anatomy of the basal ganglia. I. The cortico–basal ganglia–thalamo–cortical loop. Brain Res Rev 20, 91–127.

134. Paulmann S, Pell MD (2010) Dynamic emotion processing in Parkinson's disease as a function of channel availability. J Clin Exp Neuropsychol 32(8):822-35.

135. Pell MD, Leonard CL (2005) Facial expression decoding in early Parkinson's disease. Brain Res Cogn Brain Res 23:327-40.

136. Péron J, Dondaine T, Le Jeune F, Grandjean D, Vérin M (2012) Emotional processing in Parkinson's disease: a systematic review. Mov Disord 27:186-99.

137. Phan KL, Wager T, Taylor SF, Liberzon I (2002) Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. Neuroimage 16:331-48.

138. Philips LH, Henry JD (2005) An evaluation of the frontal lobe theory of cognitive aging. Duncan, J. Phillips, LH, Mc Leod, P (Eds) Measuring the Mind: Speed, Contro, Age. Oxford University Press, Oxford, pp. 191-216.

139. Phillips ML, Young AW, Senior C, Brammer M, Andrew C, Calder AJ, Bullmore ET, Perrett DI, Rowland D, Williams SC, Gray JA, David AS (1997) A specific neural substrate for perceiving facial expressions of disgust. Nature 389:495-8.

140. Phillips ML, Young AW, Scott SK, Calder AJ, Andrew C, Giampietro V, Williams SC, Bullmore ET, Brammer M, Gray JA (1998) Neural responses to facial and vocal expressions of fear and disgust. Proc Biol Sci 265:1809-17.

141. Poewe W, Seppi K (2001) Treatment options for depression and psychosis in Parkinson’s disease. J Neurol 248: III12–21.

142. Poewe W (2008) Non-motor symptoms in Parkinson's disease. Eur J Neurol 15:14-20.

143. Ponsen MM, Stoffers D, Booij J, van Eck-Smit BLF, Wolters ECh, Berendse HW (2004) Idiopathic hyposmia as a preclinical sign of Parkinson's disease. Ann Neurol 56:173–81.

144. Posamentier MT, Abdi H (2003) Processing faces and facial expressions. Neuropsychol Rev. 13:113-43.

145. Postuma RB, Gagnon JF, Montplaisir JY (2012) REM sleep behavior disorder: from dreams to neurodegeneration. Neurobiol Dis 46:553-8.

146. Porrino LJ, Crane AM, Goldman-Rakic PS (1981) Direct and indirect pathways from the amygdala to the frontal lobe in rhesus monkeys. J. Comp. Neurol 198: 121–136.

147. Raz N, Lindenberger U, Rodrigue KM, Kennedy KM, Head D, Williamson A, Dahle C, Gerstorf D, Acker JD (2005) Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. Cereb Cortex 15:1676-89.

148. Robbins T, Evritt B (1996) Neurobehavioural mechanism of reward and motivation. Curr Opin Neurobiol 6:228–36.

149. Robert G, Le Jeune F, Dondaine T, Drapier S, Péron J, Lozachmeur C, Sauleau P, Houvenaghel JF, Travers D, Millet B, Vérin M, Drapier D (2014) Apathy and impaired emotional facial recognition networks overlap in Parkinson's disease: a PET study with conjunction analyses. J Neurol Neurosurg Psychiatry 85:1153-8.

150. Rolls ET (2015) Taste, olfactory, and food reward value processing in the brain. Prog Neurobiol 127-128:64-90

151. Romanelli P, Esposito V, Schaal DW, Heit G (2005) Somatotopy in the basal ganglia: experimental and clinical evidence for segregated sensorimotor channels. Brain Res Brain Res Rev 48:112–28.

152. Ross GW, Petrovitch H, Abbott RD, Tanner CM, Popper J, Masaki K, Launer L, White LR (2008) Association of olfactory dysfunction with risk for future Parkinson's disease. Ann Neurol 63:167–73.

153. Ruffman T, Henry JD, Livingstone V, Phillips LH (2008) A meta-analytic review of emotion recognition and aging: implications for neuropsychological models of aging. Neurosci Biobehav Rev 32:863-81.

154. Russell JA (1994) Is there universal recognition of emotion from facial expression? A review of the cross-cultural studies. Psychol Bull. 115:102-41.

155. Saenz A, Doé de Maindreville A, Henry A, de Labbey S, Bakchine S, Ehrlé N (2013) Recognition of facial and musical emotions in Parkinson's disease. Eur J Neurol 20:571-7.

156. Sato W, Kubota Y, Okada T, Murai T, Yoshikawa S, Sengoku A (2002) Seeing happy emotion in fearful and angry faces: qualitative analysis of facial expression recognition in a bilateral amygdala-damaged patient. Cortex 38:727-42.

157. Smith MC, Smith MK, Ellgring H (1996) Spontaneous and posed facial expression in Parkinson's disease. J Int Neuropsychol Soc 2:383-91.

158. Soudry, Y., Lemogne, C., Malinvaud, D., Consoli, S.M., Bonfils, P. (2011) Olfactory system and emotion: common substrates. Eur Ann Otorhinolaryngol Head Neck Dis 128:18-23.

159. Sprengelmeyer R, Young AW, Calder AJ, Karnat A, Lange H, Hömberg V, Perrett DI, Rowland D (1996) Loss of disgust. Perception of faces and emotions in Huntington's disease. Brain 119:1647-65.

160. Sprengelmeyer R, Rausch M, Eysel UT, Przuntek H (1998) Neural structures associated with recognition of facial expressions of basic emotions. Proc Biol Sci 265:1927-31.

161. Sprengelmeyer R, Young AW, Mahn K, Schroeder U, Woitalla D, Büttner T, Kuhn W, Przuntek H (2003) Facial expression recognition in people with medicated and unmedicated Parkinson's disease. Neuropsychologia 41:1047-57.

162. Stel M, van Knippenberg A (2008) The role of facial mimicry in the recognition of affect. Psychol Sci 19:984-5.

163. Stiasny-Kolster K, Doerr Y, Möller JC, Höffken H, Behr TM, Oertel WH, Mayer G (2005) Combination of 'idiopathic' REM sleep behaviour disorder and olfactory dysfunction as possible indicator for alpha-synucleinopathy demonstrated by dopamine transporter FP-CIT-SPECT. Brain 128:126-37.

164. Stiasny-Kolster K, Mayer G, Schäfer S, Möller JC, Heinzel-Gutenbrunner M, Oertel WH (2007) The REM sleep behavior disorder

screening questionnaire--a new diagnostic instrument. Mov Disord 22:2386-93.

165. Suzuki A, Hoshino T, Shigemasu K, Kawamura M (2006) Disgust-specific impairment of facial expression recognition in Parkinson's disease. Brain 129:707-17.

166. Takahashi H, Yahata N, Koeda M, Takano A, Asai K, Suhara T, Okubo Y (2005) Effects of dopaminergic and serotonergic manipulation on emotional processing: a pharmacological fMRI study. Neuroimage 27:991-1001.

167. Tessitore A, Hariri AR, Fera F, Smith WG, Chase TN, Hyde TM, Weinberger DR, Mattay VS (2002) Dopamine modulates the response of the human amygdala: a study in Parkinson's disease. J Neurosci 22:9099-103.

168. Tisserand DJ, Pruessner JC, Sanz Arigita EJ, van Boxtel MP, Evans AC, Jolles J, Uylings HB (2002) Regional frontal cortical volumes decrease differentially in aging: an MRI study to compare volumetric approaches and voxel-based morphometry. Neuroimage 17:657-69.

169. Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE (2010) Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord 25:2649-53.

170. Ventura MI, Baynes K, Sigvardt KA, Unruh AM, Acklin SS, Kirsch HE, Disbrow EA (2012) Hemispheric asymmetries and prosodic emotion recognition deficits in Parkinson's disease. Neuropsychologia 50:1936-45.

171. Vytal K, Hamann S (2010). Neuroimaging support for discrete neural correlates of basic emotions: A voxel-based mate-analysis. Journal of Cognitive Neuroscience 22: 2864–2885.

172. Wieser MJ, Klupp E, Weyers P, Pauli P, Weise D, Zeller D, Classen J, Mühlberger A (2012) Reduced early visual emotion discrimination as an index of diminished emotion processing in Parkinson's disease? - Evidence from event-related brain potentials. Cortex 48:1207-17.

173. Wolters EC, de Munter H., Steinbuch H. Parkinson's Disease. (2014) In B. C. Wolters E (Ed.) Parkinson Disease and other movement disorders. Motor behavioural disorders and behavioural motor disorders (pp. 149-156). VU University Press, Amsterdam/The Netherlands.

174. Yip JT, Lee TM, Ho SL, Tsang KL, Li LS (2003) Emotion recognition in patients with idiopathic Parkinson's disease. Mov Disord 18:1115-22.

175. Yoshimura N, Kawamura M, Masaoka Y, Homma I (2005) The amygdala of patients with Parkinson's disease is silent in response to fearful facial expressions. Neuroscience 131:523–534.

176. Young AW, Aggleton JP, Hellawell DJ, Johnson M, Broks P, Hanley JR (1995) Face processing impairments after amygdalotomy. Brain 118:15-24.

177. Young AW, Hellawell DJ, Van De Wal C, Johnson M (1996) Facial expression processing after amygdalotomy. Neuropsychologia 34:31-9.

178. Zald DH, Pardo JV. (1997) Emotion, olfaction, and the human amygdala: amygdala activation during aversive olfactory stimuli. Proc Matl Acad Sc U S A 94:4119-24

179. Zgaljardic DJ, Borod JC, Foldi NS, Mattis P (2003) A review of the cognitive and behavioral sequelae of Parkinson's disease: relationship to frontostriatal circuitry. Cogn Behav Neurol 16:193-210.

Appendix

Hoehn and Yahr scale

The **Hoehn and Yahr scale** is a widely used scale for describing the progression of symptoms of Parkinson's disease. It was originally published in 1967 in the journal *Neurology* by Melvin Yahr and Margaret Hoehn and included stages 1 to 5. Since then, a modified Hoehn and Yahr scale was proposed with the addition of stages 1.5 and 2.5 in order to describe the intermediate course of the disease.

Stage	Hoehn and Yahr Scale	Modified Hoehn and Yahr Scale
1	Unilateral involvement only usually with minimal or no functional disability	Unilateral involvement only
1.5	-	Unilateral and axial involvement
2	Bilateral or midline involvement without impairment of balance	Bilateral involvement without impairment of balance
2.5	-	Mild bilateral disease with recovery on pull test
3	Bilateral disease: mild to moderate disability with impaired postural reflexes; physically independent	Mild to moderate bilateral disease; some postural instability; physically independent
4	Severely disabling disease; still able to walk or stand unassisted	Severe disability; still able to walk or stand unassisted
5	Confinement to bed or wheelchair unless aided	Confinement to bed or wheelchair unless aided

Modified Schwab and England Activities of Daily Living Scale

100% – Completely independent. Able to do all chores without slowness, difficulty or impairment. Essentially normal. Unaware of any difficulty.

90% – Completely independent. Able to do all chores with some degree of slowness, difficulty and impairment. Might take twice as long. Beginning to be aware of difficulty.

80% – Completely independent in most chores. Takes twice as long. Conscious of difficulty and slowness.

70% – Not completely independent. More difficulty with some chores. Three to four times as long in some. Must spend a large part of the day with chores.

60% – Some dependency. Can do most chores, but exceedingly slowly and with much effort. Errors; some impossible.

50% – More dependent. Help with half of the chores, slower, etc. Difficulty with everything.

40% – Very dependent. Can assist with all chores, but few alone.

30% – With effort, now and then does a few chores alone or begins alone. Much help needed.

20% – Nothing alone. Can be a slight help with some chores. Severe invalid.

10% – Total dependent, helpless. Complete invalid.

0% – Vegetative functions such as swallowing, bladder and bowel functions are not functioning. Confined to bed.

Publication

A short version of the Dissertation entitled ´´Facial emotion recognition in Parkinson's disease: association with age and olfaction´´ is accepted for publication in the *Journal of Clinical and Experimental Neuropsychology* on 30th May 2017.

Acknowledgments

I would like to thank my supervisor Prof. Dr. K. Fassbender, director of the department of Neurology, University of Saarland, for the excellent cooperation as well as my advisor PD Dr. M. Unger, senior physician of the department of Neurology, University of Saarland, for his helpful contribution and availability during all the time of processing of my dissertation. Furthermore, i would like to thank Mr. Schöpe Jakob from the Institute for Medical Biometry, Epidemiology and Medical Informatics, Saarland University, for his advising regarding statistical matters. I would also like to thank Ms M. Luley, former neuropsychologist in the department of Neurology, University of Saarland for advising regarding neuropsychological tests. Last but not least, i would like to thank my husband and colleague Dr. E. Lyros for his support.