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HIGH ORDER VISUOPERCEPTUAL IMPAIRMENTS UNDERSCORE SPECIFIC PERCEPTUAL PERFORMANCES ON ILLUSORY FIGURES IN PATIENTS WITH PARKINSON'S DISEASE: IMPLICATIONS FOR VISUAL HALLUCINATIONS

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DESCRIZIONE DELLO STUDIO

La malattia di Parkinson rappresenta la seconda malattia neurodegenerativa più diffusa al mondo dopo la malattia di Alzheimer, coinvolgente all'incirca dieci milioni di individui al mondo. Classicamente, essa si caratterizza come disordine del movimento, dal momento che i segni e i sintomi cosiddetti "cardinali", che ne consentono cioè l'identificazione e la diagnosi, sono precipuamente motori e comprendono bradicinesia, tremore a riposo, insabilità posturale, disturbi della marcia e rigidità muscolare. Tuttavia, è ormai conoscenza ampiamente consolidata che la malattia di Parkinson possa manifestarsi con una pletora di disturbi di natura non-motoria, la cui prevalenza e impatto sulla qualità di vita del malato variano in relazione allo stato di progressione di malattia, potenziali comorbidità e concomitanti trattamenti farmacologici. In tale contesto, le alterazioni a carico della percezione visiva rappresentano oggetto di crescente interesse. I pazienti affetti da malattia di Parkinson possono infatti sperimentare alterazioni a carico di svariate funzioni percettive, tra cui l'identificazione e il riconoscimento delle immagini, l'elaborazione della configurazione e dell'orientamento spaziale degli stimoli visivi, la segregazione figura/contorno, il raggruppamento percettivo, il riconoscimento di figure sovrapposte, la stereopsi, l'organizzazione prospettica, la percezione della direzionalità del movimento, ecc. Alterazioni a carico di tali funzioni comportano bias percettivi con conseguenze potenzialmente rilevanti sotto il profilo clinico. Le ambiguità percettive generate da anomalie a carico dei meccanismi preposti alla corretta processazione e integrazione dell'informazione visiva possono, tra l'altro, favorire l'insorgere di fenomeni di tipo illusorio e allucinatorio.

Le allucinazioni visive sono definibili come esperienze percettive che si producono in assenza di stimolazione effettiva dell'organo di senso. Esse costituiscono un sintomo non-motorio particolarmente prevalente e potenzialmente invalidante della malattia di Parkinson, che può interessare sino al 70% di questi pazienti. La fisiopatologia di questi fenomeni non è ancora nota nel dettaglio. Si ritiene che il progressivo deterioramento delle funzioni visive afferenti possa comportare la graduale attivazione di meccanismi percettivi superiori coinvolti nella modulazione dell'attenzione visiva, nel reperimento di referenze visive pregresse e nella soppressione di potenziali stimoli interferenti. Tali funzioni "top-down" non sarebbero però sufficienti nè adeguate per compensare sistematicamente alla perdita di qualità dell'informazione visiva. Ciò faciliterebbe, nel tempo, l'emergere di esperienze percettive erronee.

In psicologia percettiva, le illusioni rappesentano fenomeni di erronea interpretazione dello stimolo visivo. Esse possono essere elicitate sistematicamente attraverso la manipolazione parametrica di alcune variabili dello stimolo visivo quali luminanza, colore, risoluzione temporale, configurazione spaziale ecc. Tali fenomeni non possiedono valenza patologica di per se, in quanto sono attribuili alle fisiologiche caratteristiche computazionali del sistema visivo umano. In tale contesto, la performance percettiva dell'individuo in risposta a stimoli illusori può fornire importanti informazioni circa i processi neurofisiologici alla base della percezione visiva cosciente.

Il presente progetto di ricerca si è articolato attraverso uno studio esplorativo osservazionale in singolo cieco avente come scopo la caratterizzazione della performance percettiva di una popolazione di pazienti affetti da malattia di Parkinson di grado moderato e senza significativa disfunzione cognitiva. I pazienti sono stati suddivisi in due gruppi, rispettivamente con (PD_Hal) e senza (PD-NonHal) storia di allucinazioni visive, sulla base del punteggio a un questionario dedicato (University of Miami Parkinson's Disease Hallucinations Questionnaire), ottimizzato per il riconoscimento delle allucinazioni visive tipicamente sperimentate da questi pazienti. Successivamente, sono state somministrate due figure illusorie computerizzate ritenute in grado di ingaggiare direttamente funzioni percettive verosimilmente intaccate dal processo neurodegenerativo associato alla malattia di Parkinson: l'illusione di DelBoeuf e l'illusione di restringimento da completamento amodale. Le potenziali differenze nella performance percettiva elicitata in risposta a tali stimoli sono state analizzate e confrontate con quelle di un guppo di controlli sani di pari età. Inoltre, il presente progetto di ricerca ha esplorato i sostrati neurali alla base delle possibili differenze percettive trai pazienti mediante lo studio nelle differenze nel metabolismo regionale corticale con tomografia per emissione di positroni (PET).

I risultati di questa sperimentazione suggeriscono che, nei pazienti senza storia di allucinazioni visive, le alterazioni visuospaziopercettive associate alla malattia di Parkinson comportino un profilo di paradossale resilienza a stimoli illusori che nei soggetti sani normalmente implicano una integra rappresentazione della scena visiva globale e un adeguato shift attentivo. Tale pattern non risulta rilevabile nei pazienti con storia di allucinazioni visive, i quali, per contro, manifestano una maggior vulnerabilità a stimoli illusori che normalmente vengono contrastati, nei soggetti sani, da funzioni percettive quali segregazione figura/contrasto e identificazione di figure sovrapposte. Inoltre, lo studio tramite PET con fluorodesossiglucosio ha evidenziato un pattern caratterizzato da un minor deficit ipometabolico a carico di regioni corticali prefrontali

nei pazienti con allucinazioni visive rispetto ai pazienti senza storia di allucinazioni. Ciò rafforza ulteriormente l'ipotesi che la disregolazione delle funzioni percettive superiori giochi un ruolo fondamentale nella genesi dei fenomeni allucinatori in questa popolazione clinica. In sintesi, gli effetti della malattia di Parkinson sulla performance percettiva ai test illusori mostrerebbero una direzionalità variabile: quando il processo neurodegenerativo intacca le funzioni visuospaziali che sottendono al bias percettivo, il paziente dimostra una paradossale resistenza alla relativa illusione. Quando, al contrario, a essere alterati risultano i meccanismi normalmente preposti al contrasto del bias percettivo, il paziente manifesta una maggior vulnerabilità allo stimolo illusorio.

Nel complesso, i risultati di questo studio esplorativo supportano l'utilizzo sperimentale degli stimoli illusori come possibile metodica non invasiva e riproducibile per la caratterizzazione delle anomalie a carico delle funzioni percettive connesse al processo neurodegenerativo della malattia di Parkinson, fornendo nel contempo una prospettiva del tutto originale sui meccanismi fisiopatologici responsabili della comparsa delle allucinazioni visive in questi pazienti.

I. INTRODUCTION

A hallucination is a fact, not an error; what is erroneous is a judgment based upon it.
Bertand Russel (1872-1970)

Overview on Parkinson's Disease

Epidemiology

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease, with an incidence ranging from 5/100,000 to over 35/100,000 new cases yearly[1]. The current prevalence of the disease in North America is estimated to be 301 per 100,000, and approximately 194 per 100,000 in Italy[2]. The burden of the disease is poised to a dramatic growth, as PD is currently regarded as the fastest growing neurodegenerative disorder worldwide. From 1990 to 2015, the number of affected individuals increased globally by 118%, reaching 6.2 million[3]. By 2040, the number of people affected by the disease is projected to exceed 17 million worldwide[4].

This unprecedented raise of PD prevalence was recently dubbed by some Authors as the emergence of the "Parkinson's pandemic"[5]. The reasons for this phenomenon are not fully understood, although the global increase in longevity is probably one of major drivers. Indeed, aging is long recognized as the strongest risk factor for PD[6]. The disease is rare under 50 years of age, with an incidence lower than 20/100,000, accounting for less than 4% of all cases[7]. From the sixth to the ninth decade of life, incidence increases sharply by 5 to 10-fold, reaching 108-212/100,000[8]. Increased longevity alone is expected to lead to a 12% increase in age-standardized prevalence models of PD over the next 20 years[5].

The current epidemiological trend could be also fueled by changes in lifestyles. The risk of PD appears to be lower in tobacco smokers, and declining smoking rates might result in an increased number of individuals with PD. Cumulative, life-time exposure to neurotoxic byproducts of industrialization, such as pesticides, herbicides, solvents, and heavy metals, is also regarded as a potential key contributor[9]. As a case in point, the greatest increase in the rates of PD was recently observed in those countries that have undergone the most rapid industrialization, including China and India[5].

Etiology

In its etiology, PD can be conceptualized as a multifactorial disease, arising as a result of a complex interplay between genetics and environment[10]. Among environmental factors, pesticide exposure, rural living, repeated head injury, β-blocker use, agricultural occupation, and well-water drinking are linked to an increased risk of developing the disease[11]. Conversely, a negative association is reported with tobacco smoking, caffeine consumption and the use of non-steroidal anti-inflammatory drugs[9]. In approximately 80% of patients, PD shows a sporadic distribution, while in 10-15% of cases, the disease occurs in the setting of a positive family history. Only 5% of all cases are attributable to pathogenic variants in single genes inherited through a mendelian pattern[6]. The age of onset in the proband usually helps distinguishing recessive forms, typically arising before the fourth decade of life, from dominant PD, usually occurring after the age of 50[12].

The identification of monogenic mutations and their functional characterization significantly contributed to shed light on the pathophysiology of PD by highlighting molecular mechanisms relevant to neuronal degeneration. For example, mutations in the PARKIN and PINK1 genes are known causes of autosomal recessive PD, and they are both linked to impaired lysosomal degradation of dysfunctional mitochondria, a process known as mitophagy. Notably, PARKIN mutations have been found to be responsible for about 50% of all autosomal recessive cases, with a form of parkinsonism that closely resembles idiopathic PD[13]. Mutations in the LRRK2 gene are associated with a common form of autosomal dominant PD. This gene encodes for leucine-rich repeat kinase 2, a multifunctional enzymatic protein. Pathogenic mutants typically exhibit an increased kinase activity, which in turn might be linked to dopaminergic neuronal cell death, impaired proteostasis, abnormal neuroinflammatory response, and oxidative damage[14]. LRRK2 mutations can be found in approximately 2% of all patients and in approximately 5% of familial cases, thus being recognized as an important genetic risk factor for both sporadic and familial forms of PD. Mutations in the GBA gene are regarded as another common genetic risk factor for PD. These mutations are causative for Gaucher's disease, a rare autosomal recessive disorder caused by a deficiency in the lysosomal enzyme β-glucocerebrosidase, leading to the accumulation of its substrate glucosylceramide in macrophages[15]. Indeed, PD occurs in about 10% of patients with type 1 Gaucher's disease before the age of 80 years, as compared to about 3-4% in the general population. About 5% of PD patients carry a GBA mutation, and in PD patients of Ashkenazi Jewish origin, the carrier frequency is considerably higher, i.e. 15-20%. This makes GBA mutations numerically the

most important know genetic risk factor for PD[16]. GBA mutations do not cause a mendelian form of PD, but are considered a genetic risk factor, increasing the risk 20-30-fold, although the risk varies with different GBA mutations.

In addition to known monogenic causes, additional susceptibility loci have been identified through genome-wide association studies. These genetic modifiers are believed to influence individuals' lifetime risk for PD, as well as the age of onset and the likelihood to display particular clinical features such as tremor or cognitive impairment. Overall, the multifactorial etiology of PD posits that the cumulative exposure to detrimental environmental factors conspires over time to increase the likelihood of developing the disease in the setting of genetically determined individual susceptibility. This process may be driven by multiple and potentially overlapping mechanisms, including mitochondrial dysfunction, impairment of the intracellular protein clearance system, oxidative stress, and neuroinflammation, overall converging in the activation of apoptosis and, consequently, progressive neuronal loss[17].

Pathophysiology

The epicenter of neuronal loss in PD involves neuromelanin-containing dopaminergic neurons located in the ventrolateral tier of the *substantia nigra pars compacta*, and their projections to the dorsal *putamen* of the *striatum*. The *striatum* is a hub in the basal ganglia circuitry, controlling goal directed actions and habits; it receives the densest dopaminergic innervation from the *substantia nigra pars compacta,* and it projects to the basal ganglia output structures through two distinct pathways, namely the "direct" and "indirect" pathways[18]. In the direct pathway, type I medium-spiny neurons directly inhibit the internal segment of the *globus pallidus*, thus producing a disinhibition of thalamic neurons responsible for excitation of the premotor cortex. The functional net result is a facilitation of voluntary movements. In the indirect pathways, striatal type II medium-spiny neurons inhibit the external segment of the *globus pallidus*, which in turn suppresses the excitatory output of the subthalamic nucleus towards the *globus pallidus interna.* The resulting increased tonic inhibition of basal ganglia outputs to the thalamus is believed to promote the suppression of involuntary movements.

In PD, the unremitting loss of striatal dopaminergic innervation disrupts the ability of the two principal striatal projection systems to respond appropriately to cortical and thalamic signals, resulting in a progressively impaired motor behavior. This model is, admittedly, an oversimplification. For example, lesioning or stimulation of the *globus pallidum interna*

improves motor behavior, both in hypokinetic disorders like PD, and in hyperkinetic conditions such as dystonia or chorea. Further, the proposed model does not fully account for the onset of tremor, which is presumably attributable to the additional involvement of striatal-cortical-cerebellar pathways[19]. Notwithstanding its limitations, the current model is consistent with the well-established link between the reduction of dopaminergic signaling in striatal-thalamic-cortical pathways and motor impairment, and it is therefore widely adopted to describe the general pathophysiology of the disease[20].

In addition to the progressive depopulation of dopaminergic neurons in the midbrain, a further pathological hallmark of PD is the presence of abnormal cytoplasmic deposits within neuronal cell bodies which are immunoreactive for the protein α-synuclein. This 14 kDA protein is ubiquitously expressed in the brain, particularly pre-synaptically, where it is believed to regulate membrane to membrane interactions[21]. In PD, α-synuclein becomes abnormally phosphorylated and prone to aggregate into intracellular inclusions called Lewy Bodies (LB), often accompanied by axonal dystrophic neurites. LB consist of granular and fibrillar core with a surrounding halo, with a diameter ranging from 5 to 30 micrometers. Several mechanisms have been proposed to explain conformational changes that lead to abnormal α-synuclein aggregation including phosphorylation, ubiquitination, and C-terminal truncation[22]. Different species of α-synuclein are found in PD brain, including unfolded monomers, soluble oligomers and high molecular with insoluble fibrils. The most neurotoxic α-synuclein species is the early oligomeric form, which is capable of "seeding", a property presumably underlying the cell-to-cell spread of aggregated proteins and the progression of PD pathology[23]. The direct link between PD and α-synuclein was first established in 1997 by the demonstration of a missense mutation in the SNCA gene encoding for α-synuclein, leading to an autosomal dominant form of PD[24]. To date, cumulative evidence suggests that the presence of LB perturbates the functional integrity of neurons through multiple mechanisms, including mitochondrial dysfunction, lysosomal impairment, membrane disturbance, endoplasmic reticulum stress, calcium homeostasis, and synaptic dysfunction[25]. The exact pathogenicity of α-synuclein in the induction of PD, however, remains debated. Not all cases of PD are characterized by the presence of LB, as demonstrated in patients carrying mutations in the PARKIN gene; conversely, LB can be found in the absence of clinical parkinsonism. The crucial question as to whether the spread of α-synuclein instigates the neurodegenerative process underlying PD, or rather constitutes a downstream effect, remains to be conclusively addressed. Cumulative evidence from neuropathological and preclinical studies, however,

indicates that LB pathology remains central to PD progression[26]. Such process appears to involve extranigral structures, such as the nasal and intestinal *mucosa*, long before reaching the *substantia nigra*. Indeed, the intracerebral formation of LB begins in clearly identifiable anatomic sites, subsequently progressing in a topographically consistent fashion. Braak and colleagues examined the anatomic progression of α-synucleinopathy in several symptomatic and asymptomatic cases, proposing a staging system based on the distribution of LB pathology[27]. According to this system, LB pathology remains restricted to the olfactory bulb, the anterior olfactory nucleus, and the lower brainstem during premotor stages 1 and 2. In stages 3, the pathology spreads to the *substantia nigra*, the ventral tegmental area, as well as various other nuclear structures in both midbrain and forebrain. During this stage, patients display the classical motor features of the disease, eventually leading to the clinical diagnosis. At stage 4, LB pathology spreads to the temporal limbic cortex. Finally, throughout stages 5 and 6, the entire neocortex is involved, leading to the appearance of symptoms related the impairment of high order cortical functions, such as visuospatial cognition, memory, and locomotion. The Braak system remains subject to controversies, as a proportion of PD brains do not match its predicted pattern, and an accurate correlation between LB pathology and clinical phenomenology has not been conclusively established[28]. However, this staging system contributed to gain new insights into the pathological process of PD by highlighting the widespread nature of its degenerative process[29]. Consistently, positron emission tomography (PET) and single photon emission computed tomography (SPECT) studies confirmed the *in vivo* pathological involvement of various structures and brain circuitries outside of the brainstem dopaminergic system[30]. The involvement of different serotonergic, noradrenergic, and cholinergic circuitries might play a key role in the pathophysiology of common non-motor features of the disease, including constipation, depression, and cognitive impairment.

Clinical Phenomenology

To date, the diagnosis of PD relies on clinical evidence of classical motor symptoms of the disease, also known as "cardinal motor features". The central role of motor phenomenology in PD was acknowledged since the original description of the disease by James Parkinson in 1817[31]. Main motor features include bradykinesia, muscular rigidity, and tremor at rest. At their onset, motor symptoms are usually unilateral, with some degree of asymmetry persisting throughout the disease. An additional cluster of motor symptoms involves postural changes, balance impairment and gait dysfunction (PIGD)[32]. These symptoms become particularly

problematic in the most advanced stages of the disease, and they are generally regarded as poor prognostic factors.

Bradykinesia is the core clinical sign for the diagnosis of PD. This is defined as a reduction of speed, amplitude, and rhythm of movements[33]. A key feature of parkinsonian bradykinesia is the "sequence effect" whereby both amplitude and velocity of movements rapidly decrement upon their repeated execution. Several clinical tests can be used to evaluate bradykinesia, including finger tapping, foot tapping, and pronation-supination maneuvers. Initially, this symptom may affect only spontaneous movements like blinking, hand gesticulation, or arm swinging while walking; eventually, motor slowness extends to several activities of daily living, such as writing, buttoning, or using utensils. As a result, normally undemanding motor tasks become increasingly effortful and time-consuming. Bradykinesia is presumably caused by an insufficient recruitment of muscle power due to the underscaled execution of internally generated movements at basal ganglia level, the latter presumably arising as a result of striatal dopamine depletion[34].

Rigidity, or stiffness, is another cardinal motor feature of the disease. Unlike spastic hypertonia due to pyramidal tract involvement, rigidity manifests as a constant resistance to passive mobilization, remaining homogenous throughout the entire range of motion. This sign may be exacerbated and unmasked by volitional movements of the contralateral limb. The pathophysiology of rigidity is incompletely understood, and it involves both dopaminergic depletion with abnormalities affecting basal ganglia activity, and complex functional derangements of long loop reflex pathways originating at a neuromuscular spindles level and relaying to motor cortical areas[35].

Tremor at rest can be observed in approximately 60% of PD patients, with a typical frequency of 4-7 Hz[36]. In a subset of patients, coexisting emerging postural and kinetic tremors may be observed. The classic parkinsonian tremor usually involves the distal region of upper limbs, especially thumb and index fingers, thus reproducing a characteristic "money counting" movement. Subsequently, tremor may involve lips, tongue, and jaw. Passive mobilization of the tremulous limb may evoke a specific cogwheel phenomenon, usually more evident at elbows and wrists. Tremor severity does not seem to correlate with the severity of bradykinesia or rigidity, and it might even be worse contralaterally to the most bradykinetic side. The pathophysiology of tremor in PD is not fully understood, and it presumably recognizes a central genesis, as the integrity of both motor cortex and pyramidal tracts seems required for its generation[37]. According to the so called "dimmer switch hypothesis" abnormal basal ganglia

functioning might promote the initiation of tremor, which is subsequently amplified throughout reverberating cerebellar-thalamic-cortical pathways converging on motor cortical areas[38]. In this setting, the thalamus, particularly the ventral intermediate nucleus, seem to play a pivotal role in the generation of tremor, as surgical thalamotomy or thalamic DBS both suppress this sign without modifying the degree of patient's rigidity.

Due to variable combinations of the above signs and symptoms, patients with PD may display additional features including masked face, with reduced blinking and impaired swallowing causing dry, irritated eyes, and drooling. Swallowing disturbances are particularly prevalent in the most advanced stages of the disease, with about 50% of patients reporting recurrent chocking after 17 years of disease[39]. Speech impairment may affect up to 70% of patients, manifesting with a typically monotone vocal output of decreased intensity[40]. Hypophonia can significantly impair patients' ability to communicate and therefore remaining socially active. The typical parkinsonian posture involves a forwarded projection of the center of gravity, with both head and shoulders bent towards the trunk. Upper limbs tend to rest closely and internally tilted to the trunk. Postural instability may develop due to failure of postural reflexes later in the course of the disease. In these patients, recurrent falls are strong predictors for nursing home placement and overall decreased survival[41]. PD patients may also display a broad array of gait disturbances. Parkinsonian gait involves a slow, shuffling walking with tiny steps of decreased amplitude and decreased ground clearance[42]. Episodic gait problems may also occur, especially in the most advanced stages of the disease. These include festination, defined as an involuntary, sudden shortening of strides with a rapid quickening of gait, and freezing of gait (FoG); the latter manifests with a brief absence or marked reduction of forward progression of the feet despite patient's intention to walk, usually associated with the feeling to have both feet glued to the floor[43].

Motor features in PD are heterogeneous, and several attempts have been made to classify subtypes of the disease based on the prevalent motor phenotype. While a consensus has not been reached yet, long-standing empirical observations suggest the existence of three major clinical subtypes: tremor-predominant, rigid-akinetic, and PIGD[44]. Predominantly tremulous PD is characterized by a relative lack of the main other aspects of parkinsonism such as bradykinesia and rigidity; it is usually associated with a relatively benign clinical course, an unpredictable response to dopaminergic treatments, and a better long-term functional prognosis. In the rigid-akinetic subtype, appendicular bradykinesia outweighs the other cardinal motor features of the disease. The response to symptomatic treatments is pronounced

and sustained. At some point during the course of the disease, the various motor features of parkinsonism increasingly overlap, thus resulting in what is sometimes referred as a "mixed" clinical subtype. Finally, in PIGD parkinsonism, axial symptoms, including balance impairment, postural abnormalities, speech problems, and gait dysfunction predominate over other motor symptoms, especially tremor. Patients with PIGD are usually burdened by a higher cumulative disability and faster cognitive decline; the response to dopaminergic treatment is almost always suboptimal. Historically, this phenomenological classification is derived by a retrospective review of one of the largest natural history studies of PD, the DATATOP trial[44]. Such clinically driven approach holds practical utility, especially when assessing the functional impact of motor impairment. However, its biological validity remains to be ascertained. At present, it is unclear whether the three major clinical subtypes recognize specific pathogenic substrates leading to discrete symptomatic clusters, or rather represent a state marker which is dynamically influenced by salient factors occurring during the course of the disease[45].

In addition to the motor symptoms described above, PD may manifest with a broad array of non-motor manifestations. Problems in detection, discrimination and identification of odors are a common early finding in PD. The prevalence of hyposmia is approximately 80%, and olfactory impairment may be a prodromal sign in PD[46]. Among non-motor features, neuropsychiatric abnormalities are particularly prevalent and a major source for disability. The prevalence of depression in PD ranges between 20 and 50%, and approximately 40% of patients may experience anxiety disorders and panic attacks[47]. Apathy, defined as a persistent and functionally significant loss of interest and motivation, is another psychiatric manifestation of the parkinsonian syndrome[48]. Psychological and physical fatigue are reported by up to 50% of all patients suffering from PD[49]. Fatigue may herald motor symptomatology and tends to worsen during the course of disease. However, this symptom shows no clear correlation with motor signs and is therefore believed to be mainly a non-dopaminergic phenomenon. The underlying mechanisms of affective disorders in PD remain unknown. Psychosocial factors and disability likely contribute to the development of reactive depressive symptoms. However, when compared with patients burdened by other chronic disabling conditions and matched for the degree of disability, PD patients are found to display an increased risk for endogenous mood dysregulation[50]. This is presumably related to neurobiological factors associated with the underlying neurodegenerative disease. As a case in point, the degeneration of mesocortical and mesolimbic dopaminergic neurons may disrupt the serotoninergic signaling in the dorsal raphe,

thus resulting in a dysfunction of orbitofrontal-basal ganglia-thalamic circuits involved in mood regulation and reward[51].

Approximately 30% of newly diagnosed PD patients report subjective cognitive decline, and 20% have mild cognitive impairment (MCI)[52]. The conversion rate from MCI into Parkinson's dementia is about 60% after 5 years of follow-up, and the proportion of patients with dementia increases significantly over time. The overall risk of developing dementia is 2-3 times higher in patients with PD as compared to the general population, with an estimated prevalence between 15 and 40% among patients aged over 65[53]. Traditionally, two main patterns of cognitive involvement have been identified in PD. The so called "anterior" pattern arises as a consequence of the disruption of dopaminergic signaling across frontal and prefrontal areas, manifesting with a characteristic dysexecutive syndrome affecting the adaptive capacity to new contexts, problem-solving, mental speed, and cognitive flexibility[54]. Conversely, the so called "posterior" pattern is traditionally attributed to the cholinergic involvement of the temporal and parietal cortices, accounting for memory impairment and visuospatial dysfunction[55]. During the course of the disease, psychotic symptoms, including complex hallucinations and ideation disorders, can be experienced by up to 40% of patients[56]. These symptoms are particularly frequent in patients with overt dementia. Pain, either neuropathic or nociceptive, is also a common non-motor feature of PD. It is suggested that this phenomenon may be related to the involvement of the periaqueductal gay, parabrachial nucleus, coerulean complex and medial thalamic regions[49]. Pain may also be related to motor fluctuations, namely with wearing-off and ON/OFF phenomena in patients with long exposure to levodopa treatment, usually manifesting with muscle cramps and dystonia.

Autonomic disorders have been recognized in patients with PD since the original description given by James Parkinson. In PD, both the central and the peripheral autonomic nervous systems can indeed be affected[57]. Autonomic dysfunction is a common hallmark of α-synucleinopathies, including multiple system atrophy (MSA), pure autonomic failure, and dementia with Lewy bodies (DLB)[58]. The time of onset and clinical severity of autonomic symptoms is variable. In PD, these symptoms may become particularly problematic in the advanced stages of the disease, as some of them can be exacerbated by prolonged dopaminergic treatment. Dysautonomia may involve cardiovascular symptoms, gastrointestinal, urogenital, sudomotor and thermoregulatory dysfunctions. Most PD patients suffer from orthostatic hypotension with baroreflex failure, usually due to cardiac sympathetic denervation[58]. Over time, PD related gastrointestinal problems such as dysphagia and delayed gastric emptying may

induce malnutrition and affect adherence to oral treatments[59]. Increased urinary urgency and frequency are usually related to detrusor hyperactivity, and they can increase the risk for recurrent urinary infections[60]. Sleep dysfunction is another key non-motor feature of PD. Together with insomnia and excessive daytime sleepiness, sleep fragmentation may significantly affect patients' quality of life and functional independence[61]. Sleep dysfunction can be associated with cognitive dysfunction, mainly affecting executive functions, and mood disorders. Rapid eye movement (REM) sleep behavioral disorder (RBD) is characterized by the lack of motor inhibition during REM stage, leading to potentially harmful dream-enactment[62]. RBD can occur in the premotor stage of PD, thus being regarded as a prodromal symptom of the disease.

Overall, non-motor symptoms constitute a highly distinctive element of the parkinsonian syndrome. Some of these features, such as mood changes, constipation, hyposmia or REM sleep abnormalities, may precede the onset of motor symptoms by several years, overall supporting the notion of a systemic, multifaceted disease. Cumulative disability arising from both motor and non-motor symptoms of the disease negatively impacts on a broad range of activities of daily living, thus resulting in reduced functional independence and poor quality of life.

Principles of Pharmacological Treatment

To date, there are no established disease-modifying treatments addressing the underlying neurodegenerative process of PD. Despite significant advances in the understanding of its pathophysiology, the disease remains an unremitting, incurable disorder. Dopaminergic medications are the mainstay of symptomatic treatment, and they are aimed at correcting the shortage of endogenous dopamine and the resulting striatal-thalamic-cortical dysfunction driving the main motor manifestations of the disease. Pharmacological treatments are usually started when symptoms become functionally interfering. The single most effective agent for the symptomatic management of PD is levodopa (L-3,4-dihydroxyphenylalanine), the metabolic precursor of dopamine. When taken orally, levodopa is absorbed rapidly from the small intestine by the transport system for aromatic amino acids[63]. The rate and extent of absorption of levodopa depend on various factors, including rate of gastric emptying, gastric pH, length of exposure to degradative enzymes, and potential presence of competing substrates such as dietary amino acids[64]. Drug penetration into the central nervous system is also mediated

by a membrane transporter for aromatic amino acids on the blood–brain barrier. In the brain, levodopa is converted to dopamine by decarboxylation primarily within the presynaptic terminals of dopaminergic neurons in the *striatum*. After its release in the synaptic cleft, dopamine is either transported back into dopaminergic terminals by presynaptic uptake or catabolized by degradative enzymes including monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT). When administered alone, dopamine is largely decarboxylated by enzymes in the intestinal mucosa and other peripheral sites. As a result, only a negligible fraction of the drug penetrates the central nervous system. Furthermore, dopamine release into systemic circulation by peripheral conversion of levodopa is associated with various undesirable effects, including nausea and hypotension. For these reasons, levodopa is given in combination with peripherally restricted inhibitors of aromatic L-amino acid decarboxylase, such as carbidopa or benserazide, allowing for a greater fraction of the drug to reach the brain. Early in the course of the disease, the degree of responsiveness of motor symptoms to levodopa, particularly bradykinesia, is outstanding. In this stage, beneficial effects from levodopa outlast the plasma lifetime of the drug, suggesting that the nigrostriatal dopamine system retains some capacity to store and release dopamine "on demand". This initial response to levodopa, usually lasting a few years, is referred by clinicians as the "honeymoon period"[64]. As the disease progresses, however, this buffering capacity is lost, and patients' motor state begin to fluctuate, showing a pattern of alternating times characterized by adequate motoric control (ON time), and times marked by the reemergence of motor symptoms, also known as OFF periods[65]. Increasing the dose and frequency of administration of levodopa can extend the ON time duration, but this approach is often limited by the development of excessive and abnormal involuntary movements known as dyskinesias, as well as other side effects linked to dopaminergic overstimulation, including orthostatic hypotension and visual hallucinations. With the disease progression, the therapeutic window where drugs are both effective and tolerated becomes increasingly narrow, often resulting in a complex trade-off between dyskinesias and impaired motor function. According to observational surveys, the prevalence of motor fluctuations and dyskinesia ranges from 22-64% and from 26-44%, respectively[65]. Approximately 50% of PD patients will display motor fluctuations and dyskinesia 2-5 years after the initiation of symptomatic treatment. After 10 years of treatment with levodopa, the occurrence of motor complications is estimated to affect virtually 100% of patients[66].

Additional therapeutic approaches include compounds acting directly on dopaminergic receptors such as dopamine agonists, as well as the administration of catabolic inhibitors

(MAO-B inhibitors and COMT inhibitors) extending the time during which levodopa is active in the brain. Unlike levodopa, dopamine agonists do not require enzymatic conversion to active metabolites, and they do not compete with other substances for active transport across the blood–brain barrier. Because these selective agonists have a longer duration of action and may be less likely than levodopa to induce dyskinesias, they are typically used as an initial treatment for PD[67]. However, the magnitude of symptomatic effect of both dopamine agonists and catabolic inhibitors is significantly lower than levodopa. Furthermore, the use of dopamine agonists can be limited by various side effects, including behavioral complications such as impulsive-compulsive disorders (ICDs), cardiovascular abnormalities, sleep attacks, and visual hallucinations[68]. MAO inhibitors, like selegiline, rasagiline and safinamide, inhibit the B-isoform of mitochondrial enzymes degrading dopamine, thus increasing its bioavailability at the synaptic level. Taken once or twice a day, they are used in the initial stages of the disease as monotherapy, as well as an add-on to levodopa in the more advanced stages[69]. Another class of catabolic inhibitors is represented by molecules blocking COMT enzymes such as entacapone, tolcapone, and opicapone. These drugs are usually administered in combination with levodopa to prolong its effects in fluctuating patients[70].

Device-aided therapies constitute the main treatment strategies for patients affected by advanced stage PD. The so called "5-2-1" formula serves as a general screening tool to identify patients who are potentially suitable to be referred to such treatments: 5 times of oral levodopa intake/day + 2 hours of OFF time/day + 1 hour of time spent with troublesome dyskinesia/day. Advanced therapeutic strategies include deep brain stimulation (DBS), levodopa–carbidopa intestinal gel (LCIG), levodopa-carbidopa-entacapone intestinal gel, subcutaneous foslevodopa/foscarbidopa, and continuous subcutaneous apomorphine infusion. More recently, magnetic resonance imaging (MRI) guided focused ultrasounds have been applied for the management of refractory tremor[71]. These approaches show a variable degree of invasiveness, tolerability, safety, efficacy, and reversibility, and they are available only for carefully selected patients in dedicated centers[72]. Complementary approaches, including multidisciplinary intensive rehabilitation, palliative care and nursing can improve patients' quality of life and long-term functional prognosis[73]. The leading causes of death in PD include falls and respiratory infections. Infections are typically favored by a combination of symptoms directly attributable to the disease such as dysphagia and bladder dysfunction, with the long-term effects related to reduced mobility and bed-confinement[74].

Visuospatial Dysfunction in Parkinson's Disease

General considerations

Although traditionally described in terms of motor symptoms, PD involves a broad array of non-motor features significantly affecting patients' quality of life and functional independence. Mounting evidence from clinical, behavioral, neuropsychological and brain imaging studies suggests an extensive perceptual impairment in PD, potentially occurring at any stage of the disease. When specifically asked about visuospatial difficulties, patients with PD report problems such as bumping into doorways, difficulties in negotiating obstacles on their path and estimating trajectories and space distances. In questionnaires studies, 78% of non-demented patients with PD without ocular diseases reported at least one visuospatial symptom, including misjudging objects and difficulties in navigating distances[75]. The exact source for visuospatial impairment in PD is not fully known. Retinal abnormalities can contribute to a reduction in visual acuity, contrast sensitivity, and color discrimination[76]. However, perhaps with the sole exception of visual acuity which is fundamentally constrained by retinal factors, both contrast sensitivity and color discrimination imply complex bottom-up and top-down perceptual processes that are not limited to retinal level. Patients with PD may also display a number of eye movement abnormalities, mainly affecting saccadic programing and execution, with potentially significant implications on visual exploration strategies[77]. Finally, high order visual processing and visuomotor integration seem to be significantly affected by the disease, with a number of abnormalities involving visuospatial functions such as motion perception, depth perception, spatial reasoning, visual cognition, and visuo-constructional abilities[78]. Notably, these abnormalities persist after correcting for motor impairment, disease duration, and pharmacological treatment, thus suggesting their primary perceptual nature. In the following paragraphs, the main sensory and perceptual abnormalities described in patients with PD will be reviewed, from early sensory discrimination to high order perceptual functions.

Basic Sensory Impairment

In PD, the neuropathological involvement of the retina is supported by the finding of misfolded and hyperphosphorylated alpha-synuclein in the inner retinal layer, and by several pathological studies revealing dopaminergic denervation within the foveal region[76]. A substantial reduction in retinal dopamine content was also reported in experimental models of PD, including MPTP-

treated monkeys[79]. On high resolution optical coherence tomography (OCT), the inner retinal layer of PD patients appeared significantly thinner than in controls, even though the exact clinical implications of this finding are still not known[80]. Dopaminergic amacrine interneurons modulate center/surround antagonism of ganglion cells' receptive fields. Their involvement may result in the disruption of several key visual processes, particularly involving light adaptation and transition from photopic to scotopic vision. Light adaptation enables the visual system to achieve perceptual consistency by normalizing the perceived brightness of a given stimulus over background luminance conditions. Its involvement may account for some visual difficulties reported by PD patients, especially under dim light conditions[81]. PD patients may also exhibit a shortened duration of retinal afterimages, a process normally mediated by a slow-decay dopaminergic modulation occurring within the inner plexiform layer[82]. Neurophysiologic studies provided further evidence for retinal involvement in PD. Both patients and animal models of PD display abnormal responses on pattern-electroretinograms (PERG), consistent with an attenuation of tuning for medium spatial frequencies[83]. Impaired contrast sensitivity is well documented in PD patients with normal visual acuity, where it may be partially ameliorated by levodopa administration, and it appears to correlate with disease progression[75]. Achromatic contrast sensitivity tests with sinusoidal gratings in patients with PD show increased magnocellular response thresholds for stimuli with medium to low spatial frequencies, high temporal resolution and horizontal orientation[84]. Taken together, these findings suggest that the source for contrast sensitivity impairment in these patients is not confined to the retinogeniculate pathway, as both spatial-temporal tuning and orientation-specific response are well-defined firing properties of cortical neurons.

The pathological involvement of the macular region in PD may also directly affect cone photoreceptors, which are largely confined to the central retina, resulting in abnormal chromatic perception. On a retinal level, color-specific information is segregated within the red/green opponent and the blue/yellow opponent cells subpopulations[85]. Impaired color sensitivity can be documented early in drug-naïve PD patients by means of luminance noise strategies forcing subjects to rely exclusively on chromatic cues to complete visual recognition tasks. In these settings, PD patients may display decreased color sensitivity, especially along the protan and deutan axes, suggesting a peculiar pattern of retinal involvement which can be differentiated by normal aging, where errors typically occur along the tritan axis[86]. However, while retinal mechanisms can certainly contribute to abnormalities affecting color perception, emerging evidence suggests a more central process. In patients with PD, color discrimination

is strongly associated with cognitive impairment, particularly affecting visuospatial constructional abilities, stereopsis, and executive functions[87]. In this clinical population, performances on the Farnsworth-Munsell 100 hue test also correlate with white matter abnormalities affecting the temporal and parietal portions of the right superior longitudinal fasciculus and the posterior region of the *corpus callosum*[88]. Furthermore, impaired color discrimination is associated with a 3-fold increased risk of motor conversion in patients with idiopathic RBD, as well as with the presence of severe hallucinatory symptoms in patients with dementia with Lewy bodies[89]. Overall, these findings point towards extraretinal areas involved in high order visual perception as the main substrate for impaired color discrimination in these patients.

Oculomotor dysfunction

Impaired oculomotor behavior can be documented since the early stages of PD by means of eye tracking devices. This may include deficient smooth pursuit, restricted vergence, and disruption of saccadic programing, with the generation of hypometric saccades; the latter is the most consistently reported oculomotor abnormality in this clinical population[77]. Accurate saccades rely on a complex pathway involving the frontal, supplementary and parietal eye fields, as well as the posterior parietal cortex[90]. These cortical areas project via the superior colliculus to the saccadic burst generators located in the brainstem reticular formation. It has been postulated that dopamine deficiency affecting the *substantia nigra pars compacta* may disrupt the normal inhibition exerted by the *striatum* via *pars reticulata* towards the superior colliculus, resulting in an abnormal ocular response towards the presumed location of visual stimuli[91]. The exact clinical implications of this dysfunction are not clear, but hypometric saccades are known to be associated with restricted ocular scanning and increased fixation times. Interestingly, differences in saccadic behavior between cognitively intact PD patients and controls are maximized by tasks requiring the visualization of relatively simple figures. In this setting, the area scanned by patients' eye movements is significantly smaller than the one scanned by controls[92]. However, when complex figures are explored, patients' performance paradoxically improves, as indicated by an increase in the overall extension of the scanned area. This phenomenon could be attributable to the greater availability of visual cues in complex figures, which may trigger the generation of additional, compensatory saccades. This pattern was recently dubbed by some Authors as "ocular kinesie paradoxale"[92]. Restricted ocular scanning implies a reduced access to relevant spatial information, and oculomotor

abnormalities are associated with worse performances on various visual recognition tasks. Poorly efficient exploration strategies, where irrelevant visual areas are visited in preference to correct areas of interest, are documented in patients with PD, and the severity of oculomotor impairment seems greater in the presence of cognitive impairment[93]. In these patients, spatial cognition may be directly influenced by abnormal patterns of visual exploration characterized by reduced saccadic amplitude and longer fixation; alternatively, an ongoing cognitive impairment may require subjects with PD to spend longer time in each location to extract adequate visual information. Abnormalities in saccades and fixation metrics may therefore reflect both a primary subcortical oculomotor deficit as well as the top-down consequence of an impaired spatial representation upon which patients' oculomotor behavior is erroneously organized and executed.

High order perceptual functions

Patients with PD show evidence for impairment affecting various high order visual perceptual functions[77]. In this clinical population, deficits affecting visual processing, target recognition, constructional abilities and multiple components of visual attention persist after adjusting for visual acuity and contrast sensitivity, thus highlighting a specific impairment in the cognitive elaboration of afferent sensory information[94-95]. When compared to age-matched healthy controls, PD patients consistently show poorer performances in tasks assessing various visuospatial functions, such as dynamic shape perception (e.g. recognition of computer-animated rotating figures), orientation judgment, and depth perception[96-98]. Motion perception can also be affected, with patients experiencing greater difficulties in detecting moving gratings than static ones, which is a reversal of the pattern observed in healthy controls[99]. Figure to background segregation, which normally allows the observed to isolate discrete visual features when embedded into complex sensory patterns, might also be impaired in PD. According to previous results from our group, patients with PD make a greater number of errors on the Navon test, where a letter identification tasks assesses various aspects of perceptual grouping, including global advantage and global interference[100]. Both phenomena are related to the hierarchically organized perception of spatial relationships between stimuli, by virtue of which large targets are usually processed faster than local forms[101]. For this reason, the analysis of local features can be easily disrupted by incongruent information arising from the global level. Interestingly, PD patients showed little to no evidence of unidirectional global interference under incongruent stimuli conditions[100]. This is consistent with previous longitudinal studies

reporting an attenuated global preference occurring in patients with other neurodegenerative disorders, namely Alzheimer's dementia[102]. This perceptual pattern could be attributable to a deficient representation of global features, but also to an overreliance on local features analysis. Studies assessing perceptual matching judgment between differentially oriented objects provided further evidence for an abnormal perceptual grouping occurring in patients with PD. In this clinical population, deficits in shape equivalence recognition were maximized at large angular discrepancies between objects[103]. This indicates that while undergoing such tasks, PD patients erroneously judged as different two identical objects largely rotated to one another. By relying too heavily on local matching strategies, different orientations across small adjoining segments of two identical figures may be taken as evidence for shape difference, whereas an intact global exploration strategy would lead to a correct matching decision. PD patients were also found to perform poorly on modified versions of Popperlreuter-Ghent's overlapping figure tests, where the correct disentanglement of overlapping objects requires both intact figure to background segregation, and the capability to explore the various spatial configurations of each figure in order to reach an accurate perceptual decision[104].

Perception of extrapersonal space is also affected in PD, with evidence for a differential impact on visuospatial abilities depending on the dominant side of hemisphere degeneration. In studies utilizing line bisection tasks, patients with grater clinical impairment on the left hemisoma show a clear rightward selection bias by consistently deviating towards the right side of the true midpoint, hence neglecting part of the lines contralateral to the most affected hemisphere[105]. Notably, this pattern was not observed in controls and in patients with right-sided parkinsonism, in whom the normal leftward bias driven by a prevalent right-sided parietal activation was maintained. The rightward bias observed in patients with left-sided parkinsonism might result from a distorted representation of the external space or from a lateralized failure of visual attention. Consistently, patients with left-sided parkinsonism were found to judge the size of rectangles in the left hemispace as smaller than same-sized rectangles in the right hemispace, thus suggesting an asymmetric compression of the visual scene[106]. Further information regarding perception of extrapersonal space in PD can be derived by studies on spatial navigation. Spatial navigation is a complex sensorimotor behavior where information about heading can be essentially gained by the perception of optic flow and by the estimation of reference points[106]. Optic flow is defined as the pattern of apparent motion of objects, surfaces, and edges in a visual scene caused by the difference in relative motion between the observer and the visual scene[107]. The computation of relative distance between

image frames allows to gain information on relative motion. This is presumably linked to the activation of the associative parietal cortex. When heading is primarily influenced by optic flow perception, individuals move away from the side of the space perceived as faster, that is, they move towards the hemispace perceived as more static. This is a highly conserved behavior of intuitive evolutionary significance. For example, when the optic flow is asymmetrically manipulated in experimental settings, honeybees tend to fly towards the side of the space characterized by a smaller coefficient of relative motion[108]. The same pattern can be observed in healthy humans during cognitively undemanding overground walking, treadmill walking, and driving simulations[108]. An asymmetric compression of extrapersonal space may induce a perceived asymmetry in the optic flow speed, which in turn could influence heading direction. Because the optic flow in the non-compressed hemispace is perceived as faster, patients with left-sided parkinsonism and rightward visual bias should preferentially veer towards the left. However, in contrast to the results predicted by optic flow model, patients with PD do not "move away from the most affected hemisphere", and navigational veering in this population is clearly ipsilesional[109]. Indeed, kinematic gait analysis of PD patients both in open field environments and virtual reality paradigms, revealed a consistent rightward veering of patients with left-sided parkinsonism, whereas controls and patients with right-sided parkinsonism consistently veered rightward. Notably, the deviation towards the most affected hemisphere increases when subjects keep their eyes are open. Such strong influence of visual input on veering is consistent with a perceptual bias rather than an impaired motor execution or spatial akinesia.

An alternative hypothesis posits that in PD patients, veering is influenced by abnormalities in the computation of reference points rather than by optic flow asymmetries. As a case in point, in PD patients with predominant right-hemisphere degeneration, veering appears consensual to a shift in midline reference points, particularly the egocentric reference point, which divides the space into two lateral hemifields with respect to the midline of the trunk[110]. This notion is further corroborated by previous reports of whole-body rotational behaviors towards the ipsilesional hemisphere in animal models of PD[111]. The computation of egocentric spatial references involves visually responsive areas within the posterior parietal cortex, with particular respect towards retino-topically identified elements within the right intraparietal sulcus[112]. The exact reason on why, in PD patients, veering seems more influenced by a biased rightward computation of egocentric reference points rather than by a perceived asymmetry in optic flow is not fully known. A possible explanation rests on a restricted capability to

formulate texture analysis due to impaired contrast sensitivity. Healthy contrast sensitivity serves as the basis for the computation of second-order statistics defining the joint probability that a pair of points separated by a given distance and orientation will differ from one another by a particular amount of luminance[113]. It is conceivable that in presence of a defective texture analysis, PD patients rely more on the estimation of egocentric topographic coordinates than on optic flow equalization strategies. This hypothesis, however, remains to be formally tested.

The exact substrates of visuospatial dysfunction in PD are not fully known. Impaired orientation judgment is associated with posterior parietal lobe dysfunction, whereas the capability of recognizing and isolating multiple overlapping objects is mediated by the interplay between the lateral occipital and posterior parietal cortex[114]. The neurophysiological correlates of figure to background segregation imply feedback loops between frontal and prefrontal areas and lower areas within the early visual cortex. Both optic flow perception and computation of reference points involve the activation of different areas within the parietal cortex. Previous imaging studies reported a correlation between performance in visual recognition tasks and reduction in cortical thickness in occipital-parietal regions in patients with PD[115]. Metabolic and perfusion deficit affecting extrastriate visual areas have been reported by fluorodeoxyglucose-PET studies and arterial spin labelled perfusion MRI in the same clinical population[116-118]. Changes in functional connectivity between networks that are strongly implicated in visual processing and perceptual modulation have also been reported in the early stages of the disease by means of resting state functional magnetic resonance imaging (RS fMRI). Specifically, reduced connectivity between occipital and temporo-parietal regions was observed in PD patients within 3 years of the diagnosis, with connectivity deficits strongly correlating with poor visuospatial performances[118]. Overall, converging evidence from neuropsychological and brain imaging studies, suggests that the pathophysiology of visuospatial symptoms in these patients involve both bottom-up processing of upcoming sensory information within the extrastriate visual cortex, and top-down perceptual modulation in distributed frontal, temporal, and occipital-parietal regions.

Visuospatial dysfunction and motor behavior

The relationship between visuospatial functions and regulation of complex motor functions is particularly relevant in PD. In primates, the balance system heavily relies on integrated sensory information arising from three major sources: the vestibular channel for head positioning, the visual system for the estimation of reference points and optic flow perception, and the

proprioceptive system for information regarding joint rotation and the kinematic aspects of limb movements like azimuth, lateral displacement, and relative distance from the trunk[119-120]. These components show a significant degree of interdependence. Indeed, the balance system dynamically adjusts the loads on each sensory channel based on predictions elaborated at multisensory integration levels. For example, the magnitude of balance response, i.e. lateral sway, to galvanic vestibular stimulation increases dramatically when visual information is removed[120]. Hence, in a setting of progressively reduced kinesthetic feedback, an increasing reliance on visual information is expected. In healthy individuals, this may be sufficient to compensate for impaired proprioception. However, when restricted sensory-motor integration is compounded with impaired perceptual judgment, an even greater perturbation of motor behavior is expected.

PD involves a generalized dysfunction of sensorimotor integration and proprioception due to impaired basal ganglia functions integrating multisensory input and motor behavior[121]. This typically results in an overreliance on visual information to guide locomotion, and it is consistent with the beneficial effects on step length and gait velocity commonly experienced by these patients with the use of visual cues in rehabilitation settings[122]. However, episodic gait abnormalities can also be precipitated by the need to solve sudden visuospatial problems. FoG is one of the most disabling features of PD, and it is characterized by a severe, sudden, difficulty in the forward progression of gait, usually lasting a few seconds[43]. The pathophysiology of FoG is still debated due to its clinical complexity, variety of coexisting pathologies and lack of a clear neuropathological substrate on *post-mortem* examinations[43]. FoG is not exclusive to PD, as it may be experienced by patients suffering from various neurodegenerative conditions[123]. Furthermore, the response to dopaminergic therapy is frequently suboptimal, thus suggesting the involvement of non-dopaminergic pathways[124]. One possibility is that impaired integration of visual information may prevent patients with FoG from adapting the ongoing motor behavior to solve sudden visuospatial problems[125].

Visual Hallucinations in Parkinson's Disease

Definition and Classification

Hallucinations are sensory perceptions occurring without external stimulation of the relevant sensory organ[126]. This definition allows to differentiate hallucinations from illusions, in which an external stimulus is perceived, but misinterpreted[127]. In PD, visual hallucinations, in turn, may be categorized into "simple" versus "complex" hallucinations[128]. Simple hallucinations are characterized by the absence of a recognizable form. They include photopsias such as flashes of light or color, or geometric patterns like tessellations, i.e. brick-like patterns, which may move around in space. Conversely, complex or major hallucinations have a clearly recognizable form, and they may involve humans, animals, or objects[128]. In patients with PD, secondary hallucinations may occur in the setting of delirium due to metabolic disorders, infections, or exposure to pharmacological agents, particularly anticholinergic medications[129]. Secondary hallucinations usually develop acutely, in close proximity to an acute overlapping illness or intoxication, and they are commonly associated with clouded sensorium, agitation, lethargy, and delusions. For these reasons, secondary hallucinations can be usually differentiated, on medical history, from primary hallucinations occurring as part of the underlying neurodegenerative disease.

Illusions and simple hallucinations are clinically grouped under the broad category of "minor hallucinations"[128]. This categorization is driven by cumulative observations suggesting fundamental differences in clinical profiles between patients with minor and complex hallucinations. Indeed, illusions and simple hallucinations are generally regarded as benign phenomena, typically experienced by otherwise cognitively intact patients retaining full insight on their percepts[129]. Conversely, complex hallucinations tend to occur in patients with various degrees of cognitive impairment, longer disease duration, and greater cumulative disability[130].

Lumping illusions and simple hallucinations together, however, remains problematic when considering that the perceptual nature of these phenomena is fundamentally different. Illusions arise as a consequence of an abnormal interpretation of a real sensory stimuli. Parametric manipulations of luminance, geometrical configurations, and spatial relations between stimuli, consistently elicit illusory percepts in healthy individuals[131]. These illusions are inherent to the physiological properties of the human visual system and, as such, they do not hold pathological relevance *per se*. Rather, these misinterpretations assume the integrity of various physiologic

mechanisms subserving conscious and unconscious perception, thus highlighting discrepancies between the physical properties of external information and its final percept[132-134].

Epidemiology

Epidemiological studies on primary hallucinations in PD produced variable results, mainly due to the paucity of standardized assessments. Furthermore, the majority of epidemiological observations were conducted in movement disorders clinics, with only a few studies carried out in community-based samples, with the inherent risk of selection bias. The prevalence of visual hallucinations in PD ranges from 8 to 40%[135-136]. It is generally acknowledged that the risk for hallucinations increases with the disease duration. In patients with less than 5 years of PD history, the aggregated prevalence of various types of visual hallucinations was found to be 9.2%, as compared to 17.9% and 38.3% in patients with 5-10 years or with more than a decade of disease, respectively[136]. In a longitudinal study, the point prevalence of visual hallucinations in PD reached 74% over 20 years long follow-up[137]. The real prevalence of hallucinations in PD, however, is likely underestimated. Simple hallucinations, such as flickering lights, can be erroneously attributed to ophthalmologic problems, like age-related macular degeneration or vitreous detachment[138]. Indeed, the prevalence of hallucinations raises from 22%-38% when only complex hallucinations are surveyed, up to 40-75% when pathological illusions and simple hallucinations are also considered[136,139]. Furthermore, hallucinations may be underreported in light of their potential for stigma, especially when not particularly disruptive. Various risk factors for the development of visual hallucinations were identified in patients with PD. When compared to non-hallucinators, PD patients with a history of hallucinations display greater motoric impairment and more severe depressive symptoms[136,140]. However, both findings could be due to a correlation with the duration of the disease. According to logistic regressions studies, two independent predictive factors for the onset of hallucinations persist after factoring out disease duration and severity: sleep disorders and cognitive impairment[141-142]. Among sleep disorders, day-time somnolence and RBD are independently associated with a higher incidence of hallucinations[143]. An impaired brainstem regulation of sleep-wake cycle, with fluctuating vigilance, was proposed by some Authors as the potential link between sleep dysfunction and hallucinations. In this setting, hallucinatory phenomena would be interpretable as episodes of REM sleep intrusions into wakefulness[144]. However, available clinical data do not support a directly shared pathophysiology between RBD and hallucinations. The highly stereotypical nature of visual hallucinations in PD stands

in sharp contrast with the notoriously heterogeneous content of dreams. Furthermore, while RBD may benefit from dopaminergic optimization, increasing the dose of these medications may result in an opposite effect on visual hallucinations[145].

Cognitive disorders are another major, independent predictive factor for visual hallucinations in PD. Indeed, dementia is the most consistently identified risk factor for the development of hallucinations, and patients with a history of hallucinations are known to develop dementia more rapidly than non-hallucinators[146]. Even in the absence of overt dementia, PD patients experiencing visual hallucinations show poorer performances on various cognitive functions, including verbal learning, semantic and phonologic fluency, inhibitory control, and selective memory[147].

Finally, in PD patients, hallucinations may be exacerbated by the dopaminergic therapy. Indeed, all dopaminergic agents used for the treatment of PD have the potential to elicit adverse psychotic reactions. The risk for psychosis following the exposure to dopamine agonists, however, seems comparatively higher than the one associated with levodopa. In a cross-sectional retrospective study, the highest risk for psychotic episodes was observed in association with the use of pramipexole, followed by ropinirole, and finally levodopa, with adjusted odds ratios of 1.05, 0.94 and 0.11, respectively[148]. The precipitating effect of dopaminergics towards hallucinations is usually observed in the setting of a chronic pharmacological exposure and a relatively advanced disease. Early hallucinations arising before or shortly after the initiation of dopaminergic treatments, should raise suspicion towards primary dementing illnesses rather than PD, particularly for dementia with Lewy Body. The frequent occurrence of visual hallucinations in the setting of exposure to the dopaminergic treatments led some Authors to hypothesize that, in PD patients, hallucinations might simply be a drug-induced event due to the overstimulation of mesolimbic dopaminergic receptors[149]. However, extensive evidence suggests that in these patients, hallucinations cannot be merely characterized as a iatrogenic syndrome. Records of visual hallucinations were documented prior to the levodopa era, although their interpretation is challenged by the lack of accurate diagnostic characterization and the frequent use of anticholinergic medications. More recent reports of minor hallucinations occurring in *de novo* patients further support the notion that dopaminergic treatments are not strictly required for the emergence of these phenomena[150]. In addition, no clear dose-effect relationship between dopaminergic treatment and hallucinations was ever established, and in most observational studies, the mean daily levodopa-equivalent dose (LEDD) did not statically differ between hallucinators and non-hallucinators. Finally, the

prevalence of hallucinations in patients treated with dopamine agonists for pituitary adenoma or restless leg syndrome is remarkably lower than what in PD, ranging from 1% to 9%, overall suggesting a specific disease-related substrate[151].

Phenomenology

In PD, visual hallucinations occur while patients are alert and with eyes open. Hallucinatory percepts appear suddenly, filling a limited area of the visual field, and have a short duration, typically lasting a few seconds[128]. The most frequent pathological illusions reported by patients with PD include kinetopsia, object misidentification and pareidolia[152]. Kinetopsia involves the misperception of stationary visual stimuli as they were in motion. This illusion usually involves inanimate objects, like curtains or leaves. In a recent study, kinetopsia was the most frequent type of illusion in PD, reported by 25.8% of patients experiencing minor hallucinations[153]. Object misidentifications are also common, and they involve the erroneous perception of inanimate objects as unfamiliar persons or other objects. The erroneous percept may have different degrees of complexity, ranging from other same-sized objects to complex animate visions[154]. Common patterns of complex misinterpretations include seeing small animals, such as bugs or worms, moving on table covers, walls or floors and replacing their geometric design. Other patients may report perceiving inanimate objects such as clocks or flowers as starring faces or animals. Pareidolic illusions, in which meaningless visual patterns are recognized as meaningful, are a phenomenon similar to object misidentification[153]. Simple hallucinations are described as blurred, stereotyped patterns of light or color, usually with no stereotyped localization within the visual field. They seem to be more frequent under dim light conditions, or during states of reduced vigilance[136]. Complex hallucinations involve formed visual percepts consisting of persons, animals or objects. These hallucinations may have a meaningful content, involving - for example - deceased relatives, friends, or pets. The personal significance of hallucinatory contents suggests top-down influences from high-level cognitive areas involved in memory and affective regulation[154]. A frequently reported hallucination is the so called "presence hallucination". This percept involves the vivid sensation of somebody located in the patients' immediate surroundings even though nobody is really present[136]. The specific attributes of these presences are usually not recognizable. However, patients can guess their anthropomorphic or zoomorphic nature, based on general contextual elements. In some cases, these presences have a familiar nature, as they may involve patients' loved ones, friends, neighbors, or pets. In a study conducted on 216 patients with mild stage PD and approximately

10 years of disease history, presence hallucinations were the most frequent type of hallucinatory percept, reported by 64% of hallucinators[155]. "Passage hallucinations" are another common type of hallucination. They consist of brief visions of poorly defined animate entities, either humans or animals, quickly passing sideways[155]. When animals are seen, patients can usually guess their species and size. Structured hallucinations with clearly defined shapes involve animate characters, either persons or animals. Because of their stereotypical and generally non-threatening nature, these hallucinations become familiar to patients, who may even observe them with interest and actively examine them, for example by walking towards them or trying to grab them, at which point they tend to disappear[135]. At times, complex hallucinations contain physical incongruencies providing patients with clues on their non-veridical nature. On the other hand, frightening complex hallucinations are rare, and they usually occur in the setting of paranoid delusions and comorbid dementia[156]. In PD, delusions usually involve jealousy, persecution and abandonment. Misidentification syndromes such as Capgras syndrome where patients believe that their loved ones or others they know have been replaced by doubles or imposters, may occur in combination with complex hallucinations and delusions within the spectrum of PD related psychosis[157].

Conceptual framework

Due to their transient nature, phenomenological heterogeneity and the complex relationship with other symptoms, hallucinations in PD have been challenging to investigate, and although many theories have been proposed, a unified pathophysiological model is still lacking. Over the recent years, multiple lines of evidence converged on a predictive-coding framework suggesting that in PD, pathological illusions and simple hallucinations would mostly result from an abnormal data-driven, bottom-up acquisition of sensory evidence, whereas complex hallucinations would arise as a consequence of a disrupted integration of both bottom-up sensory processing and top-down perceptual modulation[158-160]. Therefore, in these patients, the gradual transition from minor hallucinations into complex hallucinations would signal a symptomatic progression of the neurodegenerative process underlying PD. Although in PD complex hallucinations may occur without a preexisting history of pathologic illusions or simple hallucinations, a continuum progression across these phenomena is generally acknowledged[161]. In this clinical population, minor hallucinations are usually followed, over a period of months or years, by the occurrence of visions of growing complexity, which eventually become pervasive and increasingly distressing. Even though there is little evidence

directly supporting a sequential relationship between minor and complex hallucinations, this pattern appears consistent with the neuropathological staging proposed by Braak, with Lewy bodies pathology gradually spreading from subcortical structures to various cortical regions involved in different stages of perception.

Normal perception arises as a dynamic integration of bottom-up sensory information and top-down perceptual modulation. Upcoming sensory information obtained by the retina is processed through the optic tract, lateral geniculate nucleus, striate cortices and, from there, to the thick-stripe regions of extrastriate cortex projecting to higher-order areas concerned with object recognition, motion perception and spatial processing, within the dorsal and ventral visual systems[162-163]. In the traditional description of bottom-up perception, visual information flows from lower-level regions to higher-level regions until semantic analysis is performed and final recognition accomplished. The dorsal pathway is concerned with spatial and kinetic information of objects, arising from the occipital visual cortex and running through the parietal cortices[164]. The ventral system, assessing colors and forms, extends from the occipital visual cortex through the temporal cortices towards the hippocampus and amygdala[165]. Given the broad array of possible variations in the physical properties of stimuli, perceptual ambiguities cannot be uniquely resolved by systematic bottom-up analyses. Consequently, top-down feedback projections from higher-level regions are needed to unify locally-processed information into global percepts. Top-down modulation relies on long-range inputs from control networks mostly located in the frontal, prefrontal, parietal, and temporal cortices. These include the left middle frontal gyrus, the dorsolateral prefrontal cortex, the anterior cingulate cortex, the frontal eye fields, the superior temporal cortex, the hippocampal and parahippocampal regions, and the lateral parietal cortex[166-168]. Expectations generated by predictive cues enhance perceptual performances such as speed and accuracy in target recognition, and they are mediated by prefrontal and parietal regions. Attentional modulation during sensory encoding involves the enhancement of relevant sensory regions and the suppression of activity generated by distractors[167]. This function is presumably mediated by different regions within the frontal cortex. In addition, objects sharing same low-level attributes, are processed differently on the basis of their perceived emotional content[168]. Visual information expected to hold emotional significance based con contextual cues and mnemonic resonance, is prioritized to allow for a rapid evaluation and response. The network subserving top-down modulation of emotionally meaningful information likely involves the amygdala and its conspicuous, bidirectional connections with the orbitofrontal cortex[169]. Top-down

influences also allow for proper perceptual decisions through analogies between upcoming information and most similar representations stored in memory. The degree of matching between the expected perception and priors activates association areas relevant to the specific context, leading to a final perceptual decision[170]. In this setting, the medial temporal lobe, including the hippocampus and parahippocampal gyrus, is known to be critical for long-term memory and retrieval of high-resolution, view-invariant priors[171]. Finally, once a perceptual decision has been made, a reality monitoring system determines whether the final percept was driven by true external sensory information, or it was generated through internal imagery. When discriminating between external perceptual events, and internal thoughts, regions of the medial temporal lobes, parietal cortices, and prefrontal cortices are strongly activated, suggesting their direct involvement in cortical networks concerned with reality monitoring[172].

Pathophysiology

Evidence for bottom-up sensory impairment in PD patients with hallucinations arises from various experimental modalities. Electroretinogram studies involving face recognition tasks reported an increased latency of P2 and P3 waves in PD patients with hallucinations as compared to non-hallucinators. P2 and P3 waves latencies reflect the time required for object identification, a process involving temporo-occipital regions within the ventral pathway[173]. Furthermore, PD patients with visual hallucinations display impairments affecting shape perception and object recognition, thus further supporting an impairment of relatively low-level perceptual dimensions[77]. Cumulative evidence from brain imaging studies conducted in hallucinating PD patients point towards the involvement of brain regions that are anatomically and functionally integrated within the dorsal and ventral systems, including the superior parietal lobe, the posterior and inferior temporal cortex, the fusiform gyrus, and the occipital-parietal cortices[174-177]. In this setting, kinetopsia would be attributable to abnormalities in visual areas concerned with motion perception and spatial processing. Indeed, a recent fluorodeoxyglucose PET study suggest the involvement of the posterior parietal cortex, the middle temporal area (V5), and the medial superior temporal area in PD patients reporting this type of illusion[178]. These findings are consistent with prior case reports of patients reporting kinetopsia during epileptic seizures involving temporo-parietal and occipital cortices[179]. Indeed, kinetopsia can be directly induced in patients with pharmaco-resistant focal epilepsy through the electrical stimulation of the right superior parietal lobule and the intraparietal sulcus[180]. Defining the neural substrates for object misidentification and pareidolic illusions is

more challenging. While misidentification of simple objects may be favored by low-level sensory abnormalities, including reduced contrast sensitivity or impaired color discrimination, a more extensive perceptual dysfunction presumably underlines complex misidentifications. As a case in point, complex identifications and pareidolias were associated with a pattern of hypometabolism affecting areas of the temporoparietal cortices normally involved in shape recognition and semantic categorization of visual stimuli in PD patients[181].

When the quality and reliability of afferent visual information is affected, the recruitment of higher processing areas boosting selective attention, suppressing distraction, and retrieving relevant priors stored in visual memory is expected to increase[168]. These functions are sustained by complex, large scale networks providing top-down perceptual modulation, involving distributed regions within the frontal, temporal and parietal cortices. Different models focused on the role of top-down influences in the onset of complex hallucinations. The "cortical release" model originally postulated by Ffytche and Howard in 1999 assumes the primarily inhibitory nature of bottom-up visual inputs towards view-invariant representations of object shapes that are located at higher stages of perception[182]. These abstract representations are stable, non-sensory, and therefore independent from low-level defining attributes. View-invariant representations involve abstract, non-accidental perceptual dimensions localizing with different areas of the ventral visual system, mostly the inferior temporal cortex[183]. According to this model, the visuospatial impairment occurring in PD would cause a progressive loss of stimulus-driven inhibition, ultimately leading to the release of view-invariant templates. In other words, the lack of perceptual clarity would not allow PD patients to revolve potential visual ambiguities, which in turn would lead to the release of previously stored schemata. This model has been also used to explain hallucinations reported by patients affected by Charles Bonnet syndrome, a condition where complex visual hallucinations are experienced in the setting of a partial or total visual loss[184]. However, sensory deprivation only rarely produces complex hallucinations in the general population, and conversely, complex hallucinations can be reported by PD patients in the absence of demonstrable sensory impairment.

Another possibility involves a defective attentional binding resulting in incorrect perceptual decisions. In healthy individuals, bottom-up visual inputs activate several proto-objects stored in higher visual processing regions[185]. These proto-objects are not in conscious awareness, and they are potential abstract representations of the same stimulus in mutual competition for further processing. Top-down processes will influence this competition to allow for one of

these templates to enter conscious awareness and be finally perceived[186]. These top-down influences involve attentional modulation and perceptual expectations based, among other factors, on visual memory and familiarity. According to the Perception and Attention Deficit model proposed by Collerton et al. in 2005, hallucinations would arise as a combination of impaired perceptual clarity due to defective sensory input and impaired attentional binding, in conjunction with a relatively intact scene representation[187]. Patients with PD experiencing visual hallucinations show decreased visual attention as compared to non-hallucinators, independently of visual acuity or disease severity[188]. Furthermore, decreased levels of sustained visual attention were correlated with a decreased object and space perception in these patients. In this setting, impaired sensory input would favor multiple proto-objects to be projected into the visual scene, while a failure of attentional modulation would prevent these erroneous representations to be filtered out. This model has the merit to emphasize the combined role of impaired perception and attentional modulation in erroneous perceptual decisions. However, it does not explain the possibility for physical incongruencies within hallucinatory percepts. In addition, this model does not explain why properly perceived objects with preserved visual attention are not always capable to replace erroneous proto-objects and make hallucinations disappear.

Recent evidence from functional connectivity studies and network computational modelling suggests that in PD patients, hallucinations may be a consequence of aberrant connectivity affecting large scale networks subserving attention and conscious perception. Among these, the Default Mode Network (DMN), the Ventral Attention Network (VAN), and the Dorsal Attention Network (DAN) play a major role in regulating conscious perception[189]. The DMN is mainly associated with internally focused activities that are closely linked to the activation of limbic structures such as the parahippocampal cortex[190]. These areas are believed to support the generation of spontaneous thoughts in the absence of the attentional modulation required during externally focused tasks[191]. The VAN includes the temporoparietal junction and the ventral frontal cortex. The right temporoparietal junction is frequently associated with attention shifts towards unexpected stimuli (reorienting of attention) as well as false beliefs recognition. The ventromedial prefrontal cortex is critically involved in risk evaluation and decision making[192]. Finally, the DAN comprises the intraparietal sulcus and the frontal eye fields of each hemisphere. These areas contain retinotopically organized maps of contralateral space and are active when attention is externally oriented in space to generate priority maps for spatial attention, saccade planning, and visual working memory[193]. According to the "attentional

networks" hypothesis, an unconstrained activity of the DMN due to a concomitant decreased activation of the DAN results in an abnormal top-down attentional influence towards the ventral system, thereby priming the individual to hallucinate in the setting of impaired bottom-up sensory processing[185]. In patients with hallucinations, previous fMRI studies reported an increased connectivity in frontal-parietal regions included in the DMN[194]. Furthermore, though a dynamic causal model generated with a Bayesian approach involving the estimation of effective connectivity, Thomas et al. observed a decreased effective connectivity between the lateral geniculate nucleus to the medial thalamus and V1 in PD patients with hallucinations[195]. This finding was associated with an increased effective connectivity from the left prefrontal cortex to the medial thalamus and V1. This study provided compelling evidence that both reduced bottom-up and increased top-down effective connectivity is key to the pathophysiology of hallucinations. In addition, this study highlighted the role played by the thalamus as a crucial hub for the synchronization of simultaneous streams of information during visual processing.

Neuroimaging

Neuroimaging studies in PD patients with history of complex hallucinations reported findings consistent with the involvement of occipital-parietal, temporo-limbic structures and frontal-prefrontal areas concerned with both sensory elaboration and perceptual modulation. Voxel-based morphometry is a structural brain imaging technique utilizing T1-weighted MRI scans to perform statistical tests across a number of voxels in order to compare the regional gray matter (GM) volume of two or more groups. So far, VBM studies investigating neural correlates of hallucinations in PD led to variable and sometimes conflicting results, presumably reflecting the clinical heterogeneity of participants and the different tools utilized to assess patients' hallucinatory status. In recent studies, patients with a history of minor hallucinations exhibit a pattern of GM atrophy affecting areas involved in visuospatial functions, orienting response, and object recognition, such as the superior occipital gyrus, the inferior occipital gyrus, the right cuneus and precuneus, the superior colliculus, and the superior parietal lobule[175]. A more diffuse pattern of GM volume reduction is reported in patients with complex visual hallucinations, with atrophy extending to areas involved in complex perceptual functions such as visual attention and syntactic analysis. These areas include the lingual gyrus, the limbic and paralimbic cortex, the dorsolateral prefrontal cortex and the inferior frontal cortex[177].

Brain perfusion single-photon emission computed tomography (SPECT) imaging is a functional nuclear imaging technique assessing regional cerebral perfusion. Because cerebral blood flow is closely linked to neuronal activity, the activity distribution presumably reflects neuronal activity in different areas of the brain. Results from SPECT studies showed significant perfusion deficits in occipital cortices, inferior temporal cortices, and precuneus gyri in non-demented PD patients with hallucinations compared to patients with non-hallucinatory PD[196]. F-18 fluoro-deoxy-glucose (^{18}FDG) PET is an imaging modality assessing the relative regional glucose metabolic rate. In the first ^{18}FDG PET study conducted on hallucinating PD patients, the cerebral rate for glucose consumption was found to be significantly increased in various frontal regions[178]. In a subsequent study on 24 PD patients, a decreased glucose metabolism was observed in occipital-parietal-temporal regions of hallucinators[194]. Somewhat conflicting results were reported in a later ^{18}FDG PET study where, the hypometabolic pattern involved occipital-parietal areas, but with a sparing of the occipital lobe[198].

Different modalities of fMRI have been utilized to explore the neural basis of illusions and hallucinations in patients with PD. In these studies, patterns of brain connectivity are identified by looking at time-varying changes in blood-oxygen-level-dependent (BOLD) signal across different brain regions. These changes are caused by temporal variations of deoxyhemoglobin levels, which in turn are driven by localized changes in brain perfusion. Because of neurovascular coupling, changes in blood oxygenation reflect underlying changes in neuronal activity. Hence, spatially distributed areas showing temporally correlated changes in BOLD signal are deemed to be functionally connected. The first fMRI studies exploring the neural correlated of hallucinations examined differences in resting-state (RS) connectivity between PD patients with and without hallucinations[199]. Resting state functional connectivity (RS-Fc) is defined as a significantly correlated signal between functionally related brain regions, in the absence of specific stimuli or tasks[200]. Significantly higher levels of RS-Fc were found in the right middle frontal gyrus, bilateral posterior cingulate gyrus and precuneus in PD patients with history of hallucinations as compared to non-hallucinators. These findings supported a key role played by an abnormal top-down perceptual modulation in the occurrence of complex hallucinations[177]. However, the main limitation of RS fMRI studies lies in their inability to assess real time changes in Fc occurring while patients are experiencing hallucinatory percepts. Task-related fMRI can overcome this limitation by assessing changes in functional connectivity occurring during the administration of various paradigms engaging patients' perceptual functions. Network activity levels are determined by analyzing the percent signal

change from the average BOLD intensity within each network during the execution of a given task[201]. Using an apparent motion inducing paradigm involving alternating stationary and moving concentric circles, a task-related fMRI study conducted on PD patients with history of hallucinations found a decreased activation of the inferior parietal lobe as well as a significantly greater activation of the inferior frontal cortex as compared to non-hallucinating patients[204]. These findings supported the hypothesis that hallucinations may arise as a consequence of two interconnected phenomena: an impaired sensory processing, as highlighted by a reduced activation of posterior brain regions, in combination with an abnormal top-down perceptual modulation, the latter indicated by an increased frontal activation.

Similar results were partially replicated by a small task-related fMRI study on 6 PD patients with a paradigm involving colored geometric shapes moving in random directions across a black background[159]. However, the utilized task was designed primarily to activate posterior cortical areas involved in low-level perceptual functions, and not specifically to elicit illusory percepts. The same limitation concerns a subsequent study with a task involving the repeated vision of face pictures where, compared to non-hallucinators, hallucinating patients showed a decreased activation of extrastriate visual regions, but not an increased activation of anterior cortical areas[203].

More sophisticated paradigms were recently developed to elicit illusory percepts in susceptible individuals while avoiding the same effect in healthy subjects. These induced illusions are regarded as surrogates for spontaneous hallucinatory phenomena occurring in clinical populations. In this setting, bistable percept paradigms reliably induce illusory phenomena in inviduals who are prone to hallucinate. While undergoing these computer-based tasks, participants are generally asked to view a series of monochromatic images appearing in either stable or multistable configurations. In the former case, images are made of stimuli with only one possible perceptual interpretation. In the latter case, images are presented in multistable configurations associated with multiple perceptual interpretations. When looking at stable images, patients with hallucinations typically report multiple perceptual interpretations, highlighting a specific deficit in solving ambiguities and reach a perceptual decision. In 2015, Shine et al. utilized a task-related fMRI approach with a bistable percept paradigm to investigate patterns of bran activation underlying visual hallucinations in 35 patients with PD[204]. In patients misinterpreting stable images, therefore labeled as "hallucinators", an increased activation of the DMN and the VAN was found, alongside a significantly decreased activation of the DAN. The Authors concluded that illusory percepts in PD patients could be

caused by a failure to recruit exogenous attention systems in the absence of externally-driven inputs, and in the setting of a concomitant increase in endogenous attentional systems involved with reality monitoring. These findings provided the basis for the "attentional networks" model described in the previous paragraph.

Diagnosis and Clinical Relevance

There is no accepted diagnostic gold standard for visual hallucinations in PD. In clinical settings, the identification and characterization of hallucinatory percepts commonly relies on medical history. The Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) is one of the most frequently used clinical assessments in PD[205]. The Item 1.2 of the MDS-UPDRS Part I evaluates both hallucinations and delusions using a clinician-administered, patient-report or informant-report measure on a rank-ordered scale. The reliability of this item is limited by the lack of differentiation between the various types of hallucinations. Furthermore, Item 1.2 of MDS-UPDRS Part I does not accurately characterize the peculiar phenomenology of low-complexity abnormal percepts, thus potentially underestimating illusions and minor hallucinations. The North East Visual Hallucinations Interview is a 17-item, clinician-administered interview assessing frequency, intensity, and content of visual hallucinations[206]. The validity of this tool remains to be ascertained in large clinical populations as well as in patients experiencing multimodal hallucinations. Indeed, the possibility for hallucinations involving more than one sensory modality is not uncommon in PD. In these patients, the cumulative percentage of various non-visual hallucinations modalities (i.e. tactile, olfactory and acoustic) was recently found to be 54.8%[207].

Disease-specific tools such as the Scales for Outcomes in Parkinson's Disease – Psychiatric Complications (SCOPA-PC), Parkinson's Psychosis Rating Scale (PPRS), and the Non-motor Symptom Questionnaire (NMSS), include only a limited number of items specifically assessing visual hallucinations, and they may not fully disentangle the specific core of hallucinatory experiences from related constructs like psychosis or dementia[208-210]. Other inventories characterizing hallucinations in a more detailed fashion may be time-consuming and, as such, they are not easily administrable in clinical settings. The Rush Behavioral interview assesses the severity of hallucinations across all modalities focusing on frequency in the past month, with a score ranging from 0 (none) to 3 (at least three times weekly), but it does not provide detailed information about the type and nature of hallucinations[211]. The University of Miami

Parkinson's disease Hallucinations Questionnaire (UM-PDHQ) is 20-item, clinician-administered questionnaire consisting of two groups of questions: a quantitative group of 6 questions assessing modality, frequency, duration, insight and emotional burden, and a qualitative group consisting of 14 questions assessing clinical phenomenology, potential association with dopaminergic medications, and concomitant ocular abnormalities[212]. The UM-PDHQ surveys peculiar aspects of the hallucinatory phenomenology in these patients, including motion, size, texture, color, and content of abnormal percepts, thus potentially representing a more accurate and sensitive tool. In a recent study conducted on 70 PD patients with a mean Mini Mental Status Exam (MMSE) score of 25.6 ±4.5 and a mean disease duration of 9.0 ±5.4 years, the UM-PDHQ classified 44.3% of the sample as hallucinators, as compared to only 37.1% of patients identified as hallucinators according to the relevant item of MDS-UPDRS Part I[212]. Notably, the UM-PDHQ is designed as a screening tool to optimize the detection of hallucinatory experiences in this clinical population, but it does not provide a graded scoring, thus not being suited to assess quantitative variations of severity over time.

Cumulative disability related to visual hallucinations significantly impacts the quality of life of both patients with PD and caregivers. Apart from their association with cognitive decline and reduced functional independence, hallucinations are linked to increased mortality, and they are the strongest predictor of earlier nursing home placement[213]. Quality of life is significantly poorer in hallucinators as compared to non-hallucinators, independently from disease duration and disease severity[214]. Pharmacological options for persistent or disabling hallucinations are limited to atypical antipsychotic agents, which can be particularly detrimental in these patients in light of their well-known side-effects, including falls, sedation, worsening of cognitive and motor function, and abnormalities affecting cardiac conduction[215]. Once the possibility for secondary hallucinations due to acute overlapping illnesses is ruled out, the therapeutic management of hallucinations involves the progressive reduction of potential pharmacological triggers. A judicious dopaminergic withdrawal is therefore pursued, with medications deemed as less effective in controlling motor symptoms being discontinued first. This usually involves the tapering of anticholinergic drugs, followed by amantadine, MAO-B inhibitors, dopamine agonists, and COMT-inhibitors. In particularly challenging case, reducing levodopa doses might be needed, with the inherent risk of worsening PD motor symptoms and related disability. For all these reasons, visual hallucinations are regarded as a great unmet need in this clinical population.

II. STUDY METHODOLOGY

Background: Illusory Figures

Visuospatial functions and Illusions

As reviewed in the previous sections, impairments affecting high order visuoperceptual functions are a key component of the pathophysiology of visual hallucinations in PD. In the early stages of disease, before the onset of a general deficit in cognition, such impairments can be detected by means of dedicated tasks assessing different visuoperceptual domains. Results from a recent metanalysis conducted on 99 neuropsychological studies, overall including 7826 PD patients, indicate restricted visual apperception and impaired visuospatial functions are indeed neuropsychological hallmarks of hallucinations in this clinical population[129]. Poorer performances of hallucinators is reported in tasks assessing judgement of line orientation, visuospatial constructional abilities, position discrimination, perceptual differentiation and organization, and different components of visuospatial attention[126]. As the disease progresses, deficient sensory accumulation due to impaired bottom-up processing leads to an overactivation of top-down modulatory functions aimed at preserving perception by boosting selective attention, suppressing distraction, and retrieving relevant priors stored in visual memory. These functions, however, are not optimized to systematically fill the gap of perceptual ambiguities resulting from poor quality sensory information. As a result, erroneous percepts with growing layers of complexity may occur[195].

Illusory figures have the potential to elicit illusions in healthy individuals through perceptual biases related to systematic manipulations in geometrical configurations, contrast, color, or spatial relationships between visual stimuli[131-133]. To avoid ambiguities, the term "illusory figures" will be used in this thesis to refer to configurations purposefully eliciting visual illusions in healthy individuals, whereas the term "illusions" will be used to denote the perceptual experience of observers exposed to such figures. The Delboeuf illusion is a visual phenomenon fist described by the Belgian philosopher Franz Joseph Delboeuf occurring when two circles (test figures) of equal radius are presented next to each other and surrounded by concentric circles (inducers) of different radii[216]. In this illusion, the test figure is overestimated or underestimated depending on the size of its inducer **(Figure 1)**. Specifically, if the inducer is only slightly larger than the target, the latter is overestimated. Conversely, if the inducer is

much larger than the test figure, the target's sized is underestimated. The first type of distortion is described as the "assimilation illusion": in this case the outer and inner circles are placed in close proximity to each other due to the short radius of the inducer. The target is therefore assimilated to the inducer and hereby perceived as bigger than its real size. The second type of distortion is known as "size contrast illusion": the relative long distance between test figure and inducer elicits a downscaling of the former, which is therefore perceived as smaller than its real size[217]. The magnitude of both distortions is related to the diameter ratio between the two concentric circles: the largest overestimation and underestimation of targets are determined by ratios of 3:2 and 5:1, 6:1, respectively[218]. Particularly relevant is the role of attentional prioritization in modulating the perceptual performance on assimilation illusion. Indeed, the overestimation of the target is greater when the observer reports the size of the inducer first, whereas the magnitude of overestimation is smaller if the target is attended before the inducer[219]. The reason for this phenomenon, known as effect of judgment order, presumably lies on the persistence of spatial scaling from the prioritized stimulus. In the first case, the size of the inducer is assumed as a spatial reference to estimate the size of the target. Hence, the assimilation of the target is facilitated[220]. Conversely, if the observer attends the target first, a further attentional effort is required to integrate the new spatial scale of the inducer, thus reducing the strength of the illusory overestimation. Notably, the judgment order effect differs from the classical time-order error, where the stimulus judged as second is systematically overestimated, in that the overestimation obtained under sequential judgement with Delboeuf illusion cannot be reversed when observers make their judgement in the opposite order. The specific attentional basis of the effect of judgment order are not fully known. However, the effect of judgement order appears significantly influenced by task-dependent attentional modulation[220]. The assimilation of the target is indeed facilitated when the observer attends the inducer through relevant attentional tasks such as the estimation of the area enclosed by the outer circle, whereas its mere inspection or segmentation does not lead to the same facilitation. Conceivably, visual information deemed relevant to an ongoing task, like the estimation of the area of the inducer, is enhanced to generate the spatial framework for the subsequent stimulus, therefore magnifying the overestimation bias[220].

Further illusions can be experienced by healthy individuals as a result of perceptual biases related to illusory filling and amodal completion. The illusory filling is a perceptual phenomenon whereby the invisible contours of partially occluded objects is perceived despite the absence of corresponding retinal stimulation[221]. This phenomenon enables the viewer to

bypass the physiological constrains of tridimensional space, where the majority of objects naturally lies in a partially or totally occluded configuration. The perceptual basis of illusory filling is presumably linked to the phenomenological persistence of priors, and recent evidence suggests that its neural substrates may involve higher tier visual areas within the posterior parietal and lateral occipital cortices[222]. The amodal completion process, on the other hand, is perceptual phenomenon where two modally visible elements of an occluded object are erroneously perceived as a unitary object[223]. The proclivity of the visual system to amodally complete objects results in well-documented perceptual distortions[224]. In a classic example of such distortions, a square lying behind an occluding rectangle is perceived as smaller than its non-occluded copy (**Figure 2**). Impairments in stereopsis were originally believed to play a role in driving this illusory bias: as the occluded element is projected in the background behind the inducer, the application of size-distance invariance may indeed lead to its illusory shrinking. According to the principle of size constancy, the perceived size of an object is proportional to its distance; therefore, the observer may assume that the occluded element lying behind the inducer is smaller than its non-occluded copy. However, an erroneous size judgement driven by depth constancy is likely to affect both dimensions of the occluded element, whereas the illusion due to amodal shrinking typically involves only one single dimension. The exact mechanisms underlying this illusion, therefore, remain unknown. When attending these figures, observers appear to disregard the perceptual evidence supporting the existence of two same-sized squares by erroneously perceiving the amodally completed object as shrunk. Kanisza famously noted that the perceived extension of surfaces depends only partially on their actual geometric extension, as the size representation of objects also depends on the low intensity and homogeneity of the stimulation of the occluded surface[225]. This might favor the size underestimation of amodally completed objects. Effective figure to background segregation may counteract this bias, by allowing for the disentanglement of the occluded square from the overlapping rectangle. This would enable the observer to scrutinize each element of the object separately[226]. In this setting, impairments affecting figure to background segregation leading to a biased representation of overlapping figures might prevent an accurate perceptual decision regarding the size of the occluded element and its non-occluded copy[227].

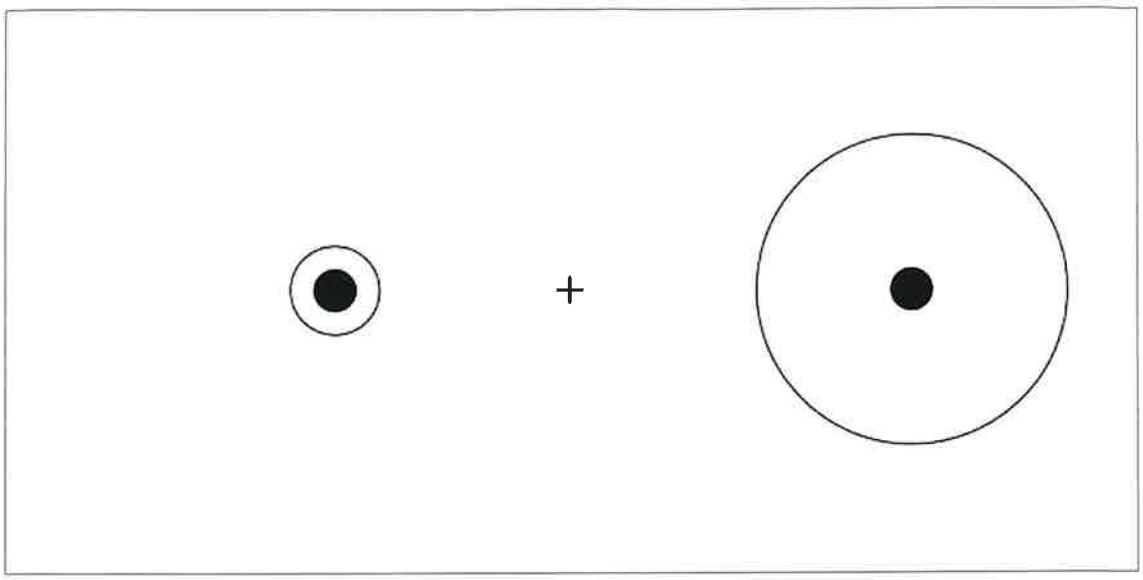


Figure 1: size distortions in Delboeuf illusion: when the outer circle is slightly larger than the inner circle (left-side), the latter is overestimated due to assimilation; when the outer circle is considerably larger than the inner circle (right-side), the latter is underestimated due to size contrast.

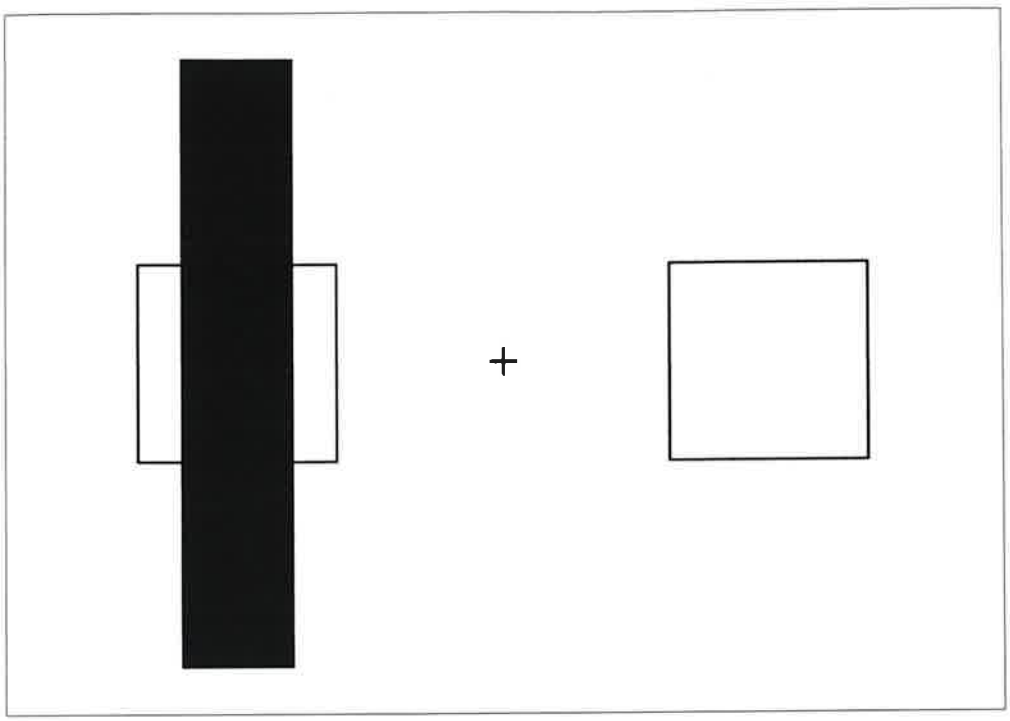


Figure 2. Illusory shrinkage of amodally completed objects: the occluded square can be erroneously perceived as smaller than its non-occluded copy.

Study Rationale and Research Questions

Rationale for the present study

Perceptual biases driving physiologic illusions in the general population assume the *a priori* integrity of various bottom-up and top-down perceptual functions. For example, the overestimation distortion in the Delboeuf illusions involves physiologic mechanisms of assimilation and attentional prioritization, whereas the vulnerability to shrinking distortions of amodally completed figures presumably involves mechanisms of edge detection, illusory filling, and perceptual grouping[218, 220, 222, 224]. Critically, these function can be variably targeted by the neurodegenerative process underlying PD. Computer-generated illusory figures are non-invasive, cost-effective, and reproducible modalities to probe some of the physiologic mechanisms underlying perception. Different performances on these illusory figures might therefore highlight perceptual mechanisms relevant to the pathophysiology of hallucinations in this clinical population. In the present study, we investigated perceptual performances of non-demented PD patients on illusory figures, with and without a history of hallucinations, and compared them with those of age-matched healthy individuals. To this end, we selected the Delboeuf illusion and the size shrinkage due to amodal completion. Perceptual biases driving these illusions were indeed deemed likely to be influenced by visuoperceptual impairments occurring in PD.

Final perception results from the dynamic interplay between mechanisms preventing the misinterpretation of sensory information (e.g. perceptual constancies) and mechanisms generating illusory biases. Different profiles of vulnerability to illusions can be hypothesized in PD, depending on patients' visuoperceptual impairment. An increased vulnerability to illusions should be observed when relevant protective mechanisms are targeted by the disease. Conversely, a paradoxical profile of decreased vulnerability should be expected when mechanisms driving the occurrence of illusions are affected by the underlying neurodegenerative process. Furthermore, potential neural substrates linked to perceptual performances in both hallucinating and non-hallucinating PD patients were explored by means of extensive clinical characterization and analysis of brain metabolic patterns on ^{18}FDG PET.

Research Questions and Hypotheses

1. Is perceptual performance on illusory figures different between healthy controls, non-hallucinating PD patients, and PD hallucinators?

Hypothesis. Performance on illusory figures relies on visuospatial and visuoperceptual functions that can be variably affected by the underlying neurodegenerative process of PD; in the same clinical population, some of these perceptual functions are involved in the pathophysiology of hallucinations. We hypothesized that performance on experimentally induced illusions will be significantly different across the three groups.

2. Which profile of vulnerability to illusory figures is expected in PD patients?

Hypothesis. Variable effects of the disease on perceptual performance of these patients can be expected, depending on the relation between the prevalent perceptual deficit and the perceptual biases driving illusions. Specifically, an increased vulnerability to illusions was expected when the impaired function normally counteracts the perceptual bias driving the illusion. Conversely, a decreased vulnerability to illusions was expected when the impaired function is normally required to generate the perceptual bias driving the illusion.

3. What are the neural substrates underlying potential differences in perceptual performances between PD patients with and without hallucinations?

Hypothesis. We hypothesized that abnormal perceptual performances on illusory figures of PD patients with complex hallucinations was accompanied by the involvement of cortical areas concerned with high order perceptual functions, including visual attention, perceptual decision, and reality monitoring.

Methods

Study Design

This was an observational, cross-sectional, controlled, exploratory study conducted on three groups of age-matched individuals: PD patients with history of complex hallucinations (PD_Hal), PD patients with no history of hallucinations (PD_NonHal), and healthy controls (HC). Eligibility criteria for study participation are summarized in **Table 1.** Main inclusion criteria were a Montreal Cognitive Assessment (MoCA) corrected score ≥24 and, for PD patients, a clinically established diagnosis of PD according to the United Kingdom Parkinson's Disease Society (UKPDS) Brain Bank criteria[228,229]. Main exclusion criteria were a history of clinically significant ocular pathology or ophthalmic disease, and impaired visual acuity as indicated by a Snellen chart acuity test <20/20, despite potential correction. Specific exclusion

criteria for PD patients included recent changes in dopaminergic medications, unpredictable motor fluctuations, psychosis, delirium, or any contraindication to undergo ^{18}FDG PET study.

Patients were prescreened telephonically to determine their potential eligibility. On Visit 1, eligibility criteria were reviewed, and PD patients were categorized as PD_Hal and PD_NonHal based on the score of their University of Miami Parkinson's disease Hallucinations Questionnaire (UM-PDHQ). The UM-PDHQ is 20-item clinician-administered questionnaire consisting of two groups of questions: a quantitative group of 6 questions assessing modality, frequency, duration, insight and emotional burden, and a qualitative group consisting of 14 questions assessing clinical phenomenology as well as the potential association with dopaminergic medications and concomitant ocular abnormalities[212]. For the present study, a non-validated Italian translation of the UMPDHQ was developed by the Author (see in **Supplemental Materials**). Patients scoring ≥1 were categorized as PD_Hal, whereas patients scoring 0 were categorized as PD_NonHal. UM-PDHQ was chosen to determine patients' hallucinatory status in light of its relatively higher sensitivity, accuracy in describing disease-specific hallucinatory percepts, and nominal time requirements for its administration.

Upon successful verification of eligibility, participants were scheduled with Visit 2, during which the remaining experimental procedures of the study took place. In PD patients experiencing motor fluctuations, all assessments performed during Visit 2 were conducted in the ON therapeutic state in order to minimize fatigue and potential physical discomfort. Study personnel involved in the assessments of Visit 2 was kept blind to the specific PD group allocation.

Study Setting and Participants

The study was carried out between February and September 2022 at the Neurology Clinic of Cattinara Teaching Hospital in Trieste, in collaboration with the Department of Life Sciences of the University of Trieste, Italy. Thirty-three subjects were consecutively screened, and 31 of them were deemed eligible to participate in the study. Ten healthy subjects and 21 PD patients with and without history of hallucinations were enrolled in the study. Informed consent for data collection was undersigned by all participants, and the study was approved by the local institution review board (Comitato Etico Unico Regionale FVG, CEUR). All experimental activities were performed in accordance with relevant regulations and in compliance with the Declaration of Helsinki.

Illusory figures: Apparatus

Two sets of illusory figures were used in the present experiments: the Delboeuf illusion, and the size shrinkage of amodal completion. The former was chosen to explore potential differences in perceptual performance related to spatial scaling (size contrast), perceptual grouping (assimilation), and attentional modulation (judgement order effect). The illusion of size shrinkage induced by amodal completion was selected to explore potential differences in perceptual performances related to perceptual filling and overlapping figures judgement. For each illusion, a set of stimuli was created by keeping constant a part of the configuration, and systematically manipulating one variable of the second part of the configuration. The perceptual variable of interest was expressed in terms of degrees of visual angle. The visual angle of an object is a measure of the size of its retinal representation depending on both the relative distance between the object and the observer and the actual object's size. For the Delboeuf illusion, the diameter of the target enclosed by the larger inducer (on the right side) was manipulated ranging from 0.95° to 2.29° of visual angle (with a variation of 0.09° for each figure); the size of the inner disk on the left was constant (1.09°). For the size shrinkage of amodal completion, the width of the non-occluded square (on the right side) was manipulated ranging from 4.39° to 7.81° of visual angle (with a variation of 0.19° for each figure); the size of the occluded square on the left was constant (5.72°). Stimuli were generated using a vector graphics editor (Inkscape). The experiment was programmed through an open source software package written in Python (PsychoPy). Illusory figures were administered with participants sitting in front of a computer screen of 31.5 x 54 cm placed in front of them on a distance of approximately 50 cm. A five-buttons response box was used to collect responses, using the extreme left and right keys for responses.

Illusory figures: Procedures

Participants were exposed to a set of illusory figures (one by one) and were asked to provide their answer by pressing the corresponding key on the response box in front of them, using the left hand for pressing the left key and right hand for the right key. When performing the task related to the Delboeuf illusion, participants were asked to answer the following question: "*can you tell me which one of the two inner circles is larger?*". Similarly, when performing the task relevant to the amodal completion illusion, participants were asked to answer the following

question: *"can you tell me which one of the two squares is larger?"*. In both tasks, participants were instructed to press the left key when the left target was perceived larger than the right one, and the right key when the right target was perceived larger. A familiarization session was run before starting the experiment, for each perceptual task. No specific time constraints were given, but participants were prompted to undergo the tasks in a timely fashion and at best of their capability. A staircase method was employed, with the initial stimulus always eliciting a perceptually obvious judgement, either a maximally amplified illusion or its opposite perceptual effect. The perceptual variable relevant to each illusion was then systematically manipulated by showing figures that progressively reduced the effect until the participant's initial perceptual judgement was reversed and the reversal was confirmed in a subsequent trial. At this point, a new set of stimuli was administered, this time starting from the opposite end of the range of the stimuli. The same procedure was repeated four times for each illusion, with the starting condition being randomized across trials. For each set of stimuli, the average value of the two figures before and after the reversal was calculated. This value represents the subject's point of subjective equality (PSE), i.e. the value of comparison stimulus equally likely to be judged higher or lower than that of the standard stimulus. An average PSE close to the point of physical equality was taken as evidence for an accurate perceptual performance. Conversely, the greater the difference between PSE and point of physical equality, the more vulnerable participants were deemed towards the relevant illusory effect. The overall time for the administration of both illusory figures was approximately 10 minutes.

Clinical Assessments

Clinical assessments were performed by neurologists with expertise on Movement Disorders. Patient's pharmacological profile was characterized in terms of levodopa equivalent dose (LEDD) and dopamine-agonist equivalent dose (DA-LED) as in Tomlinson et al.[230] Disease burden and clinical severity were assessed by means of MDS-UPDRS, in its four sections exploring mentation, behavior and mood, activities of daily living (ADL), motor severity, and complications of therapy, respectively[231]. Sections I to III of this rating tool are scored on a 0-4 rating scale. Section IV is scored with yes and no ratings. Higher scores indicate increased severity. A specific sub-score was derived for each patient by pooling together scores on item 1 and 9-13 of MDS-UPDRS Part III in order to explore potential differences in terms of axial impairment between PD_NonHal and PD_Hal. The MDS-UPDRS also includes the Hoehn and Yahr (H&Y) staging, describing the progression of the disease through various grades of

functional disability, from I (unilateral disease) to V (patient is wheelchair bound or bedridden unless aided). The 39 item PD questionnaire (PDQ-39) was administered to assess patient's perceived quality of life[229]. PDQ-39 is the most widely used disease specific patient completed rating scale in PD, and it comprises 39 questions from 8 dimensions, including mobility, ADL, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort. Questions explore patient's perceived functional impact on each dimension, and answers are scored between 0 (never) to 4 (always or cannot do at all). The total score is calculated after adding the individual scores. A higher score indicates poorer quality of life.

Study of brain metabolism with F-18 fluoro-deoxy-glucose positron emission tomography

Regional cerebral metabolic rate of glucose utilization was measured using ^{18}FDG PET in PD patients exclusively. All patients fasted for more than 6 hours before the scan and were injected with a mean ^{18}FDG dose of 200 MBq intravenously 40 minutes prior to scanning. To minimize the effects of external stimuli during the 40 minutes ^{18}FDG-uptake period, subjects were confined in a quiet room. Scans were obtained with patients under resting conditions, wearing eye masks. PET images were obtained using a PET/TC Discovery MI DR scanner (G.E. Healthcare) for 8 minutes. Image reconstruction was performed using an ordered subset expectation maximization and 32 subsets and a 5-iteration reconstruction algorithm and displayed in a 128X128 matrix (pixel size 2.35 mm). Multiple automated approaches for alignment to the database were employed, including linear affine registration to account for global position and scaling differences as well as a deformable registration algorithm to allow for localized adjustments. On each of the spatially and globally normalized images of patients, Z-scores were obtained through a dedicated post-processing software (Cortex Suite, G.E.) for each of the following region of interest (RoI), bilaterally: lateral prefrontal cortex (LPFC), medial prefrontal cortex (MPFC), superior parietal cortex (SPC), inferior parietal cortex (IPC), lateral temporal cortex (LTC), mesial temporal cortex (MTC), lateral occipital cortex (LOC), precuneus, and primary visual cortex (PVC) as in Tzourio-Mazoyer et al.[232] Negative Z scores indicated relative hypometabolism and positive Z scores indicated relative hypermetabolism. Semiquantitative assessments were obtained through and reviewed by expert nuclear medicine physicians.

Statistics

Participants' PSE was calculated from each sequence of illusory figures by averaging the value of the stimulus before and after the inversion, considering the dimension being manipulated (i.e., the degree of visual angle). A set of one-way ANOVAs were conducted for the individual sets of each illusory figure; the dependent variable was the PSE of each individual series. Tuckey's correction (Honestly Significant Difference) was applied in post-hoc tests. The threshold value for significance was set at $P<0.05$. Clinical variables across the two PD groups were compared with two-tailed t-test for unequal variance. Statistical significance threshold was set at $\alpha= 0.05$. For comparisons that did not meet the criteria for using parametric tests, the corresponding non-parametric tests were utilized. Between group differences in brain metabolic patterns on ^{18}FDG PET were analyzed by calculating the values of mean regional abnormalities in relative regional cerebral glucose metabolic rate for each RoI. Statistical analyses were performed by means of t testing for the two PD groups across each region, with significance level set at $P< 0.05$.

Table 1: Eligibility Criteria

	Common	Specific to HC	Specific to PD patients
Inclusion criteria	Female or male. Age 30 – 80. MoCA ≥24.		Diagnosis of PD according to UK PDS Brain Bank Criteria, reviewed and confirmed by an MDS expert neurologist. Hoehn&Yahr staging 1-3. No changes in dopaminergic treatment in the 4 weeks prior to screening.

Exclusion criteria	Visual acuity <20/20 on Snellen Chart test despite correction. Active ophthalmic disease or clinically significant ocular problems (e.g. symptomatic cataract, glaucoma, recent periorbital trauma, diabetic retinopathy, etc.). Major unstable illness. Major surgery in the 3 months prior to screening.	Any history of neurologic or psychiatric disease.	Chronic pain or severe dyskinesia limiting participation in behavioral tasks. Severe and unpredictable motor fluctuations. Signs and symptoms suggesting an ongoing significant progression of PD per investigator's judgement. History of/ ongoing psychosis and delirium. PET contraindications[1].

[1]PET specific contraindications: renal insufficiency, diabetes mellitus, dehydration or volume depletion, concurrent treatment with nephrotoxic drugs, morbid obesity, claustrophobia, prior allergic reactions to radiotracer administrations.

III. RESULTS

Demographic and Clinical Characteristics

Ten healthy subjects, 10 PD patients with UMPDHQ score of 0, and 11 PD patients with UMPDHQ ≥1 were enrolled and assigned to the HC, PD_NonHal, and PD_Hal groups, respectively. Demographic characteristics and clinical features of study population are summarized in **Table 2**. Subjects in the three groups were comparable in terms of age, gender distribution, and general cognition as assessed by MoCA. Comparatively longer education was observed in HC and PD_Hal as compared to PD_NonHal. Disease duration was comparable between PD patients with and without hallucinations. General Motor impairment as assessed by MDS-UPDRS part III was comparable between PD patients with and without hallucinations, but a trend towards a worse axial involvement was found in PD_Hal as compared to PD_NonHal (mean UPDRS Part III axial subscore: 5.63 ±2.37 Vs 3.08 ±2.09; P=0.07; see also **Figure 3**). Patients in the PD_Hal group showed significantly worse quality of life and perceived functionality in various ADL compared to PD_NonHal, as indicated by total scores in PDQ-39 (**see also Figure 4**), PDQ-39 mobility, PDQ39-ADL, PDQ-39 cognition, MDS-UPDRS part I, and MDS-UPDRS part II. No significant differences in LEDD and DA-LEDD emerged between the two PD groups.

All patients in the PD_Hal group reported full insight on their hallucinations; 5/11 of them endorsed pure visual hallucinations, while in the remaining cases visual hallucinations occurred in combination with other sensory modalities (acoustic, olfactory, or tactile). Most of multisensory hallucinations involved visual and either auditive (3/11) or olfactory (2/11) percepts. In the majority of patients, hallucinations occurred frequently, more than once a week (4/11) or even more than once per day (2/11), while in the remaining cases they were less frequent occurring less than once per week. In all cases, hallucinations had abrupt onset, and a duration shorter than 10 seconds. Hallucinations were stereotyped and mostly perceived as non-threatening or only slightly disturbing. No discernible association between dopaminergic intake (ON and OFF phases) and onset of hallucinations was reported. 81% of hallucinating patients (9/11) reported fully formed visual perceptions, with their content involving animated anthropomorphic or zoomorphic subjects, such as relatives, strangers, pets, insects, or wild animals. In 2/11 hallucinated patients, visual hallucinations were not formed, and were involving a sense of shadow or presence unfolding in the periphery of the visual field. Hallucinations usually emerged during night-time or under dim light conditions (7/11). In most

cases, hallucinations were suppressible by volitional control (8/11). In the majority of PD_Hal, hallucinations were normal-sized, transparent and non-colored.

Differences in Perceptual Performances on Experimentally-induced illusions

Differences in perceptual performances on Delboeuf illusion and amodal completion illusions between PD_NonHal, PD_Hal and HC are highlighted on **Figure 5** and **Figure 6**, respectively. On the size estimation task of the Delboeuf illusion, PD patients without hallucinations performed significantly better than healthy controls (physical equality: 1.09°; mean PSE in PD_NonHal 1.30°; mean PSE in HC: 1.39°; $P<0.05$). Non-hallucinating patients also performed better than hallucinators, though not significantly so. Performance of hallucinating patients was substantially similar to healthy controls (mean PSE in PD_Hal 1.36°). Perceptual performance on amodal completion illusion was significantly worse in hallucinating PD patients as compared to healthy controls (physical equality: 5.72°; mean PSE in PD_Hal: 5.36°; mean PSE in HC: 5.53°; $P <0.05$). Hallucinators also performed poorly when compared to non-hallucinating PD patients, though not significantly so (mean PSE in PD_NonHal: 5.44°). Mean reaction times (RT) did not significantly differ across participants' groups for neither illusory task (Delboeuf, mean RT: HCs 450±190 msec; PD_NonHal 370±210 msec; PD_Hal 460±350 msec; $P > 0.4$. Amodal Completion, mean RT: HCs 350±80 msec; PD_NonHal 930±830 msec; PD_Hal 610±64 msec; $P > 0.5$).

^{18}FDG PET Study

Mean Z-scores for each RoI are summarized in **Table 3**. Upon visual reads, both groups showed similar hypometabolic patterns involving the following regions: SPC, LPC, LTC, MTC, LOC and PVC, bilaterally. Different findings between the two groups emerged at the level of left MPFC. Here, the degree of hypoactivation was lower in hallucinating PD patients compared to non-hallucinating patients, as indicated by higher Z scores in the relevant RoI of the formers (0.478±1.821 Vs -1.602±1.909; $P=0.033$ by independent t-test, see also exemplary **Figure 7**). No other significant differences were noted across the two PD groups.

Table 2: Demographics and general clinical features

	PD_Hal	PD_NonHal	HC	P value[a]	P value[b]	P value[c]
Age (yrs); mean (±SD)	65.8 (±7.68)	69.3 (±6.22)	69.2 (±5.16)	0.27	0.255	0.969
Gender (F:M)	3:8	2:8	3:7	-	-	-
Education (yrs); mean (±SD)	14.63 (±3.41)	11.1 (±3.35)	15.1 (±3.07)	0.027*	0.748	0.012*
MoCA_raw; mean (±SD)	26.68 (±2.51)	27 (±1.94)	26.9 (±2.51)	0.36	0.5	0.51
MoCA_ corrected; mean (±SD)	26.72 (±2.53)	28.3 (±1.34)	27.2 (±2.15)	0.127	0.651	0.131
Disease Duration (yrs); mean (±SD)	7.64 (±5.02)	5.4 (±2.67)	N/A	0.387	-	-
Hoehn and Yahr	3 HY1, 8 HY2	3 HY1, 5 HY2, 2 HY3	N/A	-	-	-
UMPDHQ, questions 1-6 mean subscore (±SD) (min. 0 max. 14)	6.72 (±3.10)	0	-	-	-	-

LEDD; mean (±SD)	683 (±268)	633 (±296)	N/A	0.973	-	-
DA-LEDD; mean (±SD)	218.18 (±76)	127.5 (±141.64)	N/A	0.152	-	-
MDS-UPDRS I; mean (±SD)	12.27 (±5.53)	6.88 (±3.1)	N/A	0.024≠	-	-
MDS-UPDRS-II; mean (±SD)	9.63 (±3.41)	4 (±3.35)	N/A	0.001*	-	-
MDS-UPDRS III; mean (±SD)	34.72 (±11.67)	27 (±11.66)	N/A	0.14	-	-
UPDRS III_axial; mean (±SD)	5.63 (±2.37)	3.08 (±2.09)	N/A	0.08≠	-	-
MDS-UPDRS IV; mean (±SD)	2.18 (±2.27)	3.01 (±1.88)	N/A	0.80	-	-
MDS-UPDRS Total; mean (±SD)	58.81 (±15.36)	39 (±17.95)	N/A	0.01*	-	-
PDQ39_total; mean (±SD)	36.72 (±14.17)	19.77 (±8.49)	N/A	0.020*	-	-
PDQ39_mobility; mean (±SD)	7.72 (±4.94)	3 (±3.04)	N/A	0.028≠	-	-

PDQ39_ADL; mean (±SD)	6.18 (±3.57)	2.7 (±2.04)	N/A	0.025*	-	-
PDQ39_Stigma; mean (±SD)	2.63 (±2.24)	1.66 (±1.65)	N/A	0.296	-	-
PDQ39_Cognition; mean (±SD)	6.18 (±3.37)	3.22 (±1.71)	N/A	0.028*	-	-

Between group comparison (a), PD_Hal vs. PD_NonHal; (b), PD_Hal vs. HC; (c), PD_NonHal vs. HC. $p<0.05$ (*) by 2-tailed independent t-test; (≠) by Mann–Whitney/Wilcoxon test. Abbreviations: MoCA: Montreal Cognitive Assessment; UMPDHQ: The University of Miami Parkinson's Disease Hallucinations Questionnaire; LEDD: Levodopa Equivalent Dose; DA-LEDD: dopamine agonist adjusted equivalent dose; MDS-UPDRS: Movement Disorders Society United Parkinson's Disease Rating Scale; PDQ39: Parkinson's Disease Questionnaire 39; N/A: non-applicable as relevant data was not collected; -: test not performed.

Table 3: mean Z scores obtained for each designated RoI in PD patients without (PD_NonHal) and with history of visual hallucinations (PD_Hal).

RoI	**PD_NonHal** mean Z-score (±SD)	**PD_Hal** mean Z-score (±SD)	P value[a]
LPFC_R	-1.032 (±0.823)	-0.42 (±1.672)	0.245
LPFC_L	-1.48 (±1,296)	-1.222 (±1.055)	0.65
MPFC_R	-1.18 (±1.476)	0.2 (±1.782)	0.106
MPFC_L	-1.602 (±1.903)	0.478 (±1.821)	0.033*
SPC_R	-3.707 (±1.938)	-2.461 (±1.711)	0.171
SPC_L	-2.845 (±1.752)	-2.499 (±1.658)	0.677
IPC_R	-3.254 (±2.326)	-3.509 (±2.212)	0.636
IPC_L	-3.955 (±1.878)	-3.705 (±2.182)	0.701
LTC_R	-1.855 (±0.574)	-1.758 (±1.267)	0.851
MTC_L	-2.08 (±1.358)	-1.944 (±1.647)	0.858
TMC_R	0.984 (±1.251)	1.609 (±1.814)	0.438
TMC_L	1.231 (±1.592)	1.804 (±1.830)	0.506
LOC_R	-3.995 (±1.878)	-4.068 (±2.66)	0.95
LOC_L	-3.738 (±0.988)	-4.263 (±2.88)	0.651
Precuneus_R	4.155 (±1.955)	-2.832 (±2.256)	0.221
Precuneus_L	-3.254 (±2.326)	-0.884 (±2.635)	0.069

PVC_R	-1.83 (±1.031)	-2.321 (±1-101)	0.358
PVC_L	-1.765 (±1.045)	-2.53 (±1.053)	0.151

Abbreviations: (a): means Z scores comparison between PD_NonHal and PD_Hal by independent t-test; LPFC: lateral prefrontal cortex; MPFC: medial prefrontal cortex; SPC: superior parietal cortex; IPC: inferior parietal cortex; LTC: lateral temporal cortex; MTC: mesial temporal cortex; LOC: lateral occipital cortex; PVC: primary visual cortex; R: right-side; L_ left-side.

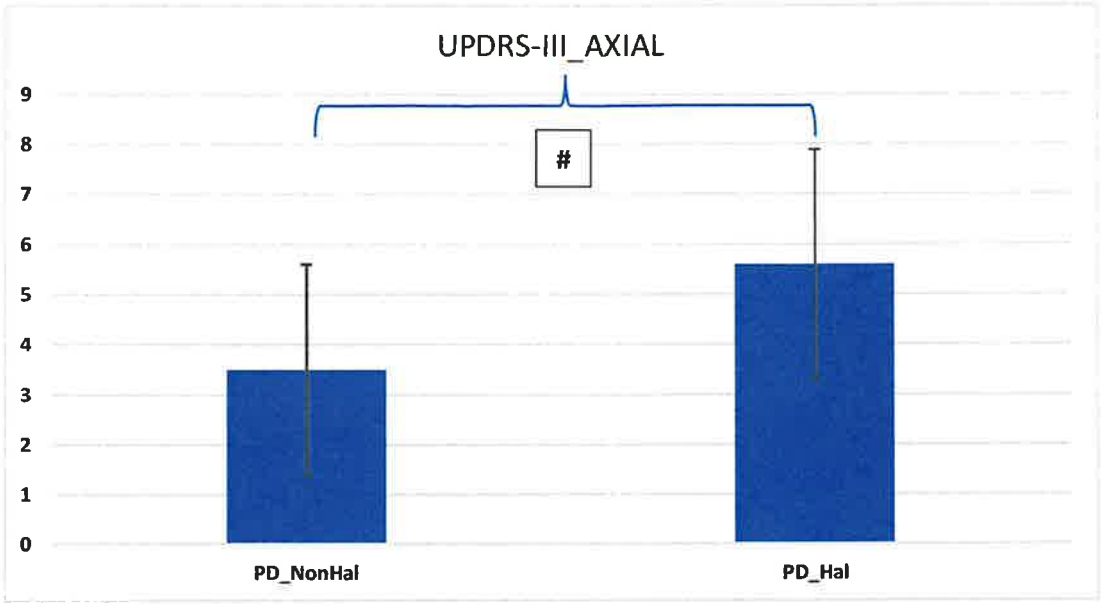


Figure 3: mean UPDRS-III axial subscores; PD_NonHal: 3.08 ±2.09 Vs PD_Hal: 5.63 ±2.37; #: P=0.07 by independent t-test.

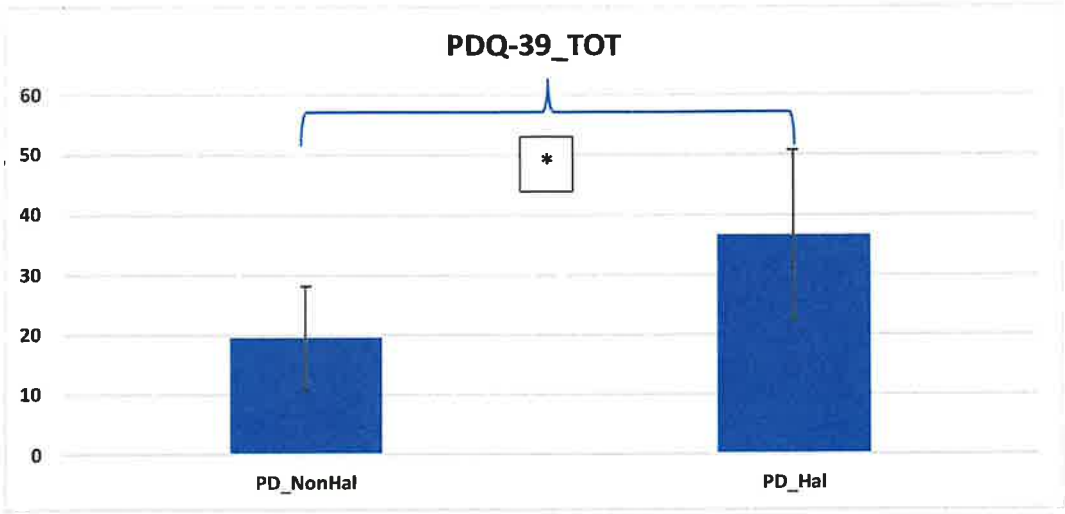


Figure 4: mean PDQ-39 total scores; PD_NonHal: 19.77±8.49 Vs PD_Hal: 36.72±14.17; *: P=0.005 by independent t-test.

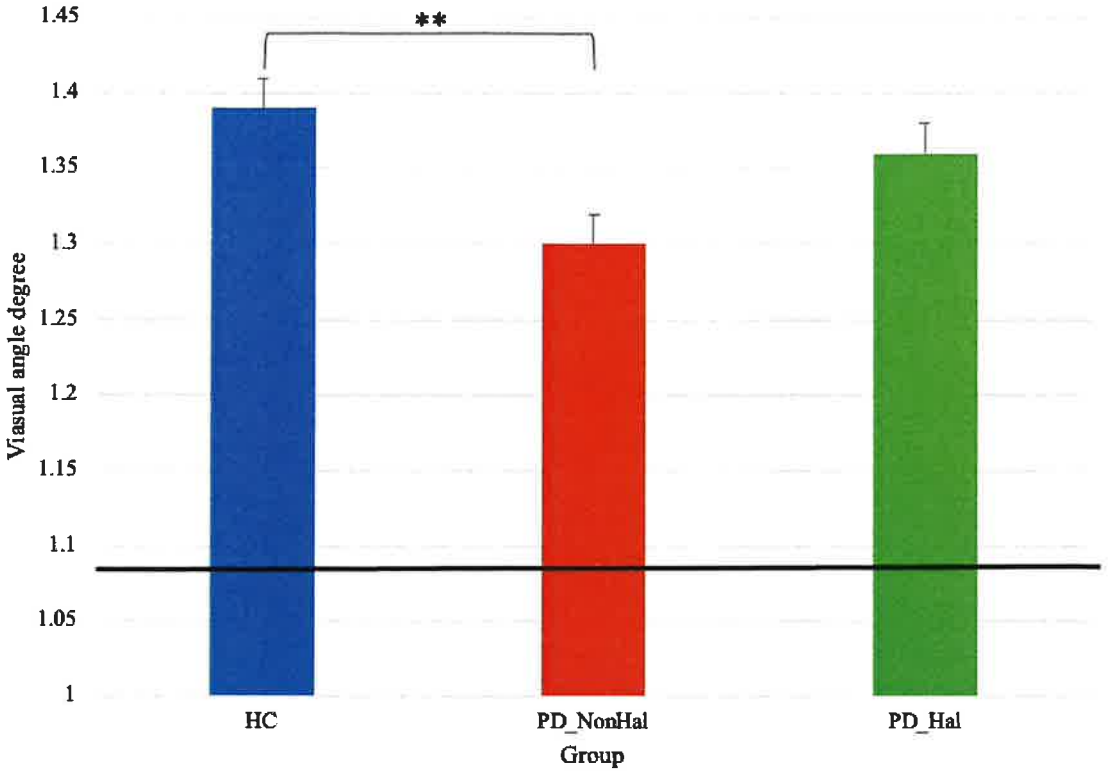


Figure 5: Perceptual performance on Delboeuf illusory figure: mean PSE (vertical bars) Vs point of physical equality (horizontal black bar) across the three groups. In this illusion, the lower the visual angle degree, the better the performance, as this is closer to the point of physical equality. **: $P < 0.05$ by one-way ANOVA.

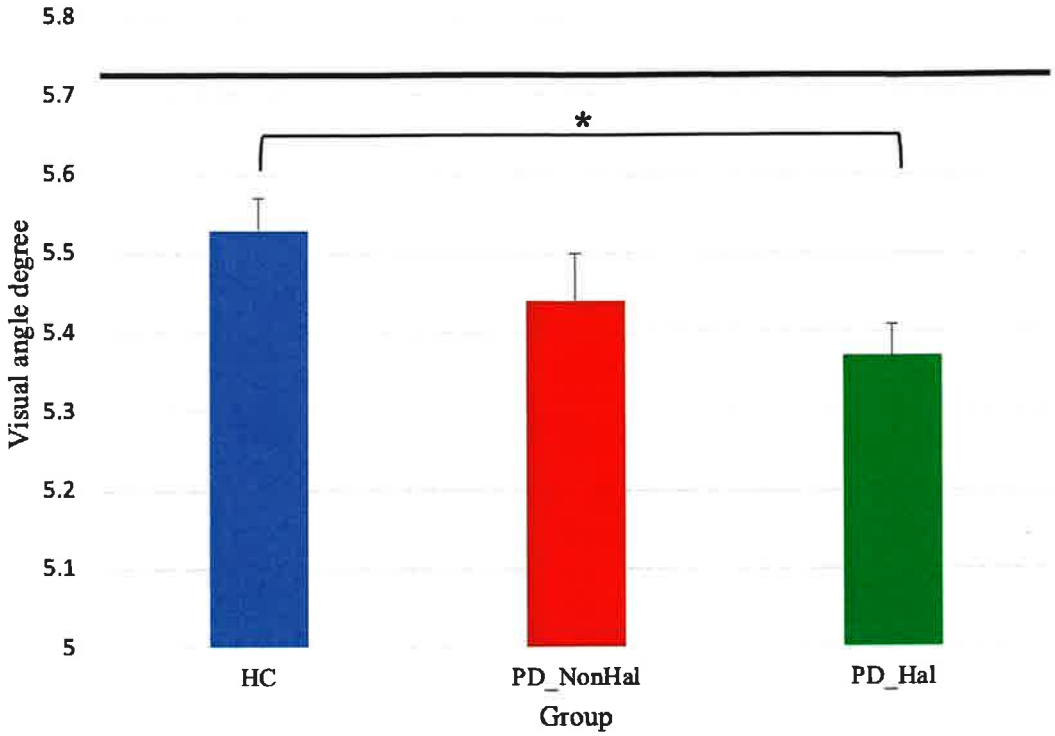
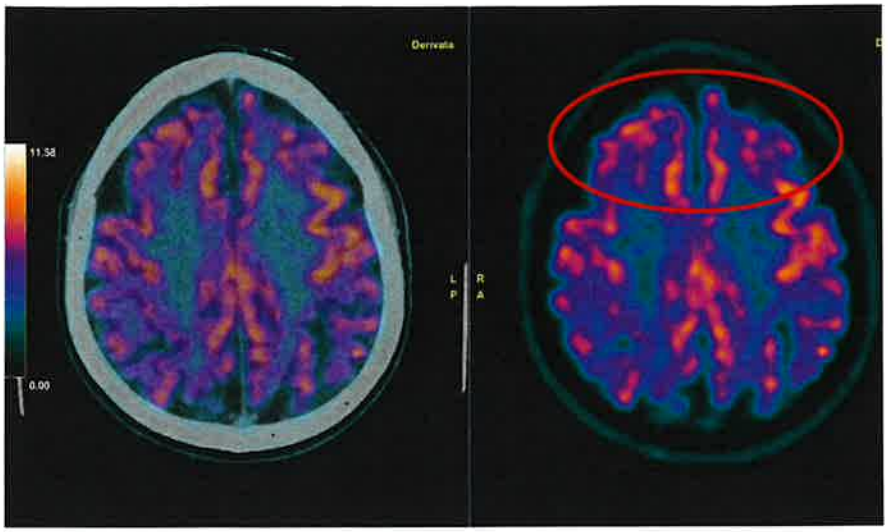
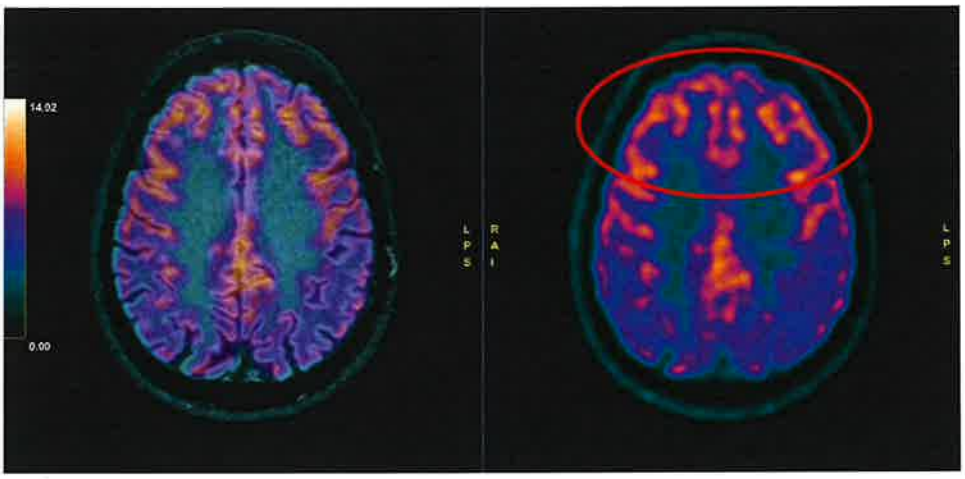


Figure 6: Perceptual performance on amodal completion illusory figure: mean PSE (vertical bars) Vs point of physical equality (horizontal black bar) across the three groups. In this illusion, the higher the visual angle degree, the better the performance, as this is closer to the point of physical equality. *: $P < 0.05$ by one-way ANOVA.



a. **PD_NonHal** (axial section; left: MRI-reconstructed)



b. **PD_Hal** (axial section; left: MRI-reconstructed)

Figure 7: Exemplary PET scans of a PD_NonHal (a. above) and a PD_Hal (b. below) participant. The PD patient with hallucinations displays a lower degree of hypoactivation in the frontal cortex as compared to the PD patients without history of hallucinations (see red circles).

IV. DISCUSSION

"The Universe is written in mathematical language, and the letters are triangles, circles and other geometrical figures, without which means it is humanly impossible to comprehend a single word".

Galileo Galilei (1564 – 1642)

The most striking finding of this study was that visuospatial deficits in PD appear to differentially affect systematic perceptual biases driving illusions, thus resulting in variable performances on computer-generated illusory figures. Compared to age-matched controls, non-hallucinating PD patients exhibited a paradoxical resistance to the Delboeuf illusion, while a greater vulnerability towards the illusory shrinkage illusion was observed in PD patients with history of hallucinations.

Indeed, a significantly smaller gap between the mean PSA and the point of physical equality was observed in non-hallucinating PD patients when attending the Delboeuf size estimation task, thus indicating a more accurate perceptual performance in these patients than in healthy controls. We interpreted this pattern as the result of differences in the effect of judgement order between the two groups. Indeed, when undergoing the size estimation task, subjects were asked to attend the inner circles prior to the inducers. In this setting, an additional attentional effort is required for the overestimation of the inner circle through its assimilation with the inducer. The assimilation of the target is facilitated when observers attend the inducer through relevant attentional tasks such as the estimation of the area enclosed by the outer circle. PD patients are known to consistently exhibit a pattern of impaired visual attention characterized by exaggerated, rigid selective attention and impaired set shifting[233]. Furthermore, visual exploration strategies in PD patients heavily rely on local rather than global visual exploration[234]. Conceivably, an impaired attentional modulation required to shift the visual exploration from the local scale of the inner circle towards the global scale of the outer circle might have resulted in an attenuation of the Delboeuf illusory effect due to assimilation. Differences in perceptual performances between PD patients and healthy controls may also be partially driven by psychobehavioral symptoms influencing task engagement and task execution, such as impulsivity, mental fatigue, or apathy. While this possibility cannot be ruled-out due to lack of formal neuropsychological assessments, analysis of mean reaction times did not reveal any significant difference across the three groups of participants, indeed suggesting

comparable levels of task engagement. Interestingly, the paradoxical resistance to the Delboeuf illusions observed in PD_NonHal was no longer recognizable in PD hallucinators, whose performance appeared substantially comparable with the one observed in healthy controls. These findings suggest a potential disruptive effect of hallucinations on the paradoxical resistance to the Delboeuf illusions observed in non-hallucinating PD patients. Whether an abnormal top-down attentional modulation in PD hallucinators might be responsible for the loss of such pattern, remains to be formally addressed with dedicated visuoperceptual tasks.

Substantially different findings emerged when analyzing performances on the amodal completion illusion. Here, a greater vulnerability towards the illusory shrinkage was found in hallucinating PD patients, as indicated by a significantly greater difference between their mean PSE and the point of true equivalence compared to controls. Although differences between PD_Hal and PD_NonHal did not meet statistical significance, a pattern of increased vulnerability clearly emerged across the three groups whereby the perceptual performance was poorer in non-hallucinating PD patients as compared to age-matched controls, and it further deteriorated in PD hallucinators. As previously outlined, the ability to perform figure to background segregation is key to accurate perceptual decisions regarding the size of overlapping figures, as this function allows the observer to attend each element of the visual scene separately. From a perceptual viewpoint, this process can be conceptualized as a modulatory force counterbalancing the mechanisms of amodal completion leading to the illusory shrinkage of the occluded element. Figure to background segregation relies on three complementary processes: boundary detection (i.e., edge modulation), region filling (i.e., center modulation), and background suppression[235-236]. The first component detects feature discontinuities between overlapping stimuli. The second component allows for the grouping of regions with similar features. Finally, background suppression inhibits the perception of similar features, thereby maximizing discontinuities between figures and backgrounds. Both region filling and background suppression are strongly influenced by top-down attentional modulation. Specifically, previous computational models and recent functional connectivity studies suggested that iso-feature detection and iso-feature suppression heavily rely on feedback loops projecting from higher cortical areas within the frontal and dorsolateral prefrontal cortices towards the primary visual cortex[237]. Interestingly, PD patients were previously found to perform poorly on modified versions of Popperlreuter-Ghent's overlapping figure tests, where the disentanglement of overlapping objects requires both intact figure to background segregation and the capability to explore each figure across various spatial

configurations in order to perform an accurate matching[127]. Furthermore, a specific impairment in the ability of PD patients to isolate discrete visual features when embedded into complex sensory patterns was recently found in PD patients as indicated by poorer performances on Navon test[100]. We hypothesized that the increased vulnerability to amodal completion illusions in PD patients might be related to the pathological involvement of cortical areas boosting perceptual attention during figure to background segregation. As these high order areas are also involved in the modulation of perceptual grouping, hallucinating PD patients may become increasingly vulnerable to this particular illusory bias. A key role played by abnormalities affecting top-down attentional modulation in the perceptual performance of PD patients with complex hallucinations is further suggested by our ^{18}FDG PET findings. Here, a pattern of relative hypermetabolism in prefrontal cortical regions concerned with attentional modulation of upcoming sensory information was observed, a finding overall in agreement with previous literature[178]. From a phenomenological viewpoint, 82% of hallucinating PD patients reported fully formed percepts with animate characters carrying emotional content (e.g. pets or wild animals). In PD, complex hallucinations typically have a meaningful content, involving - for example - deceased relatives or pets. The personal significance of hallucinatory contents in these phenomena further suggests top-down influences from high-level cognitive areas involved in emotional memory and affective functioning[238].

Regarding clinical outcomes, PD patients with and without visual hallucinations were comparable in terms of disease staging, disease duration, general cognition, and overall motor impairment. These findings support the primary perceptual nature of the differences in performance on illusory figures observed between the two groups. Given the nature of our perceptual tasks, their inherently simple instructions, and the familiarization trials provided to all participants, differences in education (HCs > PD_Hal > PD_NonHal) were not regarded as a likely source for distortion. When compared to non-hallucinators, hallucinating PD patients exhibited a trend towards a worse axial involvement. This finding is consistent with previous literature suggesting a shared pathology affecting both perceptual functions and complex visually guided behaviors such as locomotion and balance in this clinical population[239]. Systematic perceptual biases can lead to abnormalities affecting space navigation, postural control and gait maintenance. Specifically, an impaired integration of perceptual information may prevents PD patients from adapting their ongoing motor behavior to solve sudden visuospatial problems[240]. Notably, in PD patients, episodes of FoG are usually observed during changes in trajectory or while negotiating obstacles, as well as while walking through narrow

and obstructed spaces. Early kinematic abnormalities preceding the onset of FoG can be detected in freezers before passing through narrow doorways, thus suggesting a disrupted online perceptual processing[125]. Several clinical-correlational and brain imaging studies report an association between FoG and visuospatial impairments in patients with PD, further suggesting a common visual-stream neuropathology[240]. In addition, while LEDD and DA-LEDD were not statistically different between the two groups of PD participants, the higher exposure to dopamine agonists observed in PD_Hal raises the intriguing question as to whether hallucinations reported by these patients were driven, at least partially, by their dopaminergic treatment. The cross-sectional nature of the present study does not allow to speculate on the nature of the association between dopaminergic treatment and visual hallucinations. While a iatrogenic component appears certainly plausible, the mere exposure to dopaminergic treatment *per se* is not regarded as a sufficient factor to trigger visual hallucinations, which typically require a neuropathologically permissive substrate (as reviewed in previous sections). Finally, PD patients with history of visual hallucinations perceived a worse functional impairment in multiple domains of daily living as compared to patients without hallucinations, despite an otherwise comparable degree of motor impairment. A worse axial involvement may have contributed to this finding, as axial symptoms are well-known determinants of poor quality of life and reduced functional independence. In addition, these findings suggest the disabling nature of visual hallucinations, with a related disability potentially extending to multiple functional domains. Cumulative disability related to visual hallucinations was previously reported to significantly impact the quality of life of both patients with PD and caregivers[214,241]. In this clinical population, hallucinations are regarded as the strongest predictor of earlier nursing home placement, independently from disease duration and disease severity[213].

V. Conclusions and Future Directions

The present study addressed the following experimental questions: 1. Is the perceptual performance on illusory figures different between healthy controls, PD non-hallucinating patients, and PD hallucinators? 2. Which profile of vulnerability to illusions is observed in PD patients with and without history of visual hallucinations? 3. What are the potential substrates underlying potential differences in perceptual performance between participants?

Overall, our findings support the hypothesis that perceptual performance on illusory figures is different across PD patients with and without hallucinations and healthy controls. Specifically, a variable directionality of effects on perceptual performance is observed, depending on the main perceptual deficit and its relation to the perceptual bias driving the relevant illusion. Illusions relying on adequate attentional modulation and global visual perception are paradoxically attenuated in PD patients without hallucinations, and such pattern is no longer recognizable in hallucinating patients. Conversely, illusory effects potentially counteracted by the ability to effectively operate figure to background segregation and recognition of overlapping figures are enhanced in PD patients with hallucinations and, to a lower extent also in PD patients without hallucinations. Furthermore, findings from our ^{18}FDG PET study suggest that perceptual differences between the two PD groups could be linked to abnormalities affecting top-down perceptual functions. Indeed, the analysis of differences in regional cerebral glucose metabolic rate revealed a lower degree of hypometabolism in frontal cortical regions concerned with attentional modulation of upcoming sensory information occurring in hallucinators compared to non-hallucinating PD patients. According to our experience, computer-generated illusory figures can be administered to non-demented patients with mild to moderate PD, with nominal time requirements and ease of recruitment. Computer-generated illusory tasks are non-invasive, reproducible, and relatively inexpensive. Perceptual performance on these tasks could be a suitable tool to systematically characterize the neural underpinnings of hallucinations in these patients and complement available neuropsychological and clinical scales for a prompt detection and characterization of these phenomena.

We acknowledge some limitations in our study, mostly inherent to its exploratory nature. First, the cross-sectional nature of this study prevents from drawing conclusions about the nature of the potential association between clinical, behavioral, and brain imaging variables. Correlational analyses on a larger sample size are warranted to address this specific aspect.

In order to limit the length of the study procedures and minimize participants' burden, a formal neuropsychological evaluation, including domain-specific assessments of cognitive functions such as attention, cognitive flexibility and visuospatial functions, was not conducted. This may have limited the interpretability of our findings. Similarly, the potential influence of non-motor symptoms of PD cannot be fully ruled-out due to the lack of specific clinical assessments. Careful review of participants' medical records coupled with a restrictive MoCA entry criterion of 24 or higher (well above the cut-off identified in the Italian population) should have reduced the risk for major distortions due to severe cognitive or psychiatric comorbid factors. However, the potential contribution of psychobehavioral abnormalities frequently linked to PD (e.g. apathy, impulsivity, fatigue etc.) will need to be specifically addressed in future studies. Another potential limitation concerns the lack of a formal neuro-ophthalmological assessment, which does not allow to exclude the potential contribution of peripheral and retinal abnormalities. For the present study, we opted for a more feasible and yet less accurate approach based on review of medical history and assessment of visual acuity. Future studies should take this limitation into account, for example by incorporating ophthalmoscopic examination and neurophysiological assessments of retinal function into the study procedures. In addition, our illusory tasks implied the motor engagement of the subjects, who were required to operate on a keyboard in order to provide their perceptual feedback. Although practice trials were allowed for familiarization and assessments in fluctuating patients were performed during the ON therapeutic state, it is still possible that the performance of PD patients might have been influenced by some degree of hypokinesia.

In the present study, we focused on the two illusions of Delboeuf and amodal completion, which were selected from a broader battery of illusory tasks administered as part of our protocol. We chose these two particular illusions because we hypothesized that their underlying neural mechanisms were more likely to be affected by the neurodegenerative process of PD. In doing so, we may have introduced a selection bias. A broader analysis of behavioral data from the whole battery of illusory tasks is warranted to expand the current findings of the study. Finally, we did not control for potential errors due to multiplicity, which may restrict the generalizability of our findings, particularly from the brain imaging component of the study. Given the exploratory nature of this project, we opted to maximize chances for signal detection. Further, properly designed and adequately sized studies are warranted to confirm our preliminary findings.

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When you are no longer able to clearly see real things, you will soon start seeing things that are not real. This could be a fair lay-language summary of some of the main findings from this study. This statement may also serve as a reminder on not losing sight on things that are both true and important. On this topic, I would like to thank my advisor, Prof. Paolo Manganotti, and all the team of the Movement Disorders Unit at the Neurology Clinic of the University of Trieste, particularly Dr. Mauro Catalan for supporting this study. I would also like to extend my gratitude to the bright and motivated neurology residents and medical students who collaborated to this study, including Dr. Marco Liccari, Dr. Tiziana Lombardo, Dr. Valentina Cenacchi, and Dr. Sophie Rangan.

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VII. REFERENCES

1. Tysnes, O.-B. & Storstein, A. Epidemiology of Parkinson's disease. J. Neural Transm. (Vienna) 124, 901–905 (2017).

2. de Lau, L. M. L. & Breteler, M. M. B. Epidemiology of Parkinson's disease. Lancet Neurol. 5, 525–535 (2006).

3. Lee, A. & Gilbert, R. M. Epidemiology of Parkinson disease. Neurol. Clin. 34, 955–965 (2016).

4. Bloem, B. R., Okun, M. S. & Klein, C. Parkinson's disease. Lancet 397, 2284– 2303 (2021).

5. Dorsey, E. R., Sherer, T., Okun, M. S. & Bloem, B. R. The emerging evidence of the Parkinson pandemic. J. Parkinsons. Dis. 8, S3–S8 (2018).

6. Kalia, L. V. & Lang, A. E. Parkinson's disease. Lancet 386, 896–912 (2015).

7. Poewe, W. et al. Parkinson disease. Nat. Rev. Dis. Primers 3, 17013 (2017).

8. Baldereschi, M. et al. Parkinson's disease and parkinsonism in a longitudinal study: Two-fold higher incidence in men. Neurology 55, 1358–1363 (2000).

9. Tsalenchuk et al. Linking environmental risk factors with epigenetic mechanisms in Parkinson's disease. Npj Parkinson's Disease 9, 123(2023)

10. Brown, T. P., Rumsby, P. C., Capleton, A. C., Rushton, L. & Levy, L. S. Pesticides and Parkinson's disease—is there a link? Environ. Health Perspect. 114, 156–164 (2005).

11. Balestrino, R. & Schapira, A. H. V. Parkinson disease. Eur. J. Neurol. 27, 27–42 (2020).

12. Lees, A. J., Hardy, J. & Revesz, T. Parkinson's disease. Lancet 373, 2055–2066 (2009).

13 von Coelln J. et al. Parkin-associated Parkinson's Disease. Cell. Tissue Res. 318, 175–184 (2004)

14. Quin Rui et al. The Role of LRRK2 in Neurodegeneration of Parkinson Disease. Curr Neuropharmacol. 16(9): 1348-1357 (2018).

15. Smith L, Schapira Anthony H.V. GBA Variants and Parkinson's Disease: Mechanisms and treatments. Cells 11(8): 1261 (2022).

16. Billingsey K.J. et al. Genetic Risk Factors in Parkinson's Disease. Cell Tissue Res. 373(1): 9-20 (2018).

17. Jankovic J. Eng King Tan. Parkinson's Disease: etiopathogenesis and treatment. J Neurol Neurosurg Psychiatry; 91:795–808 (2020).

18. McGregor M. Nelson, A.B. Circuit Mechanisms of Parkinson's Disease. Neuron; 101 (6): 1042-1056 (2019).

19. Cui G, Jun SB, Jin X, Pham MD, Vogel SS, Lovinger DM, Costa RM. Concurrent activation of striatal direct and indirect pathways during action initiation. Nature. 2013 14;494(7436):238-42.

20. Mathai A, Smith Y. The corticostriatal and corticosubthalamic pathways: two entries, one target. So what? Front Syst Neurosci. 2011; 5:64.

21. Norris, E. H., Giasson, B. I. & Lee, V. M.-Y. Alpha-synuclein: normal function and role in neurodegenerative diseases. Curr. Top. Dev. Biol. 60, 17–54 (2004).

22. Spillantini, M. G. et al. Alpha-synuclein in Lewy bodies. Nature 388, 839–840 (1997).

23. Choi, B.-K. et al. Large α-synuclein oligomers inhibit neuronal SNARE-mediated vesicle docking. Proc. Natl. Acad. Sci. U. S. A. 110, 4087–4092 (2013).

24. Rocha, E. M., De Miranda, B. & Sanders, L. H. Alpha-synuclein: Pathology, mitochondrial dysfunction and neuroinflammation in Parkinson's disease. Neurobiol. Dis. 109, 249–257 (2018).

25. Melki, R. Alpha-synuclein and the prion hypothesis in Parkinson's disease. Rev. Neurol. (Paris) 174, 644–652 (2018).

26. Brundin, P., Melki, R. & Kopito, R. Prion-like transmission of protein aggregates in neurodegenerative diseases. Nat. Rev. Mol. Cell Biol. 11, 301–307 (2010).

27. Braak, H. et al. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol. Aging 24, 197–211 (2003).

28. Goedert, M., Spillantini, M. G., Del Tredici, K. & Braak, H. 100 years of Lewy pathology. Nat. Rev. Neurol. 9, 13–24 (2013). 63

29. Bongianni M. et al. Olfactory swab sampling optimization for α-synuclein aggregate detection in patients with Parkinson's disease. Transl Neurodegener. 2022 Jul 28;11(1):37.

30. Miguelez C. et al. Non-Dopaminergic Systems in Parkinson's Disease. Front. Pharmacol. 11: 593822 (2020).

31. Armstrong, M. J. & Okun, M. S. Diagnosis and treatment of Parkinson disease: A review. JAMA 323, 548–560 (2020).

32. Postuma, R. B. et al. MDS clinical diagnostic criteria for Parkinson's disease. Mov. Disord. 30, 1591–1601 (2015).

33. Postuma, R. B. Prodromal Parkinson disease: do we miss the signs? Nat. Rev. Neurol. 15, 437–438 (2019).

34. Bologna, M., Paparella, G., Fasano, A., Hallett, M. & Berardelli, A. Evolving concepts on bradykinesia. Brain 143, 727–750 (2020).

35. Bologna, M. & Paparella, G. Pathophysiology of rigidity in Parkinson's disease: Another step forward. Clinical neurophysiology: official journal of the International Federation of Clinical Neurophysiology vol. 131 1971–1972 (2020).

36. Dirkx, M. F. & Bologna, M. The pathophysiology of Parkinson's disease tremor. J. Neurol. Sci. 435, 120196 (2022).

37. Hallett, M. Parkinson's disease tremor: pathophysiology. Parkinsonism Relat. Disord. 18 Suppl 1, S85-6 (2012).

38. Dirkx, M. F. et al. The cerebral network of Parkinson's tremor: An effective connectivity fMRI study. J. Neurosci. 36, 5362–5372 (2016).

39. Suttrup I, Warnecke T. Dysphagia in Parkinson's Disease. Dysphagia. 31(1):24-32 (2016).

40. Dashtipour K, Tafreshi A, Lee J, Crawley B. Speech disorders in Parkinson's disease: pathophysiology, medical management and surgical approaches. Neurodegener Dis Manag.;8(5):337-348 (2018).

41. Pelicioni PHS, Menant JC, Latt MD, Lord SR. Falls in Parkinson's Disease Subtypes: Risk Factors, Locations and Circumstances. Int J Environ Res Public Health. 23;16(12):2216 (2019).

42. Mirelman A, Bonato P, Camicioli R, Ellis TD, Giladi N, Hamilton JL, Hass CJ, Hausdorff JM, Pelosin E, Almeida QJ. Gait impairments in Parkinson's disease. Lancet Neurol. Jul;18(7):697-708 (2019).

43. Cucca A, Biagioni MC, Fleisher JE, Agarwal S, Son A, Kumar P, Brys M, Di Rocco A. Freezing of gait in Parkinson's disease: from pathophysiology to emerging therapies. Neurodegener Dis Manag.;6(5):431-46 (2016).

44. Jankovic, J. et al. Variable expression of Parkinson's disease: a base-line analysis of the DATATOP cohort. The Parkinson Study Group. Neurology 40, 1529–1534 (1990).

45. Jankovic, J. Parkinson's disease: clinical features and diagnosis. J. Neurol. Neurosurg. Psychiatry 79, 368–376 (2008).

46. Ponsen, M. M. et al. Idiopathic hyposmia as a preclinical sign of Parkinson's disease. Ann. Neurol. 56, 173–181 (2004).

47. Schapira, A. H. V., Chaudhuri, K. R. & Jenner, P. Non-motor features of Parkinson disease. Nat. Rev. Neurosci. 18, 509 (2017).

48. Poewe, W. Non-motor symptoms in Parkinson's disease. Eur. J. Neurol. 15 Suppl 1, 14–20 (2008).

49. Pfeiffer, R. F. Non-motor symptoms in Parkinson's disease. Parkinsonism Relat. Disord. 22 Suppl 1, S119-22 (2016).

50. Cong, S. et al. Prevalence and clinical aspects of depression in Parkinson's disease: A systematic review and meta-analysis of 129 studies. Neurosci. Biobehav. Rev. 141, 104749 (2022).

51. Remy, P., Doder, M., Lees, A., Turjanski, N. & Brooks, D. Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system. Brain 128, 1314–1322 (2005). 67

52. Postuma, R. B. et al. Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: a multicentre study. Brain 142, 744–759 (2019).

53. Aarsland, D., Andersen, K., Larsen, J. P., Lolk, A. & Kragh-Sørensen, P. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. Arch. Neurol. 60, 387–392 (2003).

54. Hanagasi, H. A., Tufekcioglu, Z. & Emre, M. Dementia in Parkinson's disease. J. Neurol. Sci. 374, 26–31 (2017).

55. Tolosa, E., Wenning, G. & Poewe, W. The diagnosis of Parkinson's disease. Lancet Neurol. 5, 75–86 (2006).

56. Archibald, N. K., Clarke, M. P., Mosimann, U. P. & Burn, D. J. Visual symptoms in Parkinson's disease and Parkinson's disease dementia. Mov. Disord. 26, 2387– 2395 (2011).

57. Chen, Z., Li, G. & Liu, J. Autonomic dysfunction in Parkinson's disease: Implications for pathophysiology, diagnosis, and treatment. Neurobiol. Dis. 134, 104700 (2020).

58. Kaufmann, H. & Goldstein, D. S. Autonomic dysfunction in Parkinson disease. Handb. Clin. Neurol. 117, 259–278 (2013).

59. Cucca A. et al. Amino acid supplementation in levodopa treated Parkinson's Disease Patients. Clin. Nutr. 34(6): 1189-1194 (2015).

60. Hogg et al. Urinary Tract Infections in Parkinson's Disease. J. Parkinsons Dis. 12(3): 743-757 (2022).

61. Zoccolella, S. et al. Sleep disorders and the natural history of Parkinson's disease: the contribution of epidemiological studies. Sleep Med. Rev. 15, 41–50 (2011).

62. Xu, Z., Anderson, K. N. & Pavese, N. Longitudinal studies of sleep disturbances in Parkinson's disease. Curr. Neurol. Neurosci. Rep. 22, 635–655 (2022).

63. Fahn, S. The history of dopamine and levodopa in the treatment of Parkinson's disease. Mov. Disord. 23 Suppl 3, S497-508 (2008).

64. Salat, D. & Tolosa, E. Levodopa in the treatment of Parkinson's disease: current status and new developments. J. Parkinsons. Dis. 3, 255–269 (2013).

65. Constantinescu, R., Richard, I. & Kurlan, R. Levodopa responsiveness in disorders with parkinsonism: a review of the literature. Mov. Disord. 22, 2141–8; quiz 2295 (2007).

66. Freitas et al. Motor Complications of Dopaminergic Medications in Parkinson's Disease. Semin Neurol. 2017 Apr; 37(2): 147–157.

67. Blandini, F. & Armentero, M.-T. Dopamine receptor agonists for Parkinson's disease. Expert Opin. Investig. Drugs 23, 387–410 (2014).

68. Stocchi, F., Torti, M. & Fossati, C. Advances in dopamine receptor agonists for the treatment of Parkinson's disease. Expert Opin. Pharmacother. 17, 1889–1902 (2016).

69. Rascol, O. et al. Rasagiline as an adjunct to levodopa in patients with Parkinson's disease and motor fluctuations (LARGO, Lasting effect in Adjunct therapy with Rasagiline Given Once daily, study): a randomised, double-blind, parallel-group trial. Lancet 365, 947–954 (2005).

70. Kaakkola, S. Clinical pharmacology, therapeutic use and potential of COMT inhibitors in Parkinson's disease. Drugs 59, 1233–1250 (2000).

71. Deuschl, G. et al. A randomized trial of deep-brain stimulation for Parkinson's disease. N. Engl. J. Med. 355, 896–908 (2006).

72. Weaver, F. M. Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease. A randomized controlled trial. JAMA 301, 63 (2009).

73. Kulisevsky, J., Oliveira, L. & Fox, S. H. Update in therapeutic strategies for Parkinson's disease. Curr. Opin. Neurol. 31, 439–447 (2018). 71

74. Sharma Shaidbat et al. Causes, factors, and complications associated with hospital admissions among patients with Parkinson's disease Front. Neurol. 14: in press. (2023).

75. Davidsdottir, S., Cronin-Golomb, A. & Lee, A. Visual and spatial symptoms in Parkinson's disease. Vision Res. 45, 1285–1296 (2005).

76. Weil, R. S. et al. Visual dysfunction in Parkinson's disease. Brain 139, 2827–2843 (2016).

77. Matsumoto H. et al. Small saccades restrict visual scanning area in Parkinson's disease. Mov. Dis. 26 1619-1626).

78. Shao X. et al. Outcome of visuospatial dysfunction assessment in patients with Parkinson's disease using mobile application software. Front. Ag. Neurosci. 15 (2023).

79. Campello L. et al. Alterations in Energy Metabolism, Neuroprotection and Visual Signal Transduction in the Retina of Parkinsonian, MPTP-Treated Monkeys. PLoS One 8(9) e74439 (2013).

80. Schmoll, C., Lascaratos, G., Dhillon, B., Skene, D. & Riha, R. L. The role of retinal regulation of sleep in health and disease. Sleep Med. Rev. 15, 107–113 (2011).

81. Lee, J.-Y. et al. Retinal nerve fiber layer thickness and visual hallucinations in Parkinson's Disease. Mov. Disord. 29, 61–67 (2014). 129.

82. Khadjevan F. et al. Reduction of negative afterimage duration in Parkinson's disease patients: a possible role for dopaminergic deficiency in the retinal Interplexiform cell layer. Vision Res. 8; 50(3): 279-83 (2010).

83. Tagliati M., Bodis-Wollner I., M.D Yahr. The pattern electroretinogram in Parkinson's disease reveals lack of retinal spatial tuning. Electroencephalogr Clin Neurophysiol 100(1):1-11 (1996).

84. Arakawa K. et al. Parvocellular and magnocellular visual processing in spinocerebellar degeneration and Parkinson's disease: an event-related potential study. Clin Neurophysiol110(6):1048-57 (1999).

85. Rowe MH. Trichromatic color vision in primates. News Physiol Sci. Jun;17:93-8 (2002).

86. Werner et al. Effects of ageing on postreceptoral short-wavelength gain control: Transient tritanopia increases with age. Vis. Res. 50(17): 1641-1648.

87. Bertand JA et al. Color discrimination deficits in Parkinson's disease are related to cognitive impairment and white-matter alterations. Mov. Dis. 27(14): 1781-1788 (2012).

88. Müller T. et al. Motor impairment influences Farnsworth-Munsell 100 Hue test error scores in Parkinson's disease patients. J Neurol Sci. 213(1-2):61-5 (2003).

89. Matar E. et al. Impaired Color Discrimination-A Specific Marker of Hallucinations in Lewy Body Disorders. J Geriatr Psychiatry Neurol. 32(5):257-264 (2019).

90. Sjaikh A.G. et al. Physiology and pathology of saccades and gaze holding. NeuroRehab. 32(3) 493-505 (2013).

91. Krishnan R. et al. Modeling the role of basal ganglia in saccade generation: is the indirect pathway the explorer? Neural Netw. 24(8):801-13. (2011).

92. Matsumoto et al Ocular paradoxical movement and severity of Parkinson's disease. Brain 136(10), e-250 (2013).

93. Wong WH et al. Eye movement parameters and cognitive functions in Parkinson's Disease patients without dementia. Parkinsonism Relat. Disord. 52: 43-48 (2018).

94. Boller et al. Visuospatial Impairment in Parkinson's Disease. Role of Perceptual and Motor Factors. Arch. Neurol. 41(5): 485-490 (1984).

95. Norton D.J. et al. Visuospatial Attention to Single and Multiple Objects is Independently Impaired in Parkinson's Disease. PLoS One 11(3) e0150013 (2016).

96. Bek, J., Humphries, S., Poliakoff, E. *et al.* Mental rotation of hands and objects in ageing and Parkinson's disease: differentiating motor imagery and visuospatial ability. *Exp Brain Res* 240, 1991–2004 (2022).

97. Montse A, Pere V, Carme J, Francesc V, Eduardo T. Visuospatial deficits in Parkinson's disease assessed by judgment of line orientation test: error analyses and practice effects. J Clin Exp Neuropsychol. Oct;23(5):592-8. (2001)

98. Ba F, Sang TT, He W, Fatehi J, Mostofi E, Zheng B. Stereopsis and Eye Movement Abnormalities in Parkinson's Disease and Their Clinical Implications. Front Aging Neurosci. Feb 8;14 (2022).

99. Armstrong RA. Visual symptoms in Parkinson's disease. Parkinsons Dis. 2011:908306. (2011)

100. Cucca, A. et al. Art therapy for Parkinson's disease. Parkinsonism Relat. Disord. 84, 148–154 (2021).

101. Gerlach C, Poirel N. Navon's classical paradigm concerning local and global processing relates systematically to visual object classification performance. Sci Rep. 10;8(1):324 (2018).

102. Álvarez-San Millán A, Iglesias J, Gutkin A, Olivares EI. Progressive attenuation of visual global precedence across healthy aging and Alzheimer's disease. Front Aging Neurosci. Sep 20; 14:893818 (2022).

103. Lee AC, Harris JP, Calvert JE. Impairments of mental rotation in Parkinson's disease. Neuropsychologia. Jan;36(1):109-14 (1998).

104. Katsarou Z, Bostantjopoulou S, Alevriadou A, Mentenopoulos G, Avraam X, Kiosseoglou G. A longitudinal study of visuospatial discrimination in parkinsonian patients. Percept Mot Skills. 86(1):171-80 (1998).

105. Lee AC, Harris JP, Atkinson EA, Fowler MS. Evidence from a line bisection task for visuospatial neglect in left hemiparkinson's disease. Vision Res. Sep;41(20):2677-86 (2001).

106. Putcha D, Ross RS, Rosen ML, Norton DJ, Cronin-Golomb A, Somers DC, Stern CE. Functional correlates of optic flow motion processing in Parkinson's disease. Front Integr Neurosci. Jul 8;8:57 (20014)

107. Niehorster DC. Optic Flow: A History. Iperception. ;12(6):20416695211055766 (20021).

108. E. Baird et al. The effect of optic flow cues on honeybee flight control in wind.Proc. R. Soc. B288: 20203051 (20021).

109. Davidsdottir S, Wagenaar R, Young D, Cronin-Golomb A. Impact of optic flow perception and egocentric coordinates on veering in Parkinson's disease. Brain. 2008 Nov;131(Pt 11):2882-93

110. Ren X, Salazar R, Neargarder S, Roy S, Ellis TD, Saltzman E, Cronin-Golomb A. Veering in hemi-Parkinson's disease: Primacy of visual over motor contributions. Vision Res. Oct;115(Pt A):119-27 (2015).

111.Konnova EA, Swanberg M. Animal Models of Parkinson's Disease. In: Stoker TB, Greenland JC, editors. Parkinson's Disease: Pathogenesis and Clinical Aspects. Brisbane (AU): Codon Publications; Chapter 5 (2018).

112. Stein JF. The representation of egocentric space in the posterior parietal cortex. Behav Brain Sci. 15 Spec No 4:691-700 (1992).

113. Lin CC, Wagenaar RC, Young D, Saltzman EL, Ren X, Neargarder S, Cronin-Golomb A. Effects of Parkinson's disease on optic flow perception for heading direction during navigation. Exp Brain Res. Apr;232(4):1343-55. (2014).

114. recognition of overlapping figures neural substrate parietal cortex

115. Nieto-Escamez F, Obrero-Gaitán E, Cortés-Pérez I. Visual Dysfunction in Parkinson's Disease. Brain Sci. Aug 7;13(8):1173 (2023).

116. Booth S, Park KW, Lee CS, Ko JH. Predicting cognitive decline in Parkinson's disease using FDG-PET-based supervised learning. J Clin Invest. 17;132(20):e157074 (2022).

117. Collerton D. Disorders of Visual Perception in Parkinson's Disease and Other Lewy Body Disorders. Book Series: Advances in Biological Psychiatry, vol. 27. Book chapter. ISBN electronic: 978-3-8055-9801-9.

118. Loayza FR, Villagra F, et al. Cortical hypoperfusion in Parkinson's disease assessed using arterial spin labeled perfusion MRI. Neuroimage 2012; 59: 2743–50.

119. Britton Z, Arshad Q. Vestibular and Multi-Sensory Influences Upon Self-Motion Perception and the Consequences for Human Behavior. Front Neurol. Mar 7;10:63 (2019).

120. Pavlik AE, Inglis JT, Lauk M, Oddsson L, Collins JJ. The effects of stochastic galvanic vestibular stimulation on human postural sway. Exp Brain Res. 24(3):273-80 (1999).

121. Ferrazzoli D, Ortelli P, Volpe D, Cucca A, Versace V, Nardone R, Saltuari L, Sebastianelli L. The Ties That Bind: Aberrant Plasticity and Networks Dysfunction in Movement Disorders-Implications for Rehabilitation. Brain Connect.;11(4):278-296 (2021).

122. Schlick C, Ernst A, Bötzel K, Plate A, Pelykh O, Ilmberger J. Visual cues combined with treadmill training to improve gait performance in Parkinson's disease: a pilot randomized controlled trial. Clin Rehabil. 30(5):463-71 (2016).

123. Nutt JG, Bloem BR, Giladi N, Hallett M, Horak FB, Nieuwboer A. Freezing of gait: moving forward on a mysterious clinical phenomenon. Lancet Neurol. 10(8):734-44 (2011).

124. Giladi N. Medical treatment of freezing of gait. Mov Disord.;23 Suppl 2:S482-8. doi: 10.1002/mds.21914. Erratum in: Mov Disord. 15;23(11):1639-40 (2008).

125. Peterson DS, King LA, Cohen RG, Horak FB. Cognitive Contributions to Freezing of Gait in Parkinson Disease: Implications for Physical Rehabilitation. Phys Ther.;96(5):659-70 (2016).

126. Lefebvre, S. et al. Hallucinations and conscious access to visual inputs in Parkinson's disease. Sci. Rep. 6, (2016).

127. Jazayeri M, Movshon JA. A new perceptual illusion reveals mechanisms of sensory decoding. Nature. 19;446(7138):912-5 (2007).

128. Barnes J, David AS. Visual hallucinations in Parkinson's disease: a review and phenomenological survey. J Neurol Neurosurg Psychiatry;70(6):727-33 (2001).

129. Kuzuhara S. Drug-induced psychotic symptoms in Parkinson's disease. Problems, management and dilemma. J Neurol.;248 Suppl 3:III28-31 (2001).

126. Koerts, J. et al. Attentional and perceptual impairments in Parkinson's disease with visual hallucinations. Parkinsonism Relat. Disord. 16, 270–274 (2010).

127.Mosimann, U. P. et al. Visual perception in Parkinson disease dementia and dementia with Lewy bodies. Neurology 63, 2091–2096 (2004).

128. Ramirez-Ruiz, B., Junque, C., Marti, M.-J., Valldeoriola, F. & Tolosa, E. Cognitive changes in Parkinson's disease patients with visual hallucinations. Dement. Geriatr. Cogn. Disord. 23, 281–288 (2007).

129. Montagnese, M., Vignando, M., Ffytche, D. & Mehta, M. A. Cognitive and visual processing performance in Parkinson's disease patients with vs without visual hallucinations: A meta-analysis. Cortex 146, 161–172 (2022).

130. Galvin, J. E., Pollack, J. & Morris, J. C. Clinical phenotype of Parkinson disease dementia. Neurology 67, 1605–1611 (2006).

131. Makowski D, Lau ZJ, Pham T, Paul Boyce W, Annabel Chen SH. A Parametric Framework to Generate Visual Illusions Using Python. Perception. 50(11):950-965 (2021).

132. Coren, S., Girgus, J. S., Erlichman, H. & Hakstian, A. R. An empirical taxonomy of visual illusions. Percept. Psychophys. 20, 129–137 423 (1976).

133. Coren, S., & Girgus, J. S. Seeing Is Deceiving: The Psychology Of Visual Illusions. (Lawrence Erlbaum Associates, 1978).

134. Gregory, R. L. Perceptual illusions and brain models. Proc. R. Soc. Lond. B Biol. Sci. 171, 279–296 (1968).

135. Weil RS, Reeves S. Hallucinations in Parkinson's disease: new insights into mechanisms and treatments. Adv Clin Neurosci Rehabil.;19(4):ONNS5189 (2020).

136. Fénelon G, Mahieux F, Huon R, Ziégler M. Hallucinations in Parkinson's disease: prevalence, phenomenology and risk factors. Brain.;123 (Pt 4):733-45 (2020).

137. Goetz CG, Leurgans S, Pappert EJ, Raman R, Stemer AB. Prospective longitudinal assessment of hallucinations in Parkinson's disease. Neurology. 11;57(11):2078-82 (2001).

138. Brda D, Tang EC. Visual hallucinations from retinal detachment misdiagnosed as psychosis. J Psychiatr Pract. 7(2):133-6 (2011).

139. Gryc W, Roberts KA, Zabetian CP, Weintraub D, Trojanowski JQ, Quinn JF, Hiller AL, Chung KA, Poston KL, Yang L, Hu SC, Edwards KL, Montine TJ, Cholerton BA.

Hallucinations and Development of Dementia in Parkinson's Disease. J Parkinsons Dis.;10(4):1643-164 (2020).

140. Santangelo, G. et al. A neuropsychological longitudinal study in Parkinson's patients with and without hallucinations. Mov. Disord. 22, 2418–2425 (2007).

141. Pappert, E. J., Goetz, C. G., Niederman, F. G., Raman, R. & Leurgans, S. Hallucinations, sleep fragmentation, and altered dream phenomena in Parkinson's disease. Mov. Disord. 14, 117–121 (1999).

142. Ramírez-Ruiz, B., Junqué, C., Martí, M.-J., Valldeoriola, F. & Tolosa, E. Neuropsychological deficits in Parkinson's disease patients with visual hallucinations. Mov. Disord. 21, 1483–1487 (2006).

143. Pacchetti, C. et al. Relationship between hallucinations, delusions, and rapid eye movement sleep behavior disorder in Parkinson's disease. Mov. Disord. 20, 1439– 1448 (2005).

144. Manni R, Terzaghi M, Ratti PL, Repetto A, Zangaglia R, Pacchetti C. Hallucinations and REM sleep behaviour disorder in Parkinson's disease: dream imagery intrusions and other hypotheses. Conscious Cogn.;20(4):1021-6 (2011).

145. Effectiveness of pramipexole, a dopamine agonist, on rapid eye movement sleep behavior disorder. AU Sasai T, Inoue Y, Matsuura M SO Tohoku J Exp Med. 2012;226(3):177.

146. Lenka, A. et al. Predictors of onset of psychosis in patients with Parkinson's disease: Who gets it early? Parkinsonism Relat. Disord. 44, 91–94 (2017).

147. Barrett, M. J. et al. Characteristics, correlates, and assessment of psychosis in Parkinson disease without dementia. Parkinsonism Relat. Disord. 43, 56–60 (2017).

148. Ecker D, Unrath A, Kassubek J, Sabolek M. Dopamine Agonists and their risk to induce psychotic episodes in Parkinson's disease: a case-control study. BMC Neurol. 0;9:23 (2009).

149. Goetz CG, Vogel C, Tanner CM, Stebbins GT. Early dopaminergic drug-induced hallucinations in parkinsonian patients. Neurology.;51(3):811-4 (1998).

150. Pagonabarraga J, Martinez-Horta S, Fernández de Bobadilla R, Pérez J, Ribosa-Nogué R, Marín J, Pascual-Sedano B, García C, Gironell A, Kulisevsky J. Minor hallucinations occur in

drug-naive Parkinson's disease patients, even from the premotor phase. Mov Disord.;31(1):45-52 (2016).

151. Ali S, Miller KK, Freudenreich O. Management of psychosis associated with a prolactinoma: case report and review of the literature. Psychosomatics.;51(5):370-6 (2010).

152. Sasaki C, Yokoi K, Takahashi H, Hatakeyama T, Obara K, Wada C, Hirayama K. Visual illusions in Parkinson's disease: an interview survey of symptomatology. Psychogeriatrics.;22(1):38-48 (2022).

153. Nishio Y, Yokoi K, Hirayama K, Ishioka T, Hosokai Y, Gang M, Uchiyama M, Baba T, Suzuki K, Takeda A, Mori E. Defining visual illusions in Parkinson's disease: Kinetopsia and object misidentification illusions. Parkinsonism Relat Disord.;55:111-116 (2018).

154. Hermanowicz N. Delusional misidentification in Parkinson's disease: report of two cases and a review. Postgrad Med.130(2):280-283 (2018).

154. Kveraga, K., Ghuman, A. S. & Bar, M. Top-down predictions in the cognitive brain. Brain Cogn. 65, 145–168 (2007). 134.Aarsland, D. et al. The rate of cognitive decline in Parkinson disease. Arch. Neurol. 61, 1906–1911 (2004).

155. Lenka A, Pagonabarraga J, Pal PK, Bejr-Kasem H, Kulisevsky J. Minor hallucinations in Parkinson disease: A subtle symptom with major clinical implications. Neurology. 6;93(6):259-266 (2019).

156. Marsh, L. et al. Psychiatric comorbidities in patients with Parkinson disease and psychosis. Neurology 63, 293–300 (2004).

157. Groth CL, Pusso A, Sperling SA, Huss DS, Elias WJ, Wooten GF, Barrett MJ. Capgras Syndrome in Advanced Parkinson's Disease. J Neuropsychiatry Clin Neurosci. ;30(2):160-163 (2018).

158. Snowden, R., Thompson, P. & Troscianko, T. Basic vision. An Introduction to Visual Perception. (Oxford University Press, 2006).

159. Holroyd, S. & Wooten, G. F. Preliminary FMRI evidence of visual system dysfunction in Parkinson's disease patients with visual hallucinations. J. Neuropsychiatry Clin. Neurosci. 18, 402–404 (2006).

160. Pagonabarraga, J. et al. Neural correlates of minor hallucinations in non-demented patients with Parkinson's disease. Parkinsonism Relat. Disord. 20, 290–296 (2014).

161. Marques A, Taylor NL, Roquet D, Beze S, Chassain C, Pereira B, O'Callaghan C, Lewis SJG, Durif F. Structural and Functional Correlates of Hallucinations and Illusions in Parkinson's Disease. J Parkinsons Dis.12(1):397-409 (2022).

162. Hebart MN, Hesselmann G. What visual information is processed in the human dorsal stream? J Neurosci. Jun 13;32(24):8107-9. (2012).

163. Kravitz DJ, Saleem KS, Baker CI, Ungerleider LG, Mishkin M. The ventral visual pathway: an expanded neural framework for the processing of object quality. Trends Cogn Sci.;17(1):26-49. doi: 10.1016/j.tics.2012.10.011 (2013).

164. Righi, G., Vettel, J. Dorsal Visual Pathway. In: Kreutzer, J.S., DeLuca, J., Caplan, B. (eds) Encyclopedia of Clinical Neuropsychology. Springer, New York, NY (2011).

165. Goddard E. A step toward understanding the human ventral visual pathway. J Neurophysiol. 1;117(3):872-875 (2017).

166. Riener, C. New Approaches and Debates on Top-Down Perceptual Processing. Teaching of Psychology, *46*(3), 267-272 (2019).

167. Gilbert CD, Li W. Top-down influences on visual processing. Nat Rev Neurosci.;14(5):350-63 (2013).

168. Kveraga K, Ghuman AS, Bar M. Top-down predictions in the cognitive brain. Brain Cogn.;65(2):145-68 (2007).

169. Liang X, Zebrowitz LA, Aharon I. Effective connectivity between amygdala and orbitofrontal cortex differentiates the perception of facial expressions. Soc Neurosci.4(2):185-96 (2009).

170. Hohwy J. Priors in perception: Top-down modulation, Bayesian perceptual learning rate, and prediction error minimization. Conscious Cogn.47:75-85 (2017).

171. Hardstone R, Zhu M, Flinker A, Melloni L, Devore S, Friedman D, Dugan P, Doyle WK, Devinsky O, He BJ. Long-term priors influence visual perception through recruitment of long-range feedback. Nat Commun. 1;12(1):6288 (2021).

172. Metzak P.D. et al. Functional brain networks involved in reality monitoring, Neuropsychologia, 75; 50-60, ISSN 0028-3932 (2015).

173. Asanowicz D, Gociewicz K, Koculak M, Finc K, Bonna K, Cleeremans A, Binder M. The response relevance of visual stimuli modulates the P3 component and the underlying sensorimotor network. Sci Rep. 2;10(1):3818 (2020).

174. Ramírez-Ruiz, B. et al. Cerebral atrophy in Parkinson's disease patients with visual hallucinations. Eur. J. Neurol. 14, 750–756 (2007).

175. Watanabe, H. et al. Cortical and subcortical brain atrophy in Parkinson's disease with visual hallucination. Mov. Disord. 28, 1732–1736 (2013).

176. Goldman, J. G. et al. Visuoperceptive region atrophy independent of cognitive status in patients with Parkinson's disease with hallucinations. Brain 137, 849–859 (2014).

177. Lenka, A., Jhunjhunwala, K. R., Saini, J. & Pal, P. K. Structural and functional neuroimaging in patients with Parkinson's disease and visual hallucinations: A critical review. Parkinsonism Relat. Disord. 21, 683–691 (2015).

178. Nagano-Saito, A. et al. Visual hallucination in Parkinson's disease with FDG PET. Mov. Disord. 19, 801–806 (2004).

179. Perumal MB, Chinnasami S, Shah A, Rodionov R, Maglajlija V, Miserocchi A, McEvoy AW, Wehner T, Diehl B. Epileptic kinetopsia localizes to superior parietal lobule and intraparietal sulcus. Neurology. 19;83(8):768-70 (2014).

180. Chowdhury FA, Silva R, Whatley B, Walker MC. Localisation in focal epilepsy: a practical guide. Pract Neurol.;21(6):481-491. (2021).

181. Ishioka T, Hirayama K, Hosokai Y, Takeda A, Suzuki K, Nishio Y, Sawada Y, Takahashi S, Fukuda H, Itoyama Y, Mori E. Illusory misidentifications and cortical hypometabolism in Parkinson's disease. Mov Disord. 26(5):837-43 (2011).

182. Ffytche DH, Howard RJ. The perceptual consequences of visual loss: 'positive' pathologies of vision. Brain.;122 (Pt 7):1247-60 (1999).

183. Nam, Y., Sato, T., Uchida, G. *et al.* View-tuned and view-invariant face encoding in IT cortex is explained by selected natural image fragments. Sci Rep 11, 7827 (2021).

184. Schadlu AP, Schadlu R, Shepherd JB 3rd. Charles Bonnet syndrome: a review. Curr Opin Ophthalmol.;20(3):219-22 (2009).

185. Shine JM, Halliday GM, Naismith SL, Lewis SJ. Visual misperceptions and hallucinations in Parkinson's disease: dysfunction of attentional control networks? Mov Disord. 2;26(12):2154-9 (2011).

186. Muller AJ, Shine JM, Halliday GM, Lewis SJ. Visual hallucinations in Parkinson's disease: theoretical models. Mov Disord.;29(13):1591-8 (2014).

187.Collerton, D., Perry, E. & McKeith, I. Why people see things that are not there: a novel Perception and Attention Deficit model for recurrent complex visual hallucinations. Behav. Brain Sci. 28, 737–57; discussion 757-94 (2005).

188. Diederich NJ, Goetz CG, Raman R, Pappert EJ, Leurgans S, Piery V. Poor visual discrimination and visual hallucinations in Parkinson's disease. Clin Neuropharmacol. 21(5):289-95. (1998).

189. Kronemer, S.I., Aksen, M., Ding, J.Z. *et al.* Human visual consciousness involves large scale cortical and subcortical networks independent of task report and eye movement activity. *Nat Commun 13*, 7342 (2022).

190. Smallwood, J., Bernhardt, B.C., Leech, R. *et al.* The default mode network in cognition: a topographical perspective. Nat Rev Neurosci 22, 503–513 (2021).

191. Vossel S, Geng JJ, Fink GR. Dorsal and ventral attention systems: distinct neural circuits but collaborative roles. Neuroscientist. 20(2):150-9 (2014).

192. Spaniol J, Di Muro F, Ciaramelli E. Differential impact of ventromedial prefrontal cortex damage on "hot" and "cold" decisions under risk. Cogn Affect Behav Neurosci. 19(3):477-489 (2019).

193. Christiane S. Rohr, Sarah A. Vinette, Kari A.L. Parsons, Ivy Y. K. Cho, Dennis Dimond, Alina Benischek, Catherine Lebel, Deborah Dewey, Signe Bray, Functional Connectivity of the Dorsal Attention Network Predicts Selective Attention in 4–7 year-old Girls, *Cerebral Cortex*, 27(9); 4350–4360 (2017).

194. Yao, N. et al. The default mode network is disrupted in Parkinson's disease with visual hallucinations. Hum. Brain Mapp. 35, 5658–5666 (2014).

195. Thomas GEC, Zeidman P, Sultana T, Zarkali A, Razi A, Weil RS. Changes in both top-down and bottom-up effective connectivity drive visual hallucinations in Parkinson's disease. Brain Commun. 4;5(1):fcac329 (2022).

196. Kiferle L, Ceravolo R, Giuntini M, Linsalata G, Puccini G, Volterrani D, Bonuccelli U. Caudate dopaminergic denervation and visual hallucinations: evidence from a ^{123}I-FP-CIT SPECT study. Parkinsonism Relat Disord.;20(7):761-5 (2014).

197. Oishi N, Udaka F, Kameyama M, Sawamoto N, Hashikawa K, Fukuyama H. Regional cerebral blood flow in Parkinson disease with nonpsychotic visual hallucinations. Neurology. 13;65(11):1708-15 (2005).

198. Boecker H, Ceballos-Baumann AO, Volk D, Conrad B, Forstl H, Haussermann P. Metabolic alterations in patients with Parkinson disease and visual hallucinations. Arch Neurol. 64(7):984-8 (2007).

199. Spinosa V, Brattico E, Campo F, Logroscino G. A systematic review on resting state functional connectivity in patients with neurodegenerative disease and hallucinations. Neuroimage Clin ;35:103112 (2022).

200. Li K, Guo L, Nie J, Li G, Liu T. Review of methods for functional brain connectivity detection using fMRI. Comput Med Imaging Graph.;33(2):131-9 (2009).

201. Buracas GT, Fine I, Boynton GM. The relationship between task performance and functional magnetic resonance imaging response. J Neurosci. 23;25(12):3023-31 (2005).

202. Stebbins GT, Goetz CG, Carrillo MC, Bangen KJ, Turner DA, Glover GH, Gabrieli JD. Altered cortical visual processing in PD with hallucinations: an fMRI study. Neurology. 26;63(8):1409-16 (2004).

203. Bhome R, Thomas GEC, Zarkali A, Weil RS. Structural and Functional Imaging Correlates of Visual Hallucinations in Parkinson's Disease. Curr Neurol Neurosci Rep.;23(6):287-299 (2023).

204. Shine, J. et al. Abnormal connectivity between the default mode and the visual system underlies the manifestation of visual hallucinations in Parkinson's disease: a task-based fMRI study. *npj* Parkinson's Disease 1, 15003 (2015).

205. Starkstein, S. E. & Merello, M. The Unified Parkinson's Disease Rating Scale: validation study of the mentation, behavior, and mood section. Mov. Disord. 22, 2156–2161 (2007).

206. Holiday KA, Pirogovsky-Turk E, Malcarne VL, Filoteo JV, Litvan I, Lessig SL, Song D, Schiehser DM. Psychometric Properties and Characteristics of the North-East Visual Hallucinations Interview in Parkinson's Disease. Mov Disord Clin Pract. 4(5):717-723 (2017).

207. Toh WL, Yolland C, Gurvich C, Barnes J, Rossell SL. Non-visual hallucinations in Parkinson's disease: a systematic review. J Neurol.;270(6):2857-2889 (2023).

208. Visser M, Verbaan D, van Rooden SM, Stiggelbout AM, Marinus J, van Hilten JJ. Assessment of psychiatric complications in Parkinson's disease: The SCOPA-PC. Mov Disord. 15;22(15):2221-8 (2007).

209. Friedberg G, Zoldan J, Weizman A, Melamed E. Parkinson Psychosis Rating Scale: a practical instrument for grading psychosis in Parkinson's disease. Clin Neuropharmacol. 21(5):280-4 (1998).

210. Romenets SR, Wolfson C, Galatas C, Pelletier A, Altman R, Wadup L, Postuma RB. Validation of the non-motor symptoms questionnaire (NMS-Quest). Parkinsonism Relat Disord. 18(1):54-8 (2012).

211. Goetz CG, Stebbins GT, Ouyang B. Visual plus nonvisual hallucinations in Parkinson's disease: development and evolution over 10 years. Mov Disord. 26(12):2196-200 (2011).

212. Papapetropoulos, S. et al. A questionnaire-based (UM-PDHQ) study of hallucinations in Parkinson's disease. BMC Neurol. 8, 21 (2008).

213. Goetz, C. G. & Stebbins, G. T. Mortality and hallucinations in nursing home patients with advanced Parkinson's disease. Neurology 45, 669–671 (1995).

214. El Haj M, Roche J, Jardri R, Kapogiannis D, Gallouj K, Antoine P. Clinical and neurocognitive aspects of hallucinations in Alzheimer's disease. Neurosci Biobehav Rev. 83:713-720 (2017).

215. Divac N, Stojanović R, Savić Vujović K, Medić B, Damjanović A, Prostran M. The Efficacy and Safety of Antipsychotic Medications in the Treatment of Psychosis in Patients.

216. Parrish AE, Brosnan SF, Beran MJ. Do you see what I see? A comparative investigation of the Delboeuf illusion in humans (Homo sapiens), rhesus monkeys (Macaca mulatta), and capuchin monkeys (Cebus apella). J Exp Psychol Anim Learn Cogn.41(4):395-405 (2015).

217. Coren, S. & Enns, J. T. Size contrast as a function of conceptual similarity between test and inducers. Percept. Psychophys. 54, 579–588 (1993).217. Goto T. Uchiyama I. Imai A. et al. Assimilation and contrast in optical illusions. Jap. Psych. Res. 49(1) 33-44 (2007).

218. Girgus, J. S. & Coren, S. Assimilation and contrast illusions: differences in plasticity. Percept. Psychophys. 32, 555–561 (1982).

219. Nicolas S. Joseph Delboeuf on Visual Illusions: A Historical Sketch. Am. Journal of Psychology. 108(4): 563-574 (1995).

220. Kawahara JI et al. Area-specific attentional effect in the Delboeuf illusion. Perception. 36: 670-685 (2007).

221. De Weerd P. Perceptual filling-in: More than the eye can see. Prog Brain Res. 54:227-45 (2006).

222. Mendola JD, Dale AM, Fischl B, Liu AK, Tootell RB. The representation of illusory and real contours in human cortical visual areas revealed by functional magnetic resonance imaging. J Neurosci. 1;19(19):8560-72 (1999).

223. Purghé, F. & Coren, S. Amodal completion, depth stratification, and illusory figures: a test of Kanizsa's explanation. Perception 21, 325–335 (1992).

224. Gerbino W. Amodal Completion Revisited. Iperception. 30;11(4):2041669520937323 (2020).

225. Kanizsa, G. Amodal completion and phenomenal shrinkage of surfaces in the visual field. Italian Journal of Psychology 2, 187–195 (197).

226. Dimiccoli M. Figure–ground segregation: A fully nonlocal approach. Vis. Res. 126: 308-217 (2016).

227. Zhang B, Hu S, Zhang T, Hai M, Wang Y, Li Y, Wang Y. Different patterns of foreground and background processing contribute to texture segregation in humans: an electrophysiological study. PeerJ. 2;11:e16139 (2023).

228. Julayanont P., Ziad S.N. Cognitive screening instruments; Book chapter; 139-195; Spring. (2017).

229. Berg D, Lang AE, Postuma RB, et al. Changing the research criteria for the diagnosis of Parkinson's disease: obstacles and opportunities. Lancet Neurol; 12:514–52 (2013).

230. Tomlinson, C. L. et al. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov. Disord. 25, 2649–2653 (2010).

231. Postuma, R. B. et al. Validation of the MDS clinical diagnostic criteria for Parkinson's disease. Mov. Disord. 33, 1601–1608 (2018). 68

232. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage. 2002 Jan;15(1):273-89.

233. Fallon, S. J., Hampshire, A., Barker, R. A. & Owen, A. M. Learning to be inflexible: Enhanced attentional biases in Parkinson's disease. Cortex 82, 24–34 (2016).

234. Archibald N.K. et al. Visual exploration in Parkinson's disease and Parkinson's disease dementia, Brain, 136(3), 739–750 (2013).

235. Huang L, Wang L, Shen W, Li M, Wang S, Wang X, Ungerleider LG, Zhang X. A source for awareness-dependent figure-ground segregation in human prefrontal cortex. Proc Natl Acad Sci U S A. 1;117(48):30836-30847 (2020).

236. Shishikura M, Tamura H, Sakai K. Correlation between neural responses and human perception in figure-ground segregation. Front Syst Neurosci. 12;16:999575 (2023).

237. Layton OW, Mingolla E, Yazdanbakhsh A. Neural dynamics of feedforward and feedback processing in figure-ground segregation. Front Psychol. 10;5:972 (2014).

238. Mohanty A, Sussman TJ. Top-down modulation of attention by emotion. Front Hum Neurosci. 1;7:102 (2013).

239. Stuart, S., Galna, B., Delicato, L. S., Lord, S. & Rochester, L. Direct and indirect effects of attention and visual function on gait impairment in Parkinson's disease: influence of task and turning. Eur. J. Neurosci. 46, 1703–1716 (2017).

240. Fasano A, Herman T, Tessitore A, Strafella AP, Bohnen NI. Neuroimaging of Freezing of Gait. J Parkinsons Dis. 5(2):241-54 (2015).

241. McKinlay A, Grace RC, Dalrymple-Alford JC, Anderson T, Fink J, Roger D. A profile of neuropsychiatric problems and their relationship to quality of life for Parkinson's disease patients without dementia. Park Relat Disord.;14(1):37–42 (2008).

Supplemental Materials: Italian Translation of The University of Miami Parkinson's disease Hallucinations Questionnaire (UM-PDHQ).

QUESITO	CARATTERISTICHE	PUNTEGGIO
1. Le capita mai di avere delle allucinazioni? *(Ha mai notato qualcosa di strano nella sua vista? Le è mai capitata qualche esperienza visiva insolita? Le è mai capitato di vedere, udire, sentire, odorare o gustare cose che non sono realmente presenti o che comunque gli altri non vedono?)*	1. Visive 2. Acustiche 3. Somatiche/ cutanee 4. Gustative 5. Olfattorie	0 = nessuna allucinazione 1 = un solo tipo di allucinazione 2 = combinazione di più tipi C: non nell'ultimo mese, ma è capitato in passato.
2. Quante volte le capita di sperimentare allucinazioni?		0 = solo raramente 1 = occasionalmente (meno di una volta alla settimana ma in modo protratto) 2 = spesso (circa una volta alla settimana) 3 = frequentemente (molte volte alla settimana ma meno di una volta ogni giorno) 4 = molto frequentemente (una o più volte ogni giorno)
3. Di solito quanto durano queste esperienze?		0 = breve durata (<1 secondo) 1 = durata media (< 10 secondi) 2 = durata prolungata (>10 secondi)
4. Ritiene che ciò che le capita di vedere o sperimentare sia reale?		0 = non e´reale 1 = talvolta penso sia reale 2 = penso sempre sia reale
5. Quanti tipi di immagini o sensazioni le capita di sperimentare?		1 = sempre lo stesso tipo 2 = pochi tipi (due o tre) 3 = molti tipi (più di tre)
6. Quanto gravi, disturbanti o stressanti le paiono queste visioni o sensazioni?		0 = nessun effetto negativo o addirittura piacevoli 1 = lievemente stressanti 2 =moderatamente stressanti (infastidiscono e sono intrusive) 3 = gravemente stressanti (molto disturbanti, possono richiedere trattamento farmacologico).
Punteggio (min 0 / max 14)		

SEGNI LA RISPOSTA PIU' APPROPRIATA ED EVENTUALMENTE DESCRIVA	
7. Le è mai stato diagnosticato un problema agli occhi? (es. problemi di vista, visione doppia, cataratta, glaucoma, retinite, distacco di retina, retinopatia diabetica o ipertensiva)	**SI (descriva):** _____ **NO**
8. Che medicine assume?	**COMPILARE NELLA SCHEDA RACCOLTA DATI**
9. Ha modificato medicine recentemente?	**SI (descriva):** _____ **NO**
10. Il cambiamento delle medicine è stato dovuto alla comparsa o a cambiamenti nelle sue allucinazioni?	**SI** **NO** **NON SAPREI**
11. Le allucinazioni capitano durante fasi di ON o di OFF?	**SOPRATTUTTO IN ON** **SOPRATTUTTO IN OFF** **SEMPRE, A PRESCINDERE DA ON E OFF**
12. Di solito cosa le capita di vedere?	**LE ALLUCINAZIONI NON HANNO FORMA, NON SAPREI DESCRIVERLE** **VOLTI:** **a. interi** **b. frammentati b1. familiari / b2 estranei** **PERSONE INTERE:** **a. familiari** **b. estranee** **ANIMALI** **INSETTI / RETTILI** **OGGETTI**
13. C'è qualcosa che può fare cessare queste immagini/sensazioni?	**SI (descriva):** _____ **NO**
14. In che momento del giorno o con quali condizioni di luminosità si verificano di solito?	**IN MOMENTI SPECIFICI DEL GIORNO** - **Di giorno / in piena luce** - **Di notte / nell'oscurità** - **Al crepuscolo** **SI VERIFICANO IN QUALSIASI MOMENTO**
15. Le immagini che vede producono qualche suono o rumore?	**SI** **NO** **N/A (assenza di allucinazioni visive)**

16. Le immagini che vede si muovono?	**SI** **NO** **N/A (assenza di allucinazioni visive)**
17. Le immagini che vede hanno dimensioni normali?	**SI, sono piu' piccole del normale** **SI, sono piu' grandi del normale** **NO** **N/A (assenza di allucinazioni visive)**
18. Le immagini che vede sono evanescenti o solide?	**EVANESCENTI** **SOLIDE** **N/A (assenza di allucinazioni visive)**
19. Le immagini che vede sono colorate?	**SI** **NO (bianche e nere)** **N/A (assenza di allucinazioni visive)**
20. Le immagini che vede compaiono in modo graduale o improvviso?	**GRADUALE (compaiono e scompaiono lentamente)** **IMPROVVISO (compaiono e scompaiono improvvisamente)** **NON SAPREI** **N/A (assenza di allucinazioni visive)**

DISCLAIMER: This is an original, non-validated translation developed by Alberto Cucca M.D. for the Department of Life Sciences of the University of Trieste for the sole scientific purposes of the present study. For further information: alberto.cucca@phd.units.it.

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