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# *[BEHAVIORAL AND NEUROIMAGING APPROACHES AS TOOLS TO DISSECT NON-MOTOR MANIFESTATIONS IN PARKINSON´S DISEASE: A FOCUS ON THE VISUAL SYSTEM]*

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**ABSTRACT**

In recent years, evidence has been accumulating regarding the existence of neurosensory deficits in Parkinson´s disease, suggesting early changes of visual function at the retinal level. However the involvement of visual cortical pathways is still not very clear. There is some evidence that visual dysfunction in Parkinson´s disease may be related to changes in dopaminergic neurotransmission within retinocortical pathways. Disease-related changes in visual parallel processing have also been documented in Parkinson´s disease. This review aims to expose changes in cortical and subcortical structures related to visual manifestations in Parkinson´s disease. For this purpose, we have organized this review in two chapters. On the first chapter we will start by giving a conceptual background about visual manifestations in Parkinson´s disease and describe the underlying neural mechanisms. The second chapter is divided in two sections: on the first we will enlighten possible related cortical and subcortical changes found through novel neuroimaging studies; on the second section, we will address other sensory systems and possible relations with visual impairment in Parkinson´s disease.

**Keywords**: Parkinson´s disease, cortical, subcortical, basal ganglia, neuroimaging, visual symptoms, visual cortex, MRI, fMRI, SPECT, PET

**LIST OF ACRONYMS AND ABBREVIATIONS**

BA- Broadman Area

DSM- Diagnostic and Statistical Manual of Mental Disorders

FDG-PET- Flurodeoxyglucose - Positron emission tomography

fMRI- Functional Magnetic Resonance Imaging

MRI-Magnetic Resonance Imaging

MRS- Magnetic Resonance Spectroscopy

MT+- Mediotemporal

NMS-Non-motor symptoms

NMSQuest- Non-motor symptoms questionnaire

PD- Parkinson´s disease

PET-Positron Emission Tomography

REM- Rapid eye movement

SI- Substantia innominata

SPECT- Single Photon Emission Computed Tomography

VBM- Voxel-Based Morphometry

VEP- Visual Evoked Potentials

VH- Visual Hallucinations

VOI- Volume of Interest

## INTRODUCTION

Growing ageing population and associated neurodegenerative disorders, are increasingly common realities in the developed world, Parkinson´s Disease is one of the most common neurodegenerative disorders, after Alzheimer's disease, and is characterized by a progressive and selective loss of nigrostriatal dopaminergic neurons (Kempster *et al*., 2007). The prevalence in industrialized countries is accepted to be 0.3% in the general population and about 1% in people over 60 years of age (Lau and Breteler, 2006). It affects people of all ethnic origins and both sexes with slight preponderance for males. Its incidence increases with age, the disease manifesting itself around the fifth or sixth decade of life, only exceptionally earlier. A distinction between normal ageing and disease has diagnostic and potential therapeutic relevance in Parkinson´s Disease since this might allow for the early diagnosis and treatment of alterations in the spatial and temporal proprieties of the ocular structures and of the brain (Antal *et al.*, 2007).

Parkinson´s disease can be idiopathic (the vast majority) or familial, with some of the genetic causes already identified such as highly-penetrant mutations in different genes (SNCA, LRRK2, VPS35, Parkin, PINK1, and DJ-1) that may cause monogenic forms of the disease. Also, different variants with incomplete penetrance in the LRR2 and GBA genes have already been identified as strong risk factors for developing Parkinson´s disease (Bonifati, 2014). Other forms of Parkinsonism have been described but they will not be considered in this review.

A more complete picture of the clinical phenotype of Parkinson´s disease has emerged nowadays as a "multi-system neurodegenerative disorder" with a wide variety of motor and non-motor symptoms. Motor features have been the hallmark of the disease and include: resting tremor, rigidity, postural instability, akinesia or bradykinesia and gait difficulty (Thomas and Flint, 2007; Jankovic, 2008). Non-motor features arise in over

90% of patients across all stages (Chaudhuri *et al*., 2011) and play a large role in degradation of their quality of life (Suzuki *et al.*, 2009) which may actually occur early on, even before the onset of motor manifestations.

Multisensory deficits have been documented early in the course of Parkinson's disease, in particular within the visual domain, ranging from ocular manifestations to sensory deficits, colour vision, motion perception and abnormal perceptual phenomena (Barnes and David, 2001; Silva *et al*., 2005; Castelo-Branco *et al*., 2009; Van Asselen *et al*., 2009; Goldman *et al*., 2014). The brain areas that are devoted to processing of low-level visual functions as well as higher-order areas are as well affected in the disease. Evidence has been accumulating by neuroimaging studies, suggesting early changes of visual function at the retinal level and involvement of cortical pathways, occipital cortex and high-order areas in the dorsal (parietal and frontal cortices) and ventral (occipitotemporal cortex) visual processing streams (Bar *et al.*, 2006; Castelo-Branco *et al*., 2009; Van Asselen *et al*., 2009; Niethammer *et al.*, 2012)

The neural origin of such deficits still remains controversial. It has also been questioned whether the reported deficits are truly sensory, since ageing factors related to the brain and also to ocular structures could explain some of the reported results. Despite the fact that retinal dopaminergic dysfunction is reflected by the low tyrosine hidroxylase imunorreactivity in central retinal dopaminergic cells (Nguyen-Legros, 1988), the known dopaminergic innervation of lateral geniculate nucleus and visual cortex (García-Cabezas *et al*., 2009) raises the question that these structures may as well be directly affected in Parkinson´s disease patients with visual impairment. It has been established that some Parkinson´s disease patients are also unable to learn implicit information contained in visual scenes, this might be due to basal ganglia dysfunction, since it´s believed that the basal ganglia is not only involved in movement control, but also in associative learning,

planning, working memory and emotion. This loss leads to compromised attentional search of an object in a repeated visual scene with repeated contextual content (Van Asselen *et al*., 2009). Visual hallucinations occur in some patients with Parkinson´s disease, we will provide some considerations of the circumstances under which hallucinations arise and of their brain substrates, focusing on visual cortex.

Frequently used neuroimaging techniques in Parkinson´s disease include Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) which assess striatal dopamine terminal dysfunction. Conventional Magnetic Resonance Imaging (MRI) is of little interest in clinical practice, however developments in structural and functional imaging have improved the capacity of MRI to detect cerebral changes, such as Voxel Based Morphometry (VBM) (Pyatigorskaya *et al.,* 2013). These novel neuroimaging techniques have helped unveiling visual impairment related cerebral changes and have also pointed to a possible relation between visual and other non-motor symptoms that we will approach in the course of this review (Meral *et al*., 2007; Shokur *et al.,* 2013). Such relations could help understanding non-striatal and striatal dopaminergic pathways in Parkinson´s disease (without overlooking the possible involvement of other neurotransmitter systems) and could possibly play an important role on early diagnosis and therapy of Parkinson´s disease.

Dissecting the underlying physiopathology of visual manifestations in Parkinson's disease with novel neuroimaging techniques may have an outstanding interest, since it can help to differentiate normal ageing cerebral changes from those related to Parkinson´s disease processes and other neurodegenerative disorders (Antal *et al*., 2007). Notwithstanding, much of the current research is focused on visual hallucinations and subtle aspects of visual processing impairment are not as frequently addressed.

This review addresses the cerebral changes in Parkinson´s disease patients with visual impairment and their possible role as a progression biomarker of Parkinson´s disease. For this purpose, we organized this review in two chapters. On the first we will start by giving a conceptual background about visual manifestations in Parkinson´s disease and how they can act as locators of brain disturbances. The second chapter is divided in two sections: on the first we will enlighten possible related cortical and subcortical changes found through novel neuroimaging studies; on the second section, we will address other sensory systems and possible relations with visual impairment in Parkinson´s disease.

# CHAPTER I

## VISUAL SYMPTOMS AS IDENTIFIERS OF THE SOURCE OF BRAIN DISTURBANCES

Visual symptoms are indeed common and several studies have reported impairment in the retina, early visual pathways, as well as in visual cortical areas in Parkinson´s disease patients. The most described visual deficits are compromised eye movements, visual acuity, colour vision, contrast sensitivity, motion perception, visuoperception and visuospatial dysfunction (see Silva *et al*., 2005 and references therein; see review by Archibald *et al.*, 2009; Terao *et al.*, 2013; Caproni *et al.*, 2014). Underlying structural brain abnormalities implicated in visual stimulus analysis have also been described (Caproni *et al.*, 2014). It has been estimated that these deficits may play a role in motor manifestations of the disease and may also be associated with the development of visual hallucinations (Caproni *et al.*, 2014). In this chapter, we will focus on the most reported visual symptoms in Parkinson´s disease and their role as a potential tracer of mechanisms of cerebral changes.

### EYE MOVEMENTS IN PD

Eye movements are influenced by an extensive network of brain regions that converge on the midbrain, more specifically, in the superior colliculus. The superior colliculus is not only responsible for the subconscious guidance of the eyes movements but is also responsible for updating the different brain regions about the ongoing eye movement, contributing to the stability of the visual field (Wurtz *et al.*, 1972). It receives a strong inhibitory projection from the basal ganglia, originating in the substantia nigra pars reticulata and also receives input from the retina in the upper layers (Pierrot-Deseilligny *et al*., 2004). The lower part of the superior colliculus is more concerned with

saccadic eye movements, while the upper part of the superior colliculus receives feedback from the frontal eye fields and contributes for the correction of saccades (Anderson *et al*., 2013). In the majority of time, the superior colliculus is inhibited by the basal ganglia, but movement initiation requires this inhibition to stop. Sometimes this mechanism is compromised such as in Parkinson´s disease leading to impairment of visual guided and memory-guided saccades (Anderson *et al*., 2013). A recent study showed that triggered saccades (required for visually keeping up with the moving object) are hypometric in Parkinson´s disease patients, requiring several saccades to reach the target (Terao *et al*., 2013). Hypermetric reflexive saccades can also occur when the inhibition becomes inconsistent (Terao *et al*., 2011). An increased dopaminergic inhibition in the indirect pathway which consequently may lead to impaired superior collicus modulation has been pointed as an explanation for a deficit in the initiation of visually-guided saccades. Memory-guided saccades are also impaired in Parkinson´s disease patients suggesting a dysfunction in the frontal cortex-superior colliculus loops (Cubizolle *et al.*, 2013; Terao *et al*., 2013).

**VISUAL PERCEPTION IMPAIRMENT IN PD**

Visual perception is divided in two different neuroanatomical and functional pathways: the occipito-temporal (ventral) pathway or the "what" loop; and the visuospatial or "where" loop, represented by the occipito-parietal (dorsal) pathway (Caproni *et al.*, 2014). Previous work addressing the separation of low from high level alterations in PD have shown that damage of the visual magnocellular pathway coexists with the upstream occipito-parietal pathway deficits and could be separated. Concerning high level motion perception, these deficits are not only dissociable, but in fact have been shown to be independent (Castelo-Branco *et al*., 2009). This study suggested that both

retinal and visual cortical dysfunction may trigger visual deficits in Parkinson disease´s patients. Visuospatial symptoms that regularly occur in Parkinson´s disease are: difficulties in estimating spatial relations; double vision; freezing in narrow spaces; bumping into objects and experiencing visual hallucinations (Davidsdottir *et al*., 2005). Difficulties in judging motion in everyday experience, especially in detecting and following rapidly moving objects in their lateral visual field have been well-reported (Trick *et al*., 1994; Lee and Harris, 1999). A "motion blur" has also been described in contrast perception of Parkinson´s disease patients with decreased spatiotemporal contrast sensivity to moving gratings, compared to age-matched controls (Masson *et al*., 1993). Nevertheless, older adults also exhibit decreased ability in discriminating motion and in detecting moving objects, on given the ageing effect on visual processing of target´s motion (Ball and Sekuler, 1986). However, when compared to age-matched controls, Parkinson´s disease patients have demonstrated worse performance in visual attention, spatial and motion detection tasks (Uc *et al*., 2005). Hence, Parkinson´s disease patients besides having changes in visual acuity and contrast sensivity (Brandies and Yehuda, 2008; Bodis-Wolner *et al*., 2014), might also have motion perception impairment, suggesting an involvement of the visual cortex since this task is more related with cortical impairment than with retina dysfunction. (Mosimann *et al*., 2004; Uc *et al.*, 2005).

Colour vision and in particular, chromatic contrast sensitivity is often disturbed in Parkinson disease´s (Silva *et al*., 2005; Terao *et al*., 2013). In the retina, colour vision starts through the routing of wavelength selective signals which just triggers the first steps in colour information processing. It is in the visual cortex that colour perception occurs and, in particular, colour constancy which consist in the ability to perceive the same colour, regardless of changes in illumination (Kolb *et al*., 2008). Color discrimination

deficits and impairment in performing visuospatial tasks in Parkinson´s disease are associated with level of motor functioning and with difficulties in realizing activities of daily living (Davidsdottir *et al.,* 2005). Parkinson´s disease patients may have increased reliance on visual feedback especially in complex tasks as a compensatory mechanism for reduced kinesthetic feedback. However, in some Parkinson´s disease patients the visual function is poorly reliable and is likely that exaggerated disturbances of posture and gait may occur (Davidsdottir *et al*., 2005). Evidence of impairment of motor performance in sequence tasks (e.g. finger taping) and in assessing event duration, which might involve the basal ganglia and thalamocortical connections was also supported by the study of Terao *et al*., 2013.

Spatial-temporal visual dysfunction in Parkinson´s Disease patients is often characterized by contrast sensitivity loss which depends on the concentration of dopamine (Uc *et al*., 2005). Contrast processing abnormalities are possibly related with dopamine dysfunction and are likely associated to damage in early visual cortical areas (Castelo-Branco *et al.,* 2009; Caproni *et al.,* 2014). The question whether involvement of these areas contributes to the contrast sensitivity deficits observed in this disease remains open (Antal *et al*, 2002). Studies associating electroretinography and visual evoked potentials (VEP) have shown that other points in the visual pathways (besides the already approached lack of dopamine in the retina) might also be implicated in the establishment of contrast sensitivity impairment in Parkinson´s disease patients (Cardoso *et al.,* 2010). Some abnormalities in the VEP could not be explained by the ones found in the electroretinography, suggesting that impairment in other locations besides the retina might be involved (Cardoso *et al.*, 2010). Processing problems in MT+ related motion circuits, might cause motion coherence deficits, as well as in perception of rapidly moving stimuli and are likely to cause problems in tracking fast moving targets (Castelo-Branco

*et al*., 2009; Jones and Jahanshashi, 2009). This all contributes to inaccurate perception of movement and may evince not only a basal ganglia dopaminergic dysfunction, but may also suggest a possible involvement of cortico-superior colliculus circuitries. In our mind, if these circuitries are dysfunctional, inaccurate misinterpretation of peripherally located visual stimuli could lead to abnormal activity in the visual cortex and even lead to experiencing illusions and hallucinations in the peripheral visual field.

The complex visual stimulus processing which demands "bottom-up" and "top-down" visual processing have been the focus of fMRI studies in Parkinson´s disease patients with visual hallucinations and researches have pointed that the latter is activated not only in optimal conditions, but also in suboptimal visual circumstances. This process involves a fast initial projection of visual information to the prefrontal cortex, activating an "initial guess" which is then projected back to the temporal cortex (Bar *et al.,* 2006). A possible impairment in "bottom-up" visual pathways might be a cause to higher reliance on 'top-down' mechanisms, where the frontal lobe seems to play a role in activating the visual cortices, releasing previously seen images, which do not match up with the external world (Jenner, 2010). This way, relative impairment in visual processing could lead to compensatory visual processing and internal image generation, leading e.g to the appearance of visual hallucinations in Parkinson´s disease patients (Jenner, 2010). Since retinal dysfunction has been well addressed in previous studies (Silva *et al*., 2005; Brandies and Yehuda, 2008; Archibal *et al*., 2009; Bodis-Wolner *et al*., 2014), the studies we will focus on the second chapter will mostly concern the visual cortex.

## VISUAL HALLUCINATIONS

Visual hallucinations (VH) are a common feature among Parkinson´s disease patients, occurring in up to half of patients with this disease (Williams and Lees, 2005).

Patients with visual hallucinations have a higher risk of institutionalization and mortality compared to those without VH. Also, greater degree of disability, higher caregiver burden and increased mortality has been associated with Parkinson´s disease patients with cognitive impairment (Stephenson et al., 2010). VH may be characterized as a "sensory perception, without external stimulation of the relevant sensory organ", according to DSM IV criteria. They can be classified based on content: simple: characterized by the absence of form, often photopsias, most of them possibly arising from early visual cortex; and complex (the more frequent in Parkinson´s disease patients), perceived as visions that are clearly defined, such as objects or animals, probably arising from inferotemporal visual cortex (Feinberg and Rapcsack, 1989; Ffytche *et al*., 1998; Barnes and David, 2001). They occur while the patient is alert with the eyes open and last a few seconds (Cummings, 1991). Sometimes it starts with the sense of presence, they feel that there is something in the corner of their eye and they turn to see what´s there. When they start to perceive it as real, they become clinically relevant. Parkinson´s disease patients with hallucinations exhibit a lower contrast sensitivity, suggesting that retinal dysfunction may be a predisposing factor (Diederich *et al*., 1998). Also, visual acuity reduction and retinal disease per se may lead to visual hallucinations in Parkinson´s disease, so one cannot postulate that there is a pathognomonic evidence of cortical involvement in Parkinson´s disease patients with visual hallucinations (Holroyd *et al*., 2001; Castelo-Branco, 2005). Nevertheless, visual object categorization deficits were found by Antal *et al*., (2002) suggesting a potential link to object processing deficits and visual hallucinations. It is possible that cognitive impairment may have some relation with the occurrence of hallucinations since some studies have revealed that cognitive decline plays a role in chronic evolution of hallucinations being the latter a risk factor for worsening of cognitive aptitudes (Factor *et al*., 2003). Several mechanisms have been proposed to explain VH in

Parkinson´s disease patients: sleep disorders; interaction between visual impairment and compensatory "top-down" regulation (Davidsdottir *et al.*, 2005) that we will address in the second section of chapter two. Dopaminergic medication is also mentioned as an often cause of VH in Parkinson´s disease (Barnes and David, 2001). Opposingly, other studies proposes VH as an intrinsic part of Parkinson´s disease (Fénelon *et al*., 2000; Davidsdottir *et al.*, 2005) since PD patients already had VH in the pre-Dopa era, which suggests that VH may occur independently of dopaminergic medication and that it might not be the direct cause but a precipitating factor (Fénelon *et al*., 2000; Jenner, 2010). Nonetheless, excessive dopaminergic stimulation may play a role in inappropriate signaling of the retino-geniculo-extrastriate pathway, leading to inaccurate perception of motion in the peripheral visual field. Foveation of the peripheral perception, in order to dissect a disturbance of the receptive visual field, could be a great approach to confirm or reject this theory (Diederich *et al.*, 2014). Also, increased excitability and disinhibition of neural structures such as the visual cortex, with subsequently spontaneous activity, is one of the hypothesis that has been pointed to explain VH (Onofrj *et al*., 2007).

Several neuroimaging studies have been done in order to understand the physiopathology of visual impairment and, more specifically, VH in Parkinson´s disease whose results we will discuss in the second chapter.

# CHAPTER II

## 1. BRAIN REGIONS AFFECTED IN PARKINSON´S DISEASE WITH VISUAL MANIFESTATIONS

Early diagnosis of Parkinson´s disease is very important, although there are no current medications with the potential to modify the curse of this neurodegenerative disease, it may play an important role in future disease modifying approaches. Misdiagnosis is very common in early Parkinson´s disease with prevalence of non-motor symptoms, including visual manifestations, and may lead to unwarranted therapeutics. Some visual manifestations may initiate years before the onset of the disease, such as impairment in colour vision that has shown to have 73% sensitivity and 50% specificity for identifying underlying neurodegenerative disease (Postuma *et al*., 2011). Their early acknowledgment gives a window to apply the right approach and since some pharmacological modifying diseases are being well studied, this will be of particularly importance when they´ll became available (Gasior *et al.*, 2006).

Recent advances in neuroimaging technology with PET, SPECT, MRS and fMRI imaging have permitted new understanding of the neuroanatomical basis of pathophysiological phenomena of vision (Niethammer *et al.*, 2012). PET and SPECT imaging use a number of radiotracers for in vivo assessment of the brain function. They may assess postsynaptic dopaminergic function with D1 and D2 receptor ligands, making it an extremely important resource whereas in early disease stage there is an elevation of D2 receptor binding in the striatum contralateral to the more affected limb in Parkinson´s disease, which has been interpreted as compensation dopaminergic deficit. In later stages, D2 receptor binding values fall back in the normal range, indicating a long-term down-regulation of the receptors (Meyer *et al*., 2006).These techniques have been widely used

to study the dopaminergic system in Parkinson´s disease but other neurochemical systems can also be investigated (Niethammer *et al.*, 2012).

In this section, we will focus on the main cortical and subcortical findings revealed using neuroimaging techniques applied nowadays in Parkinson´s disease and their role in understanding visual manifestations.

## CORTICAL FINDINGS

### Occipital cortex and temporal extrastriate visual cortices

Meppelink and his colleagues (2009), specified a relation between the function of visual cortex and VH in non-demented Parkinson´s disease patients. Aiming to identify activation changes in circuitry particularly related to visual processing preceding image recognition, they submitted Parkinson´s disease patients with history of VH to an fMRI study. Reduced activation of the lateral occipital cortex and temporal extrastriate visual cortices seconds before an image recognition task was found in Parkinson´s disease patients with VH. This was not seen in patients without visual hallucinations, supporting the idea of impairment in bottom-up visual pathways on the former group (Meppelink *et al.*, 2009). This may point to a disturbance at a processing stage beyond V1 in which the normal brain uses scarce information to predict the structure of features in poor scenery (Meppelink *et al.*, 2009). Despite this reduction found in ventral/lateral extrastriate visual cortices in Parkinson´s disease with VH, no differences in cortical grey matter volume were seen between Parkinson´s disease patients with and without VH (Meppelink *et al.*, 2011). This may suggest specific neurochemical deficits preceding structural changes, e.g cholinergic deficiency which may be the cause of impairment in selection of subcortical information streams, consequently predisposing to hallucinations (Meppelink *et al.*, 2011).

Further insight in possible occipito-temporal pathology associated with VH was given by Cardoso and his colleagues (2010) who performed two fMRI studies in Parkinson´s disease patients without visual complaints and without dementia for evaluation of neural responses to flickering checkerboards and a facial perception paradigm and compared it to controls responses. In the former, Parkinson´s disease patients showed decreased bilaterally activity in the primary visual cortex compared to healthy controls. Previous studies have also shown similar decreased glucose metabolism in the primary visual cortex of Parkinson´s disease patients with VH when compared to healthy controls (Holroyd and Wooten, 2006). Furthermore, when Cardoso *et al.*, submitted the Parkinson´s disease patients with VH to the facial perception paradigm, an increased activity of fusiform gyrus was found. This supports the idea that visual discrimination may not be entirely determined by the visual cortex alone (Cardoso *et al.*, 2010). Moreover, since greater occipital glucose metabolic reduction was found in the hemisphere contralateral to the side of the body affected, a global dysfunction in visual pathways is suggested by these findings. If Parkinson´s disease related retinopathy was here concerned, we would expect symmetric reduction in glucose metabolism in occipital lobe not correlated with contralateral motor impairment (Cardoso *et al.*, 2009).

The Positron Emission Tomography (PET) allows the use of molecularly specific tracers and it is an important molecular imaging tool to explore pre- and post-synaptic dopamine function in Parkinson´s disease (Nandhagopal *et al.*, 2008). Metabolic alterations have also been assessed to try to understand which brain regions are affected in Parkinson´s disease with and without visual hallucinations (Boecker *et al.*, 2007). Positron emission tomography with $^{18}$F-Fluorodeoxyglucose (FDG-PET) is a diagnostic imaging procedure used to evaluate the pattern of cerebral glucose metabolism. A FDG-PET study done by Boecker *et al.* (2007) in order to determine whether functional changes

in Parkinson´s disease with VH (discontinued from dopaminergic medication for at least 12 hours before FDG-PET) occur in visual association areas, as suggested by the complex symptomatology, revealed impairment within cortical visual pathways processing, with evidence of hypometabolism in the temporal gyri and the occipital cortex of Parkinson´s disease patients with VH in comparison to patients without VH (Boecker *et al*., 2007). Also, one study with fMRI suggested that different cerebral areas are abnormal depending on the type of hallucinations: facial hallucinations were associated with temporal lobe changes, while objects and moving scenes were associated with occipital lobe alterations (Factor *et al.*, 2007).

This way, future studies should address the impairment of the ventral and lateral extrastriate visual cortex in more detail with PET addressing possible underlying molecular mechanisms of disease in extrastriate visual areas. Since all this evidence support that this impairment may be one of the risk factors for the occurrence of VH in Parkinson´s disease patients, with an important role in the deterioration of their quality of life (Meppelink *et al.*, 2009).

**Temporoparietal association cortices and ventral visual pathways**

With the aim to study pattern of glucose metabolism in Parkinson´s disease patients with VH and its relation with cognitive impairment, Park *et al.*, (2013) performed FDG PET with later statistical parametric mapping comparison between 3 groups: the first was constituted by Parkinson´s disease patients with visual hallucinations without cognitive impairment; the second by Parkinson´s disease patients with visual hallucinations and cognitive impairment and the third by Parkinson´s disease patients without visual hallucinations. The FDG PET revealed a glucose hypometabolism in the temporoparietal association cortices; in dispersed frontal areas and in the fusiform gyri of

Parkinson´s disease patients with visual hallucinations who had no cognitive impairment, suggesting an engagement of the ventral visual pathway. This was previously seen in a pathological study made by Gallagher *et al*., in 2011 that also revealed temporal and cortical dysfunction but, particularly, the greater impairment was found in ventral visual pathways which are strongly implicated in reality discrimination and emergence of VH. Dysfunction of ventral visual pathway involving the temporal lobe may be a key point in VH development in Parkinson´s disease patients. Notwithstanding, evolving distribution from the ventral visual pathway to more extensive posterior cortices may be a predictor of cognitive impairment in Parkinson´s disease patients (Park *et al.,* 2013).

**Frontal cortex**

Top-down projections originate in the frontal lobe and can enhance stimulus-related activity, but they also modulate neural activation in striate and extrastriate visual areas which emphasizes the importance of high level mechanisms (Rosa *et al.,* 2013). An increasing number of studies are suggesting an interconnection between visual perception deficits and frontal disturbances besides the classical correlation with posterior visual regions (Koshino *et al*., 2008). It is known that feedback signals into primary visual cortex arise from higher order visual areas, frontal and parietal cortices, and are involved in attention, visual imagery, and task-related visual processing (Rosa *et al.*, 2013).

There is also evidence that greater cerebral glucose metabolic rate may be enhanced in frontal areas of Parkinson´s disease patients with VH (Nagano-Saito *et al.*, 2004; Jenner, 2010). Nagano-Saito *et al.,* 2004 used FDG PET to compare cerebral glucose metabolism between Parkinson´s disease with VH and Parkinson´s disease without VH (24 hours after discontinuing their Parkinson´s disease medications in the off state). The results revealed a significant increase of glucose metabolic rate, more

specifically, in the left superior frontal gyrus that may unveil compensatory "top-down" mechanisms to overcome defective visual input, e.g. to fill missing or unclear details in Parkinson´s disease patients with VH or spontaneous compensatory neural firing in visual pathways that has been pointed as a possible causal factor for hallucinations in Parkinson´s disease (Davidsdottir *et al.,* 2005; Jenner, 2010). These findings support the hypothesis that areas beyond the visual cortex (e.g in this situation, frontal areas associated with the control of executive function and attention) may take part in the pathophysiology of VH.

Somewhat contrarily to these findings, decreased activity of frontal regions has been found in Parkinson´s disease patients with VH (Ramírez-Ruiz *et al.,* 2008 and references within). Ramírez-Ruiz and his colleagues in 2008, made a study in which response to complex visual stimuli was measured with fMRI. A hypoactivation of frontal areas associated with control of attention was detected in patients with VH and related to a decreased response to complex visual stimuli. Additionally, when the deactivation pattern was analyzed, an increased response to non-meaningful simple visual stimuli was also suggested. Therefore, impairment in perception and visual attention might play a role in improper differentiation between relevant and irrelevant visual information and may predispose the development of visual hallucinations (Ramírez-Ruiz *et al.,* 2008; Van der Hoorn A *et al.,* 2014).

Parkinson´s disease patients show impairment both at pre-attentional visual processing and later at the level of saccade execution (Lieb *et al.,* 1999). Execution and correction of the saccades are planned through feedback pathways from the frontal eye fields to the superior colliculus (Diederich *et al.,* 2014). Hypoactivity of the frontal brain involved in eye movement planning, execution and monitoring, along with a hypoactivity of supplementary eye fields was found in an fMRI study done by Rieger *et al*., (2008)

where Parkinson´s disease patients executed voluntary saccades, in comparison to healthy participants. Both had activation in the superior parietal cortex and the occipital cortex. According to this study, cortical frontal eye fields involved in saccade direction selection are profoundly affected in Parkinson´s disease patients, while activation in several posterior brain areas associated with saccades is increased. These reciprocal effects may evidence a shift in relative activity between frontal and posterior brain regions as a result of possible reorganization of related cortical areas for voluntary saccades (Rieger *et al*., 2008).

**The parietal lobe and lingual gyrus impairment**

Ramírez-Ruiz *et al.,* (2007), were the first to give an in vivo evidence of atrophic alterations in Parkinson´s disease with VH. Using MRI with voxel-based morphometry (VBM), they reported that compared with both controls and with a non-hallucinating Parkinson´s disease group, patients with complex visual hallucinations had grey matter volume reductions in the left lingual gyrus and superior parietal lobe, bilaterally. The lingual gyrus has been implicated in the visual processing at different levels of complexity, such as colour perception, visual discrimination and attention (Lee *et al.*, 2000). Impairment in this area could lead to compromised visuoperceptive function, which has been referred as a contributing factor for the appearance of VH (Ramírez-Ruiz *et al.,* 2007). Damage in the superior parietal lobe may be related to visuospatial working memory and visual attentional tasks deficits (Wurtz *et al.*, 1972; Ramírez-Ruiz *et al.*, 2007) and might be caused by secondary effect of basal ganglia disease (Meppelink *et al*., 2011). These underlying changes in visual attention pathways may lead to the wrong incorporation of stereotyped form-objects into the visual field and predisposing to VH (Ramírez-Ruiz *et al.,* 2007). This seeming discrepancy with the results of Meppelink *et*

*al*, (shown in the beginning of the second chapter) that didn´t associate VH in Parkinson´s disease with grey matter reductions may be explained by an earlier stage of Parkinson´s disease in their study.

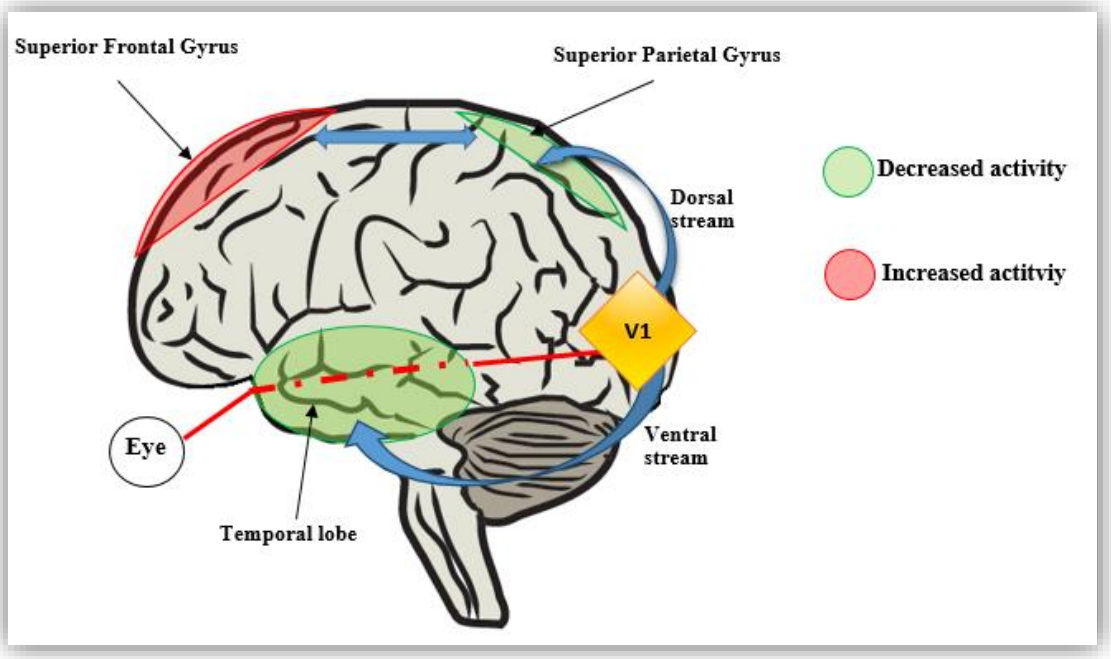


**FIGURE 1**. *Decreased activity in the primary visual cortex and temporal extrastriate visual cortices has been detected in an fMRI study of PD patients with VH (Meppelink et al., 2009). Dysfunction of ventral visual pathway concerning the temporal lobe may be a key point in the development of VH in PD patients since it involves processing stage beyond V1 in which the normal brain uses scarce information to predict the structure of features in poor scenery (Meppelink et al., 2009). Increased activity in superior frontal gyrus may unveil compensatory "top-down" mechanisms to overcome defective visual input (Davidsdottir et al., 2005; Jenner, 2010). Superior frontal areas have functional reciprocal connections with the parietal lobe and prefrontal cortex, intervening, this way, in visual attention processes. They also have functional connections with the basal ganglia, receiving input from the striatum, this way it may be hypothesized that patients with more severe basal ganglia dysfunction may be predisposed to the development of VH (Kiferle et al., 2014).*

## SUBCORTICAL FINDINGS

Recently, abnormalities of subcortical regions implicated in visual stimuli analysis have been observed in Parkinson´s disease patients with cognitive decline and visual hallucinations (Caproni *et al.,* 2014). Studies have also highlighted the importance of various connections among these regions, specifically those that are part of basal ganglia networks, involved in attention and cognitive functions (Caproni *et al.,* 2014). Superior frontal areas have functional connections with the basal ganglia, receiving input from the striatum, and form reciprocal connections with the parietal lobe and prefrontal cortex, intervening, this way, in visual attention processes (Kiferle *et al*., 2014). According to this and also considering that early executive dysfunction has been linked to nigrostriatal dysfunction in Parkinson´s disease patients, it may be hypothesized that patients with more severe basal ganglia dysfunction may be predisposed to the development of VHs (Kiferle *et al*., 2014). In order to study this interactions, some neuroimaging studies have been performed that, whose results we will contextualize next.

### Striatum

Death of dopaminergic neurons in the substantia nigra pars compacta may lead to functional changes that involve all components of the fronto-thalamo-striatal circuit (Davidsdottir *et al.,* 2005). Deficient activation in caudate (bilaterally) and left putamen has been confirmed in Parkinson´s disease patients with visual hallucinations by Caproni et al., 2014. These findings are in agreement with the pathophysiology of the disease, since impairment in this region affects the expression of frontal-lobe functions by interrupting normal transmission through frontostriatal circuitries and may influence making decisions in ambiguous contexts (Caproni *et al.,* 2014). In this study, the right

insula and right hippocampus also showed decreased activation that we will discuss in the next sections. In agreement with this hypothesis are also the results of a SPECT scan made by Kiferle *et al*., in which they studied Parkinson´s disease patients with VH and a group of Parkinson´s disease patients without VH and dementia. They performed SPECT scan with $^{123}$I-FP-CIT (a radioligand for imaging of dopamine transporters) in Parkinson´s disease patients as soon as VH emerged. The results showed a significant decrease in right caudate uptake in Parkinson´s disease patients with VH when compared with patients without VH. Since the caudate is connected to the frontal cortex through neuronal loops, as said above, these findings suggest that right dopamine dysfunction may contribute to frontal impairment in Parkinson´s disease patients with VH (Kiferle *et al.*, 2014).

**Hippocampus**

The hippocampus contributes mostly to processing within allocentric frames of reference, with a specific role in processing and storage of spatial information, as part of the top–down visual processing system that might be impaired in Parkinson´s disease (Caproni *et al*., 2014). Notwithstanding, hippocampal hypoactivation in Parkinson´s disease has been related to reduced efficiency in executive and attentional functions. Caproni *et al.*, used a specific visuoperceptual/visuospatial paradigm to compare Parkinson´s disease patients and controls. Due to the specificity of the test they used, their results suggested an association between the hippocampus and subclinical visuospatial dysfunction in Parkinson´s disease, not setting aside the possibility of an overlap with levodopa therapy (Caproni *et al*., 2014).

**Substantia innominata**

An interesting study was done by Shin *et al*. (2012) that performed VBM for grey matter volume and a region-of-interest-based volumetric analysis (VOI) of the substantia innominata (SI) of non-demented Parkinson´s disease patients with visual hallucinations. This study described a significantly reduced volume in the frontal, temporal and thalamic areas as well as the substantia innonimata which is known to receive afferents from structures known to be part of the limbic system such as the amygdala (Shin *et al*., 2012). Choi *et al*, 2012 reported that the volume of SI is correlated with frontal executive function, memory, attention, visuoconstructional and object-naming performance. Furthermore, in the SI of the basal forebrain, exists a nucleus called Meynert that is the major source of cholinergic input to the cerebral cortex. This cholinergic system has been suggested to be important in the development of VH in patients with Parkinson´s disease (Shin *et al,* 2012). Future studies using functional imaging with a cholinergic ligand could be significant to elucidate the role of the cholinergic system in the development of VH (Shin *et al*, 2012).

**Insula**

The insula has been under-recognized in the pathogenesis of non-motor symptoms in Parkinson´s disease (Christopher *et al*., 2014). fMRI studies have revealed hypoactivation of the insula in Parkinson´s disease patients with cognitive impairment and, in particular, in the presence of hallucinations (Caproni *et al.*, 2014). It is a region that seems to be involved in attentional and long-range functional interactions with visual perception networks (Caproni *et al.*, 2014). Hypoactivation of the insula may suggest an initial loss of efficiency in "switching" between attentional and visuospatial networks when Parkinson´s disease patients are submitted to specific tasks to study visuospatial

judgment, anticipating the development of cognitive impairment and visual hallucinations (Caproni *et al.*, 2014). Also, inability to activate the anterior insula was related to capacity of viewing bistable images in a study done by Shine *et al*., (2013) exploring possible mechanisms underlying visual misperceptions in Parkinson's disease. Misperceptions or hallucinations were found to be possibly associated with impairment in attentional networks involving the anterior insula (Christopher *et al.*, 2014 and references within).

## 2. OTHER NON-MOTOR SYMPTOMS INVOLVED IN PARKINSON´S DISEASE AND POSSIBLE RELATIONS WITH VISUAL SYMPTOMS

Non-motor symptoms of Parkinson´s disease may often be an excellent key to support the identification of populations at higher risk of developing the disease and to understand its early onset. Several non-motor symptoms of Parkinson´s disease have the same fundamental etiology, sharing similar pathways related to the basal ganglia. According to this, it is expected that reciprocal associations between symptom components might exist (Davidsdottir *et al*., 2005). For this reason, we will contextualize the latest findings about the most common NMS and unveil possible relations with the visual system impairment.

### 2.1 OTHER SENSORY SYSTEMS

#### OLFACTORY DYSFUNCTION

Parkinson´s disease patients rarely mention olfactory loss spontaneously, but between 22% and 70% of Parkinson´s disease patients may indicate hyposmia or anosmia when directly asked and it was detected in 70-100% of specifically tested patients (Chaudhary *et al*., 2009). Olfactory loss in Parkinson´s disease occurs in early stages and might be present in untreated Parkinson´s disease patients with mild motor symptoms, occurring independently of the duration and severity of the disease. This lack of association suggests that olfactory deficits reach a maximum early in the course of the disease and for this reason may have a role as a biomarker in future approaches since it may expose subjects at risk, who are in the pre-motor phase of Parkinson´s disease,

helping antedate the appearance of motor symptoms in 2-7 years. (Chaudhary *et al*., 2009; Rolheiser *et al.,* 2011).

The hypothesis that pathological changes start extending from the lower brainstem and olfactory pathways to the midbrain and the cortex has been supported by recent findings suggesting that changes in the olfactory function may be among the earliest abnormalities that occur in Parkinson´s disease (Stephenson *et al.,* 2010; Haehner *et al.*, 2011). Though the mechanisms of olfactory lesions are still unclear, some studies have revealed that patients with great olfactory impairment (nearly complete anosmia) are at a higher risk of developing visual hallucinations and cognitive decline over the course of the disease, since there was a pattern of increasing risk of neuropsychiatric complications with each quartile drop in olfactory performance (Stephenson *et al.,* 2010). Therefore, in the future olfactory testing may be a useful prognostic indicator of Parkinson´s disease neuropsychiatric features since it can help in the identification of these target patients at an early stage of Parkinson´s disease. This way, disease-modifying medications could be applied to help postponing the development of dementia and psychosis in Parkinson´s disease (Stephenson *et al.,* 2010).

**HAPTIC SYSTEM**

Maintaining equilibrium implies sensorimotor integration tasks which involves complex integration of sensory inputs and coordination of multiple motor outputs that allow quiet-standing posture. Sensory information and timing operations processing may be affected in Parkinson´s disease, even at early disease stages, who have shown an inaccurate calibration of postural responses with severely depressed frontal responsiveness to sensory stimuli, as tested with sensory evoked potential (Honeine and Schieppati, 2014; Zhao *et al*., 2014). Studies have indicated that to prepare for and

accomplish an action successfully, information from separate sensory systems that are involved in motor planning, such as the haptic, visual and auditory systems must somehow be integrated (Zhao *et al*., 2014). De Nunzio *et al.,* tested Parkinson´s disease patient's balance while continuously riding a moving platform, under eyes-closed and latter under eyes-open. A delay in the implementation of the vision-dependent behavior was found while Parkinson´s disease patients were submitted to kinesthetic-to vision-dependent tests, which is consistent with abnormal temporal features. This was unexpected since the advantage of having vision in the test with eyes-open was supposed to benefit motor performance in Parkinson´s disease. According to this, Parkinson´s disease patients performing dynamic postural tasks under changing sensory conditions might become more unstable due to an insufficient integration of a new sensory information or a delay in the implementation of the change in the appropriate balancing strategy. The interaction between vision and the proprioceptive input is essential to achieve balance (Shokur *et al.,* 2013). These two sensory inputs have different time-period necessary to access the brain and in a variety of situations, we may witness that vision dominates over the proprioceptive input (Murnaghan *et al.,* 2011) such as the example above. Zhao *et al.,* examined through fMRI which brain regions of Parkinson´s disease patients were involved in the integration of tactile–motor information. Their study revealed an activation in extrastriate visual cortical areas during tactile tasks and, essentially, during movement and integration tasks in neurologically normal controls. However, their findings revealed significantly decreased activity in the right Broadman Area (BA) 18 and BA 19, which are involved in the translation and interpretation of visual impressions transmitted from the primary visual cortex, in patients with early Parkinson´s disease compared with neurologically normal controls. Surprisingly, they also found decreased activity in the middle temporal gyrus/V5 in Parkinson´s disease patients during

a movement task. Since this area is thought to play a main role in motion perception and the guidance of some eye movements, this could suggest that this region may play a key role in Parkinson´s disease sensorimotor computation and movement dysfunction. These findings indicate that extrastriate visual cortex is a multisensory region essential in sensorimotor integration.

Lack of studies have been done in this field, multisensory fMRI could be done to explore which brain regions are involved in the integration of visual-haptic-motor information and to determine whether activity in the extrastriate visual cortex in perception and cognition tasks differs when patients with early Parkinson´s disease are compared with normal controls.

**AUDITORY SYSTEM**

Evidence has pointed that auditory hallucinations occur in 8% to 13% of patients with Parkinson´s disease and when they occur are generally accompanied by visual hallucinations (Kataoka and Ueno, 2014). Most auditory hallucinations are a repetitive human voice. Auditory musical hallucinations are rare complex auditory hallucinations in Parkinson´s disease that have been reported in few patients (Kataoka and Ueno, 2014). Greater cognitive deficits have been related to Parkinson´s disease patients with hallucinations in comparison with patients without hallucinations (Fénelon *et al*., 2000). What is not known is whether Parkinson´s disease patients who experience hallucinations in more than one modality are more cognitively impaired than individuals whose hallucinations are limited to a single type (Katzen *et al*., 2010). Katzen *et al*., employed a comprehensive neuropsychological battery ("*Premorbid Intellectual Functioning Language"; "Boston Naming Test*"; "*Memory"; "Visuospatial"; "Attention and Executive"; "Mood and affect"; "Hallucinations Questionnaire"* and *"Medication*

*Data")* in Parkinson´s disease patients with visual hallucinations to address whether patients with multi-modal hallucinations were at higher risk for cognitive and emotional dysfunction. Their findings were consistent with previous work demonstrating that when comparing with non-hallucinating Parkinson´s disease patients, in general, patients with hallucinations exhibited greater difficulty formulating spatial judgments and demonstrated executive dysfunction characterized by working memory and set shifting difficulties. Notwithstanding, it appeared that the presence of hallucinations in more than one modality was not necessarily associated with a greater risk of either cognitive or affective impairment among Parkinson´s disease patients with comparable disease severity and duration (Katzen *et al*., 2010) but additional investigations with larger samples could be made in order to support these findings. Some common pathways in visual and auditory processing have been exposed by Karabanov *et al*., 2009. They used an fMRI study in order to investigate the effect of two factors on the neural control of temporal sequence performing. One of them was the influence of rhythms learned by different modalities (by visual or auditory pacing). The other was the modality of the pacing stimuli preceding performance. Each participant had to learn two rhythms, one presented visually and the other auditorily, some days before scanning. During fMRI, the rhythms were performed in blocks. In each block, beats of a visual or auditory pacing metronome were followed by repetitive self-paced rhythm performance from memory. A key finding of the study was that reproduction of rhythms that were both trained and paced in visual and auditory modalities activated essentially the same network of brain regions. Furthermore, this set of areas included auditory-motor areas of the dorsal auditory stream which is related to sequencing and transformation of auditory representations into motor responses (Karabanov *et al*., 2009). This has not been applied to Parkinson´s disease patients with both visual and auditory hallucinations, but future

studies could investigate the neural circuitry underlying single versus multi-modal Parkinson´s disease hallucinators in order to understand the processing relation between this sensory system and how it can influence the appearance of multi-modal hallucinations in Parkinson´s disease patients. Despite the fact that no neuroimaging study was made in the study of Katzen *et al*., the authors conclude that even if patients with multi-modal hallucinations had neuroanatomical dysfunction, it would not necessarily require different approaches by clinicians than those patients with a single type hallucinations have, since no additional cognitive impairment or emotional disruption was found in multi-modal hallucinators in comparison with those with single type hallucinations (Katzen *et al*., 2010).

To our knowledge no further investigations were made with the purpose to study a possible relation between other auditory manifestations and visual symptoms in Parkinson´s disease.

## 2.2 OTHER NON-MOTOR SYMPTOMS

### DEPRESSION

Depression may occur at any stage of the disease and affects up to 68.1% of Parkinson´s disease patients (Blonder and John, 2011). In early stages it affects up to 27.6% the patients and has direct implications in their quality of life (Cummings, 1992), including facets such as apathy, lack of motivation, flattened mood that contribute to considerably morbidity (Chaudhuri *et al.,* 2009).

There are few neuronal systems seemed to be involved in the genesis of depression in Parkinson´s disease, among them are the dopaminergic and serotoninergic

systems. It is believed that the reduction in striatal dopamine availability leads to a compensatory reduction of serotonin levels (Mayeux *et al*., 1984). This reduction can precede the development of motor manifestations up to 3-6 years before the diagnosis of Parkinson´s disease (Gaenslen *et al*., 2011). The D2 receptor binding is as well elevated in the putamen of patients with major depression without Parkinson´s disease (Meyer *et al*., 2006). There is also evidence of an interconnection between the visual and the limbic system, processing emotional information, with an association between the superior colliculus and the amygdala via thalamus. This could be an explanation of the suggested link between visuomotor disturbances and depression in Parkinson disease´s (Gurvich *et al.*, 2007). According to this, there may be a link between these two major complex pathologies which waits for further studies to understand how it can affect each other (Leentjens, 2004).

### COGNITIVE IMPAIRMENT AND DEMENTIA

Cognitive impairment and dementia in Parkinson's disease have vast detrimental impact on the quality of life of Parkinson´s disease patients (Goldman *et al.*, 2014). Executive function, motor learning, working memory are the most common impaired features. These deficits are more subtle at an early stage of Parkinson´s disease, yet worse prognostic comes when they appear early on the onset of the disease. With Parkinson´s disease´s progression, these symptoms start to interfere with the socio-occupational function of the patient and along with other neurobiological underpinnings may contribute to dementia´s development (YorkWilliams and Poston, 2014).

Brück *et al.*, (2004) found an association between brain atrophy and cognitive impairment. Their study revealed that at an early stage of Parkinson´s disease patients without medication and non-demented already had atrophy the hippocampus and in the

prefrontal cortex. In this study left hippocampal atrophy seemed to be related to impaired memory and prefrontal cortex atrophy was associated with prolonged reaction time in tests evaluating vigilance (sustained attention). This frontal dysfunction that often accompanies Parkinson´s disease cognitive decline, with reduction of inhibitory output, might also explain VH in this disease (Onofrj *et al*., 2007). Also, recent fMRI studies demonstrated that dorsal and ventral frontoparietal networks constitute the anatomical substrates of attention (Stebbins *et al.,* 2004). This way, the frontal lobe dysfunction observed in Parkinson´s disease patients might therefore contribute to abnormal preattentive processes with impairment of spotlight focusing attention, improper perception of images and inaccurate afferent information through the dorsal and ventral corticocortical pathways. This premise enhances a lack of rostral inhibitory input to visual loss as causative mechanisms of VH, but doesn´t explain why some kinds of hallucinations never occur in Parkinson´s disease and why visual impairment is often corrected with drug administrations, while VH develop chronically and seem to be induced by dopaminergic treatment (Onofrj *et al*., 2007). In our opinion, longitudinal investigation of dorsal and ventral networks through neuroimaging techniques such as fMRI or PET could probably be a great resource to understand the role of cognitive decline in attentional processes impairment leading to VH.

**AUTONOMIC DYSFUNCTION**

Currently, it is believed that dysautonomia may herald the onset of Parkinson´s disease (Fereshtehnejad and Lökk., 2014) and may be as disabling as the motor symptoms in early stages of the disease (Chaudhuri *et al.,* 2009).

Previous studies have shown an association between autonomic dysfunction and visual hallucinations (Williams and Lees, 2005). Simple VH are rare or absent in

Parkinson´s disease, most of the time they are complex and kinematic (Onofrj *et al.*, 2007). This type of VH has been described secondary to lesions of the thalamus, striatocapsular regions and the rostral brainstem that also plays a role in the pathogenesis of dysautonomia (Benke, 2006). Unfortunately these regions are too small to be evaluated by FDG-PET (Arahata *et al*., 1999). Thus, further pathological studies in these areas will be required to clarify the role of brainstem in the pathogenesis of autonomic dysfunction and visual hallucinations in Parkinson's disease.

**SLEEP DISORDERS**

REM sleep behavior disorder (RBD) has been documented to precede idiopathic Parkinson´s disease in 3 to 13 years, but it can also occur concomitantly with the disease (Meral *et al.*, 2007). Sinforiani *et al.* have found that RBD in Parkinson´s disease can be considered as a risk factor of hallucinations and also of cognitive abnormalities. Neuronal loss in the brainstem, hypothalamus, thalamus and basal forebrain have been indicated as a possible cause since these regions are implicated in sleep-wake regulation and cognitive processes (Goldman *et al.*, 2014). Shared neurobiological substrates such as those concerning striatal and extra-striatal regions, including the limbic system and non-dopaminergic systems may underlie a possible association between RBD and visual hallucinations (Meral *et al*., 2007) that might reflect disturbed internal/external perception dependent on visual impairment and on dysfunction of the control system for rapid eye movement (REM) sleep (Onofrj *et al.*, 2007). REM sleep produces visual experiences theorically similar to those of hallucinating Parkinson´s disease which may be related to dysregulation of the inhibitory control of the ponto-geniculate-occipital system (Benke, 2006). Another theory supports that loss of serotonergic inhibition to the visual pathways from the raphe nuclei might lead to unrestrained excitatory cholinergic activity to the

visual cortices conducing to VH (Onofrj *et al.*, 2007). Notwithstanding, Meral *et al*, could not find significant association between RBD and VHs, since the percentages among patients with VH and RBD and those without RBD in their study were very similar. Despite some studies postulations about a possible relation between RBD and visual hallucinations, supportive evidence has not yet been consistent. This hypothesis needs to be strengthened through longitudinal evaluations (Sinforiani *et al.*, 2005).

## CONCLUSION AND FINAL REMARKS

This review focused on evidence for behavioral and neuroimaging correlates of visual manifestations of Parkinson´s disease, in particular those related with visual hallucinations. In fact, the large majority of the visual information processed in the brain escapes conscious control. This process combines an integration of relevant stimuli in time and space, arousing latter into consciousness. Any dysfunction in this vast neuronal network may lead to visual processing impairment and compensatory mechanisms with incorrect processing of the visual stimuli, leading to misperception or even VH. Poor fidelity of visual mapping is significant in influencing overall motor function, having a great impact in Parkinson´s disease patients' quality of life. Although not the focus of this review, this may occur even at the retinal level. Henceforth, correcting visual problems sooner as possible can significantly benefit PD patients. It is important that symptoms due to treatment adverse reactions might be distinguished from those due to the disease process itself. Distinguish Parkinson´s disease visual map deficits due to retinal impairment from those concerning higher order processing deficits is of great importance since many patients have visual impairment without retinal dysfunction and this would help framing the distinct patterns of degeneration that starts at a retinal or at a cortical level in Parkinson´s disease.

In general, MRI was largely exceeded by PET and SPECT imaging in the investigation of visual system impairment. Functional neuroimaging with dopaminergic tracers and FDG PET are possibly the best available approach to study disease progression in clinical trials of neuroprotection in Parkinson´s disease. Mapping of Population Receptive Visual Fields using fMRI could also be great to approach Parkinson´s disease patients with visual manifestations. Great progress in this field has been seen, still many findings remain unexplained. The existence of a variety of top-down

and bottom-up influences and their effect in the neuronal processing gives a lot of research questions and opportunities to future investigations. In other words, abnormal inhibitory modulation of center responses by surround fields may lead to abnormal visual contrast enhancement and disturbed visual function. Analyzing the pathways in which these process are affected can be performed through neuroimaging methods, bearing in mind that impairment ate different areas along the visual perception pathway may ultimately manifest as visual misperceptions and visual hallucinations. Overall, the aim of this review was to address possible brain changes associated with visual impairment and visual hallucinations. No specific associations were found, but generally, patients with hallucinations exhibited greater difficulty formulating spatial judgments and executive dysfunction characterized by working memory and set shifting difficulties. This way, visual discrimination may not be entirely determined by the visual cortex alone. The frontal lobe can enhance stimulus-related activity through top-down influences. Impairment in perception and visual attention might play a role in improper differentiation between relevant and irrelevant visual information and may lead to the appearance of VH. Also, patients with more severe basal ganglia dysfunction seem to have more predisposition for the development of VHs.

Future studies should address the impairment of the ventral and lateral extrastriate visual cortex in more detail. A combination of markers (dopaminergic and non-dopaminergic) would provide greater reliability for more specific understanding of Parkinson´s disease physiopathology and this could enlighten symptom modifying therapies. More and more studies are now being performed with other neurotransmitters such as acetylcholine and serotonin and this is a very promising approach since evidence has been accumulated of these pathways being involved in pre-motor symptoms. Right

now, we are in a progression stage in what neuroimaging Parkinson´s disease approach is concerned.

Dissecting underlying cerebral changes of visual manifestations is of great importance for better understanding the pathophysiology of the disease and with more evidence, innovative pharmacological disease modifying approaches may be explored.

In conclusion, the role of molecular imaging in illuminating models of pathophysiological dysfunction in Parkinson´s disease will definitely be an important research trend in the future. Nonetheless much of the current research is focused on visual hallucinations and, in the future, subtle aspects of visual processing impairment should also be considered.

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