Brain Imaging and Behavior (2019) 13:323–332
DOI 10.1007/s11682-017-9764-1

ADVANCES IN IMAGING (HADASSAH CONFERENCE)

Imaging behavioural complications of Parkinson's disease

Mikaeel Valli[1,2,3] · **Alexander Mihaescu**[1,2,3] · **Antonio P. Strafella**[1,2,3,4]

Published online: 30 August 2017

Abstract In addition to motor symptoms, behavioural complications are commonly found in patients with Parkinson's disease (PD). Behavioural complications, including depression, anxiety, apathy, impulse control disorder and psychosis, together have a large impact on PD patient's quality of life. Many neuroimaging studies using PET, SPECT and MRI techniques have been conducted to study the underlying neural mechanisms of PD pathogenesis and pathophysiology in relation to its behavioural complications. This review will survey these PET, SPECT and MRI studies to describe the current understanding of the neurochemical, functional and structural changes associated with behavioural complications in PD patients.

Keywords Parkinson's disease · Neuroimaging · Depression · Apathy · Impulse control disorder · Psychosis

✉ Antonio P. Strafella
antonio.strafella@uhn.ca; antonio.strafella@camh.ca

1 Research Imaging Centre, Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, University of Toronto, Toronto, ON, Canada

2 Division of Brain, Imaging and Behaviour – Systems Neuroscience, Krembil Research Institute, UHN, University of Toronto, Toronto, ON, Canada

3 Institute of Medical Science, University of Toronto, Toronto, ON, Canada

4 Morton and Gloria Shulman Movement Disorder Unit & E.J. Safra Parkinson Disease Program, Neurology Division, Department of Medicine, Toronto Western Hospital, UHN, University of Toronto, Toronto, ON, Canada

Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative disorders. Globally, PD becomes more prevalent with age: 428 per 100,000 people between ages 60 to 69 years have the disease compared to 1087 per 100,000 people between ages 70 to 79 years, an increase of 154% (Pringsheim et al. 2014). PD is a debilitating disorder characterized typically by its motor symptoms including tremor, rigidity, slowness of movement and postural instability (Jankovic 2008). However, coupled with these motor symptoms are behavioural complications including depression, anxiety, apathy, impulse control disorder and psychosis (Schneider et al. 2008). It is estimated that upwards of 60% of PD patients suffer from at least one behavioural complication (Riedel et al. 2008; Schneider et al. 2008).

The classic underlying feature of PD is the gradual loss of midbrain neurons within the substantia nigra towards to the striatum, leading to a significant deficit of the neurotransmitter dopamine in the brain (Hirsch et al. 1988). However, through reviews of the literature of PD (Tang and Strafella 2012) and PD with dementia (Gratwicke et al. 2015), it has been recently established that the effects of PD are not localized to specific brain regions and instead have far-reaching effects on the whole brain. The Braak staging classification model describes this widespread progressive degeneration where the pathophysiological changes first occur in the olfactory bulb and medulla oblongata, then spread rostrally towards the brainstem, affecting the raphe nucleus, locus ceruleus, and the reticular zone (Braak et al. 2004). In later stages of disease progression, neocortical regions of the brain begin to degenerate as well (Braak et al. 2004). The primary understanding of the pathophysiology of non-motor symptoms is based on the basal ganglia-thalamocortical circuitry model. This model contains closely linked loop circuits involving the basal ganglia, thalamus and cortices that are grouped together into motor, cognitive, associative, orbitofrontal and limbic loops (Tang and Strafella 2012). Neuro-chemical changes also play a role in giving rise to the non-motor symptoms (Tang and Strafella 2012) and behavioural symptoms are a critical part of PD disease pathology.

The behavioural symptoms of PD are both very distressing and widespread in the patient population (Schneider et al. 2008). Depression is one of the most common non-motor symptoms in PD, occurring in 30–40% of PD patients (Cummings and Masterman 1999; Kano et al. 2011), causing a loss of pleasure and anhedonia (Antonelli et al. 2010). Anxiety is also pervasive and occurs in 31% of PD patients, with general anxiety disorder and phobia being common symptoms (Broen et al. 2016). Depression and anxiety often co-occur, possibly due to similar underlying pathophysiology, with 14% of PD patients reporting both depression and anxiety (Dissanayaka et al. 2010). Apathy is another common behavioural complication which is characterized by reduced interest and motivation in goal-directed behaviours, indifference towards daily tasks and lack of emotional responsiveness (Aarsland et al. 2009). Apathy occurs in up to 65% of PD patients and often co-occurs with depression in 14% of PD patients (Tang and Strafella 2012). In addition to the mood disorders that emerge, PD patients also report psychosis and especially visual hallucinations (Aarsland et al. 2009). Fifty percent of PD patients have some form of visual hallucination ranging from mild to severe (Aarsland et al. 2009). Another behavioural complication that can arise in 30% of the PD patients is impulse control disorder (Antonini et al. 2017). Impulse control disorder manifests in PD patients either through excessive gambling, compulsive sexual behaviour, compulsive shopping or binge-eating (Ray and Strafella 2010). The behavioural complications may not only arise from the PD pathology, but also from the treatments used to manage patients' motor symptoms. The treatments include either dopaminergic medication to increase dopamine levels or deep brain stimulation (DBS) of the subthalamic nucleus (STN) to reduce dopamine receptor stimulation. The side effects of medications can lead to depression, anxiety and impulse control disorder (Tang and Strafella 2012). DBS of the STN has shown to be associated with the dopamine agonist withdrawal syndrome, a syndrome that frequently includes apathy along with depression and anxiety as symptoms (Tang and Strafella 2012; Thobois et al. 2010). These behavioural symptoms greatly reduce the quality of life of PD patients and investigators and clinicians must remain cognizant of their impact.

Neuroimaging techniques allow an in vivo investigation of the underlying neural mechanisms of PD pathogenesis and pathophysiology in relation to the behavioural complications. This paper will review the current neuroimaging literature in regards to understanding the neuro-chemical, functional and structural changes associated with behavioural complications of depression, anxiety, apathy, impulse control disorder and psychosis in PD patients. It will focus on studies performed through positron emission tomography (PET), single-photon emission computed tomography (SPECT) and magnetic resonance imaging (MRI) modalities to explore this emerging topic of PD research.

Neuroimaging of PD patients with depression and anxiety

PET and SPECT imaging studies examining depression (dPD) and anxiety in PD patients have shown some overlap in neuro-chemical changes when compared to healthy controls and PD patients without depression or anxiety. Studies performed using radiotracers have found dysfunction of dopamine receptors (Joutsa et al. 2013), transporters and presynaptic dopamine (Antonelli et al. 2010). In dPD patients, SPECT studies have shown inverse relationships between depression score and symptoms with dopamine transporter availability in the left cingulate cortex (Frosini et al. 2015), right caudate nucleus (Vriend et al. 2014b) and left caudate (Di Giuda et al. 2012). However, a different SPECT study examining dPD patients has shown a positive relationship between depression score and dopamine transporter availability in the striatum (Ceravolo et al. 2013), while another found increased transporter density in the left caudate and right putamen compared to non-dPD patients (Felicio et al. 2010). Similarly for PD patients with anxiety, SPECT studies tracking dopamine transporters found a negative correlation—lower dopamine transporter levels in the striatum as anxiety score increased (Erro et al. 2012; Picillo et al. 2017). However, other studies have instead shown a positive correlation between dopamine transporter levels and anxiety scores in the striatum (Ceravolo et al. 2013), putamen and the left caudate (Moriyama et al. 2011). In addition to dopaminergic changes, there is also a dysfunction of the serotonergic system in dPD patients. Using [^{18}F]MPPF, a selective serotonin 1A receptor antagonist, the investigators found reduced uptake of the radiotracer in the limbic system—which included the left hippocampus, right insula, superior temporal cortex and orbitofrontal cortex (Ballanger et al. 2012). The binding of [^{11}C]-DASB, a radiotracer tracking serotonin transporter availability, was elevated alongside increasing depression symptom scores in the limbic system including the amygdala and hypothalamus (Politis et al. 2010)—possibly suggesting a presynaptic dysfunction of serotonin. Other brain networks are also affected in dPD patients, with one study finding increased brain perfusion in the left cuneus as well as reductions in brain perfusion in the right superior temporal gyrus, right medial superior temporal gyrus, medial orbitofrontal cortex. Furthermore, dPD also showed reduced perfusions in the limbic region including the anterior cingulate cortex, amygdala, hippocampus, and parahippocampal gyrus (Kim et al. 2016). Along with the serotonergic, dopaminergic and brain perfusion changes in dPD, an increase in glucose metabolism was also found, especially within the amygdala (Huang et al. 2013). Furthermore, Huang and colleagues (2013) found that PD patients with increasing severity of anxiety had decreasing caudate metabolism. The dysregulation of dopamine and serotonin in PD patients is believed to play an integral role in the development of behavioural symptoms.

Structural imaging also provides invaluable insight of PD patients with depression and anxiety through the use of MRI studies. Through voxel-based morphometry, dPD showed regions of white matter loss within the right frontal lobe including the anterior cingulate bundle and the inferior orbitofrontal region relative to non-dPD and healthy controls (Kostic et al. 2010). In another study using surface-based morphometry, they found increased cortical areas in the orbitofrontal region and insula in dPD compared to non-dPD—which implicates white matter loss in these areas (Huang et al. 2016). Luo et al. (2016) observed that with increasing depression scores, there was a decreasing cortical thickness in the left prefrontal cortex. A study examining mild dPD patients showed that these patients had an intact hippocampus, uncinate fasciculus and corpus callusum but atrophied amygdala (Surdhar et al. 2012). However with increasing depression, the volumes of the hippocampus was also reduced (van Mierlo et al. 2015). There was also a negative correlation in PD patients with anxiety and amygdala volume size (Vriend et al. 2016). Within the basal ganglia and periventricular regions, white matter hyperintensities were found to be higher in dPD patients compared to non-dPD patients and controls (Petrovic et al. 2012). Together, these studies strongly suggest the role of gray and white matter changes in causing the behavioural symptoms in PD patients.

Coupled with structural changes are functional changes that contribute to the depressive complications in PD patients. There have been no studies which have explored the functional connectivity of PD patients with anxiety. Recent studies found that functional connectivity was reduced between the right amygdala and fronto-parietal areas—including the orbitofrontal gyrus, left gyrus rectus and right putamen in dPD patients (Hu et al. 2015; Huang et al. 2015). The functional connectivity within the prefrontal-limbic system was also shown to be decreased (Sheng et al. 2014), while increased connectivity was observed from the bilateral anterior insula and posterior orbitofrontal cortices to the right basal ganglia in dPD patients (Liang et al. 2016). While completing a task-based fMRI study, dPD patients on dopaminergic medication showed decreased activation in the ventromedial prefrontal cortex, however, non-dPD patients showed an increased deactivation in the same region while off the dopaminergic medication (Andersen et al. 2015). Using mirrored homotopic connectivity approach, investigators found a greater inter-hemispheric desynchronized connectivity between the right and left dorsal lateral prefrontal cortices and the calcarine cortices in depressed compared to non-dPD patients (Zhu et al. 2016) suggesting atypical connectivity in the brains of PD patients.

The method known as "amplitude of low frequency fluctuations" (ALFF), which indexes the blood-oxygen levels dependent (BOLD) through functional MRI (fMRI), has been used in dPD patients to detect the spontaneous neural activity within the brain (Huang et al. 2015). Through ALFF, a recent study found that increasing depression scores in PD patients resulted in greater hyperactivity in the left amygdala (Huang et al. 2015). This finding was consistent with a PET study that demonstrated increased glucose consumption within the amygdala of dPD patients (Huang et al. 2013). Compared to non-dPD patients, dPD patients showed an increase in spontaneous activity within the orbitofrontal regions (Luo et al. 2014). However, there was a decrease in spontaneous activity in the dorsolateral prefrontal cortex, ventral medial prefrontal cortex and rostral anterior cingulate cortex (Wen et al. 2013), which could explain the reduced functional connectivity in the prefrontal-limbic network (Luo et al. 2014). "Complementary ensemble empirical mode decomposition" (CEEMD) is an adaptive time–frequency analysis of fMRI data and has been used to study dPD patients (Song et al. 2015). With this method, reduction in the efficiency of nodes within the basal ganglia network was observed in dPD compared to non-dPD patients (Qian et al. 2016). The fMRI band signals were also found to be associated with motor and depressive symptoms within certain brain regions in PD patients (Song et al. 2015). Both depression and anxiety have substantial support for their importance in PD pathology, however the nature of their etiology remains unclear.

In summary, many neuroimaging techniques have been applied to delineate the underlying neural substrates especially for dPD and to a lesser extent for PD patients with anxiety. The results from these studies indicates no uniform model for the neuropathology of dPD or PD with anxiety, but rather a wide-range of potential causes that includes the dysregulation of the cortico-limbic and nigrostriatal pathways. However, despite the pervasiveness of anxiety in the PD population, neuroimaging in this area is under-studied. Hence, there is a need for further exploration to better elucidate the underlying pathology of PD with anxiety using different imaging modalities including, PET, fMRI and different MRI sequences including diffusion tensor imaging (DTI).

Neuroimaging of PD patients with apathy

Converging evidence from PET imaging studies have shown dysfunction of both the dopaminergic and serotonergic systems in PD patients with apathy (aPD). A PET study using radiotracers tracked dopamine and serotonin presynaptic transporters [^{11}C]-PE2I and [^{11}C]-DASB respectively. The study found widespread dopaminergic and serotonergic degeneration in aPD patients in the bilateral caudate nuclei, putamen, ventral striatum, pallidum and thalamus. Serotoninergic disruption in aPD was specifically found within the limbic regions, including the insula, orbitofrontal and subgenual anterior cingulate cortices. Dopaminergic abnormalities were observed in the substantia nigra–ventral tegmental area complex (Maillet et al. 2016). In a recent SPECT study, aPD patients showed reduced striatal dopamine transporter density compared PD patients without apathy (Santangelo et al. 2015). With increasing apathy severity in PD patients, there is a decreasing performance on the emotional facial recognition task. This study found that the apathy network was associated with an increase of glucose metabolism within the left posterior cingulate cortex. Conversely, emotional facial recognition network was associated with decreases in metabolic activity within the bilateral posterior cingulate gyrus, right superior frontal gyrus and left superior frontal gyrus (Robert et al. 2014). PD patients with apathy showed diminished response in the amygdala, ventral medial prefrontal cortex, striatum and midbrain which are brain regions critical for representation of reward value and goal-directed behaviour (Lawrence et al. 2011). Similarly, PD patients that became apathetic following STN DBS had impaired glucose levels prior to DBS in several limbic regions including the insula, amygdala, subgenual anterior cingulate and inferior frontal gyrus (Gesquière-Dando et al. 2015) suggesting certain PD patient groups are more susceptible to acquiring aPD.

There are many structural and functional changes that occur in aPD patients. Using ALFF, a study found increased regional response in the middle orbital gyrus and subgenual cingulate, but also found decreased BOLD activity in the supplementary motor region, inferior parietal lobule and fusiform gyrus in aPD patients (Skidmore et al. 2013). Apathetic PD patients showed lower functional connectivity primarily within the left-sided circuits including the limbic, striatal and frontal regions (Baggio et al. 2015). Structural atrophy was observed within the nucleus accumbens (Carriere et al. 2014), caudate nucleus (Carriere et al. 2014; Martinez-Horta et al. 2016) and several cortical regions including the precentral gyrus, inferior parietal gyrus, inferior frontal gyrus, insula, right posterior cingulate gyrus and right precuneus in aPD patients (Reijnders et al. 2010). In addition, a recent study showed reduced gray matter volume in the left inferior, middle and medial frontal gyrus, right anterior cingulate and the left superior temporal gyrus (Alzahrani et al. 2016).

Results from neuroimaging studies of aPD patients indicates the involvement of both structural and functional changes in the frontal, limbic and striatal areas of the brain, along with both dopaminergic and serotonergic dysfunction. Although aPD is better studied compared to PD with anxiety, there are still knowledge gaps in the pathology to address at the network level, with a need to identify clusters of brain regions critical for aPD through more advanced neuroimaging analysis such as graph-theory.

Neuroimaging of PD patients with impulse control disorder

Impulse control disorders in PD patients (ICD-PD) have been shown to be due to dopaminergic dysfunction especially within areas of the limbic and ventral striatum—regions associated with decision making and reward behaviours (Cerasa et al. 2014). PD patients are at a higher risk for experiencing ICD symptoms when patients at untreated baseline have lower dopamine transporter availability in the right caudate (Smith et al. 2016). Furthermore, the ICD symptom severity correlated negatively with untreated baseline dopamine transporter availability in the right ventral and anterior-dorsal striatum (Vriend et al. 2014a). An increased ventral striatal dopamine release has been observed in ICD-PD patients compared to non-ICD-PD patients in response to reward cues and gambling tasks (O'Sullivan et al. 2011; Steeves et al. 2009; Wu et al. 2015). ICD-PD patients have been observed to have a D3 dopamine receptor reduction (Payer et al. 2015) as well as reductions of the dopamine transporter within the ventral striatum (Cilia et al. 2010; Lee et al. 2014) and bilateral striatum (Voon et al. 2014). In ICD-PD patients with pathological gambling addiction, an abnormal binding potential of the extrastriatal D2 dopamine receptors was found in the anterior cingulate cortex (Ray et al. 2012). These dopaminergic changes were paralleled by reduced activity within the control inhibitory networks, which included the lateral orbitofrontal cortex, rostral cingulate region, amygdala, and external pallidum (Van Eimeren et al. 2010). When ICD-PD patients were tasked with making riskier choices, there was a decreased activity within the orbitofrontal cortex, anterior cingulate cortex (Voon et al. 2011) and right ventral striatum (Rao et al. 2010; Voon et al. 2011). However, when PD patients diagnosed with pathological gambling viewed gambling-related visual cues, there was an increase of activity in the ventral striatum, anterior cingulate cortex, medial and superior frontal gyri, precuneus and the right inferior parietal lobule (Frosini et al. 2010). PD patient gamblers show a disconnection between anterior cingulate cortex and cingulate gyrus. Gambling severity was associated with a dysfunction of the brain network implicated in decision making, risk processing, and response inhibition, including the ventrolateral prefrontal cortex, anterior and posterior cingulate cortex, medial prefrontal cortex, insula and striatum, as observed through brain perfusion SPECT (Cilia et al. 2011). During resting state functional imaging, ICD-PD patients showed decreased functional connectivity between the striatal regions, including the left anterior putamen, and the limbic system, including the left inferior temporal gyrus and left anterior cingulate gyrus (Carriere et al. 2015). Another study using SPECT to index cerebral perfusion in PD patients with pathological gambling found resting state overactivity in regions within the right hemisphere including the orbitofrontal cortex, hippocampus, amygdala, insula, and the ventral pallidum (Cilia et al. 2008). In PD patients without ICD performing a delay discounting task, dopamine agonists increased impulsive choices, and activated the medial prefrontal cortex and posterior cingulate cortex but reduced activation in the ventral striatum (Antonelli et al. 2014), suggesting that normal activation of these cortical regions may prevent the manifestation of ICD-PD.

Structural changes were observed through MRI in PD patients that gave rise to ICD compared to PD patients without ICD. With increasing gambling symptoms in PD patients, there was an increase in gray matter loss in the orbitofrontal cortex and reduced degrees of gyri folding in this region (Cerasa et al. 2014). Similarly, the cortical thickness examined in ICD-PD patients found thinning in the frontal striatal circuitry, specifically the right superior orbitofrontal, left rostral middle frontal, bilateral caudal middle frontal region and corpus callosum (Biundo et al. 2015). Conversely, two studies showed increasing cortical thickness in ICD-PD patients within the anterior cingulate cortex (Pellicano et al. 2015; Tessitore et al. 2016), frontal pole (Pellicano et al. 2015) and orbitofrontal cortices (Tessitore et al. 2016) compared to non-ICD-PD patients. The white matter tract integrity in the reward-related behaviour regions were shown to also be affected in ICD-PD patients compared to non-ICD-PD patients (Yoo et al. 2015).

Neuroimaging of ICD-PD patients has shown network dysregulation mainly within the striatal and limbic brain regions. Neuroimaging studies suggest dopaminergic dysfunction to be the underlying pathology of ICD-PD, however, it remains unclear if other neurotransmitter systems such as the serotonergic network are also involved. Additional functional imaging studies are needed to better understand the complex interactions between various neural networks. In addition to using molecular imaging to explore other neuro-chemical systems, there is a need for more studies to elucidate the conflicting results found in the structural changes of ICD-PD, with some studies showing increased cortical thickness in some brain regions while others show decreased cortical thickness in the same region.

Neuroimaging of PD patients with visual hallucinations

A common form of psychosis experienced by PD patients is visual hallucination (VH-PD) which is shown to be associated with significant neurochemical abnormalities. A PET study with VH-PD patients found increased serotonin 2A receptor binding in the ventral visual pathway which includes the bilateral inferior-occipital gyrus, right fusiform gyrus, inferior-temporal cortex and prefrontal regions (Ballanger et al. 2010). These serotonergic changes occur alongside reduced glucose metabolic activity within the ventral visual pathway, including the inferior and middle temporal cortex, fusiform gyrus and frontal regions (Park et al. 2013). In VH-PD patients with cognitive impairment, studies have confirmed a reduced glucose metabolic activity within the frontal, temporal, parietal (Gasca-Salas et al. 2016; Park et al. 2013) and occipital regions (Gasca-Salas et al. 2016).

Structural changes were also observed in the gray and white matter of VH-PD patients compared to non-VH-PD patients and healthy controls. The data however is more inconsistent in this topic. A study found no differences in gray matter volume between VH-PD and non-VH-PD patients (Meppelink et al. 2011), while other studies found regions within the limbic system and mesolimbic system showing gray matter atrophy (Gama et al. 2014; Goldman et al. 2014; Ibarretxe-Bilbao et al. 2011; Shin et al. 2012). The atrophy in VH-PD was shown to extend to the right parahippocampal gyrus, posterior cingulate gyrus, parietal lobe, primary and secondary visual cortex (Goldman et al. 2014; Watanabe et al. 2013). White matter degeneration in VH-PD patients was also found with higher diffusivity in the posterior hippocampus (Yao et al. 2016).

Functional changes have also been observed in VH-PD patients. An fMRI study found that when VH-PD patients viewed flashing light stimuli, there were increased activations in the superior and inferior frontal gyrus and caudate nucleus while reduced activation was seen in the visual cortices (Stebbins et al. 2004). A different study using face stimuli found that VH-PD patients showed a reduced activation in the right prefrontal regions including the inferior, superior, middle frontal, and anterior cingulate gyrus compared to non-PD-VH. However, when these patients viewed the control stimuli, hyperactivation was observed in the right inferior frontal gyrus relative to non-VH-PD patients (Ramírez-Ruiz et al. 2008). Shine et al. (2014) suggests that VH-PD patients may show decreased ability to recruit critical regions in the dorsal attention network, which includes the bilateral frontal eye fields, dorsolateral prefrontal cortex, superior parietal lobule, caudal midbrain, midline pre-supplementary motor area and the right parietal-occipital cortex. The connectivity of the dorsal attention network with the ventral attention network, including the anterior cingulate cortex and insula, was predicted to decrease based on the amount of misperceptions made in a behavioural paradigm that measures visual hallucinations and voluntary mental imagery (Shine et al. 2015). On the other hand, within the default mode network, functional connectivity was increased in VH-PD compared to non-VH-PD patients (Franciotti et al. 2015; Yao et al. 2014, 2016) leaving the role of brain connectivity in VH-PD unclear.

Metabolic, structural and functional changes were observed in VH-PD patients mainly within the frontal, limbic and visual brain regions. Contrary to PD patient motor symptoms and ICD-PD, neuroimaging studies suggest serotonergic dysfunction to be the underlying pathology of VH-PD. It is unclear whether the neuropathology of VH-PD is also associated with dopaminergic changes and exploration into this area would be needed. Given that functional imaging studies have shown the recruitment of the default mode, dorsal and ventral attention network, future studies should use more advanced imaging analysis including graph theory to possibly identify clusters of brain regions critically involved in VH-PD. In the similar vain, using multiple structural and functional neuroimaging modalities may help elucidate the discrepancies observed with structural changes associated with VH-PD.

Conclusions

Neuroimaging studies including PET, SPECT and MRI have provided a deeper understanding of the pathophysiology of behavioural complications in PD patients. However, many unanswered questions remain regarding the interaction of different neural networks and how their dysregulation causes these distressing symptoms. The lack of functional connectivity studies on anxiety in PD is a glaring omission in the understanding of the disease symptoms. Additionally, future studies of the behavioural symptoms of PD should incorporate concepts of modern neuroimaging including graph-theory analysis which may help to identify important behavioural hubs in the brain. An integrated approach that includes other neuroimaging techniques is a promising future venture to provide new ways to understand the complex pathology of PD.

Acknowledgements This work was supported by Canadian Institutes of Health Research (MOP 136778). A.P.S is supported by the Canada Research Chair program.

Compliance with ethical standards

Conflict of interest MV, AM and APS declare that they have no conflict of interest.

Human and animal rights and informed consent This article does not contain any studies with human participants or animals performed by any of the authors.

References

Aarsland, D., Marsh, L., & Schrag, A. (2009). Neuropsychiatric symptoms in Parkinson's disease. *Movement Disorders, 24*(15), 2175–2186. https://doi.org/10.1002/mds.22589.Neuropsychiatric.

Alzahrani, H., Antonini, A., & Venneri, A. (2016). Apathy in Mild Parkinson's disease: neuropsychological and neuroimaging evidence. *Journal of Parkinson's Disease, 6*(4), 821–832. https://doi.org/10.3233/JPD-160809.

Andersen, A. H., Smith, C. D., Slevin, J. T., Kryscio, R. J., Martin, C. A., Schmitt, F. A., & Blonder, L. X. (2015). Dopaminergic Modulation of medial prefrontal cortex deactivation in Parkinson depression. *Parkinson's Disease, 2015*. https://doi.org/10.1155/2015/513452.

Antonelli, F., Ko, J. H., Miyasaki, J., Lang, A. E., Houle, S., Valzania, F., Ray, N. J., & Strafella, A. P. (2014). Dopamine-agonists and impulsivity in Parkinson's disease: impulsive choices vs. impulsive actions. *Human Brain Mapping, 35*(6), 2499–2506. https://doi.org/10.1002/hbm.22344.

Antonelli, F., Ray, N., & Strafella, A. P. (2010). Imaging cognitive and behavioral symptoms in Parkinson's disease. *Expert Review of Neurotherapeutics, 10*(12), 1827–1838. https://doi.org/10.1586/ern.10.173.

Antonini, A., Barone, P., Bonuccelli, U., Annoni, K., Asgharnejad, M., & Stanzione, P. (2017). ICARUS study: prevalence and clinical features of impulse control disorders in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry, 88*(4), 317–324. https://doi.org/10.1136/jnnp-2016-315277.

Baggio, H. C., Segura, B., Garrido-Millan, J. L., Marti, M. J., Compta, Y., Valldeoriola, F., Tolosa, E., & Junque, C. (2015). Resting-state frontostriatal functional connectivity in Parkinson's disease-related apathy. *Movement Disorders, 30*(5), 671–679. https://doi.org/10.1002/mds.26137.

Ballanger, B., Klinger, H., Eche, J., Lerond, J., Vallet, A. E., Le Bars, D., Tremblay, L., Sgambato-Faure, V., Broussolle, E., & Thobois, S. (2012). Role of serotonergic 1A receptor dysfunction in depression associated with Parkinson's disease. *Movement Disorders, 27*(1), 84–89. https://doi.org/10.1002/mds.23895.

Ballanger, B., Strafella, A. P., van Eimeren, T., Zurowski, M., Rusjan, P. M., Houle, S., & Fox, S. H. (2010). Serotonin 2A receptors and visual hallucinations in Parkinson disease. *Archives of Neurology, 67*(4), 416–421. https://doi.org/10.1001/archneurol.2010.35.

Biundo, R., Weis, L., Facchini, S., Formento-Dojot, P., Vallelunga, A., Pilleri, M., ,Weintraub, D., & Antonini, A. (2015). Patterns of cortical thickness associated with impulse control disorders in Parkinson's disease. *Movement Disorders, 30*(5), 688–695. https://doi.org/10.1002/mds.26154.

Braak, H., Ghebremedhin, E., Rüb, U., Bratzke, H., & Del Tredici, K. (2004). Stages in the development of Parkinson's disease-related pathology. *Cell and Tissue Research, 318*(1), 121–134. https://doi.org/10.1007/s00441-004-0956-9.

Broen, M. P. G., Narayen, N. E., Kuijf, M. L., Dissanayaka, N. N. W., & Leentjens, A. F. G. (2016). Prevalence of anxiety in Parkinson's disease: a systematic review and meta-analysis. *Movement Disorders, 31*(8), 1125–1133. https://doi.org/10.1002/mds.26643.

Carriere, N., Besson, P., Dujardin, K., Duhamel, A., Defebvre, L., Delmaire, C., & Devos, D. (2014). Apathy in Parkinson's disease is associated with nucleus accumbens atrophy: a magnetic resonance imaging shape analysis. *Movement Disorders, 29*(7), 897–903. https://doi.org/10.1002/mds.25904.

Carriere, N., Lopes, R., Defebvre, L., Delmaire, C., & Dujardin, K. (2015). Impaired corticostriatal connectivity in impulse control disorders in Parkinson disease. *Neurology, 84*(21), 2116–2123. https://doi.org/10.1212/WNL.0000000000001619.

Cerasa, A., Salsone, M., Nigro, S., Chiriaco, C., Donzuso, G., Bosco, D., Vasta, R., & Quattrone, A. (2014). Cortical volume and folding abnormalities in Parkinson's disease patients with pathological gambling. *Parkinsonism and Related Disorders, 20*(11), 1209–1214. https://doi.org/10.1016/j.parkreldis.2014.09.001.

Ceravolo, R., Frosini, D., Poletti, M., Kiferle, L., Pagni, C., Mazzucchi, S., Volterrani, D., & Bonuccelli, U. (2013). Mild affective symptoms in de novo Parkinson's disease patients: relationship with dopaminergic dysfunction. *European Journal of Neurology, 20*(3), 480–485. https://doi.org/10.1111/j.1468-1331.2012.03878.x.

Cilia, R., Cho, S. S., van Eimeren, T., Marotta, G., Siri, C., Ko, J. H., Pellecchia, G., Pezzoli, G., Antonini, A., & Strafella, A. P. (2011). Pathological gambling in patients with Parkinson's disease is associated with fronto-striatal disconnection: a path modeling analysis. *Movement Disorders, 26*(2), 225–233. https://doi.org/10.1002/mds.23480.

Cilia, R., Ko, J. H., Cho, S. S., van Eimeren, T., Marotta, G., Pellecchia, G., Pezzoli, G., Antonini, A., & Strafella, A. P. (2010). Reduced dopamine transporter density in the ventral striatum of patients with Parkinson's disease and pathological gambling. *Neurobiology of Disease, 39*(1), 98–104. https://doi.org/10.1016/j.nbd.2010.03.013.

Cilia, R., Siri, C., Marotta, G., Isaias, I. U., De Gaspari, D., Canesi, M., Pezzoli, G., & Antonini, A. (2008). Functional abnormalities underlying pathological gambling in Parkinson disease. *Archives of Neurology, 65*(12), 1604–1611. https://doi.org/10.1001/archneur.65.12.1604.

Cummings, J., & Masterman, D. (1999). Depression in patients with Parkinson's disease. *International Journal of Geriatric Psychiatry, 14*(9), 711–718. https://doi.org/10.1002/(sici)1099-1166(199909)14:9<711::aid-gps4>3.0.co;2-1.

Di Giuda, D., Camardese, G., Bentivoglio, A. R., Cocciolillo, F., Guidubaldi, A., Pucci, L., Bruno, I., Janiri, L., Giordano, A., & Fasano, A. (2012). Dopaminergic dysfunction and psychiatric symptoms in movement disorders: a 123I-FP-CIT SPECT study. *European Journal of Nuclear Medicine and Molecular Imaging, 39*(12), 1937–1948. https://doi.org/10.1007/s00259-012-2232-7.

Dissanayaka, N. N. W., Sellbach, A., Matheson, S., O'Sullivan, J. D., Silburn, P. A., Byrne, G. J., Marsh, R., & Mellick, G. D. (2010). Anxiety disorders in Parkinson's disease: prevalence and risk factors. *Movement Disorders, 25*(7), 838–845. https://doi.org/10.1002/mds.22833.

Erro, R., Pappatà, S., Amboni, M., Vicidomini, C., Longo, K., Santangelo, G., Picillo, M., Vitale, C., Moccia, M., Giordano, F., Brunetti, A., Pellecchia, M. T., Salvatore, M., & Barone, P. (2012). Anxiety is associated with striatal dopamine transporter availability in newly diagnosed untreated Parkinson's disease patients. *Parkinsonism and Related Disorders, 18*(9), 1034–1038. https://doi.org/10.1016/j.parkreldis.2012.05.022.

Felicio, A. C., Moriyama, T. S., Godeiro-Junior, C., Shih, M. C., Hoexter, M. Q., Borges, V., Silva, S. M., Amaro-Junior, E., Andrade, L. A., Ferraz, H. B., & Bressan, R. A. (2010). Higher dopamine transporter density in Parkinson's disease patients with depression. *Psychopharmacology, 211*(1), 27–31. https://doi.org/10.1007/s00213-010-1867-y.

Franciotti, R., Delli Pizzi, S., Perfetti, B., Tartaro, A., Bonanni, L., Thomas, A., Weis, L., Biundo, R., Antonini, A., & Onofrj, M. (2015). Default mode network links to visual hallucinations: a comparison between Parkinson's disease and multiple system atrophy. *Movement Disorders, 30*(9), 1237–1247. https://doi.org/10.1002/mds.26285.

Frosini, D., Pesaresi, I., Cosottini, M., Belmonte, G., Rossi, C., Dell'Osso, L., Murri, L., Bonuccelli, U., & Ceravolo, R. (2010). Parkinson's disease and pathological gambling: results from a functional MRI study. *Movement Disorders, 25*(14), 2449–2453. https://doi.org/10.1002/mds.23369.

Frosini, D., Unti, E., Guidoccio, F., Del Gamba, C., Puccini, G., Volterrani, D., Bonuccelli, U., & Ceravolo, R. (2015). Mesolimbic dopaminergic dysfunction in Parkinson's disease depression: evidence from a 123I-FP-CIT SPECT investigation. *Journal of Neural Transmission, 122*(8), 1143–1147. https://doi.org/10.1007/s00702-015-1370-z.

Gama, R. L., Bruin, V. M. S., Távora, D. G. F., Duran, F. L. S., Bittencourt, L., & Tufik, S. (2014). Structural brain abnormalities in patients with Parkinson's disease with visual hallucinations: a comparative voxel-based analysis. *Brain and Cognition, 87*(1), 97–103. https://doi.org/10.1016/j.bandc.2014.03.011.

Gasca-Salas, C., Clavero, P., García-García, D., Obeso, J. A., & Rodríguez-Oroz, M. C. (2016). Significance of visual hallucinations and cerebral hypometabolism in the risk of dementia in Parkinson's disease patients with mild cognitive impairment. *Human Brain Mapping, 37*(3), 968–977. https://doi.org/10.1002/hbm.23080.

Gesquière-Dando, A., Guedj, E., Loundou, A., Carron, R., Witjas, T., Fluchère, F., Delfini, M., Mundler, L., Regis, J., Azulay, J. P., & Eusebio, A. (2015). A preoperative metabolic marker of parkinsonian apathy following subthalamic nucleus stimulation. *Movement Disorders, 30*(13), 1767–1776. https://doi.org/10.1002/mds.26349.

Goldman, J. G., Stebbins, G. T., Dinh, V., Bernard, B., Merkitch, D., Detoledo-Morrell, L., & Goetz, C. G. (2014). Visuoperceptive region atrophy independent of cognitive status in patients with Parkinson's disease with hallucinations. *Brain, 137*(3), 849–859. https://doi.org/10.1093/brain/awt360.

Gratwicke, J., Jahanshahi, M., & Foltynie, T. (2015). Parkinson's disease dementia: a neural networks perspective. *Brain, 138*(6), 1454–1476. https://doi.org/10.1093/brain/awv104.

Hirsch, E., Graybiel, A. M., & Agid, Y. A. (1988). Melanized dopaminergic neurons are differentially susceptible to degeneration in Parkinson's disease. *Nature, 334*(6180), 345–348. https://doi.org/10.1038/334345a0.

Hu, X., Song, X., Yuan, Y., Li, E., Liu, J., Liu, W., & Liu, Y. (2015). Abnormal functional connectivity of the amygdala is associated with depression in Parkinson's disease. *Movement Disorders, 30*(2), 238–244. https://doi.org/10.1002/mds.26087.

Huang, C., Ravdin, L., Nirenberg, M., Piboolnurak, P., Severt, L., Maniscalco, J., Solnes, L., Dorfman, B. J., & Henchcliffe, C. (2013). Neuroimaging markers of motor and nonmotor features of Parkinson's disease: an [18F]fluorodeoxyglucose positron emission computed tomography study. *Dementia and Geriatric Cognitive Disorders, 35*(3–4), 183–196. https://doi.org/10.1159/000345987.

Huang, P., Lou, Y., Xuan, M., Gu, Q., Guan, X., Xu, X., Song, Z., Luo, W., & Zhang, M. (2016). Cortical abnormalities in Parkinson's disease patients and relationship to depression: a surface-based morphometry study. *Psychiatry Research: Neuroimaging, 250*, 24–28. https://doi.org/10.1016/j.pscychresns.2016.03.002.

Huang, P., Xuan, M., Gu, Q., Yu, X., Xu, X., Luo, W., & Zhang, M. (2015). Abnormal amygdala function in Parkinson's disease patients and its relationship to depression. *Journal of*

Affective Disorders, 183, 263–268. https://doi.org/10.1016/j.jad.2015.05.029.

Ibarretxe-Bilbao, N., Junque, C., Marti, M. J., & Tolosa, E. (2011). Cerebral basis of visual hallucinations in Parkinson's disease: structural and functional MRI studies. *Journal of the Neurological Sciences, 310*(1–2), 79–81. https://doi.org/10.1016/j.jns.2011.06.019.

Jankovic, J. (2008). Parkinson's disease: clinical features and diagnosis. *Journal of Neurology, Neurosurgery & Psychiatry, 79*(4), 368–376. https://doi.org/10.1136/jnnp.2007.131045.

Joutsa, J., Rinne, J., Eskola, O., & Kaasinen, V. (2013). Movement activation and inhibition in Parkinson's disease: a functional imaging study. *Journal of Parkinson's Disease, 3*(3), 325–329. https://doi.org/10.3233/JPD-130205.

Kano, O., Ikeda, K., Cridebring, D., Takazawa, T., Yoshii, Y., & Iwasaki, Y. (2011). Neurobiology of depression and anxiety in Parkinson's disease. *Parkinson's Disease, 2011*, 143547. https://doi.org/10.4061/2011/143547.

Kim, Y.-D., Jeong, H. S., Song, I.-U., Chung, Y.-A., Namgung, E., & Kim, Y.-D. (2016). Brain perfusion alterations in depressed patients with Parkinson's disease. *Annals of Nuclear Medicine, 30*(10), 731–737. https://doi.org/10.1007/s12149-016-1119-2.

Kostic, V. S., Agosta, F., Petrovic, I., Galantucci, S., Spica, V., Jecmenica-Lukic, M., & Filippi, M. (2010). Regional patterns of brain tissue loss associated with depression in Parkinson disease. *Neurology, 75*(10), 857–863. https://doi.org/10.1212/WNL.0b013e3181f11c1d.

Lawrence, A. D., Goerendt, I. K., & Brooks, D. J. (2011). Apathy blunts neural response to money in Parkinson's disease. *Social Neuroscience, 6*(5–6), 653–662. https://doi.org/10.1080/17470919.2011.556821.

Lee, J.-Y., Seo, S. H., Kim, Y. K., Yoo, H.B., Kim, Y. E., Song, I. C., Lee, J. S., & Jeon, B. S. (2014). Extrastriatal dopaminergic changes in Parkinson's disease patients with impulse control disorders. *Journal of Neurology, Neurosurgery & Psychiatry, 85*(1), 23–30. https://doi.org/10.1136/jnnp-2013-305549.

Liang, P., Deshpande, G., Zhao, S., Liu, J., Hu, X., & Li, K. (2016). Altered directional connectivity between emotion network and motor network in Parkinson's disease with depression. *Medicine, 95*(30), 1–9. https://doi.org/10.1097/MD.0000000000004222.

Luo, C., Chen, Q., Song, W., Chen, K., Guo, X., Yang, J., Huang, X., Gong, Q., & Shang, H.-F. (2014). Resting-state fMRI study on drug-naive patients with Parkinson's disease and with depression. *Journal of Neurology, Neurosurgery & Psychiatry, 85*, 675–683. https://doi.org/10.1136/jnnp-2013-306237.

Luo, C., Song, W., Chen, Q., Yang, J., Gong, Q., & Shang, H.-F. (2016). Cortical thinning in drug-naïve Parkinson's disease patients with depression. *Journal of Neurology, 263*(10), 2114–2119. https://doi.org/10.1007/s00415-016-8241-x.

Maillet, A., Krack, P., Lhommée, E., Météreau, E., Klinger, H., Favre, E., Le Bars, D., Schmitt, E., Bichon, A., Pelissier, P., Fraix, V., Castrioto, A., Sgambato-Faure, V., Broussolle, E., Tremblay, L., & Thobois, S. (2016). The prominent role of serotonergic degeneration in apathy, anxiety and depression in de novo Parkinson's disease. *Brain, 139*(Pt 9), 2486–2502. https://doi.org/10.1093/brain/aww162.

Martinez-Horta, S., Sampedro, F., Pagonabarraga, J., Fernandez-Bobadilla, R., Marin-Lahoz, J., Riba, J., & Kulisevsky, J. (2016). Non-demented Parkinson's disease patients with apathy show decreased grey matter volume in key executive and reward-related nodes. *Brain Imaging and Behavior*, 1–9. https://doi.org/10.1007/s11682-016-9607-5.

Meppelink, A., de Jong, B., Teune, L., & van Laar, T. (2011). Regional cortical grey matter loss in Parkinson's disease without dementia is independent from visual hallucinations. *Movement Disorders, 26*(1), 142–147. https://doi.org/10.1002/mds.23375.

Moriyama, T. S., Felicio, A. C., Chagas, M. H. N., Tardelli, V. S., Ferraz, H. B., Tumas, V., Amaro-Junior, E., Andrade, L. A., Crippa, J. A., & Bressan, R. A. (2011). Increased dopamine transporter density in Parkinson's disease patients with social anxiety disorder. *Journal of the Neurological Sciences, 310*(1–2), 53–57. https://doi.org/10.1016/j.jns.2011.06.056.

O'Sullivan, S. S., Wu, K., Politis, M., Lawrence, A. D., Evans, A. H., Bose, S. K., Djamshidian, A., Lees, A. J., & Piccini, P. (2011). Cue-induced striatal dopamine release in Parkinson's disease-associated impulsive-compulsive behaviours. *Brain, 134*(4), 969–978. https://doi.org/10.1093/brain/awr003.

Park, H., Kim, J., Im, K., Kim, M., Lee, J.-H., Lee, M., Kim, J., & Chung, S. (2013). Visual hallucinations and cognitive impairment in Parkinson's disease. *Canadian Journal of Neurological Sciences, 40*(5), 657–662. https://doi.org/10.1017/S0317167100014888.

Payer, D. E., Guttman, M., Kish, S. J., Tong, J., Strafella, A., Zack, M., Adams, J. R., Rusjan, P., Houle, S., Furukawa, Y., Wilson, A. A., & Boileau, I. (2015). [11C]-(+)-PHNO PET imaging of dopamine D2/3 receptors in Parkinson's disease with impulse control disorders. *Movement Disorders, 30*(2), 160–166. https://doi.org/10.1002/mds.26135.

Pellicano, C., Niccolini, F., Wu, K., O'Sullivan, S. S., Lawrence, A. D., Lees, A. J., Piccini, P., & Politis, M. (2015). Morphometric changes in the reward system of Parkinson's disease patients with impulse control disorders. *Journal of Neurology, 262*(12), 2653–2661. https://doi.org/10.1007/s00415-015-7892-3.

Petrovic, I. N., Stefanova, E., Kozic, D., Semnic, R., Markovic, V., Daragasevic, N. T., & Kostic, V. S. (2012). White matter lesions and depression in patients with Parkinson's disease. *Journal of the Neurological Sciences, 322*(1–2), 132–136. https://doi.org/10.1016/j.jns.2012.07.021.

Picillo, M., Santangelo, G., Erro, R., Cozzolino, A., Amboni, M., Vitale, C., Barone, P., & Pellecchia, M. T. (2017). Association between dopaminergic dysfunction and anxiety in de novo Parkinson's disease. *Parkinsonism & Related Disorders, 37*, 106–110. https://doi.org/10.1016/j.parkreldis.2017.02.010.

Politis, M., Wu, K., Loane, C., Turkheimer, F. E., Molloy, S., Brooks, D. J., & Piccini, P. (2010). Depressive symptoms in PD correlate with higher 5-HTT binding in raphe and limbic structures. *Neurology, 75*(21), 1920–1927. https://doi.org/10.1212/WNL.0b013e3181feb2ab.

Pringsheim, T., Jette, N., Frolkis, A., & Steeves, T. D. L. (2014). The prevalence of Parkinson's disease: a systematic review and meta-analysis. *Movement Disorders, 29*(13), 1583–1590. https://doi.org/10.1002/mds.25945.

Qian, L., Zhang, Y., Zheng, L., Fu, X., Liu, W., Shang, Y., Zhang, Y., Xu, Y., Liu, Y., Zhu, H., & Gao, J.-H. (2016). Frequency specific brain networks in Parkinson's disease and comorbid depression. *Brain Imaging and Behavior, 11*(1), 1–16. https://doi.org/10.1007/s11682-016-9514-9.

Ramírez-Ruiz, B., Martí, M., Tolosa, E., Falcín, C., Bargallo, N., Valldeoriola, F., & Junque, C. (2008). Brain response to complex visual stimuli in Parkinson's patients with hallucinations: a functional magnetic resonance imaging study. *Movement Disorders, 23*(16), 2335–2343. https://doi.org/10.1002/mds.22258.

Rao, H., Mamikonyan, E., Detre, J. A., Siderowf, A. D., Stern, M. B., Potenza, M. N., & Weintraub, D. (2010). Decreased ventral striatal activity with impulse control disorders in parkinson's disease. *Movement Disorders, 25*(11), 1660–1669. https://doi.org/10.1002/mds.23147.

Ray, N., Miyasaki, J. M., Zurowski, M., Ko, J. H., Cho, S. S., Pellecchia, G., Antonelli, F., Houle, S., Lang, A. E., & Strafella, A. P. (2012). Extrastriatal dopaminergic abnormalities of DA homeostasis in Parkinson's patients with medication-induced pathological gambling: a [11C] FLB-457 and PET study. *Neurobiology of Disease, 48*(3), 519–525. https://doi.org/10.1016/j.nbd.2012.06.021.

Ray, N., & Strafella, A. (2010). Dopamine, reward, and frontostriatal circuitry in impulse control disorders in Parkinson's disease: insights from functional imaging. *Clinical EEG and Neuroscience, 41*(2), 87–93. https://doi.org/10.1177/155005941004100208.

Reijnders, J. S. A. M., Scholtissen, B., Weber, W. E. J., Aalten, P., Verhey, F. R. J., & Leentjens, A. F. G. (2010). Neuroanatomical correlates of apathy in Parkinson's disease: a magnetic resonance imaging study using voxel-based morphometry. *Movement Disorders, 25*(14), 2318–2325. https://doi.org/10.1002/mds.23268.

Riedel, O., Klotsche, J., Spottke, A., Deuschl, G., Förstl, H., Henn, F., Heuser, I., Oertel, W., Reichmann, H., Riederer, P., Trenkwalder, C., Dodel, R., & Wittchen, H. U. (2008). Cognitive impairment in 873 patients with idiopathic Parkinson's disease: results from the German Study on Epidemiology of Parkinson's Disease with Dementia (GEPAD). *Journal of Neurology, 255*(2), 255–264. https://doi.org/10.1007/s00415-008-0720-2.

Robert, G., Le Jeune, F., Dondaine, T., Drapier, S., Péron, J., Lozachmeur, C., Sauleau, P., Houvenaghel, J. F., Travers, D., Millet, B., Vérin, M., & Drapier, D. (2014). Apathy and impaired emotional facial recognition networks overlap in Parkinson's disease: a PET study with conjunction analyses. *Journal of Neurology, Neurosurgery & Psychiatry, 85*(10), 1061–1066. https://doi.org/10.1136/jnnp-2013-307025.

Santangelo, G., Vitale, C., Picillo, M., Cuoco, S., Moccia, M., Pezzella, D., Erro, R., Longo, K., Vicidomini, C., Pellecchia, M. T., Amboni, M., Brunetti, A., Salvatore, M., Barone, P., & Pappatà, S. (2015). Apathy and striatal dopamine transporter levels in de-novo, untreated Parkinson's disease patients. *Parkinsonism and Related Disorders, 21*(5), 489–493. https://doi.org/10.1016/j.parkreldis.2015.02.015.

Schneider, F., Althaus, A., Backes, V., & Dodel, R. (2008). Psychiatric symptoms in Parkinson's disease. *European Archives of Psychiatry and Clinical Neuroscience, 258*(Suppl 5), 55–59. https://doi.org/10.1007/s00406-008-5012-4.

Sheng, K., Fang, W., Su, M., Li, R., Zou, D., Han, Y., Wang, X., & Cheng, O. (2014). Altered spontaneous brain activity in patients with Parkinson's disease accompanied by depressive symptoms, as revealed by regional homogeneity and functional connectivity in the prefrontal-limbic system. *PLoS ONE, 9*(1). https://doi.org/10.1371/journal.pone.0084705.

Shin, S., Lee, J. E., Hong, J. Y., Sunwoo, M.-K., Sohn, Y. H., & Lee, P. H. (2012). Neuroanatomical substrates of visual hallucinations in patients with non-demented Parkinson's disease. *Journal of Neurology, Neurosurgery & Psychiatry, 83*(12), 1155–1162. https://doi.org/10.1136/jnnp-2012-303391.

Shine, J. M., Halliday, G. M., Gilat, M., Matar, E., Bolitho, S. J., Carlos, M., Naismith, S. L., & Lewis, S. J. G. (2014). The role of dysfunctional attentional control networks in visual misperceptions in Parkinson's disease. *Human Brain Mapping, 35*(5), 2206–2219. https://doi.org/10.1002/hbm.22321.

Shine, J. M., Keogh, R., O'Callaghan, C., Muller, A. J., Lewis, S. J. G., & Pearson, J. (2015). Imagine that: elevated sensory strength of mental imagery in individuals with Parkinson's disease and visual hallucinations. *Proceedings of the Royal Society B: Biological Sciences, 282*(1798), 20142047. https://doi.org/10.1098/rspb.2014.2047.

Skidmore, F. M., Yang, M., Baxter, L., von Deneen, K., Collingwood, J., He, G., Tandon, R., Korenkevych, D., Savenkov, A., Heilman, K. M., Gold, M., & Liu, Y. (2013). Apathy, depression, and motor symptoms have distinct and separable resting activity patterns in idiopathic Parkinson disease. *NeuroImage, 81*, 484–495. https://doi.org/10.1016/j.neuroimage.2011.07.012.

Smith, K. M., Xie, S. X., & Weintraub, D. (2016). Incident impulse control disorder symptoms and dopamine transporter imaging in Parkinson disease. *Journal of Neurology, Neurosurgery & Psychiatry, 87*(8), 864–870. https://doi.org/10.1136/jnnp-2015-311827.

Song, X., Hu, X., Zhou, S., Xu, Y., Zhang, Y., Yuan, Y., Liu, Y., Zhu, H., Liu, W., & Gao, J.-H. (2015). Association of specific frequency bands of functional MRI signal oscillations with motor symptoms and depression in Parkinson's disease. *Scientific Reports, 5*, 16376. https://doi.org/10.1038/srep16376.

Stebbins, G. T., Goetz, C. G., Carrillo, M. C., Bangen, K. J., Turner, D. A., Glover, G. H., & Gabrieli, J. D. E. (2004). Altered cortical visual processing in PD with hallucinations: an fMRI study. *Neurology, 63*(8), 1409–16. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/15505157.

Steeves, T. D. L., Miyasaki, J., Zurowski, M., Lang, A. E., Pellecchia, G., Van Eimeren, T., Rusjan, P., Houle, S., & Strafella, A. P. (2009). Increased striatal dopamine release in Parkinsonian patients with pathological gambling: a [11C] raclopride PET study. *Brain, 132*(5), 1376–1385. https://doi.org/10.1093/brain/awp054.

Surdhar, I., Gee, M., Bouchard, T., Coupland, N., Malykhin, N., & Camicioli, R. (2012). Intact limbic-prefrontal connections and reduced amygdala volumes in Parkinson's disease with mild depressive symptoms. *Parkinsonism and Related Disorders, 18*(7), 809–813. https://doi.org/10.1016/j.parkreldis.2012.03.008.

Tang, J., & Strafella, A. P. (2012). The frontostriatal circuitry and behavioral complications in PD. *Parkinsonism & Related Disorders, 18 Suppl 1*, S104–6. https://doi.org/10.1016/S1353-8020(11)70033-5.

Tessitore, A., Santangelo, G., De Micco, R., Vitale, C., Giordano, A., Raimo, S., Corbo, D., Amboni, M., Barone, P., & Tedeschi, G. (2016). Cortical thickness changes in patients with Parkinson's disease and impulse control disorders. *Parkinsonism & Related Disorders, 24*, 119–125. https://doi.org/10.1016/j.parkreldis.2015.10.013.

Thobois, S., Ardouin, C., Lhommée, E., Klinger, H., Lagrange, C., Xie, J., Fraix, V., Coelho Braga, M. C., Hassani, R., Kistner, A., Juphard, A., Seigneuret, E., Chabardes, S., Mertens, P., Polo, G., Reilhac, A., Costes, N., LeBars, D., Savasta, M., Tremblay, L., Quesada, J. L., Bosson, J. L., Benabid, A. L., Broussolle, E., Pollak, P., & Krack, P. (2010). Non-motor dopamine withdrawal syndrome after surgery for Parkinson's disease: predictors and underlying mesolimbic denervation. *Brain, 133*(Pt 4), 1111–1127. https://doi.org/10.1093/brain/awq032.

Van Eimeren, T., Pellecchia, G., Cilia, R., Ballanger, B., Steeves, T. D. L., Houle, S., Miyasaki, J. M., Zurowski, M., Lang, A. E., & Strafella, A. P. (2010). Drug-induced deactivation of inhibitory networks predicts pathological gambling in PD. *Neurology, 75*(19), 1711–1716. https://doi.org/10.1212/WNL.0b013e3181fc27fa.

van Mierlo, T. J., Chung, C., Foncke, E. M., Berendse, H. W., & van den Heuvel, O. A. (2015). Depressive symptoms in Parkinson's disease are related to decreased hippocampus and amygdala volume. *Movement Disorders, 30*(2), 245–252. https://doi.org/10.1002/mds.26112.

Voon, V., Gao, J., Brezing, C., Symmonds, M., Ekanayake, V., Fernandez, H., Dolan, R. J., & Hallett, M. (2011). Dopamine agonists and risk: impulse control disorders in Parkinson's disease. *Brain, 134*(5), 1438–1446. https://doi.org/10.1093/brain/awr080.

Voon, V., Rizos, A., Chakravartty, R., Mulholland, N., Robinson, S., Howell, N. A., Harrison, N., Vivian, G., & Ray Chaudhuri, K. (2014). Impulse control disorders in Parkinson's disease: decreased striatal dopamine transporter levels. *Journal of Neurology, Neurosurgery & Psychiatry, 85*(2), 148–152. https://doi.org/10.1136/jnnp-2013-305395.

Vriend, C., Nordbeck, A. H., Booij, J., van der Werf, Y. D., Pattij, T., Voorn, P., Raijmakers, P., Foncke, E. M., van de Giessen, E., Berendse, H. W., & van den Heuvel, O. A. (2014a). Reduced dopamine transporter binding predates impulse control disorders in Parkinson's disease. *Movement Disorders, 29*(7), 904–911. https://doi.org/10.1002/mds.25886.

Vriend, C., Raijmakers, P., Veltman, D. J., van Dijk, K. D., van der Werf, Y. D., Foncke, E. M. J., Smit, J. H., Berendse, H. W., & van den Heuvel, O. A. (2014b). Depressive symptoms in Parkinson's disease are related to reduced [123I]FP-CIT binding in the caudate nucleus. *Journal of Neurology, Neurosurgery & Psychiatry, 85*(2), 159–164. https://doi.org/10.1136/jnnp-2012-304811.

Vriend, C., Boedhoe, P. S., Rutten, S., Berendse, H. W., van der Werf, Y. D., & van den Heuvel, O. A. (2016). A smaller amygdala is associated with anxiety in Parkinson's disease: a combined FreeSurfer-VBM study. *Journal of Neurology, Neurosurgery & Psychiatry, 87*(5), 493–500. https://doi.org/10.1136/jnnp-2015-310383.

Watanabe, H., Senda, J., Kato, S., Ito, M., Atsuta, N., Hara, K., Tsuboi, T., Katsuno, M., Nakamura, T., Hirayama, M., Adachi, H., Naganawa, S., & Sobue, G. (2013). Cortical and subcortical brain atrophy in Parkinson's disease with visual hallucination. *Movement Disorders, 28*(12), 1732–1736. https://doi.org/10.1002/mds.25641.

Wen, X., Wu, X., Liu, J., Li, K., & Yao, L. (2013). Abnormal baseline Brain activity in non-depressed Parkinson's disease and depressed Parkinson's disease: a resting-state functional magnetic resonance imaging study. *PLoS ONE, 8*(5), 1–8. https://doi.org/10.1371/journal.pone.0063691.

Wu, K., Politis, M., O'Sullivan, S. S., Lawrence, A. D., Warsi, S., Bose, S., Lees, A. J., & Piccini, P. (2015). Single versus multiple impulse control disorders in Parkinson's disease: an 11C-raclopride positron emission tomography study of reward cue-evoked striatal dopamine release. *Journal of Neurology, 262*(6), 1504–1514. https://doi.org/10.1007/s00415-015-7722-7.

Yao, N., Shek-Kwan Chang, R., Cheung, C., Pang, S., Lau, K. K., Suckling, J., et al. (2014). The default mode network is disrupted in Parkinson's disease with visual hallucinations. *Human Brain Mapping, 35*(11), 5658–5666. https://doi.org/10.1002/hbm.22577

Yao, N., Cheung, C., Pang, S., Shek-kwan Chang, R., Lau, K. K., Suckling, J., et al. (2016). Multimodal MRI of the hippocampus in Parkinson's disease with visual hallucinations. *Brain Structure and Function, 221*(1), 287–300. https://doi.org/10.1007/s00429-014-0907-5.

Yoo, H.B., Lee, J. Y., Lee, J. S., Kang, H., Kim, Y. K., Song, I. C., Lee, D. S., & Jeon, B. S. (2015). Whole-brain diffusion-tensor changes in Parkinsonian patients with impulse control disorders. *Journal of Clinical Neurology (Korea), 11*(1), 42–47. https://doi.org/10.3988/jcn.2015.11.1.42.

Zhu, Y., Song, X., Xu, M., Hu, X., Li, E., Liu, J., Yuan, Y., Gao, J. H., & Liu, W. (2016). Impaired interhemispheric synchrony in Parkinson's disease with depression. *Scientific Reports, 6*, 27477. https://doi.org/10.1038/srep27477.