Affective disorders in Parkinson's disease

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Abstract

Purpose of review—This review explores recent literature pertaining to affective disorders associated with Parkinson's disease.

Recent findings—Nonmotor symptoms including affective disorders are becoming more widely recognized as complications of Parkinson's disease. As awareness of these symptoms increases, and new neuroimaging tools are developed and become more accessible, more studies are being conducted pertaining to behavioral complications in Parkinson's disease. The functional connectivity of the basal ganglia can predispose people with Parkinson's to develop affective disorders. Furthermore, dopaminergic treatments may exacerbate or trigger behavioral symptoms. It is now understood that changes associated with Parkinson's disease are widespread, affecting striatal and extrastriatal regions and resulting in alterations in gray matter, white matter, blood flow, metabolism, and dopaminergic and serotonergic function.

Summary—Neuroimaging is advancing our knowledge of the mechanisms involved in Parkinson's disease, and their role in the development of behavioral disorders. An increased understanding of these disorders may lead to the discovery of new therapeutic targets, or the identification of risk factors for the development of these disorders. If preventive therapies become available, identification of risk factors will be important for the identification and treatment of susceptible individuals.

Keywords

affective disorders; neuroimaging; Parkinson's disease

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Conflicts of interest

There are no conflicts of interest.

INTRODUCTION

The increase in lifespan for people with Parkinson's disease has resulted in increased recognition of the neuropsychiatric symptoms of Parkinson's disease over the last few decades [1]. Affective disorders in Parkinson's disease include depressive disorders, apathy, mania, anxiety disorders, psychosis, impulse control disorders, dopamine dysregulation syndrome, and dopamine agonist withdrawal syndrome (DAWS) [2,3[■],4[■]]. Although many of these are inherent to the disease process, others are side-effects of Parkinson's disease treatments [3[■]]. It is now understood that in addition to dopamine depletion, Parkinson's disease also results in acetylcholine, norepinephrine, and serotonin abnormalities. Although the majority of nuclear imaging studies in Parkinson's disease still focus on the dopaminergic system, new studies are examining the role of other neurotransmitter systems.

DEPRESSION AND APATHY

It is believed that depression in Parkinson's disease is mainly related to the disease course and not secondary to being diagnosed with a progressive, neurodegenerative illness. Depression often occurs before the motor onset and diagnosis of Parkinson's disease [5]. Additionally, when Parkinson's disease patients are compared with other patients with chronic disabilities, the incidence of depression in Parkinson's disease is higher [1]. Depression can be underdiagnosed in people with Parkinson's disease, as they may not meet the Diagnostic and Statistical Manual of Mental Disorders criteria for depression [6]. Furthermore, depression and Parkinson's disease share common symptoms such as bradykinesia, fatigue, sleep disturbance, and loss of productivity, desire, and libido [6,7[■]]. Despite this, it has been suggested that endogenous and Parkinson's disease-related depression have distinct clinical profiles [6], and neuroimaging studies have provided insight into the neurobiological mechanisms of depression in Parkinson's disease.

A [99mTc] hexamethylpropyleneamineoxime single-photon emission computed tomography (SPECT) study measuring regional cerebral blood flow (rCBF) before and after treatment with citalopram, a selective serotonin reuptake inhibitor, showed that people with primary depression and those with depression secondary to Parkinson's disease responded differently to citalopram. Patients with primary depression showed an area of relative hypoperfusion in the basal right frontal lobe when compared with Parkinson's disease groups. This showed a trend toward normalization with citalopram treatment. Conversely, in depressed Parkinson's disease patients, at baseline, rCBF was increased bilaterally in the frontoparietal region, the right dorsolateral frontal lobe, and the left anterior frontal lobe. This also normalized following citalopram treatment, suggesting a different neuro-biological basis for primary depression and depression secondary to Parkinson's disease [8].

There is some evidence suggesting that major depression in Parkinson's disease is associated with more widespread neurodegenerative processes. SPECT imaging of rCBF showed reduced perfusion in the preoccipital area in Parkinson's disease patients when compared with healthy controls. This was especially true of Parkinson's disease patients with major depression [8]. A voxel-based morphometry (VBM) study comparing healthy controls and Parkinson's disease patients with and without depression found that depressed patients

showed white matter loss in the right anterior cingulate cortex (ACC) bundle, orbitofrontal cortex, and left parietal lobe. Thus, depression in Parkinson's disease may represent a disconnection syndrome [9]. Indeed, diffusion tensor imaging (DTI) studies support this claim. The first DTI study of depression in Parkinson's disease noted reduced fractional anisotropy values in frontal areas, possibly corresponding to the anterior cingulate bundles, in depressed individuals [10]. Subsequent investigations noted decreased fractional anisotropy values bilaterally in the mediodorsal thalamus correlating with increasing depression severity in Parkinson's disease patients, as assessed by the Hamilton Depression Scale. This suggests decreased viability of neurons or white matter fibers projecting to or from the mediodorsal thalamus [11]. A more recent DTI study, examining only the uncinate fasciculus as a region of interest, was unable to find a difference between depressed and nondepressed Parkinson's disease groups, in terms of fractional anisotropy values. The authors did however acknowledge the limitations of DTI in measuring subtle changes in fibers [12].

Nuclear imaging studies suggest involvement of the dopaminergic and serotonergic systems in depression in Parkinson's disease. A SPECT study using the dopamine transporter (DAT) radioligand [99mTc] 2[[2-[[[3-(4-chlorophenyl)-8-methyl-8-aza-bicyclo[3,2,1]-oct-2-yl]-methyl](2-mercaptoethyl) amino]ethyl]amino]ethanethiolato(3-)-N₂,N₂',S₂, S₂]oxo-[1R-exo-exo)] (TRODAT-1) found significantly higher DAT density in depressed Parkinson's disease patients, compared to Parkinson's disease controls. This was especially prominent in the left caudate and right putamen. It is hypothesized that this may be because of DAT upregulation resulting in decreased dopaminergic transmission at the synapse [9]. A positron emission tomography (PET) study of the serotonin transporter demonstrated reduced serotonergic neurotransmission in the raphe nuclei and limbic structures in antidepressant-naïve Parkinson's disease patients with depression. This finding correlated with depression symptom severity [6].

Apathy occurs in up to 40% of people with Parkinson's disease [1], and although clinically distinct from depression, the two are often comorbid [1,13,14,15[■]]. A resting-state functional magnetic resonance imaging (fMRI) study suggested a neurobiological basis for the differentiation of these disorders in Parkinson's disease. Apathy was associated with decreased activity in the lateral geniculate nucleus and parietal areas, as well as increased activity in the right orbitofrontal cortex. Depression was associated with increased activity in the subgenual cingulate. The authors suggest that changes in goal-oriented behavior underlie apathy, which may be classified as a disconnectional, amotivational syndrome [16]. An [18F] fluorodeoxyglucose (FDG) PET study found apathy severity to be positively correlated with metabolic activity in the left anterior insula, and right cuneus and middle frontal cortex, and negatively correlated with metabolism in the posterior cerebellum [17[■]]. This study is significant as it examined apathy in Parkinson's disease patients without dementia or depression, as these disorders are often comorbid [15[■],17[■]]. Another study demonstrated, using VMB, that increased apathy scores in people with Parkinson's disease were associated with reduced gray matter density in the bilateral precentral gyrus, parietal gyrus, inferior frontal gyrus, insula, and the right cingulate gyrus and precuneus. Increased apathy scores were not, however, associated with decreased motor performance, supporting

the role of nondo-paminergic systems. Furthermore, the cingulate and inferior frontal gyri are also affected in people with apathy and Alzheimer's disease or depression [18].

Deep brain stimulation may also be associated with depression, apathy [15[■]], and suicide [1]. A PET study using [11C] raclopride demonstrated that Parkinson's disease patients who developed postoperative apathy and depression had increased mesocorticolimbic dopaminergic denervation, demonstrated by a reduced ability to release dopamine in response to methylphenidate administration. This was especially true for projections to the orbitofrontal, prefrontal, and dorsolateral pre-frontal cortices, as well as the left ventral striatum and right amygdala. This suggests the origin of apathy in Parkinson's disease is mesolimbic rather than nigrostriatal. Postoperative apathy may also be secondary to reductions in dopaminergic medications [14], and represents a type of withdrawal syndrome [4[■],14]. Conversely, an [18F] FDG study of postoperative apathy suggested that apathy is unrelated to medication decreases and microlesioning of the subthalamic nucleus. In this study, modified apathy scores correlated with hypometabolism bilaterally in the cingulate gyrus and the left middle gyrus, and hypermetabolism in the right post-central, inferior, inferior frontal, and middle frontal gyri, and the left fusiform gyrus [19].

MANIA

Few neuroimaging studies have been conducted pertaining to mania in Parkinson's disease. A small study examined deep brain stimulation-treated patients who developed mania and hypomania and had electrodes completely or partially located in the substantia nigra. Mania was associated with increased rCBF in the bilateral dorsal ACC, as well as the right primary motor cortex, medial prefrontal cortex, and globus pallidus, and decreased rCBF bilaterally in the occipital cortex, and in the left temporal cortex. The results were highly asymmetric, with increases in rCBF primarily in the right hemisphere and decreases primarily in the left. These findings suggest that post-deep brain stimulation hypomania is primarily mediated by the substantia nigra's effect on the ACC and provide support for the basal ganglia's role in the limbic loop and modulation of mood [20].

ANXIETY

Up to 40% of people with Parkinson's disease experience symptoms of anxiety [1]. Anxiety in Parkinson's disease may manifest as generalized anxiety disorder, panic attacks, social anxiety disorder (SAD), phobic disorders, obsessive-compulsive disorder, or other anxiety disorders [1,7[■]]. These symptoms occur in tandem with nonmotor fluctuations, especially during 'off' periods [1,21[■]]. Like depression, anxiety in Parkinson's disease appears to be a consequence of Parkinson's disease pathology rather than a response to disability, as people with Parkinson's disease show higher rates of anxiety when compared with similarly disabled people [22]. Nevertheless, psychosocial factors likely play a role, especially in young-onset Parkinson's disease patients who may find the burden of social isolation, loss of productivity and income, and impact on family members more stressful [21[■]]. Despite the burden of anxiety in Parkinson's disease, relatively few neuroimaging studies have been performed.

A TRODAT-1 study of SAD in Parkinson's disease failed to find significant differences in DAT density between Parkinson's disease patients with and without SAD, although social anxiety scores showed a significant positive correlation with DAT binding in the left caudate and putamen. The findings provide support for a neurobiological basis for SAD in Parkinson's disease and may indicate less neurodegeneration in this patient population or alternatively decreased dopamine release at the synapse [23].

PSYCHOSIS AND VISUAL HALLUCINATIONS

A recent demographic study of nondemented Parkinson's disease patients reported the incidence of psychosis to be 21.5%, and reported visual hallucinations as the most common symptom, occurring in 13.6% of patients [24[■]]. Parkinson's disease psychosis is primarily ascribed to dysfunction in dopaminergic, serotonergic, or cholinergic neuro-transmission [2] through the modulation of psychotic symptoms in addition to cognition, mood, and sleep [2,25[■]], as well as impaired visual input processing [25[■]]. Furthermore, psychotic symptoms in Parkinson's disease can be brought about or exacerbated by dopaminergic medications, which hypersensitize mesolimbic dopaminergic receptors [2]. The recognition of psychosis as a nonmotor feature of Parkinson's disease is relatively recent, coinciding primarily with the widespread use of dopamine replacement therapy [1], although such symptoms were reported before dopaminergic drugs were used [26]. Interestingly, there is no clear correlation between dosage, treatment duration, and psychosis [1,27].

A SPECT study was conducted to determine the effect of electroconvulsive therapy on motor and psychotic features of Parkinson's disease. Although improvement of psychotic symptoms was associated with increased rCBF in the right middle frontal gyrus, motor improvement was not. Thus, it is likely that different brain areas modulate motor and psychotic features [27].

Several neuroimaging studies have been conducted to examine visual hallucinations in Parkinson's disease. An fMRI study demonstrated several processing abnormalities in people with Parkinson's disease experiencing visual hallucinations, primarily just prior to image recognition. Findings suggested impaired bottom-up processing and that impairment of the ventral and lateral extrastriate visual association areas is a risk factor for the development of visual hallucinations [26]. Ventral visual pathway abnormalities have also been noted in studies of the serotonergic system. A study using [18F] setoperone PET and MRI scans found that patients with visual hallucinations experienced significant increases in serotonin-2A binding potential in the bilateral infero-occipital gyrus, dorsolateral prefrontal cortex, and insula, and the right fusiform gyrus, inferotemporal cortex, and posterior cingulate cortex [28]. Gray matter atrophy is also observed in people with Parkinson's disease and visual hallucinations, and this is a risk factor for the development of dementia. Visual hallucinations and dementia may be part of the same degenerative process with visual hallucination symptomatology presenting first, with atrophy of the posterior neo-cortical areas, and onset of dementia corresponding to more widespread atrophy. This is based on a VBM study that reported 75% of patients with visual hallucinations met the diagnostic criteria for dementia at 2.5-year follow-up, and exhibited extensive gray matter atrophy in

limbic, paralimbic, and neocortical regions. Those who did not progress to dementia showed smaller regions of atrophy limited to frontal areas and the cerebellum [29].

IMPULSE CONTROL DISORDERS

Impulse control disorders (ICDs) include binge eating, compulsive shopping, pathological hypersexuality, and gambling. To date, the most comprehensive study on ICDs reports a prevalence of 13.6% [30]. Despite this wide variation in ICD phenotype, most studies focus on compulsive gambling.

A H₂[15]O PET study before and after administration of a dopamine agonist in Parkinson's disease patients with and without gambling behavior found that dopamine agonist-related activity change in brain areas that are implicated in impulse control and response inhibition (lateral orbitofrontal cortex, rostral cingulate zone, amygdala) distinguished gamblers from controls. Although the agonist significantly increased rCBF in these areas in controls, gamblers showed, in contrast, a significant reduction of activity [31].

Another study comparing Parkinson's disease gamblers with a Parkinson's disease control group, using voxel-wise covariance analysis and structural equation modeling, revealed a disconnection between the striatum and the ACC, and also between the ventrolateral prefrontal cortex and both the anterior and posterior cingulate. Gamblers exhibited impaired response inhibition but also failure of associative learning with respect to the processing of negative outcomes. This is consistent with the imaging findings, as the ACC plays an essential role in integrating information in decision-making and impulse control, and the ventrolateral prefrontal cortex is important to link negative feedback learning with negative outcomes [32]. A recent PET imaging study of Parkinson's disease patients with pathological gambling suggested that changes in ACC function in this patient population may have a dopaminergic basis [33[■]]. Another study found that Parkinson's disease patients are impaired with respect to negative feedback learning when compared with healthy controls, and this was associated with reduced activation of the parietal lobe while integrating information pertaining to incentive, in an fMRI paradigm [34]. In addition, a region of interest analysis of Parkinson's disease patients with pathological gambling and shopping and a Parkinson's disease control group suggested that the striatum, orbitofrontal cortex, and anterior insula may be important for negative outcome learning. While supporting dopamine's role in reward learning, the authors also proposed that serotonergic mechanisms might be involved [35]. A recent fMRI study of hypersexual Parkinson's disease patients and Parkinson's disease controls found that hypersexual patients demonstrated increased activity in several brain areas (ACC, posterior cingulate, orbitofrontal, and anterior prefrontal cortices, as well as the superior parietal lobule, hypothalamus and amygdala) when presented with sexual visual cues, but not other reward stimuli. This occurred regardless of whether patients were on or off levodopa [36[■]].

In a DAT imaging study, when Parkinson's disease controls were compared with Parkinson's disease gamblers, reduced binding was seen in the nucleus accumbens of the right ventral striatum in gamblers. These changes may be because of decreased terminals, functional downregulation, or genetic factors influencing the expression of the DAT gene and can

contribute to pulsatile dopaminergic stimulation, decreases in dopamine turnover, and sensitization of dopamine neurotransmission in the limbic circuitry [37]. A [11C] raclopride PET study noted reduced binding in the ventral striatum of Parkinson's disease gamblers in response to an active gambling task. Furthermore, gamblers exhibited reduced binding at baseline, suggesting either increased dopamine release in the resting state, or fewer D2/D3 receptors. This is thought to be the biological basis for addiction, as low dopamine binding in the ventral striatum may trigger a drive for dopamine-releasing behaviors [38]. A recent study used the [11C] FLB-457 radio-ligand to measure extrastriatal dopamine binding in Parkinson's disease gamblers and controls. Results demonstrated reduced binding to midbrain auto-receptors in Parkinson's disease gamblers. These autoreceptors are involved in negative feedback control of dopamine release in the striatum. Furthermore, binding potential was increased in the ACC, which may also be related to reduced control of impulses [33].

Taken together, imaging studies of ICD in Parkinson's disease suggest that changes in dopamine levels predispose individuals to ICD-type behaviors [37,39,40]. These changes could be because of underlying predispositions [38,39], or sensitization of dopaminergic circuitry by repeat stimulation by dopamine agonists [38,39]. Interactions between the basal ganglia and cortex, especially between the medial prefrontal cortex and subthalamic nucleus, are important, and deep brain stimulation of the subthalamic nucleus can result in changes in conflict evaluation and decreased decision thresholds, leading to impulsivity [41].

Recently, a strong link has been found between ICD and DAWS. DAWS manifests similarly to withdrawal from other drugs, and does not respond to treatment with levodopa. A chart review of 84 patients withdrawn from dopamine agonists found a 15.5% frequency of DAWS. All patients who developed DAWS were withdrawn from dopamine agonists because of ICD, whereas only 41% of the group who did not develop DAWS were withdrawn for this reason. Development of ICD on dopamine agonists may therefore be a risk factor for DAWS [4].

CONCLUSION

As awareness of nonmotor features of Parkinson's disease increases and new neuroimaging techniques [42] emerge and become more commonplace, understanding of the underlying pathological processes in Parkinson's disease will increase. This has the potential to positively impact patient quality of life and may lead to new therapeutic targets. Although neuroimaging for the premotor diagnosis of Parkinson's disease is generally not feasible because of cost and availability issues, several PET ligands are now available [5]. If neuroprotective treatments become available in the future, these imaging techniques will be important for the identification of susceptible individuals, and therapies may focus on prevention rather than treatment.

Acknowledgments

This work was supported by the Canadian Institutes of Health Research (MOP 110962). A.P.S. is also supported by the Canada Research Chair program and E.J. Safra Foundation.

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KEY POINTS

- The functional connectivity of the basal ganglia can lead to affective disorders in people with Parkinson's disease, and imaging studies are capable of elucidating neural circuitry.
- New radioligands are being used to study not only the dopaminergic system but also other neurotransmitter systems and their roles in affective disorders in Parkinson's disease.
- Imaging studies are now able to identify individuals at risk for the development of affective disorders. In the future, imaging techniques may play a role in identifying candidates for preventive therapies, should these therapies become available.