Nucleus accumbens and Parkinson’s disease: Exploring the role of Mavridis atrophy.

IN Mavridis*1

Abstract

Introduction

The human nucleus accumbens (NA), a limbic-motor interface, plays an important role in motivation and emotional processes and is involved in some of the most disabling neuropsychiatric disorders such as Parkinson’s disease (PD). PD, a common disorder of dopamine (DA) dysfunction, is characterised by motor, psychiatric and autonomic symptoms. Mavridis’ atrophy (MA) is called the parkinsonism-related shrinkage of the human NA. The purpose of this article was to review the literature regarding the NA involvement in PD in order to explore the role of MA.

The existing literature about the involvement of the NA in PD was carefully reviewed with emphasis on cellular and molecular changes of this nucleus in PD patients, as well as on psychiatric and motor symptoms of PD related to the NA. Review-based suggestions for possible causes, clinical consequences and other aspects of MA are in turn provided.

Discussion

The NA is critically involved in PD, not only in its pathogenesis and clinical manifestations but in the effects of several treatment efforts as well. DAergic degeneration seems to precede clinical phenotype. Some motor and psychiatric symptoms may share a common pathophysiological process mediated by the NA. Neuronal loss due to DAergic degeneration is probably the major cause of MA. Functional NA changes accompany MA. Degeneration of limbic areas is considered as a pathological consequence of MA. Its clinical effects include neuropsychiatric and motor symptoms. MA, as an imaging finding, could be used as a predictive factor for the development of psychiatric manifestations such as depression. MA probably begins in early PD.

Conclusion

There are important studies confirming the finding of MA in PD and, thanks to several new basic science and clinical data, the clarification of its role has begun. Future studies are expected to improve our understanding of the significance of this phenomenon.

Introduction

The striatum, the first relay of the basal ganglia system, is critically involved in motor functions and motivational processes. The dorsal striatum is central to the motor control and motor learning and the ventral striatum, especially the nucleus accumbens (NA), is essential for motivation, the reward system and reinforcement by drugs. This system is dysfunctional in movement disorders such as Parkinson’s disease (PD) and in psychiatric disorders1.

The human NA (Figure 1), having dopamine (DA) as a principal neurotransmitter and dominating the reward system as a ‘pleasure centre’, is connected to the limbic and extrapyramidal motor system2. Acting as a limbic-motor interface, it plays an important role in motivation and emotional processes and is involved in some of the most disabling neuropsychiatric disorders such as PD2,3.

Table 1 summarises the main neurological and psychiatric conditions where the NA is involved. PD, a common neurological disease, is an archetypal disorder of DA dysfunction characterised by motor, cognitive, behavioural and autonomic symptoms4. Beside the classically described motor manifestations, neuropsychiatric symptoms occur in the majority of patients and should be considered as an integral part of the disease5,6.

PD neuropsychiatric sequelae include dementia (subcortical or cortical) and cognitive impairment (including executive, visuospatial, attentional and memory dysfunctions), depression (common in early as well as advanced PD7), dysthymia, anxiety disorders (including panic attacks), psychosis, apathy, sleep disorders (insomnia, parasomnias, somnolence, sleep attacks), sexual disorders and treatment-related psychiatric symptoms (ranging from vivid dreams and hallucinations to delusions, mania, affective episodes, hypersexuality, DA dysregulation syndrome and delirium)6,7,8,9,10,11,12.

Neuropsychiatric symptoms are important determinants of mortality, disease progression and patients’ and caregivers’ quality of life6,9,10,11.

PD has been associated with well-documented morphological changes in basal ganglia nuclei13. The role of the NA neurotransmitters and neurons in PD has been established14,15,16,17.

Mavridis’ atrophy (MA) is called the parkinsonism-related shrinkage of the human NA14,18. The primary purpose of this article was to review the literature regarding the NA involvement in PD, from the level of neurons and neurotransmitters to clinical level, in order to explore the role of MA.

The existing literature regarding the involvement of the NA in PD was carefully reviewed with emphasis on

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All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript. All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

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cellular and molecular changes of this nucleus in PD patients, as well as on psychiatric and motor symptoms of PD related to the NA. Review-based suggestions for possible causes, clinical consequences and other aspects of MA are in turn provided.

**Discussion**

The author has referenced some of his own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed.

**Cellular and molecular NA changes in PD**

Oyanagi et al. reported that the number of large neurons in parkinsonism-dementia complex of Guam was reduced by more than 90% in the NA. The remaining large neurons and many of the medium-sized neurons in the NA were immunopositive for tau protein and contained varying amounts of paired helical filaments admixed with straight tubules. Curly fibres and circularly arranged reactive astrocytes were seen in the NA of many parkinsonism-dementia complex patients. Their findings suggested that in Guam parkinsonism-dementia complex the large neurons in the neostriatum and NA degenerate and that extremely severe loss of large neurons in the NA may be linked to marked degeneration of limbic areas, ventral tegmental area (VTA) and nucleus dorsal raphe.

PD models (produced with neurotoxins that selectively lesion DA neurons) are characterised by acute removal and gradual recovery of DA. Teicher et al. reported slowly progressive loss of DA in ipsilateral NA following profound acute unilateral depletion of DA in the caudate-putamen of neonatal rats. Metabolic turnover of DA markedly increased in ipsilateral NA.

Casteels et al., studying a rat model of PD, found severely decreased DA transporter binding in the ipsilateral caudate-putamen, NA and substantia nigra.

Kumakura et al. searched for regions of elevated 6-[18F]fluoro-l-DOPA utilization and steady-state trapping in a group of patients with early, asymmetric PD. They found increased 6-[18F]fluoro-l-DOPA utilisation in the bilateral medial NA, suggesting hyperfunction of catecholamine fibres innervating specifically the limbic striatum. In contrast, the positron emission tomography (PET) study of Eggers et al. in PD patients showed normal metabolic activity of the NA.

Yagi et al. examined in vivo changes in the brain DAergic system using PET with a DA transporter radiotracer, to elucidate the pathophysiologic characteristics of the DA system in early PD converters. They found that the level of radiotracer binding in the NA and orbitofrontal cortex on the unaffected side was positively correlated with the conversion (from unilateral to bilateral parkinsonism) interval.

This correlation indicates that the more severe a dysfunction presents in the mesocortical DA system (NA, caudate, orbitofrontal cortex) on the seemingly intact side, the more rapidly the parkinsonism proceeds to the intact side (bilateral parkinsonism). The finding of bilateral reduction in the striatal radiotracer binding even in early stage (Hoehn and Yahr stage 1) PD patients confirms that molecular changes in the DA system precede clinical phenotype.

In the same direction, Lin et al. evaluated the capability of PET in detecting the monoaminergic degeneration in early PD in vivo. PD patients at early stage of disease with mild and unilateral motor symptoms underwent (18)F-9-fluoropropyl-(-)-dihydrotetrabenazine (a useful imaging marker to measure DAergic integrity) PET scans. Interestingly the specific uptake ratios of bilateral (in contrast to the unilateral nature of symptoms) caudate, putamen, substantia nigra and NA were significantly lower in PD.

<table>
<thead>
<tr>
<th>Table 1: Neurological and psychiatric disorders where the NA is involved</th>
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<tbody>
<tr>
<td><strong>Psychiatric disorders</strong></td>
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<tr>
<td>Obsessive-compulsive disorder</td>
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<tr>
<td>Depression</td>
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<tr>
<td>Tourette syndrome</td>
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<tr>
<td>Addiction (drugs, alcohol, etc.)</td>
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<td>Schizophrenia</td>
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<tr>
<td>Bipolar disorder</td>
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<tr>
<td>Attention deficit-hyperactivity disorder</td>
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<tr>
<td>Post-traumatic stress disorder</td>
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<tr>
<td>Apathy</td>
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<td>NA, nucleus accumbens; PD, Parkinson’s disease</td>
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</table>

**Figure 1:** The cerebral structures where the NA belongs and the two major functional systems wherein this nucleus is involved.
Consequently DAergic degeneration seems to take place in the premotor phase of PD.36

Adenyl cyclase supersensitivity has been observed in the NA of mice pretreated with twice-daily pramipexole and quinpirole, a finding possibly related to the exacerbation of gambling in PD that is provoked by antiparkinsonic agents acting as selective D2/D3 receptor agonists, notably pramipexole.27

**NA-related neuropsychiatric symptoms of PD**

Neuropsychiatric symptoms that occur in PD such as depression, apathy and anhedonia have a DAergic basis28. Interestingly, involvement of the NA in such neuropsychiatric conditions has been reported29,30,31.

Further, levodopa administered in a pulsatile manner may lead to the induction of synaptic plasticity within the DA systems. In the ventral mesolimbic system, this could lead to loss of behavioural flexibility, impulsive behaviour and cognitive impairment32. Impulse control disorders and DA dysregulation syndrome in PD are motivation-based behaviours that involve repetitive occurrences of impulsive and uncontrolled activity33.

Interestingly, DAergic replacement therapy in PD patients is among the most common causes of punding. Punding, drug-induced stereotypes, addiction and dyskinesias all share a common pathophysiological process. Punding may be related to plastic changes in the ventral and dorsal striatal structures, including the NA, and linked to psychomotor stimulation and reward mechanisms34.

It is suggested that DAergic therapy interacts with existing neuroanatomical and/or neurochemical abnormalities, to produce impulsive behaviour in certain vulnerable PD patients.35

O’Callaghan et al.35 investigated whether grey matter atrophy in fronto-striatal brain regions contributes to inhibitory dysfunction (a key feature of impulsive behaviour) in PD. Frontal atrophy was correlated with verbal disinhibition and striatal atrophy (right NA) was associated with response disinhibition. Their results provided evidence that disinhibition in PD is related to fronto-striatal grey matter atrophy. They supported the hypothesis that fronto-striatal structural abnormalities contribute to impulsive behaviours in PD patients35.

Lee et al.36 investigated the extrastriatal DAergic neural changes in relation to the medication-related impulse control disorders in PD and found that PD patients with impulse control disorders showed tendency to lower binding potentials at the left NA.36

O’Callaghan et al.37 explored the relationship between fronto-striatal grey matter atrophy and learning in PD. They confirmed that learning rates were reduced in patients relative to controls. Moreover, voxel-based morphometry imaging analysis demonstrated that this learning impairment was directly related to grey matter loss in discrete fronto-striatal regions including the NA.37

Many studies showed executive impairments, apathy, depression, hypomania and impairment of recognition of negative facial emotions after chronic subthalamic nucleus (STN) deep brain stimulation (DBS) in PD patients. The medial tip of the STN represents its limbic part.38

Haegelen et al.38 proposed a new function scheme of the limbic system, establishing connections between limbic cortical structures and limbic part of the basal ganglia.

This could be composed of a minor part based on the model of cortico-basal ganglia-thalamo-cortical loop and of a major part linking the STN with the mesolimbic DAergic pathway via the VTA and NA, and with limbic cortical structures. This scheme could explain limbic impairments after STN DBS by disruption of limbic information inside the STN and VTA.38

<table>
<thead>
<tr>
<th>NA changes</th>
<th>Clinical effects</th>
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<tbody>
<tr>
<td>Neuronal loss</td>
<td>Limbic dysfunction symptoms (degeneration of limbic areas)</td>
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<tr>
<td>Decreased DA</td>
<td>Akinesia</td>
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<tr>
<td>Dysfunction</td>
<td>Depression, apathy, anxiety, anhedonia, bradyphrenia, hypokinesia</td>
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<tr>
<td>Atrophy</td>
<td>Learning impairment</td>
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<tr>
<td>DAergic degeneration</td>
<td>(Precedes clinical phenotype)</td>
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<tr>
<td>Hyperfunction of catecholamine fibres</td>
<td>(Precedes clinical phenotype)</td>
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<tr>
<td>Treatment-related</td>
<td></td>
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<tr>
<td>Medical treatment</td>
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<tr>
<td>Atrophy</td>
<td>Impulsive behaviour</td>
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<tr>
<td>Increased DA</td>
<td>Dyskinesia</td>
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<tr>
<td>Adenyl cyclase supersensitivity</td>
<td>Gambling</td>
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<tr>
<td>Changes in synaptic plasticity</td>
<td>Punding</td>
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<tr>
<td>Increased DA synthesis and release</td>
<td>Exercise-related benefit of movement behaviour</td>
</tr>
<tr>
<td>STN DBS</td>
<td>Depression, apathy, hypomania</td>
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<tr>
<td>Dysfunction</td>
<td>Motor loop activation</td>
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<tr>
<td>DA release</td>
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<td>DA, dopamine; DBS, deep brain stimulation; PD, Parkinson’s disease; STN, subthalamic nucleus.</td>
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NA-related motor symptoms of PD

Despite the denial of the depressive state and the absence of obvious cognitive disorder, PD patients lack ambition and spend their time idly. However, although their motor function remains subliminal, such patients can carry out motor activities when the situation requires, but usually they do not have the drive to move. The DA system of the dorsal striatal pathway projecting from the substantia nigra pars compacta to the dorsal part of the striatum (motor striatum) functions in the control of speed and dexterity of movement. On the other hand, the DA system, through the medial forebrain bundle projecting from the VTA to the NA, ventral striatum (limbic striatum) and cerebral cortex, is associated with hypokinesia and bradyphrenia.

The DA levels have been found relatively high in the NA of PD patients treated with levodopa, a finding possibly responsible for the occurrence of dyskinesias. In contrast, Rose et al. suggested that the transient and reversible DA loss in the NA may contribute to the initial profound akinesia exhibited by common marmosets treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

To elucidate the dynamic effects of STN DBS on the DAergic system during activity, Nozaki et al. studied with PET scans 12 PD patients (who underwent STN DBS operations) during right-foot movement in DBS-off and DBS-on conditions. The STN DBS during exercise significantly reduced the [11C]raclopride binding potential in the caudate and NA, but not in the putamen. The magnitude of DA release in the NA correlated negatively with the magnitude of motor load, indicating that STN DBS facilitated motor behaviour more smoothly and at less expense to DA neurons in the region. The lack of DA release in the putamen and the significant DA release in the ventromedial striatum by STN DBS indicated DAergic activation occurring in the motivational circuit during action, suggesting a compensatory functional activation of the motor loop from the non-motor system.

Endurance exercise has a beneficial effect on reactivity and movement behaviour in PD patients following cued application of levodopa probably due to an augmented synthesis and release of DA and other catecholamines in the prefrontal cortex, the NA and basal ganglia.

Finally, the normal pattern of greater activation of some brain areas including the left NA/caudate during motor timing was not observed in PD patients.

The role of MA in PD

According to the present review, it is clear that the NA is involved in several not only psychiatric but also motor symptoms occurring in PD patients, which fits better the functional profile of this nucleus (limbic-motor interface). The exact nature of this involvement is not fully understood. Table 2 summarises the role of the NA in clinical expression of PD. We see that its effects are associated with several pathological and pathophysiological changes.

Regarding MA, we note that two recent studies of O’Callaghan et al. and O’Callaghan et al. confirmed the finding of NA atrophy in PD. A combination of neuronal loss, neuronal shrinkage and reduction of synaptic terminals into the NA has been proposed as potential cause of MA.

According to the present review, neuronal loss due to DAergic degeneration seems to be the major cause of MA. Functional NA changes such as decreased DA, dysfunction (decreased activation) and changes in its synaptic plasticity are expected to accompany MA.

Degeneration of limbic areas could be easily considered as a pathological consequence of MA. It has been proposed that MA could be related to comorbidity with other psychiatric conditions such as depression. Based on the above mentioned cause and changes related to MA, its clinical effects should include neuropsychiatric (mainly due to limbic dysfunction) and motor symptoms (mainly negative). Table 3 presents the possible clinical consequences of MA.

Finally, other issues raised in the past regarding MA include its potential role as a predictive factor in PD comorbidity with other psychiatric conditions, as well as whether this phenomenon is observed in patients with early PD too. The present review approaches the answer to these questions. MA, as an imaging finding, could be safely considered as a predictive factor for the development of psychiatric manifestations such as depression (and probably of other symptoms too). Given that DAergic degeneration takes place in the premotor phase and that molecular changes in the DA system precede clinical phenotype of PD, MA probably begins in early PD.

Conclusion

The human NA, a limbic-motor interface, is crucially involved in PD, not only in its pathogenesis and clinical manifestations but in the effects of several treatment efforts as well.

Table 3: The possible clinical consequences of MA

<table>
<thead>
<tr>
<th>Neuropsychiatric symptoms</th>
<th>Motor symptoms</th>
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<tbody>
<tr>
<td>Limbic dysfunction</td>
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<tr>
<td>Apathy</td>
<td>MA, Mavridis’ atrophy</td>
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DAergic degeneration seems to precede clinical phenotype. Some motor and psychiatric PD symptoms may share a common pathophysiological process mediated by the NA. Fronto-striatal structural abnormalities, including NA atrophy, contribute to impulsive behaviours and learning impairment in PD patients.

Neuronal loss due to DAergic degeneration is probably the major cause of MA. Functional NA changes such as decreased DA, dysfunction and changes in its synaptic plasticity are expected to accompany MA. Degeneration of limbic areas could be easily considered as a pathological consequence of MA. Its clinical effects include neuropsychiatric (limbic dysfunction) and motor symptoms (negative). MA, as an imaging finding, could be considered as a predictive factor for the development of psychiatric manifestations such as depression. MA probably begins in early PD.

Four years after the discovery of MA, there are important studies confirming this finding and, thanks to several new basic science as well as clinical data, the clarification of its role has begun. Future studies are expected to improve our understanding of the significance of this phenomenon.

Abbreviations list
AD, Alzheimer’s disease; DA, dopamine; DBS, deep brain stimulation; MA, Mavridis’ atrophy; NA, nucleus accumbens; PD, Parkinson’s disease; PET, positron emission tomography; STN, subthalamic nucleus; VTA, ventral tegmental area.

References


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