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The Vulnerable Ventral Tegmental Area in Parkinson's Disease

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Abstract

Introduction—The involvement of dopaminergic neurons in the ventral tegmental area (VTA) in Parkinson's disease (PD) has not been universally recognized by neuroscientists and neurologists. Here, we conduct a review of previous research documenting dopaminergic neuronal loss in both the substantia nigra pars compacta (SNpc) and VTA and add three new post-mortem PD cases to the literature.

Methods—PD and control brains were sectioned, stained for tyrosine hydroxylase, and cells in the SNpc and VTA were counted.

Results—Based on the review, we report two main results: 1) the VTA does degenerate in PD, and 2) the VTA degenerates less than the SNpc.

Conclusion—Inconsistent clinical information about these cases limits our ability to interpret how the VTA contributes to PD symptoms. However, our data in combination with prior PD neuropathological cases in the literature unequivocally establish that the VTA is involved in PD, and could be relevant for future investigation of non-motor symptoms in PD.

Keywords

Ventral tegmental area; Parkinson's disease

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder that causes motor disabilities and cognitive dysfunction due to the degeneration and loss of dopaminergic neurons in the midbrain. There is no debate as to whether the loss of neurons in the substantia nigra pars compacta (SNpc) is directly causative of the motor symptoms of PD [1]. While the ventral tegmental area (VTA) has long been suggested to be involved in PD

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[2], some authors have stated that the VTA is relatively spared [3–6] and some textbooks of neurology, neuroscience, and movement disorders state that the VTA is "affected little or not at all" [7,8]. Our motivation for this study was to review the existing literature and investigate the degree to which the VTA is involved in PD.

Previous research has provided several theories explaining this relative sparing, such as the variety of neurons found in the VTA [3,4], lower expression of the dopamine transporter [5], differences in calcium channel expression, as well as in levels of cytosolic dopamine and the presence of α-synuclein [6,9]. Here, we conduct a review of eight previous neuropathological studies in humans that directly quantified dopamine neurons in both the SNpc and VTA and add three new PD cases to the literature. We conclude, unequivocally, that the VTA degenerates in PD. This information could be helpful in understanding the pathophysiology of non-motor symptoms of Parkinson's disease. This line of evidence is consistent with widespread degeneration of ascending projection systems in PD including cholinergic, noradrenergic, serotonergic, and dopaminergic nuclei [10].

The VTA extends laterally from the midline (0 mm) to 4 mm and from 4 mm caudal to the mammillary bodies to 9 mm [11]. It contains dopamine neurons that project mainly to the ventral striatum and prefrontal cortex, with some projections to the amygdala. The VTA integrates information from a variety of cortical, brainstem, and peripheral centers, and contains a diversity of dopaminergic, GABAergic, and glutamatergic neurons, while the SNpc does not express glutamatergic neurons [3,4,12,13]. Due to the diversity of neurons, the VTA responds to local and distant neuromodulators [5]. The VTA has been implicated in a variety of behaviors and psychopathological states, including depression, anxiety, drug addiction, feeding, reward processing, and executive function [14]. Crucially, many PD patients have non-motor symptoms that include disorders associated with the VTA. For instance, 25% of PD patients have anxiety and/or depression [15] and nearly 30% of PD patients have executive dysfunction [16]. We present evidence from 43 previous PD cases and three new ones to explicitly test the hypothesis that the VTA is extensively involved in PD.

METHODS

Literature review

The following key words were used to collect published journal articles on the degeneration of the VTA in PD: ventral tegmental area, Parkinson's disease, dopamine, and degeneration. The articles were then analyzed for content of dopaminergic degeneration in the VTA and SNpc.

Collection

Seven perfusion-fixed (4% formaldehyde) human midbrains (from superior colliculus to cerebral peduncles) were collected. Brain blocks were post-fixed for at least one week in formaldehyde. For cryoprotection, midbrains were maintained in 30% sucrose. Midbrains were sectioned on a sliding microtome at 40 μm. All procedures complied with the University of Iowa Deeded Body Program guidelines [17].

Staining

Sections were blocked at room temperature for 1 hour in 0.1% Triton-X with normal horse serum (10 drops/ 30 mL) and then washed three times with 0.1 M PBS. Sections were then incubated in the primary antibody, rabbit anti-tyrosine hydroxylase (TH) (Abcam, 1:2000), on a shaker at 4°C for 48 hours. Following three washes with 1XPBS, sections were incubated in the secondary antibody, biotinylated anti-rabbit IgG (made in horse) (1:200), at room temperature for 2 hours. For DAB staining, the ABC mix kit (Vector) was used. Sections were mounted on subbed slides, subsequently dehydrated, and cover-slipped with Permount for imaging and storage [18,19].

Imaging and counting

Images were uploaded using Adobe Photoshop for TH positive cell counts. The SNpc and VTA were outlined using previously described parameters [11,20]. Cells positive for TH were counted in the SNpc and VTA and the average dopaminergic degeneration was calculated by comparing the mean number of TH positive cells in the PD group to the control group. Cell counts were compared via a t-test.

RESULTS

We reviewed eight studies in which TH expression was quantified in the VTA and SNpc. Though all of the previous studies reported here aimed to quantify TH differences between PD and controls, not all used the same methods. For instance, most studies used haematoxylin-eosin staining to label neuromelanin [11,21,22], which Bogerts had established as an appropriate marker for catecholaminergic neurons [23]. One only characterized pigmented neurons [20], another used immunostaining for specific proteins such as TH [24]. Only one of the studies reported here used radioenzymatic methods to quantify TH activity [25].

Of these studies, Bogerts et al. reported the lowest average VTA dopamine loss, as measured by TH expression, at 40 percent (3,100 cell in PD vs. 5,155 cells in controls) [21]. Additionally, in 1984 Javoy-Agid et al. reported the highest average loss at 77 percent (6,235 cells in PD vs 27,440 cells in controls) [26]. Across all reported studies, the VTA had significantly less cell loss compared to the SNpc ($p<0.05$). Unfortunately, not all studies reported clinical data on the PD cases. Of those that did, the widest range of disease duration was from months to 37 years [21]. Bogerts et al., Hirsch et al., and German et al. reported mean disease durations of 11, 7, and 14 years, respectively [11,21,22]. Additionally, of the studies providing patient symptoms, two stated that all cases exhibited tremor, rigidity, and akinesia/hypokinesia [21,22], while another reported that approximately half of the cases presented with these symptoms [24]. Interestingly, only one study mentioned cognitive symptoms and reported that two cases showed intellectual impairment while one case suffered from hallucinations [22].

In our cases, we characterized the VTA based on Uhl et al. [20] and German et al. [11], identified the VTA in all possible sections, and counted the TH-positive cells (Figure 1A). We report that, on average, PD brains showed a 49 percent decrease in TH-positive cells in

the VTA when compared to controls ($p < 0.01$), and a 41 percent decrease in the SNpc ($p < 0.01$) (Figure 1B). These differences are notable in the images (Figure 1C). Due to the fact that the cases used in this study were obtained from the Deeded Body Program at the University of Iowa, no clinical data was available from donors.

DISCUSSION

We report that both in previous literature and in our new data, the VTA consistently degenerates in PD. Our new cases indicate a 49 percent decrease, on average, of TH positive cells (Table 1), which falls in the 40–77 percent range reported in previous studies [21,26]. These data clearly and unequivocally establish that the VTA is involved in PD. We used TH as a marker of dopamine neurons; however, it should be noted that this enzyme is also found in other catecholaminergic neurons. Furthermore, there is a diversity of cell types in the VTA; thus, future work is required to account for this diversity to better study the differential dopamine loss in the VTA. Our review of the literature suggests that the VTA does appear to degenerate less than the SNpc. Since very little clinical data was provided in the literature, it is unclear if these differences can be accounted for by the clinical heterogeneity of the disease.

Two purported reasons for the differential loss of VTA dopamine neurons in PD have been proposed. First, Reyes et al. recently reported lower levels of calbindin in the SNpc when compared to the VTA in both mice and humans [27], consistent with previous studies [28]. They also reported that more neurons in the VTA co-express TH and calbindin than in the SNpc [27]. In cultured dopaminergic midbrain neurons from rats, higher levels of calbindin resulted in lower vesicular release, thus, VTA dopaminergic neurons release lower levels of dopamine [9]. This may result in fewer reactive oxygen species and less neurotoxicity. Secondly, SNpc neurons express $Ca_v1.3$ channels while those in the VTA express hyperpolarization-activated, cyclic nucleotide-regulated cation channels [29,30]. *In vivo*, blocking $Ca_v1.3$ channels decreases the levels of cytosolic dopamine following exposure to L-Dopa in SNpc neurons but not in VTA neurons, suggesting that the SNpc is more vulnerable to degeneration because of cellular mechanisms that increase intracellular dopamine [6]. However, most neurons in the central nervous system express $Ca_v1.3$ channels, including degenerating populations in the basal forebrain and locus coeruleus; thus, this reason alone cannot explain the difference.

Executive and cognitive functions have consistently been localized to the prefrontal cortex. , thus deficits in behaviors requiring executive function show abnormal activity in this area [31–33]. Moreover, lesions to the ventral midbrain have been associated with dysexecutive syndrome and dementia. Two lesion studies support the role of the VTA in executive function [34,35]. In these two case studies, patients presented with behavioral changes representative of dysexecutive syndrome and magnetic resonance imaging demonstrated, in both cases, a lesion to the VTA [34,35]. These case studies provide evidence for the importance of the VTA in cognition.

Notably, PD patients are clinically heterogeneous. Over 80% develop non-motor symptoms affecting mood, cognition, and sleep [15,36]. Though several studies have reported

improvements in cognition in PD patients while on dopamine replacement therapy (e.g. levodopa) when compared to off treatment [37,38], these results are not consistent [39], supporting the notion that PD is a complex disease. In the literature reported here, only one study provided information on non-motor symptoms: two patients had intellectual impairment and only one subject presented with hallucinations [22]. Goetz et al. and Forsaa et al. identified the development of psychotic symptoms as a risk factor for mortality, as those patients with psychotic symptoms died at earlier ages following PD diagnosis [40,41]. Similarly, PD patients demonstrating executive impairments exhibited lower prefrontal cortex activity as measured by fMRI during a working memory task [42]. An idea that grows out of this insight is that VTA dopamine loss contributes to non-motor symptoms such as depression [43]. Many of the PD patients in pathological studies in the literature, in this and previous studies, die before non-motor symptoms are routinely investigated, thus rendering it impossible to assess the significance of VTA cell loss in PD. Neuroimaging studies, however have shed some light on this question by documenting abnormalities in mesocortical and mesolimbic circuits. For instance, Frosini et al. demonstrated decreased dopaminergic innervation of the anterior cingulate cortex in PD patients with depression as compared to PD patients without depression, measured by dopamine transporter density [43]. Moreover, extensive animal work has indicated that dopamine dysfunction in mesocortical and mesolimbic pathways can consistently impair behaviors that are impaired in PD patients [44].

One specific hypothesis that grows out of this review is that PD patients with anxiety, depression, and executive dysfunction have substantial VTA/medial nigral dopamine loss. However, this hypothesis is made with caution as the dopaminergic system is not the only one affected during disease progression [10]. It has been reported in PD patients that dopamine levels are decreased by 70–90% [45,46], serotonin levels by 60% [46], norepinephrine levels by 80% [47], and acetylcholine levels by 70% [48]. Although these systems have been implicated in the non-motor symptoms of PD, it is possible that they also play a role in the emergence of certain motor symptoms, such as those that do not respond to dopamine replacement therapy. Additionally, some of these systems have also been demonstrated to degenerate with aging, specifically the dopaminergic system. Histological and imaging studies in humans and animal models of aging demonstrate decreases in dopamine in several nuclei [49–52]. However, on average the extent of dopaminergic degeneration is negligible when compared to that seen in PD [49]. Therefore, aging alone cannot explain the decreases in dopaminergic neurons in the VTA found in the present study and the literature.

Our patient samples and the studies we reviewed here did not reliably investigate the many nuclei containing the varying neurotransmitters. Our conclusions are limited because our patients and previous studies did not examine the level of Lewy bodies, tau, or other toxic proteins in the midbrain or cortex which have been previously associated with PD [53–55]. Unfortunately, detailed clinical information was not available for the present or past studies. Future work will explore these issues and will help establish the significance of cell loss in the VTA by combining detailed clinical phenotyping over the disease course with emerging structural, neurochemical, and pathological markers.

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Highlights

- We ran a literature review on degeneration of the VTA in PD and added new cases.
- The literature unequivocally demonstrates that the VTA is involved in PD.
- Our new cases support previous ones with significant degeneration in the VTA.

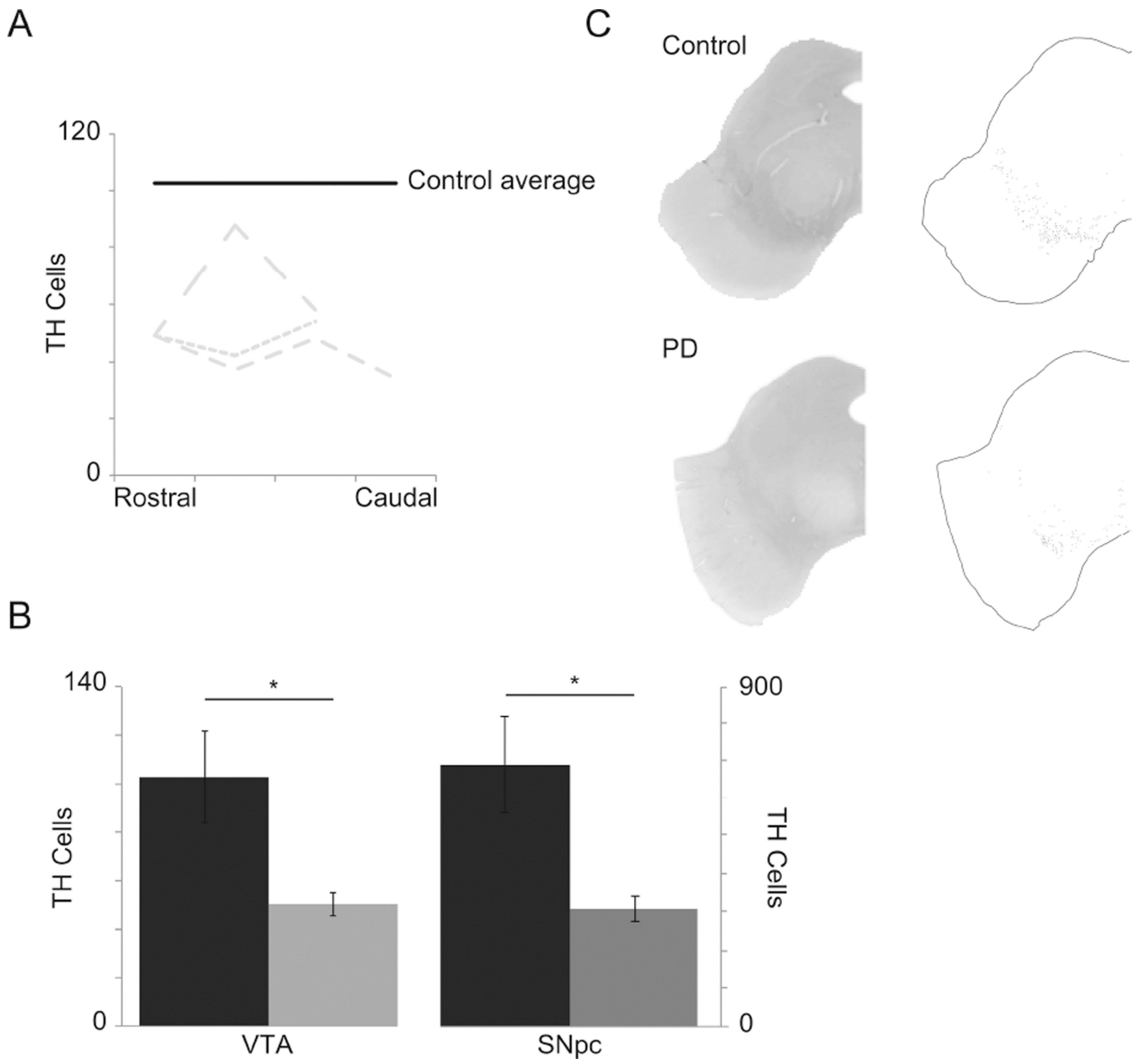

Figure 1.

A. Mean number of TH positive cells for controls (black line) and individual case TH positive cell counts from rostral to caudal (grey dashed lines). B. Average TH positive cell counts in the VTA and SNpc of controls (black) and PD cases (grey). C. Representative images of staining (left) for TH of a Control (top) and PD (bottom) cases and the respective cell labeling (right).

Table 1

Literature Data and New Cases.

Author, Year	Number of cases			
	Control	PD	Average decrease in SN (%)	Average decrease in VTA (%)
Javoy-Agid & Agid, 1980	13	7	70	57
Bogerts et al., 1983	9	5	65	40
Javoy-Agid et al., 1984	2	2	NA	77
Uhl et al., 1985	4	4	NA	55
Waters et al., 1988	15	12	57	45
Hirsch et al., 1988	3	4	77	48
German et al., 1989	3	5	73	58
Graybiel et al., 1990	3	4	88	48
Present study	3	3	41	49
Total:	**55**	**47**	**67**	**53**

The average decrease of SN and VTA dopaminergic cells was calculated in each paper by comparing the number of SN and VTA dopaminergic cells in PD brains and healthy controls. NA: not available.