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MEDICAL SCIENCES / DAHİLİ TIP BİLİMLERİ

The Mediating Effect of Caudate Nucleus Dopaminergic Activity on the Relationship Between Age and Cognitive Functions in Parkinson's Disease Patients

Parkinson Hastalarında Kaudat Çekirdek Dopaminerjik Aktivitesinin Yaş ve Bilişsel İşlevler Arasındaki İlişkiye Aracılık Etkisi

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Abstract

Objectives: Advancing age is the primary risk factor for Parkinson's disease (PD). In PD patients, dopaminergic activity is impaired, and cognitive dysfunctions are observed. This study investigated the mediating effect of caudate nucleus dopamine transporter binding score on the relationship between age and cognition in PD patients.

Materials and Methods: The open database of the Michael J. Fox Association was used, and data on 1,099 PD patients were accessed. Cognitive function scores and single-photon emission tomography findings assessing caudate nucleus dopaminergic activity were used.

Results: The caudate nucleus dopamine transporter binding score mediated the relationship between age and attention, processing speed, linguistic function, working memory, verbal episodic memory, and visual-spatial functions.

Conclusion: The cumulative neurodegenerative effect of age and PD requires monitoring of cognitive function. This study emphasizes the significance of considering dopaminergic activity in the caudate nucleus for diagnosing, monitoring, and treating cognitive functions in Parkinson's disease.

Keywords: Parkinson's disease, mediation analysis, cognition, caudate nucleus, dopamine transporter

Öz

Amaç: İlerleyen yaş, Parkinson hastalığı için birincil risk faktörüdür. Parkinson hastalarında, dopaminerjik aktivite bozulur ve bilişsel işlev bozuklukları görülür. Bu çalışmanın amacı, Parkinson hastalarında yaş ve biliş ilişkisinde, kaudat çekirdek dopamin taşıyıcısı bağlanma skorunun aracılık etkisinin araştırılmasıdır.

Gereç ve Yöntem: Michael J. Fox Derneğinin erişime açık veritabanı kullanılmış, 1.099 Parkinson hastasının verilerine erişim sağlanmıştır. Hastaların bilişsel işlev puanları ve kaudat çekirdek dopaminerjik aktivitesini değerlendiren tek foton emisyon tomografisi bulguları kullanılmıştır.

Bulgular: Kaudat çekirdek dopamin taşıyıcısı bağlanma skoru, yaş ile dikkat, işlem hızı, dilsel işlev, çalışma belleği, sözel epizodik bellek ve görsel-uzamsal işlevler arasındaki ilişkiye aracılık etmiştir.

Sonuç: Yaş ve Parkinson hastalığının kümülatif nörodejeneratif etkisi, bilişsel işlevlerin takibini gerektirmektedir. Bu çalışma, Parkinson hastalığında bilişsel işlevlerin tanı, takip ve tedavisinde, kaudat çekirdek dopaminerjik aktivitesinin dikkate alınmasının önemini vurgulamaktadır.

Anahtar Kelimeler: Parkinson hastalığı, aracılık analizi, biliş, kaudat çekirdek, dopamin taşıyıcısı

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Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra, affecting more than 6 million people worldwide (1). In addition to motor symptoms, including bradykinesia, rigidity, tremors, and postural instability, non-motor symptoms, including cognitive dysfunctions, pain, fatigue, and autonomic disorders, accompany the course of the disease and worsen the prognosis (2).

The aging process and neurodegeneration are associated, with advanced age being the primary risk factor for PD (3). Several molecular features of aging, including oxidative damage and mitochondrial dysfunction, loss of protein homeostasis, neuroinflammation, genomic instability, and impaired stress responses, overlap with mechanisms involved in PD neurodegeneration (4). Studies have suggested that dopaminergic neurons are more sensitive to age-related loss of mitochondrial function and more vulnerable to resulting bioenergetic stress (5). The Rotterdam study, one of the early and comprehensive studies on the relationship between age and PD, was conducted with approximately 7,000 individuals over 55 years of age. It reported that the prevalence of PD was 0.3%, 1%, 3.1%, and 4.3% in the 55-64, 65-74, 75-84, and 85-94 age ranges, respectively (6). Many subsequent studies have consistently confirmed the association between aging and the development of PD (7-9).

It has been documented that non-motor symptoms were present in patients with an advanced age of onset at the time of PD diagnosis, and many patients had previously sought medical advice for these symptoms (10). Due to its combined impact on dopaminergic and non-dopaminergic pathways, advanced age may lead to a more prevalent and severe course of PD-related functional disorders. Indeed, it has been reported that older individuals with PD exhibit more extensive involvement of extra-striatal and non-dopaminergic systems compared to younger ones (11). Since non-motor symptoms are resistant to levodopa treatment, it has been suggested that PD-related disability is broadly related to these symptoms (12). Cognitive impairments, which are considered non-motor symptoms, develop six times more frequently in patients with PD than in the healthy population (13). A longitudinal study showed that approximately half of PD patients with normal cognition developed cognitive impairment within six years of their initial visit (14). Frequent cognitive complaints include impairments in attention, executive functions, visual-spatial skills, language, and memory functions (15,16). Cognitive decline may occur before or at the time of diagnosis of PD, as well as many years after the diagnosis, and shows high variability in terms of clinical severity, related cognitive domains, and rate of progression (16). However, age itself is the greatest risk factor for the development of dementia in PD (11).

The striatum, comprising the caudate nucleus and putamen, is a key component of the basal ganglia. In PD, the loss of dopaminergic neurons in the striatum leads to dysfunction and structural changes in basal ganglia-thalamocortical circuits, which are modulated by dopamine (17). The caudate nucleus is linked to the dorsolateral prefrontal cortex and lateral orbitofrontal cortex. Dopaminergic input to the caudate nucleus has been linked to brain circuit activity associated with cognitive functioning in early PD (18). Indeed, several studies have associated cognitive deficits in PD with dopaminergic dysfunction in the caudate nucleus (18-21). For instance, dopamine depletion in the caudate nucleus has been suggested to lead to early impairment of executive functions in PD, as evidenced by changes in dorsolateral prefrontal and anterior cingulate metabolism (19). Furthermore, individuals diagnosed with PD and cognitive impairment exhibited reduced presynaptic dopamine binding in the right caudate in comparison to those without cognitive impairment (20). Relatedly, impaired dopaminergic function of the caudate nucleus has been associated with impaired memory functions (21). Moreover, the dorsal caudate nucleus is a major target of the nigrostriatal pathway, and abnormal modulation in nigrostriatal dopaminergic circuits has also been connected to cognitive impairments in the early stages of PD (22,23). In this context, the shrinkage of the caudate nucleus with age, along with the reduction of both dopamine receptors and transporters (24,25), may further exacerbate the negative effects of PD on cognitive functions.

One important element of the dopaminergic system is the dopamine transporter (DAT), a protein located in the presynaptic terminal of dopaminergic neurons responsible for dopamine reuptake (26). The DAT is crucial in controlling synaptic dopamine levels, making it a key regulator of dopaminergic neuron connectivity. The DAT single-photon emission computed tomography (DAT-SPECT) is a new imaging technique used to assess the activity of dopamine in the striatum of the brain in individuals with PD. The DAT scan involves the injection of Ioflupane I-123 to visualize dopamine transporters in the striatum (27). The amount of Ioflupane I-123 binding to dopamine transporters indicates the levels of bound striatal DAT and, consequently, the dopamine levels in the striatum. The DAT scan has a high sensitivity (84.4%) and specificity (96.2%) and is used for differential diagnosis (28). The degree of striatal dopaminergic deficiency, measured by striatal binding ratios, is associated with the severity of motor symptoms of PD, overall disease severity, and some non-motor symptoms (29,30). Early dysfunction of caudate dopaminergic activity is also reported to be a predictor for future cognitive impairment (31-33).

Cognitive decline in individuals with PD leads to a lower quality of life and increased burden for both the patients and their caregivers (34). Thus, identifying the reasons behind this decline in cognitive functions may help develop new strategies for managing the disease. This study aims to investigate whether the level of dopaminergic activity in the caudate nucleus mediates the relationship between age and cognitive functions in early-stage PD patients.

Materials and Methods

The data for this study was obtained from the Parkinson's Progression Markers Initiative (PPMI) database (35). PPMI is an international multicentric cohort study and it has been collecting data from newly diagnosed PD patients, people at risk, and unaffected controls since 2010. The study is based on a longitudinal design, with assessments taken at regular intervals. The findings in this study are based on the patients' initial assessment. Patients included in the study were over 30 years old and had not yet started medication such as levodopa, MAO-B inhibitors, dopamine agonists, and/or amantadine. The dataset was acquired from the PPMI website on 1.7.2024, and it only included data from PD patients. We accessed demographic data, caudate nucleus dopamine transporter binding score information, and cognitive test results of 1099 PD patients in the database. The PPMI protocol was reviewed and approved by the Institutional Review Board and the Independent Ethics Committee (IRB/IEC) at each center and the study followed the Guideline for Good Clinical Practice. Each participant provided written informed consent before being included in the study. This study obtained the right to use the PPMI database data.

Assessments

The cognitive functions were assessed using the following tests: Trail Making Test-A (TMT-A) (attention, executive functions), Digit Symbol Substitution Test (DSST) (processing speed), Montreal Cognitive Assessment (MoCA) (general cognition), Semantic Fluency Test (SFT) (linguistic function), Number Letter Sequencing Test (NLST) (executive function-working memory), Hopkins Verbal Learning Test (HVLT) (verbal episodic memory), and Line Orientation Test (LOT) (visual-spatial skills). TMT-A measured the time to complete the test, where a longer completion time indicates worse cognitive performance. All other cognitive tests measured accuracy scores, where a higher score indicates better cognitive performance.

DAT-SPECT analysis was conducted using Ioflupane I-123 to target the dopamine transporter during the scan as per the imaging technical manual (www.ppmi-info.org). The scans were performed at various imaging centers and then sent to the PPMI imaging central laboratory at the Neurodegenerative Disorders Institute in New Haven, where two expert readers visually interpreted the results. To ensure consistency of the reconstructions for all imaging centers, the SPECT raw data was reconstructed using HERMES (Hermes Medical Solutions, Skeppsbron 44, 111 30 Stockholm, Sweden) and then processed in PMOD (PMOD Technologies, Zurich, Switzerland). Attenuation correction and filtering (a standard Gaussian 3D 6.0 mm) were applied, and the images were normalized to a standard anatomical alignment. Next, the highest striatal uptake slice was identified, and the eight hottest striatal slices around it were averaged. Regions of interest were placed on the left and right caudate, and the count densities were extracted for each striatal region, and the specific binding ratio for the caudate was calculated as [(target region/reference region)-1]. In this study, the mean DAT binding scores (DATbs) of the caudate nucleus were used as DATbs.

Statistical Analysis

We used IBM Statistical Package for Social Sciences (SPSS) v26.0 software for all analyses. To investigate whether the caudate nucleus DATbs mediates the relationship between age and cognition, we applied the mediation model proposed by Hayes using the SPSS PROCESS macro (35). In this mediation model, the indirect effect is the impact of the independent variable (age) on the outcome variable (cognitive functions) through the mediator variable (caudate DATbs), while the direct effect is the impact of the independent variable on the outcome without considering the mediator. The total effect (c) is calculated as the sum of the direct (c') and indirect effects (ab) (Figure 1). We included gender and years of education as covariates in the model to account for their potential influence on the DATbs and cognitive outcomes in PD (36,37). To test the significance of indirect effects, we used a bootstrapping procedure with 5,000 samples. This method provides point estimates of the indirect effect and 95% confidence intervals. Indirect effects were considered significant when the 95% confidence interval did not contain zero (38). The significance level was set at <0.05.

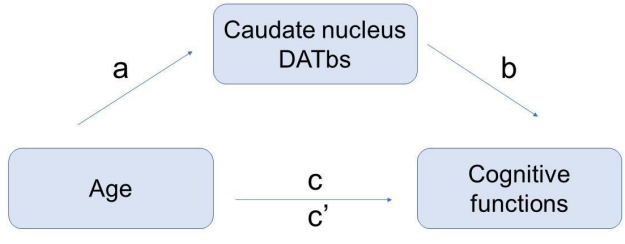

Figure 1: Simple mediation model. a, The effect of age on caudate nucleus DATbs; b, The effect of caudate nucleus DATbs on cognitive functions; c, The total effect of age on cognitive functions; c', The direct effect of age on cognitive functions

DATbs: Dopamine transporter binding scores

Results

In this study, data from 1,099 PD patients, including demographic, cognitive, and neuroimaging data, were analyzed. Participants had an average age of 62.64 (±9.56) years, and 41.2% were female. The demographic and clinical information of the participants, along with the cognitive test results, are presented in Tables 1 and 2, respectively.

Table 1: Demographic and clinical characteristics of patients

Age	62.64±9.56
Sex, n (%)	
Female Male	466 (41.2%) 663 (58.8%)
Hand preference, n (%)	
Right-handed Left-handed Ambidextrous	997 (88.3%) 93 (8.2%) 36 (3.2%)
Education years (year)	16.06±3.47
Diagnosis time (day)	406.12±634.75
Symptom time (day)	1338.94±3805.94
Caudate nucleus DATbs	0.86±0.33

Values are presented as %, mean (SD)
SD: Standard deviation, DATbs: Dopamine transporter binding scores

Table 2: Cognitive test scores

Trail Making Test-A (s)	40.54±21.45
Digit Symbol Substitution Test	42.39±10.80
Semantic Fluency	32.44±16.22
Number Letter Sequencing Test	4.05±5.36
Hopkins Verbal Learning Test	18.30±23.77
Line Orientation Test	9.70±12.51
Montreal Cognitive Assessment	26.76±2.62

Values are presented as mean (SD). TMT-A score represents the time required to complete the test, while the scores on all other tests denote accuracy
TMT-A: Trail Making Test-A, SD: Standard deviation, s: In seconds

The analysis revealed a significant total effect of age on TMT-A, indicating that older age was associated with a longer completion time (c=0.4487, standardized error (SE): 0.0658, p<0.001). Additionally, the direct effect of age on TMT-A remained significant (c'=0.4301, SE: 0.0660, p<0.001), suggesting partial mediation. The total effect of age on DSST was significant, and older age was associated with lower scores (c=-0.4362, SE: 0.0303, p<0.001). The direct effect of age on DSST was also significant, indicating partial mediating effect (c'=-0.4203, SE: 0.0302, p<0.001). The total effect of age on SFT was significant, and older age was associated with lower scores (c=-0.3596, SE: 0.0498, p<0.001). The direct effect of age on SFT was also significant, indicating partial mediating effect (c'=-0.3759, SE: 0.0499, p<0.001). The total effect of age on NLST was significant, and older age was associated with lower scores (c=-0.1124, SE: 0.0165, p<0.001). The direct effect of age on NLST was also significant, indicating partial mediating effect (c'=-0.1175, SE: 0.0166, p<0.001). The total effect of age on HVLT was significant, and older age was associated with lower scores (c=-0.3156, SE: 0.0741, p<0.001). The direct effect of age on HVLT was also significant, indicating partial mediating effect (c'=-0.3397, SE: 0.0743, p<0.001). The total effect of age on LOT was significant, and older age was associated with lower scores (c=-0.2144, SE: 0.0388, p<0.001). The direct effect of age on LOT was also significant, indicating partial mediating effect (c'=-0.2277, SE: 0.0388, p<0.001). The total effect of age on MoCA was significant, with older age associated with lower scores (c=-0.0732, SE: 0.0078, p<0.001). The direct effect of age on MoCA remained significant after accounting for the mediator (c'=-0.0715, SE: 0.0078, p<0.001), while the indirect effect was not significant. Table 3 presents the results of the simple mediation analysis, showing the total and direct effects on cognitive functions. Accordingly, caudate nucleus DATbs partially mediated the effect of age on TMT-A, DSST, SFT, NLST, HVLT, and LOT scores. Table 4 summarizes the caudate nucleus DATbs mediation findings for the effect of age on cognitive functions (indirect effects).

Table 3: Total and direct effects of age on cognitive functions

Cognitive tests	Total effect			Direct effect		
	β	SE	p	β	SE	p
TMT-A	0.4487	0.0658	<0.001	0.4301	0.0660	<0.001
Digit Symbol Substitution Test	-0.4362	0.0303	<0.001	-0.4203	0.0302	<0.001
Semantic Fluency	-0.3596	0.0498	<0.001	-0.3759	0.0499	<0.001
Number Letter Sequencing Test	-0.1124	0.0165	<0.001	-0.1175	0.0166	<0.001
Hopkins Verbal Learning Test	-0.3156	0.0741	<0.001	-0.3397	0.0743	<0.001
Line Orientation Test	-0.2144	0.0388	<0.001	-0.2277	0.0388	<0.001
Montreal Cognitive Assessment	-0.0732	0.0078	<0.001	-0.0715	0.0078	<0.001

β: Unstandardized regression coefficient
TMT-A: Trail Making Test-A, SE: Standardized error, p: Statistical significance

Table 4: Indirect effect findings			
Cognitive tests	β	95% CI	
		LLCI	ULCI
Trail Making Test - A	0.0186	**0.0036**	**0.0385**
Digit Symbol Substitution Test	-0.0160	**-0.0293**	**-0.0061**
Semantic Fluency	0.0163	**0.0042**	**0.0336**
Number Letter Sequencing Test	0.0051	**0.0011**	**0.0106**
Hopkins Verbal Learning Test	0.0241	**0.0061**	**0.0493**
Line Orientation Test	0.0133	**0.0037**	**0.0268**
Montreal Cognitive Assessment	-0.0017	-0.0042	0.0001

Bold indicates significant mediation effects
β: Unstandardized regression coefficient
LLCI: Lower level confidence interval, ULCI: Upper level confidence interval

Discussion

This study demonstrated that the effect of age on cognitive functions in patients with PD is mediated by caudate nucleus dopaminergic activity. This finding suggests that caudate nucleus dopaminergic activity may be an important factor in explaining age-related cognitive decline in PD patients.

The cognitive tests in which caudate nucleus dopaminergic activity showed a significant mediation effect were TMT-A, DSST, Semantic Fluency Test, Number Letter Sequencing Test, Hopkins Verbal Learning Test and Line Orientation Test, which assess attention-executive functions, processing speed, verbal function, working memory, verbal episodic memory, and visual-spatial functions, respectively.

The caudate nucleus plays a crucial role in the cortico-striato-thalamic-cortical circuit, serving as a central hub for information processing (39) and playing a key role in cognitive functions (40). Research has demonstrated a connection between DAT binding in the caudate nucleus and cognition, with longitudinal studies suggesting that this binding may be a predictor of future cognitive decline (20,41,42). Relatedly, this study's results align with previous research indicating that attention, working memory, processing speed, verbal fluency, verbal memory, and visuospatial functions are linked to dopaminergic activity within the caudate nucleus (19,21,43,44).

Supportingly, studies have shown that the decline in dopamine levels plays a crucial role in the impact of aging on cognitive function (45,46). Regarding PD, observations have highlighted that individuals with cognitive impairment exhibit lower striatal DAT binding, indicating a more pronounced dopamine denervation compared to those without cognitive impairment (19,31,47).

The precise role of dopaminergic regulation in cognition is not completely understood, but it is believed to affect cognitive functions through the nigrostriatal pathway and mesocortical dopaminergic projections (48,49). There is a dopaminergic connection between the substantia nigra and striatum in the nigrostriatal pathway, as well as between the ventral tegmental area and prefrontal cortex in the mesocortical pathway. Physiologically regulated dopamine neurotransmission is important for the proper functioning of these dopaminergic pathways. Diminished dopaminergic neurons and/or dopamine neurotransmitter levels may result in impaired connectivity between regions and possibly underlie cognitive dysfunction.

It is important to note that the striatum exhibits a topographical organization and has reciprocal connections with the neocortex. Changes in any part of the frontostriatal network can lead to structural and functional changes in other parts. Studies have shown that stimulating the dorsolateral prefrontal cortex increases neural activity and dopamine release in the caudate nucleus, indicating a connection between executive frontal areas and the caudate nucleus (50). Therefore, the association observed in this study between memory, visuospatial function, and the presence of DAT in the caudate nucleus may indicate a disruption in frontostriatal dopaminergic function. It is also worth noting that memory and visuospatial dysfunctions in PD are thought to be secondary to impairments in working memory and executive function (51).

Finally, the caudate nucleus receives indirect anatomical connections from the superior colliculus, a midbrain structure recognized for its key role in controlling visual attention (52). This structural relationship may help to explain how reduced dopamine levels in the caudate nucleus mediate the regulation of visual attention.

Unlike other cognitive assessments, this study found no significant mediation effect of caudate nucleus DATbs on the relationship between age and the MoCA score. One possible explanation is that as a global cognitive assessment tool, MoCA provides an overall measure of cognitive function across various domains, whereas the other assessments are more domain-specific. While MoCA is valuable for detecting mild cognitive impairment, it may not be sensitive enough to detect specific cognitive processes that depend on caudate nucleus function or dopaminergic activity. Additionally, MoCA may have a ceiling effect, particularly in patients with less severe cognitive impairment, making it less likely to capture subtle differences in cognitive function related to dopamine levels in the caudate nucleus. As a result, in early-stage PD without significant cognitive impairment, MoCA scores may not reflect subtle cognitive differences linked to caudate nucleus dopamine activity.

Given the cross-sectional nature of this study's design, it is important to consider the hypothesis that cognitive decline may occur before dopamine loss. Although most literature suggests that dopamine loss causes cognitive decline, it is

possible that cognitive decline could precede the degradation of the dopamine system through neuroplasticity and a feedback mechanism between cognition and neurotransmitter systems. This could potentially worsen both cognitive and dopaminergic impairments. Hence, this study's cross-sectional design limits the ability to establish causal relationships between age, cognitive functions, and dopamine transporter binding scores in PD. Future research should employ a longitudinal design to confirm these findings. Additionally, a regional analysis of dopaminergic activity in the caudate nucleus and its relationship with cognitive functions could provide more detailed insights. Lastly, further studies are needed to elucidate the impact of anomalies in other neurotransmitter systems in mediating cognitive function losses in PD.

Conclusion

This study provides insights into the interplay between age, cognitive function, and dopaminergic activity in the caudate nucleus, offering potential implications for the monitoring and managing of cognitive symptoms in PD. Further longitudinal studies are warranted to validate the mediating role of dopaminergic activity in cognitive decline and its clinical relevance for PD patients.

Ethics

Ethics Committee Approval: The PPMI protocol was reviewed and approved by the Institutional Review Board and the Independent Ethics Committee (IRB/IEC) at each center and the study followed the Guideline for Good Clinical Practice. This study obtained the right to use the PPMI database data.

Informed Consent: Each participant provided written informed consent before being included in the study.

Footnotes

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