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Review Article

Spatial memory deficits in Parkinson's disease: neural mechanisms and assessment

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Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder that primarily affects motor function. However, PD may also result in substantial cognitive impairments, including spatial memory deficits. Spatial memory, defined as the ability to encode, store, and retrieve information about environmental spatial orientation, is a critical component of daily functioning. A comprehensive understanding of the neural mechanisms underlying these deficits is imperative for the development of targeted interventions. This narrative review explores the neural basis of spatial memory deficits in PD, summarizing evidence from neuroimaging and neurophysiological studies. In addition, it examines current assessment methods and their clinical applications. Spatial memory is primarily governed by the hippocampus and interconnected cortical and subcortical structures, including the basal ganglia, the prefrontal cortex, and the anterior cingulate cortex. In PD, dopaminergic degeneration in the substantia nigra leads to functional disruptions in these networks. The basal ganglia, particularly the striatum, play a crucial role in procedural aspects of spatial navigation, while the hippocampus is essential for allocentric mapping. The utilization of functional neuroimaging techniques has yielded evidence of altered activity in these regions, which is concomitant with spatial memory deficits. Traditional neuropsychological assessments, laboratory-based tasks, and recent advancements, including virtual reality-based tasks, have been employed in the evaluation of spatial memory. The identification of spatial memory deficits in PD is of significant diagnostic and therapeutic importance. Future research should focus on integrating multimodal assessment tools to enhance diagnostic accuracy and explore novel therapeutic approaches targeting spatial memory dysfunction. The cause of spatial memory deficits in PD is multifactorial, arising from complex interactions between dopaminergic depletion and dysfunction in hippocampal-cortical networks. Advancements in assessment methodologies and targeted interventions hold considerable potential for enhancing spatial cognitive outcomes in patients diagnosed with PD. However, further research is required to refine diagnostic tools and develop effective rehabilitation strategies that are targeted at spatial memory impairments in PD.

Keywords: Parkinson's disease, spatial memory, assessment, central nervous system, intervention

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder traditionally characterized by motor symptoms such as bradykinesia, rigidity, tremor, and postural instability [1]. These symptoms are primarily due to dopaminergic neuronal degeneration in the substantia nigra [1]. However, increasing evidence has established PD as a multisystem disorder that includes a wide range of non-motor features, most notably cognitive impairments that may precede or co-occur with motor onset [2, 3].

Among these cognitive changes, spatial memory deficits, which affect an individual's ability to encode, store, and retrieve information about spatial orientation and navigation, have received increasing attention due to their significant impact on functional independence and safety [4, 5]. Spatial memory involves both egocentric (body-centered) and allocentric (environment-centered) reference frames and relies on a distributed neural network involving the hippocampus, basal ganglia, prefrontal cortex, and parietal regions [5, 6].

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Despite the growing recognition of cognitive impairments in PD, research on spatial memory deficits remains fragmented and inconsistent. While some studies have identified spatial memory alterations in PD [7, 8], a more comprehensive and systematic review is needed to elucidate the full extent of these alterations and their implications for patient care and research. This narrative review addresses this gap by integrating multidisciplinary findings from neuroimaging, neurophysiology, and clinical research. In particular, we focus on how dopaminergic depletion, hippocampal-cortical disconnection, and basal ganglia dysfunction collectively contribute to egocentric and allocentric navigation impairments. In addition, we emphasize the importance of motor subtypes and explore the use of novel assessment methods, including virtual reality-based tools, that may offer greater ecological validity and diagnostic precision.

The objective is to provide clinicians and researchers with a synthesis of the current evidence on spatial memory deficits in PD, providing a timely and comprehensive resource for clinicians and researchers seeking to better understand and treat spatial memory deficits in individuals with PD.

Neural basis of spatial memory

Spatial memory is supported by a network of interconnected brain structures that encode, store, and retrieve spatial information. The hippocampus, entorhinal cortex, and associated cortical regions play a central role in the formation of cognitive maps, integrating egocentric and allocentric reference frames to facilitate navigation and spatial reasoning [9].

The hippocampus plays a crucial role in spatial memory, with place cells that fire when an individual is at a specific location, effectively encoding spatial representations [10]. These cells interact with grid cells in the medial entorhinal cortex that fire at multiple locations, thereby forming a grid and providing a metric system for spatial navigation [11]. Consequently, these cells facilitate the encoding of locations and paths within an environment. The existence of additional cell types contribute to spatial representation. Head-direction cells, located in regions such as the anterior thalamus and postsubiculum, encode the direction of an animal's head, thereby providing a stable orientation system [12]. Boundary vector cells and border cells, located in the subiculum and medial entorhinal cortex, respectively, encode proximity to environmental boundaries and play a critical role in defining spatial relationships between landmarks [13].

The conceptualization of spatial information can be approached through two distinct frames of reference: the egocentric (body-centered) or allocentric (world-centered) frames. These frames are supported by different brain networks. The posterior parietal cortex has been shown to process egocentric representations by integrating sensory inputs and the coordination of spatial perception with movement [14]. The precuneus has been implicated in the integration of multiple egocentric spatial representations and their transformation into action-relevant information [15]. Conversely, allocentric representations are dependent on the retrosplenial cortex and the parahippocampal place area, which respond to large-scale environmental features and encode stable viewpoint-independent spatial layouts [9, 14, 15]. The integration of egocentric and allocentric representations is crucial for efficient navigation, allowing individuals to dynamically update their spatial orientation [15].

The ability to switch between egocentric and allocentric spatial frames is critical for navigation and flexible spatial memory. The posterior parietal cortex (area 7a) contributes to this transformation by integrating visual and proprioceptive information [9, 14, 16]. The retrosplenial cortex has also been implicated in reference frame transformation, as it receives input from both the hippocampus and parietal cortex, facilitating the conversion of egocentric sensory input into allocentric spatial memory [9, 11, 17].

Research has demonstrated that spatial memory is influenced by reward-based learning. The medial prefrontal cortex has been shown to encode goal locations, thereby playing a role in decision-making and adaptive behavior [10, 11, 18]. The orbitofrontal cortex, amygdala, and ventral striatum have been identified as critical components of reward-based spatial learning, facilitating the association of locations with anticipated rewards [11, 18, 19]. The dopaminergic system has been shown to refine

spatial learning by modulating reinforcement signals and enabling optimal decision-making strategies [19, 20].

Neural mechanisms of spatial memory deficits in PD

Spatial memory deficits in PD are the result of disruptions in multiple neural circuits, including the basal ganglia, hippocampus, dopaminergic pathways, and frontal cortical regions. The use of functional neuroimaging techniques, including functional Magnetic Resonance Imaging (fMRI) and Positron Emission Tomography (PET), has provided insight into the interactive nature of these regions and their contribution to spatial cognition [20, 21]. Due to the involvement of these structures, the cognitive domains most commonly affected include executive function, attention, memory, and visuospatial abilities [21].

Basal ganglia

The basal ganglia, particularly the striatum (caudate nucleus and putamen), have been demonstrated to play a fundamental role in procedural learning and spatial navigation [22, 23].

The striatum integrates sensory and motor inputs to facilitate goal-directed spatial behavior. In PD, the progressive loss of dopaminergic neurons in the substantia nigra pars compacta results in striatal dysfunction, thereby impairing the selection and execution of spatially guided actions [22-24]. The caudate nucleus, which has strong connections to the prefrontal cortex, is critical for allocentric (map-based) navigation, given its role in cognitive functions such as planning, decision making, and working memory [20]. Individuals with PD show caudate atrophy and decreased activation during spatial learning tasks [20, 22]. In addition, it has been observed that patients diagnosed with PD and exhibiting an akinetic-rigid subtype demonstrate a more significant deterioration in this strategy [8]. Conversely, the putamen plays a more important role in egocentric navigation, which depends on immediate sensory feedback. Putaminal degeneration in PD has been demonstrated to affect spatial working memory and motor coordination [24]. Therefore, patients diagnosed with PD exhibit a heightened propensity for impaired ability to comply with directives and to recall routes [8].

Regarding dopaminergic pathways, neurophysiological evidence suggests that dopaminergic modulation of the basal ganglia is critical for maintaining spatial memory performance [20, 21]. Dopaminergic dysfunction in this area results in abnormal processing throughout the cortico-basal circuit, contributing to the cognitive deficits observed in PD [25]. A decline in DA levels has been observed to result in a diminished capacity to encode and retrieve spatial relationships. Thus, in turn, has been shown to lead to impaired navigation and cognitive flexibility [20, 21].

Hippocampus and related structures

The hippocampus plays a fundamental role in allocentric spatial memory, a process that involves the formation of cognitive maps. Hippocampal atrophy and dysfunction in PD have been demonstrated to contribute significantly to deficits in spatial navigation [14]. The involvement of the hippocampus and related areas has been demonstrated to alter the ability to convert spatial goals (allocentric ability) into concrete movements (egocentric ability) and vice versa [22].

The entorhinal cortex has been shown to provide input to the hippocampus, thereby providing information about the travel distance [26]. This region experiences early degeneration in PD, leading to the disruption of spatial representations and grid cell activity [20, 22]. The grid cells, which are located in the entorhinal cortex, specifically in the dorsolateral part, are essential for spatial navigation and the formation of cognitive maps [11, 22]. These cells, in conjunction with the place cells located in the hippocampus, are essential in the development and correct functioning of the allocentric strategy [15]. In PD, the alterations in grid cells and place cells are attributable to the depletion of DA, affecting spatial perception and movement [8, 22]. This dysfunction gives rise to a phenomenon known as conceptual hypometry, which involves a compression of space that results in delayed perception of distances and sizes, as well as errors in the calculation of positions due to the failure of the grid cells. Some of the manifestations of this dysfunction are bradykinesia or hyperkinesia and bottleneck, characterized by an arrest or freezing before entering narrow spaces, as well as walking close to the edges [22].

On the other hand, the dentate gyrus, which is the hippocampal region responsible for pattern separation (the differentiation of similar spatial locations), is affected by α-synuclein pathology in PD, resulting in impaired recognition of previously visited locations [27, 28].

Dopaminergic pathways

DA has been shown to play a critical role in spatial learning by regulating interactions between the basal ganglia and hippocampus. Two major dopaminergic pathways have been identified as contributing to spatial memory: the nigrostriatal pathway, which connects the substantia nigra to the striatum, and the mesolimbic pathway, which projects from the ventral tegmental area to the hippocampus and cortex [28]. The striatum and the hippocampal-entorhinal cortex are functionally interconnected, a process that is dependent on DA and modulated by the locus coeruleus [22]. DA plays a critical role in facilitating communication between these structures, which is fundamental to the translation of spatial information into goal-directed motor actions [22].

DA depletion in the nigrostriatal pathway has been demonstrated to disrupt motor control, resulting in rigidity and reduced adaptability in spatial navigation [28]. Conversely, depletion of DA in the mesolimbic pathway has been demonstrated to compromise the function of the hippocampus [29], thereby impairing spatial encoding and memory retrieval [20, 29].

The effects of levodopa (L-DOPA) on spatial cognition have been reported to be contradictory. While it has been demonstrated to enhance motor function, excessive stimulation of the dorsal striatum has been demonstrated to reinforce habitual navigation strategies, thereby hindering flexible spatial learning and route adaptation [22]. Regarding the effects of dopaminergic modulation on visuoperceptual and perceptuomotor functions, Hanna-Pladdy et al. [30] observed that L-DOPA has differential effects on spatial accuracy, depending on whether the task involves perception or movement. Furthermore, their findings suggest that visuoperceptual deficits in PD may be linked to dysfunctions in corticostriatal circuits.

In the early stages of PD, the degeneration of striatal DA follows a spatiotemporal pattern, progressing from the dorsal to the lateral-ventral regions [31]. The dorsal striatal DA terminals in the caudate nucleus and putamen experience the most severe depletion, while the ventral striatum, including the nucleus accumbens, which is innervated by the ventral tegmental area, remains preserved [32]. As the disease progresses, the depletion of DA extends further, progressively impairing the mesolimbic pathway and leading to more widespread cognitive and behavioral dysfunction [33].

Frontal lobe and cortex

A correlation between PD and cortical atrophy has been established. The aforementioned alterations in the cerebral cortex can exert a direct or indirect influence on spatial memory, thereby further exacerbating navigation-related challenges [20, 44].

Prefrontal cortical atrophy, particularly in the dorsolateral prefrontal cortex, plays a critical role in the executive control of spatial memory [7, 23]. The dorsolateral prefrontal cortex has been shown to coordinate working memory for spatial locations and integrate sensory inputs for navigation [34]. Patients diagnosed with PD and exhibiting frontal atrophy have difficulty planning routes and adapting to changing environments [25, 30]. The dysfunction of the frontostriatal circuit, which involves the prefrontal cortex, has been associated with a profile of cognitive impairment characterized by deficits in planning and working memory [8]. The reduction in β-oscillations during memory encoding in individuals with cognitive impairment also affects the cortico-striatal circuitry [20]. Impaired functional connectivity between the prefrontal cortex and the hippocampus is also responsible for spatial memory deficits in PD. Reduced communication between the prefrontal cortex and the hippocampus has been demonstrated to contribute to disorganized spatial representations in this population [25]. In addition, alterations in functional connectivity within the frontal and parietal regions were identified in patients with PD-MCI [35]. Investigations in animal models of PD have also supported the association between prefrontal dysfunctions and deficits in spatial memory [25]. Lesions in the prefrontal cortex have been shown to disrupt oscillatory signatures involved

in spatiotemporal integration within working memory [36].

The anterior cingulate cortex is a pivotal structure within the medial prefrontal cortex that plays a critical role in spatial decision-making, conflict monitoring, and cognitive flexibility [37]. It is involved in evaluating choices, adjusting behavior based on feedback, and selecting optimal navigational strategies [37]. In PD, neurodegenerative changes result in reduced anterior cingulate cortex activation, which significantly impairs spatial cognitive processes [30, 38]. The anterior cingulate cortex plays a pivotal role in regulating error detection and adaptive decision-making in spatial tasks. It facilitates the recognition of erroneous navigational choices and enables adjustments, thereby ensuring optimal performance and adaptation in dynamic environments. However, in PD, reduced anterior cingulate cortex activation has been shown to impair error monitoring, thereby compromising the capacity to modify behavior based on feedback [39, 40]. The anterior cingulate cortex is also involved in reward-based learning, which is essential for reinforcing effective navigational strategies. DA depletion in PD has been demonstrated to diminish the capacity of the anterior cingulate cortex to assign appropriate value to correct versus incorrect spatial choices, resulting in perseverative errors rather than flexible spatial exploration [39, 41].

Insights from neuroimaging studies

Neuroimaging techniques have provided critical insights into the neural mechanisms underlying spatial memory impairments in PD. A comprehensive review of the literature reveals that functional and structural imaging studies have consistently demonstrated widespread alterations across key brain regions implicated in spatial cognition, including the hippocampus, basal ganglia, anterior cingulate cortex and white matter tracts. Indeed, a substantial body of research has demonstrated the presence of these alterations using fMRI, PET, EEG, and Diffusion Tensor Imaging (DTI) [42].

The findings from fMRI have revealed reduced activation in the hippocampus, caudate nucleus and anterior cingulate cortex during spatial navigation tasks in PD. The hippocampus, a structure that is critical for forming and retrieving allocentric spatial representations, exhibits reduced fMRI activation in this population, which correlates with deficits in cognitive mapping and episodic spatial recall [43]. The caudate nucleus, a critical structure within the basal ganglia, exhibits hypoactivity in PD, resulting in difficulties in planning and executing spatial movements [41]. Similarly, patients diagnosed with PD exhibit a marked decrease in activation within the anterior cingulate cortex during spatial learning tasks. This finding is associated with elevated rates of perseveration rates and impaired task-switching abilities [44, 45].

Neuroimages obtained with PET have provided further evidence for a link between dopaminergic dysfunction and spatial memory deficits in patients with PD [21]. PET scans have demonstrated reduced DA metabolism in the anterior cingulate cortex, thus supporting the hypothesis that the anterior cingulate cortex plays a role in spatial cognitive impairment. Given the role of the anterior cingulate cortex in decision-making and spatial navigation, its hypometabolism is likely to contribute to the decision-making difficulties and spatial disorientation experienced in PD [21]. PET imaging also reveals diminished reduced DA transporter binding in the nigrostriatal pathway. This finding indicates a depletion of DA in the substantia nigra and striatum. This reduction has been found to correlate with impaired spatial working memory and navigational deficits, thus further confirming the role of DA in spatial cognition [7].

DTI has provided structural evidence of white matter integrity in PD. The findings from DTI studies suggest the presence of fornix degeneration and disruptions in hippocampal output [46]. The fornix, a major white matter tract connecting the hippocampus to the prefrontal cortex, exhibits reduced structural integrity in PD [47]. This degeneration has been demonstrated to contribute to deficits in episodic spatial memory, as the fornix plays a crucial role in retrieving spatial information and guiding goal-directed navigation [46].

EEG studies have revealed neural oscillatory changes associated with spatial memory impairments in PD, which consist of diminished Theta-band oscillations (2-7 Hz) in the medial temporal lobe [36]. These oscillations are criti-

cal for the encoding of spatial information by the hippocampus. In PD, EEG recordings show reduced theta power within the medial temporal lobe, indicative of impaired neural synchronization and diminished spatial representations [20, 27].

Clinical and experimental evidence of spatial memory deficits in PD

Spatial memory deficits in PD have been documented in both clinical and experimental studies, particularly regarding impairments in allocentric (map-based) and egocentric (self-referenced) spatial representations.

Altered spatial representations in PD

Spatial representations have been observed to be impaired in patients with PD. Cammisuli and Crowe [48] explored spatial memory in non-demented PD patients and healthy controls employing the Route Learning Task (RLT) from the Rivermead Behavioral Memory Test (RBMT). The investigation revealed that patients diagnosed with PD exhibited substandard spatial memory performance in comparison to the control group. Additionally, the study by Schneider et al. [49] assessed spatial learning in patients with PD, PD-MCI, and healthy subjects using a computerized virtual version of the Morris water maze. A learning effect was observed in both healthy subjects and PD patients over reversal learning trials, with the improvement being more evident in the latter group, indicating the use of more landmark-dependent strategies (i.e., allocentric representations). In contrast, patients diagnosed with PD-MCI did not demonstrate compensatory use of allocentric strategies. Furthermore, at the end of the reversal learning trials, PD patients exhibited performance levels comparable to those of healthy subjects, while PD-MCI patients did not reach the same level of performance. Their search strategies required a greater duration and resulted in more extensive routes. These results suggest an egocentric impairment in both PD and PD-MCI patients, with an additional allocentric impairment in the latter.

A number of studies have focused on the assessment of egocentric representations in patients with PD, and they have found alterations in this strategy. For instance, Paquette et al. [50] examined the impact of DA medication on spatial navigation in patients with PD, cerebellar ataxia, and healthy subjects. The study compared the performance of patients with PD who were on medication (ON condition) and those who were not on medication (OFF condition) when navigating with their eyes open or closed. The findings indicated that all groups exhibited equivalent navigation performance with eyes open. In contrast, when the subjects were instructed to navigate with their eyes closed, patients receiving the OFF medication exhibited a greater walking radius compared to the control group, while the ON medication patients demonstrated a similar walking radius, albeit with earlier stops at the initial position. Furthermore, the cerebellar ataxia patients displayed noteworthy performance with their eyes closed, suggesting that the basal ganglia, but not the cerebellum, plays a substantial role in non-visual navigation. The hypothesis suggests that alterations in egocentric representations in patients with PD may be attributable to dysfunction in the caudate nucleus, a brain structure critical to egocentric representations.

Other studies have examined allocentric representations in PD. Thurm et al. [51] conducted a study that explored the allocentric frame of reference with a computerized spatial navigation task. The study's participants were patients with PD who had been receiving stable dopaminergic treatment for at least three months at the time of admission to the study. The study manipulated the DA medication during testing (ON and OFF medication conditions), as well as in healthy age-matched controls. The study revealed that the allocentric spatial navigation performance of the PD patients was comparable to that of the healthy controls when they were not on medication. This phenomenon can be partially explained by the ongoing DA treatment of patients diagnosed with PD, which has been demonstrated to enhance cognitive functions, including spatial memory, to a level comparable to that of non-PD subjects of a similar age. Thurm et al. [51] also found differences between the effects of DA medication on two different types of spatial memory: striatal-dependent spatial memory and hippocampal-dependent spatial memory. Specifically, the study observed that DA medication exhibited a more pronounced effect on the striatal-depen-

dent system compared to the hippocampal-dependent system, which was found to be more influenced by prior task experience.

A substantial body of literature has suggested that PD is characterized by an alteration of egocentric representations, with allocentric representations preserved [48, 50]. However, other studies assessing allocentric frames of reference in PD patients also found this strategy to be impaired. The study by Fernandez-Baizan et al. [8] aimed to separately assess both egocentric and allocentric representations in PD patients, comparing their performance with that of healthy subjects. The experimental protocol was divided in two sections. In part A, which was designed to assess participants' spatial short-term memory, subjects were tasked with memorizing the location of three cards, which were positioned in three of eight possible locations. Following a 10-second delay, the subjects were required to return the cards to their original locations. In part B, which was designed for the assessment of egocentric representations, participants were required to memorize the same three cards. However, immediately following the memorization stage, the cards were removed, and the participants were rotated to the right or to the left by 90° or 180°, depending on the trial. Conversely, the allocentric real-based task was conducted in a room with distal spatial cues, and participants were required to first memorize the location of the three cards. Following the encoding phase, the cards were removed, the subjects were blindfolded, and they were relocated to a different position. From this new position, the subjects were tasked with replacing the cards in their original locations. The results obtained demonstrated that patients with PD exhibited poorer performance compared to healthy controls in both parts of the egocentric task and the allocentric task. The authors proposed that while egocentric representations may be impaired due to concurrent impairments in related capacities, such as visual and spatial processing skills or vestibular signals, allocentric representations may be altered due to difficulties in visually exploring complex environments. Furthermore, the study proposes that the volume loss and hypoactivation of specific brain regions implicated in these spatial representations (i.e., the hippocampus for allocentric strategies and the striatum for egocentric strategies) could underlie the observed impairments. In relation to the impairments in allocentric representations in PD patients, Reinshagen offers an additional potential explanation [22]. The present author hypothesized that the depletion of DA affects grid cells, neurons located in the entorhinal cortex that function in the generation of external spatial allocentric references, resulting in symptoms of PD related to motor control and spatial memory.

Spatial memory impairments in PD: spatial and visual memory, contributing factors, and motor subtype differences

Spatial memory and visual memory are both components of the visuospatial memory system. Spatial memory is defined as the ability to recall the location of stimuli, while visual or object memory refers to the retention of the physical characteristics of the stimuli. The study by Possin et al. [52] explored whether spatial working memory and visual working memory were differentially impaired in PD patients using a computerized delayed response paradigm. In this task, participants were presented with two shapes in specific locations. Following a delay of 1, 5, or 10 seconds, they were required to determine whether a third shape corresponded to one of the two previous shapes. This correspondence could be determined in terms of shape (object condition) or location (spatial condition). The results indicated discrepancies in the performance of object and spatial working memory in patients with PD. Specifically, the impairment in object working memory was only evident after a 10-second delay, suggesting difficulties in maintaining the information. Conversely, impairment in spatial working memory was observed across all delay intervals. Notably, spatial working memory deficits in PD patients were only evident in trials that demanded precise location parameters. The experimental trials incorporated target and probe stimuli that exhibited a high degree of similarity in their location, though not an exact match. The results of this study indicate that spatial working memory deficits in PD are attributable to impairments in earlier stages of processing, such as encoding or spatial attention difficulties. These deficits do not appear to be caused by alterations in the maintenance of spatial information.

A body of research has emerged exploring the correlation between motor symptoms and spatial memory impairment. Given the prevalence of asymmetrical motor manifestations in PD, which are indicative of asymmetric subcortical dopaminergic degeneration, the study by Foster et al. [53] explored the association between motor asymmetry and spatial memory in subjects with mild PD. The experimental task employed a computerized spatial delayed response task, which has been demonstrated to reflect the functioning of the dorsolateral prefrontal cortex and the dopaminergic system. The findings revealed that patients with PD who predominantly exhibited motor dysfunction on the left side demonstrated significantly poorer performance compared to those with predominant right-side motor dysfunction. Notably, the latter group demonstrated spatial memory task performance analogous to that of non-PD participants. The collective results of the aforementioned studies indicated an association between the severity of right-brain disease and the extent of spatial memory impairment.

Lally et al. [54] investigated the relationship between the two PD motor subtypes and spatial memory performance. To that end, patients with PD were divided into two groups: the akinetic-rigid PD subtype and the tremor-dominant subtype. Both groups completed three spatial memory and spatial working memory tasks: the Brooks Spatial Memory Task (BSMT), the reverse Corsi Block Tapping Test (rCBTT), and the Body Position Spatial Task (BPST). The results indicated that the akinetic-rigid subgroup exhibited poorer performance on all three tasks, suggesting that this motor subtype is particularly impaired in spatial memory functioning. These findings are consistent with those reported in the study by Fernandez-Baizan et al. [8], which showed poorer performance in the allocentric task in the akinetic-rigid PD subgroup compared to the tremor-dominant subgroup.

Furthermore, the study of Fernandez-Baizan et al. [8] investigated the association between the duration since PD diagnosis and spatial memory performance. The findings indicated alterations in allocentric strategies during the initial years of the disease. In contrast, egocentric strategies and spatial short-term memory exhibited impairment between the ages of 9 and 11 years following diagnosis.

Assessment methods of spatial memory in patients with PD

A variety of paradigms have been used to assess spatial memory in Parkinson's disease, including real-world tasks, computer-based tools, and immersive virtual reality (iVR) environments. These methods provide insight into the nature and progression of spatial memory deficits, particularly impairments in egocentric and allocentric navigation, and allow the identification of subtle dysfunction across different stages and phenotypes of the disease.

The Morris water maze is a reliable tool for assessing spatial memory. This learning test, developed for rats, is based on long distances from a starting point along the perimeter of an open swimming area to an underwater exit platform. It is one of the most widely used paradigms to assess hippocampus-based learning and memory. While traditionally this task has been used in experimental paradigms with animal models, its adaptation for humans in both real-world and computerized versions allows evaluation of allocentric navigation and flexible spatial learning. A real-world based version of the Morris water maze task was employed in the study conducted by Leplow et al. [55]. This version of the task consisted of a circular platform in a room with different distal and proximal cues. Participants were instructed to find and remember five correct locations out of 20 possible locations. The learning phase was defined as the point at which participants performed two successive trials without errors. The experiment incorporated two probe phases: during the first phase, the starting position and the proximal cues were rotated, whereas in the second phase, the starting position was rotated and the proximal cues were completely removed. In both probe conditions, participants were tasked with identifying the five previously learned locations. The results indicated that, in comparison to the control group, PD patients exhibited a significantly higher number of errors only in the second probe phase, when the proximal cues were removed. A computerized version by Schneider et al. [56] introduced reversal learning phases, showing that deep brain stimulation improved performance, particularly in spatial flexibility tasks. The task comprised a spatial learning phase, a recall phase, and a spatial reversal learning phase. The results of the study suggest that deep brain stimulation

of the subthalamic nucleus may be a beneficial intervention for spatial reversal learning in patients with PD.

Another task typically used to assess visuospatial memory is the CBTT, which has two different forms: the direct form (dCBTT) and the reverse form (rCBTT), to assess short-term visuospatial memory and working memory, respectively. In both forms, participants are presented with a panel containing nine randomly arranged blocksd. The blocks are labeled on one side, ensuring that the numbers are only visible to the researcher. The dCBTT form is used to assess short-term visuospatial memory and requires the maintenance of both a movement sequence and a visuospatial pattern. In this form, the researcher must tap the blocks in a specific order, and subsequently, the participants are then instructed to reproduce the block sequence in the same order [54]. In the rCBTT form, which is used to assess visuospatial working memory, participants are instructed to tap the block sequence in the reverse order in which it is presented. In both forms, the block sequences gradually increase in length. As with the Morris water maze task, the CBTT is administered via computerized versions that display the blocks on a monitor or laptop. For instance, in the study by Stoffers et al. [57], a computerized version of the dCBTT was administered to treated PD patients, untreated PD patients, and healthy controls. The results indicated that treated PD patients exhibited poorer visuospatial memory performance compared to the control group. Ramos et al. [58] used a computerized version of the CBTT to assess visuospatial short-term memory and visuospatial working memory in PD patients and in healthy subjects at two time points 1 year apart. The dCBTT and rCBTT were employed for this purpose. The results demonstrated that PD patients exhibited poorer performance than healthy subjects at both time points. However, these differences were not statistically significant. A notable finding was the variation in the effect sizes of visuospatial dysfunction across the two CBTT forms and the assessment points. Specifically, the dCBTT form indicated moderate visuospatial dysfunction in PD patients at both baseline and the 1-year follow-up, whereas the rCBTT form reflected small dysfunction at baseline and moderate dysfunction at the 1-year follow-up. These results suggest that visuospatial working memory is more challenging for PD patients 1 year after their baseline assessment.

Other tasks analogous to the CBTT that have been utilized for the evaluation of spatial memory in patients with PD include the Spatial Span Task (SST) from the Cambridge Neuropsychological Assessment Battery (CANTAB) [59], the BPST [60], and the BSMT [61]. These tasks examine memory span, motor-cognitive integration, and mental imagery, offering complementary insights. Collectively, these tasks highlight how visuospatial dysfunction in PD extends beyond simple recall and frequently encompasses body-based navigation and executive control. The SST can be considered analogous to the computerized version of the CBTT. Both consist of white squares presented on a screen, and some of them briefly change color in a variable sequence. The direct form of the SST assesses visuospatial short-term memory and requires participants to select the boxes whose color changed in the same order that was displayed. Conversely, the reverse form of the SST assesses visuospatial working memory and requires subjects to select the boxes in the reverse order. The study by Fernandez-Baizan et al. [8] revealed that patients with PD exhibited lower performance levels in the direct form of the SST when compared to healthy subjects. However, no significant differences were observed in the reverse form of the SST. The BPST is structurally analogous to the dCBTT, yet it also demands whole body spatial cognition [60]. This real-world based task has been demonstrated to be both feasible and reliable in measuring spatial cognitive function and motor-cognitive interaction in patients with PD [60]. It requires stepping and turning in a spatial arrangement of five possible moves: step forward, step left, step right, quarter turn left, quarter turn right. The task's progression in difficulty, as measured by the number of movements and the span, culminates in a failure of the participants in two consecutive trials within a specific level of the span [54]. The BSMT is another real-based task that assesses spatial working memory; however, it also requires mental imagery. The task requires the memorization and subsequent recall of the placement of numbers in a matrix, with the numbers being presented by verbal descriptions (e.g., "there is a six in the top left") [54]. It is noteworthy that

both the BPST and the BSMT involve cognitive abilities beyond spatial memory, which can be compromised in patients with PD. This aspect makes their application in this population particularly relevant.

The RLT was employed for the assessment of spatial memory in individuals with PD [48]. This task is available in both real-based formats and in computerized versions. For instance, the RLT from the RBMT [62] is a real-based spatial memory task that includes immediate recall and a delayed recall of spatial information. In the immediate recall, the researcher performs a route to walk around a room and then requests that participants perform it. In the delayed condition, participants are required to complete the route previously demonstrated by the researcher. A computerized version of the RLT for spatial memory assessment in PD is provided by Yang et al. [63]. The task was conducted within a three-dimensional environment comprising a series of hallways with turns and objects serving as landmarks. During the learning phase of the study, participants observed a first-person video of a specific route through the environment and were instructed to memorize it. The test phase was comprised of three trials. In the initial two trials, designated as the forward trials, the researcher played the video and stopped it at each choice point, subsequently requesting the participant's selection. In the third trial, designated as the backward trial, participants traversed the route from the finish to the starting positions, requesting guidance at each choice point to return. Subsequent to the completion of these three trials, participants were asked to recall the objects (i.e., landmarks) in their specific locations within the 3-D environment. The aim of the study was to assess spatial memory in patients with PD and in two control groups: an age-matched group and a young-adult group. The results demonstrated that patients with PD exhibited poorer spatial memory performance compared to young adults. However, when performance differences were compared to the age-matched group, no significant differences were observed. This study highlights the potential of the RLT as a valuable tool for investigating spatial learning in large scale environments, thereby providing insight into the role of age-related cognitive decline in contributing to the wayfinding difficulties observed in PD patients.

The use of immersive Virtual Reality (iVR) for cognitive assessment, with a particular emphasis on spatial memory, remains limited. Nevertheless, iVR offers novel possibilities for ecological and body-centered assessment of spatial memory. The objective of the study by Tuena et al. [64] was to explore whether spatial representations are differently affected in PD patients with and without visual hallucinations (VHa). In order to achieve this objective, a patient diagnosed with PD and recurrent VHa, as well as five PD patients without VHa, participated in a Morris water iVR maze-based task. In this task, the participants were required to collect and memorize the position of four objects by utilizing a boundary of the arena, an intra-arena landmark, and distal cues. The study incorporated an immersive condition, wherein participants performed the task with an iVR device, and a passive condition, in which participants observed the navigation of a researcher on a screen. The results demonstrated a greater impairment in the egocentric representations compared to the allocentric representations in the PD patient with VHa compared to the PD group without VHa. However, the findings also revealed that, while the passive condition significantly influenced egocentric representations compared to allocentric representations, particularly in the PD patient with VHa, these differences in spatial representations were not observed in the immersive condition. The findings demonstrated that, in both the PD patients with VHa and in the PD patient without VHa, egocentric representations exhibited less impairment compared to allocentric representations when performing the task with iVR. These results suggest that iVR can provide body-based information during spatial navigation, a phenomenon that is particularly advantageous for egocentric representations.

The utilization of iVR for the assessment of spatial memory has experienced a marked increase in recent years. A recent systematic review examined studies that utilized iVR to assess visuospatial memory, concurrently registering brain activity during task performance. This analysis revealed activations in the prefrontal cortex, the medial temporal lobe, the parietal cortex, and the occipital cortex [65]. A substantial body of research suggests that iVR devices have potential as promising tools in the

cognitive neuroscience field. However, there is a lack of research on the application of these technologies in patients with PD. A scoping review explored the use of VR in cognitive rehabilitation [66]. The studies analyzed suggested that VR and other innovative tools may be more beneficial for the cognitive and behavioral alterations in PD than traditional tools and could have a positive effect on PD patients' quality of life [66]. The potential benefits of VR on cognitive functions in PD may be attributable to the activation of specific neurological mechanisms within the virtual environment. This activation has the potential to enhance the strength of the cholinergic and dopaminergic pathways, which have undergone alterations during the course of the disease [66]. Furthermore, the implementation of cognitive rehabilitation in the context of VR has the potential to impact brain reorganization processes and promote neuroplasticity [66].

Implications for clinical practice and future directions

Spatial memory impairments in PD have been associated with an increased frequency of navigation errors, difficulty in planning routes, frequent freezing episodes, and falls. These factors have a detrimental impact on daily functioning and autonomy. These deficits frequently precede the onset of overt dementia and are associated with frontal and hippocampal atrophy, dopaminergic depletion, and cortico-subcortical disconnection. Researchers have observed discrepancies between PD motor subtypes, such as akinetic-rigid versus tremor-dominant, with the former demonstrating heightened impairments in both allocentric and egocentric tasks. Furthermore, the duration of the disease, the medication status of the patient, and hemispheric asymmetry have also been demonstrated to influence spatial performance, thereby emphasizing the necessity for individualized assessment approaches.

The comprehension of the neural mechanisms of spatial memory and the neuropsychological assessment methods employed in individuals with PD are imperative to the formulation of practice guidelines in both clinical and research contexts.

Van Halteren et al. [67] have proposed a care management model for PD patients which contemplates the following five key aspects: care coordination, patient navigation, information provision, early detection of symptoms through proactive monitoring, and process monitoring. The early detection of initial changes in signs or symptoms is of particular importance, as it allows for earlier interventions, which prevent further exacerbation of problems and avoid potential complications [67]. The recognition that spatial memory deficits emerge in early stages of PD [68] emphasizes the need for an early assessment of spatial memory in this condition.

The integration of spatial memory tasks within cognitive training programs designed for patients suffering from PD has been demonstrated to be an effective strategy for addressing spatial memory deficits. This approach is exemplified in the study conducted by Peña et al. [69]. This study examined the effectiveness of a structured cognitive training and paper-and-pencil-based program in individuals with PD. The program was grounded in restoration, compensation, and optimization strategies of rehabilitation, incorporating visual learning, recall, and recognition tasks. In comparison to a group of PD patients engaged in occupational activities, the PD group that underwent the cognitive training program exhibited significant enhancements in visual memory. Furthermore, an additional study developed by the same research group revealed that these visual memory benefits persisted following an 18-month follow-up, thereby supporting the long-term efficacy of cognitive training [70]. The impact of cognitive training programs on spatial memory can vary depending on the specific characteristics of the program. A study by De Luca et al. [71] examined the effects of two distinct cognitive training programs on cognition in patients with PD. One group participated in a traditional paper-and-pencil program, while the other group engaged in a computer-assisted program that provided feedback to enhance motivation and awareness. The experimental design entailed the administration of spatial memory tasks, which were designed to elicit the memorization and subsequent recall of a sequence of symbols, the pairing of identical figures, and the recollection of specific locations. The findings of the study indicated that both programs resulted in improvements in scores from the baseline to the conclusion of

the training period. However, a more pronounced enhancement was observed in the PD group that underwent the computer-assisted cognitive training program. The study suggests that the implementation of PC-based and advanced technology tools in cognitive training for PD patients could be a promising avenue for research. These devices allow for the modification of various variables, including the duration of the session and the difficulty level of the activity. However, further research is necessary to draw stronger conclusions regarding the use of cognitive training and spatial memory tasks with advanced technologies, such as iVR devices.

Conclusions

Spatial memory deficits represent a critical yet frequently disregarded cognitive impairment in PD. While this disease is traditionally characterized by its motor symptoms, increasing evidence reveals the importance of non-motor symptoms, particularly spatial impairments. These deficits, which involve both egocentric and allocentric navigation strategies, are the result of the degeneration of key neural structures, including the hippocampus, basal ganglia, and cortical areas, as well as disruptions in dopaminergic pathways.

A growing body of research has demonstrated that neuroimaging g studies have revealed widespread alterations in brain networks responsible for spatial cognition in PD. These impairments manifest in challenges associated with routine activities, such as navigating new routes, maintaining spatial orientation, and interacting with the environment. Evidence suggests that while egocentric impairments are more prevalent in PD, allocentric deficits also emerge as the disease progresses. Moreover, differences in spatial memory performance have been observed between motor subtypes, with the akinetic-rigid subtype exhibiting greater impairments.

Given the growing recognition of spatial memory deficits in PD, its assessment has expanded to include a variety of tools, from real-world and computerized tasks to iVR paradigms. Emerging research suggests that VR-based assessments and interventions hold promise for improving spatial cognition, enhancing neuroplasticity, and mitigating disease-related cognitive decline. However, future research should focus on refining assessment tools and developing targeted rehabilitation protocols. A more profound comprehension of spatial memory deficits in PD will not only enhance diagnostic precision but also facilitate the development of strategies that promote patient autonomy, independence, and overall well-being.

From a clinical perspective, the early detection of spatial memory impairments is crucial for the implementation of effective interventions. The incorporation of spatial memory evaluations into cognitive screening for PD has the potential to enhance diagnosis, optimize rehabilitation strategies, and improve patient-centered care management. Cognitive training programs, particularly those integrating advanced technologies, may offer an effective approach to maintaining spatial memory and navigation abilities in PD patients. However, more research is needed to determine the effectiveness of different spatial memory training programs and their long-term benefits. For this purpose, a close collaboration between clinicians and researchers is essential to minimize the impact of spatial memory deficits in people with PD and enhance their quality of life.

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Disclosure of conflict of interest

None.

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