Emerging Concepts of Motor Reserve in Parkinson's Disease

Seok Jong Chung,1,2 Jae Jung Lee,3 Phil Hyu Lee,1,4 Young H. Sohn1

1Department of Neurology, Yonsei University College of Medicine, Seoul, Korea
2Department of Neurology, Yongin Severance Hospital, Yonsei University Health System, Yongin, Korea
3Department of Neurology, Ilsan Paik Hospital, Inje University College of Medicine, Goyang, Korea
4Severance Biomedical Science Institute, Yonsei University College of Medicine, Seoul, Korea

ABSTRACT

The concept of cognitive reserve (CR) in Alzheimer's disease (AD) explains the differences between individuals in their susceptibility to AD-related pathologies. An enhanced CR may lead to less cognitive deficits despite severe pathological lesions. Parkinson's disease (PD) is also a common neurodegenerative disease and is mainly characterized by motor dysfunction related to striatal dopaminergic depletion. The degree of motor deficits in PD is closely correlated to the degree of dopamine depletion; however, significant individual variations still exist. Therefore, we hypothesized that the presence of motor reserve (MR) in PD explains the individual differences in motor deficits despite similar levels of striatal dopamine depletion. Since 2015, we have performed a series of studies investigating MR in de novo patients with PD using the data of initial clinical presentation and dopamine transporter PET scan. In this review, we summarized the results of these published studies. In particular, some premorbid experiences (i.e., physical activity and education) and modifiable factors (i.e., body mass index and white matter hyperintensity on brain image studies) could modulate an individual's capacity to tolerate PD pathology, which can be maintained throughout disease progression.

Key Words: Dopamine transporter; Motor reserve; Parkinson's disease; Positron-emission tomography.

The concept of reserve was introduced to explain the mismatch between the degree of observed pathological changes in the brain and clinical manifestations.1 The most representative form of reserve is cognitive reserve (CR) that explains the differences between individuals in their susceptibility to age-related brain changes or Alzheimer's disease (AD)-related pathologies.2 Epidemiological studies suggest that lifelong experiences, including educational and occupational attainment and participation in leisure activities in later life, can enhance CR.2 Patients with high CR may exhibit fewer cognitive deficits despite having a similar level of AD pathology compared with those with low CR.2

Parkinson's disease (PD) is also a common neurodegenerative disease that affects the elderly. The main symptom of PD manifests as motor deficits, which is primarily related to striatal dopaminergic depletion. Motor symptoms in PD do not develop until 50–60% of nigral dopaminergic neurons are lost,3 suggesting the presence of compensatory mechanisms in the motor system. This compensatory ability (i.e., the ability of the brain to perform without functional impairment until damage reaches a critical threshold) is known as neural reserve4,5 and may differ among patients, reflecting an individual's capacity to tolerate neuropathological lesions. In addition, the amount of motor deficits may differ among patients who have a similar level of striatal dopamine depletion. These features suggest the presence of motor reserve (MR) in PD, which explains the individual differences in parkinsonian motor deficits at similar levels of pathological changes. Here, we summarize a series of our publications investigating MR in PD.
ASSESSMENT OF MR IN PD

Since 2009, dopamine transporter (DAT) scan using an $[^{18}F]$ N-(3-fluoropropyl)-2β-carbon ethoxy-3β-(4-iodophenyl) nor- tropane (FP-CIT) positron emission tomography (PET) scan was performed as an initial evaluation for the diagnosis of PD in Yonsei Parkinson Center. When patients were drug-naïve, Part III of Unified Parkinson’s Disease Rating Scale (UPDRS-motor) and the Mini-Mental State Examination (MMSE) were assessed in each patient to estimate their baseline PD motor severity and baseline cognitive function, respectively. The final diagnosis of PD was made according to the clinical criteria of the UK Brain Bank,6 the presence of appropriate DAT defects on FP-CIT PET scans,7 and the presence of PD drug response during follow-up (≥ 6 months). Patients with cognitive dysfunction (MMSE score < 24) were excluded from data analysis.

The detailed methods of PET-CT image acquisition and quantitative analyses of FP-CIT PET data were described previously.8 DAT activity was calculated in six striatal subregions: the ventral striatum, anterior caudate, posterior caudate, anterior putamen, ventral putamen and posterior putamen.7 Baseline UPDRS motor score and DAT activity in the posterior putamen or in the sensorimotor striatum were used to assess MR in each patient with PD. The degree of CR in AD is represented by clinical severity and AD pathology.2 If the same concept is applied to PD, MR may be represented by the initial UPDRS motor score (i.e., clinical severity) and the level of dopamine depletion (i.e., PD pathology) (Figure 1A). However, because we could not measure the level of dopamine depletion based on FP-CIT PET data, the X-axis of the graph should be replaced by DAT activity in the posterior putamen, and MR could be plotted as demonstrated in Figure 1B. In this figure, patients with high MR exhibited fewer motor deficits, i.e., lower UPDRS motor score, compared with those with low MR despite similar levels of DAT activity in the posterior putamen.

PREMORBID EXPERIENCES AND MR

Exercise engagement

Animal experiments have demonstrated that physical training may protect dopamine neurons from various parkinsonism-inducing neurotoxins.9,10 Additionally, epidemiological studies have demonstrated that long-term strenuous exercises are associated with reduced development of PD in humans.11,12 Accordingly, just as premorbid cognitive activity enhances an individual’s CR,2 premorbid physical activity (i.e., engagement in exercise) may enhance MR in individuals with PD. To address this hypothesis, premorbid engagement of leisure-time exercise was assessed in 102 patients using the Physical Activity Scale for the Elderly.13 Among patients with mild to moderate reductions in striatal dopaminergic activity (greater than the median DAT activity in the posterior putamen), the group with the highest exercise engagement showed significantly lower UPDRS motor scores (i.e., less parkinsonian motor deficits) despite having similar levels of DAT activity compared to the middle and the lowest exercise engagement groups combined (Figure 2A).
Meanwhile, among the patients with severe reduction in striatal dopaminergic activity, the highest tertile exercise group showed significantly higher UPDRS motor scores, suggesting a more rapid decline in motor function related to decreases in striatal DAT activity compared with the other two groups. These results suggest that engagement in premorbid exercise acts as a proxy for an active reserve in the motor domain (i.e., MR) in patients with PD. A recent paper demonstrated delayed clinical manifestation of PD among physically active skiers, which supports the above conclusion.\textsuperscript{14}

**Figure 2.** Premorbid experiences and MR. A: A scatterplot showing the relationship between DAT activity in the posterior putamen and motor deficits according to the premorbid physical activity. The highest tertile group (red) showed a significantly steeper slope compared with the middle tertile (green, \( p = 0.002 \)) and the low tertile group (blue, \( p = 0.001 \)), suggesting that engagement in premorbid exercise acts as a proxy for an active reserve in patients with PD [Adapted from Sunwoo et al. Parkinsonism Relat Disord 2017;34:49-53 (13)]. B: A scatterplot showing the relationship between DAT activity in the posterior putamen and motor deficits according to the level of education. Patients with higher education (closed circle) exhibited lower UPDRS motor scores compared to those with lower education (open circle) despite having a similar DAT activity in the posterior putamen (\( p = 0.032 \)) [Adapted from Sunwoo et al. J Neurol Sci 2016;362:118-120 (18)]. C: I. A scatterplot showing the relationship between DAT activity in the posterior putamen and motor deficits according to smoking status. Although mean DAT activity in the posterior putamen (\( p = 0.016 \)) and ventral putamen (\( p = 0.028 \)) was higher in current smokers (red) compared to ex-smokers (green) and never-smokers (blue), a similar slope of motor deficits relative to DAT activity among the groups suggests that current smoking does not enhance MR in individuals with PD. II. Comparison of longitudinal increases in LED according to smoking status. No significant differences in changes in LED were noted among the smoking groups (interaction between group and time, \( p = 0.948 \)), suggesting that current smoking has no additional clinical benefits in prognostic aspects [Adapted from Lee et al. Ann Neurol 2017;82:850-854 (28)]. MR: motor reserve, DAT: dopamine transporter, PD: Parkinson’s disease, UPDRS: Unified Parkinson’s Disease Rating Scale, LED: levodopa-equivalent dose.
Educational attainment

Educational attainment is a main factor that enhances CR in AD. Therefore, similar to CR in AD, higher educational dose (LED) did not differ among the smoking groups (Figure PD (Figure 2C–I). Longitudinal change of levodopa-equivalent relative to DAT activity in the posterior putamen suggests that protective effect on dopamine neurons that are most affected was more pronounced in the more affected side than the less affected side, suggesting that smoking preferentially exerts a sparing of DAT activity in the posterior and ventral putamen despite a similar duration of PD symptoms. The difference in motor deficits between the groups remained significant after adjusting for potential confounding factors (i.e., age, sex, disease duration, and MMSE scores) as well as DAT activity in the posterior putamen as covariates (Figure 2B). These results suggest that high education attainment could lead to enhanced MR in individuals with PD. Educational attainment has also been proposed as an MR proxy in other previous studies. and a higher level of education possibly enhances MR via greater cerebral volume or white matter integrity, increased synaptic plasticity, more efficient recruitment of brain networks or recovery mechanisms, and beneficial effects on general health or environmental risk factors.

Smoking habits

Cigarette smoking is associated with a reduced risk of PD; a meta-analysis showed that current smokers have a relative risk of 0.39 for the development of PD. However, whether smoking protects against the development of PD or PD itself protects against smoking remains controversial. In experimental animals, cigarette smoke protects against toxin-induced dopamine neuronal damage. However, it remains unknown whether smoking protects dopamine neuronal degeneration and subsequently enhances MR in humans with PD. Of the total 282 male patients with PD, current-smokers (n = 44) showed higher DAT activity in the posterior and ventral putamen but exhibited similar motor deficits compared to ex-smokers (n = 105) and never-smokers (n = 133). Selective sparing of DAT activity in the posterior and ventral putamen was more pronounced in the more affected side than the less affected side, suggesting that smoking preferentially exerts a protective effect on dopamine neurons that are most affected by PD pathology. However, a similar slope of motor deficits relative to DAT activity in the posterior putamen suggests that smoking status is not associated with MR in individuals with PD (Figure 2C–I). Longitudinal change of levodopa-equivalent dose (LED) did not differ among the smoking groups (Figure 2C–II), which suggests no additional clinical benefits related to current smoking.

DEMOGRAPHIC VARIABLES AND MR

Age

Ample evidence suggests that age at PD onset is a major determinant of clinical heterogeneity in patients with PD. Young-onset PD has consistently demonstrated slower disease progression, better response to dopaminergic medications, more frequent motor complications, and less frequent cognitive impairments compared to old-onset PD. However, the mechanism underlying the age at onset-dependent differences in PD remains unknown. Few reports have demonstrated that age at onset is associated with different patterns of striatal dopamine depletion in PD; however, these studies were limited by small sample size, confounding effects of PD medication, and less detailed segmentation of the striatum. To investigate the relationship between age at onset and MR in PD, a total of 205 patients were subdivided into tertile groups according to their age at onset of PD symptoms. The old-onset PD group (the highest tertile group, > 66 years, n = 73) exhibited higher UPDRS motor scores than the young-onset PD group (the lowest tertile group, < 58 years, n = 66), but DAT activity in the posterior putamen was comparable between the two groups. The old-onset PD group exhibited an increased risk for developing freezing of gait and required higher doses of dopaminergic medications for symptom control over time than the young-onset group (Figure 3A–I and II). In an additional analysis, a general linear model showed that the old-onset group had significantly more severe motor deficits than the young-onset group after controlling for sex, disease duration, and DAT activity in the posterior putamen (p < 0.05) (Figure 3A–III). This finding suggests that the old-onset group represents poor MR in PD compared to the young-onset group.

Sex

PD develops more often in males than in females; a meta-analysis showed an increased relative risk of 1.5 in males. Age at PD onset is later in females than in males, which partly correlates with the fertile life span in females. Clinically, female PD patients exhibit less severe parkinsonian motor features and better levodopa responses with more severe levodopa-induced dyskinesia. However, whether sex is a critical risk factor for developing levodopa-induced dyskinesia remains controversial. These sex differences suggest a beneficial influence of the female sex hormones (i.e., estrogen) against the development and progression of PD. The beneficial effect of estrogen could also enhance MR in individuals with PD, which may depend on
the patients’ age. Among a total of 307 patients, 45 female PD patients (n = 155) exhibited greater DAT activity in all the striatal subregions than male PD patients (n = 152). Age-related DAT decline was greater in the anterior and posterior caudate and in the anterior putamen in female PD patients compared to male PD patients but similar in other subregions (Figure 3B). Sex differences in age-related DAT decline in the antero-dorsal striatum is presumably due to age-related decline in estrogen. However, this difference was not observed in the sensorimotor striatum, suggesting that female PD patients do not have a greater MR

**Figure 3.** Demographic variables and motor reserve. A: I. Survival curves of the development of FOG in patients with young-onset PD (n = 66) and old-onset PD (n = 73). The old-onset group demonstrated an increased risk for developing FOG compared with the young-onset group (p = 0.007). II. Comparison of longitudinal increases in LED according to age at onset. The old-onset group required higher doses of dopaminergic medications for symptom control compared with the young-onset group (interaction between group and time, p < 0.001). III. A scatterplot showing the relationship between DAT activity in the posterior putamen and motor deficits according to age of onset. The old-onset group (green circle) exhibited more severe motor deficits than the young-onset group (red circle) after controlling for sex, disease duration, and DAT activity in the posterior putamen (p = 0.016) [Adapted from Chung et al. J Mov Disord 2019;12:113-119 (36)]. B: Scatterplots showing the relationship between DAT activity in the striatal subregions and age of onset according to sex. Women (closed triangle) exhibited higher DAT activity in all the striatal subregions compared with men (open circle). Women (dotted line) exhibited a more rapid decrease in DAT activity in the striatal subregions and age of onset according to sex. Women (closed triangle) showed lower UPDRS motor scores compared with nondominant-side onset PD (open circle) despite exhibiting a similar level of DAT activity in the posterior putamen (p = 0.013) [Adapted from Ham et al. Mov Disord 2015;30:1921-1925 (52)]. FOG: freezing of gait, PD: Parkinson’s disease, LED: levodopa-equivalent dose, DAT: dopamine transporter, UPDRS: Unified Parkinson’s Disease Rating Scale.
Handedness is the most prominent human behavioral asymmetry. Compared to the nondominant primary motor cortex (M1), the dominant M1 exhibits a greater dispersion of elementary movement representations with more profuse horizontal connections. Therefore, it is conceivable that the dominant hemisphere could have more efficient motor networks with a greater neural reserve to cope with the pathological changes related to PD. Unilateral onset and persistent asymmetry of motor signs are unique features of PD. To evaluate whether dominant-side onset PD patients showed greater MR compared to nondominant-side onset PD patients, 118 PD patients with significant asymmetric motor deficits were included for analysis. Among them, dominant-side onset patients (n = 57) exhibited fewer motor deficits despite exhibiting a similar level of DAT activity in the posterior putamen than the nondominant-side onset patients (n = 61) (Figure 3C), which suggests greater MR in dominant-side onset patients.

Body mass index

Patients with PD have a lower body mass index (BMI) than healthy subjects, which can be traced back almost 10 years before the diagnosis of PD. In addition, a low BMI in PD is more pronounced in patients with greater disease severity. Therefore, a low BMI could be associated with PD-related pathology (i.e., dopamine neuronal degeneration). A total of 398 patients were divided into five quintile groups according to their BMI. This study demonstrated that BMI was associated with DAT activity in all striatal subregions (Figure 3D–I, II, III, IV, and V), which suggests that a lower BMI might be related to a lower density of nigrostriatal dopaminergic neurons in PD. In an additional analysis, we compared MR between the low BMI group (the first and second quintile group) and the high BMI group (the fourth and fifth quintile group). This analysis showed that the low BMI group exhibited greater motor deficits than the high BMI group after controlling for age, sex, and DAT activity in the posterior putamen. DAT: dopamine transporter, BMI: body mass index, UPDRS: Unified Parkinson’s Disease Rating Scale.

PRECLINICAL AND CLINICAL PRESENTATION AND MR

Olfactory dysfunction

Olfactory dysfunction is present in approximately 70–90% of patients with early-stage PD and can precede the onset of motor symptoms by several years. The pathologic process of PD spreads from the olfactory bulb, anterior olfactory nucleus, and...
lower brainstem to different brain areas.\textsuperscript{39,60} Olfactory dysfunction is typically nonprogressive once motor symptoms develop;\textsuperscript{57,58} thus, predetermined olfactory involvement may have an impact on PD progression. Furthermore, the olfactory bulb is the main source for neurogenesis in adults.\textsuperscript{62} Thus, patients with spared olfaction (i.e., normosmic PD) may have a greater potential for neurogenesis and greater MR against the neuro-pathological processes of PD compared to hyposmic PD. Among a total of 208 patients who performed a Cross Cultural Smell Identification Test (CCSIT), normosmic patients (CCSIT score $\geq 9; n = 53$) exhibited a cut-off of 6/7 was used to minimize the false positives compared to hyposmic PD.

A clinical phenotype with greater MR and a more benign course in the posterior putamen, compared to hyposmic patients (CCSIT score $\leq 6, n = 96$) (Figure 4A). The LED during follow-up tended to be lower in normosmic compared with hyposmic PD patients. These findings suggest that normosmic PD is a unique clinical phenotype with greater MR and a more benign course compared to hyposmic PD.

**REM sleep behavioral disorder**

Rapid eye movement sleep behavior disorder (RBD) is an important biomarker of prodromal PD.\textsuperscript{63} Polysomnography-proven RBD exhibits a 130-fold increased likelihood ratio for PD.\textsuperscript{64} Accordingly, striatal DAT activity is reduced in patients with idiopathic RBD compared to healthy controls.\textsuperscript{65} PD patients without RBD exhibited a different pattern of striatal DAT activity compared to those with RBD.\textsuperscript{66} Furthermore, a prospective cohort study demonstrated that the presence of RBD in patients with PD at baseline indicates a more rapid disease progression of PD.\textsuperscript{67} Therefore, PD without RBD may represent a benign motor phenotype of PD similar to normosmic PD. Among a total of 122 patients who performed the RBD Screening Questionnaire (RBDSQ)\textsuperscript{68} at baseline, patients with clinically probable RBD (RBDSQ score $\geq 7, n = 39$; a cut-off of 6/7 was used to minimize the false positives for the presence of RBD in patients with PD\textsuperscript{69}) exhibited greater parkinsonian motor deficits predominantly in the less-affected side and axial symptoms and required higher LEDs during the follow-up period compared to those without clinically probable RBD (RBDSQ score $\leq 4, n = 58$).\textsuperscript{70} These differences in motor deficits remained significant after controlling for DAT activity in the putamen and other confounding variables (Figure 4B), suggesting that the presence of RBD at baseline may represent a distinct PD subtype with a malignant motor phenotype and low MR in individuals with PD.

**Depression**

Depression is a representative nonmotor symptom (NMS) that may precede the onset of parkinsonian motor symptoms.\textsuperscript{45} The presence of depression at early-stage PD has been proposed to result from the pathological involvement of the monoaminergic brainstem nuclei.\textsuperscript{71} Accordingly, early accompaniment of depression in PD may indicate widespread involvement of PD pathologies, which subsequently may limit compensatory ability and reduce MR in individuals with PD. A previous study that showed more physical impairments in depressed than nondepressed patients with PD\textsuperscript{72} supports the above hypothesis. A total of 474 patients who performed the Beck Depression Inventory (BDI) at baseline were divided into tertiles based on their BDI score.\textsuperscript{73} The highest tertile group (BDI score $\geq 15; n = 157$) showed more severe motor deficits and a lower level of cognitive performance than the lowest tertile group (BDI score $\leq 7, n = 158$). This difference in motor deficits remained significant after controlling for DAT activity in the posterior putamen and other confounding factors (Figure 4C–I). In addition, the highest tertile group received higher LEDs for symptom control during follow-up than the lowest tertile group after controlling for age, sex, and initial motor deficit severity (Figure 4C–II). These findings indicate that the presence of depression at baseline represents reduced MR in PD.

**Nonmotor burden**

A variety of NMS are frequently accompanied by PD, which occur across all stages of PD, including the prodromal stage.\textsuperscript{74,75} The involvement of PD-related pathology in widespread brainstem and cortical regions could be responsible for various NMS.\textsuperscript{76,77} Therefore, patients with greater nonmotor burden at baseline may have more widespread involvement of PD pathology and limited MR in PD compared to those with fewer nonmotor burden. A cluster analysis study has demonstrated that nonmotor dominant patients with PD exhibit a more rapid motor progression than either pure-motor or mixed motor/nonmotor PD patients,\textsuperscript{78} which supports the above hypothesis. A total of 151 patients who performed the Korean version of Non-Motor Symptom Scale (K-NMSS)\textsuperscript{79} at baseline were classified into two groups: high nonmotor burden group (K-NMSS score $\geq 41, n = 71$) and low nonmotor burden group (K-NMSS score < 41, $n = 80$).\textsuperscript{80} Patients in the high nonmotor burden group were older, had a longer disease duration, exhibited more severe parkinsonian motor deficits, and received higher doses of dopaminergic medications during follow-up than those in the low nonmotor burden group despite similar levels of striatal DAT activity. The difference in motor deficits remained significant after controlling for potential confounding factors, including DAT activity, in the sensorimotor striatum (Figure 4D). These results suggest that low nonmotor burden at baseline represents a greater MR in PD compared to high

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Figure 4. Preclinical and clinical presentation and motor reserve. A: A scatterplot showing the relationship between DAT activity in the posterior putamen and motor deficits according to olfactory function. Normosmic PD patients (blue) exhibited lower UPDRS motor scores than hyposmic PD patients (red) at similar levels of DAT activity \( (p = 0.016) \) [Adapted from Lee et al. Neurology 2015;85:1270-1275 (8)]. B: A scatterplot showing the relationship between DAT activity in the posterior putamen and motor deficits according to the presence of RBD. PD patients with clinically probable RBD (closed circle) exhibited higher UPDRS motor scores than those without clinically probable RBD (open circle) at similar levels of DAT activity \( (p = 0.046) \) [Adapted from Chung et al. Eur J Neurol 2017;24:1314-1319 (70)]. C: I. A scatterplot showing the relationship between DAT activity in the posterior putamen and motor deficits according to the BDI scores. The highest tertile group (red circle) exhibited higher UPDRS motor scores than the lowest tertile group (blue circle) after controlling for DAT activity in the posterior putamen \( (p = 0.046) \). II. Comparison of longitudinal increases in LED according to the BDI scores. The highest tertile group required higher doses of dopaminergic medications for symptom control compared with the lowest tertile group [Adapted from Lee et al. PLoS One 2018;13:e0203303 (73)]. D: A scatterplot showing the relationship between DAT activity in the sensorimotor striatum and motor deficits according to the NMS burden. The high NMS burden group (closed circle) exhibited higher UPDRS motor scores compared with the low NMS burden group (open circle) at similar levels of DAT activity \( (p = 0.004) \) [Adapted from Chung et al. PLoS One 2016;11:e0161316 (80)]. DAT: dopamine transporter, PD: Parkinson’s disease, UPDRS: Unified Parkinson’s Disease Rating Scale, RBD: rapid eye movement sleep behavior disorder, BDI: Beck Depression Inventory, LED: levodopa-equivalent dose, NMS: nonmotor symptoms.
nonmotor burden at baseline.

**NEUROIMAGING MARKERS AND MR**

**Dopamine depletion patterns**

Selective and asymmetric involvement of the posterior putamen is the principal pathological feature of the nigrostriatal pathway in patients with PD; however, the mechanism underlying this regional vulnerability remains unclear. The spatial patterns of striatal dopaminergic denervation are maintained as the disease progresses and vary extensively among individuals with PD. Therefore, the pattern of striatal dopamine depletion might represent a consistent and specific characteristic of each patient with PD and could provide information on the clinical profiles; few studies have demonstrated that residual dopamine in the associative/limbic and contralateral striatum can act as a compensatory mechanism for parkinsonian motor symptoms. A total of 634 patients were divided into tertile groups according to their patterns of striatal dopamine depletion, i.e., 1) the degree of dopamine loss found in the other striatal subregions compared to the posterior putamen [intersubregional ratio (ISR)] and 2) the interhemispheric asymmetry of dopamine deficits in the posterior putamen [asymmetry index (AI)] (Figure 5A–I). The highest tertile group of patients with PD according to AI exhibited milder parkinsonian motor signs than the lowest tertile group despite their greater decrease in DAT activity in the more affected posterior putamen (Figure 5A–II). In addition, the highest tertile group according to either ISR or AI values received lower doses of dopaminergic medications for symptom control than the corresponding lowest tertile group during the follow-up period (> 2 years). These findings suggest that the baseline patterns of striatal dopamine depletion can act as a marker for MR in PD, while high ISR and AI values represent a greater MR.

**White matter hyperintensity signals**

White matter hyperintensities (WMHs) are commonly observed in brain imaging studies of the healthy elderly. Ample evidence has suggested that WMHs have a clinical impact on motor disability in the elderly, which might be associated with interruption of frontal subcortical motor circuits. Moreover, white matter integrity appears to be related to the nigrostriatal synaptic dopamine function via common biological mechanisms. Accordingly, WMH might contribute to the clinical severity in patients with PD. Indeed, a number of studies have demonstrated that severe WMH is associated with greater motor deficits, especially axial motor impairments in patients with PD, whereas some studies failed to demonstrate this association. Our data revealed that the PD group with moderate to severe WMH (n = 109) exhibited more severe motor deficits than the PD group with minimal WMH (n = 227) despite comparable striatal DAT activity. Furthermore, the PD group with moderate to severe WMH required higher doses of dopaminergic medications for symptom control compared to the PD group with minimal WMH (Figure 5B–I). The moderate to severe WMH group also exhibited an increased risk of developing freezing of gait (Figure 5B–II). These results suggest that baseline WMH severity can be used as an imaging marker for MR as well as a prognostic marker for motor outcomes in individuals with PD.

**Functional brain network associated with MR**

In patients with AD, several neuroimaging studies have demonstrated that neural substrates of CR are closely linked to AD pathology-prone regions. We hypothesized that the neural correlates of MR in PD populations might be coupled with the network associated with motor function. Among 134 patients who performed resting state functional MRI at baseline, we calculated the ‘MR estimate’ of each patient based on the UPDRSmotor scores and DAT activity in the posterior putamen using a residual model with high MR estimates indicating high MR. Then, we applied a network-based statistic (NBS) analysis to identify the functional brain network associated with the MR estimate (i.e., MR network) using resting-state functional MRI data. NBS analysis identified that the MR network comprised of the basal ganglia (putamen, caudate, pallidum), inferior frontal cortex, insula, cerebellar vermis, hippocampus, and amygdala (Figure 5C–I), which could share the core components of the network associated with motor function in PD. Patients with an increased degree of functional connectivity within the MR network exhibited a greater MR. Moreover, higher MR network strength (i.e., increased functional connectivity within the MR network) was associated with a slower longitudinal increase in doses of dopaminergic medications (Figure 5C–II). These findings suggest that functional connectivity within the MR network could indicate an individual’s capacity to cope with neurodegenerative processes in PD.

**Prognostic implications of MR**

In AD populations, it is well established that patients with high CR exhibit a greater capacity to tolerate AD pathology but exhibit a more rapid cognitive decline once the critical threshold is reached. This is presumably due to more advanced pathologies at the critical threshold coupled with the shorter time frame required to reach the point when AD pathology overwhelms cognitive function. However, the impact of the initial MR on the long-term prognosis in PD remains unclear. A total of 205 patients were classified into two groups based on their...
Figure 5. Neuroimaging markers and MR. A: I. Examples of PD groups according to ISR and AI. The ISR-H exhibited a slower longitudinal increase in doses of dopaminergic medications than the ISR-L (p = 0.003). The AI-H exhibited milder parkinsonian motor signs than the AI-L despite their greater decrease in DAT activity in the posterior putamen. The AI-H group also showed a slower longitudinal increase in doses of dopaminergic medications than the AI-L group (p < 0.001) [Adapted from Chung et al. Clin Nucl Med 2018;43:787-792 (88)]. II. A scatter-plot showing the relationship between DAT activity in the posterior putamen and motor deficits according to the AI value. The highest tertile AI group (sky-blue circle and solid line) exhibited lower UPDRS motor scores than the lowest tertile AI group (dark blue circle and dashed line) despite a greater decrease in DAT activity in the posterior putamen. B: WMH signals. I. Longitudinal increases in LED. The PD group with moderate to severe WMH received higher doses of dopaminergic medications compared with the PD group with minimal WMH [Adapted from Chung et al. Parkinsonism Relat Disord 2019;66:105-109 (100)]. II. Curves of Kaplan-Meier estimates of the onset of FOG in PD patients with moderate to severe WMH and matched PD patients with minimal WMH. The moderate to severe WMH group exhibited an increased risk for developing FOG than the minimal WMH group (p < 0.001). C: I. Functional brain network associated with MR (MR network) at a primary threshold of p-value 0.001. A network-based statistic analysis identified that the MR network is composed of the basal ganglia, hippocampus, amygdala, inferior frontal cortex, insula, and cerebellar vermis. II. Spaghetti plot showing longitudinal changes in LED according to the MR network strength. The MRN-L (lower quartile, red line) exhibited a steeper increase in LED at 1-year and 2-year follow-up visits than the MRN-H (upper quartile, black line) [Adapted from Chung et al. Mov Disord 2020;35:577-586 (22)].
MR estimate, including those with high MR ($n = 65$) and those with low MR ($n = 57$), which was determined by initial motor deficits and striatal DAT activity (Figure 6A). As expected, the low MR group exhibited higher baseline motor deficits than the high MR group despite having comparable levels of DAT activity in the posterior putamen. During the follow-up period, the low MR group received higher doses of dopaminergic medications for symptom control than the high MR group (Figure 6B–I). Moreover, the low MR group exhibited an increased risk for the early development of levodopa-induced dyskinesia compared with the high MR group ($P_{\text{log-rank}} < 0.001$). III. Curves of Kaplan-Meier estimates of the onset of FOG in the PD groups. The low MR group exhibited an increased risk of developing FOG compared with the high MR group with low MR, LED: levodopa-equivalent dose, FOG: freezing of gait, LID: levodopa-induced dyskinesia.

**Table 1. Summary of factors affecting MR in patients with PD**

| MR-related factors | Comment |
|--------------------|---------|
| **Modifiable** | |
| Physical activity | Premorbid exercise → MR↑ |
| Education | Higher education attainment → MR↑ |
| Smoking | No association with MR |
| BMI | Low BMI → MR↓ |
| WMH | Moderate to severe WMH → MR↓ |
| **Nonmodifiable** | |
| Age | Old age → MR↓ |
| Sex | No association with MR |
| Hand dominance | Dominant-side-onset PD → MR↑ |
| Olfactory dysfunction | Normosmic PD → MR↑ |
| RBD | Presence of RBD → MR↓ |
| Depression | Presence of depression → MR↓ |
| Nonmotor burden | High nonmotor burden → MR↓ |
| Striatal DAT loss pattern | Antero-posterior gradient ↑, asymmetry ↑ → MR↑ |

MR: motor reserve, PD: Parkinson’s disease, BMI: body mass index, WMH: white matter hyperintensity, RBD: rapid eye movement sleep behavior disorder, DAT: dopamine transporter.

**Summary**

In this review, we discussed several factors that can enhance or reduce the MR in patients with PD (Table 1). In particular, some premorbid experiences (i.e., physical activity and education) and modifiable factors, such as BMI and WMH (which might be related to vascular risk factors), could modulate an individual’s capacity to tolerate PD pathology, which can be maintained throughout disease progression. Therefore, modification of these MR-related factors may be a reasonable treatment strategy for delaying parkinsonian symptom onset or improving the long-term motor outcomes of PD. Further studies are also needed to determine whether an active or passive reserve model will work in the strategy of enhancing each MR proxy.
Conflicts of Interest
The authors have no financial conflicts of interest.

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Ethical Standard
All procedures performed in our previous studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1975 Helsinki declaration and its later amendments or comparable ethical standards.

Author Contributions
Conceptualization: Young H. Sohn. Data curation: Seok Jong Chung, Jae Jung Lee, Phil Hyu Lee, Young H. Sohn. Formal analysis: Seok Jong Chung, Jae Jung Lee, Young H. Sohn. Investigation: all authors. Methodology: Seok Jong Chung, Young H. Sohn. Project administration: Young H. Sohn. Visualization: Seok Jong Chung, Jae Jung Lee, Young H. Sohn. Writing—original draft: Seok Jong Chung, Y och Jong Chung, Young H. Sohn. Writing—review & editing: Jae Jung Lee, Phil Hyu Lee. Approval of final manuscript: all authors.

ORCID iDs
Seok Jong Chung https://orcid.org/0000-0001-6086-3199
Jae Jung Lee https://orcid.org/0000-0003-4254-1289
Phil Hyu Lee https://orcid.org/0000-0001-9931-8462
Young H. Sohn https://orcid.org/0000-0001-6533-2610

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