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Longitudinal Response Patterns to a Combined Motor–Cognitive Intervention in Parkinson's Disease: An Exploratory Single-Arm Study

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Abstract

Background

Combined motor–cognitive exercise is a promising non-pharmacological intervention for both motor and non-motor symptoms in Parkinson's disease (PD). However, many exercise trials do not meet their primary endpoints, possibly because of substantial inter-individual variability in treatment response. In this exploratory single-arm study, we aimed to evaluate the overall effects of a combined motor–cognitive intervention and the heterogeneity of intervention responsiveness.

Methods

Thirty-eight individuals with PD completed a specialist-led combined motor–cognitive training program and were assessed at baseline, 8 weeks, and 20 weeks. Linear mixed-effects models were used to assess overall changes over time. To identify latent response subgroups that were not detected by group-level analyses, a multivariate latent class linear mixed model was applied to Unified Parkinson's Disease Rating Scale Part III and Montreal Cognitive Assessment scores. Elastic net logistic regression was used to identify predictors of subgroup membership.

Results

Significant improvements were observed in Unified Parkinson's Disease Rating Scale Part II, depressive symptoms, lower-extremity functional performance, and balance, whereas Unified Parkinson's Disease Rating Scale Part III and 6-minute walk distance worsened over time. Latent class analysis identified two distinct response subgroups that were primarily differentiated by divergent trajectories of Unified Parkinson's Disease Rating Scale Part III scores. Key predictors of subgroup membership were anxiety, grip strength, and the cognitive domain of quality of life, with the model accounting for 54.9% of the variance.

Conclusions

These findings indicate substantial heterogeneity in response to combined motor–cognitive interventions in PD and support the identification of response-based subgroups. Accounting for this heterogeneity may improve intervention design, refine outcome evaluation, and support more personalized rehabilitation strategies.

Trial registration:

Clinical Research Information Service of the Republic of Korea (CRIS), KCT0009353, registered on April 19, 2024.

Background

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by degeneration of dopaminergic neurons in the substantia nigra of the midbrain. It is characterized by both motor and non-motor symptoms that progressively worsen over time, substantially impairing health-related quality of life (HRQoL) and functional independence [1–3]. Given its multifaceted clinical presentation, optimal management of PD requires a multidisciplinary approach that integrates pharmacological and non-pharmacological interventions [4]. To date, most non-pharmacological interventions have focused primarily on motor symptoms, with exercise-based approaches widely recommended [5, 6]. Evidence from randomized controlled trials indicates that exercise modalities, including endurance, resistance, balance, and flexibility training, can improve physical function, gait performance, balance, and activities of daily living (ADL) in individuals with PD [5, 7]. More recently, the role of cognitive processes in enhancing exercise interventions has gained increasing recognition [8]. Cognitive–motor interventions integrate cognitive and physical tasks and aim to improve cognitive function or attenuate cognitive decline while also improving motor outcomes such as postural control and gait performance [8]. Despite these advances, findings across studies remain inconsistent. Several trials have reported no significant improvements in physical function or HRQoL at the group level, and systematic reviews have reported considerable variability in intervention outcomes [9]. One explanation for these inconsistencies is the marked heterogeneity inherent in PD, where individuals exhibit highly variable responses to identical interventions [10]. Such inter-individual variability may reduce statistical power and obscure clinically meaningful effects in conventional group-level analyses [10]. Accordingly, increasing interest has been observed in characterizing individual differences in treatment responsiveness [11, 12]. However, most studies have adopted dichotomous classifications of participants as responders or non-responders, which provide a limited representation of the complexity of intervention effects [10]. A more comprehensive understanding of factors underlying differential responsiveness is essential to inform optimal intervention strategies and advance personalized rehabilitation approaches [13]. For example, Albrecht et al. evaluated responsiveness to a highly challenging balance and gait intervention in individuals with PD using predefined cut-off values derived from prior literature [14]. Their findings indicated that responsiveness varied according to baseline characteristics, with greater improvements observed in individuals with slower gait velocity and lower self-perceived walking ability, whereas reduced responsiveness was associated with recent fall history or impaired gait [14]. Although informative, such approaches remain constrained by predefined domains and binary classifications, thereby limiting their ability to capture the full spectrum of response patterns [15].

Moreover, most prior studies have relied on pre–post comparisons, capturing simplified representations of responsiveness, such as improvement, deterioration, or stability. These approaches do not account for the dynamic and longitudinal nature of treatment responses. To address this limitation, data-driven approaches such as latent class modeling of longitudinal trajectories have been proposed to identify

latent subgroups characterized by distinct response patterns over time. This approach enables more nuanced characterization of response heterogeneity and provides clinically relevant insights for treatment stratification and precision rehabilitation [14, 16]. These approaches may identify clinically meaningful response phenotypes that are not detectable using conventional analytical methods. Accordingly, in this exploratory single-arm study, we aimed to evaluate the effects of a combined motor–cognitive exercise intervention in individuals with PD, and identify latent response patterns across motor and cognitive domains, as well as factors associated with differential responsiveness. We hypothesized that distinct latent subgroups with differential response trajectories would be identified.

Methods

Participants

This study included individuals diagnosed with idiopathic PD according to the 2015 Movement Disorder Society (MDS) diagnostic criteria by a clinician. Inclusion criteria were age > 50 years and modified Hoehn and Yahr stage 1–3, indicating independent walking and mobility without assistive devices. Exclusion criteria included a history of cardiovascular, musculoskeletal, vestibular, or other neurological disorders; use of mobility-assistive devices; and pharmacotherapy-refractory dyskinesia. All participants were assessed in the medication “ON” state during the exercise program and experimental procedures to ensure the full therapeutic effect of their medication. The study was approved by the Institutional Review Board of Dong-A University Hospital (IRB number: DAUHIRB–22–089). All participants received a full explanation of the study procedures and provided written informed consent. The study was registered in the Clinical Research Information Service of the Republic of Korea (KCT0009353) on April 19, 2024.

Intervention

The combined motor–cognitive intervention consisted of a 20-week program, including an initial 8-week adaptation phase (T1) followed by a 12-week progressive training phase (T2). During the initial 8 weeks, participants focused on safely learning and adapting to the exercise tasks. During the subsequent phase, exercise intensity was progressively increased every 3 weeks according to individual performance and tolerance [17].

The program was delivered in a group-based format, with sessions conducted twice weekly for 60 minutes under the supervision of an exercise specialist. The intervention was based on established exercise and dual-task training protocols for individuals with PD. The program aimed to improve physical function, mobility, and cognitive function. Each session followed a standardized structure comprising a 10-minute warm-up, a 40-minute main exercise phase, and a 10-minute cool-down. Participants rated their perceived exertion using the modified Borg Rating of Perceived Exertion (RPE) scale after each

session [18]. RPE was used to monitor and adjust exercise intensity to ensure it remained within a safe and tolerable range [17].

The warm-up phase included breathing exercises, marching in place, and dynamic stretching to prepare participants for the main exercise phase, with a focus on increasing range of motion and reducing muscle stiffness. The main exercise phase targeted muscle strength, coordination, dynamic balance, and functional mobility. It included stepping exercises combined with cognitive tasks, upper- and lower-limb resistance exercises, and trunk flexibility exercises. Stepping exercises incorporated dual-task components requiring motor coordination and cognitive processes such as memory and executive function [19, 20]. The cool-down phase included stretching for recovery, relaxation, and prevention of muscle stiffness. A detailed description of the intervention is provided in Supplementary Table 1.

Measurements

All participants underwent standardized physical assessments and clinician-administered evaluations of clinical characteristics. Assessments were conducted at baseline (T0), after 8 weeks (T1), and after 20 weeks (T2) [21]. Changes over time were defined as follows: Δ1 represented the change from T0 to T1, Δ2 represented the change from T1 to T2, and Δ3 represented the overall change from T0 to T2.

Cognitive function was assessed using the validated Korean version of the Montreal Cognitive Assessment (MoCA-K) [22, 23]. Motor function was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) Parts I–IV [24, 25], Hoehn and Yahr (H&Y) scale [26], Mini Balance Evaluation Systems Test (Mini-BESTest) [27], grip strength measurement, Five Times Sit-to-Stand Test (FTSTS) [28], and 6-minute walk test (6MWT) [29]. Fall-related concerns were assessed using the Falls Efficacy Scale-Korean (FES-K) [30]. Depression and anxiety levels were assessed using the Beck Depression Inventory (BDI) [31] and Beck Anxiety Inventory (BAI) [32], respectively. HRQoL was assessed using the Parkinson's Disease Questionnaire-39 (PDQ-39), which includes eight domains: mobility, ADL, emotional well-being, social stigma, social support, cognition, communication, and physical discomfort [33].

Statistical analysis

All data were tested for normality using the Shapiro–Wilk test. Statistical analyses were conducted using both parametric and nonparametric methods as appropriate. Demographic and clinical characteristics were summarized using mean and standard deviation (SD). Continuous variables were compared using independent t-tests or Mann–Whitney U tests, and categorical variables were analyzed using the chi-square test. Analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA) and Python (version 3.10) with Pandas, NumPy, and Scikit-learn libraries.

Overall time effects and inter-individual variability

Time effects following the intervention were analyzed using linear mixed-effects models, with time points (T0, T1, T2) included as categorical fixed effects [34, 35]. A random intercept was included to account for baseline differences among individuals, and random slope variance was included to evaluate variability in individual trajectories. Likelihood ratio tests were used to assess model fit and evaluate the contribution of additional model components. Effect size (ES) was calculated as the mean change divided by the standard deviation of baseline values. ESs were interpreted as follows: ≥0.80 large, 0.50–0.79 moderate, 0.20–0.49 small, and 0.00–0.19 very small [36, 37]. Analyses were conducted using the lme4 package in R [38].

To evaluate clinically meaningful changes not apparent at the group level, participants were classified as responders or non-responders based on established criteria. For UPDRS Parts I–IV, responder status was defined using minimal clinically important difference (MCID) thresholds. The MCID represents the smallest change in an outcome perceived as beneficial by the patient [39, 40]. Use of the MCID helps researchers and clinicians design and interpret treatment protocols and evaluate treatment response. For all other variables, distribution-based thresholds were defined as 0.5 times the baseline standard deviation [41]. All change scores were coded such that positive values represented improvement.

Response trajectory identification and predictors of responsiveness

Latent class mixed modeling (LCMM) aims to provide estimation functions that address these different extensions of the linear mixed model [42]. Among its key estimation functions, multivariate latent class linear mixed model (MLCLMM) was employed to identify the heterogeneous subgroups based on longitudinal trajectories across multiple outcomes [42, 43]. A multivariate latent class linear mixed model (MLCLMM) was applied using UPDRS Part III and MoCA scores as outcome variables. Models with two and three classes were evaluated to preserve adequate sample size and clinical interpretability within each subgroup. The optimal class solution was determined using the Akaike Information Criterion and Bayesian Information Criterion, with lower values indicating better model fit [44].

Following latent trajectory analysis, linear regression was performed to identify the time-specific changes associated with the overall trajectories of motor symptom severity and cognitive function. The dependent variables were Δ3 values for UPDRS Part III and MoCA, whereas the independent variables were changes at Δ1 and Δ2.

Prediction model

Elastic net–regularized logistic regression was used to identify predictors of latent subgroup membership. The elastic net combines L1 (LASSO) and L2 (Ridge) penalties of the LASSO and Ridge, which adds quadratic regularization via L2 penalties regressions, overcoming their respective implementation problems, effectively setting some coefficients to zero and, enabling variable selection while addressing multicollinearity. Bootstrapping with 300 resamples was performed to assess the

stability of variable selection. Variables with selection frequencies > 0.75 were retained. Multivariate logistic regression was then used to identify independent predictors of subgroup classification [45].

Finally, network analysis was conducted to examine associations between selected predictors and variables at Δ1, Δ2, and Δ3 based on partial correlations. A graphical lasso model was applied to estimate regularized partial correlations and to shrink less relevant edges to zero [46, 47]. Node positions were determined using the Fruchterman–Reingold algorithm, and edge thickness indicated the strength of associations (Fig. 1) [48].

Results

Participant characteristics

Of the 48 individuals with PD who met the inclusion criteria, 46 enrolled in the program. A total of 38 participants completed the 20-week intervention and follow-up assessment (Fig. 2). Table 1 summarizes the demographic and clinical characteristics of the cohort (n = 38).

Table 1. Demographic and clinical characteristics of individuals with Parkinson's disease (n = 38).

Characteristics	Mean ± SD or n
Sex (male/female)	22/16
Age (years)	68.66 ± 5.08
Height (cm)	161.58 ± 8.44
Body weight (kg)	63.64 ± 10.90
BMI (kg/m^2)	24.24 ± 2.78
MoCA score	26.1 1± 3.14
Hoehn and Yahr scale	1.88 ± 0.54
UPDRS Part □ (score)	9.39 ± 5.93
UPDRS Part □ (score)	9.95 ± 6.48
UPDRS Part □ (score)	24.78 ± 11.55
UPDRS Part □ (score)	1.18 ± 2.73
UPDRS total score	45.30 ± 18.06
L-Dopa equivalent dose (mg/day)	545.89 ± 306.30
Treatment duration (years)	5.63 ± 4.17
Symptom duration (years)	6.55 ± 4.02
BDI score	12.76 ± 8.33
BAI (scores)	29.18± 7.63
FES-K (scores)	28.13± 10.54
Number of falls	1.92 ± 2.50
PDQ-39 total (scores)	26.47 ± 21.38
PDQ-39 mobility (scores)	6.21 ± 8.08
PDQ-39 ADL (scores)	4.47 ± 5.09
PDQ-39 emotional well-being (scores)	4.37 ± 5.07
PDQ-39 stigma (scores)	4.71 ± 4.25
PDQ-39 social support (scores)	1.53 ± 2.20
PDQ-39 cognition (scores)	3.55 ± 3.15
PDQ-39 communication (scores)	1.29 ± 2.30
PDQ-39 bodily discomfort (scores)	2.50 ± 2.72

Grip_L (kg)	28.19 ± 8.82
Grip_R (kg)	28.94 ± 8.31
FTSTS (seconds)	8.94 ± 3.98
6MWT distance (m)	438.04 ± 93.77
Mini-BESTest (scores)	24.55 ± 2.66

Data are presented as mean ± standard deviation for continuous variables and n for categorical variables. BMI: Body mass index; MoCA: Montreal cognitive assessment; UPDRS: Unified Parkinson's disease rating score; BDI: Beck depression inventory; BAI: Beck anxiety inventory; FESK: Fall efficacy scale-Korean; PDQ39: the 39-item Parkinson's disease questionnaire; ADL: activities of daily living; Grip_L: Left grip strength; Grip_R: Right grip strength; FTSTS: five times sit-to-stand test; 6MWT: 6-minute walk test; Mini-BESTest, Mini Balance Evaluation Systems Test.

Overall effects of intervention over time

Linear mixed-effects analysis showed significant improvement in UPDRS Part II scores over time relative to baseline, with significant improvement at T1 (β = 1.63, 95% CI 0.239 to 3.024, p = 0.016, ES = 0.25) and further improvement at T2 (β = 1.97, 95% CI 0.581 to 3.366, p = 0.003, ES = 0.30). BDI scores also improved at T1 (β = 3.18, 95% CI 1.006 to 5.363, p = 0.002, ES = 0.38) and remained improved at T2 (β = 2.26, 95% CI 0.085 to 4.442, p = 0.039, ES = 0.27). FTSTS significantly improved at T1 (β = 0.98, 95% CI 0.077 to 1.881, p = 0.029, ES = 0.25) and further improved at T2 (β = 1.15, 95% CI 0.244 to 2.048, p = 0.008, ES = 0.29). Mini-BESTest scores improved significantly at T2 (β = -1.34, 95% CI -2.347 to -0.338, p = 0.005, ES = 0.50). In contrast, UPDRS Part III scores worsened significantly at T1 (β = -2.74, 95% CI -5.386 to -0.088, p = 0.040, ES = 0.24) and T2 (β = -3.00, 95% CI -5.649 to -0.351, p = 0.021, ES = 0.26). The 6MWT scores also significantly reduced at bothT1 (β = 33.18, 95% CI 3.453 to 62.898, p = 0.023, ES = 0.35) and T2 (β = 32.54, 95% CI 2.814 to 62.258, p = 0.027, ES = 0.35). (Fig. 3, Supplementary Fig. 1). Model comparisons using likelihood ratio tests indicated that random intercept–random slope models provided improved fit for UPDRS Part IV (p = 0.028), FTSTS (p < 0.001), right grip strength (p = 0.011), PDQ-39 total score (p = 0.033), the ADL domain (p = 0.018), and the communication domain (p = 0.003) (Supplementary Table 2).

Clinically meaningful responsiveness to the intervention

At the individual level, clinically meaningful changes were assessed by examining the distribution of responders and non-responders across all outcome measures. For Δ3, non-responders predominated in the 6MWT scores (31.6% responders vs. 68.4% non-responders). For most other variables, responders were more frequent than non-responders. For UPDRS Part III, responder and non-responder proportions were similar (52.6% responders vs.47.4 non-responders) (Fig. 4, Supplementary Table 3). The corresponding results for Δ1 and Δ2 are presented in Supplementary Fig. 2.

Latent response subgroups

Two distinct latent response subgroups were identified. Subgroup 1 (n = 22) and Subgroup 2 (n = 16) both showed relatively preserved cognitive function over time. However, the subgroups were primarily distinguished by their UPDRS Part III trajectories. Subgroup 1 showed progressively worsening motor scores from Δ1 onward and was therefore categorized as the improved cognition with motor worsening group. In contrast, Subgroup 2 showed progressively improving motor scores from Δ1 onward and was categorized as the improved cognition with motor improvement group (Fig. 5, Table 2). Linear regression analysis indicated that early change (Δ1) in UPDRS Part III scores was the variable most associated with the overall trajectory of motor symptom severity. For cognitive outcomes, early change (Δ1) in MoCA scores was the variable most associated with the overall cognitive trajectory (Table 3).

Table 2. Demographic and clinical characteristics of response subgroups.

Characteristics	Improved cognition with motor improvement (n = 22)	Improved cognition with motor worsening (n = 16)	P value
Sex (male/female)	11/11	11/5	0.330
Age (years)	69.05 ± 4.72	68.13 ± 5.66	0.588
Height (cm)	160.10 ± 7.57	163.61 ± 9.37	0.211
Body weight (kg)	62.35 ± 10.14	65.41 ± 11.97	0.400
BMI (kg/m^2)	24.17 ± 2.44	24.34 ± 3.28	0.860
MoCA (scores)	26.09 ± 3.38	26.13 ± 2.90	0.872
Hoehn and Yahr scale	1.75 ± 0.57	2.06 ± 0.44	**<0.001[c]**
UPDRS Part □ (scores)	8.36 ± 5.78	10.81 ± 6.01	0.213
UPDRS Part □ (scores)	8.95 ± 5.64	11.31 ± 7.47	0.274
UPDRS Part □ (scores)	22.30 ± 10.61	28.19 ± 12.25	0.122
UPDRS Part □ (scores)	1.00 ± 2.02	1.44 ± 3.54	0.942
UPDRS total score	40.61 ± 16.92	51.75 ± 18.07	0.059
L-Dopa equivalent dose (mg/day)	489.50 ± 281.66	623.44 ± 330.57	0.187
Treatment duration (years)	5.29 ± 4.52	6.11 ± 3.72	0.145
Symptom duration (years)	6.17 ± 4.32	7.08 ± 3.63	0.223
BDI (scores)	12.00 ± 8.21	13.81 ± 8.64	0.473
BAI (scores)	29.23 ± 7.89	29.13 ± 7.50	0.872
FES-K (scores)	25.82 ± 9.19	31.31 ± 11.71	0.073
Number of falls	2.14 ± 2.71	1.63 ± 2.22	0.529
PDQ-39 total (scores)	23.36 ± 18.61	30.75 ± 24.66	0.421
PDQ-39 mobility (scores)	5.09 ± 6.69	7.75 ± 9.71	0.404
PDQ-39 ADL (scores)	3.91 ± 4.73	5.25 ± 5.60	0.356
PDQ-39 emotional well-being (scores)	3.59 ± 5.07	5.44 ± 5.05	0.181
PDQ-39 stigma (scores)	4.82 ± 4.11	4.56 ± 4.57	0.693

PDQ-39 social support (scores)	1.41 ± 1.89	1.69 ± 2.63	0.919
PDQ-39 cognition (scores)	2.68 ± 2.53	4.75 ± 3.59	0.084
PDQ-39 communication (scores)	0.86 ± 1.49	1.88 ± 3.05	0.609
PDQ-39 bodily discomfort (scores)	2.32 ± 2.61	2.75 ± 2.93	0.693
Grip_L (kg)	26.81 ± 7.44	30.09 ± 10.39	0.263
Grip_R (kg)	27.47 ± 7.52	30.96 ± 9.15	0.206
FTSTS (seconds)	9.00 ± 4.90	8.86 ± 2.35	0.372
6MWT distance (m)	441.54 ± 92.99	433.22 ± 97.68	0.715
Mini-BESTest (scores)	24.59 ± 2.44	24.50 ± 3.01	0.804

Data are presented as mean ± standard deviation for continuous variables and n (%) for categorical variables. BMI: body mass index; MoCA: Montreal Cognitive Assessment; UPDRS: Unified Parkinson's Disease Rating Scale; BDI: Beck Depression Inventory; BAI: Beck Anxiety Inventory; FES-K: Falls Efficacy Scale-Korean; PDQ-39: 39-item Parkinson's Disease Questionnaire; ADL: activities of daily living; Grip_L: Left grip strength; Grip_R: Right grip strength; FTSTS: Five Times Sit-to-Stand Test; 6MWT: 6-minute walk test; Mini-BESTest: Mini Balance Evaluation Systems Test. [a] Mann–Whitney U test; [b] independent samples t-test; [c] chi-square test, $p < 0.05$.

Table 3. Associations between early (Δ1) and total change (Δ3) in UPDRS Part III and MoCA

Variable	β (SE)	T value	*P* value	R^2
UPDRS Part III (Δ3)	0.875 (0.081)	10.862	**< 0.001**	0.760
UPDRS Part III (Δ1)				
MoCA (Δ3)	0.590 (0.135)	4.385	**< 0.001**	0.330
MoCA (Δ1)				

UPDRS: Unified Parkinson's Disease Rating Scale; MoCA: Montreal Cognitive Assessment; β: regression coefficient; SE: standard error; CI: confidence interval; R², coefficient of determination. $p < 0.05$ was considered statistically significant.

Predictors of latent response subgroup membership

Elastic net logistic regression identified H&Y stage, BAI, FES-K, UPDRS total score, the cognition domain of the PDQ-39, and left grip strength as the most important variables for subgroup classification

(Supplementary Fig. 3). Using these selected variables, multivariable logistic regression analysis showed that BAI (odds ratio [OR]:0.180, p = 0.015), left grip strength (OR: 3.005, p = 0.034), and the cognition domain of the PDQ-39 (OR: 10.275, p = 0.008) were significant predictors of subgroup membership, with a model the model accounting for 54.9% of the variance (Table 4, Supplementary Fig. 4). Given the small sample size, however, this estimate should be interpreted cautiously.

Network analysis suggested different patterns of association between predictors and outcome-related variables in the two subgroups. In the improved cognition with motor worsening group, BAI was associated with grip strength (r = -0.853), H&Y stage (r = 0.826), 6MWT (r = -0.865), and BDI (r = 0.641) at Δ1. In this subgroup, PDQ-39 cognition was also associated with grip strength (r = -0.850). In the improved cognition with motor improvement group, BAI was associated with PDQ-39 total score (r = -0.493) and PDQ-39 cognition (r = 0.359) at Δ1. In addition, PDQ-39 cognition was associated with left grip strength (r = -0.481) and right grip strength (r = 0.265) (Fig. 6). The network analysis was conducted in a small sample; hence, these findings should be regarded as exploratory.

Table 4. Results of elastic net–regularized binary logistic regression analysis.

Variable	β	SE	OR	95% CI for OR	*P* value	R_N^2
PDQ-39 cognition	2.33	0.88	10.28	1.833–57.588	0.008	**0.549**
BAI	-1.72	0.71	0.18	0.045–0.717	0.015	
Left grip strength	1.10	0.52	3.01	1.085–8.320	0.034	

PDQ-39: 39-item Parkinson's Disease Questionnaire; BAI: Beck Anxiety Inventory; SE: standard error; OR: odds ratio; CI: confidence interval; R_N^2 is the fit statistic for the Nagelkerke model; $p < 0.05$ was considered statistically significant.

Discussion

In this exploratory study, we evaluated the effects of a combined motor–cognitive intervention and identified latent subgroups of responsiveness, as well as factors associated with differential response patterns.

At the group level, improvements were observed in UPDRS Part II, depressive symptoms, balance, and functional performance, whereas UPDRS Part III and walking capacity showed worsening or variable trajectories over time. These findings should be interpreted cautiously, as PD is characterized by progressive declines in motor function, including muscle strength, balance, and postural control, which contribute to impairments in mobility and functional performance [49]. Exercise programs incorporating resistance and mobility training can improve muscle strength, postural stability, and functional capacity, while reducing fall risk in individuals with PD [50]. In addition, reduced trunk mobility—particularly in axial extension and rotation—is a common feature of PD and is strongly associated with functional limitations [51]. Targeted strength and flexibility training may therefore improve these impairments, contributing to

enhanced ADL performance and reduced fear of falling [52, 53]. However, the motor outcomes may reflect disease progression, insufficient training intensity, or a lack of task-specific targeting of motor symptoms. Physical exercise alleviates depressive symptoms in PD, potentially through modulation of neurotransmitter systems, including dopaminergic and serotonergic pathways [54]. Combined exercise interventions incorporating strength, balance, and flexibility components have been associated with improvements in depressive symptoms [54], consistent with the present findings. Collectively, these findings suggest that a 20-week combined motor–cognitive intervention may improve physical and psychological outcomes. However, consistent with previous studies, effects on motor symptoms and walking capacity at the group level were variable and, in some cases, limited, highlighting the importance of considering inter-individual variability in treatment response.

At the individual level, the findings indicate that a subset of participants achieved clinically meaningful improvements across several outcomes. Nevertheless, only 34.3% of participants reached the MCID for the 6MWT, whereas 65.8% did not, demonstrating substantial heterogeneity in responsiveness. Previous meta-analyses have reported that multidisciplinary exercise programs can improve mobility-related functional capacity, as assessed by the 6MWT, in individuals with PD after approximately 8 weeks of intervention [55, 56]. The 6MWT reflects aerobic capacity and functional mobility and is widely used to monitor disease progression and evaluate rehabilitation outcomes [57, 58]. Current recommendations suggest moderate- to high-intensity aerobic exercise (Borg RPE 14–17) for 30–40 minutes, three times weekly, to improve aerobic capacity in PD [59, 60]. However, motor–cognitive interventions inherently require simultaneous cognitive engagement and physical execution, which necessitates careful balancing of task complexity and physical load [61]. In the present study, the intervention prioritized safety and feasibility over intensity, which may have limited improvements in walking performance, suggesting that gait-specific and intensity-targeted components may need to be more explicitly incorporated into future intervention protocols [62].

Using longitudinal latent class modeling, two distinct subgroups characterized by different trajectories of motor symptom severity were identified. In both subgroups, cognitive function showed modest improvement over time; however, motor outcomes diverged. Subgroup 1 exhibited progressively worsening motor symptoms, whereas Subgroup 2 demonstrated gradual improvement. These findings highlight the presence of distinct response phenotypes within the PD population, even when participants are exposed to the same intervention. Baseline anxiety, grip strength, and the cognitive domain of quality of life were identified as predictors of subgroup membership. These findings are consistent with previous studies indicating that non-motor symptoms—including anxiety, depression, cognitive function, and fatigue—are associated with changes in motor outcomes in PD [63]. However, given the relatively small sample size and the use of regularized modeling techniques, these estimates should be interpreted cautiously, as the risk of overfitting cannot be excluded. Higher baseline anxiety was associated with a lower likelihood of motor improvement, whereas better cognitive function and greater grip strength were associated with a higher likelihood of favorable response. Anxiety negatively affects gait and motor performance, potentially through its effects on attentional resources and motor control [64, 65]. In addition, individuals with greater baseline motor impairment may exhibit greater

responsiveness to intervention, as suggested by prior studies [66], although this relationship may depend on the type and intensity of the intervention.

Network analysis further supported these findings by demonstrating associations between anxiety and changes in motor severity, physical function, and depressive symptoms, particularly in the subgroup with worsening motor outcomes. However, given the limited sample size and the exploratory nature of this analysis, these findings should be interpreted with caution. Anxiety possibly interacts with disease severity and physical limitations to reduce adaptability to intervention [67–70]. In contrast, individuals with better preserved cognitive function and higher physical capacity appeared more capable of benefiting from the intervention, potentially reflecting greater cognitive and physical reserve. Preserved executive function and attentional capacity may facilitate engagement in cognitively demanding motor tasks, while greater muscle strength may support sustained participation in exercise programs [71–73].

Taken together, these findings suggest that responsiveness to combined motor–cognitive interventions in PD is influenced by a complex interplay of psychological, cognitive, and physical factors. Identifying such predictors may inform patient stratification and support the development of more targeted and individualized rehabilitation strategies [74]. These results further support a shift toward phenotype-driven or precision rehabilitation approaches in PD.

Several limitations should be considered. First, the exploratory single-arm design without a control group limits the ability to establish causal relationships between the intervention and observed outcomes. Second, the relatively small sample size—particularly after subgroup classification—may reduce statistical power, increase the risk of overfitting in predictive models, and limit generalizability. Third, assessments were conducted in the medication “ON” state, which reflects real-world clinical conditions but may confound the effects of the intervention with those of dopaminergic medication. Future studies should consider evaluating participants in both medications “ON” and “OFF” states to better isolate intervention-specific effects. Finally, future research should incorporate more detailed gait parameters, a broader range of cognitive domains, and larger sample sizes to comprehensively characterize motor and cognitive changes and validate the identified response subgroups.

Conclusion

Herein, we demonstrated that a combined motor–cognitive intervention may improve functional and psychological outcomes in individuals with PD while revealing substantial heterogeneity in motor symptom responses. Although improvements were observed at the group level in functional and psychological outcomes, motor severity and walking capacity showed variable and, in some cases, inconsistent trajectories. Two distinct response subgroups were identified, indicating that individuals with PD may exhibit markedly different response patterns under the same intervention. These findings underscore the limitations of relying solely on average treatment effects and highlight the importance of incorporating individual response trajectories into evaluation frameworks. Incorporating baseline factors such as anxiety, cognitive function, and physical capacity into clinical decision-making may support the

development of more precise and individualized rehabilitation strategies. Identifying response phenotypes may facilitate the development of precision rehabilitation approaches in PD.

Abbreviations

ADL
activities of daily living
AUC
area under the curve
BAI
Beck Anxiety Inventory
BDI
Beck Depression Inventory
BMI
body mass index
CI
confidence interval
ES
effect size
FES-K
Falls Efficacy Scale-Korean
FTSTS
Five Times Sit-to-Stand Test
HRQoL
health-related quality of life
H&Y
Hoehn and Yahr
IRB
Institutional Review Board
KCT
Clinical Research Information Service registration number
LCMM
latent class mixed modeling
LMM
linear mixed-effects model
MCID
minimal clinically important difference
MDS
Movement Disorder Society
Mini-BESTest

Mini Balance Evaluation Systems Test
MLCLMM
multivariate latent class linear mixed model
MoCA-K
Korean version of the Montreal Cognitive Assessment
NRF
National Research Foundation of Korea
OR
odds ratio
PD
Parkinson’s disease
PDQ-39
Parkinson’s Disease Questionnaire-39
ROC
receiver operating characteristic
RPE
Rating of Perceived Exertion
SD
standard deviation
UPDRS
Unified Parkinson’s Disease Rating Scale
6MWT
6-minute walk test
Δ1
change from baseline (T0) to 8 weeks (T1)
Δ2
change from 8 weeks (T1) to 20 weeks (T2)
Δ3
change from baseline (T0) to 20 weeks (T2)
T0
baseline
T1
8 weeks
T2
20 weeks

Declarations

Ethics approval and consent to participate

All procedures involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The study protocol and supplementary information files were approved by the Institutional Review Board of Dong-A University Hospital (IRB No. DAUHIRB-22-089) (see ethics approval letter in the related file). All patients provided written informed consent before data collection. The study is registered with the Clinical Research Information Service in the Republic of Korea (KCT0009353).

Consent for publication

Not applicable.

Availability of data and materials

The datasets that support the findings of this study are available from the corresponding author upon reasonable request.

Code availability

There is no available open-source code. The code used for training and testing the machine learning models was developed in Python 3.8 using PyTorch (version 1.9.1) and Torch vision (version 0.10.1). Data management and feature processing were performed using Pandas (version 1.3.3) and NumPy (version 1.21.2). The datasets and code supporting the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no conflict of interest.

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Author's contributions

JH and CY conceived and designed the study. JH, CY, HP, BK, HC, MK, and SC recruited participants and performed data acquisition. JH and CY conducted data analysis and interpretation. JH and CY drafted

the manuscript. All authors reviewed and approved the final version of the manuscript.

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Figures

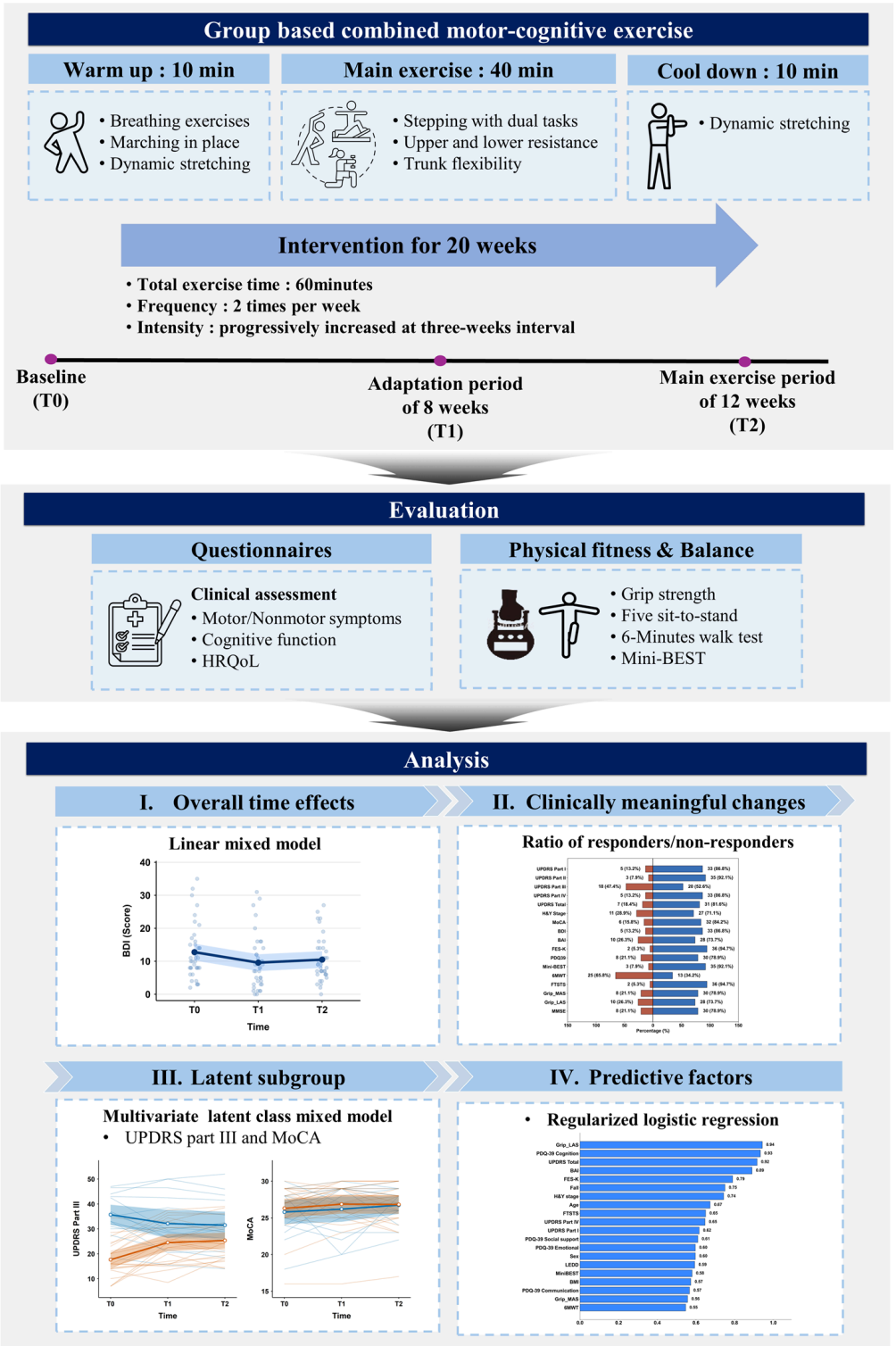


Figure 1

Schematic overview of the proposed approach. Min: minutes; HRQoL: health related quality of life; UPDRS: Unified Parkinson's Disease Rating Scale; MoCA: Montreal Cognitive Assessment.

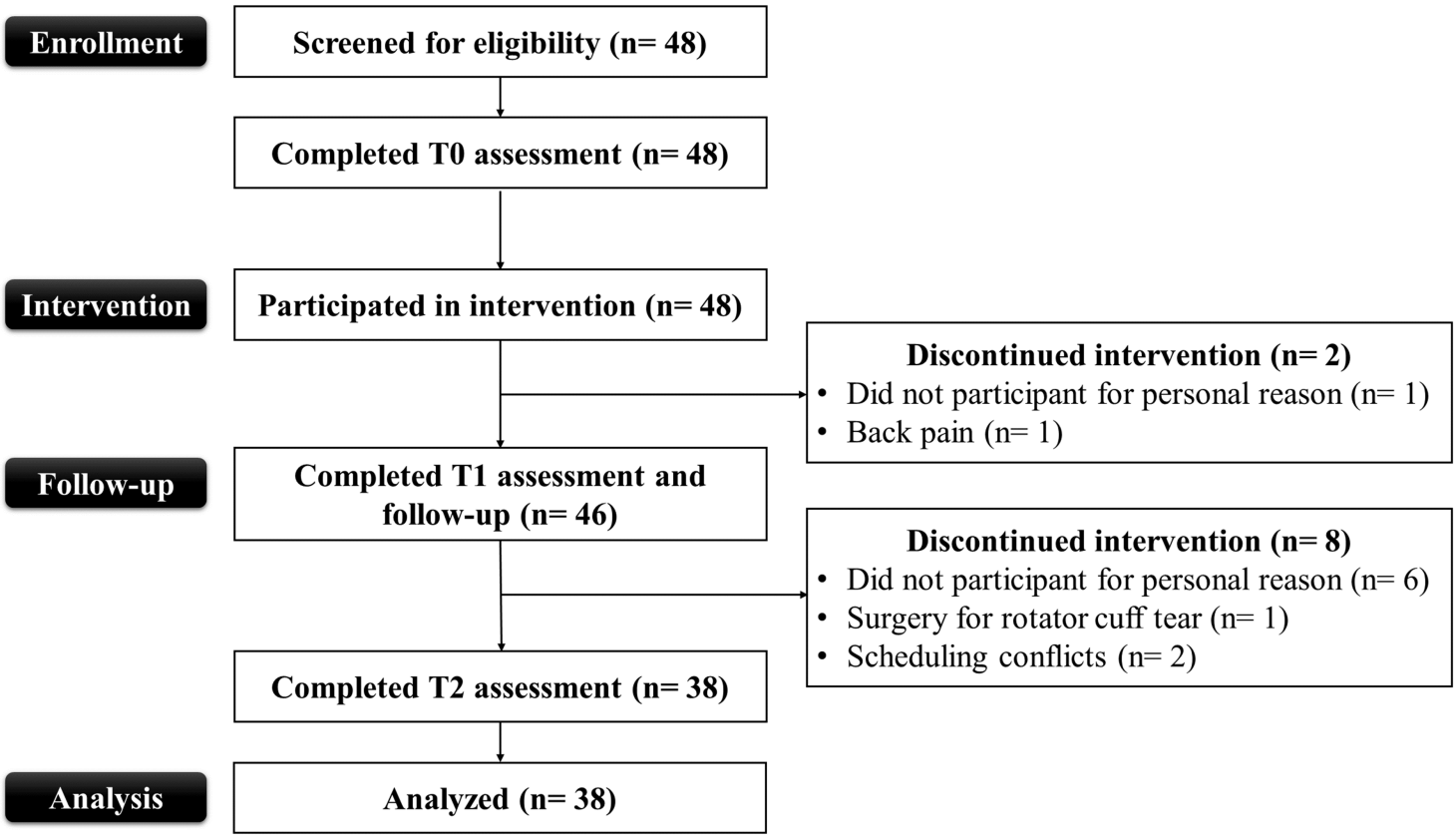


Figure 2

Participant flow diagram. T0: baseline; T1: 8 weeks; T2: 20 weeks.

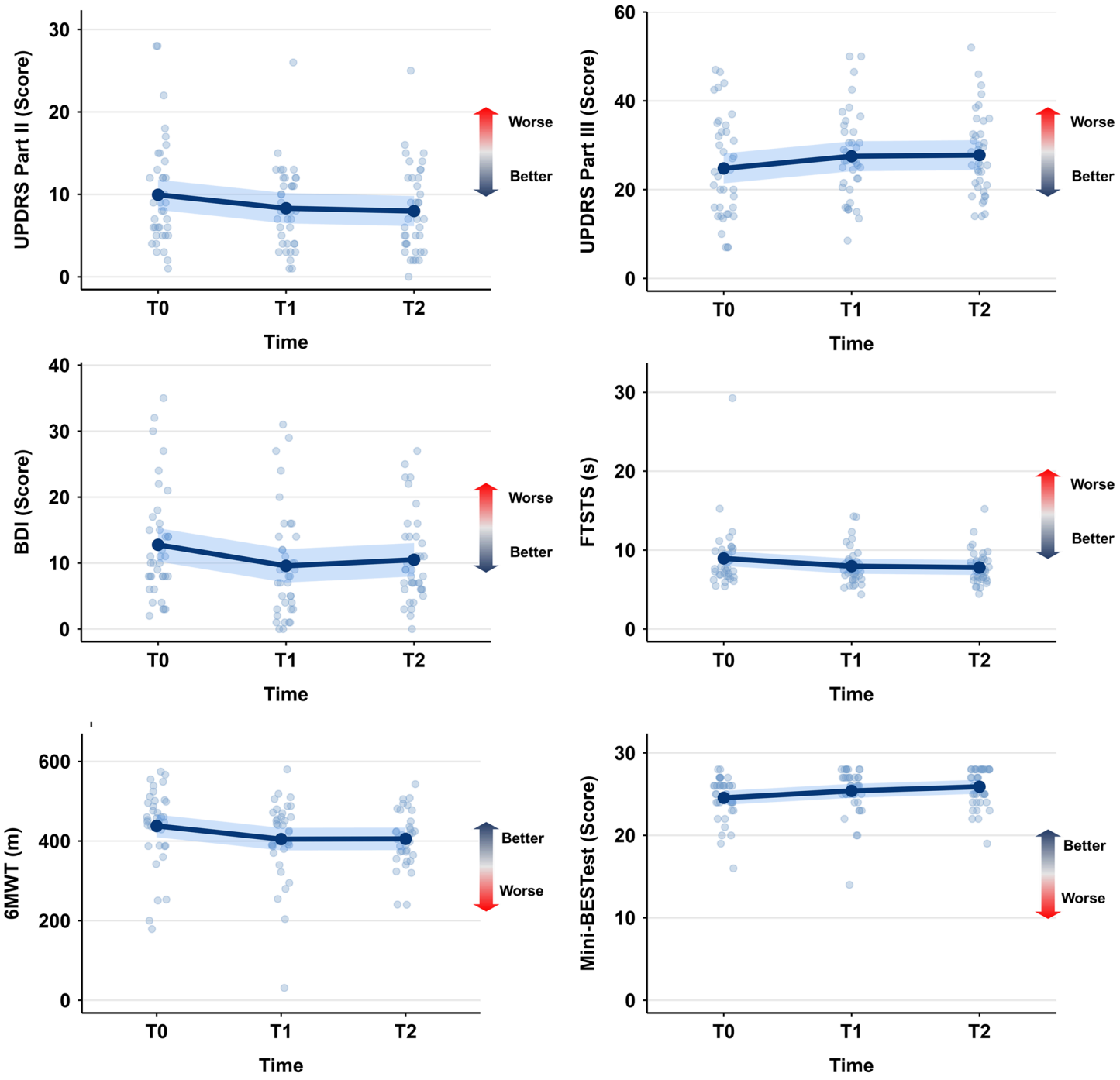


Figure 3

Linear mixed-effects model results for variables with significant time effects. UPDRS: Unified Parkinson's Disease Rating Scale; BDI: Beck Depression Inventory; FTSTS: Five Times Sit-to-Stand Test; 6MWT: 6-minute walk test; Mini-BESTest: Mini Balance Evaluation Systems Test.

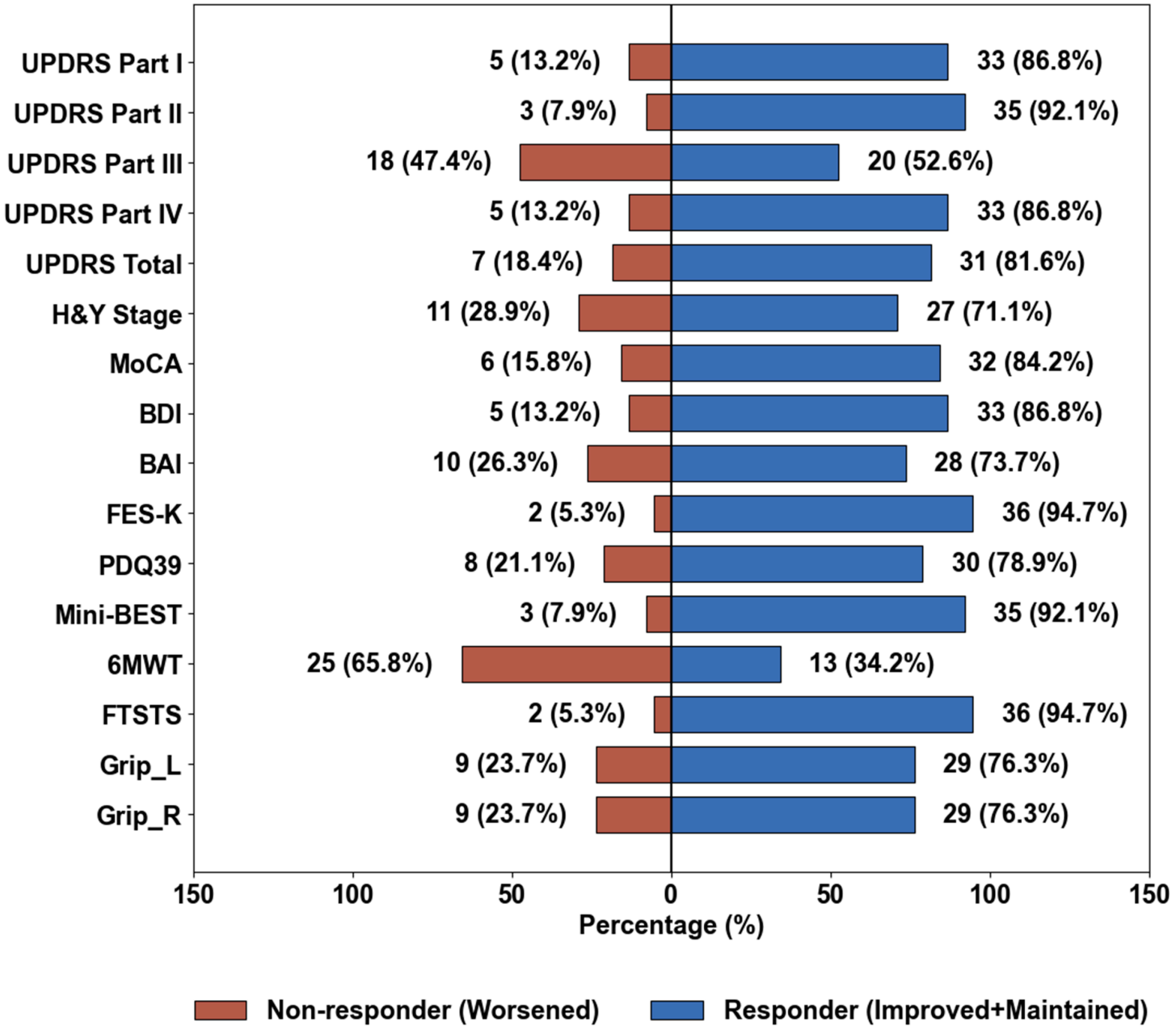


Figure 4

Distribution of clinically meaningful responsiveness over 20 weeks. UPDRS: Unified Parkinson's Disease Rating Scale; BDI: Beck Depression Inventory; BAI: Beck Anxiety Inventory; MoCA: Montreal Cognitive Assessment. FES-K: Falls Efficacy Scale-Korean; PDQ-39: 39-item Parkinson's Disease Questionnaire; FTSTS: Five Times Sit-to-Stand Test; 6MWT: 6-minute walk test; Mini-BESTest: Mini Balance Evaluation Systems Test; Grip_L: Left grip strength; Grip_R: Right grip strength.

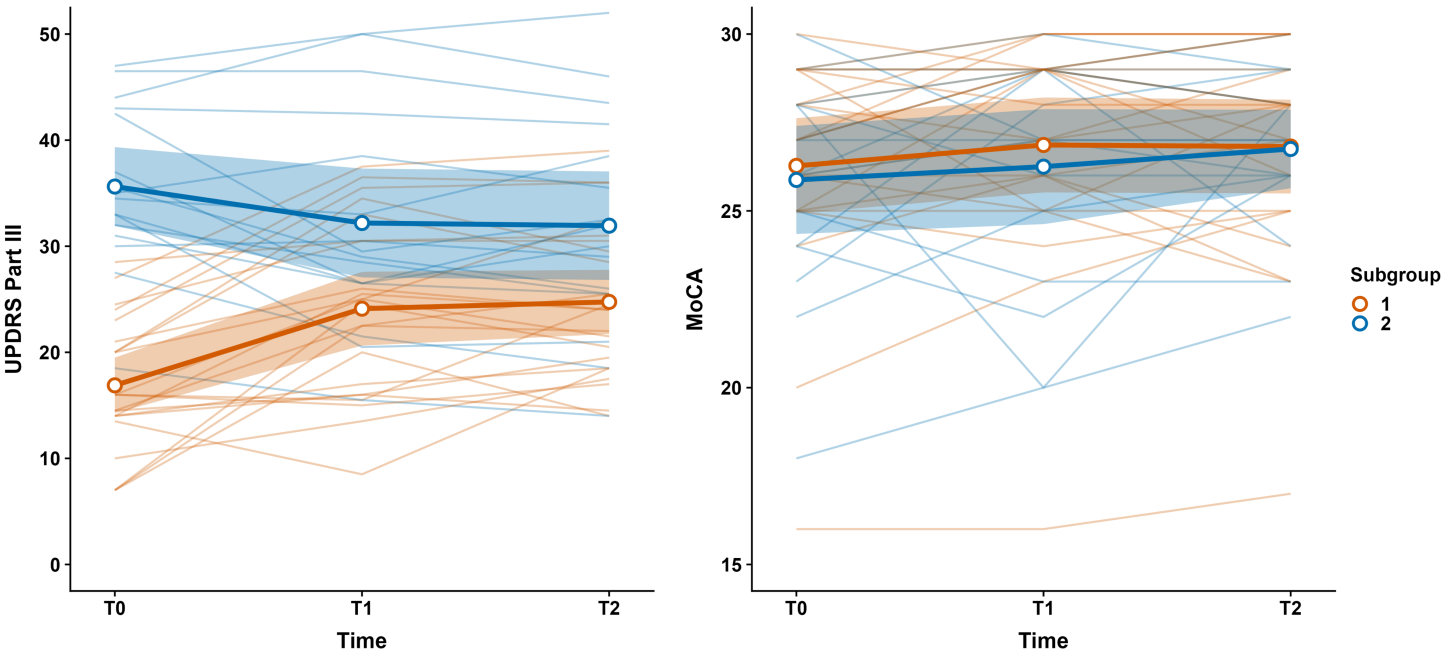


Figure 5

Distinct longitudinal trajectories of motor and cognitive function using multivariate latent class mixed modeling. UPDRS: Unified Parkinson's Disease Rating Scale; MoCA: Montreal Cognitive Assessment; T0: baseline; T1: 8 weeks; T2: 20 weeks.

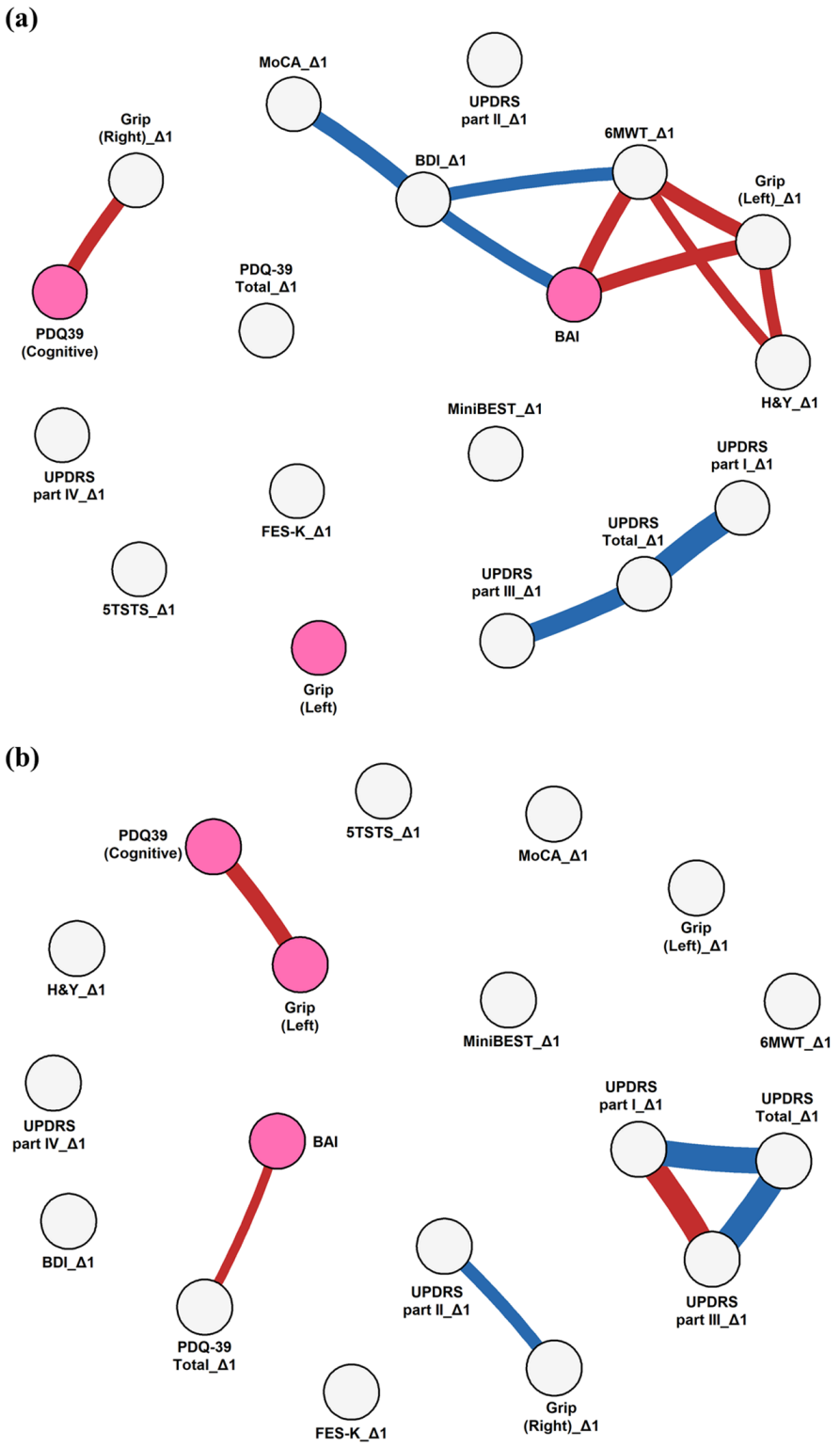


Figure 6

Network plots for each subgroup. UPDRS: Unified Parkinson's Disease Rating Scale; BDI: Beck Depression Inventory; BAI: Beck Anxiety Inventory; FES-K: Falls Efficacy Scale-Korean; PDQ-39: 39-item Parkinson's Disease Questionnaire; FTSTS: Five Times Sit-to-Stand Test; 6MWT: 6-minute walk test; Mini-BESTest: Mini Balance Evaluation Systems Test; Δ1: change from T0 to T1.

Supplementary Files

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