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Divergent Neural Correlates of Clinician-Rated and Self-Reported Depressive Symptoms in Parkinson's Disease

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Abstract

Depressive symptoms in Parkinson's disease reflect large-scale brain network dysfunction. Clinician-rated instruments such as the seventeen-item Hamilton Depression Rating Scale and patient-reported measures such as the Beck Depression Inventory second edition target distinct somatic versus cognitive-affective symptom profiles. This retrospective study investigated the resting-state functional magnetic resonance imaging correlates underlying these divergent clinical assessments. We examined thirty-eight patients with Parkinson's disease during the clinically confirmed medicated state using a hypothesis-driven seed-based region-of-interest approach. Evaluated regions included the posterior cingulate cortex, medial prefrontal cortex, anterior cingulate cortex, left amygdala, left middle frontal gyrus, and left caudate. Multiple linear regression models adjusting for age, sex, Hoehn and Yahr stage, and daily pramipexole dosage revealed that functional connectivity between the posterior cingulate cortex—a core hub of the default mode network—and the left amygdala exhibited a strong positive association with clinician-rated depression severity. In contrast, no significant functional connectivity alterations correlated with self-reported depression scores. Furthermore, attenuated left caudate–left amygdala and medial prefrontal cortex–anterior cingulate cortex connectivity was associated with advanced age, whereas enhanced medial prefrontal cortex–left amygdala connectivity was linked to higher daily pramipexole intake. These findings demonstrate that somatically weighted clinician ratings uniquely correspond to hyperconnectivity between the default mode network and limbic structures. Differentiating somatic from cognitive-affective dimensions is essential for accurate clinical evaluation, neuroimaging biomarker discovery, and targeted pharmacological management in Parkinson's disease depression.

Introduction

Parkinson's disease (PD) is the second most prevalent neurodegenerative disorder, primarily driven by dopaminergic loss in the substantia nigra pars compacta alongside multisystem non-dopaminergic degeneration (Armstrong & Okun, 2020; Fox et al., 2009; Homayoun, 2018; Kotagal et al., 2012). In addition to cardinal motor features—bradykinesia, rigidity, and resting tremor—non-motor symptoms (NMS) such as sleep disturbance, autonomic dysfunction, cognitive decline, and depression severely impair patient quality of life (Duncan et al., 2014; Homayoun, 2018; Martinez-Martin et al., 2011). Depression affects 40% to 50% of PD patients, often preceding motor onset and compounding disability through chronic fatigue and cognitive deficits (Kalia & Lang, 2015; Ray & Agarwal, 2020; Reijnders et al., 2008).

Evaluating depression in PD is challenging due to the clinical tools employed. The clinician-rated 17-item Hamilton Depression Rating Scale (HAM-D) and self-reported Beck Depression Inventory-II (BDI-II) capture distinct constructs: HAM-D accentuates somatic and neurovegetative manifestations, which frequently overlap with primary PD symptoms, whereas BDI-II emphasizes subjective cognitive-affective distress (Broen et al., 2015; Reijnders et al., 2010; Seemüller et al., 2023; Uher et al., 2012).

Resting-state functional magnetic resonance imaging (rs-fMRI) has delineated circuit abnormalities in PD depression (Younce et al., 2021). Prior investigations demonstrated hyperactivation in the orbitofrontal cortex (OFC) and median cingulate cortex correlated with HAM-D scores (Hu, Song, Li, et al., 2015; Luo et al., 2014), reduced interhemispheric functional connectivity (FC) in medial frontal regions (Hu, Song, Li, et al., 2015; Liao, Fan, et al., 2020), and dysregulation across the default mode network (DMN), salience network (SN), and frontoparietal networks (Q. Liu et al., 2022; Z. Liu et al., 2022; Su et al., 2022). However, most studies dichotomized patients into categorical groups, obscuring continuous neural substrates underlying specific assessment dimensions.

Unlike categorical classifications, we modeled continuous HAM-D and BDI-II scores using multiple linear regression. We employed a hypothesis-driven region-of-interest (ROI) approach targeting the left-lateralized fronto-striatal-limbic circuit and core hubs of the DMN and SN to discern whether somatic versus cognitive-affective depressive dimensions correspond to distinct functional connectivity alterations.

Methods

Participants

We retrospectively screened 432 patients from the Parkinson's Disease Registry at Hualien Tzu Chi Hospital (January 2015 – April 2023). Inclusion criteria were: (1) PD diagnosis by UK Brain Bank criteria; (2) completed 3T rs-fMRI; and (3) completed concurrent HAM-D and BDI-II assessments. Exclusion criteria were: (1) current or recent antidepressant therapy; (2) cognitive impairment by education-adjusted Mini-Mental State Examination (MMSE) thresholds; and (3) excessive head motion (absolute translation > 1.5 mm or rotation > 1.5°). Applying these criteria yielded 38 eligible patients. The study protocol was approved by the Institutional Review Board of Hualien Tzu Chi Hospital (IRB112-112-B) with informed consent waived due to retrospective registry design.

Clinical Assessments

Clinical evaluations and MRI acquisitions were conducted during the confirmed 'ON' medication state to assess habitual functioning and prevent levodopa withdrawal stress. Assessments included Unified Parkinson's Disease Rating Scale (UPDRS), HAM-D, BDI-II, MMSE, Hoehn and Yahr (H&Y) staging, and daily pramipexole dosage.

MRI Data Acquisition

Imaging was conducted on a 3.0T scanner (Discovery MR750w, GE Healthcare, Milwaukee, WI, USA) with head foam padding and earplugs. Patients remained still with eyes closed. Functional images were acquired using echo-planar imaging (EPI): TR = 2,000 ms, TE = 21 ms, flip angle = 90°, FOV = 220 × 220 mm^2, matrix = 64 × 64, 42 axial slices, slice thickness = 3.4 mm (no gap), voxel size = 3.4 × 3.4 × 3.4 mm^3, and 180 volumes (6 min). High-resolution T1-weighted structural scans were acquired using 3D BRAVO: TR = 8.5 ms, TE = 3.2 ms, flip angle = 12°, inversion time = 450 ms, FOV = 256 × 256 mm^2, matrix = 256 × 256, 180 slices, and voxel size = 1.0 × 1.0 × 1.0 mm^3.

Data Preprocessing

Imaging data were preprocessed using SPM12 (Friston et al., 2007) and CONN toolbox release 22a (Whitfield-Gabrieli & Nieto-Castanon, 2012) in MATLAB. Preprocessing included slice-timing correction, rigid-body realignment, coregistration to structural T1 images, MNI normalization, bandpass filtering (0.01–0.08 Hz), and 6-mm FWHM Gaussian smoothing. Quality assurance and aCompCor physiological noise reduction parameters are detailed in Supplementary Material.

ROI Selection and Functional Connectivity Analysis

Based on affective circuitry and the approach-withdrawal valence model (Bruder et al., 2017; Liao, Cai, et al., 2020), six a priori ROIs were defined from the Harvard-Oxford and CONN default network atlases: posterior cingulate cortex (PCC; posterior DMN hub), medial prefrontal cortex (MPFC; anterior DMN hub) (Raichle, 2015), anterior cingulate cortex (ACC; SN interface) (Seeley, 2019), Left Amygdala, Left Middle Frontal Gyrus (Left MidFG/DLPFC), and Left Caudate. Prioritizing left-lateralized fronto-striatal-limbic nodes reflects hypothesized deficits in approach motivation and emotional regulation in depression. Left laterofrontal hypofunction is tied to core depressive symptoms (Akiyama et al., 2018), and left amygdala dysfunction is characteristic of PD depression (Hu, Song, Yuan, et al., 2015). Although dopamine transporter imaging implicated right caudate (Vriend et al., 2014), recent rs-fMRI demonstrated that left caudate FC specifically tracks depressive severity (Wang et al., 2022). MNI stereotactic coordinates and atlas details are provided in Supplementary Table S1.

ROI-to-ROI functional connectivity matrices were estimated in CONN 22a by computing Fisher-z–transformed bivariate correlation coefficients between residual BOLD time series using a weighted general linear model (Nieto-Castanon, 2020; Nieto-Castanon & Whitfield-Gabrieli, 2022).

Statistical Analysis

Multiple linear regression models were estimated across pairwise connections. Two parallel models assessed continuous depression measures:

Model 1 (Clinician-Rated): Entered HAM-D total score as primary predictor.

Model 2 (Self-Reported): Entered BDI-II total score as primary predictor.

Both models included age, sex, H&Y stage, and daily pramipexole dosage (≥ 1 mg/day vs. < 1 mg/day) as covariates. Total Levodopa Equivalent Daily Dose was excluded to prevent overparameterization and collinearity with H&Y stage. Pramipexole was included due to its D3-preferring antidepressant properties, dichotomized at the validated 1.0 mg/day clinical threshold (Corrigan et al., 2000). Standardized beta coefficients (β), 95% confidence intervals (CI), and two-tailed p-values were calculated (significance: $p < 0.05$).

Results

Demographic and Clinical Characteristics

The cohort included 38 patients with PD (mean age: 58.63 ± 7.16 years). Clinical evaluations showed mean HAM-D of 12.05 ± 5.51, mean BDI-II of 20.61 ± 11.44, and mean H&Y stage of 2.50 ± 0.46. Seventeen patients (44.7%) received pramipexole < 1 mg/day, and 21 (55.3%) received ≥ 1 mg/day. As shown in Table 1, no significant differences were observed between sexes regarding age, depression scores, H&Y stage, or pramipexole dosage (all $p > 0.05$).

[Insert Table 1 here]

Functional Connectivity Associated with HAM-D

Multiple linear regression outcomes for Model 1 are detailed in Table 2.

HAM-D Main Effects: Higher clinician-rated HAM-D scores were significantly associated with increased FC between the PCC and left amygdala (β = 0.0127, 95% CI: 0.0009 to 0.0244, p = 0.036). No other ROI pairs exhibited significant associations with HAM-D.

Covariate Effects: Chronological age showed significant negative correlations with MPFC–ACC connectivity (β = -0.0154, 95% CI: -0.0268 to -0.0041, p = 0.009) and left caudate–left amygdala connectivity (β = -0.0140, 95% CI: -0.0251 to -0.0029, p = 0.015). Sex, H&Y stage, and pramipexole dosage were not significant in Model 1.

[Insert Table 2 here]

Functional Connectivity Associated with BDI-II

Multiple linear regression outcomes for Model 2 are presented in Table 3.

BDI-II Main Effects: In contrast to HAM-D, self-reported BDI-II scores revealed no statistically significant associations with FC across any evaluated ROI pairs (all $p > 0.05$).

Covariate Effects: Higher pramipexole dosage (≥ 1 mg/day) was significantly associated with increased MPFC–left amygdala FC (β = 0.1449, 95% CI: 0.0021 to 0.2877, p = 0.047). This effect was unique to Model 2. The negative effect of age

on MPFC–ACC connectivity (β = -0.0144, 95% CI: -0.0262 to -0.0027, p = 0.018) and left caudate–left amygdala connectivity (β = -0.0140, 95% CI: -0.0250 to -0.0029, p = 0.015) remained robust and directionally identical to Model 1.

[Insert Table 3 here]

Discussion

We investigated resting-state functional connectivity correlates of clinician-rated versus self-reported depressive symptoms in PD. Clinician-rated depression severity (HAM-D) was specifically associated with enhanced PCC–left amygdala functional connectivity. Conversely, self-reported depressive symptoms (BDI-II) exhibited no significant associations across the analyzed circuits. Across both models, older age was associated with reduced connectivity in MPFC–ACC and caudate–amygdala pathways, whereas higher pramipexole dosage (≥ 1 mg/day) was linked to enhanced MPFC–left amygdala connectivity in the self-report model.

HAM-D Severity and PCC–Left Amygdala Hyperconnectivity

The hyperconnectivity between the PCC and left amygdala provides mechanistic insight into the neurobiology of PD depression. The PCC is a core hub of the default mode network mediating autobiographical memory and self-referential cognition (Raichle, 2015; Summerfield et al., 2009), while the amygdala processes emotional salience and negative valence (Fox et al., 2015; West et al., 2021). Enhanced coupling between these regions indicates abnormal integration of negative affective salience into internal mentation, reflecting depressive rumination (Hamilton et al., 2015; Philippi et al., 2018).

Our finding of positive PCC–left amygdala coupling contrasts with Lin et al. (2020), who reported negative FC between the PCC and a combined bilateral hippocampus–amygdala complex. This discrepancy likely stems from seed definition: whereas Lin et al. evaluated an aggregated bilateral complex, we specifically isolated the left amygdala. Abundant evidence demonstrates lateralized vulnerability of the left amygdala in depression (Hu, Song, Yuan, et al., 2015; Wen et al., 2023). In PD, disrupted fronto-amygdalar regulation selectively compromises left amygdala connectivity (Hu, Song, Yuan, et al., 2015). Isolating this node uncovered focal DMN-limbic hyperconnectivity that may be obscured in composite bilateral analyses.

Furthermore, our findings align conceptually with Zhang et al. (2019), who linked amygdala-DMN coupling to affective distress in PD. In PD, anxiety and depressive symptoms display high clinical comorbidity, frequently presenting as a mixed anxious-depressive phenotype (Cui et al., 2017; Weintraub et al., 2022). Transdiagnostic frameworks indicate that aberrant amygdala-DMN connectivity marks generalized affective distress across internalizing disorders (Coutinho et al., 2016; Feurer et al., 2021). Moreover, the HAM-D contains prominent items assessing somatic anxiety, psychomotor agitation, and gastrointestinal symptoms (Broen et al., 2015; Lopez et al., 2018; Reijnders et al., 2010). Thus, PCC–left amygdala hyperconnectivity likely reflects a transdiagnostic negative valence network capturing the somatic-affective distress characteristic of PD depression.

Importantly, evaluations were conducted during the 'ON' medication state. Examining patients in the 'ON' state ensures feasibility, avoids acute withdrawal distress, and minimizes motor artifacts. That DMN-limbic hyperconnectivity remained detectable in the 'ON' state suggests that PD depression involves non-dopaminergic or structural circuit dysfunctions not fully corrected by dopaminergic regimens (Fox et al., 2009).

Discrepancy Between Clinician-Rated and Self-Reported Assessments

The divergence between HAM-D and BDI-II findings underscores fundamental differences in psychometric construction (Seemüller et al., 2023; Uher et al., 2012). The clinician-administered HAM-D heavily weights somatic, vegetative, and psychomotor features, which closely intersect with subcortical and limbic dysfunction in PD (Broen et al., 2015; Uher et al., 2012; Zu et al., 2019). Because our a priori ROIs targeted limbic and DMN hubs, they proved sensitive to the somatic burden

captured by HAM-D. Conversely, the self-reported BDI-II emphasizes subjective cognitive-affective distortions such as guilt and pessimism (Seemüller et al., 2023). The absence of significant BDI-II correlations suggests that subjective cognitive distress may distribute across broad frontoparietal networks not sampled by our seed selection.

Age-Related Decoupling in Fronto-Striatal and Cingulate Circuits

Advancing age was significantly associated with reduced FC in MPFC–ACC and left caudate–left amygdala pathways across both models. The MPFC and ACC are critical for cognitive control and emotion regulation (Sheline et al., 2009); their age-associated decoupling mirrors functional alterations documented in cognitive aging and mild cognitive impairment (Huang et al., 2024). Concurrently, reduced caudate–amygdala connectivity indicates an age-related breakdown in coordinating striatal approach motivation and amygdalar affective processing. While amygdalar-prefrontal connectivity remains relatively stable during early adulthood (Xiao et al., 2018), aging in neurodegenerative disease precipitates progressive network decoupling. Aging-related dedifferentiation in striatal circuits (Rieckmann et al., 2018) interacts with parkinsonian mesolimbic denervation to impair striato-amygdalar communication (Schott et al., 2007), establishing age as an essential biological covariate.

Pramipexole Dosage and Prefrontal-Amygdala Connectivity

In Model 2, higher daily pramipexole dosage (≥ 1 mg/day) was associated with enhanced MPFC–left amygdala FC. The MPFC provides top-down inhibitory modulation over amygdaloid reactivity (d'Arbeloff et al., 2018). While dopamine agonists modulate reward pathways and may alter frontostriatal loops (Ye et al., 2011), our findings indicate that therapeutic pramipexole strengthens prefrontal-limbic regulation. This association attained significance only in Model 2, likely because HAM-D shares extensive variance with somatic symptoms responsive to dopaminergic therapy, confounding medication effects; controlling for cognitive symptoms (BDI-II) unmasks pramipexole's contribution to prefrontal-limbic regulation, consistent with its established antidepressant efficacy (Corrigan et al., 2000; Mah et al., 2011).

Limitations

Several limitations should be noted. First, the retrospective cross-sectional design and sample size (N = 38) restrict statistical power. Second, evaluations were conducted exclusively in the 'ON' medication state; future studies incorporating paired 'ON' and 'OFF' scans are needed to distinguish acute pharmacological effects from intrinsic neuropathology. Third, our hypothesis-driven ROI approach precluded identifying connectivity alterations across other cerebral systems. Finally, longitudinal studies with larger prospective cohorts and multiple comparison corrections are warranted to substantiate these findings.

Conclusions

In conclusion, resting-state functional connectivity alterations in Parkinson's disease depression are fundamentally shaped by the clinical assessment instrument. Clinician-rated depression severity (HAM-D), reflecting somatic and neurovegetative symptom burdens, is specifically linked to hyperconnectivity between the default mode network (PCC) and limbic system (left amygdala), reflecting pathological emotional rumination. In contrast, self-reported cognitive distress (BDI-II) did not correlate with these circuits. Furthermore, advancing age drives decoupling across fronto-striatal-limbic pathways, whereas higher pramipexole dosage reinforces top-down prefrontal-amygdala regulation. Differentiating somatic from cognitive-affective symptom dimensions is critical for refining neuroimaging biomarkers in PD depression.

Declarations

Competing Interests:

The authors have no relevant financial or non-financial interests to disclose.

Ethics Approval:

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Institutional Review Board of Hualien Tzu Chi Hospital (Approval number: IRB112-112-B).

Consent to Participate:

The requirement to obtain informed consent was waived by the Institutional Review Board of Hualien Tzu Chi Hospital due to the retrospective nature of the study using registry data.

Consent to Publish:

Not applicable.

Use of Generative AI Tools

During the preparation of this work, the authors used Gemini to improve linguistic clarity and expression. The authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Author Contribution

LC and HYC contributed equally to this work. LC, HYC, SYC, and SHL contributed to the conceptualization and methodology of the study, as well as writing the main manuscript text. LCH and LGC contributed to data curation and rs-fMRI image preprocessing. JHW performed the formal analysis, specifically the multiple linear regression. SHL supervised the project and contributed to project administration. All authors reviewed and edited the manuscript, and approved the final version for publication.

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Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to patient privacy and institutional ethics committee regulations (Institutional Review Board of Hualien Tzu Chi Hospital).

Code Availability:

The custom analysis scripts and batch pipelines for resting-state fMRI preprocessing and connectivity calculation (CONN toolbox / SPM) are available from the corresponding author upon reasonable request.

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Tables

Table 1. Demographics (n = 38)

	Sex		Total	P-value
	Female	Male		
N	16	22	38	
Age	61.06 ± 6.82	56.86 ± 7.02	58.63 ± 7.16	0.074
HAM-D score	12.69 ± 4.14	11.59 ± 6.38	12.05 ± 5.51	0.552
BDI-II score	19.19 ± 10.30	21.64 ± 12.34	20.61 ± 11.44	0.522
Hoehn & Yahr Stage (on)	2.66 ± 0.51	2.39 ± 0.41	2.50 ± 0.46	0.077
Dosage of Pramipexole, n (%)	-	-	-	0.444
Daily dose < 1mg	6(37.5%)	11(50.0%)	17(44.7%)	
Daily dose ≧ 1mg	10(62.5%)	11(50.0%)	21(55.3%)	
Data are presented as n or mean ± standard deviation. *p-value < 0.05 was considered statistically significant after test				

Table 2. Multiple Linear Regression Analysis of Functional Connectivity and Depressive Symptoms (Model 1: HAM-D)

Connectivity (ROI pairs)	Age		Sex (M vs. F)		HAM-D		Daily pramipexole dosage (≥ 1 vs. <1 mg)		H&Y Stage	
	β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value
MPFC – MidFG L	0.0111 (-0.0034, 0.0255)	0.128	0.0438 (-0.1377, 0.2254)	0.626	-0.0017 (-0.0180, 0.0145)	0.830	0.0802 (-0.0960, 0.2565)	0.361	-0.1612 (-0.3851, 0.0628)	0.153
MPFC – AC	-0.0154 (-0.0268, -0.0041)	0.009*	-0.0617 (-0.2043, 0.0809)	0.385	-0.0104 (-0.0231, 0.0024)	0.108	-0.0489 (-0.1873, 0.0896)	0.477	0.0286 (-0.1473, 0.2045)	0.742
MPFC – PC	-0.0045 (-0.0206, 0.0115)	0.569	0.0537 (-0.1487, 0.2561)	0.592	-0.0029 (-0.0211, 0.0152)	0.744	0.05160 (-0.1449, 0.2481)	0.596	-0.1028 (-0.3524, 0.1468)	0.408
MPFC – Caudate L	0.0035 (-0.0100, 0.0169)	0.603	0.0645 (-0.1046, 0.2336)	0.443	-0.0006 (-0.0158, 0.0145)	0.932	-0.0527 (-0.2168, 0.1115)	0.518	-0.0513 (-0.2599, 0.1572)	0.620
MPFC – Amygdala L	-0.0028 (-0.0147, 0.0091)	0.633	-0.0139 (-0.1639, 0.1361)	0.851	-0.0002 (-0.0136, 0.0133)	0.979	0.1388 (-0.0068, 0.2844)	0.061	-0.0912 (-0.2762, 0.0938)	0.323
MidFG L – AC	0.0052 (-0.0079, 0.0183)	0.428	0.0088 (-0.1560, 0.1737)	0.914	0.0092 (-0.0055, 0.0240)	0.212	-0.0888 (-0.2488, 0.0712)	0.267	0.0393 (-0.1640, 0.2426)	0.696
MidFG L – PC	0.0071 (-0.0048, 0.0191)	0.234	0.0773 (-0.0732, 0.2278)	0.303	-0.0060 (-0.0195, 0.0075)	0.373	-0.0168 (-0.1629, 0.1292)	0.816	-0.0693 (-0.2548, 0.1163)	0.453
MidFG L – Caudate L	0.0106 (-0.0020, 0.0232)	0.096	0.0043 (-0.1538, 0.1624)	0.956	-0.0040 (-0.0182, 0.0102)	0.568	-0.0779 (-0.2314, 0.0756)	0.309	-0.1201 (-0.3151, 0.0750)	0.219
MidFG L – Amygdala L	0.0023 (-0.0067, 0.0112)	0.611	0.0222 (-0.0905, 0.1348)	0.691	-0.0045 (-0.0146, 0.0056)	0.373	0.0010 (-0.1083, 0.1104)	0.985	-0.0784 (-0.2174, 0.0605)	0.259
AC – PC	-0.0124 (-0.0266, 0.0018)	0.084	-0.1670 (-0.3454, 0.0115)	0.066	-0.0071 (-0.0231, 0.0089)	0.374	-0.0999 (-0.2731, 0.0733)	0.249	-0.0662 (-0.2863, 0.1539)	0.544
AC – Caudate L	-0.0063 (-0.0163, 0.0036)	0.205	0.1027 (-0.0225, 0.2279)	0.104	-0.0010 (-0.0122, 0.0102)	0.861	0.0585 (-0.0630, 0.1800)	0.334	0.0980 (-0.0564, 0.2524)	0.205
AC – Amygdala L	-0.0102 (-0.0210, 0.0006)	0.064	-0.0418 (-0.1778, 0.0943)	0.536	-0.0011 (-0.0133, 0.0111)	0.860	0.0797 (-0.0524, 0.2118)	0.228	-0.0510 (-0.2188, 0.1168)	0.540
PC – Caudate L	-0.0026 (-0.0140, 0.0088)	0.646	0.0999 (-0.0435, 0.2432)	0.166	0.0009 (-0.0119, 0.0138)	0.883	-0.0997 (-0.2389, 0.0394)	0.154	-0.0835 (-0.2604, 0.0933)	0.343
PC – Amygdala L	-0.0053 (-0.0158, 0.0051)	0.307	-0.0293 (-0.1609, 0.1023)	0.654	0.0127 (0.0009, 0.0244)	0.036*	-0.0181 (-0.1459, 0.1096)	0.774	-0.0713 (-0.2336, 0.0911)	0.378

Abbreviations: AC, Anterior Cingulate Gyrus; CI, Confidence Interval; F, Female; HAM-D, Hamilton Depression Rating Scale; H&Y, Hoehn and Yahr scale; M, Male; MidFG L, Middle Frontal Gyrus Left; MPFC, Medial Prefrontal Cortex; PC, Posterior Cingulate Gyrus; ROI, Region of Interest.

Caudate L – Amygdala L	-0.014 (-0.0251, -0.0029)	0.015*	-0.1086 (-0.2479, 0.0306)	0.122	0.0009 (-0.0116, 0.0133)	0.890	0.0706 (-0.0645, 0.2058)	0.295	0.0291 (-0.1427, 0.2009)	0.732

*p-value < 0.05 was considered statistically significant

Abbreviations: AC, Anterior Cingulate Gyrus; CI, Confidence Interval; F, Female; HAM-D, Hamilton Depression Rating Scale; H&Y, Hoehn and Yahr scale; M, Male; MidFG L, Middle Frontal Gyrus Left; MPFC, Medial Prefrontal Cortex; PC, Posterior Cingulate Gyrus; ROI, Region of Interest.

Table 3. Multiple Linear Regression Analysis of Functional Connectivity and Depressive Symptoms (Model 2: BDI-II)

Connectivity (ROI pairs)	Age		Sex (M vs. F)		HAM-D		Daily pramipexole dosage (≥ 1 vs. <1 mg)		H&Y Stage	
	β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value
MPFC – MidFG L	0.0112 (-0.0032, 0.0255)	0.124	0.0459 (-0.1363, 0.2281)	0.611	-0.0006 (-0.0082, 0.0069)	0.864	0.0788 (-0.0962, 0.2538)	0.366	-0.1669 (-0.3830, 0.0493)	0.126
MPFC – AC	-0.0144 (-0.0262, -0.0027)	0.018*	-0.0549 (-0.2035, 0.0938)	0.458	-0.0012 (-0.0074, 0.0049)	0.686	-0.0637 (-0.2065, 0.0791)	0.371	-0.0080 (-0.1843, 0.1683)	0.927
MPFC – PC	-0.0044 (-0.0204, 0.0117)	0.581	0.0569 (-0.1463, 0.2601)	0.572	-0.0010 (-0.0094, 0.0075)	0.818	0.0489 (-0.1463, 0.2441)	0.614	-0.1126 (-0.3537, 0.1284)	0.348
MPFC – Caudate L	0.0039 (-0.0095, 0.0172)	0.561	0.0618 (-0.1074, 0.2310)	0.463	0.0014 (-0.0056, 0.0085)	0.683	-0.0572 (-0.2197, 0.1054)	0.479	-0.0550 (-0.2557, 0.1457)	0.581
MPFC – Amygdala L	-0.0034 (-0.0151, 0.0084)	0.562	-0.0082 (-0.1569, 0.1404)	0.911	-0.0027 (-0.0089, 0.0035)	0.382	0.1449 (0.0021, 0.2877)	0.047*	-0.0894 (-0.2658, 0.0870)	0.310
MidFG L – AC	0.0047 (-0.0086, 0.0179)	0.480	-0.0009 (-0.1686, 0.1668)	0.992	0.0028 (-0.0041, 0.0098)	0.414	-0.0798 (-0.2409, 0.0814)	0.321	0.0704 (-0.1285, 0.2694)	0.476
MidFG L – PC	0.0079 (-0.0041, 0.0200)	0.189	0.0788 (-0.0740, 0.2316)	0.301	0.0004 (-0.0059, 0.0068)	0.888	-0.0281 (-0.1749, 0.1187)	0.699	-0.0915 (-0.2727, 0.0898)	0.312
MidFG L – Caudate L	0.0111 (-0.0015, 0.0237)	0.083	0.0059 (-0.1535, 0.1653)	0.941	0.0000 (-0.0066, 0.0066)	0.994	-0.0848 (-0.2380, 0.0683)	0.268	-0.1347 (-0.3238, 0.0544)	0.157
MidFG L – Amygdala L	0.0027 (-0.0063, 0.0117)	0.546	0.0250 (-0.0894, 0.1393)	0.660	-0.0005 (-0.0052, 0.0043)	0.844	-0.0056 (-0.1154, 0.1043)	0.919	-0.0943 (-0.2300, 0.0413)	0.166
AC – PC	-0.0116 (-0.0259, 0.0027)	0.109	-0.1636 (-0.3449, 0.0176)	0.075	-0.0002 (-0.0077, 0.0073)	0.956	-0.1115 (-0.2856, 0.0626)	0.201	-0.0918 (-0.3068, 0.1232)	0.391
AC – Caudate L	-0.0055 (-0.0152, 0.0042)	0.255	0.0963 (-0.0261, 0.2187)	0.119	0.0033 (-0.0018, 0.0083)	0.201	0.0491 (-0.0685, 0.1667)	0.401	0.0915 (-0.0537, 0.2367)	0.208
AC – Amygdala L	-0.0104 (-0.0211, 0.0004)	0.058	-0.0384 (-0.1744, 0.0976)	0.569	-0.0014 (-0.0070, 0.0043)	0.618	0.0812 (-0.0494, 0.2119)	0.215	-0.0536 (-0.2150, 0.1077)	0.503
PC – Caudate L	-0.0022 (-0.0135, 0.0090)	0.691	0.09460 (-0.0478, 0.2371)	0.186	0.0023 (-0.0036, 0.0082)	0.430	-0.1037 (-0.2405, 0.0332)	0.133	-0.0822 (-0.2512, 0.0868)	0.329
PC – Amygdala L	-0.0065 (-0.0176, 0.0046)	0.245	-0.0384 (-0.1790, 0.1021)	0.581	0.0019 (-0.0039, 0.0077)	0.511	-0.0010 (-0.1361, 0.1340)	0.988	-0.0269 (-0.1937, 0.1399)	0.745

Abbreviations: AC, Anterior Cingulate Gyrus; BDI-II, Beck Depression Inventory-II; CI, Confidence Interval; F, Female; H&Y, Hoehn and Yahr scale; M, Male; MidFG L, Middle Frontal Gyrus Left; MPFC, Medial Prefrontal Cortex; PC, Posterior Cingulate Gyrus; ROI, Region of Interest.

Caudate L – Amygdala L	-0.0140 (-0.0250, -0.0029)	0.015*	-0.1103 (-0.2499, 0.0293)	0.117	0.0006 (-0.0052, 0.0064)	0.828	0.0706 (-0.0635, 0.2048)	0.292	0.0317 (-0.1340, 0.1973)	0.700

*p-value < 0.05 was considered statistically significant

Abbreviations: AC, Anterior Cingulate Gyrus; BDI-II, Beck Depression Inventory-II; CI, Confidence Interval; F, Female; H&Y, Hoehn and Yahr scale; M, Male; MidFG L, Middle Frontal Gyrus Left; MPFC, Medial Prefrontal Cortex; PC, Posterior Cingulate Gyrus; ROI, Region of Interest.

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