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Gender-based analysis of cortical thickness and structural connectivity in Parkinson's disease

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Abstract

Parkinson's disease (PD) is a progressive neurological disorder and appears to have gender-specific symptoms. Studies have observed a higher frequency for development of PD in male than in female. In the current study, we evaluated the gender-based changes in cortical thickness and structural connectivity in PD patients. With informed consent, 64 PD (43 males and 21 females) patients, and 46 (12 males and 34 females) age-matched controls underwent clinical assessment including MiniMental State Examination (MMSE) and magnetic resonance imaging on a 1.5 Tesla clinical MR scanner. Whole brain high-resolution T1-weighted images were acquired from all subjects and used to measure cortical thickness and structural network connectivity. No significant difference in MMSE score was observed between male and female both in control and PD subjects. Male PD patients showed significantly reduced cortical thickness in multiple brain regions including frontal, parietal, temporal, and occipital lobes as compared with those in female PD patients. The graph theory-based network analysis depicted lower connection strengths, lower

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Compliance with ethical standards

Conflicts of interest: The authors declare no conflict of interest.

Ethical standard: All human studies have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All persons gave their informed consent prior to their inclusion in the study.

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clustering coefficients, and altered network hubs in PD male than in PD female. Male-specific cortical thickness changes and altered connectivity in PD patients may derive from behavioral, physiological, environmental, and genetical differences between male and female, and may have significant implications in diagnosing and treating PD among genders.

Keywords

Parkinson's disease; Magnetic resonance imaging; Brain; Cortical thickness; Structural network connectivity

Introduction

Parkinson's disease (PD) is a progressive, neurological disorder affecting movements, muscle control, balance, cognitive functions, and consequently affecting the overall quality of life. These symptoms appear to have gender-specific directions in PD patients [19, 21, 31, 38, 45, 47]. Epidemiological studies have shown that male has 1.4–3.7 times higher frequency for developing PD than female [38, 42, 45, 47]. Further, a large meta-analysis study revealed that in any specific time period, approximately twice the number of males suffer from PD than do females [3].

In addition to differences in PD frequency, multiple studies have discovered differences in the clinical and cognitive profile of PD among genders. For example, onset of clinical symptoms of PD appears approximately 2 years earlier in male than in female [1, 21]. Studies have also observed sex-specific pattern in cognitive domains, where male showed more deficits in verbal fluency and recognition of facial emotions, while female depicted higher impairment in visuospatial functions [21, 31]. Additionally, the effect of drugs in terms of tolerability, efficacy, and pharmacokinetics for treating PD has different impacts in male and female [38].

Different genetic components such as gender-specific sex chromosome-linked genes, presence of sex hormones and environmental conditions are hypothesized to distinctly affect PD pathogenesis between male and female. Gene expression profile from post mortem brain of subjects who had been diagnosed with the late-stage idiopathic PD has revealed that the genes implicated in the pathogenesis of PD were up-regulated in male, while genes responsible for neuronal maturation were more pronounced in female [11, 39].

Brain's structural and functional changes have been widely studied in PD patients using multiple imaging modalities. Magnetic resonance imaging (MRI) is the most commonly used noninvasive imaging modality to study the structural and functional changes in the brain of PD patients. With structural brain MR imaging, atrophy in multiple brain regions including cortical and subcortical structures was observed in PD patients [25, 26, 29, 32, 44]. Studies based on diffusion MR imaging depicted higher brain's tissue changes in PD patients than in healthy controls [17, 33]. Contradictory findings were observed on cortical thickness analysis in PD patients. While some studies reported reduced cortical thickness in multiple brain sites [29, 32] others reported no significant changes in cortical thickness in PD patients compared with healthy controls [36].

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Although, no in vivo information is available showing the gender-based changes in cortical thickness in PD patients, however, studies based on clinical, behavioral and molecular examination clearly observed that female is more protected than male from PD pathology. Gender-based characterization of brain tissue changes in PD patients during the disease progression is crucial for the effective treatment of PD as both male and female have different disease symptoms, and progression and treatment outcomes. In the current study, we investigated gender-based differences in cortical thickness and structural connectivity in PD patients. Our hypothesis was that the difference in PD onset frequency and degree of PD disease severity in male and female might result in differences in cortical thickness and structural network connectivity.

Materials and methods

Participants

Institutional review board committee approved the current study protocol; 64 PD patients (43 males, mean age = 71.2 ± 6.3 years; 21 females, mean age = 69.5 ± 7.0 years), and 46 controls (12 males, mean age = 73.0 ± 10 years; 34 females, mean age = 69.3 ± 10 years) were included in this study. Informed consent was obtained from all subjects before they underwent clinical assessment and whole brain MRI. For cognitive assessment, Mini-Mental State Examination (MMSE) was performed in all subjects. A team of experts including a neurologist, a neuropsychologist, a neurophysiologist and a psychiatrist made the diagnosis for PD as per the UK Parkinson's Disease Society Brain Bank criteria for Parkinson's disease [27]. All PD patients met the clinical diagnostic criteria for Parkinson's disease. The control group consisted of subjects who visited the clinic with subjective complaints, and underwent exactly the same diagnostic work-up as PD patients.

MRI study

MRI was performed on a 1.5-Tesla, Siemens Sonata clinical-scanner (Siemens Medical Systems, Malvern, PA, USA) using a vendor-supplied head coil. Conventional imaging including T1-weighted, T2-weighted and fluid-attenuated-inversion-recovery was performed to examine any gross brain pathology. High-resolution T1-weighted 3D image volumes were acquired using magnetization-prepared rapid acquisition gradient-echo (MPRAGE) pulse sequence covering whole brain with repetition time (TR)/echo time (TE) = 3000 ms/3.5 ms, slice thickness = 1.2 mm, field of view (FOV) of 240 × 240 mm^2 and 192 phase encode steps, and flip angle = 8°.

Cortical thicknesses analysis—High-resolution T1-weighted brain images were processed for cortical thickness measurement in all subjects using well-established FreeSurfer pipeline (v 5.3.0). The image-processing methods are described in detail elsewhere [16]. Briefly, non-brain tissue (skull) removal followed by Talairach transformation, intensity normalization, segmentation, tessellation of the gray and white matter boundaries, topology correction, and surface deformation (http://surfer.nmr.mgh.harvard.edu/) were performed. For the quality control assessments all processed data were carefully evaluated to ensure that skull and dura matter were excluded from the analysis. After final processing, gray matter surface maps were smoothed using a

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Gaussian kernel (full width of half maximum, 15 mm). Vertex-by-vertex general linear model approach was used to evaluate regional cortical thickness changes among different groups using age and gender as covariates in the analysis (ANCOVA; $p < 0.05$, false discovery rate corrections for multiple comparisons). The statistical parametric maps for regional cortical thickness differences were generated individually for both left and right hemispheres. For structural identification of various brain regions, significant clusters between groups were overlaid onto averaged inflated cortical surface maps.

Network analysis—The Graph Analysis Toolbox was used for the structural network construction. Pearson correlation coefficient was used to generate interregional regions of interests (ROIs) correlations metrics for both groups. Clustering coefficient (C) and characteristic path length (L) of the network at different densities starting from 0.42 to 0.50 with interval of 0.01 were measured to evaluate the global network topology between groups. The C and L values of both networks were compared with the corresponding mean values of a random graph including same number of nodes, total edges, and degree distribution [30, 41]. The small-world index (SW) was computed as $(C/C_{rand})/(L/L_{rand})$, where Crand and Lrand are the mean C and L of the random network [6]. The characteristic of SW networks, C must be significantly higher than C_{rand} (C/C_{rand} ratio greater than 1), and L should comparable to L_{rand} [24] (L/L_{rand} ratio close to 1). The nodal characteristic (betweenness) of the structural networks at threshold density of 0.42 was measured to detect anatomical or functional connections. The network hubs were also identified in each group as nodes with degree at least two standard deviation higher than the mean network degree [5, 24]. Network hub is considered as a crucial regulator of effective information flow in the brain [34]. Clustering coefficient (Gamma) measures the number of connections that exists between the nearest neighbors of a node. The path length (Lambda) defines the number of points required for moving from a given node to another. Generally, the shortest path is considered. The small-world network (Sigma) is characterized by the presence of abundant clustering of connections combined with short average distances between neuronal elements. These networks maximize information processing while minimizing wiring costs, support segregated and integrated information processing, and present resilience against pathology.

Statistical analyses

All the statistical computations were performed using the Statistical Package for Social Sciences (SPSS) version 16.0 (SPSS Inc., Chicago, USA). Subjects' demographic and MMSE scores were assessed by one way analysis of variance (ANOVA) and Chi square. A p value less than 0.05 was considered statistically significant.

Results

Demographic and cognitive variable

No significant difference in age ($p = 0.84$) was observed between control and PD patients. The mean MMSE score (control = 29.1 ± 1.1, PD = 27.6 ± 3.2) was significantly decreased in PD patients ($p = 0.008$). No significant difference in PD disease duration at the time of MRI was observed between male and female patients [male: mean ± SD (3.67 ± 2.17 years); female: mean ± SD (3.69 ± 2.13 years); p value = 0.97]. No gender-based difference in age

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and mean MMSE score (control; males 29.0 ± 1.1; females, 29.2 ± 1.1; $p = 1$; PD, males 27.5 ± 3.2; females, 27.8 ± 3.1; $p = 0.75$) was observed both in PD and control.

Cortical thickness

Significantly lower cortical thickness bilaterally in multiple brain sites including caudal middle frontal, fusiform, inferior parietal, postcentral, rostral middle frontal, superior frontal, superior parietal, superior temporal, supramarginal was observed in PD male than PD female (Table 1; Fig. 1). Unilaterally, decreased cortical thickness was noted in inferior temporal, medial orbitofrontal, and paracentral in the right brain hemisphere, and in caudal middle frontal, lingual, middle temporal, precentral, precuneus in the left brain hemisphere in PD male compared with those in PD female (Table 1; Fig. 1).

PD male showed significantly decreased cortical thickness bilaterally in inferior parietal, precentral, rostral middle frontal, superior parietal, supramarginal (Table 2; Fig. 2), and unilaterally in fusiform, middle temporal (Table 2; Fig. 2) in the right hemisphere, and in inferior temporal, parsorbitalis, postcentral, superior frontal in the left hemisphere as compared with control female (Table 2; Fig. 2). No significant difference in cortical thickness was observed between control female versus PD female, control male versus control female, and control male versus PD male.

Network analysis

Both PD male and female showed widespread positive and negative interregional ROIs correlations (Fig. 3). The correlation strength was lower in PD male (0.40 ± 0.09) than in PD female (0.43 ± 0.11); however, the difference was not statistically significant ($p = 0.12$). A trend of lower clustering coefficients [gamma, PD male (1.116), PD female (1.135), p = 0.67), and (sigma, PD male (1.046), PD female (1.122); p = 0.53)], and higher path length [lambda, PD male (1.067), PD female (1.012); p = 0.48)] was observed in PD male than PD female (Fig. 4). The normalized gamma was greater than 1 across a wide range of densities in both PD male and PD female (Fig. 4a), while the normalized lambda in both groups was close to 1 (Fig. 4b, c). The cortical correlation network followed an SW property across a wide range of densities in both PD male and PD female.

Lower nodal betweenness was observed in left caudal middle frontal, left rostral middle frontal, and right parahippocampal in PD male than in PD female (Fig. 5). On the basis of nodal betweenness, the network hubs were identified in left inferior temporal, left rostral anterior cingulate, right fusiform, and right isthmus cingulate area in PD male, while in PD female, network hubs were in left rostral middle frontal, right parahippocampal, and right superior temporal regions (Fig. 6).

Discussion

Studies have shown that impaired cognition and dementia in PD patients are associated with the structural and functional brain changes [2, 9, 14, 20, 25]. However, no study so far has defined cortical thickness changes among PD genders. In the current study, we observed gender-based changes in cortical thickness and structural network connectivity in PD

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patients, where male PD patients are more affected than female PD patients suggestive of higher brain's tissues' impairment in male PD.

There are contradictory findings on gender-based clinical and behavioral differences among PD patients [19, 31, 38, 42, 47]. Indeed most of the studies have observed gender-based differences in PD symptoms' appearance and frequency [19, 21, 45, 47]. In male, symptoms appear earlier than in female with tremor as a primary indication, while in female the initial signs are bradykinesia and rigidity [21]. Gender-based rapid eye movement (REM) sleep behavior disorder (RBD) was examined in PD patients, which depicted higher prevalence of RBD in male than in female [49]. A cross-sectional study over 24,402 PD patients showed that male PD patients have more wandering, verbal and physical abusiveness, and inappropriate behavior, whereas female PD patients have more depression; moreover, there were gender-based differences with respect to pharmacologic therapies, where most of the male PD patients were on antipsychotic drugs, while female PD patients received antidepressants [19].

The current study observed gender-based differences in regional cortical thickness in multiple brain sites depicting lower cortical thickness in PD male than in PD female. Since these regions are primarily involved in critical roles including autonomic, cognitive, affective, language, and visual functions we anticipate more behavioral and brain functional changes in PD male. For example, the medial orbitofrontal cortex, which plays a crucial role in sensory integration, decision-making, showed significantly decreased cortical thickness in PD male than in PD female. The other brain areas with decreased cortical thickness in PD male include temporal, frontal, occipital, and parietal, and caudal region, and changes in these regions may responsible for the gender-specific differences in clinical, cognitive and behavioral profiles in PD patients. Gender-based changes in gray matter were previously measured in Alzheimer's disease (AD), where male AD patients showed higher gray matter loss in anterior cingulate than did female AD patients [4], whereas, based on the cortical thickness analyses, no gender-based difference in AD patients was observed [37]. Other studies on patients with temporal lobe epilepsy and schizophrenia depicted lower cortical thickness in female than in male patients [18, 22]. We suggest that the differential disease pathology in PD affects the male more than it does the female.

PD male showed lower structural network correlations than PD female due to altered cortical thickness. Structural network in both PD male and PD female showed SW topology, which is consistent with the previous studies on other pathologies including Alzheimer's disease, schizophrenia, mild cognitive impairment, and epilepsy [8, 23, 46, 48]. We did not observe any significant difference for the normalized clustering coefficient, and normalized path length between PD male and PD female.

A node with high betweenness is present at the intersection of many short paths and may control the information flow. In a brain structural network, a node with high betweenness has the potential to participate in large number of functional interactions [40]. In the current study, the nodal betweenness in PD male was significantly altered than in PD female suggestive of decreased structural brain connectivity, which may contribute to the differential behavioral and brain's functional changes in PD male. PD male showed alerted

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hubs compared to PD female. Although there has been no gender-based study on the hub locations in PD patients, we suggest that altered location of hubs in PD male might be due to change in the regional cortical thickness.

The various effects of PD disease pathology on the brain structural organization and network connectivity among genders can be well explained on the basis of involvement of the sex hormones and genes in neurodevelopment and regulation of the brain's functional activities. Sex hormones are shown to be a very important factor in gender-based differentiation of structural and functional changes in the brain. The most important sex hormone in the female is estrogen; especially 17β-estradiol has been thoroughly studied in relation to their neuroprotective effects [10]. Several studies have observed neuroprotective effect of estrogen on dopamine systems and resulting reduction of risk for PD in female. Other studies have suggested that the estrogen-based hormone therapy relieves PD symptoms when given in the early stage of the disease, and PD symptoms may deteriorate when the treatment is discontinued [7, 15, 28, 35]. The genes involved in the pathogenesis of PD including α-synuclein and PINK-1 are shown to be overexpressed in male, while the genes responsible for the neuronal maturation and signal transduction are overexpressed in female [11, 39]. Recent study measured higher level of α-synuclein in plasma of male PD than female PD [12]. Further, they observed that increased plasma α-synuclein level correlates with cognitive impairment, hallucinations, psychosis, apathy and sleep disorders in PD patients [12]. We suggest that higher expression of genes involved in PD pathogenesis in male and neuroprotective effects of sex hormones in female might be a possible explanation for the lower cortical thickness in male PD than female PD.

Most of the patients included in the current study were on anti-Parkinson drugs treatment at the time of MRI study. However, this study does not evaluate any effect of the treatment on cortical thickness in PD patients, while the effect of anti-Parkinson drugs on cortical thickness has been reported previously. It is found that PD patients with impulse control disorder (ICD) showed increased cortical thickness in limbic regions compared with PD patients without ICD treated for the equal daily dose of levodopa [43]. Similarly, in another study, PD patients with long term treatment who developed levodopa-induced-dyskinesia (LID) showed higher cortical thickness in the inferior frontal sulcus than PD patients without LID [13].

It is important to mention some limitations of the current study including absence of clinical and neurocognitive profiles' correlation with cortical thickness changes. Nevertheless, the current study provides an in vivo imaging clinical biomarker to evaluate the gender-based changes in cortical thickness, which may help to improve the clinical management of PD patients.

Conclusions

Gender-based differences on regional cortical thickness appeared in PD patients, where male PD patients are more affected than female PD patients suggestive of greater brain tissue changes in male PD than in female PD. These male-specific brain tissue changes as reflected by decreased cortical thickness in multiple brain regions may derive from physiological,

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genetical and environmental differences between male and female and may have significant implications in diagnosing and treating PD among genders. The findings also highlight the need for gender-specific medications for better clinical management of PD patients.

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Abbreviations

PD	Parkinson's disease
MRI	Magnetic resonance imaging
MMSE	Mini-Mental State Examination
MPRAGE	Magnetization-prepared rapid acquisition gradient-echo
TR	Repetition time
TE	Echo time
FOV	Field of view
ANCOVA	Analysis of covariance
ROIs	Regions of interests
C	Clustering coefficient
L	Characteristic path length
SW	Small-world index
ANOVA	Analysis of variance
RBD	Rapid eye movement sleep behavior disorder

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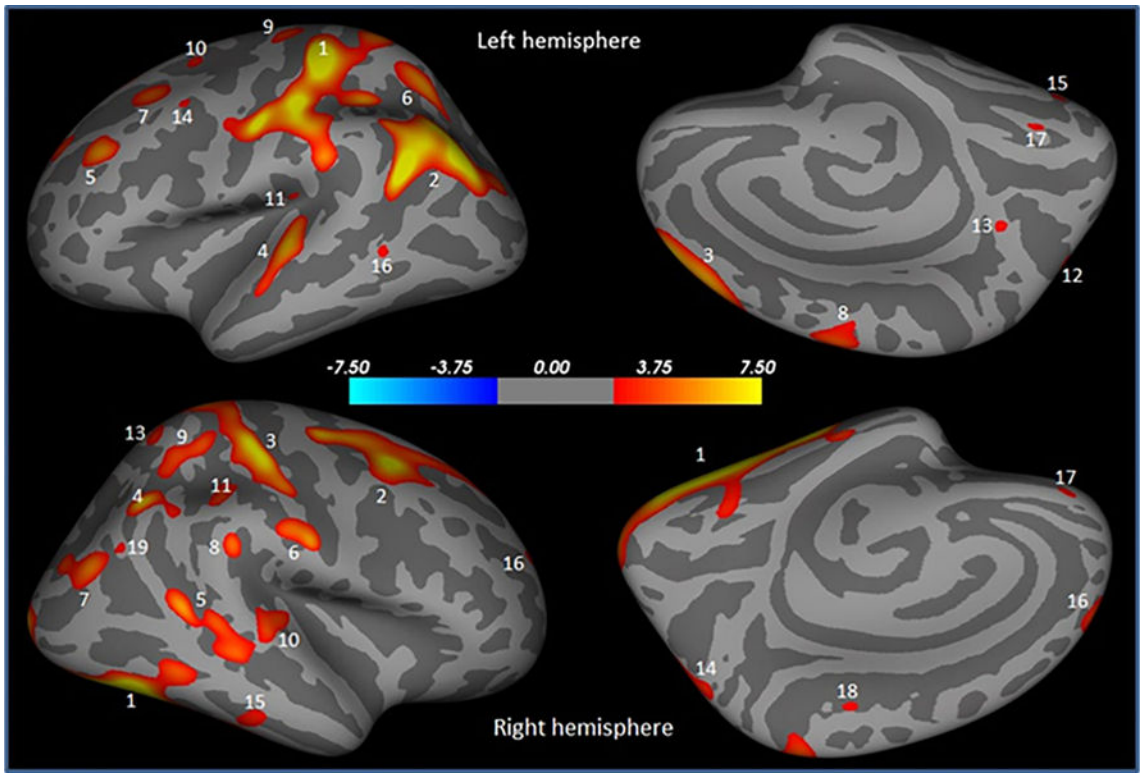

Fig. 1.

Brain regions showing significantly reduced cortical thickness in PD male compared to PD female overlaid onto inflated pial surface. These regions are postcentral (*1*), inferior parietal (*2*), superior frontal (*3*), superior temporal (*4*), rostral middle frontal (*5*), superior parietal (*6*), caudal middle frontal (*7*), precentral (*8*), superior frontal (*9*), superior frontal (*10*), supramarginal (*11*), superior parietal (*12*), precuneus (*13*), caudal middle frontal (*14*), fusiform (*15*), middle temporal (*16*), lingual (*17*) in the left hemisphere, and fusiform (*1*), caudal middle frontal (*2*), postcentral (*3*), inferior parietal (*4*), inferior parietal (*5*), postcentral (*6*), inferior parietal (*7*), supramarginal (*8*), superior parietal (*9*), superior temporal (*10*), supramarginal (*11*), superior frontal (*12*), superior parietal (*13*), superior parietal (*14*), inferior temporal (*15*), rostral middle frontal (*16*), medial orbitofrontal (*17*), paracentral (*18*), and inferior parietal (*19*) in the right hemisphere

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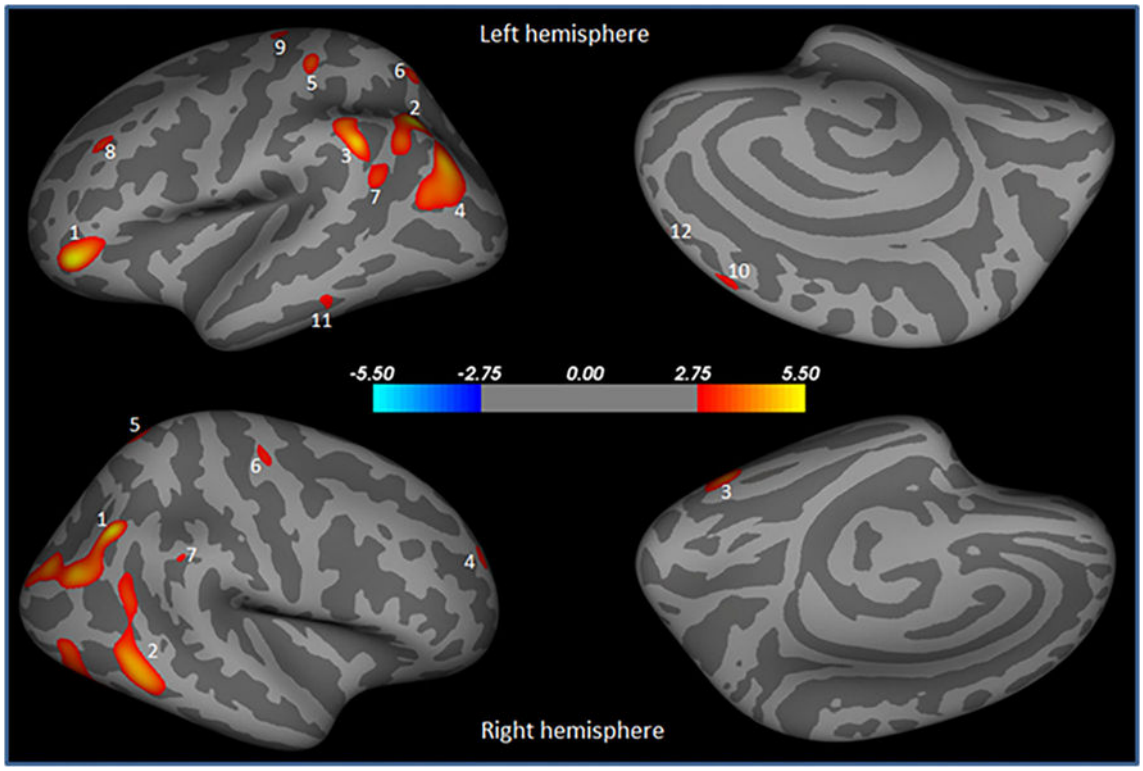

Fig. 2.

Brain regions showing significantly reduced cortical thickness in PD male compared to control female overlaid onto inflated pial surface. These areas are pars orbitalis (*1*), inferior parietal (*2*), supramarginal (*3*), inferior parietal (*4*), postcentral (*5*), superior parietal (*6*), supramarginal (*7*), rostral middle frontal (*8*), precentral (*9*), superior frontal (*10*), inferior temporal (*11*), superior frontal (*12*) in the left hemisphere, and inferior parietal (*1*), middle temporal (*2*), fusiform (*3*), rostral middle frontal (*4*), superior parietal (*5*), precentral (*6*), and supramarginal (*7*) in the right hemisphere

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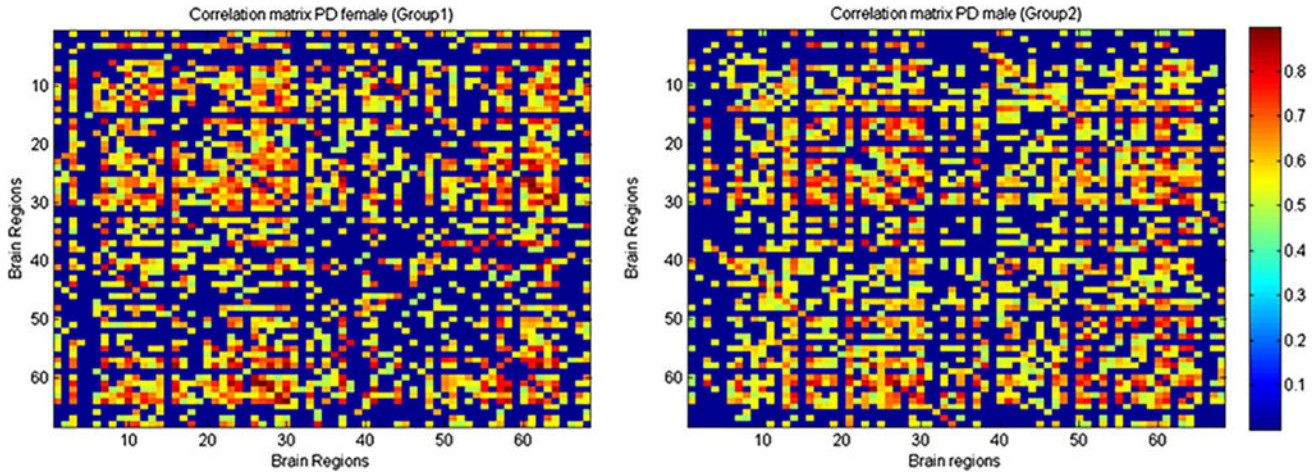

Fig. 3.

Inter-regional cortical brain regions correlation matrix of PD female and PD male. Warm colour showed connected regions. These regions are—bankssts, caudal anterior cingulate, caudal middle frontal, cuneus, entorhinal, fusiform, inferior parietal, inferior temporal, isthmus cingulate, lateral occipital, lateral orbitofrontal, lingual, medial orbitofrontal, middle temporal, parahippocampal, paracentral, pars opercularis, pars orbitalis, pars triangularis, perical-carine, postcentral, posterior cingulate, precentral, precuneus, rostral anterior cingulate, rostral middle frontal, superior frontal, superior parietal, superior temporal, supramarginal, frontal pole, temporal pole, transverse temporal, insula both in the *left* and *right* hemisphere

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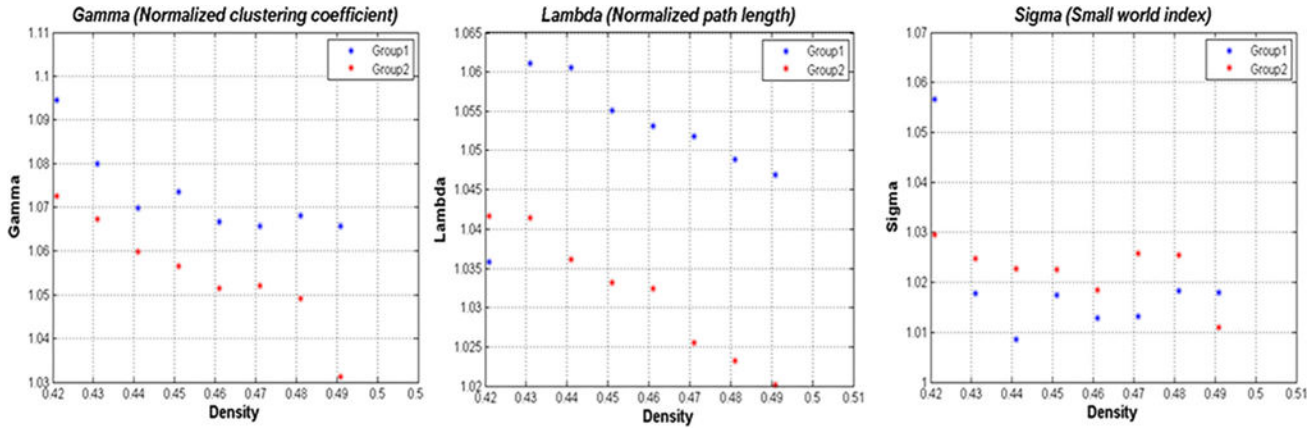

Fig. 4.

Changes in global network properties as a function of network densities in PD female and PD male (**a–c**). Both networks follow a small-world organization across the range of densities

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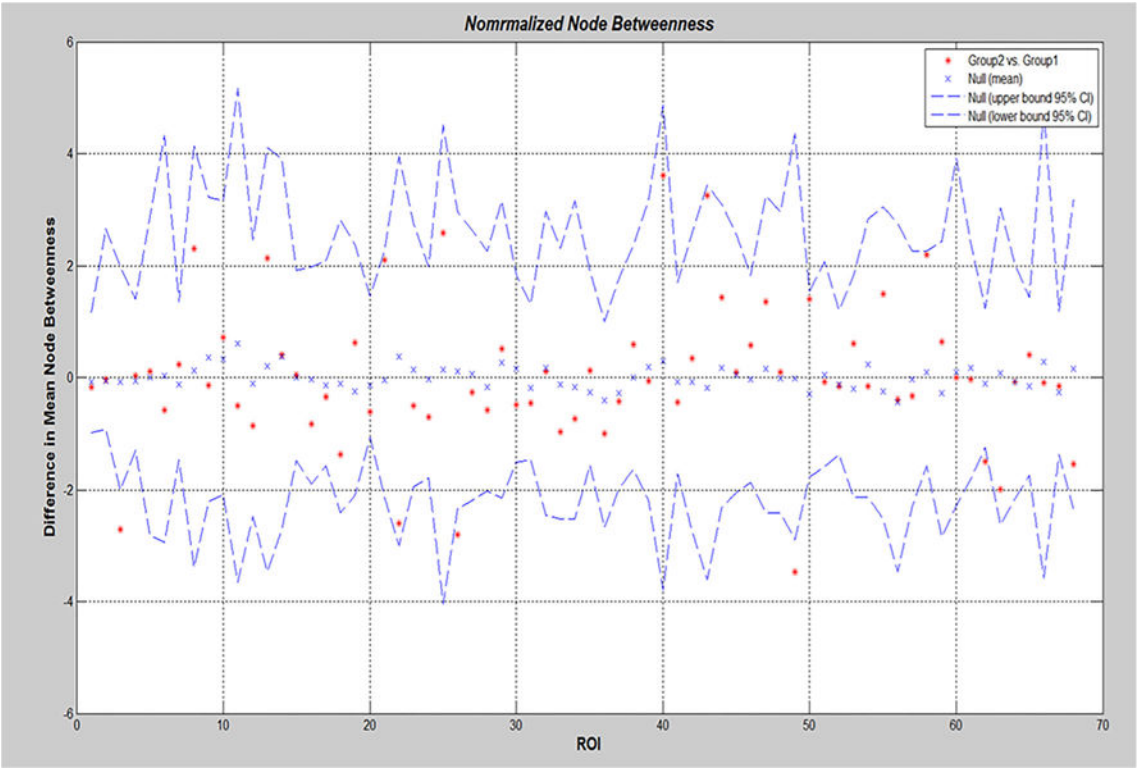

Fig. 5.

Mean node betweenness differences in regional network topology between PD female (group 1) and PD male (group 2). PD male showed lower nodal betweenness in left caudal middle frontal, left rostral middle frontal, and right parahippocampal than PD female

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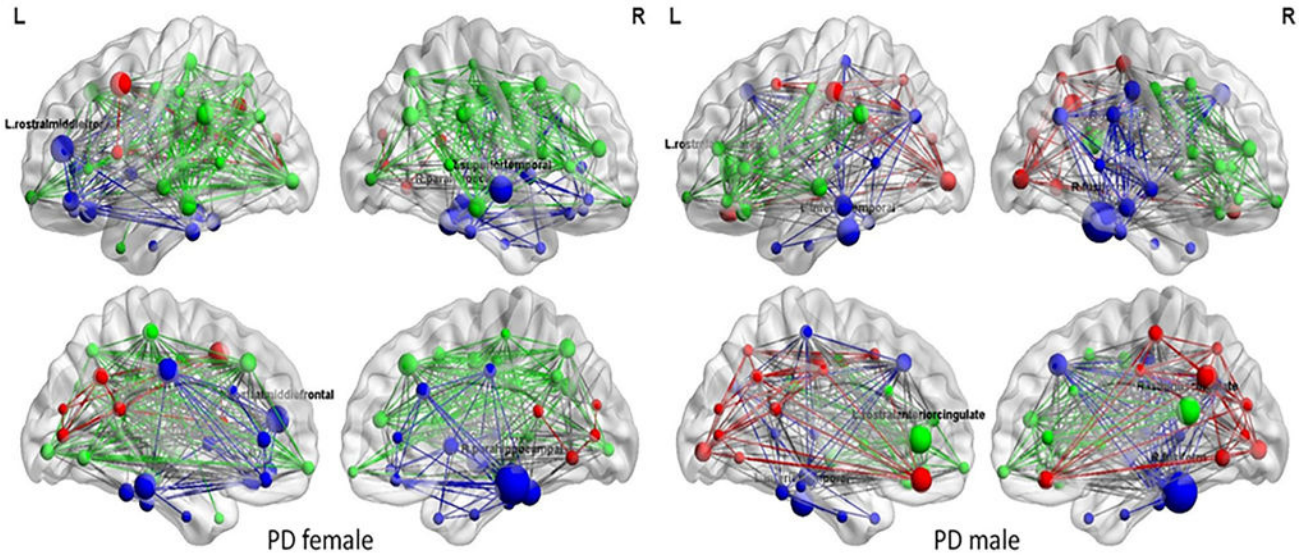

Fig. 6.

Structural correlation networks and hubs overlaid on ICBM152 brain template of PD female and PD male. *Color lines* indicate connections (edge), and spheres represent regions (node). The radius of the spheres is proportional to the nodal betweenness

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Table 1

Regional cortical thickness difference between PD male and PD female

Cluster no.		Brain sites	Max *t*-statistic	Size (mm^2)	Tal *X*	Tal *Y*	Tal *Z*	Cortical thickness, mm (mean ± SD)			
								PD male	PD female	Control male	Control female
1	L	Postcentral	−6.0326	3307.86	−37.6	−30.6	65.4	1.65 ± 0.18	1.93 ± 0.19	1.68 ± 0.19	1.80 ± 0.17
2	L	Inferior parietal	−5.7829	2373.56	−46.3	−55.6	24.1	2.03 ± 0.17	2.30 ± 0.22	2.09 ± 0.25	2.18 ± 0.22
3	L	Superior frontal	−4.0131	1122.65	−6.9	51.2	34.5	2.68 ± 0.22	2.93 ± 0.21	2.69 ± 0.14	2.84 ± 0.19
4	L	Superior temporal	−3.9891	582.57	−56.9	−19	1.2	2.22 ± 0.30	2.52 ± 0.18	2.14 ± 0.17	2.40 ± 0.27
5	L	Rostral middle frontal	−3.6413	309.39	−35.9	32.3	29.3	2.09 ± 0.20	2.32 ± 0.21	2.25 ± 0.20	2.18 ± 0.22
6	L	Superior parietal	−3.595	394.46	−24.3	−61.4	50.2	1.80 ± 0.18	2.00 ± 0.20	1.77 ± 0.23	1.93 ± 0.22
7	L	Caudal middle frontal	−3.1883	241.95	−30.5	13.1	45	2.17 ± 0.21	2.37 ± 0.16	2.21 ± 0.24	2.25 ± 0.21
8	L	Superior frontal	−2.9724	229.16	−10	−6.9	61.6	2.32 ± 0.24	2.58 ± 0.33	2.33 ± 0.21	2.45 ± 0.27
9	L	Precentral	−2.7983	144.12	−22.2	−22.6	68	1.97 ± 0.28	2.25 ± 0.33	1.95 ± 0.30	2.21 ± 0.29
10	L	Superior frontal	−2.4729	40.6	−20.4	4.5	52	2.14 ± 0.21	2.32 ± 0.21	2.22 ± 0.15	2.21 ± 0.20
11	L	Supramarginal	−2.4448	22.48	−42.4	−26	22.5	2.27 ± 0.29	2.51 ± 0.27	2.30 ± 0.18	2.42 ± 0.26
12	L	Superior parietal	−2.4134	78.28	−18.1	−80.8	39.7	1.87 ± 0.19	2.04 ± 0.26	1.92 ± 0.17	1.98 ± 0.21
13	L	Precuneus	−2.4055	25.96	−4.4	−61.7	18.9	2.32 ± 0.22	2.51 ± 0.20	2.33 ± 0.25	2.34 ± 0.23
14	L	Caudal middle frontal	−2.3645	24.97	−40.1	9.7	48.2	2.22 ± 0.19	2.38 ± 0.21	2.25 ± 0.18	2.35 ± 0.18
15	L	Fusiform	−2.3456	32.43	−32.6	−78.5	−11.1	1.97 ± 0.17	2.11 ± 0.17	1.20 ± 0.18	2.04 ± 0.21
16	L	Middle temporal	−2.3429	27.65	−61.2	−51.5	1.6	2.46 ± 0.23	2.65 ± 0.21	2.51 ± 0.19	2.57 ± 0.26
17	L	Lingual	−2.321	36.63	−17.3	−69.9	−10.2	1.81 ± 0.16	1.95 ± 0.18	1.80 ± 0.12	1.85 ± 0.21
1	R	Fusiform	−7.2254	4027.7	38.5	−66.5	−15.3	2.19 ± 0.19	2.51 ± 0.20	2.27 ± 0.14	2.36 ± 0.19
2	R	Caudal middle frontal	−4.8082	1618.82	29.7	8.8	48.9	2.19 ± 0.15	2.43 ± 0.25	2.25 ± 0.13	2.29 ± 0.21
3	R	Postcentral	−4.5131	1814.9	39.1	−29.9	64	1.65 ± 0.14	1.84 ± 0.19	1.71 ± 0.16	1.72 ± 0.17
4	R	Inferior parietal	−4.1342	341.95	42.8	−61.9	45.5	2.09 ± 0.17	2.30 ± 0.23	2.12 ± 0.27	2.27 ± 0.22
5	R	Inferior parietal	−3.6082	633.4	49.9	−50.4	8.7	2.28 ± 0.19	2.48 ± 0.20	2.28 ± 0.17	2.32 ± 0.21
6	R	Postcentral	−3.5816	335.79	59.9	−8.9	31.3	1.78 ± 0.20	1.99 ± 0.17	1.85 ± 0.17	1.90 ± 0.22
7	R	Inferior parietal	−3.3508	451.44	42.9	−78	21	2.24 ± 0.22	2.47 ± 0.24	2.25 ± 0.16	2.46 ± 0.23
8	R	Supramarginal	−3.1256	120.92	56	−37.2	32	2.16 ± 0.23	2.39 ± 0.25	2.23 ± 0.20	2.25 ± 0.18
9	R	Superior parietal	−2.9378	392.02	29.7	−43.8	54.6	1.76 ± 0.19	1.94 ± 0.20	1.77 ± 0.21	1.89 ± 0.17
10	R	Superior temporal	−2.8605	302.2	65.3	−20.5	4.2	2.52 ± 0.20	2.71 ± 0.19	2.54 ± 0.18	2.62 ± 0.22

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Cluster no.		Brain sites	Max *t*-statistic	Size (mm^2)	Tal *X*	Tal *Y*	Tal *Z*	Cortical thickness, mm (mean ± SD)			
								PD male	PD female	Control male	Control female
11	R	Supramarginal	−2.808	178.39	46	−37.6	41.4	2.02 ± 0.18	2.22 ± 0.26	2.08 ± 0.29	2.15 ± 0.18
12	R	Superior frontal	−2.6901	165	7.8	56.9	25.8	2.60 ± 0.23	2.81 ± 0.24	2.62 ± 0.16	2.70 ± 0.22
13	R	Superior parietal	−2.5623	96.16	21.5	−58.9	63.8	1.97 ± 0.24	2.17 ± 0.23	2.01 ± 0.25	2.09 ± 0.21
14	R	Superior parietal	−2.5585	269.61	18.2	−75.9	43.5	1.88 ± 0.17	2.03 ± 0.20	1.93 ± 0.19	1.20 ± 0.20
15	R	Inferior temporal	−2.4346	119.6	53.7	−28	−20.9	2.56 ± 0.23	2.76 ± 0.26	2.53 ± 0.27	2.64 ± 0.26
16	R	Rostral middle frontal	−2.3588	43.53	19.6	53.1	22.8	2.26 ± 0.17	2.41 ± 0.20	2.30 ± 0.15	2.42 ± 0.20
17	R	Medial orbitofrontal	−2.3268	28.73	7.1	48.1	−20.8	2.25 ± 0.26	2.47 ± 0.28	2.22 ± 0.21	2.33 ± 0.20
18	R	Paracentral	−2.2724	16.75	13.2	−25.6	47	2.04 ± 0.22	2.21 ± 0.19	2.13 ± 0.22	2.07 ± 0.15
19	R	Inferior parietal	−2.2692	24.24	44.9	−67	27.7	2.09 ± 0.18	2.29 ± 0.32	2.15 ± 0.25	2.26 ± 0.20

Each area consists of adjacent voxels showing a significant group difference; some brain structures have more than one area of change. The magnitude of the peak (*t* statistic) in each area and its Talairach coordinates (a standardized common brain space) are listed together with size (in normalized space) and the mean (SD) of cortical thickness at specific vertex for PD male and PD female. Cortical thickness of control male and female on same vertex is also shown

L left hemispheres, *R* right hemispheres

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Table 2

Regional cortical thickness difference between PD male and control female

Cluster no.		Brain sites	Max *t*-statistic	Size (mm^2)	Tal *X*	Tal *Y*	Tal *Z*	Cortical thickness; mm (mean ± SD)	
								Control female	PD male
1	L	Pars orbitalis	5.1623	440.75	−42.1	45.4	−9.4	2.65 ± 0.18	2.41 ± 0.23
2	L	Inferior parietal	5.1616	571.19	−36.5	−66.5	43.8	2.19 ± 0.17	1.99 ± 0.18
3	L	Supramarginal	4.6329	352.31	−57.4	−48.4	33.1	2.61 ± 0.19	2.39 ± 0.23
4	L	Inferior parietal	4.4719	758.65	−41.2	−74.7	27.9	2.44 ± 0.26	2.20 ± 0.19
5	L	Postcentral	3.6049	98.38	−39.3	−32.6	63.4	1.96 ± 0.19	1.77 ± 0.21
6	L	Superior parietal	3.3874	86.72	−20	−65.2	54.1	2.11 ± 0.24	1.92 ± 0.22
7	L	Supramarginal	3.3605	126.42	−50.8	−52.8	20.2	2.30 ± 0.26	2.11 ± 0.17
8	L	Rostral middle frontal	3.3191	81.32	−34	30.7	31	2.26 ± 0.20	2.09 ± 0.19
9	L	Precentral	3.1038	55.47	−20.4	−23	68.3	2.18 ± 0.30	1.94 ± 0.28
10	L	Superior frontal	3.0241	43.22	−7.4	29	49.8	2.80 ± 0.19	2.64 ± 0.21
11	L	Inferior temporal	2.8718	43.93	−56.4	−36	−16.1	2.71 ± 0.29	2.48 ± 0.28
12	L	Superior frontal	2.8017	0.86	−7.1	53	33.7	2.84 ± 0.20	2.67 ± 0.21
1	R	Inferior parietal	5.052	1142.64	40.3	−65.9	46.3	2.33 ± 0.20	2.12 ± 0.18
2	R	Middle temporal	4.4132	712.77	53.7	−54.5	−2.6	2.57 ± 0.21	2.32 ± 0.26
3	R	Fusiform	3.9129	638.73	39.8	−66.1	−14.8	2.35 ± 0.19	2.16 ± 0.20
4	R	Rostral middle frontal	3.2135	62.23	20.1	53.1	22.9	2.41 ± 0.20	2.25 ± 0.17
5	R	Superior parietal	3.1849	67.08	14.1	−59.4	62.8	2.10 ± 0.19	1.92 ± 0.24
6	R	Precentral	3.1614	59.88	33.8	−19.3	66.3	2.40 ± 0.32	2.13 ± 0.30
7	R	Supramarginal	2.9318	20.04	54.2	−42.9	39	2.39 ± 0.23	2.22 ± 0.19

Each area consists of adjacent voxels showing a significant group difference; some brain structures have more than one area of change. The magnitude of the peak (*t* statistic) in each area and its Talairach coordinates (a standardized common brain space) are listed together with size (in normalized space) and the mean (SD) of cortical thickness for control female and PD male

L left hemispheres, *R* right hemispheres

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