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Somatic symptoms disorders in Parkinson's disease are related to default mode and salience network dysfunction

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ABSTRACT

Background: Somatic Symptoms Disorder (SSD) has been shown to have a clinically very high prevalence in Parkinson's Disease (PD) with frequencies ranging from 7.0% to 66.7%, higher than in the general population (10%- 25%).

SSD has been associated with dysfunction in Default Mode and Salience network.

Aim: With the present study we aim to verify by means of resting state functional MRI whether possible specific abnormalities in the activation and functional connectivity of the default mode network (DMN) and salience network in cognitively intact PD patients may be more prominent in PD patients with somatic symptoms (SSD-PD) as compared with patients without SSD (PD).

Methods: Eighteen SSD-PD patients (61% male), 18 PD patients (83% male) and 22 healthy age-matched subjects (59% male) were enrolled in the study and underwent resting state functional MRI.

Results: fractional amplitude of low-frequency fluctuation (fALFF) showed reduced activity in bilateral lateral parietal cortex and in left anterior insula in both SSD-PD and PD compared to control group. Functional connectivity (FC) values in the DMN areas and between DMN and salience network areas were found to be lower in SSD-PD than in control group and PD. No significant correlation was found between fMRI results and demographic and clinical variables, excluding the effect of possible confounders on fMRI results.

The present study, showing reduced activity in bilateral parietal areas and in the left anterior insula as compared to healthy controls, suggests a dysfunction of the DMN and salience network in PD, either with or without SSD.

The FC reduction within DMN areas and between DMN and salience network areas in SSD-PD patients suggests a role of dysfunctional connectivity in the resting state network of patients with SSD.

1. Introduction

Parkinson's Disease (PD) is a progressive neurodegenerative disorder consisting of specific motor and non-motor symptoms, including different prominent psychiatric disturbances (McLaughlin et al., 2014). Among the main psychiatric comorbidities and psychological disturbances in PD,

Somatic Symptoms Disorder (SSD) (American Psychiatric Association, 2013; World Health Organization, 1992) has been shown to have a very high prevalence in PD with frequencies ranging from 7.0% to 66.7% (Bugalho et al., 2012; Carrozzino et al., 2017; Hallett, 2018; Onofrj et al., 2010, 2011; Pareés et al, 2013; Wissel et al., 2018), as compared to prevalence in the general population, which ranges between 10% and 25%, in primary care (Baizabal-Carvallo et al., 2019; Steinbrecher et al., 2011; Stone, 2009).

The high prevalence of SSD in PD patients suggests that in PD there may be a peculiar vulnerability to SSD as compared to the general population.

A large number of different functional and structural neuroimaging abnormalities have been reported in patients with SSD compared to non-clinical controls. An increased activity of limbic structures (insula and anterior cingulate cortex) was found in SSD subjects (Browning et al., 2011).

In functional MRI (fMRI) studies, patients with SSD have been

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shown to deactivate right middle frontal cortex (Li et al., 2016).

Other neuroimaging studies have shown that SSD is related to local alterations in brain regions, including the medial prefrontal cortex (Su et al., 2014), left precuneus (Lemche et al., 2013; Su et al., 2014), anterior insula, ventral anterior cingulate gyrus (Su et al., 2016), cerebellum (Garcia-Campayo et al., 2001), posterior cingulate cortex (Lemche et al., 2013), caudate nuclei (Hakala et al., 2004), and amygdalae (Atmaca et al., 2011).

These regions are part of two functional resting state networks, represented by the default mode network (DMN) (Greicius et al., 2004; Raichle et al., 2001) and salience network (Seeley et al., 2007).

A recent systematic review suggests that the DMN (Greicius et al., 2004; Raichle et al., 2001) may play an important role in the pathophysiology of SSD (Browning et al., 2011).

The disruption of the DMN can lead to alexithymia (highly frequent in PD), as well as to pain perception and fatigue (Buckner et al., 2008; Saxe et al., 2004), all symptoms related to SSD.

The salience network comprises the anterior insular cortex (AI) and dorsal anterior cingulate cortex (ACC) which are involved in detecting and orienting to both external and internal salient stimuli and events (Seeley et al., 2007) and in processing of emotions (Hoeft et al., 2012). These areas have been found to be abnormally active in subjects with SSD (Malinen et al., 2010; Otti et al., 2013).

A recent fMRI study showed that inhibition of parietal areas, which are considered essential in providing integration of internal and external space, is associated with SSD (Luo et al., 2016). The inhibition of parietal areas may lead to the so called *somatoform dissociation* – a dissociation between physical information and its bodily representation (Kienle et al., 2017; Nijenhuis and Norton, 2004; Ratcliffe and Newport, 2016).

It is conceivable that the proneness of PD to develop SSD may found a pathophysiological explanation in dysfunction of those very brain areas associated with SSD. Indeed, the resting state DMN and salience network activity and connectivity have been demonstrated to be altered in PD (Franciotti et al., 2015; Tessitore et al., 2012).

With the present study therefore, by analyzing resting state network activity, we aim to explore a possible trait of susceptibility of PD to SSD, rather than a state response to a stimulus.

We therefore analyzed by means of resting state fMRI whether possible specific abnormalities of activation and functional connectivity of DMN and salience network may be more prominent in PD patients with somatic symptoms (SSD-PD) as compared with PD patients without SSD (PD).

2. Materials and methods

This study was approved by the Local Institutional Ethics Committee and was performed according to the Declaration of Helsinki (1997) and subsequent revisions. All participants gave written informed consent. Eighteen SSD-PD patients (61% male), eighteen PD patients (83% male) and twenty-two healthy age-matched subjects (59% male) were enrolled at Neurology Clinic of the University G. d'Annunzio of Chieti-Pescara, Italy. Exclusion criteria were: left handedness, prior history of major medical conditions, head injury, psychiatric or neurological disorders (exception made for those having clinical relevance for the study), current pregnancy or breastfeeding, history of substance abuse, any MRI contraindication.

2.1. Clinical assessment

The PD diagnosis was made according to the UK Parkinson's Disease Society Brain Bank criteria (Hughes et al., 1992). None of the patients or controls subjects were treated with anxiolytic or antidepressive drugs. All the PD patients were under stable doses of dopaminomimetic treatments. However, antiparkinsonian drug treatments were withdrawn the day before MRI acquisition.

Mental health status and SSD were assessed using the DSM-5 (American Psychiatric Association, 2013) and by patient interview as detailed below. Before the inclusion in the study, all patients underwent computerized tomography/MRI and DAT scan. At enrollment, patients with mild cognitive impairment/dementia were excluded according with proposed criteria (Albert et al., 2011; McKhann et al., 2011; McKeith et al., 2005). Unified Parkinson's Disease Rating Scale III (Fahn and Elton, 1987) and Hoehn and Yahr scale (1987) assessed extrapyramidal signs. All subjects were assessed for global cognitive assessment using the Mini Mental State Examination (MMSE) (Magni et al., 1996). The presence of frontal dysfunction was evaluated using the Frontal Assessment Battery (FAB) (Appollonio et al., 2005).

2.2. Somatic symptoms evaluation

Categorization of patients into SSD-PD and PD groups was based on direct observation of symptoms in the year (six months before/after) coincident with the diagnosis of neurodegenerative diseases. As a second assessment, all patients underwent semi-structured interviews by a rater blinded to neurological diagnoses. Interviews, based on DSM-5 manual, investigated somatic complaints with examples and a checklist presented to patients and caregivers, focusing on somatic symptoms traits, like dependency, mannerism, viscosity, adoption of a sick role, histrionic dramatic descriptions of disease. Evaluations of past somatic symptoms included information from prior hospital records and reports from patient's General Practitioner over the past 4–20 years. Somatic type delusional disorders were specifically investigated as part of the Neuropsychiatry Inventory (NPI) assessment (Cummings et al., 1994).

All the subjects were also tested by the Symptoms Questionnaire (Kellner, 1987). Furthermore, to ensure a clinimetrically valid analysis of the symptoms in a neurodegenerative condition (Porcelli and Guidi, 2015), the Diagnostic Criteria for Psychosomatic Research - DCPR (Fava et al., 1995; Siri and Fava, 2013, Fava et al., 2017) was administered.

2.3. Image acquisition

MR data were collected by means of a Philips Achieva 3 Tesla scanner (Philips Medical Systems, Best, The Netherlands) using a whole-body radiofrequency coil for signal excitation and an 8-channel phased-array head coil for signal reception. Structural images were acquired using a 3D T1-weighted Turbo Field-Echo sequence (TFE, TR/TE = 11/5 ms, slice thickness of 0.8 mm). Subjects were scanned during resting state conditions by means of T2*-weighted echo planar imaging with the following parameters: 21 bi-commissural slices, 300 volumes, in-plane resolution 3.594 × 3.594 mm, slice thickness 5 mm; repetition time 1100 ms; echo time 47 ms; field of view 230 × 105 × 230 mm; no gap.

T2-weighted fluid attenuation inversion recovery (FLAIR, TR/TE = 12,000/120 ms, slice thickness of 4 mm, FOV = 230 mm × 140 mm × 190 mm) images were also acquired to exclude the presence of concomitant pathologies.

2.4. FMRI analysis

The fMRI data analyses were carried out using Brain Voyager Qx release 2.3 (Brain Innovation, The Netherlands). The first five functional volumes were discarded to account for T1 saturation effects. Data preprocessing involved slice timing correction and slice realignment for head motion correction. For each subject, the fMRI data were co-registered with their 3-D anatomic images, transformed into Talairach space. Spatial smoothing was achieved with an 8-mm Gaussian core full-width half-maximum. Spatial indipendent component analysis (ICA) was applied on single subject data by using the “FastICA” algorithm. The number of components was restricted to 30 (Damoiseaux et al., 2006), and the cluster size was fixed to 10 mm for each

dimension, and a z threshold of 2.5 was used to establish which brain regions contributed to component maps. Each IC consists of a temporal waveform and an associated z-score spatial map reflecting the degree of correlation of voxel time courses with IC waveforms. ICs corresponding to noise (De Martino et al., 2007) were removed. Coactivation of the posterior cingulate cortex (PCC), the left and right lateral parietal cortex (RLPC, LLPC), left and right inferior parietal lobule (LIPL, RIPL), and left and right superior and middle rostral frontal gyrus (LSFG, RSFG, LMFG, RMFG) was the criteria to select ICs most closely matching the DMN model. In each subject, nine regions of interest (ROIs) were identified for the DMN. Coactivation of the dorsal anterior cingulate cortex (ACC) and left and right anterior insula (LAI and RAI) was the criteria to select ICs most closely matching the salience network model. Mean blood oxygen level–dependent signal intensities across all voxels in each ROI were extracted and converted to z-score values. Fast Fourier transform was applied to the mean blood oxygen level–dependent signal to obtain the spectral power of each ROI. The integrals of the spectral power in the predominant frequency band ranging from 0.01 to 0.08 Hz and in the entire band ranging from 0.01 to 0.25 Hz were performed. Then the power ratio in the low-frequency range (0.01–0.08 Hz) versus the entire range (0.01–0.25 Hz), that is, the fractional amplitude of low-frequency fluctuation (fALFF) was used to represent the power of each ROI (Yang et al., 2007).

To perform functional connectivity (FC), Pearson product-moment correlation coefficients (r) of pairwise ROIs were calculated on time courses of z-score signals for each subject (Franciotti et al., 2013). Self-organizing clustering (Esposito et al., 2005) was applied to obtain group spatial maps.

2.5. Cortical thickness analysis

Freesurfer 6.0 (http://surfer. nmr.mgh.harvard.edu), using the "recon-all-all" command line (Fischl et al., 2004), was used to estimate cortical thickness from the T_1-weighted image of each subject. In detail, the preprocessing step included magnetic field inhomogeneity correction, affine-registration to Talairach Atlas, intensity normalization, and skull-strip. The processing step included segmentation of the subcortical white matters (WM) and grey matters (GM), tessellation of the GM and WM matter boundary, automated topology correction. Cortical brain regions affected by cortical thinning were classified by using the Desikan-Killiany Atlas integrated in FreeSurfer. The "aparcstats2table" command line was used to calculate the mean cortical thickness within DMN and salience network cortical regions.

2.6. Statistics

Demographic and clinical variables were compared among groups by means of general linear model multivariate analysis of variance (MANOVA). Bonferroni post-hoc test was used to correct for multiple comparisons. Non parametric statistics were applied for the comparison of dychotomic variables. Kruskal-Wallis test was applied for the post-hoc analyses.

MANOVA was also performed on fALFF, FC values and mean cortical thickness values evaluated for each region of the DMN and salience network. Group (controls, PD, SSD-PD) was the fixed factor and the level was set at $p = .05$. Bonferroni post-hoc test was used to correct for multiple comparisons. Pearson's correlation was performed between fMRI outcomes and clinical scores.

As second level analyses we performed multivariate analysis of covariance (MANCOVA) on fMRI data to statistically control for demographic and clinical confounding variables. The level was set at $p = .05$ and Bonferroni post-hoc test was used to correct for multiple comparisons.

Table 1
Demographic and clinical variables for all groups.

	Controls (n = 22)	PD (n = 18)	SSD-PD (n = 18)	p value
Age	63 ± 9	64 ± 8	66 ± 7	
Gender (male %)	59	83	61	
Education (years)	11 ± 3	10 ± 5	9 ± 4	
Disease duration (years)	n.a.	3.8 ± 2.0	3.7 ± 2.4	
L-dopa equivalent dose	n.a.	274 ± 107	241 ± 109	
MMSE	28.1 ± 1.1	28.6 ± 2.0	28.0 ± 2.3	
FAB	n.a.	16 ± 2	16 ± 2	
UPDRS-III	n.a.	14 ± 5	16 ± 7	
H-Y	n.a.	1.5 ± 0.5	1.6 ± 0.4	
NPI-TOTAL SCORE[a]	n.a.	1.7 ± 1.4	5.4 ± 3.2	0.001[b]
SQ-anxiety	4.5 ± 3.6	5.9 ± 3.3	6.1 ± 4.4	
SQ-depression	2.9 ± 2.2	2.4 ± 2.5	4.8 ± 3.7	
SQ-somatic	4.8 ± 2.7	5.3 ± 1.9	13.3 ± 2.0	0.0001[a,b]
SQ-anger, hostility	3.5 ± 3.2	5.5 ± 4.7	4.4 ± 2.6	
SQ-relaxation	0.5 ± 1.0	0.5 ± 0.7	1.4 ± 1.2	
SQ-contentment	0.5 ± 0.5	0.6 ± 1.1	2.0 ± 2.0	
SQ-physical wellbeing	1.9 ± 0.9	2.5 ± 0.8	4.3 ± 1.4	0.005[a] 0.01[b]
SQ-friendliness	0.4 ± 0.7	0.8 ± 1.0	0.8 ± 0.6	
DCPR	n.a.	2.5 ± 1.4	4.0 ± 1.8	0.04[b]

Abbreviations: DCPR, Diagnostic Criteria for Psychosomatic Research; FAB, Frontal Assessment Battery; H–Y, Hoehn and Yahr scale; MMSE, Mini Mental State Examination; NPI, Neuropsychiatry Inventory; PD, Parkinson's disease; SSD-PD, PD patients with somatic symptoms; SQ, Symptoms Questionnaire; UPDRS-III, Unified Parkinson's Disease Rating Scale III.

[a] p value from the post-hoc comparison between control group and PD.

[b] p value from the post-hoc comparison between PD and SSD-PD.

3. Results

3.1. Study population

Demographic variables were not different among the three groups. All variables were reported in Table 1.

Significant differences were found between SSD-PD and PD in the NPI total score and in the SQ-somatic and SQ-well being scores, as well as in the DCPR score (Table 1).

Table 2 summarizes differences in the SQ-somatic symptoms subscale items among groups.

3.2. Fractional amplitude of low-frequency fluctuation

ICA revealed the presence of typical DMN and salience network maps. Fig. 1 shows DMN and salience network group-level maps from ICA algorithm.

Significant differences among groups was found for fALFF values in LLPC ($F = 9.9$, $p = 1.5{\cdot}10^{-4}$), RLPC ($F = 3.4$, $p = .05$) and LAI ($F = 4.5$, $p = .015$). The fALFF values were lower in PD and SSD-PD than in control group in LLPC ($p = 3{\cdot}10^{-4}$, $p = 10^{-3}$), RLPC ($p = .05$, $p = .03$) and in LAI ($p = .025$, $p = .013$).

3.3. Functional connectivity

The FC values among DMN areas were different significantly for the connection between PCC and right and left SFS, IPL and SFS in the left and right hemisphere, and between RLPC and LLPC. FC values were also different significantly between DMN and salience network areas for the functional connections between PCC and ACC and RMFG and RAI. For all connections FC values were lower in SSD-PD than in control group and in PD. All statistical results were reported in Table 3.

As NPI-total score was significantly different between SSD-PD and PD patients, NPI scores were used as covariate to adjust the results for

Table 2
SQ-somatic symptoms subscale items for all groups.

SQ-somatic symptoms	Controls (%)	PD (%)	SSD-PD (%)	*p* value
Feeling healthy	100	90	58	0.02[c]
Feeling of not enough air	18	10	50	
Feeling fit	100	100	50	0.007[b]; 0.004[c]
Heavy arms or legs	36	30	83	
No pain anywhere	36	40	6	
Arms and legs feel strong	73	80	50	
Appetite poor	9	0	33	
Tight head or neck	27	30	83	0.05[b]; 0.02[c]
Choking feeling	18	10	25	
Feeling of pressure in head or body	9	10	75	0.005[b]; 0.002[c]
Weak arms or legs	9	30	100	0.007[b]; 0.0001[c]
No aches anywhere	73	70	20	
Breathing difficult	27	10	33	
Parts of the body feel numb or tingling	45	70	92	0.01[c]
Heart beating fast or pounding	18	0	33	
Pressure on head	9	0	67	0.02[b]; 0.05[c]
Nauseated, sick to stomach	9	20	50	
Upset bowels or stomach	27	20	67	
Muscle pains	27	50	92	0.005[c]
No unpleasant feelings in head or body	73	10	0	0.0001[a,c]
Headaches	27	30	67	
Cramps	36	50	75	
Head pains	27	10	50	

Abbreviations: SQ, Somatic symptoms; PD, Parkinson's disease; SSD-PD, PD patients with somatic symptoms.
[a] *p* value from the Kruskal-Wallis comparison between control group and PD.
[b] *p* value from the Kruskal-Wallis comparison between PD and SSD-PD.
[c] *p* value from the Kruskal-Wallis comparison between control group and SSD-PD.

this variable. MANCOVA showed that all the main effects on FC results were retained (supplementary material details all the statistical results).

MANCOVA was also performed on patients groups using L-dopa equivalent dose as covariate. No differences were found in the MANCOVA analysis as compared to MANOVA (supplementary material details all the statistical results).

Table 3
Significant statistical results on the comparison of the FC values among groups.

FC	F	*p* value	SSD-PD < controls	SSD-PD < PD
Between DMN areas				
PCC-RSFS	6.8	0.002	0.006	0.007
PCC-LSFS	4.2	0.02	n.s.	0.02
RIPL-RSFS	5.2	0.008	0.04	0.01
LIPL-LSFS	6.6	0.003	0.004	0.01
RLPC-LLPC	8.0	0.001	0.001	0.03
DMN-salience				
PCC-ACC	3.3	0.04	n.s.	0.05
RMFG-RAI	5.0	0.01	0.04	0.01

3.4. Correlation analyses

The correlation analysis between intra-network and inter-networks fMRI outcomes and demographic and clinical variables in all groups showed the lack of significant correlation between areas which were shown to be functionally altered in SSD-PD, excluding the effect of possible confounders on fALFF and FC results. However, significant correlations were found in areas and functional connections which resulted not to be different in the groups of subjects. Specifically, in the patient groups a significant correlation was found for fALFF of LIPL with disease duration and FC with FAB. FALFF of LIPL anticorrelated with disease duration and intra-DMN network FC correlated with FAB scores. In all groups the FC between bilateral SFS and ACC, between LIPL and ACC and between PCC and RAI were found to be reduced with age.

Pearson correlation between FC values and SQ-Anxiety was significant for the FC between LLPC and RSFS ($\rho = 0.27$, $p = .04$).

Significant correlations were found between SQ-depression and FC between PCC and RSFS ($\rho = -0.32$, $p = .01$), PCC and LSFS ($\rho = -0.25$, $p = .05$), RSFS and LAI ($\rho = 0.30$, $p = .02$). Fig. 2 shows all significant correlations.

Due to the presence of significant correlation between FC and age, FAB scores, SQ-anxiety and SQ-depression, FC results were statistically adjusted for all the aforementioned variables, separately. Specifically,

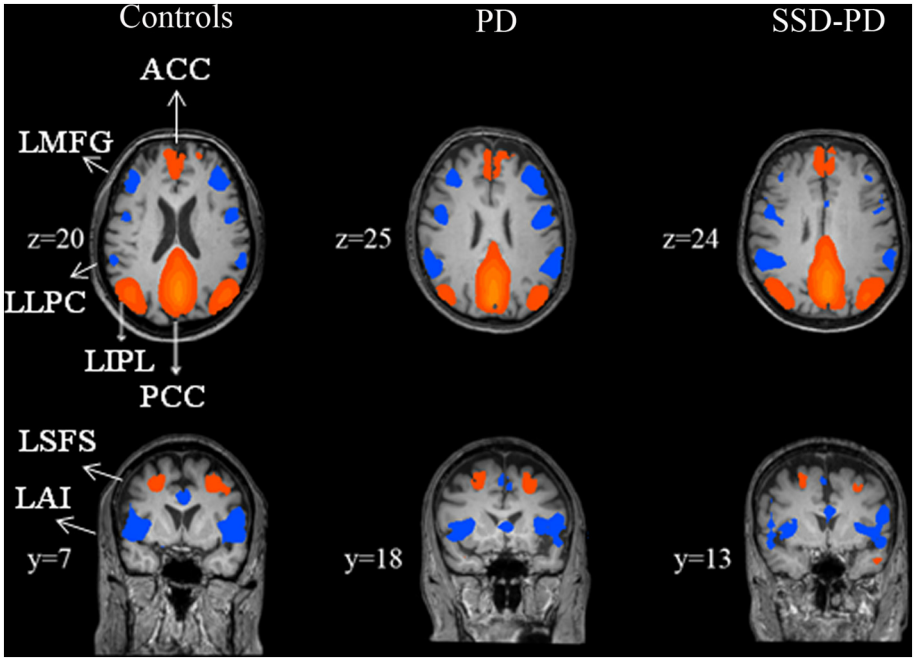

Fig. 1. Group-level ICA results representing DMN and salience network pattern for control, PD, and SSD-PD groups. Maps were overlaid onto Talairach transformed T1 image of a representative control, PD and SSD-PD patient. Abbreviations: ACC, anterior cingulate cortex, LAI, left anterior insula; LIPL, left inferior parietal lobule; LLPC, left lateral parietal cortex; LMFG, left middle frontal gyrus; LSFS, left superior frontal sulcus; PCC, posterior cingulate cortex; PD, Parkinson's disease; SSD-PD, PD patients with somatic symptoms.

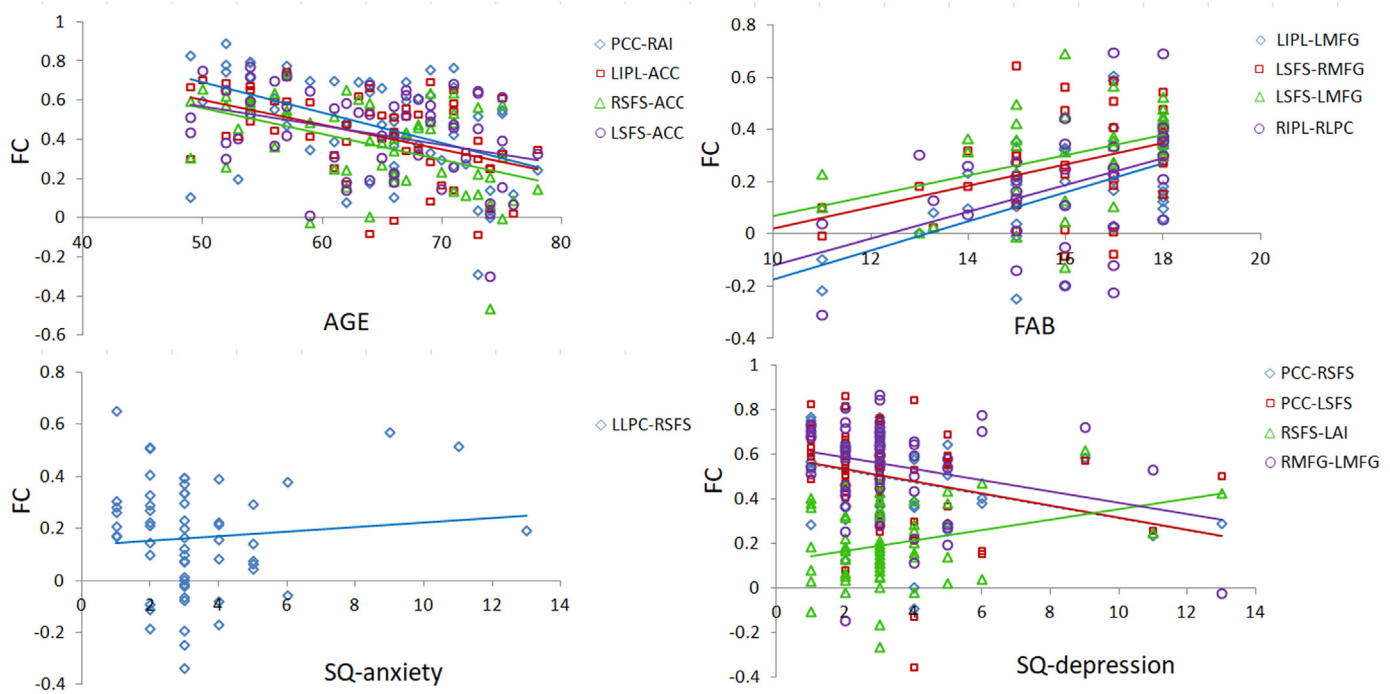

Fig. 2. Significant correlation results. Top: I Correlation between FC and age for all the three groups (left) and between FC value and FAB for the patient groups (right). Bottom: Correlation between FC values and SQ-anxiety (left) and SQ-depression (right) for all the three groups. Abbreviations: ACC, anterior cingulate cortex; FAB, frontal assessment battery, FC, functional connectivity, LIPL, left inferior parietal lobule; LLPC, left lateral parietal cortex, LMFG, left middle frontal gyrus; LSFS, left superior frontal gyrus; PCC, posterior cingulate cortex; RAI, right anterior insula; RIPL, right inferior parietal lobule; RLPC, right lateral parietal cortex; RSFS, right superior frontal gyrus; RMFG, right middle frontal gyrus.

MANCOVA was performed on FC values using groups (control, SSD-PD and PD) as fixed factor and age, SQ-anxiety and SQ-depression as separate covariates. In addition, FC values were statistically compared between patients groups using FAB scores as covariate.

All these statistical analyses showed that all the significant main effects on FC values, obtained in the analysis with MANOVA, were retained when considering age, FAB scores and SQ-anxiety as confounding factors.

All the main effects except the FC between PCC and LSFS are retained using SQ-Depression scores as covariate. Supplementary material details all the significant results by MANCOVA.

3.5. Cortical thickness

No significant difference among groups was found on cortical thickness values for DMN and salience network areas.

4. Discussion

With our study we found reduced amplitude of fALFF of RLPC, LLPC and LAI in our cohort of early, cognitively intact PD patients, either with or without SSD, as compared to healthy controls.

The two areas are parts of DMN and salience resting state networks respectively. This finding suggests that DMN and salience networks are less active in PD, in agreement with previous works (Franciotti et al., 2015; Seibert et al., 2012).

This finding was independent of cortical thickness of DMN and salience areas which were not different in the comparison among the three groups of subjects, as expected for cognitively intact patients.

The reduced activity of cortical areas of the DMN and salience network has been postulated in PD to be related to striatal disruption. Specifically, the salience network is affected by striatal disruption as striatal neurons are highly interconnected with neurons in the insular cortex (Chikama et al., 1997; Fudge et al., 2005), a key node of the salience network. Striatal dysfunction and the parallel loss of D2 signaling in the insula (Christopher et al., 2014) are thought to disrupt salience network, impairing its function in switching between other brain networks, including the DMN (Menon and Uddin, 2010).

Functional coupling between the salience network and the DMN is critical for switching attention between externally and internally salient stimuli (Fransson and Marrelec, 2008; Menon and Uddin, 2010; Sridharan et al., 2008), a function specifically impaired in subjects with SSD (de Greck et al., 2011).

SSD-PD patients showed to have impaired functional connectivity within and between DMN and salience networks as compared to PD.

In particular, within the DMN, the connections between PCC and bilateral SFS, between IPL and SFS bilaterally, RLPC and LLPC were reduced in SSD-PD patients.

Inter-network (DMN-salience) functional connectivity resulted to be altered in SSD-PD patients between PCC and ACC and RMFG and RAI.

These connections have been demonstrated to be relevant in the appearance of SSD also in the general population (Browning et al., 2011).

We propose, therefore, that the high frequency of SSD in PD (Bugalho et al., 2012; Onofrj et al., 2010; Onofrj et al., 2011; Pareés et al., 2013) may be associated with a PD-related increased vulnerability of brain areas, which, when malfunctioning, may trigger SSD. The malfunctioning is represented by reduced fALFF in bilateral parietal areas (RLPC, LLPC), and LAI, which are parts of DMN and salience network.

The functional connectivity alterations within DMN and between DMN and salience network in SSD-PD patients confirmed that reduced FC within the DMN and between the DMN and other areas may be regarded as a biomarker in patients with SSD (Loggia et al., 2013).

Our results confirm that functional alterations in the brains of SSD patients are bilateral (Atmaca et al., 2011; Garcia-Campayo et al., 2001; Hakala et al., 2004; Lemche et al., 2013; Su et al., 2014). The two cerebral hemispheres interact with each other by the brain's

commissural system, which is an important component of emotional and cognitive processing (Su et al., 2014), likely to be involved in somatic symptoms production.

As behavioural and mood disorders (specifically, depression and anxiety) are frequent in PD (Aarsland et al., 2009) and are related to SSD (Kapfhammer, 2006), an important issue in interpreting our results was to disentangle the effect of brain connectivity disruption related to SSD and to the aforementioned behavioural and mood symptoms which we solved by using NPI and SQ-depression and SQ-anxiety as confounding factors.

The positive correlation between inter-networks FC and age confirmed previous studies showing the possible vulnerability of the resting state networks to age as related to cortico-cortical and cortico-limbic dysfunctions (Vidal-Piñeiro et al., 2014). However, the effect was disjunct from the inter-network FC reduction found in SSD-PD compared to PD, suggesting that this alteration is not likely to be a reflection of brain ageing, as also confirmed by considering age as confounding factor.

As related to sex effect on the incidence of SSD which are more frequent in female individuals (Barsky et al., 2001), while the percentage of female was higher in SSD-PD than in PD, the percentage of female in PD was lower than in controls, reinforcing the result of reduced fALFF in areas relevant for SSD in PD.

Both DMN and insular networks are major large-scale cognitive brain networks and the functional connectivity both within and between these networks may reflect cognitive performance. Distinct changes in these networks have been reported in cognitively intact PD as compared to PD with mild cognitive impairment (Baggio et al., 2015; Klobušiaková et al., 2019). However, our results were independent of frontal lobe dysfunction as assessed by FAB.

Limitations:

Our PD patients were under dopaminomimetic treatment. This limited our ability to address questions related to the effects of dopamine on network interactions (Krajcovicova et al., 2012). However, dopaminergic medications used to treat Parkinson's disease have been shown to affect striatal activity, but not cortical activity (Martinu et al., 2012). Nevertheless, we performed a MANCOVA on L-dopa Equivalent Dose, excluding the effect of dopaminomimetic treatments on our results.

A further limitation lays in the impossibility to exclude the contribution of other resting state network areas in the development of SSD (including the sensorimotor area). Sensorimotor network is deemed to be involved in the development of functional paresis of somatosensory functional symptoms. The majority of our SSD-PD patients had somatosensory symptoms, but none experienced pseudo-paresis.

Finally, a population of control subjects with SSD only would have strengthened our results. However, the finding of PD related reduced activation of DMN and salience network independently of SSD makes the need of the aforementioned control population less stringent.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2019.101932.

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