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# Why Multiple System Atrophy patients do not have Visual Hallucinations?A Default Mode Network study.

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**Original investigation**

# Why Multiple System Atrophy patients do not have Visual Hallucinations? A Default Mode Network study.

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**Abstract**

Background: Studying Default Mode Network activity/connectivity in different parkinsonisms, with or without visual hallucinations, could highlight its roles in expression of clinical phenotypes. Multiple System Atrophy is the archetype of parkinsonism without visual hallucinations, variably appearing instead in Parkinson's Disease.

Methods: functional Magnetic Resonance Imaging identified Default Mode Network structures and assessed activity and connectivity in 15 Multiple System Atrophy patients, 15 controls, 15 early Parkinson's Disease patients matched for disease duration, 15 severe Parkinson's Disease patients without visual hallucinations and 15 severe Parkinson's Disease patients with visual hallucinations, matched with Multiple System Atrophy patients for disease severity. Cortical thickness and neuropsychological evaluations were compared in all groups.

Results: Multiple System Atrophy had reduced Default Mode Network activity compared to controls and Parkinson's Disease with hallucinations, no differences with Parkinson's Disease (early or severe) without hallucinations. In Parkinson's Disease with visual hallucinations, activity/connectivity was preserved compared to controls and higher than in all other groups. In early Parkinson's Disease connectivity was lower than in controls but higher than in Multiple System Atrophy and severe Parkinson's Disease without hallucinations.

Cortical thickness was reduced in severe PD, with and without hallucinations, and was only correlated with disease duration. Among neuropsychological assessments, anxiety scores differentiated patients with hallucinations from those without.

Conclusions: Multiple comparisons evidenced a pattern of Default Mode Network activity/connectivity, which was higher in Parkinson Disease with visual hallucinations and reduced in Multiple System Atrophy and Parkinson Disease without visual hallucinations.

Cortical thickness comparisons suggests that functional/inhibitory rather than structural changes underlie the activity/connectivity differences.

## 1. Introduction

The Default Mode Network (DMN) has emerged as an evolutionarily novel functional network in human brains[1] and consists of a set of cortical regions, including medial prefrontal, posterior cingulate, and lateral inferior parietal cortex, intimately connected with limbic areas[1]. Imaging studies showed that DMN areas deactivate during tasks and activate during rest[1-3], and it is posited that the DMN has roles in imagery production and incorporation of self referential information into consciousness[2,3].

The germinal studies[4-5] providing evidence of a resting state network, whose activity and connectivity could be studied in simple imaging protocols, without the requirement of performing any task, has fostered a significant body of studies investigating connectivity power in different diseases, in different cognitive, sensory, motor cortical, and subcortical areas[6-7].

More recently the original DMN role, in self-referential information production, has been reconsidered in theoretical and review studies[8-10] that seek to explain the occurrence of Visual Hallucinations- VH , on the basis that DMN could introduce self-referential information into misperceptions. From this model, it might be inferred that different DMN activity/connectivity should be evidenced in diseases characterized by presence or absence of VH.

However, definite evidence of a DMN link to VH has not been so far obtained, due to the heterogeneity of diseases studied, or to the fact that the majority of the studies were not focused specifically on the explanation of VH etiology[11-13], or as a result of the use of different methodologies applied to study the DMN, e.g. use of DMN areas as comparative, or "seed" unit of activity[14-15].

In Alzheimer's Disease (AD) patients without VH, it is well established that DMN activity/connectivity is reduced[5-16,17]. Similarly altered and reduced connectivity has been described in Progressive Supranuclear Palsy[18], a disease without VH. Conversely DMN connectivity enhancement was recently described in c9ORF72 mutation carriers[19], a variant of Frontotemporal Dementia-FTD presenting with VH.

In Parkinson Disase (PD) and Lewy Body Dementia (LBD), diseases both characterized by occurrence of VH, the evidences are controversial[11,14,16,20]. Preserved activity has been observed in Posterior Cingulate Cortex (the so called "Cingulate Island Sign") a main hub of DMN[21]. Increased or preserved (compared to controls) DMN activity or reduced inhibition during a visual task has also been seen in LBD[14,16,20], but only altered connectivity was described in other studies[22], which were not focused to VH.

In PD, earlier studies described increased connectivity[17] but more recent studies report only altered connectivity[11, 12,13,23]. One study described altered connectivity in PD either with or without VH[24]. Therefore the link between VH and DMN activity in Parkinsonisms, is a controversial issue.

One possible way to clarify the controversy is to compare DMN activity/connectivity in patients with different types of parkinsonism, in those with or without the presence of definite VH, as any evaluation restricted only to PD patients could be biased by insufficient information on VH, by variability in their onset and phenomenological quality [25-26].

Cohort studies with neuropathological assessments[27-28], evidenced that a diagnosis of Multiple System atrophy (MSA) could be excluded if VH occurred during the disease course, and thus that MSA represents an archetype of parkinsonism without VH. MSA is, moreover, an appropriate disease comparator to PD, unlike other Parkinson related disorders, because in MSA there is a responsivity, albeit reduced, to dopaminergic treatments[29-30], and thus make an ideal control comparator disease to PD, and because in MSA, REM Sleep Behavior Disorder-RBD, considered possibly linked to PD VH[10,31-32,33], is common .

We hypothesized therefore that a study of DMN resting state activity in MSA would allow us to properly test the" DMN link to VH" hypothesis.

In the present study, DMN activity in MSA patients was studied, by fMRI, in comparison with healthy subjects and with three different groups of PD patients, with or without VH, matched with MSA either for disease severity or duration.

DMN structures were identified by Independent Component analysis (ICA); only PD patients presenting with complex VH were selected for the "PD with VH" group. In addition, in order to enhance group homogeneity, matching between groups included RBD, treatments and cognitive conditions. Among clinical assessments anxiety evaluations were included, in order to explore the hypothesis suggesting that DMN reduced activity/connectivity is related to the expression of an anxiety predominant clinical phenotype[16, 34, 35,36] in contrast to a hallucinatory phenotype which is related to DMN activity enhancement.

This study design, with multiple group comparisons and matching, therefore, in summary, can address two interdependent aims: 1) evaluation of DMN activity in MSA[37], in comparison with controls and PD, 2) testing the DMN-VH hypothesis in different degenerative parkinsonisms, with and without VH.

## 2. Material and methods

### 2.1 Study population

The study population was recruited from referrals to Movement Disorder Centres of the University of Chieti-Pescara and of IRCCS San Camillo, Venezia.

Before being enrolled in the study, all subjects signed a written informed consent. The study was approved by the local ethical committees and was carried out according to revised Helsinki declaration[38]. 15 healthy elderly controls, 15 MSA (type P), 15 PD patients matched with MSA for disease duration (ePD), 30 PD patients matched with MSA for severity of symptoms and equivalent treatments (15 without VH (sPD) and 15 with VH (sPD-VH)) were selected to participate in the study, from two cohorts of 650 PD and 72 MSA patients. PD was diagnosed according to UK BBC[39]. Parkinsonian motor signs were rated with the Hoehn/Yahr scale and the motor part of the Unified Parkinson's Disease Rating Scale-UPDRS III in PD and MSA patients[40]. In MSA patients the Unified MSA Rating Scale (UMSARS) was also used[41]. $^{123}$I-FP-CIT SPECT was performed in

all patients. MSA patients were diagnosed according to consensus criteria[42] and presence of typical MRI alterations[43]. Control subjects had no evidence of clinical dementia and no evidence of any abnormality on structural neuroimaging.

All patients were tested with the MMSE, the Dementia Rating Scale 2 (DRS2)[44], the Frontal Assessment Battery (FAB)[45], the Behavioural Assessment of the Dysexecutive Syndrome (BADS6E)[46-47], the Neuropsychiatric Inventory (NPI)[48], the Geriatric Depression Scale (GDS)[49] and the State-Trait anxiety Inventory (STAI)[50].

ePD, sPD and sPD-VH were carefully matched with MSA patients for neuropsychological profiles[51-52], and presence and frequency of RBD , evaluated according to previous studies[53-54].

VH were investigated with semistructured interviews and were rated with the NPI specific item. Only patients with complex kinematic hallucinations, according to tentative classifications of VH[9,26] and to Parkinson Psychosis Scale[55], were admitted to the sPD-VH group, while patients presenting only with illusions (misperceptions) were excluded from any group. Any suspect of illusions or hallucinations excluded the diagnosis of MSA.

None of the patients received amantadine, anticholinergics, cholinesterase inhibitors, neuroleptics, all patients were treated with L-dopa-carbidopa, MAO-b inhibitors, entacapone, 6 ePD and 6 MSA patients received dopaminoagonist doses equivalent to 100mg/day of L-dopa[56].

Autonomic symptoms were rated with SCOPA-AUT scale[57] reported in supporting Table 1 of the Supporting information file.

All patients were assessed for genetic origin of parkinsonism, according to previously reported methods[58].

All patients were followed for 2-4 years after functional MRI (fMRI) acquisitions in order to confirm, challenge diagnosis.

To ensure blinding procedures, neuropsychology and fMRI raters were unaware of working hypotheses and clinical classifications, physicians from the second Unit were unaware of working hypotheses.

Table 1 reports the demographic, neuropsychological and neuropsychiatric variables of the five groups.

**2.2 Image acquisition**

MRI data were acquired with Philips scanners at 1.5 T, 24 hours after treatment withdrawal . Subjects were scanned during resting state conditions[16] by means of T2*-weighted echo planar imaging with the following parameters: 16 bicommissural slices, 200 volumes, in-plane resolution = 3.75 x 3.75 mm, slice thickness = 8 mm; repetition time = 1409 ms; echo time = 50 ms; field of view = 240 mm; no gap. Volumetric images were acquired via a 3-D T1-TFE (Turbo Field Echo) sequence.

**2.3 FMRI analysis**

FMRI data analyses were carried out using Brain Voyager Qx release 2.3 (Brain Innovation, The Netherlands). The first 5 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 fMRI data were coregistered 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 independent component analysis (ICA) was applied on single subject data using the "FastICA" algorithm. The number of components was restricted to 30[59], the cluster size was fixed to 10 mm for each dimension and 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[60] were removed. Coactivation of the posterior cingulate cortex (PCC), the left/right lateral parietal cortex (RLPC, LLPC), left/right inferior parietal lobule (LIPL, RIPL), left/right superior and middle rostral frontal gyrus (LSFG, RSFG, LMFG, RMFG) was the criterion to select ICs most closely matching the DMN model. In each subject 9 regions of interest (ROIs)

were identified. Each ROI, containing about 1000 voxels, was centered on the DMN clusters using a center of gravity approach[61]. Mean Blood Oxygen Level-Dependent (BOLD) signal intensities across all voxels in each ROI were extracted and converted to z-score values. Fast Fourier transform was applied to the mean BOLD signal to obtain power spectrum of each ROI. The power ratio of each frequency in the low-frequency range (0.01–0.08 Hz) vs. the entire range (0–0.25 Hz), i.e., fractional amplitude of low-frequency fluctuation (fALFF) was used[62].

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. Self-organizing clustering[63] was applied to obtain group spatial maps.

### 2.4 Cortical thickness analysis

Cortical thickness was estimated on $T_1$-weighted image using Freesurfer software package (http://surfer.nmr.mgh.harvard.edu).[64,65] Cortical thickness measurements were obtained by reconstructing representations of the gray/white matter boundary and the cortical surface: for each point on the white matter surface, the shortest distance to the pial surface was computed; next, for each point on the pial surface, the shortest distance to the white matter was found, and the cortical thickness at that location was set to the average of these two values providing submillimeter resolution[66].

Cortical brain regions affected by cortical thinning were classified by using the Desikan-Killiany Atlas[67] integrated in FreeSurfer. The "aparcstats2table" command line was used to calculate the mean cortical thickness within DMN cortical regions .

### 2.5 Statistics

Demographic, neuropsychological and neuropsychiatric variables were compared among groups by means of General Linear Model multivariate analysis of variance. Duncan post-hoc test was used to correct for multiple comparisons.

Two ways ANOVA was performed on fALFF with group (controls, MSA, ePD, sPD-VH and sPD) as categorical factor, ROIs as within factor.

In the between-group analysis on FC, General Linear Model multivariate analysis of variance was separately used with group as factor and age as nuisance factor, α level was set at 0.05. Multivariate ANOVA was performed on mean cortical thickness values evaluated for each region of the DMN using group as independent variable and age as nuisance factor. Duncan post-hoc test was used to correct for multiple comparisons.

Spearman's correlation, Bonferroni corrected, was performed between fMRI outcomes and neuropsychological-clinical scores .

QDEC (https:// surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/QdecGroupAnalysis_freeview) was used to individuate regions showing significant correlation between cortical thickness and neuropsychological-clinical variables. All results were corrected for multiple comparisons by using a pre-cached cluster-wise Monte-Carlo Simulation.

Correlations were performed on all patients and for patients without visual hallucinations separately.

**3. Results**

Statistical results on the intergroup comparisons for all the variables reported in Table 1 are detailed in the supporting information files. NPI hallucination scores separated sPD-VH from all groups, L-dopa equivalent doses were higher in MSA, sPD, sPD-VH than in ePD. Anxiety scores were higher in MSA than in sPD-VH and higher in sPD without VH than in sPD-VH.

In each participant ICA revealed the presence of typical DMN maps.

Fig. 1 shows DMN group-level maps from ICA algorithm, and mean patterns of power amplitudes and cortical thickness, for all DMN components averaged as a whole, in the five groups of patients. Spectral power (fALFF) was statistically higher in controls than in MSA and sPD ($p<0.01$, 0.005) and in sPD-VH than in MSA and sPD without VH ($p<0.01$, 0.005); cortical thickness was higher in

controls, MSA, ePD than in sPD with or without VH ($p<0.03$-0.01-supporting table 3 and 5 of the supporting information).

fALFF values for single DMN components in each group of subjects are detailed in fig.2: the main effect group ($F(4,70)=4.66$, $p=0.002$) and ROIs ($F(8,560)=20.11$, $p<0.0001$) and the interaction group X ROIs ($F(32,560)=1.50$, $p<0.05$) were significant.

fALFF values were significantly lower in MSA and sPD without VH than in controls ($p<0.05$-$p<0.01$) in superior and medial frontal areas, and were significantly higher in sPD-VH than in MSA and sPD ($p<0.05$ $p<0.02$).

Despite lower mean values, no statistical differences of fALFF values were found in the comparison between ePD and MSA nor between ePD and controls. The only significant comparison was for ePD vs. sPD for right inferior parietal cortex. Supporting table 4 of the supporting information reports detailed statistical results.

FC was higher in controls than in MSA and sPD without VH for all couples of areas, and higher than in ePD for frontoparietal connections. FC was higher in sPD-VH than in MSA for intra-hemispheric fronto-parietal connections, inter-hemispheric parietal connection and for connections between IPL and PCC.

FC in sPD-VH was higher than in sPD without VH for all significant couples of brain areas, but for connections between LMFG and RMFG, and higher than in ePD for LSFS-LIPL connections. FC in ePD was higher than in MSA for IPL and left PCC and was higher than in sPD without VH for fronto-parietal, fronto-cingulate and PCC connections.

Table 2 shows all statistical values and the brain areas where FC differences were found in the intergroup comparisons.

We did not find significant correlation between fMRI outcomes and neuropsychological-clinical scores.

Cortical thickness comparisons inside the DMN showed significant differences across groups in LSFS ($F(4,69)=2.52$, $p<0.05$), LMFG ($F(4,69)=2.78$, $p<0.05$), RMFG ($F(4,69)=4.31$, $p<0.005$), LLPC ($F(4,69)=2.87$, $p<0.05$), LIPL ($F(4,69)=3.30$, $p<0.05$) and PCC ($F(4,69)=3.69$, $p<0.01$).

No significant reduction of cortical thickness was found inside the DMN in MSA compared to controls and ePD. Significant cortical thinning ($p<0.046$, 0.005) was found in sPD and sPD-VH compared to controls, MSA and ePD, for all DMN areas but for RSFS. (Fig. 3, supporting Tables 2-4 of the Supporting information).

Only disease duration was correlated with mean cortical thickness ($p<0.05$) in comparisons between all groups or between groups without VH (supporting table 6 of the supporting information).

Pair-wise differences in the whole brain showed significant cortical thinning of left premotor and motor cortex, in MSA compared to controls (supporting Figure of the Supporting information).

**4. Discussion**

MSA patients had reduced activity in Superior Frontal Sulcus and Middle Frontal Gyrus DMN components and reduced inter and intra hemispheric frontoparietal and parieto-cingulate connectivity within DMN nodes, in comparison with controls. This novel finding (identified as the first study aim) is unlikely to have any diagnostic utility, as the comparison with PD patients without VH showed only minor differences..

The multiple group comparison with PD patients, matched either for disease duration or severity of symptoms, with and without VH, evidenced, however, a pattern of DMN activity and connectivity, consisting of relative enhancements or reductions, which would not have emerged from simple comparisons with controls or with a limited group of PD patients.

This pattern (Fig.1,2) is evident for DMN spectral power measurements, and was confirmed by connectivity assessments (Table 3): the pattern consists of reduced DMN activity-connectivity if VH are not present, and of increased DMN activity-connectivity (similar to controls in all DMN components) if VH are present.

This pattern was independent of cortical thickness of DMN areas and thus we would argue is more dependent upon inhibition-disinhibition mechanisms, rather than on morphometric differences (Fig1,3) between groups. Indeed increased DMN activity-connectivity separated PD patients with VH from all other groups.

Therefore, our multiple group comparison, provides evidence to support the DMN link to our VH hypothesis, as considered in our second study aim: DMN activity-connectivity is reduced if VH are not present, independently of disease type and disease duration.

Our findings are in agreement with previous studies showing that DMN is enhanced in diseases characterized by occurrence of VH, like DLB, c9ORF72 FTD and psychiatric conditions[16, 19, 68]. In PD, connectivity changes appear more variable; earlier studies described hyperconnectivity[17], and thus provided support for theoretical models of VH[8, 10], but more recent studies showed altered connectivity, which correlated with cognitive impairment[11-13,23,69] . However in these latter studies patients with VH were not included.

In our ePD and sPD without VH patients , we found reduced DMN connectivity, which was similar to findings of these studies[11-13]. However we found enhanced DMN in sPD VH, which is at variance with the hypothesized linear correlation between decreased DMN activity and cognition[11-13], as our patients with VH were just as cognitively impaired as our patients without VH (table 1). Thus we would argue that the difference between the other studies showing decreased DMN activity, and ours, is dependent on exclusion of patients with VH.

One recent study[24] compared PD patients with complex VH and without VH, with disease durations similar to our sPD groups, found “greater” DMN coactivation in VH patients, relative to non VH. Similarly as in our sPD-VH patients, the greater activity was in posterior cingulate gyrus, although in that study activity increases were evident only in right middle frontal lobe, whilst in our patients the enhancement was bilateral. Same as in our study, these authors[24] found no differences in cortical thickness between patients with enhanced or reduced DMN activity, which is consistent with our

hypothesis that functional inhibitory or facilitatory activity rather than structural change is responsible for DMN differences between hallucinators and non-hallucinators.

Our cortical thickness analysis demonstrated a correlation with disease duration, but we found no correlations with other clinical variables, and evidenced atrophy, in MSA, only in structures which were unrelated to DMN functions, which is consistent with previous cortical thickness studies in this disease[70-71]. In contrast, previous studies which have used the voxel based morphometry technique have reported widespread abnormalities in MSA[72]. We hypothesize that differences between our cortical thickness studies and the VBM based studies are largely driven by the technical limitation of the latter, which needs correction algorithms, as well as to differences in the disease durations in MSA in our study compared to others[73].

In conclusion, the comparison between different diseases, with different etiologies, suggests that DMN enhancement or inhibition is not a disease related specific process, but rather is an aspect linked to the expression of clinical phenotypes.

This hypothesis expands the possible role of DMN, by considering that DMN enhancement may underlie the expression of VH (with extreme manifestations including psychosis and delusions), whilst DMN inhibition might be linked to a phenotype characterized by hyperarousal or increased anxiety (with extreme manifestations including for example akathysia). Previous studies[16, 35,36] evidenced the correlation between reduced DMN activity and anxiety, and the present study shows that MSA patients and PD patients without VH, who had altered and reduced DMN functions, had higher anxiety scores than controls and patients with VH. Activity-connectivity and anxiety scores were not correlated with cortical thickness, suggesting that this phenomenological aspect is also dependent on functional modulation, rather than on morphometric differences.

Our results, therefore, are compatible with hypotheses on DMN functions, but one finding challenges previous attempts to explain the mechanism of DMN changes. In previous studies[16,20], the explanatory hypothesis for DMN enhancement in DLB, was that preserved DMN activity could depend on compensatory mechanisms attempting to maintain homeostatically DMN functions in the

face of developing pathology. The hypothesis considered also that DMN activity is reduced in AD[5, 16] and suggested that in this condition a lack of compensatory mechanisms may depend upon the greater cellular loss which occurs in this disease.

In MSA we observed decreased DMN activity, which was similar to reductions observed in AD[5,16], but we found no cellular loss, and this finding, again, supports our argument that functional modulatory mechanisms are relevant rather than structural differences.

Intriguingly a core question emerges from our data: does DMN power and connectivity represent a mere epiphenomenon, or might be the key driver of the clinical phenotype?

By describing DMN findings in a previously unexplored disorder, our study adds a piece of information to this puzzle.

Limitations and future directions.

A possible limitation of our study can be identified in the selection method used for the three groups of PD patients. The sPD VH group was selected on the basis of the presence of complex VH, which were specifically addressed because of their intrinsic narrative qualities, as the role of DMN is considered to consist of a narrative introduction into experience[2,3]. IIn order to reduce confounding factors, however, neuropsychological and clinical test scores were carefully matched between groups, and presence of minor hallucinations was an exclusion criterion for all groups. Restricted group selections allowed for an outcome characterized by clear-cut statistical differences between groups, but could have concealed correlations between fMRI findings and clinical variables e.g. VH severity, anxiety, cognitive level.

In order to overcome this limitation, longitudinal evaluation investigating through time DMN function changes, at rest and during tasks, should clarify how and when DMN enhancement appears, and whether it is a gradual process or a critical outbreak, in the course of PD progression or whether alternatively, it is intrinsic to specific disease subtypes (i.e. it appears only in those PD patients with greater than average DMN activity from onset of their motor symptoms).

The evidence of DMN enhancement also invites to consider whether DMN activity is a possible target for the treatment of VH: for example direct or transcranial cortical stimulation of DMN areas could be considered among future treatment research projects.

Pharmacological studies could also be designed in order to target DMN enhancement, by considering the neurotransmitters involved in cortico-cortical and thalamo-cortical projections to DMN.

We foresee, however, that the last will be a difficult task, as we know already that drugs which antagonize these glutamatergic projections, may induce[74-75], rather than reduce, VH.

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**Documentation of Author Roles**

1. Research project: A. Conception, B. Organization, C. Execution;
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

R. Franciotti: 1B, 1C, 3A.

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Figure 1.

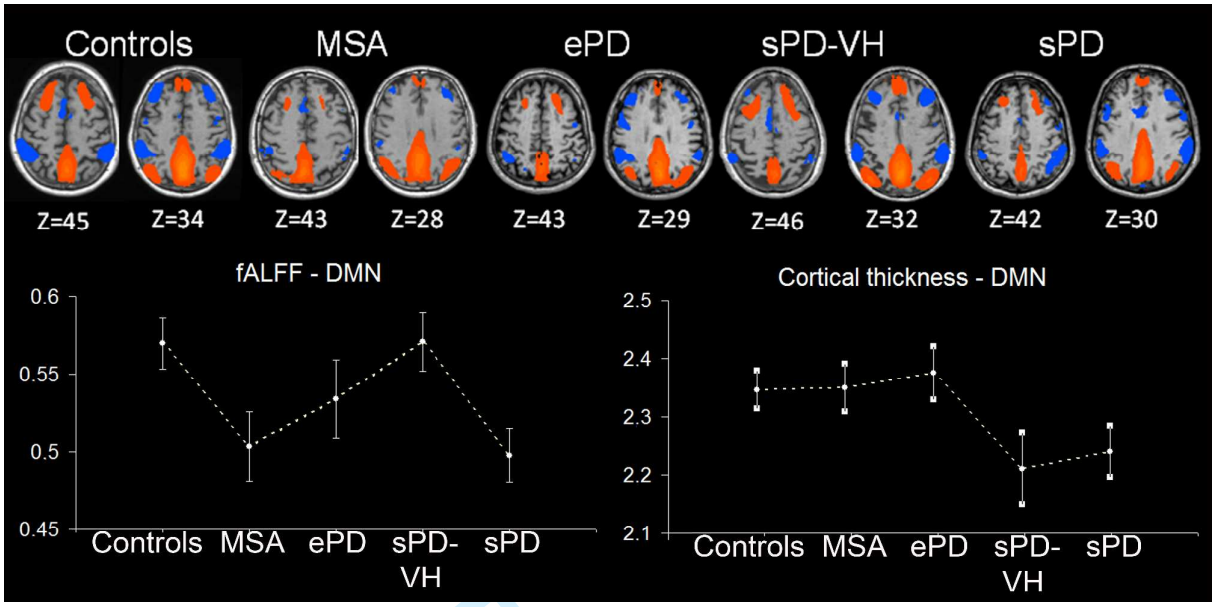



**Figure 1. Top.** Group-level ICA results representing DMN pattern for control, MSA, ePD, sPD-VH and sPD group. Maps were overlaid onto Talairach-transformed T1 image of a representative control, MSA, ePD, sPD-VH and sPD patient. Notice that DMN was clearly identified in each group.

**Bottom**. **Left:** Averaged power amplitudes of all DMN components, in each group. **Right:** averaged cortical thickness values of all DMN components in each group.

ePD = early Parkinson's Disease; MSA = Multiple System Atrophy; sPD = severe Parkinson's Disease without visual hallucinations; sPD-VH = severe PD with visual hallucinations.

Figure 2.

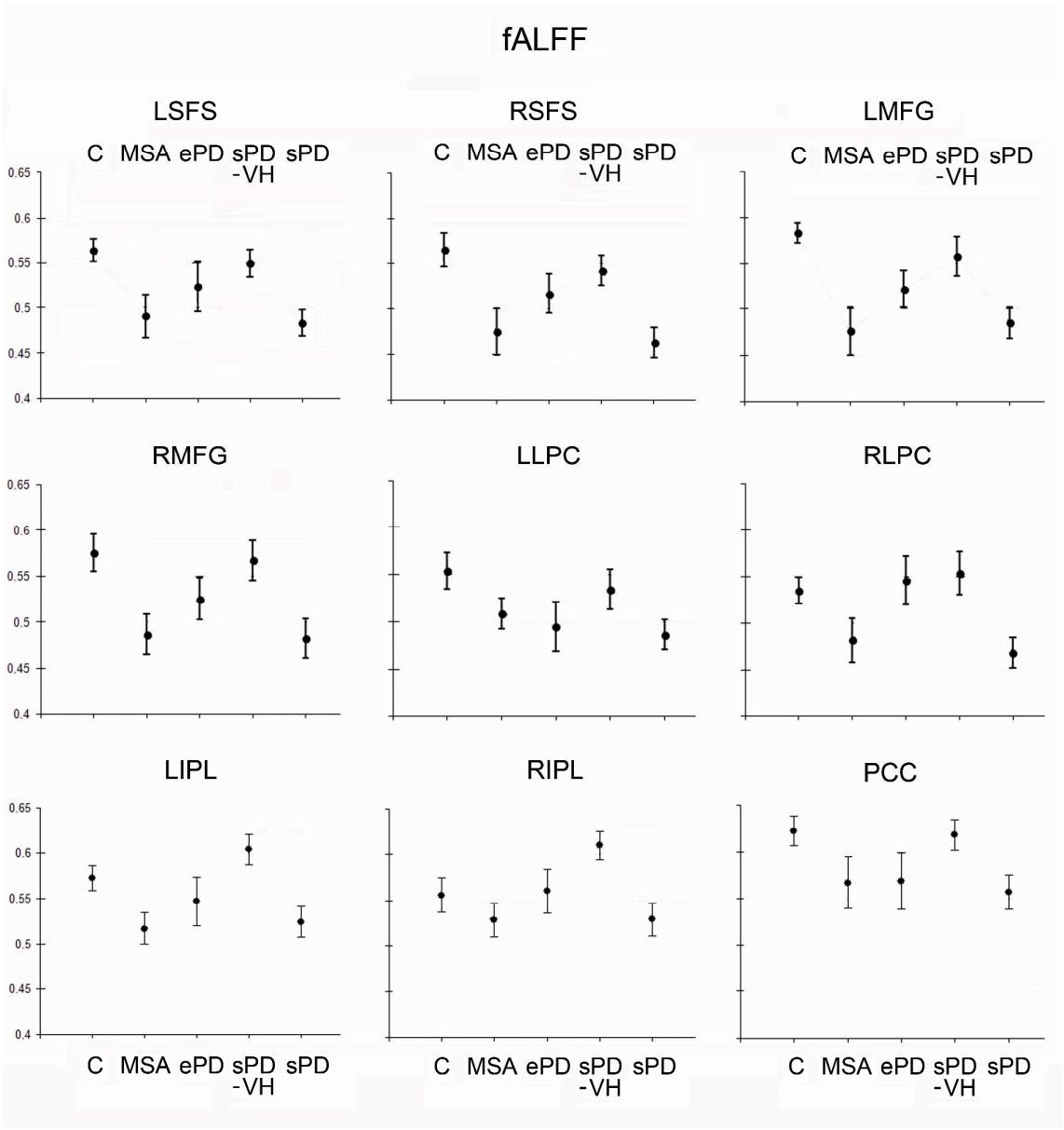



**Figure 2.** Mean fractional amplitude of low frequency fluctuations (fALFF) in the different DMN nodes, in controls, MSA, ePD, sPD-VH and sPD. Notice lower amplitude in MSA and sPD without VH, higher amplitude in sPD with VH, for all DMN nodes. Vertical bars indicate standard error. LIPL = Left Inferior Parietal Lobule; LLPC = Left Lateral Parietal Cortex; LMFG = Left Middle Frontal Gyrus; LSFS = Left Superior Frontal Sulcus; PCC = Posterior Cingulate Cortex; RIPL= Right Inferior Parietal Lobule; RLPC= Right Lateral Parietal Cortex; RMFG = Right Middle Frontal Gyrus; RSFS = Right Superior Frontal Sulcus; ePD = early Parkinson's Disease; sPD =

severe Parkinson's Disease without visual hallucinations; sPD-VH = severe PD with visual hallucinations; MSA = Multiple System Atrophy.

Figure 3.

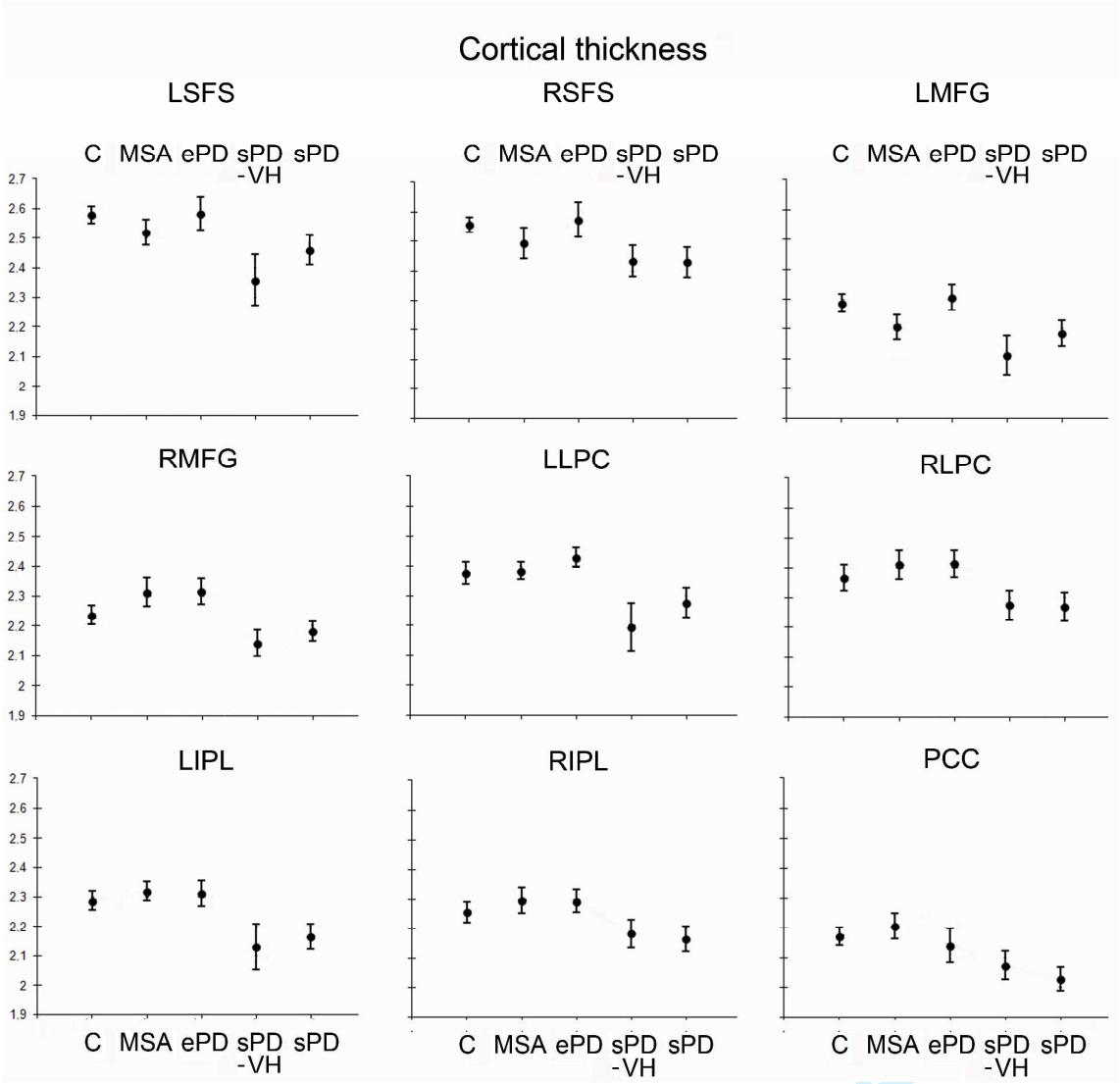



**Figure 3.** Mean **c**ortical thickness values in the different DMN nodes, in controls, MSA, ePD, sPD-VH and sPD. Notice lower cortical thickness in sPD with and without VH. Vertical bars indicate standard error.

LIPL = Left Inferior Parietal Lobule; LLPC = Left Lateral Parietal Cortex; LMFG = Left Middle Frontal Gyrus; LSFS = Left Superior Frontal Sulcus; PCC = Posterior Cingulate Cortex; RIPL= Right Inferior Parietal Lobule; RLPC= Right Lateral Parietal Cortex; RMFG = Right Middle Frontal Gyrus; RSFS = Right Superior Frontal Sulcus; ePD = early Parkinson's Disease; sPD =

severe Parkinson's Disease without visual hallucinations; sPD-VH = severe PD with visual hallucinations; MSA = Multiple System Atrophy.

**Table 1** Clinical, Cognitive, Neuropsychological, Neuropsychiatric and anxiety features (mean ± SD) for Controls, MSA, ePD, sPD-VH and sPD.

| | Controls | MSA | ePD | sPD-VH | sPD |
|---|---|---|---|---|---|
| **AGE** | 69 ± 6 | 67 ± 5 | 66 ± 9 | 70 ± 6 | 68 ± 11 |
| **Education** | 9 ± 4 | 10 ± 5 | 9 ± 3 | 10 ± 4 | 10 ± 3 |
| **MMSE** | 28.7 ± 0.7 | 25.2 ± 1.7 | 26.2 ± 1.8 | 24.3 ± 2.2 | 24.7 ± 1.8 |
| **Disease duration** | n.a. | 3.9 ± 1.8 | 3.3 ± 1.6 | 11.3 ± 4.3 | 12.0 ± 4.5 |
| **UPDRSIII** | n.a. | 36.4 ± 7.6 | 17.7 ± 4.3 | 36.3 ± 8.2 | 35.6 ± 7.4 |
| **LDED** | n.a. | 655 ± 270 | 363 ± 190 | 636 ± 199 | 645 ± 210 |
| **H&Y** | n.a. | 3.2 ± 0.8 | 2.1 ± 0.4 | 3.0 ± 0.5 | 3.0 ± 0.6 |
| **DRS-2 Total** | n.a. | 128 ± 12 | 131 ± 6 | 125 ± 7 | 121 ± 16 |
| **NPI-VH** | n.a. | 0 ± 0 | 0 ± 0 | 6.3 ± 1.7 | 0 ± 0 |
| **NPI-E. Anxiety** | 0.5 ± 0.6 | 5.3 ± 2.4 | 5.0 ± 2.1 | 1.7 ± 0.9 | 2.6 ± 1.0 |
| **NPI-K. Sleep** | 0 ± 0 | 4.1 ± 1.7 | 3.9 ± 1.5 | 3.7 ± 1.7 | 4.1 ± 1.6 |
| **NPI-TOT** | 1.7 ± 2.0 | 24.6 ± 5.4 | 21.9 ± 6.8 | 17.3 ± 3.2 | 19.0 ± 2.0 |
| **FAB** | 15.8 ± 1.5 | 12.7 ± 3.3 | 14.3 ± 1.4 | 11.7 ± 3.5 | 12.7 ± 1.5 |
| **GDS** | 6.3 ± 1.3 | 8.9 ± 2.7 | 6.4 ± 1.5 | 8.8 ± 2.6 | 9.3 ± 2.7 |
| **BADS6E*** | 5.4 ± 0.5 | 3.8 ± 1.0 | 4.1 ± 1.2 | 4.0 ± 1.1 | 4.3 ± 1.0 |
| **Stai - State** | 14.5 ± 3.5 | 43.1 ± 8.0 | 41.1 ± 8.2 | 31.2 ± 5.7 | 37.8 ± 5.2 |
| **Stai -Trait** | 14.1 ± 5.0 | 39.9 ± 7.1 | 42.1 ± 6.6 | 30.9 ± 3.8 | 34.9 ± 5.3 |
| **UMSARS I** | n.a. | 24.2 ± 6.0 | n.a. | n.a. | n.a. |
| **UMSARS II** | n.a. | 27.6 ± 8.1 | n.a. | n.a. | n.a. |
| **UMSARS tot** | n.a. | 51.8 ± 12.9 | n.a. | n.a. | n.a. |

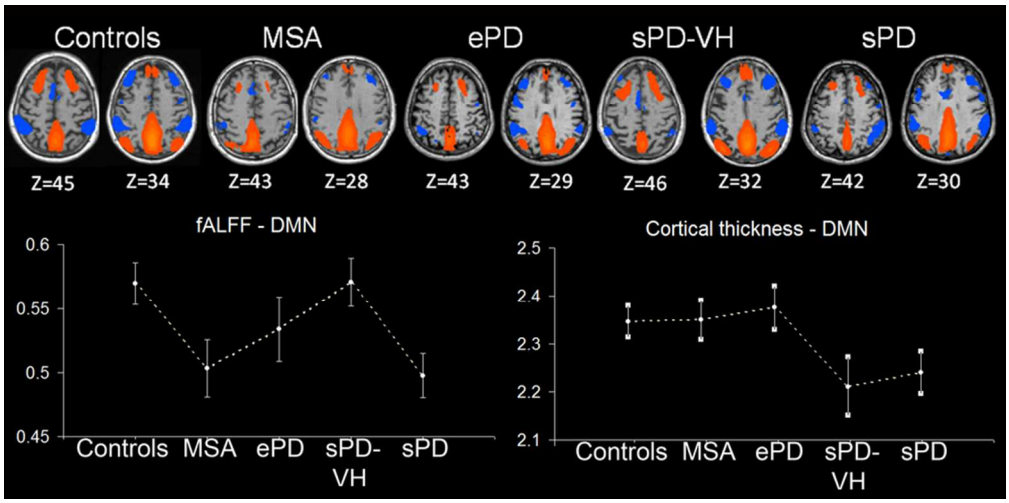
MMSE = Mini Mental State Examination; DRS-2 = Dementia Rating Scale – 2; FAB = Frontal Assessment Battery; GDS = Geriatric Depression Scale; Stai - State = State anxiety Inventory; Stai -Trait = Trait anxiety Inventory; BADS6E = Behavioural Assessment of the Disexecutive Syndrome; H&Y = Hoehn/Yahr Staging; LDED = Levo Dopa Equivalent Dose (mg); UMSARS = Unified Multiple System Atrophy Rating Scale; UPDRSIII = Unified Parkinson's Disease Rating Scale - subscale III; NPI = Neuropsychiatry Inventory; VH = visual hallucinations; ePD = early Parkinson's Disease; sPD = severe Parkinson's Disease without visual hallucinations; sPD-VH = severe PD with visual hallucinations; MSA = Multiple System Atrophy; N/A = not applicable; n.s. = not significant; SD = standard deviation.

**Table 2** Significant statistical results from the comparison of FC values among groups

| Post-hoc comparisons | p | Brain connections | F(4,69) | p | Power |
|---|---|---|---|---|---|
| Controls > MSA | 0.005 | LSFS-LIPL | 6.47 | <0.001 | 0.99 |
| | 0.02 | LSFS-RIPL | 4.23 | 0.004 | 0.91 |
| | 0.02 | RSFS-LIPL | 6.48 | <0.001 | 0.99 |
| | <0.001 | RSFS-RIPL | 6.98 | <0.001 | 0.99 |
| | 0.02 | LMFG-RMFG | 3.52 | 0.01 | 0.84 |
| | 0.01 | LLPC-RLPC | 5.40 | <0.001 | 0.97 |
| | 0.001 | LIPL-RIPL | 5.26 | <0.001 | 0.96 |
| | 0.01 | LIPL-PCC | 7.11 | <0.001 | 0.99 |
| | 0.04 | RIPL-PCC | 5.13 | 0.01 | 0.96 |
| Controls > ePD | 0.006 | LSFS-LIPL | 6.47 | <0.001 | 0.99 |
| | 0.02 | LSFS-RIPL | 4.23 | 0.004 | 0.91 |
| | 0.02 | RSFS-LIPL | 6.48 | <0.001 | 0.99 |
| | 0.04 | RSFS-RIPL | 6.98 | <0.001 | 0.99 |
| | 0.02 | LMFG-RMFG | 3.52 | 0.01 | 0.84 |
| | 0.05 | LLPC-RLPC | 5.40 | <0.001 | 0.97 |
| Controls > sPD | <0.001 | LSFS-LIPL | 6.47 | <0.001 | 0.99 |
| | <0.001 | LSFS-RIPL | 4.23 | 0.004 | 0.91 |
| | <0.001 | LSFS-PCC | 3.97 | 0.006 | 0.89 |
| | <0.001 | RSFS-LIPL | 6.48 | <0.001 | 0.99 |
| | <0.001 | RSFS-RIPL | 6.98 | <0.001 | 0.99 |
| | <0.001 | RSFS-PCC | 6.33 | <0.001 | 0.99 |
| | 0.04 | LMFG-RMFG | 3.52 | 0.01 | 0.84 |
| | <0.001 | LLPC-RLPC | 5.40 | <0.001 | 0.97 |
| | 0.004 | LIPL-RIPL | 5.26 | <0.001 | 0.96 |
| | 0.002 | LIPL-PCC | 7.11 | <0.001 | 0.99 |
| | 0.003 | RIPL-PCC | 5.13 | 0.01 | 0.96 |
| Controls > sPD-VH | 0.02 | LMFG-RMFG | 3.52 | 0.01 | 0.84 |
| MSA < ePD | 0.007 | LIPL-RIPL | 5.26 | <0.001 | 0.96 |
| | 0.047 | LIPL-PCC | 7.11 | <0.001 | 0.99 |
| MSA > sPD | 0.03 | RSFS-LIPL | 6.48 | <0.001 | 0.99 |
| | 0.03 | RSFS-PCC | 6.33 | <0.001 | 0.99 |
| MSA < sPD-VH | 0.01 | LSFS-LIPL | 6.47 | <0.001 | 0.99 |
| | 0.01 | RSFS-RIPL | 6.98 | <0.001 | 0.99 |
| | 0.006 | LIPL-RIPL | 5.26 | <0.001 | 0.96 |
| | 0.002 | LIPL-PCC | 7.11 | <0.001 | 0.99 |
| | 0.04 | RIPL-PCC | 5.13 | 0.01 | 0.96 |
| ePD > sPD | 0.03 | RSFS-LIPL | 6.48 | <0.001 | 0.99 |
| | 0.04 | RSFS-RIPL | 6.98 | <0.001 | 0.99 |
| | 0.02 | RSFS-PCC | 6.33 | <0.001 | 0.99 |
| | 0.02 | LIPL-RIPL | 5.26 | <0.001 | 0.96 |
| | 0.01 | LIPL-PCC | 7.11 | <0.001 | 0.99 |
| ePD < sPD-VH | 0.01 | LSFS-LIPL | 6.47 | <0.001 | 0.99 |
| sPD < sPD-VH | <0.001 | LSFS-LIPL | 6.47 | <0.001 | 0.99 |
| | <0.001 | LSFS-RIPL | 4.23 | 0.004 | 0.91 |
| | 0.001 | LSFS-PCC | 3.97 | 0.006 | 0.89 |
| | <0.001 | RSFS-LIPL | 6.48 | <0.001 | 0.99 |
| | 0.002 | RSFS-RIPL | 6.98 | <0.001 | 0.99 |

| | | | | | |
|---|---|---|---|---|---|
| | <0.001 | RSFS-PCC | 6.33 | <0.001 | 0.99 |
| | 0.007 | LLPC-RLPC | 5.40 | <0.001 | 0.97 |
| | 0.02 | LIPL-RIPL | 5.26 | <0.001 | 0.96 |
| | <0.001 | LIPL-PCC | 7.11 | <0.001 | 0.99 |
| | 0.002 | RIPL-PCC | 5.13 | 0.01 | 0.96 |

MSA = Multiple System Atrophy; PD = Parkinson Disease; ePD = early Parkinson's Disease; sPD = severe Parkinson's Disease without visual hallucinations; sPD-VH = severe PD with visual hallucinations; LIPL = Left Inferior Parietal Lobule; LLPC = Left Lateral Parietal Cortex; LMFG = Left Middle Frontal Gyrus; LSFS = Left Superior Frontal Sulcus; PCC = Posterior Cingulate Cortex; RIPL= Right Inferior Parietal Lobule; RLPC= Right Lateral Parietal Cortex; RMFG = Right Middle Frontal Gyrus; RSFS = Right Superior Frontal Sulcus; FC = functional connectivity. P values from Duncan post-hoc group comparison and F, p values for the main effects. Notice that all significances are reported as higher values (>), but for MSA vs ePD and sPD-VH and for ePD and sPD vs sPD-VH, where significance is inverted (<).

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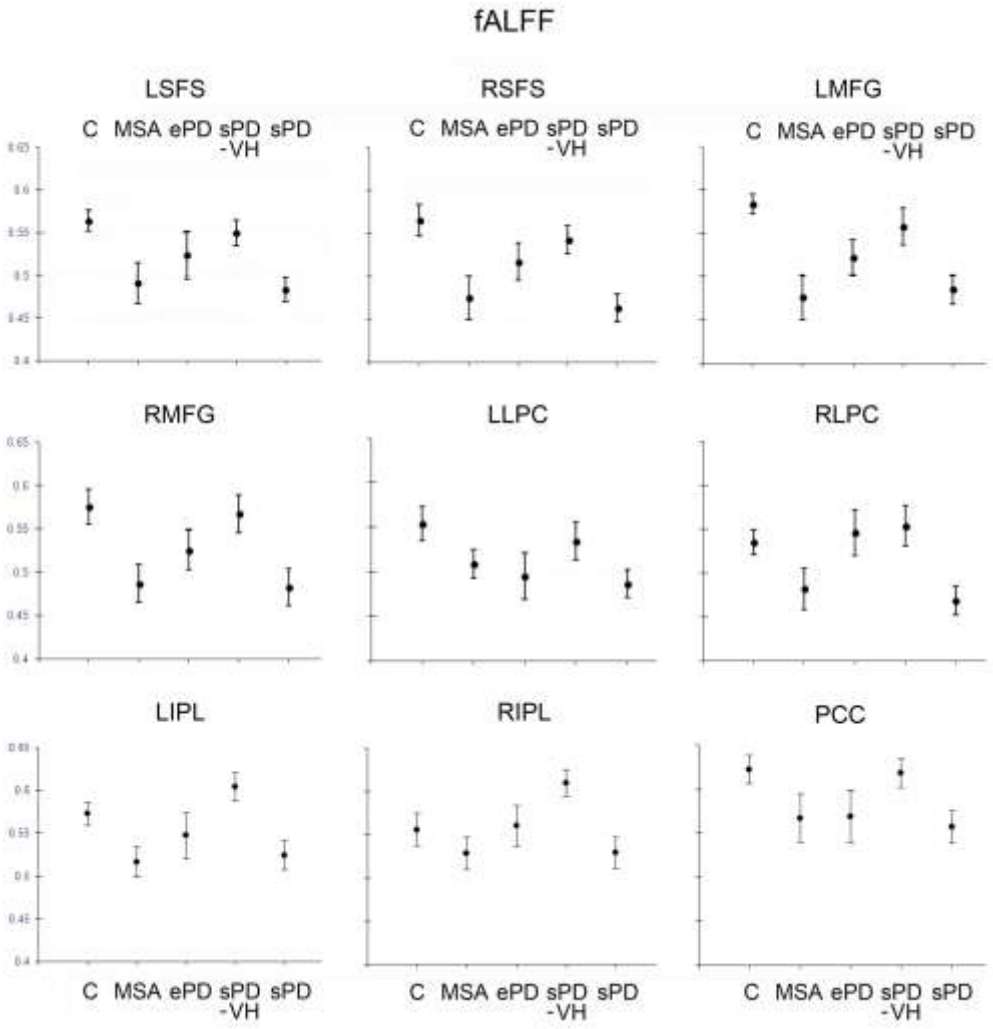


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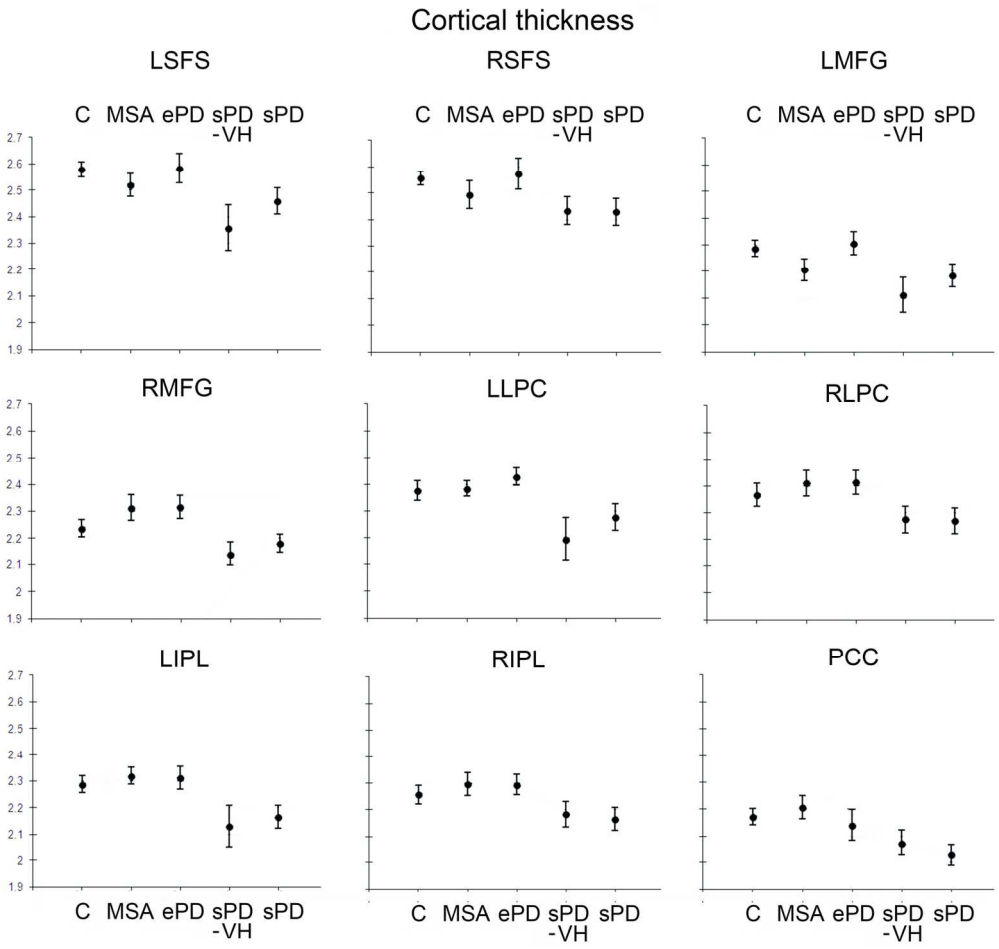


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**Table 1** Clinical, Cognitive, Neuropsychological, Neuropsychiatric and anxiety features (mean ± SD) for Controls, MSA, ePD, sPD-VH and sPD.

| | Controls | MSA | ePD | sPD-VH | sPD |
|---|---|---|---|---|---|
| **AGE** | 69 ± 6 | 67 ± 5 | 66 ± 9 | 70 ± 6 | 68 ± 11 |
| **Education** | 9 ± 4 | 10 ± 5 | 9 ± 3 | 10 ± 4 | 10 ± 3 |
| **MMSE** | 28.7 ± 0.7 | 25.2 ± 1.7 | 26.2 ± 1.8 | 24.3 ± 2.2 | 24.7 ± 1.8 |
| **Disease duration** | n.a. | 3.9 ± 1.8 | 3.3 ± 1.6 | 11.3 ± 4.3 | 12.0 ± 4.5 |
| **UPDRSIII** | n.a. | 36.4 ± 7.6 | 17.7 ± 4.3 | 36.3 ± 8.2 | 35.6 ± 7.4 |
| **LDED** | n.a. | 655 ± 270 | 363 ± 190 | 636 ± 199 | 645 ± 210 |
| **H&Y** | n.a. | 3.2 ± 0.8 | 2.1 ± 0.4 | 3.0 ± 0.5 | 3.0 ± 0.6 |
| **DRS-2 Total** | n.a. | 128 ± 12 | 131 ± 6 | 125 ± 7 | 121 ± 16 |
| **NPI-VH** | n.a. | 0 ± 0 | 0 ± 0 | 6.3 ± 1.7 | 0 ± 0 |
| **NPI-E. Anxiety** | 0.5 ± 0.6 | 5.3 ± 2.4 | 5.0 ± 2.1 | 1.7 ± 0.9 | 2.6 ± 1.0 |
| **NPI-K. Sleep** | 0 ± 0 | 4.1 ± 1.7 | 3.9 ± 1.5 | 3.7 ± 1.7 | 4.1 ± 1.6 |
| **NPI-TOT** | 1.7 ± 2.0 | 24.6 ± 5.4 | 21.9 ± 6.8 | 17.3 ± 3.2 | 19.0 ± 2.0 |
| **FAB** | 15.8 ± 1.5 | 12.7 ± 3.3 | 14.3 ± 1.4 | 11.7 ± 3.5 | 12.7 ± 1.5 |
| **GDS** | 6.3 ± 1.3 | 8.9 ± 2.7 | 6.4 ± 1.5 | 8.8 ± 2.6 | 9.3 ± 2.7 |
| **BADS6E*** | 5.4 ± 0.5 | 3.8 ± 1.0 | 4.1 ± 1.2 | 4.0 ± 1.1 | 4.3 ± 1.0 |
| **Stai - State** | 14.5 ± 3.5 | 43.1 ± 8.0 | 41.1 ± 8.2 | 31.2 ± 5.7 | 37.8 ± 5.2 |
| **Stai -Trait** | 14.1 ± 5.0 | 39.9 ± 7.1 | 42.1 ± 6.6 | 30.9 ± 3.8 | 34.9 ± 5.3 |
| **UMSARS I** | n.a. | 24.2 ± 6.0 | n.a. | n.a. | n.a. |
| **UMSARS II** | n.a. | 27.6 ± 8.1 | n.a. | n.a. | n.a. |
| **UMSARS tot** | n.a. | 51.8 ± 12.9 | n.a. | n.a. | n.a. |

MMSE = Mini Mental State Examination; DRS-2 = Dementia Rating Scale – 2; FAB = Frontal Assessment Battery; GDS = Geriatric Depression Scale; Stai - State = State anxiety Inventory; Stai -Trait = Trait anxiety Inventory; BADS6E = Behavioural Assessment of the Disexecutive Syndrome; H&Y = Hoehn/Yahr Staging; LDED = Levo Dopa Equivalent Dose (mg); UMSARS = Unified Multiple System Atrophy Rating Scale; UPDRSIII = Unified Parkinson's Disease Rating Scale - subscale III; NPI = Neuropsychiatry Inventory; VH = visual hallucinations; ePD = early Parkinson's Disease; sPD = severe Parkinson's Disease without visual hallucinations; sPD-VH = severe PD with visual hallucinations; MSA = Multiple System Atrophy; N/A = not applicable; n.s. = not significant; SD = standard deviation.

**Table 2** Significant statistical results from the comparison of FC values among groups

| Post-hoc comparisons | p | Brain connections | F(4,69) | p | Power |
|---|---|---|---|---|---|
| Controls > MSA | 0.005 | LSFS-LIPL | 6.47 | <0.001 | 0.99 |
| | 0.02 | LSFS-RIPL | 4.23 | 0.004 | 0.91 |
| | 0.02 | RSFS-LIPL | 6.48 | <0.001 | 0.99 |
| | <0.001 | RSFS-RIPL | 6.98 | <0.001 | 0.99 |
| | 0.02 | LMFG-RMFG | 3.52 | 0.01 | 0.84 |
| | 0.01 | LLPC-RLPC | 5.40 | <0.001 | 0.97 |
| | 0.001 | LIPL-RIPL | 5.26 | <0.001 | 0.96 |
| | 0.01 | LIPL-PCC | 7.11 | <0.001 | 0.99 |
| | 0.04 | RIPL-PCC | 5.13 | 0.01 | 0.96 |
| Controls > ePD | 0.006 | LSFS-LIPL | 6.47 | <0.001 | 0.99 |
| | 0.02 | LSFS-RIPL | 4.23 | 0.004 | 0.91 |
| | 0.02 | RSFS-LIPL | 6.48 | <0.001 | 0.99 |
| | 0.04 | RSFS-RIPL | 6.98 | <0.001 | 0.99 |
| | 0.02 | LMFG-RMFG | 3.52 | 0.01 | 0.84 |
| | 0.05 | LLPC-RLPC | 5.40 | <0.001 | 0.97 |
| Controls > sPD | <0.001 | LSFS-LIPL | 6.47 | <0.001 | 0.99 |
| | <0.001 | LSFS-RIPL | 4.23 | 0.004 | 0.91 |
| | <0.001 | LSFS-PCC | 3.97 | 0.006 | 0.89 |
| | <0.001 | RSFS-LIPL | 6.48 | <0.001 | 0.99 |
| | <0.001 | RSFS-RIPL | 6.98 | <0.001 | 0.99 |
| | <0.001 | RSFS-PCC | 6.33 | <0.001 | 0.99 |
| | 0.04 | LMFG-RMFG | 3.52 | 0.01 | 0.84 |
| | <0.001 | LLPC-RLPC | 5.40 | <0.001 | 0.97 |
| | 0.004 | LIPL-RIPL | 5.26 | <0.001 | 0.96 |
| | 0.002 | LIPL-PCC | 7.11 | <0.001 | 0.99 |
| | 0.003 | RIPL-PCC | 5.13 | 0.01 | 0.96 |
| Controls > sPD-VH | 0.02 | LMFG-RMFG | 3.52 | 0.01 | 0.84 |
| MSA < ePD | 0.007 | LIPL-RIPL | 5.26 | <0.001 | 0.96 |
| | 0.047 | LIPL-PCC | 7.11 | <0.001 | 0.99 |
| MSA > sPD | 0.03 | RSFS-LIPL | 6.48 | <0.001 | 0.99 |
| | 0.03 | RSFS-PCC | 6.33 | <0.001 | 0.99 |
| MSA < sPD-VH | 0.01 | LSFS-LIPL | 6.47 | <0.001 | 0.99 |
| | 0.01 | RSFS-RIPL | 6.98 | <0.001 | 0.99 |
| | 0.006 | LIPL-RIPL | 5.26 | <0.001 | 0.96 |
| | 0.002 | LIPL-PCC | 7.11 | <0.001 | 0.99 |
| | 0.04 | RIPL-PCC | 5.13 | 0.01 | 0.96 |
| ePD > sPD | 0.03 | RSFS-LIPL | 6.48 | <0.001 | 0.99 |
| | 0.04 | RSFS-RIPL | 6.98 | <0.001 | 0.99 |
| | 0.02 | RSFS-PCC | 6.33 | <0.001 | 0.99 |
| | 0.02 | LIPL-RIPL | 5.26 | <0.001 | 0.96 |
| | 0.01 | LIPL-PCC | 7.11 | <0.001 | 0.99 |
| ePD < sPD-VH | 0.01 | LSFS-LIPL | 6.47 | <0.001 | 0.99 |
| sPD < sPD-VH | <0.001 | LSFS-LIPL | 6.47 | <0.001 | 0.99 |
| | <0.001 | LSFS-RIPL | 4.23 | 0.004 | 0.91 |

| | | | | | |
|---|---|---|---|---|---|
| | 0.001 | LSFS-PCC | 3.97 | 0.006 | 0.89 |
| | <0.001 | RSFS-LIPL | 6.48 | <0.001 | 0.99 |
| | 0.002 | RSFS-RIPL | 6.98 | <0.001 | 0.99 |
| | <0.001 | RSFS-PCC | 6.33 | <0.001 | 0.99 |
| | 0.007 | LLPC-RLPC | 5.40 | <0.001 | 0.97 |
| | 0.02 | LIPL-RIPL | 5.26 | <0.001 | 0.96 |
| | <0.001 | LIPL-PCC | 7.11 | <0.001 | 0.99 |
| | 0.002 | RIPL-PCC | 5.13 | 0.01 | 0.96 |

MSA = Multiple System Atrophy; PD = Parkinson Disease; ePD = early Parkinson's Disease; sPD = severe Parkinson's Disease without visual hallucinations; sPD-VH = severe PD with visual hallucinations; LIPL = Left Inferior Parietal Lobule; LLPC = Left Lateral Parietal Cortex; LMFG = Left Middle Frontal Gyrus; LSFS = Left Superior Frontal Sulcus; PCC = Posterior Cingulate Cortex; RIPL= Right Inferior Parietal Lobule; RLPC= Right Lateral Parietal Cortex; RMFG = Right Middle Frontal Gyrus; RSFS = Right Superior Frontal Sulcus; FC = functional connectivity. P values from Duncan post-hoc group comparison and F, p values for the main effects. Notice that all significances are reported as higher values (>), but for MSA vs ePD and sPD-VH and for ePD and sPD vs sPD-VH, where significance is inverted (<).

**Supporting Table 1**

**SCOPA-autonomic (SCOPA-AUT) total scores**

**for each group.**

| | | SCOPA-AUT |
|---|---|---|
| **Controls** | **Mean ± SD** | 5.2 ± 2.0 |
| **MSA** | **Mean ± SD** | 20.9 ± 4.3 |
| **ePD** | **Mean ± SD** | 16.8 ± 2.3 |
| **sPD-VH** | **Mean ± SD** | 19.4 ± 3.4 |
| **sPD** | **Mean ± SD** | 18.9 ± 4.0 |
| **Controls vs MSA** | **p value** | $0.3*10^{-4}$ |
| **Controls vs ePD** | **p value** | $0.1*10^{-3}$ |
| **Controls vs sPD-VH** | **p value** | $0.5*10^{-4}$ |
| **Controls vs sPD** | **p value** | $0.6*10^{-4}$ |
| **MSA vs ePD** | **p value** | $0.3*10^{-2}$ |
| **MSA vs sPD-VH** | **p value** | n.s. |
| **MSA vs sPD** | **p value** | n.s. |
| **ePD vs SPD-VH** | **p value** | n.s. |
| **ePD vs sPD** | **p value** | n.s. |
| **sPD-VH vs sPD** | **p value** | n.s. |

Statistical analysis shows significant difference across groups ($F(4,70)=52.02$, $p<10^{-4}$). P-values from Duncan post-hoc comparisons. ePD = early Parkinson's Disease; MSA = Multiple System Atrophy; n.s. = not significant; sPD = severe Parkinson's Disease without visual hallucinations; sPD-VH = severe PD with visual hallucinations.

**Supporting Table 2**

**Statistical Differences across groups for Clinical and Neuropsychological Features for Controls, MSA, ePD, sPD-VH and sPD.**

| | MMSE | Disease duration | UPDRSIII | NPI-VH | NPI-E. Anxiety | NPI-K. Sleep | NPI-TOT | Stai-State | Stai-Trait | LDED | H&Y |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Controls vs. MSA** | $0.6*10^{-4}$ | n.a. | n.a. | n.a. | $0.3*10^{-4}$ | $0.5*10^{-4}$ | $0.3*10^{-4}$ | $0.3*10^{-4}$ | $0.5*10^{-4}$ | n.a. | n.a. |
| **Controls vs. ePD** | $0.5*10^{-4}$ | n.a. | n.a. | n.a. | $0.5*10^{-4}$ | $0.6*10^{-4}$ | $0.5*10^{-4}$ | $0.5*10^{-4}$ | $0.3*10^{-4}$ | n.a. | n.a. |
| **Controls vs. sPD-VH** | $0.2*10^{-3}$ | n.a. | n.a. | n.a. | $0.3*10^{-1}$ | $0.1*10^{-3}$ | $0.1*10^{-3}$ | $0.1*10^{-3}$ | $0.1*10^{-3}$ | n.a. | n.a. |
| **Controls vs. sPD** | $0.3*10^{-4}$ | n.a. | n.a. | n.a. | $0.6*10^{-3}$ | $0.3*10^{-4}$ | $0.6*10^{-4}$ | $0.6*10^{-4}$ | $0.6*10^{-4}$ | n.a. | n.a. |
| **MSA vs. ePD** | n.s. | n.s. | $0.5*10^{-4}$ | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | $0.1*10^{-2}$ | $0.6*10^{-4}$ |
| **MSA vs. sPD-VH** | n.s. | $0.1*10^{-3}$ | n.s. | $0.6*10^{-4}$ | $0.5*10^{-4}$ | n.s. | $0.8*10^{-4}$ | $0.6*10^{-4}$ | $0.1*10^{-3}$ | n.s. | n.s. |
| **MSA vs. sPD** | n.s. | $0.6*10^{-4}$ | n.s. | n.s. | $0.7*10^{-4}$ | n.s. | $10^{-3}$ | $0.4*10^{-1}$ | $0.2*10^{-1}$ | n.s. | n.s. |
| **ePD vs. SPD-VH** | $0.7*10^{-2}$ | $0.6*10^{-4}$ | $0.6*10^{-4}$ | $0.5*10^{-4}$ | $0.6*10^{-4}$ | n.s. | $0.6*10^{-2}$ | $0.2*10^{-3}$ | $0.5*10^{-4}$ | $0.1*10^{-2}$ | $0.1*10^{-3}$ |
| **ePD vs. sPD** | $0.4*10^{-1}$ | $0.5*10^{-4}$ | $0.1*10^{-3}$ | n.s. | $0.2*10^{-3}$ | n.s. | n.s. | n.s. | $0.2*10^{-2}$ | $0.1*10^{-2}$ | $0.2*10^{-3}$ |
| **sPD-VH vs. sPD** | n.s. | n.s. | n.s. | $0.1*10^{-3}$ | n.s. | n.s. | n.s. | $0.7*10^{-2}$ | n.s. | n.s. | n.s. |

Statistical differences across groups for MMSE ($F(4,70)=16.10$ $p<10^{-4}$), disease duration ($F(3,56)=29.82$ $p<10^{-4}$), UPDRSIII ($F(3,56)=25.93$ $p<10^{-4}$), NPI-VH ($F(3,56)=167.7$ $p<10^{-4}$), NPI-E. Anxiety ($F(4,70)=26.65$ $p<10^{-4}$), NPI-K. Sleep ($F(4,70)=22.20$ $p<10^{-4}$), NPI-TOT ($F(4,70)=65.01$ $p<10^{-4}$), Stai State ($F(4,70)=48.09$ $p<10^{-4}$) and Stai Trait ($F(4,70)=55.48$ $p<10^{-4}$), LDED ($F(3,56)=6.20$ $p<10^{-3}$) and H&Y ($F(3,56)=10.96$ $p<10^{-4}$). P values from Duncan post-hoc comparisons between groups. Age, Education level and DRS-2 (Dementia Rating Scale – 2) Total scores were not different across groups.

ePD = early Parkinson's Disease; H&Y = Hoehn/Yahr Staging; LDED = Levo Dopa Equivalent Dose (mg); MMSE = Mini Mental State Examination; MSA = Multiple System Atrophy; N/A = not applicable; NPI = Neuropsychiatry Inventory; Stai - State = State anxiety Inventory; Stai -Trait = Trait anxiety Inventory; n.s. = not significant; SD = standard deviation; sPD = severe Parkinson's Disease without visual hallucinations; sPD-VH = severe PD with visual hallucinations; UPDRSIII = Unified Parkinson's Disease Rating Scale - subscale III; VH = visual hallucinations.

**Supporting Table 3**

**Statistical Differences across groups for fALFF-DMN and cortical thickness from the overall DMN, calculated by averaging all the ROIs of the DMN**

| Measure | Comparison | significance |
|---|---|---|
| **fALFF-DMN F(4,70)=4.66 p=0.002** | Controls > MSA | P=0.007 |
| | controls > sPD | p=0.005 |
| | MSA < sPD-VH | p=0.007 |
| | sPD-VH> sPD | p=0.004 |
| **cortical thickness F(4,70)=3.48 p=0.01** | controls > sPD | p=0.05 |
| | controls > sPD-VH | p=0.025 |
| | MSA > sPD-VH | p=0.026 |
| | MSA > sPD | p=0.05 |
| | ePD > sPD | p=0.03 |
| | ePD > sPD-VH | p=0.01 |

MSA = Multiple System Atrophy; PD = Parkinson Disease; sPD = severe Parkinson's Disease without visual hallucinations; sPD-VH = severe PD with visual hallucinations.
P values from Duncan post-hoc group comparison.

**Supporting Table 4.**

**Significant statistical results from the comparison of fALFF values among groups.**

| Post-hoc comparisons | ROI | p |
|---|---|---|
| Controls > MSA | LSFS | 0.042 |
| | RSFS | 0.011 |
| | LMFG | 0.002 |
| | RMFG | 0.013 |
| Controls > sPD | LSFS | 0.025 |
| | RSFS | 0.003 |
| | LMFG | 0.005 |
| | RMFG | 0.010 |
| sPD-VH>MSA | LMFG | 0.023 |
| | RMFG | 0.025 |
| | RLPC | 0.048 |
| | LIPL | 0.006 |
| | RIPL | 0.015 |
| ePD>sPD | RLPC | 0.030 |
| sPD-VH>sPD | RSFS | 0.026 |
| | LMFG | 0.044 |
| | RMFG | 0.019 |
| | RLPC | 0.017 |
| | LIPL | 0.015 |
| | RIPL | 0.016 |

MSA = Multiple System Atrophy; PD = Parkinson Disease; ePD = early Parkinson's Disease; sPD = severe Parkinson's Disease without visual hallucinations; sPD-VH = severe PD with visual hallucinations; LIPL = Left Inferior Parietal Lobule; LLPC = Left Lateral Parietal Cortex; LMFG = Left Middle Frontal Gyrus; LSFS = Left Superior Frontal Sulcus; PCC = Posterior Cingulate Cortex; RIPL= Right Inferior Parietal Lobule; RLPC= Right Lateral Parietal Cortex; RMFG = Right Middle Frontal Gyrus; RSFS = Right Superior Frontal Sulcus; FC = functional connectivity.
P values from Duncan post-hoc group comparison. Notice that all significances are reported as higher values (>).

**Supporting Table 5**

**Statistical results from the comparison of cortical thickness values among groups.**

| Group comparisons | LSFS | RSFS | LMFG | RMFG | LLPC | RLPC | LIPL | RIPL | PCC |
|---|---|---|---|---|---|---|---|---|---|
| **Controls vs MSA** | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |
| **Controls vs ePD** | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |
| **Controls vs sPD** | n.s. | n.s. | n.s. | n.s. | n.s. | 0.047 | 0.042 | 0.046 | 0.008 |
| **Controls vs sPD-VH** | 0.014 | n.s. | 0.016 | 0.009 | 0.022 | 0.045 | 0.016 | n.s. | 0.042 |
| **MSA vs ePD** | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |
| **MSA vs sPD** | n.s. | n.s. | n.s. | 0.025 | n.s. | 0.044 | 0.043 | 0.042 | 0.008 |
| **MSA vs sPD-VH** | n.s. | n.s. | n.s. | 0.004 | 0.020 | 0.045 | 0.015 | n.s. | 0.045 |
| **ePD vs sPD** | n.s. | n.s. | n.s. | 0.017 | n.s. | 0.043 | 0.046 | 0.039 | n.s. |
| **ePD vs sPD-VH** | 0.014 | n.s. | 0.009 | 0.003 | 0.005 | 0.046 | 0.017 | n.s. | n.s. |
| **sPD vs sPD-VH** | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. | n.s. |

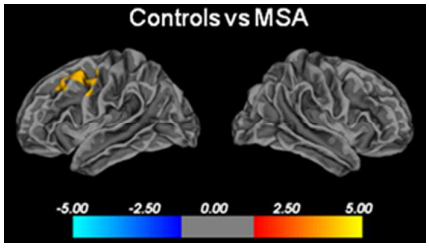
MSA = Multiple System Atrophy; PD = Parkinson Disease; ePD = early Parkinson's Disease; sPD = severe Parkinson's Disease without visual hallucinations; sPD-VH = severe PD with visual hallucinations; LIPL = Left Inferior Parietal Lobule; LLPC = Left Lateral Parietal Cortex; LMFG = Left Middle Frontal Gyrus; LSFS = Left Superior Frontal Sulcus; PCC = Posterior Cingulate Cortex; RIPL= Right Inferior Parietal Lobule; RLPC= Right Lateral Parietal Cortex; RMFG = Right Middle Frontal Gyrus; RSFS = Right Superior Frontal Sulcus; FC = functional connectivity. P values from Duncan post-hoc group comparison.

**Supporting Table 6 Correlations between cortical thickness and disease duration**

| Cortical regions | p |
|---|---|
| Left post-central gyrus [a] | 0.000003 |
| Left inferior parietal gyrus [a] | 0.00009 |
| Left supramarginal gyrus [a] | 0.0008 |
| Right superior frontal gyrus [a] | 0.0003 |
| Left post-central gyrus [a] | 0.001 |
| Left postcentral gyrus [b] | 0.00004 |
| Left precuneus [b] | 0.0001 |
| Left lateral-occipital gyrus [b] | 0.0004 |
| Left inferior parietal gyrus [b] | 0.0008 |
| Right pre-central gyrus [b] | 0.0001 |
| Right rostral-middle frontal gyrus [b] | 0.001 |
| Right caudal-middle frontal gyrus [b] | 0.001 |

**Supporting Figure 1**

**Cortical thickness comparison between MSA and controls.**




Pair-wise differences between MSA and control group in the whole brain corrected for multiple comparisons by using a pre-cached cluster-wise Monte-Carlo Simulation. Significance level was set at $p<0.05$. Notice significant areas of cortical thinning in left premotor and motor cortex.

**Original ~~Investigation~~investigation**

# Why Multiple System Atrophy patients do not have Visual Hallucinations? A Default Mode Network ~~link to visual hallucinations: evidence from MSA vs. PD patients comparison~~study

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**Word count:** ~~3023~~3698

**Keywords:** Default Mode Network, Visual Hallucinations, Multiple System Atrophy, Parkinson's Disease.



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**Abstract**

Background: ~~-~~Studying~~-~~ Default Mode Network activity/connectivity in different parkinsonisms, with or without visual hallucinations, could highlight its roles in expression of clinical phenotypes. Multiple System Atrophy is the archetype of parkinsonism without visual hallucinations, variably appearing instead in Parkinson's Disease.

Methods: ~~-~~functional Magnetic Resonance Imaging identified Default Mode Network structures and assessed ~~spectral power (~~activity~~)~~ and ~~correlation coefficients (~~connectivity~~)~~ in 15 Multiple System Atrophy patients, 15 controls, 15 early Parkinson's Disease patients matched for disease duration, 15 severe Parkinson's Disease patients without visual hallucinations and 15 severe Parkinson's Disease patients with visual hallucinations, matched with Multiple System Atrophy patients for disease severity. Cortical thickness ~~was~~and neuropsychological evaluations were compared in all groups.

Results: Multiple System Atrophy had reduced Default Mode Network activity compared to controls and Parkinson's Disease with ~~visual~~ hallucinations, no differences with Parkinson's Disease (early or severe) without ~~visual~~ hallucinations. In Parkinson's Disease with visual hallucinations ~~had increased~~, activity/connectivity was preserved compared to controls and higher than in all other groups ~~but controls. Early~~, In early Parkinson's Disease ~~had reduced~~ connectivity was lower than in ~~comparison with~~ controls ~~-~~but higher ~~connectivity~~ than in Multiple System Atrophy and severe Parkinson's Disease without ~~visual~~ hallucinations.

~~Structural results evidenced that~~ Cortical thickness was reduced ~~Default Mode Network activity/connectivity in Multiple System Atrophy was not dependent on gray matter loss, which was instead evident in~~ in severe ~~Parkinson's Disease, either~~PD, with ~~or~~and without ~~visual~~ hallucinations, and was only correlated with disease duration. Among neuropsychological assessments, anxiety scores differentiated patients with hallucinations from those without.

Conclusions: ~~Default Mode Network activity is reduced in Multiple System Atrophy.~~ Multiple comparisons evidenced ~~patterns~~ a pattern of Default Mode Network activity/connectivity, ~~increased~~



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~~with visual hallucinations and reduced in parkinsonisms without~~which was higher in Parkinson Disease with visual hallucinations~~, independently of consistency of anatomical structures~~ and reduced in Multiple System Atrophy and Parkinson Disease without visual hallucinations. Cortical thickness comparisons suggests that functional/inhibitory rather than structural changes underlie the activity/connectivity differences.

## 1. Introduction

The Default Mode Network (DMN) has emerged as an evolutionarily novel functional network in human brains[1] and consists of a set of cortical regions, including medial prefrontal, posterior cingulate, and lateral inferior parietal cortex, intimately connected with limbic ~~system~~ areas[1], ~~which~~ . Imaging studies showed that DMN areas deactivate during tasks and activate during ~~rest~~[2], ~~with a role in the~~ rest[1-3], and it is posited that the DMN has roles in imagery production and incorporation of self- referential information into ~~consciousness~~[3], consciousness[2,3]. ~~Because of this DMN role, a recent paper proposed a "DMN link to~~ The germinal studies[4-5] providing evidence of a resting state network, whose activity and connectivity could be studied in simple imaging protocols, without the requirement of performing any task, has fostered a significant body of studies investigating connectivity power in different diseases, in different cognitive, sensory, motor cortical, and subcortical areas[6-7].

More recently the original DMN role, in self-referential information production, has been reconsidered in theoretical and review studies[8-10] that seek to explain the occurrence of Visual Hallucinations- VH~~" hypothesis~~[4]~~, suggesting that the DMN acts in balance with Dorsal and Ventral Attention Networks: disinhibition of~~ , on the basis that DMN~~, introducing~~ could introduce self- referential information into misperceptions~~, could explain the occurrence of VH; however proper assessments of the~~ . From this model ~~would require recording of DMN-Attentional Networks interaction during hallucinations or during tasks , both studies scarcely feasible because of time and collaboration required.~~

~~Inferential assessments could be however proposed, comparing DMN activity-connectivity in patients with different neurodegenerative diseases with and without hallucinations.~~

, it might be inferred that different DMN activity/connectivity ~~is markedly~~ should be evidenced in diseases characterized by presence or absence of VH.

However, definite evidence of a DMN link to VH has not been so far obtained, due to the heterogeneity of diseases studied, or to the fact that the majority of the studies were not focused



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specifically on the explanation of VH etiology[11-13], or as a result of the use of different methodologies applied to study the DMN, e.g. use of DMN areas as comparative, or "seed" unit of activity[14-15].

In Alzheimer's Disease (AD) patients without VH, it is well established that DMN activity/connectivity is reduced[5-16,17]. Similarly altered and reduced ~~in Alzheimer Disease (AD)[5-6], but in~~ connectivity has been described in Progressive Supranuclear Palsy[18], a disease without VH. Conversely DMN connectivity enhancement was recently described in c9ORF72 mutation carriers[19], a variant of Frontotemporal Dementia-FTD presenting with VH.

In Parkinson ~~Disease~~Disase (PD) and Lewy ~~Bodies~~Body Dementia (LBD), diseases both characterized by occurrence of VH, the evidences are ~~controversial[6-10]. The "Cingular Island Sign" of LBD[11] evidences preserved activity~~controversial[11,14,16,20]. Preserved activity has been observed in Posterior Cingulate Cortex~~,~~ (the so called "Cingulate Island Sign") a main hub of ~~DMN~~DMN[21]. Increased or preserved (compared to controls) DMN activity or ~~disinhibition~~reduced inhibition during a visual task ~~,was described~~has also been seen in ~~LBD and PD[8,12]~~LBD[14,16,20], but only altered connectivity was described ~~-~~in other ~~studies[10, 13-14]~~studies[22], which were not focused to VH. In PD, earlier studies described increased connectivity[17], but ~~to systemic interactions~~more recent studies report only altered connectivity[11, 12,13,23]. One study described altered connectivity in PD either with or without ~~VH, but found higher activity in PD with VH[15]~~VH[24]. ~~A~~Therefore the link between VH and DMN activity in Parkinsonisms, is a controversial issue.

One possible way to clarify the controversy ~~could be~~is to compare DMN activity/~~-~~connectivity in patients with different types of ~~parkinsonisms, definitely~~parkinsonism, in those with ~~VH and~~or without ~~VH~~the presence of definite VH, as any evaluation ~~including~~restricted only to PD patients could be biased by insufficient information on VH, ~~which occur with variable timing,~~by variability in their onset and phenomenological quality~~, treatment facilitation~~[16-18 25-26].

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~~Neuropathological studies show that the best predictor of neuronal Lewy Bodies depositions and confirmation of PD diagnosis, is the occurrence of VH, which should be "added to the operational clinical criteria for the diagnosis of PD"[19-20].~~

~~These and other studies~~[21-22]Cohort studies with neuropathological assessments[27-28], evidenced that a diagnosis of Multiple System ~~Atrophy~~atrophy (MSA) could be excluded if VH occurred during the disease course, and thus that MSA ~~is the proper~~represents an archetype of ~~-~~parkinsonism without VH.

MSA is ~~also a proper target for comparison with~~, moreover, an appropriate disease comparator to PD, unlike other ~~parkinsonisms~~Parkinson related disorders, because in MSA there is a ~~response~~responsivity, albeit reduced, to dopaminergic ~~treatments[23-24],which are administered in patients and could be~~treatments[29-30], and thus make an ideal control comparator disease to PD, and because in MSA, REM Sleep Behavior Disorder-RBD, considered ~~for proper matching~~possibly linked to PD VH[10,31-32,33], is common.

We hypothesized therefore that a study of DMN resting state activity in MSA ~~could~~would allow us to properly test the" DMN link to VH" hypothesis. ~~A proper framing of DMN activity in MSA at the light of the hypothesis, requires however a comparison with PD patients, but this comparison must consider the different disease progression rates[24-25], and occurrence of VH mostly in patients with longer disease durations[16-18].~~

In the present study, DMN activity in MSA patients was studied, by fMRI, in comparison with healthy subjects and with three different groups of PD patients, with or without VH, matched with MSA either for disease severity or duration.

~~The~~ DMN structures were identified by Independent Component analysis (ICA); only PD patients presenting with complex VH were selected for the "PD with VH" group. In addition, in order to enhance group homogeneity, matching between groups included RBD, treatments and cognitive conditions. Among clinical assessments anxiety evaluations were included, in order to explore the hypothesis suggesting that DMN reduced activity/connectivity is related to the expression of an

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anxiety predominant clinical phenotype[16, 34, 35,36] in contrast to a hallucinatory phenotype which is related to DMN activity enhancement.

This study design, with multiple group ~~comparison~~comparisons and matching, therefore, in summary, can address ~~three~~two interdependent aims: 1) ~~evaluate~~evaluation of DMN activity in ~~MSA~~MSA[37], in comparison with controls and PD, 2) ~~test~~testing the DMN-VH hypothesis in different degenerative parkinsonisms, with and without VH~~; 3) assess whether DMN activity may differentiate MSA from PD~~.

## 2. Material and methods

### 2.1 Study population

The study population was recruited from referrals to Movement Disorder Centres of the University of Chieti-Pescara and of IRCCS San Camillo, Venezia.

Before being enrolled in the study, all subjects signed a written informed consent. The study was approved by the local ethical committees and was carried out according to revised Helsinki ~~declaration[26] .~~declaration[38]. 15 healthy elderly controls, 15 MSA (type P), 15 PD patients matched with MSA for disease duration (ePD), ~~15~~30 PD patients matched with MSA for severity of symptoms and equivalent treatments~~,~~ (15 without VH (sPD) and 15 ~~PD, equally matched with MSA, presenting~~ with VH (sPD-VH~~)~~)) were selected to participate in the study, from two cohorts of 650 PD and 72 MSA patients. PD was diagnosed according to UK ~~BBC[27]~~BBC[39]. Parkinsonian motor signs were rated with the Hoehn/Yahr scale and the motor part of the Unified Parkinson's Disease Rating Scale-UPDRS III in PD and MSA ~~patients[28]~~patients[40]. In MSA patients the Unified MSA Rating Scale (UMSARS) was also ~~used[29]. Dopaminergic presynaptic ligand ioflupane SPECT (~~used[41]. $^{123}$I-FP-CIT SPECT~~)~~ was performed in all patients. MSA patients were diagnosed according to consensus ~~criteria[30]~~criteria[42] and presence of typical MRI ~~alterations[31]~~alterations[43].

Control subjects had no evidence of clinical dementia and no evidence of any abnormality on structural neuroimaging.

All patients were tested with the MMSE, the Dementia Rating Scale 2 (DRS2)[~~32~~44], the Frontal Assessment Battery (FAB)[~~33~~45], the Behavioural Assessment of the ~~Disexecutive~~Dysexecutive Syndrome (BADS6E)[~~34-35~~ , 46-47, the Neuropsychiatric Inventory (NPI)[~~36~~48], the Geriatric Depression Scale (GDS)[~~37~~49] and the State-Trait anxiety Inventory (STAI)[~~38~~50].

ePD, sPD and sPD-VH were carefully matched with MSA patients for neuropsychological ~~profiles~~[39-40]profiles[51-52], and presence and frequency of ~~Rem Sleep Behavior Disorder (~~RBD~~),~~ , evaluated according to previous ~~studies~~[41-42]studies[53-54].

VH were investigated with semistructured interviews and were rated with the NPI ~~items and only~~specific item. Only patients with complex kinematic hallucinations, according to tentative classifications of ~~VH~~[17-18]-VH[9,26] and to Parkinson Psychosis Scale[55], were admitted to the sPD-VH group, while patients presenting only with illusions (misperceptions) were excluded from any group. Any suspect of illusions or hallucinations excluded the diagnosis of MSA.

None of the patients received amantadine ~~or~~, anticholinergics, cholinesterase inhibitors, neuroleptics, all patients were treated with L-dopa-carbidopa, MAO-b inhibitors, ~~entecapone~~entacapone, 6 ePD and 6 MSA patients received dopaminoagonist doses equivalent to 100mg/day of L-~~dopa~~[43-44-45-46]dopa[56].

Autonomic symptoms were rated with SCOPA-AUT ~~scale~~[47]scale[57] reported in supporting ~~Table1 in~~Table 1 of the Supporting information file.

All patients were assessed for genetic origin of parkinsonism, according to ~~methods~~ previously ~~reported~~[48]reported methods[58].

All patients were followed for 2-4 years after functional MRI (fMRI) acquisitions in order to confirm, challenge diagnosis.

To ~~attempt~~ensure blinding procedures, neuropsychology and fMRI raters were unaware of working hypotheses and clinical classifications, physicians from the second Unit were unaware of working hypotheses.

~~Tables~~Table 1 reports the demographic, neuropsychological and neuropsychiatric variables ~~for~~of the five groups. ~~Obvious statistical differences were dependent on disease duration or severity and are detailed in supporting Table2 in the Supporting information file.~~

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**2.2 Image acquisition**

MRI ~~images of participants~~data were acquired with Philips scanners at 1.5 T, 24 hours after treatment withdrawal ~~of treatment~~. Subjects were ~~in~~scanned during resting state ~~conditions[6] and were scanned~~conditions[16] by means of T2*-weighted echo planar imaging with the following parameters: 16 bicommissural slices, 200 volumes, in-plane resolution = 3.75 x 3.75 mm, slice thickness = 8 mm; repetition time = 1409 ms; echo time = 50 ms; field of view = 240 mm; no gap. Volumetric images were acquired via a 3-D T1-TFE (Turbo Field Echo) sequence.

**2.3 FMRI analysis**

FMRI data analyses were carried out using Brain Voyager Qx release 2.3 (Brain Innovation, The Netherlands). The first 5 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 fMRI data were coregistered with their 3-D anatomic images, transformed into Talairach space ~~stereotaxic coordinates, applying Talairach transformation to functional images.~~. Spatial smoothing was achieved with an 8-mm Gaussian core full-width half-maximum.

Spatial independent component analysis (ICA) was applied on single subject ~~resting state~~ data using the "FastICA" algorithm. The number of components was restricted to ~~30~~[49]30[59], the cluster size was fixed to 10 mm for each dimension and z threshold of 2.5 was used ~~as a criterion~~ 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 ~~a given~~ voxel time ~~course~~courses with ~~the corresponding~~ IC ~~waveform~~waveforms. ICs corresponding to ~~noise based on spatial patterns and temporal frequency~~[50]-noise[60] were removed. Coactivation of the posterior cingulate cortex ~~and~~(PCC), the left/right lateral parietal cortex (RLPC, LLPC), left/right inferior parietal ~~lobules~~lobule (LIPL, RIPL), left/right superior and middle rostral frontal gyrus (LSFG, RSFG, LMFG, RMFG) was the criterion to select ICs most closely matching the DMN model. In each subject 9 regions of interest (ROIs) were identified. Each ROI, containing about 1000 voxels, was centered on the DMN clusters using a center of gravity ~~approach~~[51]approach[61]. Mean Blood Oxygen Level-Dependent (BOLD) signal intensities across all voxels in each ROI were extracted and converted to z-score values. Fast Fourier transform was applied to the mean BOLD signal ~~time course of each ROI~~ to obtain power spectrum~~, the~~ of each ROI. The power ratio of ~~simple frequencies of~~each frequency in the low-frequency range (0.01–0.08 Hz) vs. the entire ~~frequency~~ range (0–0.25 Hz), i.e., fractional amplitude of low-frequency fluctuation (fALFF) was ~~used~~[52]-used[62].

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. Self-organizing ~~clustering~~[53]clustering[63] was applied ~~for each group~~ to obtain group spatial maps.

**2.4 Cortical thickness analysis**

Cortical thickness was estimated on $T_1$-weighted image using Freesurfer software package (http://surfer.nmr.mgh.harvard.edu~~), calculating thickness in a tessellated model of the cortical surface[54], by segmentation, affine registration to Talairach atlas and skull-strip, intensity normalization, tessellation and classification steps. The gray/white matter interface is tessellated, corrected by topological defects and used for accurate representation of the pial surface[55]-~~).[64,65]

Cortical thickness measurements were obtained by reconstructing representations of the gray/white

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matter boundary and the cortical surface~~, distances between these two surfaces were calculated individually~~: for each point on the white matter surface, the shortest distance to the pial surface was computed; next, for each point on the pial surface, the shortest distance to the white matter was found, and the cortical thickness at that location was set to the average of these two values providing submillimeter ~~resolution[56]~~resolution[66].

Cortical brain regions affected by cortical thinning were classified by using the Desikan-Killiany ~~Atlas[57]~~Atlas[67] integrated in FreeSurfer. The "aparcstats2table" command line was used to calculate the mean cortical thickness within ~~the~~DMN cortical regions ~~included in the DMN~~.

**2.5 Statistics**

Demographic, neuropsychological and neuropsychiatric variables were compared among groups by means of General Linear Model multivariate analysis of variance. Duncan post-hoc test was used to correct for multiple comparisons.

Two ways ANOVA was performed on fALFF with group (controls, MSA, ePD, sPD-VH and sPD) as categorical factor, ROIs as within factor. ~~Duncan post-hoc test was used to correct for multiple comparisons.~~

In the between-group analysis on FC, General Linear Model multivariate analysis of variance was separately used with group as factor and age as nuisance factor, α level was set at 0.05. Multivariate ANOVA was performed on mean cortical thickness values evaluated for each region of the DMN using group as independent variable and age as nuisance factor. Duncan post-hoc test was used to correct for multiple comparisons.

Spearman's correlation, Bonferroni corrected, was performed between fMRI outcomes and neuropsychological-clinical scores .

QDEC (https:// surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/QdecGroupAnalysis_freeview) was used to individuate regions showing significant correlation between cortical thickness and

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neuropsychological-clinical variables. All results were corrected for multiple comparisons by using a pre-cached cluster-wise Monte-Carlo Simulation.

Correlations were performed on all patients and for patients without visual hallucinations separately.

**3. Results**

Statistical results on the intergroup comparisons for all the variables reported in Table 1 are detailed in the supporting information files. NPI hallucination scores separated sPD-VH from all groups, L-dopa equivalent doses were higher in MSA, sPD, sPD-VH than in ePD. Anxiety scores were higher in MSA than in sPD-VH and higher in sPD without VH than in sPD-VH.

In each participant ICA revealed the presence of typical DMN maps~~, defined as coactivation of the posterior cingulate cortex (PCC), the left/right lateral parietal cortex (RLPC, LLPC), left/right inferior parietal lobule (LIPL, RIPL), left/right superior and middle rostral frontal gyrus (LSFG, RSFG, LMFG, RMFG).~~.

Fig. 1 shows DMN group-level maps from ICA algorithm, and mean patterns of power amplitudes and cortical thickness, for all DMN components averaged as a whole, in the five groups of patients.~~For averaged values spectral power (fALFF) is statistically higher in controls than in MSA and sPD (p<0.007,0.005)and in sPD-VH than in MSA and sPD (p<0.007,0.004);corttical thickness is higher in controls,MSA,ePD than in sPD and sPD-VH (p<0.03-0.01-appendix a).~~

Spectral power (fALFF) was statistically higher in controls than in MSA and sPD (p<0.01, 0.005) and in sPD-VH than in MSA and sPD without VH (p<0.01, 0.005); cortical thickness was higher in controls, MSA, ePD than in sPD with or without VH (p<0.03-0.01-supporting table 3 and 5 of the supporting information).

fALFF values for single DMN components in each group of ~~patients~~subjects are detailed in fig.-2~~,~~:: the main ~~effects~~effect group ($F(4,70)=4.66$, $p=0.002$) and ROIs ($F(8,560)=20.11$, $p<0.0001$) and the interaction group X ROIs ($F(32,560)=1.50$, $p<0.05$) were significant.

fALFF values were significantly lower in MSA and sPD (without VH) than in controls (p<0.04805- p<0.01) in superior and medial frontal areas,, and were significantly higher in sPD-VH than in MSA and sPD (p<0.044 05 p<0.015). 02).

Despite lower mean values, no statistical differences of fALFF values were found in the comparison between ePD and MSA nor between ePD and controls. The only significant comparison was for ePD vs. sPD for right lowerinferior parietal cortex Appendix 2. Supporting table 4 of the supporting information reports detailed statistical results.

FC was higher in controls than in MSA and sPD without VH for all couples of areas, and higher than in ePD for frontoparietal connections. FC was higher in sPD-VH than in MSA for intra-hemispheric fronto-parietal connections, inter-hemispheric parietal connection and for connections between IPL and PCC,.

FC in sPD-VH was higher than in sPD without VH for all significant couples of brain areas, but for connections between LMFG and RMFG, and higher than in ePD for LSFS-LIPL connections. FC in ePD was higher than in MSA for IPL and left PCC and was higher than in sPD without VH for fronto-parietal, fronto-cingulate and PCC connections.

Table 2 shows all statistical values and the brain areas where FC differences were found among groups.in the intergroup comparisons.

We did not find significant correlation between fMRI outcomes and neuropsychological-clinical scores.

Cortical thickness comparisons inside the DMN showed significant differences across groups in LSFS (F(4,69)=2.52, p<0.05), LMFG (F(4,69)=2.78, p<0.05), RMFG (F(4,69)=4.31, p<0.005), LLPC (F(4,69)=2.87, p<0.05), LIPL (F(4,69)=3.30, p<0.05) and PCC (F(4,69)=3.69, p<0.01).

No significant reduction of cortical thickness was found inside the DMN in MSA compared to controls and ePD. Significant cortical thinning (p<0.046, 0.005) was found in sPD and sPD-VH compared to controls, MSA and ePD, for all DMN areas but for RSFS. (Fig. 3, supporting Tables 2,3,4 inof the Supporting information file).

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Only disease duration was correlated with mean cortical thickness ($p<0.05$) in comparisons between all groups or between groups without VH (supporting table 6 of the supporting information).

Pair-wise differences in the whole brain showed significant cortical thinning of left premotor and motor cortex, in MSA compared to controls (supporting Figure ~~1in~~of the Supporting information ~~file~~).

**4. Discussion**

~~Our results show differences in DMN power and connectivity between MSA and controls. The necessary comparison with three different groups of patients~~ MSA patients had reduced activity in Superior Frontal Sulcus and Middle Frontal Gyrus DMN components and reduced inter and intra hemispheric frontoparietal and parieto-cingulate connectivity within DMN nodes, in comparison with controls. This novel finding (identified as the first study aim) is unlikely to have any diagnostic utility, as the comparison with PD patients without VH showed only minor differences..

The multiple group comparison with PD patients, matched either for disease duration ~~(ePD)~~ or ~~for~~ severity of symptoms ~~(sPD), with or without VH, and subsequent comparisons between PD groups, provided further valuable information. Intergroup comparisons showed~~, with and without VH, evidenced, however, a pattern of DMN activity and connectivity ~~which is~~, consisting of relative enhancements or reductions, which would not have emerged from simple comparisons with controls or with a limited group of PD patients.

This pattern (Fig.1,2) is evident for DMN spectral power measurements, and was confirmed by connectivity assessments (Table 3): the pattern consists of reduced DMN activity-connectivity if VH are not present, and of increased DMN activity-connectivity (similar to controls in all DMN components) if VH are present.

This pattern was independent of cortical thickness of DMN areas and ~~could~~ thus ~~depend on~~we would argue is more dependent upon inhibition-disinhibition mechanisms, rather than on

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morphometric differences. This pattern (Fig. 1, 2) is evident for DMN power measurements and is supported by FC data (Fig1,3) between groups. Indeed increased DMN activity-connectivity separated PD patients with VH from all other groups.

In early PD, only fewer connectivity differences with controls, as reported in previous literature[10,15,58], are evident, and minor connectivity differences with MSA emerge, but when VH occur (sPDVH) DMN power and connectivity is increased, is not different from controls, thus preserved, and significantly separates patients with VH from patients without VH, either MSA or PD. Increased left frontoparietal connectivity is evidenced also in the comparison between PD with VH and early PD. Conversely, when VH do not occur, despite long disease duration or because of different disease type, DMN activity and connectivity is significantly reduced.

These findings answer to the three questions asked by our study aims:

1) DMN activity and connectivity is reduced in MSA.

2) DMN activity and connectivity is significantly different if VH are or not present.

3 ) DMN activity differentiates MSA from PD only if adequate matching procedures are applied.

The minor differences with ePD, no differences with sPD without VH, despite the outstanding differences with sPD VH, suggests that DMN investigation could difficultly find a role in MSA assessment, as the selection of patients for comparisons could significantly interfere with the achievement of unequivocal statistical cut offs.

The pattern of different DMN activity/connectivity related to VH occurrence or VH inhibition is only evident because of the intergroup comparisons. Limited comparisons with controls would not show that DMN activity/connectivity is significantly increased in patients with VH, nor that MSA patients have a DMN pattern similar to sPD without VH.

The limit of our multiple group comparison is that it provides assessments of the role of DMN, which may be considered mostly inferential, as a definite demonstration of disinhibition preceding or appearing concomitantly with VH occurrence could only be obtained by a longitudinal

~~evaluation, investigating which hubs and sites of DMN are most involved in VH productions, and possibly involving evaluations of inhibition/disinhibition during specifically designed tasks.~~

~~A strength of our study is that it is performed with multiple techniques, including anatomical measurement, showing that DMN hypoactivity in MSA is not dependent on structural abnormalities (Fig. 4), whereas significant cortical thinning was detected within DMN areas in sPD patients ,with and without VH, compared to MSA, ePD and controls (Fig. 3).~~

~~The contradictory findings of preserved DMN activity/connectivity in atrophic structures (sPD-VH), and depressed DMN activity in preserved (MSA) or atrophic (sPD without VH) cortical structures, suggests that anatomical findings might be simply dependent on disease durations, while spectral power and connectivity changes should depend on functional inhibitory or facilitatory modulation.~~

~~These findings are in agreement with previous cortical thickness studies revealing atrophy in MSA only in structures unrelated to DMN functions[59-60], but~~ Therefore, our multiple group comparison, provides evidence to support the DMN link to our VH hypothesis, as considered in our second study aim: DMN activity-connectivity is reduced if VH are not present, independently of disease type and disease duration.

Our findings are in agreement with previous studies showing that DMN is enhanced in diseases characterized by occurrence of VH, like DLB, c9ORF72 FTD and psychiatric conditions[16, 19, 68]. In PD, connectivity changes appear more variable; earlier studies described hyperconnectivity[17], and thus provided support for theoretical models of VH[8, 10], but more recent studies showed altered connectivity, which correlated with cognitive impairment[11-13,23,69] . However in these latter studies patients with VH were not included.

In our ePD and sPD without VH patients , we found reduced DMN connectivity, which was similar to findings of these studies[11-13]. However we found enhanced DMN in sPD VH, which is at variance with the hypothesized linear correlation between decreased DMN activity and cognition[11-13], as our patients with VH were just as cognitively impaired as our patients without VH (table 1). Thus we

would argue that the difference between the other studies showing decreased DMN activity, and ours, is dependent on exclusion of patients with VH.

One recent study[24] compared PD patients with complex VH and without VH, with disease durations similar to our sPD groups, found "greater" DMN coactivation in VH patients, relative to non VH. Similarly as in our sPD-VH patients, the greater activity was in posterior cingulate gyrus, although in that study activity increases were evident only in right middle frontal lobe, whilst in our patients the enhancement was bilateral. Same as in our study, these authors[24] found no differences in cortical thickness between patients with enhanced or reduced DMN activity, which is consistent with our hypothesis that functional inhibitory or facilitatory activity rather than structural change is responsible for DMN differences between hallucinators and non-hallucinators.

Our cortical thickness analysis demonstrated a correlation with disease duration, but we found no correlations with other clinical variables, and evidenced atrophy, in MSA, only in structures which were unrelated to DMN functions, which is consistent with previous cortical thickness studies in this disease[70-71]. In contrast, previous studies which have used the voxel based morphometry technique have reported widespread abnormalities in MSA[72]. We hypothesize that differences between our cortical thickness studies and the VBM based studies are largely driven by the technical limitation of the latter, which needs correction algorithms, as well as to differences in the disease durations in MSA in our study compared to others[73].

In conclusion, the comparison between different diseases, with different etiologies, suggests that DMN enhancement or inhibition is not a disease related specific process, but rather is an aspect linked to the expression of clinical phenotypes.

This hypothesis expands the possible role of DMN, by considering that DMN enhancement may underlie the expression of VH (with extreme manifestations including psychosis and delusions), whilst DMN inhibition might be linked to a phenotype characterized by hyperarousal or increased anxiety (with extreme manifestations including for example akathysia). Previous studies[16, 35,36] evidenced the correlation between reduced DMN activity and anxiety, and the present study shows

that MSA patients and PD patients without VH, who had altered and reduced DMN functions, had higher anxiety scores than controls and patients with VH. Activity-connectivity and anxiety scores were not correlated with cortical thickness, suggesting that this phenomenological aspect is also dependent on functional modulation, rather than on morphometric differences.

Our results, therefore, are ~~different from results obtained with the limited voxel based morphometry techniques, which showed widespread abnormalities[61-64]. We hypothesize that differences are due to technology limitations of voxel based morphometry, needing correction algorithms[59,65] and to different disease durations of MSA[61-64].~~

~~As a final conclusion we underline that the present study considers DMN for its original role, conceived in germinal studies[3], i.e. as a resting network linked to limbic structures, introducing self referential narratives into experience.~~

~~We believe that its role in the occurrence of VH is supported by the present findings, and we hypothesize that the narrative role of DMN is a likely explanation for the complex hallucinations with florid narratives reported by PD patients[16-18].~~

~~Beyond a role in VH, DMN activity inhibition or facilitation may explain the occurrence of different clinical phenotypes,~~compatible with hypotheses on DMN functions, but one ~~with confusional hallucinatory expression due to disinhibition, one with hyperarousal and consequent agitation, anxiety or even acatisia due to DMN over-inhibition.~~

~~This hypothesis was suggested in a previous study comparing DLB and AD patients[6], and we suggest that one finding of our comparative study could be interpreted as supportive of the hypothesis. MSA patients, cPD and sPD without VH, all with reduced DMN activity and connectivity, have higher anxiety scores than sPDVH with preserved DMN activity (Table 1).~~

~~Our findings in MSA, finally, challenge~~finding challenges previous attempts to explain ~~maintenance or increase~~the mechanism of DMN ~~activity, as found in DLB~~changes. In previous ~~studies[6,8]~~studies[16,20], the explanatory hypothesis for DMN enhancement in DLB, was that preserved DMN activity could depend on compensatory mechanisms attempting to maintain homeostatically

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DMN functions in the face of developing pathology. The hypothesis ~~suggested~~considered also that ~~the~~DMN activity is reduced in AD[5, 16] and suggested that in this condition a lack of compensatory mechanisms~~, inducing DMN activity reduction in AD, might~~ may depend ~~on~~upon the greater cellular loss which occurs in this disease.

~~As~~In MSA we ~~found~~observed decreased DMN activity, which was similar to reductions observed in ~~MSA~~AD[5,16], but we found no cellular loss, ~~we~~and this finding, again, supports our argument that functional modulatory mechanisms are relevant rather than structural differences.

Intriguingly a core question emerges from our data: does DMN power and connectivity represent a mere epiphenomenon, or might ~~conclude that our~~ be the key driver of the clinical phenotype?

By describing DMN findings ~~foster further~~in a previously unexplored disorder, our study adds a piece of information to this puzzle.

Limitations and future directions.

A possible limitation of our study can be identified in the selection method used for the three groups of PD patients. The sPD VH group was selected on the basis of the presence of complex VH, which were specifically addressed because of their intrinsic narrative qualities, as the role of DMN is considered to consist of a narrative introduction into experience[2,3]. IIn order to reduce confounding factors, however, neuropsychological and clinical test scores were carefully matched between groups, and presence of minor hallucinations was an exclusion criterion for all groups. Restricted group selections allowed for an outcome characterized by clear-cut statistical differences between groups, but could have concealed correlations between fMRI findings and clinical variables e.g. VH severity, anxiety, cognitive level.

In order to overcome this limitation, longitudinal evaluation investigating through time DMN function changes, at rest and during tasks, should clarify how and when DMN enhancement appears, and whether it is a gradual process or a critical outbreak, in the course of PD progression or whether alternatively, it is intrinsic to specific disease subtypes (i.e. it appears only in those PD patients with greater than average DMN activity from onset of their motor symptoms).

The evidence of DMN enhancement also invites to consider whether DMN activity is a possible target for the treatment of VH: for example direct or transcranial cortical stimulation of DMN areas could be considered among future treatment research~~, including assessments in different diseases, with different stages of disease~~[66] projects.

Pharmacological studies could also be designed in order to target DMN enhancement, by considering the neurotransmitters involved in cortico-cortical and thalamo-cortical projections to DMN.

We foresee, however, that the last will be a difficult task, as we know already that drugs which antagonize these glutamatergic projections, may induce[74-75], rather than reduce, VH.

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1. Research project: A. Conception, B. Organization, C. Execution;
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3. Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

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Figure 1.

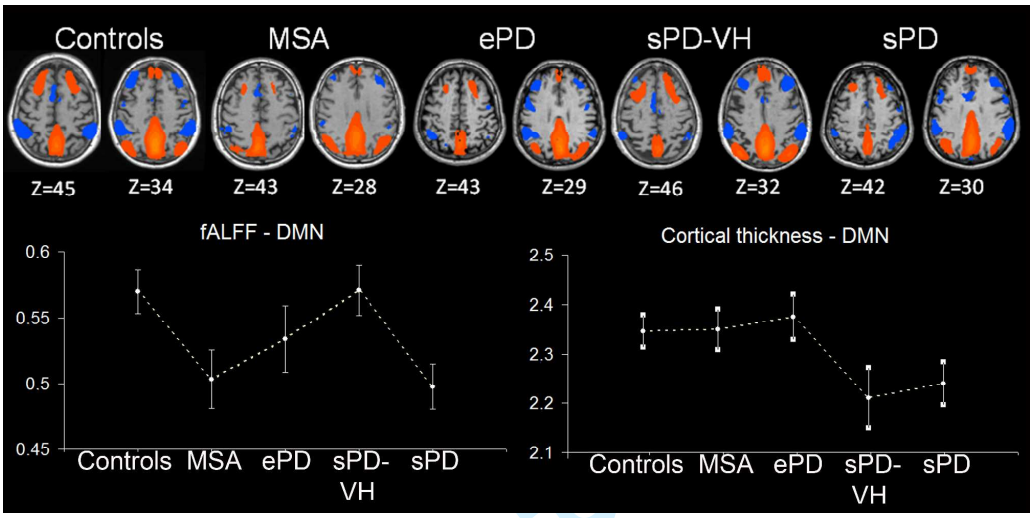


**Figure 1. Top.** Group-level ICA results representing DMN pattern for control, MSA, ePD, sPD-VH and sPD group. Maps were overlaid onto Talairach-transformed T1 image of a representative control, MSA, ePD, sPD-VH and sPD patient. Notice that DMN was clearly identified in each group.

**Bottom**. **Left:** Averaged power amplitudes of all DMN components, in each group. **Right:** averaged cortical thickness values of all DMN components in each group.

ePD = early Parkinson's Disease; MSA = Multiple System Atrophy; sPD = severe Parkinson's Disease without visual hallucinations; sPD-VH = severe PD with visual hallucinations.

Figure 2.

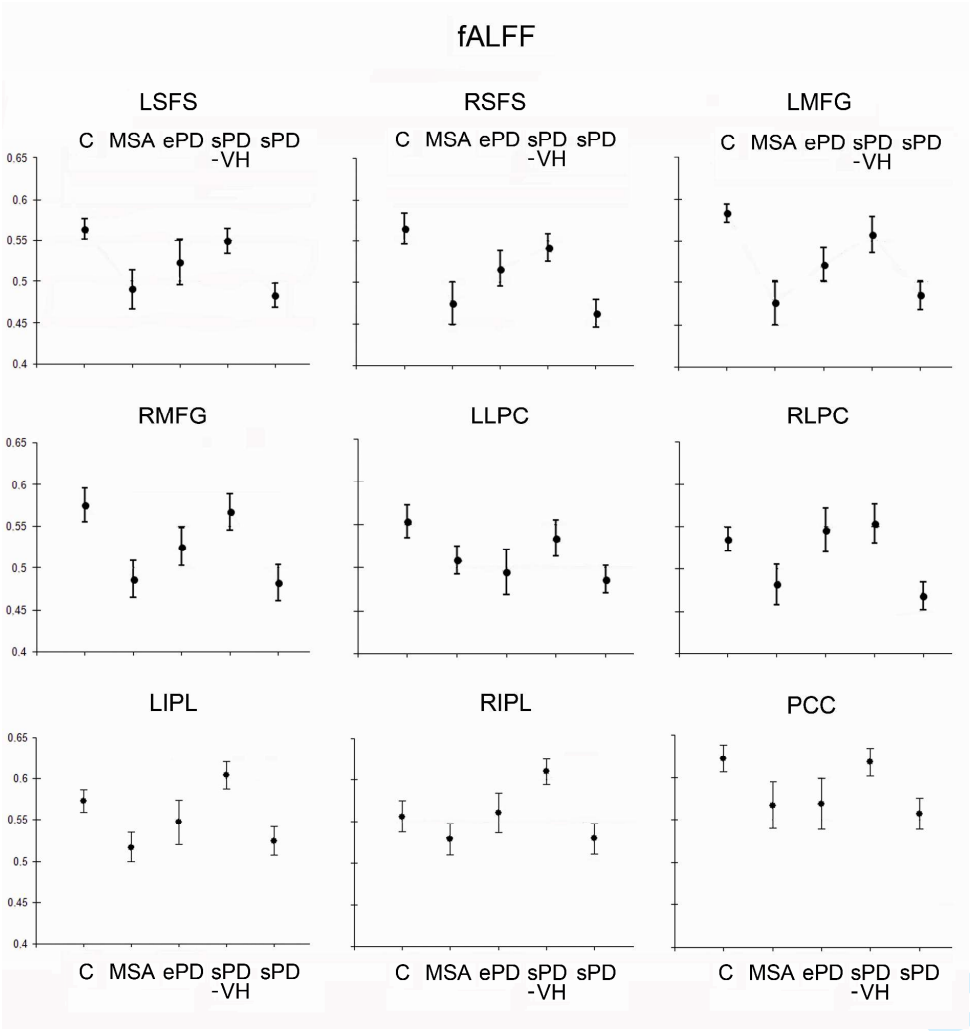


**Figure 2.** Mean fractional amplitude of low frequency fluctuations (fALFF) in the different DMN nodes, in controls, MSA, ePD, sPD-VH and sPD. Notice lower amplitude in MSA and sPD without VH, higher amplitude in sPD with VH, for all DMN nodes. Vertical bars indicate standard error. LIPL = Left Inferior Parietal Lobule; LLPC = Left Lateral Parietal Cortex; LMFG = Left Middle Frontal Gyrus; LSFS = Left Superior Frontal Sulcus; PCC = Posterior Cingulate Cortex; RIPL= Right Inferior Parietal Lobule; RLPC= Right Lateral Parietal Cortex; RMFG = Right Middle Frontal Gyrus; RSFS = Right Superior Frontal Sulcus; ePD = early Parkinson's Disease; sPD =

severe Parkinson's Disease without visual hallucinations; sPD-VH = severe PD with visual hallucinations; MSA = Multiple System Atrophy.

Figure 3.

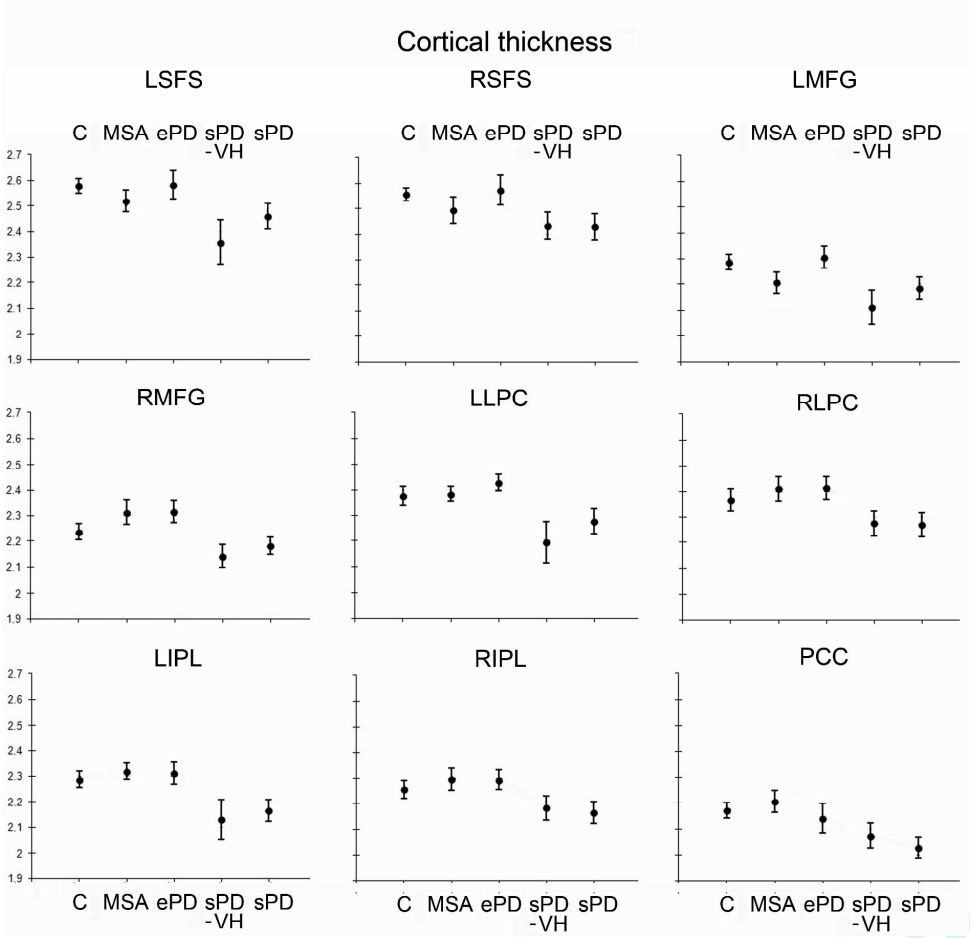


**Figure 3.** Mean cortical thickness values in the different DMN nodes, in controls, MSA, ePD, sPD-VH and sPD. Notice lower cortical thickness in sPD with and without VH. Vertical bars indicate standard error.

LIPL = Left Inferior Parietal Lobule; LLPC = Left Lateral Parietal Cortex; LMFG = Left Middle Frontal Gyrus; LSFS = Left Superior Frontal Sulcus; PCC = Posterior Cingulate Cortex; RIPL= Right Inferior Parietal Lobule; RLPC= Right Lateral Parietal Cortex; RMFG = Right Middle Frontal Gyrus; RSFS = Right Superior Frontal Sulcus; ePD = early Parkinson's Disease; sPD =

severe Parkinson's Disease without visual hallucinations; sPD-VH = severe PD with visual hallucinations; MSA = Multiple System Atrophy.

**Table 1** Clinical, Cognitive, Neuropsychological, Neuropsychiatric and anxiety features (mean ± SD) for Controls, MSA, ePD, sPD-VH and sPD.

| | Controls | MSA | ePD | sPD-VH | sPD |
|---|---|---|---|---|---|
| **AGE** | 69 ± 6 | 67 ± 5 | 66 ± 9 | 70 ± 6 | 68 ± 11 |
| **Education** | 9 ± 4 | 10 ± 5 | 9 ± 3 | 10 ± 4 | 10 ± 3 |
| **MMSE** | 28.7 ± 0.7 | 25.2 ± 1.7 | 26.2 ± 1.8 | 24.3 ± 2.2 | 24.7 ± 1.8 |
| **Disease duration** | n.a. | 3.9 ± 1.8 | 3.3 ± 1.6 | 11.3 ± 4.3 | 12.0 ± 4.5 |
| **UPDRSIII** | n.a. | 36.4 ± 7.6 | 17.7 ± 4.3 | 36.3 ± 8.2 | 35.6 ± 7.4 |
| **LDED** | n.a. | 655 ± 270 | 363 ± 190 | 636 ± 199 | 645 ± 210 |
| **H&Y** | n.a. | 3.2 ± 0.8 | 2.1 ± 0.4 | 3.0 ± 0.5 | 3.0 ± 0.6 |
| **DRS-2 Total** | n.a. | 128 ± 12 | 131 ± 6 | 125 ± 7 | 121 ± 16 |
| **NPI-VH** | n.a. | 0 ± 0 | 0 ± 0 | 6.3 ± 1.7 | 0 ± 0 |
| **NPI-E. Anxiety** | 0.5 ± 0.6 | 5.3 ± 2.4 | 5.0 ± 2.1 | 1.7 ± 0.9 | 2.6 ± 1.0 |
| **NPI-K. Sleep** | 0 ± 0 | 4.1 ± 1.7 | 3.9 ± 1.5 | 3.7 ± 1.7 | 4.1 ± 1.6 |
| **NPI-TOT** | 1.7 ± 2.0 | 24.6 ± 5.4 | 21.9 ± 6.8 | 17.3 ± 3.2 | 19.0 ± 2.0 |
| **FAB** | 15.8 ± 1.5 | 12.7 ± 3.3 | 14.3 ± 1.4 | 11.7 ± 3.5 | 12.7 ± 1.5 |
| **GDS** | 6.3 ± 1.3 | 8.9 ± 2.7 | 6.4 ± 1.5 | 8.8 ± 2.6 | 9.3 ± 2.7 |
| **BADS6E*** | 5.4 ± 0.5 | 3.8 ± 1.0 | 4.1 ± 1.2 | 4.0 ± 1.1 | 4.3 ± 1.0 |
| **Stai - State** | 14.5 ± 3.5 | 43.1 ± 8.0 | 41.1 ± 8.2 | 31.2 ± 5.7 | 37.8 ± 5.2 |
| **Stai -Trait** | 14.1 ± 5.0 | 39.9 ± 7.1 | 42.1 ± 6.6 | 30.9 ± 3.8 | 34.9 ± 5.3 |
| **UMSARS I** | n.a. | 24.2 ± 6.0 | n.a. | n.a. | n.a. |
| **UMSARS II** | n.a. | 27.6 ± 8.1 | n.a. | n.a. | n.a. |
| **UMSARS tot** | n.a. | 51.8 ± 12.9 | n.a. | n.a. | n.a. |
| ~~**SCOPA-AUT**~~ | ~~5.2 ± 2.0~~ | ~~20.9 ± 4.3~~ | ~~16.8 ± 2.3~~ | ~~19.4 ± 3.4~~ | ~~18.9 ± 4.0~~ |

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MMSE = Mini Mental State Examination; DRS-2 = Dementia Rating Scale – 2; FAB = Frontal Assessment Battery; GDS = Geriatric Depression Scale; Stai - State = State anxiety Inventory; Stai -Trait = Trait anxiety Inventory; BADS6E = Behavioural Assessment of the Disexecutive Syndrome; H&Y = Hoehn/Yahr Staging; LDED = Levo Dopa Equivalent Dose (mg); UMSARS = Unified Multiple System Atrophy Rating Scale; UPDRSIII = Unified Parkinson's Disease Rating Scale - subscale III; NPI = Neuropsychiatry Inventory; VH = visual hallucinations; ~~SCOPA-AUT = SCOPA-autonomic total scores; SD = standard deviation;~~ ePD = early Parkinson's Disease; sPD = severe Parkinson's Disease without visual hallucinations; sPD-VH = severe PD with visual hallucinations; MSA = Multiple System Atrophy; N/A = not applicable; n.s. = not significant; SD = standard deviation.

**Table 2** Significant statistical results from the comparison of FC values among groups

| Post-hoc comparisons | p | Brain connections | F(4,69) | p | Power |
|---|---|---|---|---|---|
| Controls > MSA | 0.005 | LSFS-LIPL | 6.47 | <0.001 | 0.99 |
| | 0.02 | LSFS-RIPL | 4.23 | 0.004 | 0.91 |
| | 0.02 | RSFS-LIPL | 6.48 | <0.001 | 0.99 |
| | <0.001 | RSFS-RIPL | 6.98 | <0.001 | 0.99 |
| | 0.02 | LMFG-RMFG | 3.52 | 0.01 | 0.84 |
| | 0.01 | LLPC-RLPC | 5.40 | <0.001 | 0.97 |
| | 0.001 | LIPL-RIPL | 5.26 | <0.001 | 0.96 |
| | 0.01 | LIPL-PCC | 7.11 | <0.001 | 0.99 |
| | 0.04 | RIPL-PCC | 5.13 | 0.01 | 0.96 |
| Controls > ePD | 0.006 | LSFS-LIPL | 6.47 | <0.001 | 0.99 |
| | 0.02 | LSFS-RIPL | 4.23 | 0.004 | 0.91 |
| | 0.02 | RSFS-LIPL | 6.48 | <0.001 | 0.99 |
| | 0.04 | RSFS-RIPL | 6.98 | <0.001 | 0.99 |
| | 0.02 | LMFG-RMFG | 3.52 | 0.01 | 0.84 |
| | 0.05 | LLPC-RLPC | 5.40 | <0.001 | 0.97 |
| Controls > sPD | <0.001 | LSFS-LIPL | 6.47 | <0.001 | 0.99 |
| | <0.001 | LSFS-RIPL | 4.23 | 0.004 | 0.91 |
| | <0.001 | LSFS-PCC | 3.97 | 0.006 | 0.89 |
| | <0.001 | RSFS-LIPL | 6.48 | <0.001 | 0.99 |
| | <0.001 | RSFS-RIPL | 6.98 | <0.001 | 0.99 |
| | <0.001 | RSFS-PCC | 6.33 | <0.001 | 0.99 |
| | 0.04 | LMFG-RMFG | 3.52 | 0.01 | 0.84 |
| | <0.001 | LLPC-RLPC | 5.40 | <0.001 | 0.97 |
| | 0.004 | LIPL-RIPL | 5.26 | <0.001 | 0.96 |
| | 0.002 | LIPL-PCC | 7.11 | <0.001 | 0.99 |
| | 0.003 | RIPL-PCC | 5.13 | 0.01 | 0.96 |
| Controls > sPD-VH | 0.02 | LMFG-RMFG | 3.52 | 0.01 | 0.84 |
| MSA < ePD | 0.007 | LIPL-RIPL | 5.26 | <0.001 | 0.96 |
| | 0.047 | LIPL-PCC | 7.11 | <0.001 | 0.99 |
| MSA > sPD | 0.03 | RSFS-LIPL | 6.48 | <0.001 | 0.99 |
| | 0.03 | RSFS-PCC | 6.33 | <0.001 | 0.99 |
| MSA < sPD-VH | 0.01 | LSFS-LIPL | 6.47 | <0.001 | 0.99 |
| | 0.01 | RSFS-RIPL | 6.98 | <0.001 | 0.99 |
| | 0.006 | LIPL-RIPL | 5.26 | <0.001 | 0.96 |
| | 0.002 | LIPL-PCC | 7.11 | <0.001 | 0.99 |
| | 0.04 | RIPL-PCC | 5.13 | 0.01 | 0.96 |
| ePD > sPD | 0.03 | RSFS-LIPL | 6.48 | <0.001 | 0.99 |
| | 0.04 | RSFS-RIPL | 6.98 | <0.001 | 0.99 |
| | 0.02 | RSFS-PCC | 6.33 | <0.001 | 0.99 |
| | 0.02 | LIPL-RIPL | 5.26 | <0.001 | 0.96 |
| | 0.01 | LIPL-PCC | 7.11 | <0.001 | 0.99 |
| ePD < sPD-VH | 0.01 | LSFS-LIPL | 6.47 | <0.001 | 0.99 |
| sPD < sPD-VH | <0.001 | LSFS-LIPL | 6.47 | <0.001 | 0.99 |
| | <0.001 | LSFS-RIPL | 4.23 | 0.004 | 0.91 |
| | 0.001 | LSFS-PCC | 3.97 | 0.006 | 0.89 |
| | <0.001 | RSFS-LIPL | 6.48 | <0.001 | 0.99 |
| | 0.002 | RSFS-RIPL | 6.98 | <0.001 | 0.99 |

| | | | | | |
|---|---|---|---|---|---|
| | <0.001 | RSFS-PCC | 6.33 | <0.001 | 0.99 |
| | 0.007 | LLPC-RLPC | 5.40 | <0.001 | 0.97 |
| | 0.02 | LIPL-RIPL | 5.26 | <0.001 | 0.96 |
| | <0.001 | LIPL-PCC | 7.11 | <0.001 | 0.99 |
| | 0.002 | RIPL-PCC | 5.13 | 0.01 | 0.96 |

MSA = Multiple System Atrophy; PD = Parkinson Disease; ePD = early Parkinson's Disease; sPD = severe Parkinson's Disease without visual hallucinations; sPD-VH = severe PD with visual hallucinations; LIPL = Left Inferior Parietal Lobule; LLPC = Left Lateral Parietal Cortex; LMFG = Left Middle Frontal Gyrus; LSFS = Left Superior Frontal Sulcus; PCC = Posterior Cingulate Cortex; RIPL= Right Inferior Parietal Lobule; RLPC= Right Lateral Parietal Cortex; RMFG = Right Middle Frontal Gyrus; RSFS = Right Superior Frontal Sulcus; FC = functional connectivity. P values from Duncan post-hoc group comparison and F, p values for the main effects. Notice that all significances are reported as higher values (>), but for MSA vs ePD and sPD-VH and for ePD and sPD vs sPD-VH, where significance is inverted (<).