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

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Movement Disorders

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 brains¹ and consists of a set of cortical regions, including medial prefrontal, posterior cingulate, and lateral inferior parietal cortex, intimately connected with limbic areas¹. Imaging studies showed that DMN areas deactivate during tasks and activate during rest¹⁻³, and it is posited that the DMN has roles in imagery production and incorporation of self referential information into consciousness^{2,3}.

The germinal studies⁴⁻⁵ 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 areas⁶⁻⁷. More recently the original DMN role, in self-referential information production, has been reconsidered in theoretical and review studies⁸⁻¹⁰ 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 etiology¹¹⁻¹³, 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 activity¹⁴⁻¹⁵.

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 Palsy¹⁸, a disease without VH. Conversely DMN connectivity enhancement was recently described in c9ORF72 mutation carriers¹⁹, 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 DMN²¹. 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 studies²², which were not focused to VH.

In PD, earlier studies described increased connectivity¹⁷ but more recent studies report only altered connectivity^{11, 12,13,23}. One study described altered connectivity in PD either with or without VH²⁴. 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 assessments²⁷⁻²⁸, 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 treatments²⁹⁻³⁰, 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.

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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 MSA³⁷, 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 declaration³⁸. 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 BBC³⁹. 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 patients⁴⁰. In MSA patients the Unified MSA Rating Scale (UMSARS) was also used⁴¹. ¹²³I-FP-CIT SPECT was performed in

all patients. MSA patients were diagnosed according to consensus criteria⁴² and presence of typical MRI alterations⁴³. 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 profiles⁵¹⁻⁵², and presence and frequency of RBD , evaluated according to previous studies⁵³⁻⁵⁴. 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 Scale⁵⁵, 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-dopa⁵⁶.

Autonomic symptoms were rated with SCOPA-AUT scale⁵⁷ reported in supporting Table 1 of the Supporting information file.

All patients were assessed for genetic origin of parkinsonism, according to previously reported methods⁵⁸.

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.

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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 conditions¹⁶ by means of T2*-weighted echo planar imaging with the following parameters: 16 bicommissural slices, 200 volumes, in-plane resolution = 3.75×3.75 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 30⁵⁹, 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 noise⁶⁰ 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 approach⁶¹. 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 used⁶².

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 clustering⁶³ 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 resolution⁶⁶.

Cortical brain regions affected by cortical thinning were classified by using the Desikan-Killiany Atlas⁶⁷ 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.

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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, Ldopa 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<0.05p<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 intrahemispheric 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.

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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 hyperconnectivity¹⁷, 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 studies¹¹⁻¹³. However we found enhanced DMN in sPD VH, which is at variance with the hypothesized linear correlation between decreased DMN activity and cognition¹¹⁻¹³, 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 study²⁴ 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 authors²⁴ found no differences in cortical thickness between patients with enhanced or reduced DMN activity, which is consistent with our

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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 disease⁷⁰⁻⁷¹. In contrast, previous studies which have used the voxel based morphometry technique have reported widespread abnormalities in MSA⁷². 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 others⁷³.

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).

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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 induce⁷⁴⁻⁷⁵, 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.

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- A. Antonini 1B, 3B.
- M. Onofrj 1A, 2C, 3A, 3B.



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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. 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 =

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





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 =

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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 \pm

SD) for Controls, MSA, ePD, sPD-VH and	l sPD.
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	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	n 0				
duration	11.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. Page 31 of 88

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

Post-hoc comparisons	ost-hoc comparisons p Brain connections		F(4,69)	р	Power
	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
Controls > MSA	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
	0.006	LSFS-LIPL	6.47	< 0.001	0.99
	0.02	LSFS-RIPL	4.23	0.004	0.91
Controls > aDD	0.02	RSFS-LIPL	6.48	< 0.001	0.99
Controls > ePD	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
	< 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
Controls > sPD	< 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
	0.007	LIPL-RIPL	5.26	< 0.001	0.96
MSA < ePD	0.047	LIPL-PCC	7.11	< 0.001	0.99
	0.03	RSFS-LIPL	6.48	< 0.001	0.99
MSA > sPD	0.03	RSFS-PCC	6.33	< 0.001	0.99
	0.01	LSFS-LIPL	6.47	< 0.001	0.99
	0.01	RSFS-RIPL	6.98	< 0.001	0.99
MSA < sPD-VH	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
	0.03	RSFS-LIPL	6.48	< 0.001	0.99
	0.04	RSFS-RIPL	6.98	< 0.001	0.99
ePD > sPD	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
· · · ·	< 0.001	LSFS-LIPL	6.47	< 0.001	0.99
	< 0.001	LSFS-RIPL	4.23	0.004	0.91
sPD < sPD-VH	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 (<).





83x41mm (300 x 300 DPI)







170x180mm (300 x 300 DPI)





154x150mm (300 x 300 DPI)
Table 1 Clinical, Cognitive, Neuropsychological, Neuropsychiatric and anxiety features (mean \pm

AGE Education	69 ± 6 9 ± 4 28.7 ± 0.7	$\begin{array}{c} 67\pm5\\ 10\pm5 \end{array}$	66 ± 9	70 ± 6	68 + 11
Education	9 ± 4 28 7 ± 0 7	10 ± 5			00 ± 11
	28.7 ± 0.7		9 ± 3	10 ± 4	10 ± 3
MMSE	20.7 ± 0.7	25.2 ± 1.7	26.2 ± 1.8	24.3 ± 2.2	24.7 ± 1.8
Disease	n 0				
duration	II.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	$1.7\ \pm 0.9$	$2.6\ \pm 1.0$
NPI-K. Sleep	0 ± 0	4.1 ± 1.7	$3.9\ \pm 1.5$	$3.7 \hspace{0.1in} \pm 1.7$	$4.1 \hspace{0.1in} \pm \hspace{0.1in} 1.6$
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	$4.3\ \pm 1.0$
Stai - State	14.5 ± 3.5	43.1 ± 8.0	41.1 ± 8.2	$31.2\pm~5.7$	37.8 ± 5.2
Stai -Trait	14.1 ± 5.0	$39.9\ \pm 7.1$	42.1 ± 6.6	$30.9\ \pm 3.8$	$34.9\ \pm 5.3$
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.

SD) for Controls, MSA, ePD, sPD-VH and sPD.

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	р	Brain connections	F(4,69)	р	Power
	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
Controls > MSA	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
	0.006	LSES-LIPL	6.47	<0.01	0.99
	0.02	LSFS-RIPL	4.23	0.004	0.91
~	0.02	RSFS-LIPL	6.48	< 0.001	0.99
Controls > ePD	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
	< 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
Controls > sPD	< 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
	0.01	LSFS-LIPL	6.47	< 0.001	0.99
	0.01	RSFS-RIPL	6.98	< 0.001	0.99
MSA < sPD-VH	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
	0.03	RSFS-LIPL	6.48	< 0.001	0.99
	0.04	KSFS-KIPL	6.98	<0.001	0.99
ePD > sPD	0.02	KSFS-PCC	6.33 5.20	<0.001	0.99
	0.02	LIFL-KIFL	J.20 7 1 1	<0.001	0.90
	0.01		6.17	<0.001	0.99
CLD < 200-14	0.01	LOFO-LIPL	6 17		0.99
sPD < sPD-VH	<0.001	LOFO-LIFL I SES DIDI	0.47 1 72	<0.001 0.004	0.99
	<0.001	LJLJ-KILL	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.

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 Statistical diff	n.s.	n.s.	n.s.	$0.1*10^{-3}$	n.s.	n.s.	n.s.	$0.7*10^{-2}$	n.s. $22 \text{ p} < 10^{-4}$	n.s.	n.s.

Statistical differences across groups for MMSE (F(4, 70)=16.10 p<10⁻¹), disease duration (F(3,56)=29.82 p<10⁻¹), 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	р
	LSFS	0.042
Controlo > MSA	RSFS	0.011
Controls > MSA	LMFG	0.002
	RMFG	0.013
	LSFS	0.025
Controls > gDD	RSFS	0.003
Controls > SPD	LMFG	0.005
	RMFG	0.010
	LMFG	0.023
	RMFG	0.025
SFD-VH/MSA	RLPC	0.048
	LIPL	0.006
	RIPL	0.015
ePD>sPD	RLPC	0.030
	RSFS	0.026
	LMFG	0.044
sPD-VH>sPD	RMFG	0.019
	RLPC	0.017
	LIPL	0.015
	RIPL	0.016
sPD-VH>sPD	RSFS LMFG RMFG RLPC LIPL RIPL	0.026 0.044 0.019 0.017 0.015 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	LSFS	RSFS	LMFG	RMFG	LLPC	RLPC	LIPL	RIPL	PCC
comparisons									
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-	0.014	n.s.	0.016	0.009	0.022	0.045	0.016	n.s.	0.042
VH									
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	р
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 comparisonstudy, R. Franciotti, PhD^{a,b}, S. Delli Pizzi, PhD^{a,b}, B. Perfetti, PhD^a, A. Tartaro, MD^{a,b}, L. Bonanni, MD^a, A. Thomas, MD^a, L. Weis, PhD^c, R. Biundo, PhD^c, A. Antonini, MD^c, M. Onofrj, MD^{a,*} ^aDepartment of Neuroscience, Imaging and Clinical Sciences, "G. d'Annunzio" University and Aging Research Centre, Ce.S.I., "G. d'Annunzio" University Foundation, Chieti, Italy ^bITAB, "G. d'Annunzio" University Foundation, Chieti, Italy ^cDepartment for Parkinson's Disease, "Fondazione Ospedale San Camillo", I.R.C.C.S., Venice, Italy. * Corresponding author Prof. Marco Onofrj Department of Neuroscience, Imaging and Clinical Sciences, "G. d'Annunzio" University, Via dei Vestini 33 66100 Chieti, Italy Ph:+39 0871358525; Fax:+39 0871562019 e-mail: onofrj@unich.it Disclosure statement for authors: None of the authors declare conflict of interest concerning the research related to the manuscript. Word count: 30233698 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 wasand 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 <u>Cortical thickness was</u> 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, eitherPD, with orand 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 Formatted: English (U.S.)

<text><text><text> 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.

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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 eonsciousness 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
HallucinationsVH [?] 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, 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 activitycontroversial ^{11,14,16,20} . Preserved activity has been observed in	
Posterior Cingulate Cortex, (the so called "Cingulate Island Sign") a main hub of DMNDMN ²¹ .	
Increased or preserved (compared to controls) DMN activity or disinhibitionreduced 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 interactionsmore recent	Formatted: Superscript
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 VH¹⁵VH²⁴,	Formatted: Font color: Auto
A <u>Therefore the link between VH and DMN activity in Parkinsonisms, is a controversial issue.</u>	
One possible way to clarify the controversy could beis to compare DMN activity/-connectivity in	
patients with different types of parkinsonisms, definitelyparkinsonism, in those with VH andor	
without VHthe presence of definite VH, as any evaluation includingrestricted 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.	

Movement Disorders

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 elinical criteria for the diagnosis of PD"¹⁹⁻²⁰. These and other studies²¹⁻²²Cohort studies with neuropathological assessments²⁷⁻²⁸, evidenced that a **Formatted:** Not Superscript/ Subscript diagnosis of Multiple System Atrophyatrophy (MSA) could be excluded if VH occurred during the disease course, and thus that MSA is the proper presents an archetype of -parkinsonism without VH. MSA is also a proper target for comparison with, moreover, an appropriate disease comparator to PD, unlike other parkinsonismsParkinson related disorders, because in MSA there is a responseresponsivity, albeit reduced, to dopaminergic treatments²³⁻²⁴, which are administered in patients and could betreatments²⁹⁻³⁰, and thus make an ideal control comparator disease to PD, and because in MSA, REM Sleep Behavior Disorder-RBD, considered for proper matchingpossibly linked to PD VH^{10,31-32,33}, is common. We hypothesized therefore that a study of DMN resting state activity in MSA could 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 rates²⁴⁻²⁵, and occurrence of VH mostly in patients with longer disease durations¹⁶⁻¹⁸-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

> 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 comparisoncomparisons and matching<u>therefore</u>, in summary, can address three<u>two</u> interdependent aims: 1) evaluateevaluation of DMN activity in MSAMSA³⁷, in comparison with controls and PD, 2) testtesting 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 declaration²⁶-declaration³⁸, 15 healthy elderly controls, 15 MSA (type P), 15 PD patients matched with MSA for disease duration (ePD), <u>1530</u> PD patients matched with MSA for severity of symptoms and equivalent treatments; <u>(15</u> without VH (sPD) and 15 PD, equally matched with MSA, presenting-with VH (sPD-VH))) were selected to participate in the study, from <u>two</u> cohorts of 650 PD and 72 MSA patients. PD was diagnosed according to UK <u>BBC²⁷BBC³⁹</u>. 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 patients²⁸ patients⁴⁰. In MSA patients the Unified MSA Rating Scale (UMSARS) was also used²⁹. Dopaminergic presynaptic ligand ioflupane SPECT (<u>used⁴¹</u>. ¹²³I-FP-CIT SPECT) was performed in all patients. MSA patients were diagnosed according to consensus eriteria³⁹ criteria⁴² and presence of typical MRI alterations³⁴ alterations⁴³.

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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 $(DRS2)^{\frac{3244}{2}}$, the Frontal Assessment Battery (FAB)³³⁴⁵, the Behavioural Assessment of the DisexecutiveDysexecutive Syndrome (BADS6E) $\frac{34-35}{5}$, the Neuropsychiatric Inventory (NPI) $\frac{3648}{5}$, the Geriatric Depression Scale (GDS) $\frac{3749}{3850}$ and the State-Trait anxiety Inventory (STAI) $\frac{3850}{3850}$. ePD, sPD and sPD-VH were carefully matched with MSA patients for neuropsychological profiles^{39.40} profiles⁵¹⁻⁵², and presence and frequency of Rem Sleep Behavior Disorder (RBD),_____</sup> evaluated according to previous studies⁴¹⁻⁴² studies⁵³⁻⁵⁴. VH were investigated with semistructured interviews and were rated with the NPI items and onlyspecific item. Only patients with complex kinematic hallucinations, according to tentative classifications of $\frac{VH^{17-18}-VH^{9,26}}{VH^{9,26}}$ and to Parkinson Psychosis Scale⁵⁵, 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, entecaponeentacapone, 6 ePD and 6 MSA patients received dopaminoagonist doses equivalent to 100mg/day of L-dopa43-44-45-46 dopa56. Autonomic symptoms were rated with SCOPA-AUT scale⁵⁷ reported in supporting Table1 inTable 1 of the Supporting information file. All patients were assessed for genetic origin of parkinsonism, according to methods previously reported⁴⁸reported methods⁵⁸. All patients were followed for 2-4 years after functional MRI (fMRI) acquisitions in order to confirm, challenge diagnosis.

To attempt<u>ensure</u> 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<u>Table</u> 1 reports the demographic, neuropsychological and neuropsychiatric variables for<u>of</u> the five groups. Obvious statistical differences were dependent on disease duration or severity and are detailed in supporting Table2 in the Supporting information file.

2.2 Image acquisition

MRI images of participants<u>data</u> were acquired with Philips scanners at 1.5 T,_24 hours after <u>treatment</u> withdrawal of treatment. Subjects were inscanned during resting state conditions⁶ and were scanned<u>conditions¹⁶</u> by means of T2*-weighted echo planar imaging with the following parameters: 16 bicommissural slices, 200 volumes, in-plane resolution = 3.75×3.75 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

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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 eoursecourses with the corresponding IC waveformwaveforms. ICs corresponding to noise based on spatial patterns and temporal frequency⁵⁰-noise⁶⁰ were removed. Coactivation of the posterior cingulate cortex and(PCC), the left/right lateral parietal cortex (RLPC, LLPC), left/right inferior parietal lobuleslobule (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 approach⁵⁺approach⁶¹. 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 timeeourse 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 used⁶²-used⁶².

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 clustering⁵³clustering⁶³ was applied for each group to obtain group spatial maps.

2.4 Cortical thickness analysis

Cortical thickness was estimated on T₁-weighted image using Freesurfer software package (http://surfer.nmr.mgh.harvard.edu), calculating thickness in a tessellated model of the cortical surface⁵⁴, 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 surface⁵⁵-,).^{64,65} Cortical thickness measurements were obtained by reconstructing representations of the gray/white Formatted: English (U.S.) Formatted: English (U.S.) Formatted: English (U.S.)

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 resolution⁵⁶resolution⁶⁶. Cortical brain regions affected by cortical thinning were classified by using the Desikan-Killiany

Atlas⁵⁷<u>Atlas⁶⁷</u> integrated in FreeSurfer. The "aparcstats2table" command line was used to calculate the mean cortical thickness within theDMN 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 \leftarrow 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.

<u>Spearman's correlation, Bonferroni corrected, was performed between fMRI outcomes and</u> <u>neuropsychological-clinical scores .</u> <u>QDEC (https:// surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/QdecGroupAnalysis_freeview) was</u>

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, Ldopa 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 patientssubjects are detailed in fig.-2;: the main effects 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 areas₅₅ 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 intrahemispheric 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 <u>file).</u>

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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 <u>linof</u> 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
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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 functions⁵⁹⁻⁶⁰, 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 hyperconnectivity¹⁷, 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 studies¹¹⁻¹³. However we found enhanced DMN in sPD VH, which is at variance with the hypothesized linear correlation between decreased DMN activity and cognition¹¹⁻¹³, as our patients with VH were just as cognitively impaired as our patients without VH (table 1). Thus we

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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
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<u>th</u>	at MSA patients and PD patients without VH, who had altered and reduced DMN functions
hi	gher anxiety scores than controls and patients with VH. Activity-connectivity and anxiety s
W	ere not correlated with cortical thickness, suggesting that this phenomenological aspect is a
de	ependent on functional modulation, rather than on morphometric differences.
0	ur results, therefore, are different from results obtained with the limited voxel based morph
ŧe	chniques, which showed widespread abnormalities ⁶¹⁻⁶⁴ . We hypothesize that differences are
te	chnology limitations of voxel based morphometry, needing correction algorithms ^{59,65} -
di	fferent disease durations of MSA ⁶¹⁻⁶⁴ -
A	s a final conclusion we underline that the present study considers DMN for its origin
ee	meeived in germinal studies ³ , i.e. as a resting network linked to limbic structures, introduc
re	ferential narratives into experience.
₩	Ve believe that its role in the occurrence of VH is supported by the present findings,-
h	pothesize that the narrative role of DMN is a likely explanation for the complex halluci
₩	ith florid narratives reported by PD patients ¹⁶⁻¹⁸ .
₿	eyond a role in VH, DMN activity inhibition or facilitation may explain the occurr
di	fferent clinical phenotypes, compatible with hypotheses on DMN functions, but or
ee	onfusional hallucinatory expression due to disinhibition, one with hyperarousal and con
a ę	gitation, anxiety or even acatisia due to DMN over-inhibition.
Ŧ	his hypothesis was suggested in a previous study comparing DLB and AD patients ⁶ ,
sı	uggest that one finding of our comparative study could be interpreted as supportive
h	ypothesis. MSA patients, ePD and sPD without VH, all with reduced DMN activ
ee	mnectivity, have higher anxiety scores than sPDVH with preserved DMN activity (Table 1)
θ	ur findings in MSA, finally, challengefinding challenges previous attempts to explain
m	aintenance or increase the mechanism of DMN activity, as found in DLB changes. In previo
et	$\frac{1}{1000}$ $\frac{1}{1000}$ the explanatory hypothesis for DMN enhancement in DLB was that pre-
51	adies <u>studies</u> , the explanatory hypothesis <u>tor Divity enhancement in DED</u> , was that pre

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7 8	DMN functions in the face of developing pathology. The hypothesis suggested considered also that
9	the DMN activity is reduced in AD ^{5, 16} and suggested that in this condition a lack of compensatory
10 11	mechanisms, inducing DMN activity reduction in AD, might may depend on upon the greater
12 13	cellular loss which occurs in this disease.
14 15	AsIn MSA we foundobserved decreased DMN activity, which was similar to reductions observed in
16 17	MSAAD ^{5,16} , but we found no cellular loss, we and this finding, again, supports our argument that
18 19	functional modulatory mechanisms are relevant rather than structural differences.
20 21	Intriguingly a core question emerges from our data: does DMN power and connectivity represent a
22	mere epiphenomenon, or might eonelude that our be the key driver of the clinical phenotype?
23 24	By describing DMN findings foster furtherin a previously unexplored disorder, our study adds a
25 26	piece of information to this puzzle.
27 28	Limitations and future directions.
29 30	A possible limitation of our study can be identified in the selection method used for the three groups
31 32	of PD patients. The sPD VH group was selected on the basis of the presence of complex VH,
33 34	which were specifically addressed because of their intrinsic narrative qualities, as the role of DMN
35 36	is considered to consist of a narrative introduction into experience ^{2,3} . IIn order to reduce
37 38	confounding factors, however, neuropsychological and clinical test scores were carefully matched
39 40	between groups, and presence of minor hallucinations was an exclusion criterion for all groups.
41 42	Restricted group selections allowed for an outcome characterized by clear-cut statistical differences
43	between groups, but could have concealed correlations between fMRI findings and clinical
44 45	variables e.g. VH severity, anxiety, cognitive level.
46 47	In order to overcome this limitation, longitudinal evaluation investigating through time DMN
48 49	function changes, at rest and during tasks, should clarify how and when DMN enhancement
50 51	appears, and whether it is a gradual process or a critical outbreak, in the course of PD progression or
52 53	whether alternatively, it is intrinsic to specific disease subtypes (i.e. it appears only in those PD
54 55	patients with greater than average DMN activity from onset of their motor symptoms).
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Movement Disorders

The evidence of DMN enhancement also invites to consider whether DMN activity is a possible	Formatted: Normal, Line spacing: Doub Tab stops: Not at 1.63"
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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Documentation of Author Roles	Formatted: English (U.S.)
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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S. Delli Pizzi: 1C.	
B. Perfetti: 2A, 2B.	
A. Tartaro 3B.	
L. Bonanni 1B, 3B.	
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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. 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 =

.; sPD-ν. severe Parkinson's Disease without visual hallucinations; sPD-VH = severe PD with visual

hallucinations; MSA = Multiple System Atrophy.



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 =

.; sPD-v severe Parkinson's Disease without visual hallucinations; sPD-VH = severe PD with visual

hallucinations; MSA = Multiple System Atrophy.

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sPD-VH

 70 ± 6

 10 ± 4

 24.3 ± 2.2

 11.3 ± 4.3

 36.3 ± 8.2

 636 ± 199

 3.0 ± 0.5

 125 ± 7

 6.3 ± 1.7

 1.7 ± 0.9

 3.7 ± 1.7

 17.3 ± 3.2

 11.7 ± 3.5

 8.8 ± 2.6

 4.0 ± 1.1

 31.2 ± 5.7

 30.9 ± 3.8

n.a.

n.a.

n.a.

 $\frac{19.4 \pm 3.4}{19.4 \pm 3.4}$

sPD

 68 ± 11

 10 ± 3

 24.7 ± 1.8

 12.0 ± 4.5

 35.6 ± 7.4

 645 ± 210

 3.0 ± 0.6

 121 ± 16

 0 ± 0

 2.6 ± 1.0

 4.1 ± 1.6

 19.0 ± 2.0

 12.7 ± 1.5

 9.3 ± 2.7

 4.3 ± 1.0

 37.8 ± 5.2

 34.9 ± 5.3

n.a.

n.a.

n.a.

 $\frac{18.9 \pm 4.0}{18.9 \pm 4.0}$

3 4 5 6 7 **Table 1** Clinical, Cognitive, Neuropsychological, Neuropsychiatric and anxiety features (mean \pm 8 9 SD) for Controls, MSA, ePD, sPD-VH and sPD. 10 11 MSA Controls 12 13 AGE 69 ± 6 67 ± 5 66 ± 9 14 Education 9 ± 4 10 ± 5 MMSE 28.7 ± 0.7 25.2 ± 1.7 26.2 ± 1.8 15 Disease 16 n.a. 3.9 ± 1.8 duration 17 UPDRSIII n.a. 36.4 ± 7.6 18 655 ± 270 LDED n.a. 19 H&Y 3.2 ± 0.8 n.a. 20 DRS-2 Total 128 ± 12 n.a. 21 NPI-VH n.a. 0 ± 0 22 NPI-E. Anxiety 0.5 ± 0.6 5.3 ± 2.4 23 NPI-K. Sleep 0 ± 0 4.1 ± 1.7 24 NPI-TOT 1.7 ± 2.0 24.6 ± 5.4 25 $12.7\ \pm 3.3$ FAB 15.8 ± 1.5 26 GDS 6.3 ± 1.3 8.9 ± 2.7 27 BADS6E* 5.4 ± 0.5 3.8 ± 1.0 28 Stai - State 14.5 ± 3.5 43.1 ± 8.0 41.1 ± 8.2 29 Stai -Trait 14.1 ± 5.0 39.9 ± 7.1 42.1 ± 6.6 30 UMSARS I n.a. 24.2 ± 6.0 31 UMSARS II n.a. 27.6 ± 8.1 51.8 ± 12.9 **UMSARS** tot 32 n.a. SCOPA-AUT 5.2 ± 2.0 $\frac{20.9 \pm 4.3}{100}$ 16.8 33 MMSE = Mini Mental State Examination; DRS-2 = Dementia Rating Scale -2; FAB = Frontal 34 35 Assessment Battery; GDS = Geriatric Depression Scale; Stai - State = State anxiety Inventory; Stai 36 37 -Trait = Trait anxiety Inventory; BADS6E = Behavioural Assessment of the Disexecutive 38 39 Syndrome; H&Y = Hoehn/Yahr Staging; LDED = Levo Dopa Equivalent Dose (mg); UMSARS = 40 41 Unified Multiple System Atrophy Rating Scale; UPDRSIII = Unified Parkinson's Disease Rating 42 43 Scale - subscale III; NPI = Neuropsychiatry Inventory; VH = visual hallucinations; SCOPA AUT = 44 45 SCOPA-autonomic total scores; SD = standard deviation; ePD = early Parkinson's Disease; sPD = 46 47 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.

 3.3 ± 1.6 17.7 ± 4.3 363 ± 190 2.1 ± 0.4 131 ± 6 0 ± 0 5.0 ± 2.1 3.9 ± 1.5 21.9 ± 6.8 14.3 ± 1.4 6.4 ± 1.5 4.1 ± 1.2

ePD

 9 ± 3

n.a.

n.a.

n.a.

+ 23

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Post-hoc comparisons	р	Brain connections	F(4,69)	р	Powe
	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	0.9
Controls > MSA	0.02	LMFG-RMFG	3.52	0.01	0.84
	0.01	LLPC-RLPC	5.40	< 0.001	0.9
	0.001	LIPL-RIPL	5.26	< 0.001	0.9
	0.01	LIPL-PCC	7.11	< 0.001	0.9
	0.04	RIPL-PCC	5.13	0.01	0.9
	0.006	LSFS-LIPL	6.47	< 0.001	0.9
	0.02	LSFS-RIPL	4.23	0.004	0.9
	0.02	RSFS-LIPL	6.48	< 0.001	0.9
Controls > ePD	0.04	RSFS-RIPL	6.98	< 0.001	0.9
	0.02	LMFG-RMFG	3.52	0.01	0.84
	0.05	LLPC-RLPC	5.40	< 0.001	0.9
	< 0.001	LSFS-LIPL	6.47	< 0.001	0.9
	< 0.001	LSFS-RIPL	4.23	0.004	0.9
	< 0.001	LSFS-PCC	3.97	0.006	0.89
	< 0.001	RSFS-LIPL	6.48	< 0.001	0.9
	< 0.001	RSFS-RIPL	6.98	< 0.001	0.9
Controls > sPD	< 0.001	RSFS-PCC	6.33	< 0.001	0.9
	0.04	LMFG-RMFG	3.52	0.01	0.84
	< 0.001	LLPC-RLPC	5.40	< 0.001	0.9
	0.004	LIPL-RIPL	5 26	< 0.001	0.96
	0.002	LIPL-PCC	7 11	< 0.001	0.9
	0.002	RIPL-PCC	5 13	0.01	0.90
Controls > sPD-VH	0.02	LMFG-RMFG	3 52	0.01	0.84
	0.02	LIPL-RIPL	5.26	< 0.01	0.0
MSA < ePD	0.007	LIPL-PCC	7 11	< 0.001	0.9
	0.03	RSFS-LIPL	6.48	<0.001	0.99
MSA > sPD	0.03	RSFS-PCC	6 33	<0.001	0.9
	0.03	I SES-LIPI	6.47	<0.001	0.99
	0.01	RSES_RIPI	6.98	<0.001	0.9
MSA < sPD-VH	0.01	I IPI -RIPI	5.26	<0.001	0.9
	0.000	LIPL-PCC	7 11	<0.001	0.90
	0.002	RIPL-PCC	5.13	0.001	0.9
	0.04	RES I IDI	6.48	<0.01	0.7
	0.03	RSFS PIDI	6.98	<0.001	0.92
aDD > aDD	0.04	DSES DCC	6.23	<0.001	0.9
erD > srD	0.02		5.26	<0.001	0.9
	0.02	LIFL-KIFL	5.20 7.11	<0.001	0.90
	0.01		6.47	<0.001	0.95
CLD ~ SLD-AU	0.01		6.47	<0.001	0.9
	<0.001	LOF O-LIFL	0.4/	<0.001 0.004	0.9
	<0.001	LOFO-KIPL	4.23	0.004	0.9
SPD ~ SPD-VH	0.001	LOFO-FUU	5.91		0.8
	< 0.001	KOFS-LIPL	0.48	< 0.001	0.95
	0.002	KSFS-KIPL	6.98	<0.001	0.99

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< 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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