



Large-scale network dysfunction in α -Synucleinopathy: A meta-analysis of resting-state functional connectivity

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Summary

Background Although dysfunction of large-scale brain networks has been frequently demonstrated in patients with α -Synucleinopathy (α -Syn, i.e., Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy), a consistent pattern of dysfunction remains unclear. We aim to investigate network dysfunction in patients with α -Syn through a meta-analysis.

Methods Whole-brain seed-based resting-state functional connectivity studies (published before September 1st, 2020 in English) comparing α -Syn patients with healthy controls (HC) were retrieved from electronic databases (PubMed, Web of Science, and EMBASE). Seeds from each study were categorized into networks by their location within a priori functional networks. Seed-based effect size mapping with Permutation of Subject Images analysis of between-group effects identified the network systems in which α -Syn was associated with hyperconnectivity (increased connectivity in α -Syn vs. HC) or hypoconnectivity (decreased connectivity in α -Syn vs. HC) within and between each seed-network. This study was registered on PROSPERO (CRD42020210133).

Findings In total, 136 seed-based voxel-wise resting-state functional connectivity datasets from 72 publications (3093 α -Syn patients and 3331 HC) were included in the meta-analysis. We found that α -Syn patients demonstrated imbalanced connectivity among subcortical network, cerebellum, and frontal parietal networks that involved in motor functioning and executive control. The patient group was associated with hypoconnectivity in default mode network and ventral attention network that involved in cognition and attention. Additionally, the patient group exhibited hyperconnectivity between neural systems involved in top-down emotion regulation and hypoconnectivity between networks involved in bottom-up emotion processing.

Interpretation These findings supported neurocognitive models in which network dysfunction is tightly linked to motor, cognitive and psychiatric symptoms observed in α -Syn patients.

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Keywords: α -Synucleinopathy; Resting-state functional connectivity; Meta-analysis; Brain networks; Parkinson's disease; Dementia with lewy body

Introduction

α -Synucleinopathy (α -Syn) refer to a series of neurodegenerative diseases, including Parkinson's disease (PD),

dementia with Lewy bodies (DLB), and multiple system atrophy (MSA).¹ The neuropathology of α -Syn is complicated as α -synuclein aggregation widely distributes across the brain from the brainstem to subcortical and cortical regions, which is aptly reflected by their protean clinical manifestations including motor, mood,

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Research in context

Background of previous research

α -Synucleinopathy (α -Syn) refer to a series of neurodegenerative diseases, including Parkinson's disease, dementia with Lewy bodies, and multiple system atrophy. Previous studies referring dysfunctions in large-scale functional networks in α -Syn patients have been implicated in motor, cognitive and emotional dysregulation, which may contribute to the clinical symptoms of α -Syn.

Added value of this study

Through a meta-analytic overview of 72 resting state functional connectivity studies, our study clarified the dysfunction of brain networks in α -Syn patients, which implicated widespread abnormal crosstalk across brain networks involved in motor, cognition, attention, and emotion.

Implications of the available evidence

These findings provide an empirical foundation for neurodegenerative models in which network dysfunctions underlie motor, cognitive and psychiatric symptoms in α -Synucleinopathy patients, which also suggests development of subsequent precision intervention (such as neuromodulation) targeting specific brain networks to ameliorate corresponding symptoms.

cognitive, behavioral, and autonomic disturbances. However, it remains unclear on how the neuropathology would correlate to the various symptoms complex.²

During recent years, studies detecting functional brain networks using resting-state functional magnetic resonance imaging (rs-fMRI) by analyzing the temporal correlations in blood oxygen level dependent (BOLD) signal between pairs of brain regions are well established in neuroscience and neurodegenerative diseases.³ The most prominent example is the default mode network (DMN)-involved in self-reference, spontaneous cognition and aspects of consciousness,⁴ the frontoparietal network (FPN) – associated with numerous aspects of cognitive control,⁵ the somatomotor network (SMN) – relevant for motor execution and somatosensory components,^{3,5} and some other networks such as dorsal and ventral attention networks (DAN and VAN) – dynamic control of attention,⁶ and visual network (VIS).⁶ Dysfunctions within and between these networks give rise to the symptoms that characterize neuropsychiatric disorders.

In evaluating disturbances of functional networks in the three α -Syn diseases, seed-based resting-state functional connectivity (rsFC) is the most commonly used method. However, substantial spatial variance of seeds selection and varying seeds definition in different

studies limit the establishment of coherent framework of network functioning in these diseases. A strategy raised by Kaiser and colleagues is categorizing seeds and related findings into a prior functional network parcellation⁶ based on their spatial locations, which is helpful to organize the various findings across studies to allow for direct replication and comparison.⁷ Apart from inconsistency of network selection, there is also a large variability across studies including sample size, medication, and clinical heterogeneity.⁸ Meta-analysis is an effective way to overcome the diversity and inconsistency of previously published work. To our knowledge, there was only one existing meta-analysis of seed-based rsFC studies for PD, which only focused on the corticobasal ganglia – thalamocortical network and motor dysfunction⁹ but no similar work for the less common α -Syn disorders, DLB and MSA.

Because of the large overlapping in pathology and clinical symptoms such as motor, cognitive, behavioural, and autonomic domains across the three α -Syn disorders, clinical differentiation among them remains a problematic diagnostic dilemma.¹⁰ It is increasingly recognized that existing clinical diagnostic categories may hinder the search for biomarkers in neuropsychiatric diseases because they are not clearly associated with distinct neurobiological abnormalities.¹¹ Therefore, we proposed that from the functional networks point of view to build trans-diagnostic network dysfunction patterns across α -Syn to understand clinical perspectives, instead of the rigid diagnostic categories of α -Syn, is one way to address this issue. This also emphasizes the need to examine the full spectrum of functional brain networks to understand their functional consequences, rather than isolated regions or networks. Nonetheless, to our knowledge, there was no available study to discuss the converging network involvement in three α -Syn in a quantitative manner. Thus, we conducted this meta-analysis of seed-based rsFC studies to investigate the functional network disturbances of α -Syn. In addition, we also performed subgroup analyses and meta-regression analyses to detect the clinical relevance for network functioning in α -Syn.

Methods

Search strategy

This study was registered on PROSPERO (CRD42020210133) and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹² Online search was conducted in PubMed, Web of Science, and EMBASE databases for literature published before September 1st, 2020. The keywords used in the search were (“Parkinson disease” OR “PD” OR “parkinsonism” OR “Dementia with Lewy Bodies” OR “Lewy body dementia” OR “DLB” OR “LBD” OR “Multiple system atrophy” OR “MSA”) AND

(“functional magnetic resonance imaging” OR “fMRI” OR “resting state” OR “functional connectivity”). We then manually searched the references of the included literature and pertinent review articles.

Study selection criteria

The inclusion criteria were as follows:

- (1) Original peer-viewed fMRI study written in English;
- (2) Patients included in the study were diagnosed with PD (based on well-established criteria for PD^{13,14}), DLB (on the basis of the McKeith criteria^{15,16}) or MSA (on the basis of Second consensus criteria¹⁷);
- (3) Directly compared PD/DLB/MSA patients with healthy controls (HC);
- (4) Performed whole-brain seed-based rsFC analysis;
- (5) Reported peak coordinates in standard stereotaxic spaces (e.g., Montreal Neurological Institute (MNI) or Talairach).

Studies were excluded if (1) using other whole-brain rsFC methods, such as independent components analysis, which could cause methodology bias¹⁸; (2) the coordinates of between-group effects could not be retrieved even by contacting the author; (3) the sample and seeds completely overlapping reported in another publication. Studies on the same samples while using different seeds were considered as separate datasets. Meanwhile, different group of patients vs. a single HC group in a study were coded as distinct datasets.

Data extraction

To identify alterations in rsFC in patients with α -Syn, we extracted the locations of the seeds (e.g., the coordinates, a prior template, or a standard atlas) as well as the information of effect regions. For seeds in cortex, we categorized each into one of seven seed networks by its location within the prior networks parcellation,¹⁹ which included the DMN, limbic network (LN), FPN, DAN, VAN, SMN and VIS. Seeds that located in subcortical regions were classified as subcortical network, while seeds that located in cerebellum were classified as cerebellar network (CN). Then, the peak coordinates and *t* statistic of clusters with significant between-group differences were extracted. If only the *Z* score of the cluster was reported, it was converted to *t* statistic. The effects of rsFC were also categorized into two groups according to their direction: hyperconnectivity (α -Syn patients > HC) and hypoconnectivity (α -Syn patients < HC). Meanwhile, studies with null findings (i.e. those that reported no between-group differences in rsFC or whose effects did not survive statistical correction) were also included to reduce the publication bias.

Data extractions were conducted by two investigators independently (S.T. and YL.W.) and all information were double-checked by two investigators (S.T. and YL.W.). Any inconsistent results were discussed and resolved by consensus.

Statistical analysis

Meta-analysis. The meta-analysis was conducted by using the Seed-based *d* Mapping with Permutation of Subject Images (SDM-PSI) software, version 6.21 (<https://www.sdmproject.com/>), which is based on a novel algorithm for coordinate-based meta-analysis that conducts a standard subject-based permutation test to control the family wise error (FWE) rate.²⁰ Firstly, effect size map was built for each individual experiment, by (a) converting the *t* value of each peak coordinate into an estimate of effect size (Hedge's *g*)²¹ and (b) convolving these peaks with a fully anisotropic unnormalized Gaussian kernel ($\alpha = 1$, Full width at half maximum (FWHM) = 20 mm) within the boundaries of the default gray matter template as provided by SDM-PSI (voxel size = $2 \times 2 \times 2$ mm³). The study conducted standard random-effects meta-analysis by imputing the brain maps of statistical effects for each study, which assumes the observed estimates of effect can vary across studies. We have not selected one variance covariance matrix during analysis as this is not specified in the software. Next, imputation was conducted separately for groups of experiments with different statistical thresholds as follows: (a) for each experiment, impute several study images that show realistic local spatial covariance, each set of images was named “imputed dataset”, one per experiment; (b) for each experiment, impute subject images that show realistic local spatial covariance. Then adapt them to the different imputed study images, so that the group analysis of the subject images of an imputed dataset returns the study images of that imputed dataset.²² Then, for each network, a subject-based permutation test was performed as follows: (a) creating a random permutation of the subjects and apply it to the subject images of the different imputed datasets; (b) conducting a group analysis of the permuted subject images for each imputed dataset separately to obtain a meta-analysis image; (c) obtaining a combined meta-analysis image from different imputed datasets by using Rubin's rules²³; (d) saving the largest *z*-value from the combined meta-analysis image and (e) iterating steps (a) to (d) 1000 times and using the distribution of the largest *z*-values to threshold the combined meta-analysis image obtained from unpermuted data.²⁰ Finally, the meta-analytic maps were thresholded using the FWE correction for multiple comparisons with a threshold of $p < 0.05$, and a cluster-wise extent threshold of $k > 50$ voxels to improve the reliability of the results.

Subgroup meta-analysis and meta-regression analysis.

To estimate potential medication effects on the main meta-analysis findings, we performed subgroup-analyses of medication-naïve/OFF and medication-ON patients. Furthermore, to detect potential diverging patterns in each subtype of α -Syn, we also conducted subgroup-analyses of PD, DLB and MSA for sufficient datasets in seed networks of each disorder.

In addition, to investigate the potential effects of relevant clinical variables to the main findings, we further performed meta-regression analyses in α -Syn patients with the Unified Parkinson's Disease Rating Scale Part III (UPDRS III), Hoehn & Yahr stage, duration of illness and the Mini-Mental State Examination as regressors. For studies that used Movement Disorders Society-UPDRS III, we converted it to UPDRS III based on published formulas.²⁴ The threshold was the same as the main analysis.

Sensitivity analysis, heterogeneity analysis and publication bias. Jackknife sensitivity analysis was conducted to evaluate the robustness and reliability of the results. This analysis excludes one study each time and repeats the main statistical analysis. If a previous significant main result remains significant in all or most of the combinations of studies, it can be regarded as replicable and stable.²⁵ For each cluster in the main results, τ^2 is used to account for the between-study heterogeneity. Other statistics for assessing heterogeneity include H^2 , and I^2 statistic. A value of $\tau^2 \approx 0$, $H^2 \approx 1$, $I^2 < 50\%$ indicates good homogeneity among the studies. The study heterogeneity was assessed through conversion of the Q statistic into Z scores, clusters that showed significant heterogeneity and overlapped with the main results were considered heterogeneous between studies.^{26,27} Funnel plots and Egger's test in SDM-PSI were used to test the possibility of any publication bias. Funnel plots are generated to visualize any possible publication bias, while the Egger's test is a quantitative method of assessing asymmetry in the funnel plots and can therefore be used as an indicator for the presence of publication bias. Results showing $p < 0.05$ on Egger's test were considered to have significant publication bias.²⁸

Quality assessment

To increase the quality of the current meta-analysis, we followed the 20-point checklist used in previous meta-analyses of rs-fMRI studies^{9,29} (Table S6 in Supplementary materials) to qualify each study. This checklist included quality of diagnostic procedures, assessments and reporting of critical clinical and demographic data, rs-fMRI acquisition parameters and quality of reported results and the use of statistical correction.

Role of funding source

The funders had no role in study design, data collection, analysis, interpretation, or writing of the report.

Results

Included studies and sample characteristics

This study included 72 publications,^{30–101} with a total of 3093 non-overlapping patients (2636 PD patients, 142 DLB patients and 315 MSA patients) and 3331 HC. The flow chart of the search strategy and study selection is shown in [Figure 1](#).

Summarized sample characteristics are shown in Table S1 in supplementary materials. Detailed demographic and clinical characteristics are shown in Tables S2–4 in supplementary materials. After the seeds from each study were categorized into networks, 16 datasets with FPN seeds, 29 datasets with DMN seeds, 16 datasets with CN seeds, 60 datasets with subcortical network seeds, 6 datasets with VAN seeds, and 9 datasets with LN seeds were identified, and these networks were delivered to subsequent meta-analyses. Results of relatively small datasets ($5 < n < 10$) would need to be interpreted with caution, while the VIS and DAN seeds were not subjected to a quantitative meta-analysis because of their small datasets (both $n = 3$), which may not provide adequate statistical power.

Altered connectivity of motor control related networks

Connectivity alterations in patients with α -Syn were associated with motor and motor control related regions including the subcortical network, SMN, CN, FPN, and VAN. Comparing to HC, α -Syn patients demonstrated both increased connectivity between subcortical network seeds and SMN (the left post central gyrus, postCG) and decreased connectivity between SMN seeds and subcortical network (bilateral putamen). Decreased connectivity was also observed in α -Syn patients, between CN seeds and subcortical network (the right striatum), FPN (the right dorsal lateral prefrontal cortex), and from both CN and subcortical network seeds to VAN (the right insula/operculum). Further, α -Syn patients also demonstrated hyperconnectivity between FPN seeds and SMN (the right supplementary motor area) and hypoconnectivity between FPN seeds and CN (bilateral cerebellum) and subcortical network (striatum and thalamus) (see [Table 1](#) and [Figure 2](#) for details).

Reduced connectivity of cognition related networks

As reported above, α -Syn patients showed hypoconnectivity between the subcortical network /CN seeds and executive control systems (FPN and VAN); these seeds also presented with reduced connectivity to the posterior DMN (the superior temporal gyrus, the precuneus and the posterior cingulate gyrus). In addition, reduced connectivity within DMN, i.e., between DMN seeds and posterior DMN (the superior temporal gyrus) is also observed in α -Syn patients comparing to HC (see [Table 1](#) and [Figure 2](#) for details).

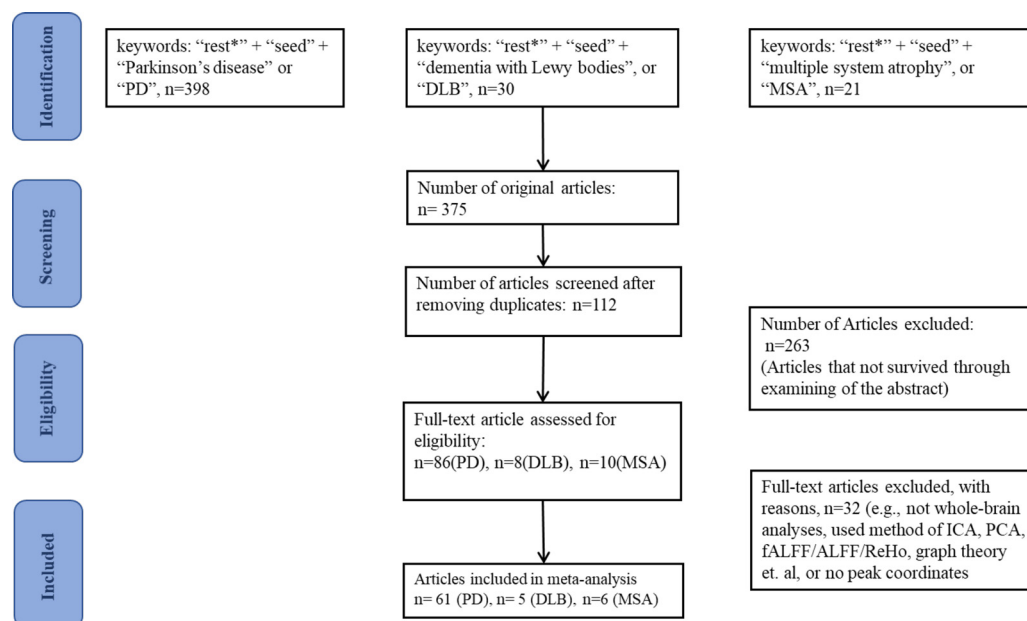


Figure 1. Flowchart of the research strategy and literature selection. Abbreviations: ICA, independent component analysis; PCA, principal component analysis; (f)ALFF, (fractional) amplitude of low frequency fluctuation; ReHo, regional homogeneity.

Reduced connectivity of attention related networks

Comparing to HC, hypoconnectivity was also present in networks involved in externally (VAN) or internally (DMN) oriented attention in α -Syn patients. Firstly, decreased connectivity was observed between DMN seeds and anterior DMN (medial prefrontal cortex) as well as VAN regions (insula and operculum). Secondly, decreased connectivity was also observed within VAN, i.e., between VAN seeds and insula, the triangular part of left inferior frontal, and the anterior cingulate cortex (ACC) (see Table 1 and Figure 2 for details).

Altered connectivity of emotion related networks

The present meta-analysis revealed increased connectivity between FPN seeds and anterior DMN region (medial prefrontal cortex) involved in “top-down” emotional regulation, and decreased connectivity between VAN seeds and LN (parahippocampal gyrus) as well as between LN seeds and VAN (subgenual ACC and operculum) involved in “bottom-up” emotional processing (see Table 1 and Figure 2 for details). A schematic overview of these disrupted functional architecture is shown in Figure 3.

Subgroup analyses and meta-regression analyses

For medication-naïve/OFF experiments, only FPN, DMN, CN and subcortical network seeds have sufficient datasets for quantitative meta-analysis. As for medication-ON experiments, only FPN, DMN, and subcortical

network seeds have sufficient datasets for quantitative meta-analysis. The results of medication-naïve/OFF experiments remained largely the same as main results, except hypoconnectivity between subcortical network and the right cerebellum in medication-ON experiments that was not present in the main results (Figs. S3,4 in supplementary materials).

Overall, it indicated there was no major medication influence on the main results.

Among all the listed articles of α -Syn, PD accounted for the largest proportion and explains most of the abnormalities. Quantitative analysis for each network was available in PD, while in MSA, CN seeds were the most frequently used and could be included into quantitative analyses. However, the literature of DLB was limited and could not be included into quantitative analyses. Thus, we summarized the findings of network abnormalities in DLB (Figure 4). Generally speaking, the effect regions of DMN and FPN in PD were similar to that of converging results, but with smaller effect size and cluster size. For CN abnormalities, PD exhibited hyperconnectivity within CN and hypoconnectivity between CN and FPN, while MSA exhibited hypoconnectivity between CN and VAN. There was common hypoconnectivity in PD and MSA between CN and precuneus (located in DMN). Hyperconnectivity between subcortical network and postCG had a larger effect size and cluster size in PD than converging results (Figs. 4 and S6 in the supplementary materials).

Meta-regression analyses showed that the UPDRS-III scores of patients were negatively

Seeds network	Connected region (peak location)	BA	Voxels	SDM-Z	MNI coordinate	Located network
FPN	Hyperconnectivity					
	R-MPFC	10	303	4.386	4,50,0	DMN
	R-SMA	6	191	4.019	2,16,54	SMN
	Hypoconnectivity					
	L-cerebellum IV / V	19	3053	-6.642	-16,-56,-16	CN
	R-IPG	40	289	-4.746	50,-48,44	FPN
	R-cerebellum IV / V	37	211	-4.354	20,-50,-28	CN
R-anterior thalamic projections	NA	213	-4.165	12,12,6	subcortical network	
L-striatum	NA	132	-3.997	-14,20,-2	subcortical network	
DMN	Hypoconnectivity					
	R-STG	NA	1131	-5.307	48,8,-12	DMN
	L-rolandic operculum	48	966	-4.705	-48,6,2	VAN
	L-MPFC	32	94	-3.975	2,34,28	DMN
R-insula	48	81	-3.831	36,18,2	VAN	
CN	Hypoconnectivity					
	R-striatum	48	568	-6.241	32,-6,8	subcortical network
	R-insula/operculum	48	459	-6.22	36,-2,12	VAN
	R-STG/MTG/ITG	20/21/22	500	-6.978	48,-10,-12	DMN
	R-STG/angular/IPG	42/39/40	1248	-6.9	52,-42,18	DMN/FPN
	R-Precuneus/PCC	23	676	-6.044	4,-46,38	DMN
	ACC/OFC	10/11	676	-5.675	-4,42,-4	DMN
R-DLPFC	9	118	-4.676	22,-10,-26	FPN	
Subcortical Network	Hyperconnectivity					
	L-postCG	4	85	4.999	-26,-30,64	SMN
	Hypoconnectivity					
	R-Precuneus	23	364	-4.688	2,-34,32	DMN
L-insula	47	166	-3.873	-26,20,-6	VAN	
L-STG	42	122	-3.967	-58,-46,20	DMN	
SMN	Hypoconnectivity					
	R-lenticular nucleus, putamen	48	240	-3.961	30,-4,0	subcortical network
L-lenticular nucleus, putamen		106	-3.738	-28,0,0	subcortical network	
VAN	Hypoconnectivity					
	R-PHG	30	229	-4.261	18,-20,-20	LN
	L-insula	48	157	-3.79	-36,-16,10	VAN
	L-IFG, triangular part	45	84	-3.319	-48,16,0	VAN
R-ACC	24	54	-3.145	6,12,38	VAN	
LN	Hyperconnectivity					
	Middle cerebellar peduncles		212	4.314	12,-28,-30	CN
	Hypoconnectivity					
L-sgACC	25	54	-3.292	-2,24,-4	VAN	
R-rolandic operculum	48	50	-3.214	46,-12,10	VAN	

Table 1: Results of meta-analysis of altered resting-state functional connectivity in α -Synucleinopathy compared with healthy control.
 Abbreviations: BA, Brodmann area; SDM-Z, seed-based d mapping-z value; MNI, Montreal Neurological Institute; FPN, frontoparietal network; R-, the right; L-, the left; DMN, default mode network; CN, cerebellar network; SMN, somatomotor network; VAN, ventral attention network; LN, limbic network, MPFC, medial prefrontal cortex, SMA, supplementary motor area, IPG, inferior parietal gyrus; STG, superior temporal gyrus; MTG, middle temporal gyrus; ITG, inferior temporal gyrus; DLPFC, dorsolateral prefrontal cortex; sgACC, subgenual anterior cingulate cortex; OFC, orbital prefrontal cortex; postCG, posterior central gyrus; PCC, posterior cingulate cortex; PHG, parahippocampal gyrus.

correlated with connectivity between FPN seeds and CN (the left cerebellum). In other words, as motor function became worse, their rsFC would decrease. There was no other effect of clinical variables on rsFC changes.

Sensitivity analysis, heterogeneity analysis and publication bias

The jackknife sensitivity analyses revealed that all clusters of main results were highly replicable. Details of the results of the sensitivity analysis were listed in Table

α -synucleinopathy diseases

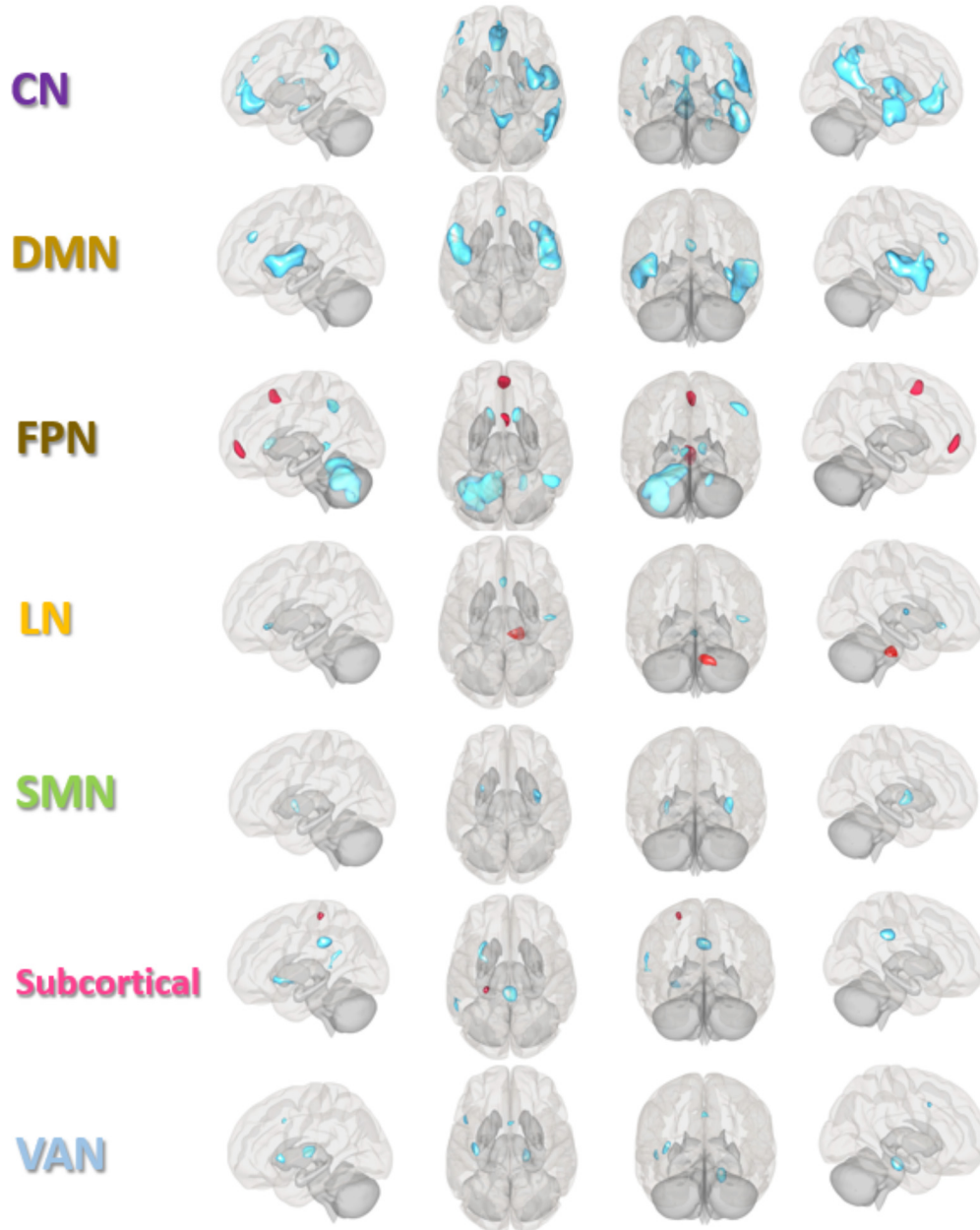


Figure 2. Meta-analysis of abnormal resting-state functional connectivity in α -Synucleinopathy. The brain regions of altered resting-state functional connectivity for each network in α -synucleinopathy (α -Syn) patients are compared with healthy controls (HC). Red refers to hyperconnectivity (α -Syn > HC), and blue refers to hypoconnectivity (α -Syn < HC). **Abbreviations:** FPN, fronto-parietal network, DMN, default mode network, CN, cerebellar network, SMN, somatomotor network, VAN, ventral attention network, LN, limbic network.

S7 (in the supplementary materials). Moreover, τ^2 , H^2 , I^2 statistics indicate there were small heterogeneities observed in the main results (see Table S7 in the supplementary materials). In addition, none of

the clusters showed significant publication bias based on Egger's test ($p > 0.05$). Funnel plots were presented in Figs. S8–38 in the supplementary materials.

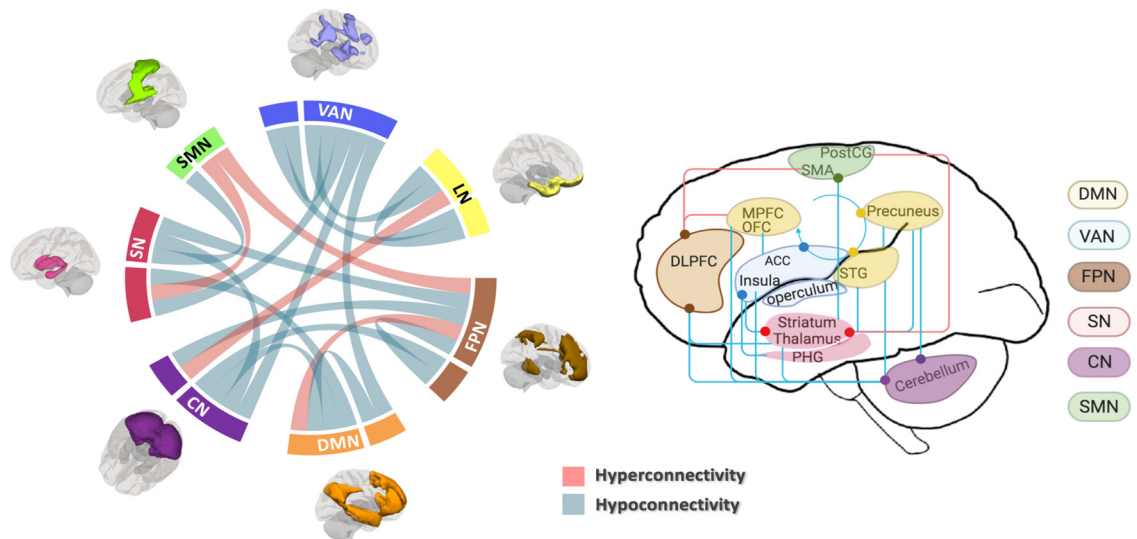


Figure 3. Schematic overview of within- and between-network connectivity changes in α -Synucleinopathy. For both graphs, pink line indicates hyperconnectivity and blue line indicates hypoconnectivity; different networks were marked with different colors. Abbreviations: FPN, frontoparietal network; DMN, default mode network; CN, cerebellar network; SN, subcortical network; SMN, somatomotor network; VAN, ventral attention network; LN, limbic network; MPFC, medial prefrontal cortex; SMA, supplementary motor area; IPG, inferior parietal gyrus; STG, superior temporal gyrus; DLPFC, dorsolateral prefrontal cortex; ACC, anterior cingulate cortex; OFC, orbital prefrontal cortex; postCG, posterior central gyrus; PHG, parahippocampal gyrus.

Quality assessment

The quality of each study was considered as good, with mean overall score of 18.84. See Figure S2 (in the supplementary materials) for further specification of the criteria of each study.

Discussion

Network models have been increasingly recognized as useful tools to study core intrinsic activity features and clinical biomarkers of neurodegenerative disorders.^{1,2} This study provided a meta-analytic overview of abnormal rsFC in patients with α -Syn, which implicated widespread abnormal crosstalk across brain networks

involved in motor, cognition, attention, and emotion. These findings supported the neurodegenerative models^{1,3} in which network dysfunction is tightly linked to motor and non-motor signs observed in α -Syn patients.

Imbalanced connectivity in networks involved in motor and “top-down” motor control

The present meta-analysis revealed alteration of connectivity in α -Syn patients: (1) both increased and decreased connectivity between subcortical network and SMN; (2) decreased connectivity between CN and subcortical network; (3) decreased connectivity between CN/subcortical network and FPN/VAN. These findings correspond

to the current understanding of parkinsonian symptoms as related to an impairment of connectivity in motor, top-down control networks, and their interactions.^{104,105}

The subcortical network and the SMN formed the so called corticobasal ganglia–thalamocortical loop, which is a fundamental circuit for motor ability and is critically related to the parkinsonism.¹⁰⁶ We found an increased connectivity of the corticobasal ganglia–thalamocortical network between subcortical network and SMN (the postCG), which has also been well-documented in PD in previous meta-analysis of rsFC studies.⁹ However, we also found decreased connectivity in this network, i.e., between SMN seeds and bilateral putamen that has not been reported before, which suggested an imbalanced network functioning influenced by the pathophysiology of parkinsonism.¹⁰⁷ The cerebellum has also been known to play an important role in the pathogenesis of α -Syn.^{108,109} The decreased cerebellar-subcortical network connectivity is likely to be a reflection of abnormal signals from the basal ganglia to influence cerebellar function, which has also influenced connectivity between the motor subsystem and large-scale cortical networks.¹¹⁰ The FPN and VAN are important in cognitive control, specifically impact motor execution.¹¹¹ Previous rs-fMRI study suggested that reorganization of FPN, VAN, and CN can contribute to problems with self-initiation and task-set maintenance in PD.¹¹² Hence, the current pattern of imbalanced or poorly coordinated functioning of networks involved in motor and “top-down” control in α -Syn patients may reflect the deficits in self-initiated, maintaining, and goal-directed movements as well as disorganized executive control.¹¹³ Our meta-regression results of the correlation of motor dysfunction severity to the hypoconnectivity between FPN and cerebellum also supports this hypothesis. Moreover, these abnormalities were robust in the subgroup of those medication-off patients, while they were not present in those medication-ON patients, which indicates that dopaminergic treatment may reverse some of these abnormalities. However, α -Syn could be treated with different medications depending on their symptoms. For example, motor symptoms were primarily treated with dopaminergic treatments, while non-motor symptoms such as dementia, depression and psychosis were treated with cholinesterase inhibitors, antidepressants and antipsychotics, respectively.^{114,115} So different active neuropharmacological interventions may have divergent effects on FC changes in α -Syn patients which should be considered more in future studies.

Reduced connectivity between networks involved in cognitive impairments

Our results also demonstrated hypoconnectivity between regions in subcortical network, CN, and

posterior DMN. This reinforced the current knowledge that subcortical rs-FC changes were not only attributed to a loss of dopaminergic neurons that was related to parkinsonism but was also associated with cognitive deficits.¹¹⁶ For example, recent studies showed that specific striatal (caudate) rsFC changes are associated with cognitive decline in PD.^{53,116} Cerebellum, as well, has a significant role beyond sensorimotor control in cognition, based on the proposed concept of the universal cerebellar transform of cerebello-basal ganglia-thalamocortical circuits.¹¹⁷ The posterior DMN is believed to play an important role in various cognitive functions,¹¹⁸ whose deficits were related to more rapid cognitive decline according to longitudinal studies in PD.¹¹⁹ Our findings appear to highlight the role of decreased synchronicity and connectivity between subcortical network, CN, and posterior DMN in impaired cognition in α -Syn patients. An interesting question is whether the FC deficiency is a cause or consequence of cognitive deficits in α -Syn? Future longitudinal studies and image-genetics analysis may map the chronological order of network dysfunction and behavioral deficits to answer this question more comprehensively. In addition, these findings indicate that another exciting direction for future research is to examine the relationship between network changes and various clinical phenotypes of α -Syn.

Reduced connectivity between networks involved in attentional control

The present meta-analysis also provided evidence of hypoconnectivity between brain networks involved in attentional control. A recent hypothesis proposed that dysfunction across attentional networks, especially in VAN and DMN, may explain visual misperception and hallucinations (VH),¹²⁰ which occur frequently in PD and DLB. Dysfunction within the VAN could result in difficulties in orienting attention to relevant stimuli,¹²¹ leading to a relative inability to “shut down” resting activity within the DMN, which is typically associated with the retrieval and manipulation of semantic and episodic memories.¹²² Indeed, both neuropathological and neuroimaging studies of PD and DLB patients have reported anomalies that were associated with a number of VAN and DMN regions in the presence of VH.^{123,124} More interestingly, our finding shows reduced connectivity between VAN and parahippocampal gyrus, the region with direct relationship to visual hallucination.¹²⁵ Thus, the demonstration of hypoconnectivity across these networks is in line with theoretical models, suggesting either a failure to recall appropriate information or select inappropriate stored information, as well as inability to communicate in the presence of an ambiguous percept, which might be the neural underpinning of VH.¹²⁰

Imbalanced connectivity between networks involved in emotion processing

The present meta-analysis revealed α -Syn patients showed increased connectivity between FPN and anterior DMN, and decreased connectivity between VAN and limbic regions. These networks are critically involved in emotional regulation and adaptive behaviors.¹²⁶ Abnormal connections of these regions are demonstrated in meta-analyses of psychiatric disorders, such as depression^{7,127} and bipolar disorder.¹²⁸ Decreased LN to VAN (subgenual ACC) connectivity might reflect an inability or interference of bottom-up emotion processing, which may constitute an increase in top-down emotional regulation reflected by hyperconnectivity between the FPN and anterior DMN.¹²⁹ This pattern of activity might also explain affective symptomatology observed in α -Syn patients.

Limitations and future directions

The major challenge is the relative rarity of studies with DLB and MSA, so the findings might be overshadowed by PD. Further studies of DLB and MSA are needed in order to better understand the clinical and neuropathological associations by transcending all α -Syn clinical phenotypes. Furthermore, in neurodegenerative diseases with similar signs, such as PD dementia, DLB, and Alzheimer's disease, a network-based taxonomy can possibly cut across traditional diagnostic boundaries and, instead, include distinct subtypes of neural network dysfunction that might better reflect the clinical homogeneity or heterogeneity of neurodegeneration.

Secondly, important clinical information such as parkinsonism laterality, autonomic and visual assessments were not systematically provided in all the included studies which have limited our analyses. Future studies should systematically study clinical symptoms in α -Syn patients to help delineate network-guided dimensions of psychopathology across clinical diagnostic categories, which could serve as a foundation for developing network-based biomarkers in α -Syn.

Finally, the age range and illness duration of included participants was quite wide which would potentially influence the results,¹³⁰ albeit we have controlled the age effect during analyses. Also, we have looked at the illness duration as a regressor in the meta-regression analysis, the result showed that there was no significant association with FC changes. A good way to understand the trajectory of rsFC changes during disease progression is to track α -Syn longitudinally.¹³¹ As rsFC changes might emerge before the clinical diagnose of α -Syn,¹³² i.e., the prodromal stage of α -Syn, it would be important to identify imaging markers at the prodromal stage. Currently, idiopathic REM sleep behavior disorder (iRBD) is considered as the most distinct prodromal phenotype of α -Syn which has been identified to highly predict the subsequent development of

PD, DLB and MSA.^{133,134} As some recent studies have shown that FC changes in iRBD patients were similar to that found in α -Syn and were associated with some cognitive aspects,^{135,136} it is anticipated that prospective rsFC study in iRBD subjects and their high-risk relatives¹³⁷ might help to monitor disease progression and phenoconversion to α -Syn. While rsFC is highly variable even within individuals, in this concern, future study using more sophisticated FC methods such as dynamic/hierarchical analyses are needed to capture the variation of FC changes in α -Syn.

Conclusion

To our knowledge, this study provides the first meta-analytic overview of large-scale network dysfunction in patients with α -Syn, including imbalanced connectivity among networks involved in motor function and executive control, decreased connectivity among networks involved in cognition and attention, and imbalanced connectivity among networks involved in emotion processing and regulation, which could potentially correlate to the motor, cognitive, and psychiatric symptoms. These findings also support the proposal to view the subcortical, cortex and cerebellum as an integrated system to understand the involvement of these areas in α -Syn.

Contributors

S.T. contributed to the conception and design of the study. S.T. and YL.W. performed study selection, data extraction and statistical analyses. S.T. and YL.W. have verified the underlying data. S.T. drafted the manuscript. Y.L., S.C. and YK.W. participated in discussion of analyses and results. J.C., W.C., J.A., and V.M. reviewed the manuscript and provided comments. Y.L. and YK.W. revised the manuscript. All authors have read and approved the final version of the submitted manuscript.

Data sharing statement

This study does not involve public datasets or codes. The data supporting the findings in this study might be requested via the corresponding author of this article upon reasonable request.

Declaration of interests

J.C. received personal fees from Eisai Co., Ltd for joining an insomnia expert forum, which is outside the submitted work.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ebiom.2022.103915.

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