A systematic review on resting state functional connectivity in patients with neurodegenerative disease and hallucinations

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ABSTRACT

Hallucinations are a complex and multidimensional phenomenon which can differ based on the involved pathology, typology and sensory modality. Hallucinations are common in patients with neurodegenerative diseases. Recent sparse evidence from resting state functional magnetic resonance imaging (rs-fMRI) studies has identified altered functional connectivity in those patients within several brain networks, such as the default mode, attentional and sensory ones, without, however, providing an organized picture of the mechanisms involved. This systematic review, following PRISMA guidelines, aims at critically analyzing the current literature on the brain networks associated with the phenomenon of hallucinations in patients with neurodegenerative diseases. Ten rs-fMRI studies fulfilled our selection criteria. All these studies focused on synucleinopathies, and most of them focused on visual hallucinations and were characterized by a heterogeneous methodology. Thus, instead of offering a definite picture of the mechanisms underlying hallucinations in neurodegeneration, this systematic review encourages further research especially concerning tauopathies. Notwithstanding, the findings overall suggest a disruption in the top-down (associated with memory intrusion and difficulty of inhibition) and in the bottom-up processes (associated with the sensory areas involved in the hallucinations). Further investigations are needed in order to disentangle the brain mechanisms involved in hallucinations and to overcome possible limitations characterizing the current literature.

1. Introduction

Neurodegenerative diseases, characterized by an irreversible and progressive degeneration and death of neuronal cells, are often concomitant with a plethora of psychological and even psychotic symptoms, such as hallucinations. The protein underlying the disease can characterize and influence the clinical course of hallucinatory symptoms. That is, there are diseases affected by the accumulation of synuclein protein (i.e., synucleinopathies) and others affected by the accumulation of other proteins like amyloid, tau protein (i.e., tauopathies) and TDP-43. Hallucinations seem to be more frequent in synucleinopathies such as Parkinson's disease (PD) and Lewy's bodies dementia (DLB) than in tauopathies such as Alzheimer's disease (AD), frontotemporal dementia (FTD) and frontotemporal dementia due to TDP (Naasan et al., 2021). In PD patients, some authors suggested that

the hallucinatory phenomena could be attributed to levodopa or dopaminergic agonist medication for parkinsonian symptoms, and that treatment suspension could reduce the symptoms (Friedman, 1991). However, medication is not the only reason for hallucinations (Merims et al., 2004; Goetz et al., 1998; Factor et al., 1995). Apart from neurodegeneration, hallucinations are present in various medical conditions (Schutte et al., 2021), and some authors suggest the existence of a psychosis continuum in order to explain the presence of hallucinations also in healthy subjects, although characterized by different severity and frequency (Badcock and Hugdahl, 2012; Van Os et al., 2009). Indeed, hallucinations can be associated with various factors, such as sleep (e.g., hypnagogic and hypnopompic hallucinations) (Asaad and Shapiro, 1986; Ohayon, 2000), sensory deficits (e.g., "Charles Bonnet syndrome''), drugs or hallucinogens use, and psychosocial factors, like in the case of post-bereavement hallucinations (Grimby, 1998, 1993).

In neurodegeneration, the type of hallucination can vary depending on the disease and the disease stage. Indeed, the early stages of Parkinson's disease are frequently characterized by minor hallucinations such as illusions, passage hallucinations (i.e., seeing something/somebody moving) and presence hallucinations (i.e., feeling the presence of somebody), whilst patients in the intermediate stages start to experience major hallucinations (i.e., seeing people, animals, objects; hearing voices, noises, sounds) with insight (Lenka et al., 2019; Ffytche et al., 2017; Pagonabarraga et al., 2016). The presence of major hallucinations characterizes DLB already in the early stages of the disease, and they represent one of the criteria for its diagnosis, differently from Alzheimer's disease (AD) in which hallucinations can occur less frequently at different stages (El Haj et al., 2017; Bassiony and Lyketsos, 2003).

Also the sensory modalities characterizing the hallucinations can vary depending on the neurodegenerative disease. Indeed, as described by Eversfield and Orton (2019) visual hallucinations have an estimated prevalence of 28.2 % in PD and 61.8 % in DLB, whereas auditory hallucinations have an estimated prevalence of 8.9 % in PD and 30.8 % in DLB. However, hallucinations may engage single or multiple senses (Asaad and Shapiro, 1986); some studies show that the sensory modality also can be associated with specific sensory dysfunction as in the case of hearing loss for the auditory hallucinations and of eye diseases for the visual hallucinations such as the "Charles Bonnet" syndrome (Waters and Fernyhough, 2017; Ffytche and Howard, 1999).

A recent *meta*-analysis focusing on voxel-based morphometry (VBM) revealed the reduced volumes of frontal, occipital, occipitotemporal and parietal brain regions in patients with neurodegenerative diseases suffering from hallucinations as compared with those without hallucinations (Pezzoli et al., 2021a). However, an influential view on brain functioning conceived the relation between structure and function based on the dynamic communication between brain regions, balancing between integration and segregation (Sporns, 2012). Such a view, reflected in findings of functional brain connectivity, is not yet systematically reported in relation to hallucinations in neurodegenerative disease. A powerful tool to investigate the neural substrates of hallucinations in neurodegeneration is functional magnetic resonance imaging (fMRI) and, more specifically, resting state fMRI (rs-fMRI), which allows for unravelling the networks involved when the subject is neither performing any task nor being exposed to any stimulus. This technique provides details about how these networks communicate with each other, though it does not provide information about the directionality of the neural communication.

The resting state (rs-fMRI) was presented for the first time by Biswal and colleagues (1995) and measures spontaneous low frequency fluctuation in the range 0.01–0.1 Hz (Fox and Raichle, 2007). This technique presents different advantages such as suitability for any population, even a not very collaborative one, and the no need for a large number of trials (Smitha et al., 2017). Some of the analysis techniques for the study of rs-fMRI connectivity are the seed-voxel- based analysis, the independent component analysis (ICA) and the amplitude of low frequency-fluctuation (ALFF) (Chen and Glover, 2015). The seed-based analysis allows for calculating the functional connectivity (FC) as the temporal synchrony between a seed region, belonging to the brain network of interest, and the rest of brain areas (Chen and Glover, 2015). The ALFF measures the spontaneous fluctuations of specific brain regions (Biswal et al., 1995). These models are strongly driven by the hypothesis to test, and so they investigate only specific regions. Conversely, the whole-brain FC does not require the pre-selection of a specific seed (i.e., region) of interest. In line with this approach, there is the independent component analysis (ICA) which identifies components independent from each other and also includes sources different from the brain (e.g., noise, movements). This approach is mainly data driven. Table 1 summarizes some of the main analysis techniques commonly used in rs-fMRI studies.

The default mode network (DMN), the attentional networks (i.e., the dorsal attention network (DAN) and the ventral attention network

Table 1
Main approaches used for resting state fMRI analysis (rs-fMRI).

rs-fMRI Analysis	Description	Driven by
Seed-based approach	Correlation between a priori region (i.e., seeds) and the rest of the brain	Hypothesis
Independent component analysis (ICA)	Identify components independent from each other	Data
Low frequency-fluctuation (ALFF)	Spontaneous fluctuation of specific regions	Hypothesis

(VAN) are among the networks which are active during the resting state. DMN includes posterior cingulate cortex precuneus, medial prefrontal cortex, medial temporal lobe, lateral and inferior parietal lobe, and it seems to orient the attention towards internal conversations, introspection, imagery and intrinsic memory (Buckner et al., 2008; Damoiseaux et al., 2008; Damoiseaux et al., 2006). DAN includes dorsolateral prefrontal cortex, superior parietal cortex and caudate, and it seems to be responsible for the executive control of attention oriented to external stimuli, while VAN includes amygdala, anterior cingulate, insula, temporo-parietal junction, ventral striatum and lateral inferior prefrontal cortex, and it seems to engage the attention towards salient and unexpected stimuli (Vossel et al., 2014; Fox et al., 2006). The brain regions associated with these networks are described in Table 2.

To date, only few recent rs-fMRI studies, comparing patients with neurodegenerative diseases experiencing hallucinations against those not experiencing hallucinations, show brain alterations in the aforementioned networks in patients experiencing hallucinations. Specifically, Shine and colleagues (2014), Shine and colleagues (2011)) have proposed a model to explain the visual hallucination in PD, suggesting an over-activation of the DMN and the VAN, which could be responsible for memory intrusion and for the incorrect attentional engagement for external stimuli, while an hypo-activation of the DAN could influence the failure in checking the salience of those stimuli (Shine et al., 2011).

Considering perception as one of the processes underlying hallucinations and as the bridge between the internal representation of the external world and the actual sensory stimuli, it seems possible to make a distinction between the top-down processes (i.e., influenced by memory and expectations) and the bottom-up ones (i.e., influenced by the perception of the actual sensory stimuli) (Friston, 2005). Recent theories converge in suggesting that an imbalance between predictions (top-down processes) and sensory inputs (bottom-up processes) could

Table 2
Main networks investigated through rs-fMRI studies.

Networks	Anatomical areas	Functions
Default Mode Network (DMN)	● Posterior cingulate ● Medial prefrontal cortex ● Medial temporal cortex ● Hippocampus ● Lateral & inferior parietal lobe ● Medial frontal gyrus	● Internal-oriented attention ● Internal conversation ● Introspection ● Imagery
Dorsal Attentional Network (DAN)	● Dorsolateral prefrontal cortex ● Superior parietal cortex ● Caudate	● External-oriented attention ● Executive control
Ventral Attentional Network (VAN)	● Basolateral amygdala ● Ventral striatum ● Ventral-frontal cortex/ lateral inferior prefrontal cortex ● Insula ● Anterior cingulate ● Temporo-parietal junction	● Salient stimuli-oriented attention ● Coordination with other networks
Visual Network (VN)	● Occipital cortex ● Retina ● Thalamic lateral geniculate nucleus	● Processing visual stimuli

underlie hallucinatory phenomena (O'Callaghan et al., 2017a) and cognitive deficits characterizing dementia (Kocagoncu et al., 2021). Specifically, behavioral studies on DLB and PD converge in showing that these patients with synucleinopathies and hallucinations tend to give more weight on prior knowledge than on actual sensory inputs (Zarkali et al., 2019; O'Callaghan et al., 2017b). Thus, a flexible system able to capture the sensory input and update the internal model is necessary in order to efficiently perceive the surroundings (Lupyan and Clark, 2015).

However, to date a consensus view on the mechanisms responsible for the pathogenesis of hallucinations in neurodegeneration is still missing, and the question remains: Which brain mechanisms are involved in the hallucination processes? There are no systematic works examining the results from resting fMRI studies under the predictive coding umbrella (Friston, 2005). Moreover, to date, it is still not clear whether hallucinations are due to a disruption in one of these processes or if it is part of the whole system, because of the interdependency of the processes. For instance, can the altered brain mechanisms involved in hallucinatory phenomena be interpreted as a second-order feature resulting from the difference between our expectation and the actual stimuli (i.e., the prediction error according to Friston's predictive coding theory; Friston, 2011)?

Hence, the aim of this review is to systematically organize the existing literature to investigate whether there are any specific brain connectivity alterations depending on the type of hallucination and on the type of neurodegenerative disease. Moreover, we wish to critically analyze whether a disruption in memory and inhibitory processes can explain the presence of hallucinations, as evidenced by alterations in resting state brain networks. Finally, we wish to better examine the top-down and bottom-up processes.

2. Methods

2.1. Literature search and study eligibility

The systematic review followed the PRISMA statement (Page et al., 2021). The registration of this work was submitted to PROSPERO on September 3rd, 2021 before the beginning of the data extraction (registration identity number, 276506).

A systematic search was carried out in July 2021 using PubMed and Scopus databases to identify resting state fMRI studies (rs-fMRI) investigating FC in patients with neurodegenerative diseases, comparing patients with and without hallucinations. We used the following keywords: "hallucinations", "brain", "cerebral cortex", "neurodegenerative disease", "Alzheimer's disease", "Parkinson's disease", "Lewy bodies dementia", "frontotemporal dementia", "synucleinopathies", "tauopathies".

Studies were included if they met the following criteria: 1) examination of hallucinations in any neurodegenerative disease; 2) inclusion of adult participants aged over 18; 3) inclusion of at least one control group; 4) inclusion of brain data from Magnetic Resonance Imaging (MRI) studies.

The following exclusion criteria were used: 1) non-peer-reviewed studies; 2) studies in languages other than English; 3) reviews; 4) *meta*-analysis; 5) animal studies; 6) post-mortem studies; 7) study participants with neurodevelopmental disorders.

After conducting the literature search, the studies were screened independently by two researchers based on titles and abstracts. Discrepancies were discussed with a third researcher. Subsequently, the full texts were retrieved and evaluated. Finally, a table was created to extract the most relevant data and to assess the methodological quality of the included studies.

2.2. Data extraction

The following variable were extracted from each study: general information about the study (author, article title, year of publication, type of publication); study characteristics (objectives, study inclusion and exclusion criteria); participant characteristics (sample size, mean age, gender, education, disease duration, hallucination duration); control conditions; overall outcome data/results (main outcomes, type of analysis, number of participants enrolled, number of participants included in the analysis); MRI related parameters (Teslas, MRI system, MRI model, head coil, rs-fMRI sequence, repetition time (TR), echo time (TE), voxel size (mm), acquisition time, analysis software, analysis method, statistical threshold, MRI quality, coordinates); behavioral-related parameters (hallucination assessment, neuropsychological tests, behavioral scales).

2.3. Quality assessment of MRI studies

We selected a set of guidelines in order to proceed with the quality assessment and guarantee the clarity and replicability of the fMRI studies (Nichols et al., 2017; Poldrack et al., 2008). The guidelines were the following: description of the MRI design, age and sex of the participants, ethical approval, image acquisition and processing, statistical MRI analysis, software package, figures and tables.

3. Results

The initial literature search of keywords produced 5235 studies of which 885 were duplicates. Due to the inclusion criteria, 4307 studies were excluded. Among the 43 studies screened for eligibility, 11 met eligibility criteria.

Eleven studies included rs-fMRI analysis. However, one of these studies was excluded because of the absence of a group differentiation between neurodegenerative patients with and without hallucinations and due to the limited sample size for the fMRI analysis (Miloserdov et al., 2020). Thus, ten studies finally met the inclusion criteria and were included in the qualitative analysis. A flow chart summarizing the selection process is depicted in Fig. 1.

3.1. Study characteristics

The characteristics of the studies included in this work are indicated in Table 3. Means and standard deviations are referring to the ten studies, although it is not clear whether the studies by Yao and colleagues (2015), Yao and colleagues (2014) were using the same sample.

3.1.1. Sociodemographic variables

3.1.1.1. Sample size. The sample size of neurodegenerative patients with hallucinations was 12.9 (interquartile range, 4.5), the sample size for those without hallucinations was 16.6 (interquartile range, 3.5), and the sample size for healthy subjects was 16.8 (interquartile range, 1.25).

3.1.1.2. Age. The age of the participants was reported in all the studies. Specifically, nine studies (90 %) reported that the mean age was 70.39 years $\pm$ 6.38 year for the patients with neurodegenerative disease with hallucinations; 67.37 $\pm$ 7.24 years for the patients with neurodegenerative disease without hallucinations, and 66.40 years $\pm$ 6.72 years old for the healthy participants. One study (10 %) reported the median age of participants was 70 years for patients with neurodegenerative disease and hallucinations, 66 years for patients with neurodegenerative disease without hallucinations and 63 years for healthy subjects.

3.1.1.3. Education. The educational level of the participants was indicated only in 60 % of the included studies, with a mean of 9.27 $\pm$ 3.69 years for the neurodegenerative patients with hallucinations, 9.82 $\pm$ 3.34 years for the neurodegenerative patients without hallucinations, 9.53 $\pm$ 2.71 years for healthy subjects.
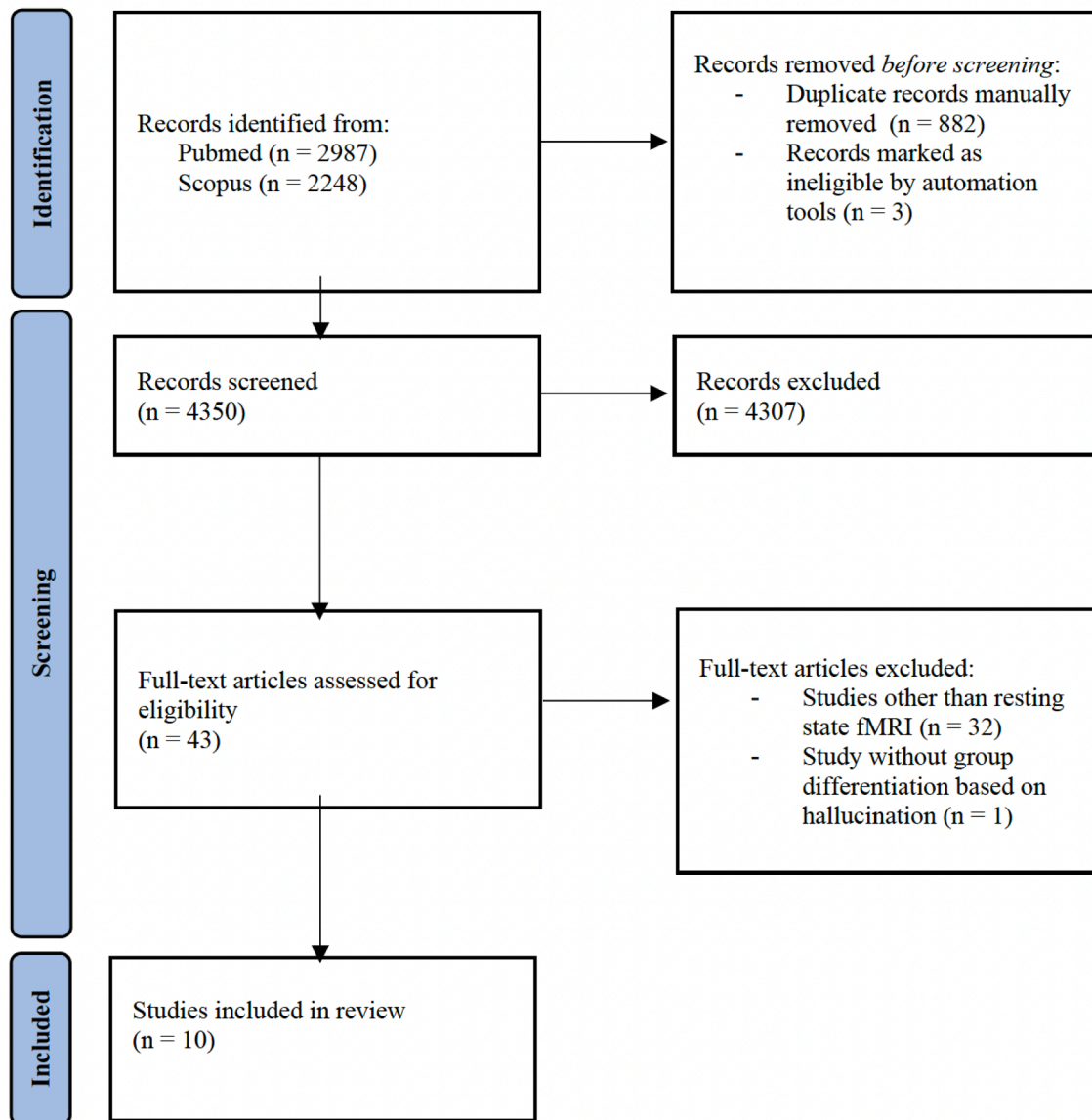
Fig. 1. Modified version of the PRISMA flow chart (Page et al., 2021). It illustrates the selection process of the ten rs-fMRI studies included in this systematic review. The number of records were identified for each database. [2-column fitting image, in color].

3.1.1.4. Sex. Twenty% of the included studies did not specify the sex of the patients (Franciotti et al., 2015; Shine et al., 2015). In the rest of the studies (80 %), the percentage of females was 48.9 % for the neurodegenerative group with hallucinations, 43.46 % for the neurodegenerative group without hallucinations, and 48.6 % for the healthy group.

3.1.1.5. Exclusion criteria. In 70 % of the studies, the authors specified the exclusion criteria, e.g.; psychiatric disorders in six studies, cognitive impairment (Mini Mental State Examination < 24) and depressive symptoms (Montgomery-Åsberg Depression Rating Scale > 6) in three studies, eye pathologies in two studies, cerebrovascular disease in three studies.

3.1.1.6. Inclusion criteria. A total of 80 % of the studies specified the inclusion criteria for the group of neurodegenerative patients with hallucinations. However, these criteria were heterogeneous and based on the aim of the study. For instance, 40 % of the studies described temporal criteria related to the occurrence of the hallucinations. Indeed, one study required complex and repetitive hallucinations once every 4 weeks for at least 4 weeks before the fMRI (Yao et al., 2016; Yao et al.,

2015; Yao et al., 2014), and another required stable hallucinations for 3 months before the study (Bejr-kasem et al., 2019). Fourty% of the studies only stated the presence of hallucinations based on specific assessments as inclusion criteria. Specifically, Pezzoli and colleagues (2021a) used the Neuropsychiatric Inventory (NPI) to determine the presence of hallucinations, Walpola and colleagues (2020) selected a score higher than 1 on the question related to hallucinations and psychosis of the Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Hepp and colleagues (2017) classified patients as hallucinator if their score was higher than 1 on the Scales for Outcomes in Parkinson Disease Psychiatric Complications, and Franciotti and colleagues (2015) examined the presence of complex hallucinations through the Parkinson Psychosis Rating Scale (PPRS).

One study used a cut-score based on a Bistable Percept Paradigm (BPP) to differentiate between non-hallucinatory and hallucinatory patients, specifying that patients from this latter group scored positively also on the MDS criteria for visual hallucinations (Shine et al., 2015). Specifically, in this paradigm participants were invited to determine whether 40 monochromatic images were stable (i.e., clear images) or bistable (i.e., ambiguous images).

Table 3

Main characteristics of the ten rs-fMRI studies included in this systematic review. DLB: Lewy bodies dementia; PD: Parkinson's disease; MSA: Multiple system atrophy; ePD: PD patients matched with MSA for disease duration; sPD: PD patients matched with MSA for severity of symptoms and equivalent treatment; H: hallucinations; HC: healthy controls; mH: minor hallucinations; VH: visual hallucinations; NPI: Neuropsychiatric Inventory; MDS-UPDRS: Movement Disorders Society-Unified Parkinson's Disease Rating Scale; PPRS: Parkinson Psychosis Rating Scale; SCOPA-PC: Scales for Outcomes in Parkinson Disease Psychiatric Complications; N.A.: not applicable.

Study	Sample	Disease Duration	Age	Hall. assessment	Hall. group: inclusion criteria	Exclusion criteria	Hall. treatment
Zorzi et al. (2021)	10 DLB VH / 13 DLB NH / 13 HC	2.7 (1.25) / 1.92 (1.11)	76.63 (7.35) / 74.44 (5.18) / 70.84 (10.85)	NPI	N.A.	Severe cerebrovascular disease; primary psychiatric disorders; severe ocular diseases	N.A.
Pezzoli et al. (2021a)	7 DLB VH / 16 DLB NH	2.57 (1.4) / 2.13 (1.31)	75.29 (5.09) / 73.5 (6.65)	NPI to assess presence, severity and frequency	Recurrent, complex hallucination	Severe cerebrovascular disease; history of psychiatric disorders; severe eye pathology impairing visual acuity	N.A.
Walpola et al. (2020)	18 PD H / 20 PD NH / 20 HC	7.6 (5) / 5.7 (3.2)	67.5 (6.7) / 63.7 (6.6) / -	MDS-UPDRS (question 2)	Score ≥ 1, having VH (including minor (passage or illusions) or complex hallucinations	N.A.	0/18 PD H
Bejr-kasem et al. (2019)	18 PD mH / 14 PD NmH	5.2 (3.8) / 4 (2)	70.4 (5.5) / 65.8 (6.9)	MDS-UPDRS	Minor hallucinations (i.e., sense of presence, passage h., visual illusions, pareidolias) weekly during the last month | stable h. 3 months before the study	History of psychiatric disorders; cerebrovascular disease; conditions impairing mental status other than PD; factors impeding MRI scanning	0/18 PD mH
Hepp et al. (2017)	15 PD VH / 40 PD NVH / 15 HC	12 (4) / 11 (4)	69 (4) / 67 (7) / 67 (8)	SCOPA-PC (1st item)	Based on the SCOPA-P score	Previous stereotactic surgery; white matter lesions and tumors at MRI	N.A.
Yao et al. (2016)	12 PD VH / 15 PD NH / 14 HC	9 (3.5) / 7.1 (5.1)	70 / 66 / 63	PPRS	Repetitive and complex VH of well-formed persons, animals or objects, lasting for at least 4 weeks, occurring once every 4 weeks	Neurological disorders other than PD; major psychiatric disorders; depressive symptoms (MADRS ≥ 6); cognitive impairment with a MMSE < 24; left-handedness	3/12 PD VH
Franciotti et al. (2015)	15 sPD VH / 15 sPD NH / 15 HC NH / 15 MSA / 15 ePD NH	11.3 (4.3) / 12 (4.5)	70 (6) / 68 (11) / 69 (6) / 67 (5) / 66 (9)	PPRS / NPI	Complex kinematic hallucinations based on the PPRS | patients with illusions (misperceptions) were excluded from any group	Minor hallucinations	0/15 sPD VH
Yao et al. (2015)	12 PD VH / 12 PD NH / 14 HC NH	10 (3.5) / 8.4 (5.1)	67.6 (7.4) / 63.4 (7.4) / 64.1 (4)	PPRS	Repetitive and complex VH of well-formed persons, animals or objects, lasting for at least 4 weeks, occurring once every 4 weeks	Neurological disorders other than PD; major psychiatric disorders; depressive symptoms (MADRS > 6); cognitive impairment with a MMSE < 24; left-handedness	3/12 PD VH
Shine et al. (2015)	10 PD VH / 9 PD NH	6.9 (4) / 4.4 (3.3)	69.5 (8) / 67.1 (7)	MDS-UPDRS	BPP error score of 11 % used as cut-score	N.A.	N.A.

(continued on next page)

Table 3 (*continued*)

Study	Sample	Disease Duration	Age	Hall. assessment	Hall. group: inclusion criteria	Exclusion criteria	Hall. treatment
Yao et al. (2014)	10 HC NH		63.5 (8)				
	12 PD VH	10 (3.5)	67.6 (7.4)	PPRS	Repetitive and complex VH of well-formed persons, animals or objects, lasting for at least 4 weeks, occurring once every 4 weeks	Neurological disorders other than PD; major psychiatric disorders; depressive symptoms (MADRS > 6); cognitive impairment with a MMSE < 24; left-handedness	3/12 PD VH
	12 PD NH	8.4 (5.1)	63.4 (7.4)				
	14 HC NH		64.1 (4)				

3.1.1.7. Geographic location of studies. The studies were conducted in five different countries. Three studies were conducted in Hong Kong (Yao et al., 2016; Yao et al., 2015; Yao et al., 2014), three in Italy (Zorzi et al., 2021; Pezzoli et al., 2021a; Franciotti et al., 2015), two in Australia (Walpola et al., 2020; Shine et al., 2015), one in Spain (Bejr-kasem et al., 2019), and one in The Netherlands (Hepp et al., 2017).

3.1.2. Disease characteristics

3.1.2.1. Type of neurodegenerative disease. We searched for studies investigating hallucinations in all neurodegenerative diseases; however, the selected inclusion and exclusion criteria allow us to use only studies investigating patients with DLB and PD. Specifically, among the ten studies included in this review, two studies focused on patients with DLB and eight studies focused on PD. Thus, the total number of participants was 321. Specifically, there are 17 patients with DLB and hallucinations, 29 patients with DLB without hallucinations, 112 patients with PD and hallucinations, 153 patients with PD without hallucinations, 115 healthy controls and 15 patients with multiple system atrophy.

3.1.2.2. Disease duration. The disease duration was reported in all the included studies. The mean disease duration was 7.7 ± 3.4 years for neurodegenerative patients with hallucinations, and 6.5 ± 3.63 years for neurodegenerative patients without hallucinations.

3.1.2.3. Comparisons between diseases. The neurodegenerative patients with hallucinations were compared with patients with the same neurodegenerative disease but without hallucinations in only 20 % of the included studies. The rest of the studies (80 %) compared the neurodegenerative patients, with and without hallucinations, also with healthy subjects. Among these latter studies, in the study by Franciotti and colleagues (2015), the PD patients with hallucinations were also compared with patients with multiple system atrophy (MSA) and PD patients matched with MSA for disease duration.

3.1.2.4. Comorbidity. No data about comorbidity were found.

3.1.3. Hallucination characteristics

3.1.3.1. Type. A total of 90 % of the studies included a detailed description related to the type of hallucination, distinguishing between minor and major hallucinations. Hepp and colleagues (2017) does not specify the type of hallucination of the participants in the study. The study by Bejr-kasem and colleagues (2019) is the only one which has focused on minor hallucinations.

3.1.3.2. Sensory modality. Overall, 80 % of the studies focused on visual hallucinations, and another 10 % focused on hallucinations grouping different sensory modalities (Walpola et al., 2020), 10 % focused on minor hallucinations (Bejr-kasem et al., 2019) without specifying the modality.

3.1.3.3. Content. Thirty% of the included studies provided further details about the content of the hallucinations. Yao and colleagues (2016), Yao and colleagues (2015) reported participants experiencing visual hallucinations of people, animals and objects, and one participant with minor hallucinations (i.e., "presence of a person"). Bejr-kasem et al. (2019) reported 11 patients with presence hallucinations and 10 patients with passage hallucinations.

3.1.3.4. Duration. Only three out of the ten studies have reported the duration of the hallucinations (Yao et al., 2016; Yao et al., 2015; Yao et al., 2014), with a mean duration of 24.6 months.

3.1.4. Assessment and treatments

3.1.4.1. Hallucination assessment. The hallucination assessment was conducted through different scales: 30 % of the studies used the Neuropsychiatric Inventory Questionnaire (NPI, Cummings et al., 1994) (Zorzi et al., 2021; Pezzoli et al., 2021a; Franciotti et al., 2015), 30 % used the Parkinson Psychosis Rating Scale (PPRS) (Yao et al., 2016; Yao et al., 2015; Yao et al., 2014), 30 % used the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS, Goetz et al., 2008) (Walpola et al., 2020; Bejr-kasem et al., 2019; Shine et al., 2015), and only 10 % used the Scales for Outcomes in Parkinson Disease Psychiatric Complications (Hepp et al., 2017). Only one study also used a semi-structured interview in order to further examine the different types of minor hallucinations (Bejr-kasem et al., 2019).

3.1.4.2. Hallucination treatment. In 30 % of the studies, it was not specified whether the participants were taking medications for the hallucinations (Pezzoli et al., 2021a; Hepp et al., 2017; Shine et al., 2015). In 30 % of the studies, three patients per study were medicated against hallucinations (Yao et al., 2016; Yao et al., 2015; Yao et al., 2014). In another 30 % of the studies no patients were on medication (Walpola et al., 2020; Bejr-kasem et al., 2019; Franciotti et al., 2015). In 10 % of the studies the exact number of patients under medication was not reported (Zorzi et al., 2021).

3.1.4.3. Neuropsychological assessment. Overall, 80 % of the studies used neuropsychological tools to assess differences at a cognitive level between participants with and without hallucinations. However, only 40 % of the studies found significant differences between the group of neurodegenerative patients with hallucinations and the group without hallucinations. That is, hallucinatory patients had worse scores in visual attention (i.e., in the digit cancellation test) (Zorzi et al., 2021), attentional set-shifting and memory retention (Walpola et al., 2020), orientation, language, memory and perception (Cambridge Cognitive Examination revised test), semantic fluency, spatial span and working memory (Hepp et al., 2017), attentional set-shifting (i.e., slower performance in Trail Making Test B-A) and elevated imagery strength (Shine et al., 2015).

3.1.4.4. Behavioral assessment. Three out of ten studies have not assessed behavioral disorders (Zorzi et al., 2021; Pezzoli et al., 2021a; Hepp et al., 2017). The rest of the studies used different scales to assess depression, anxiety and apathy: three studies used Montgomery-Åsberg Depression Rating Scale - Self-assessment (MADRS-S) (Yao et al., 2016; Yao et al., 2015; Yao et al., 2014), two studies used the Beck Depression Scale (BDI-II) (Walpola et al., 2020; Shine et al., 2015); one study used the Geriatric Depression Scale and the State-Trait anxiety Inventory (Franciotti et al., 2015) and another one the Hospital Anxiety & Depression Scale and the apathy through the Starkstein Apathy Scale (Bejr-kasem et al., 2019). Thus, seven studies assessed depression, two studies assessed anxiety, and one study assessed apathy.

3.1.4.5. Treatment for motor symptoms. In 20 % of the studies, it is not specified whether participants were taking levodopa medication (Pezzoli et al., 2021b; Shine et al., 2015). In the rest of the studies, participants were under treatment for motor symptoms.

3.1.5. MRI characteristics

3.1.5.1. MRI acquisition and rs-fMRI analysis. In order to acquire neuroimaging data, 30 % of the studies used 1.5 T scanners (Zorzi et al., 2021; Pezzoli et al., 2021b; Franciotti et al., 2015), while the rest of the studies used 3 T scanners. Among the MRI scanners 70 % of the studies used Philips, and 30 % used General Electric (Walpola et al., 2020; Hepp et al., 2017; Shine et al., 2015).

Only 70 % of the included studies reported the mean duration of the resting state fMRI acquisition, which was around 7.5 min.

The ten studies included in this review were characterized by an heterogeneous methodology for the data analysis. Indeed, six studies used seed-based/regions of interest (ROI) analyses, three studies used independent component analysis (ICA) (Pezzoli et al., 2021b; Franciotti et al., 2015; Yao et al., 2014), two studies used amplitude of low-frequency fluctuation (ALFF) (Franciotti et al., 2015; Yao et al., 2015), and one study used a whole brain approach (Hepp et al., 2017).

3.1.5.2. A priori hypothesis. All authors specified the hypothesis of their studies. However, only 10 % of the studies were characterized by a clear direction in the a priori hypothesis (Franciotti et al., 2015). For instance, Franciotti and colleagues (2015) decided to test the hypothesis that an anxiety phenotype is characterized by a reduced activity in the DMN, and a hallucinatory phenotype is characterized by an enhanced activity in the DMN.

3.1.5.3. Structural analysis. A total of 50 % of the studies examined structural differences between groups of patients with hallucinations and those without (Zorzi et al., 2021; Bejr-kasem et al., 2019; Yao et al., 2016; Yao et al., 2014). Specifically, only Bejr-kasem and colleagues (2019) found that minor hallucinations were associated with greater atrophy in visual areas and DMN. Conversely, in 2016, Yao and colleagues found a smaller hippocampus in PD patients without hallucinations, but they did not find any difference in gray matter in the hippocampus of these patients. Moreover, whole brain analysis did not show any gray matter intensity difference between groups. In 2014, Yao and colleagues examined the cortical thickness in order to understand if the structural changes could influence a DMN dysfunction, but they did not find any difference between groups. Also, Franciotti and colleagues (2015) found no differences in structures related with DMN functions. Finally, only one study analyzed the white matter and found a reduction in the frontoparietal superior longitudinal fasciculus in patients with hallucinations (Zorzi et al., 2021).

3.1.6. Findings from the comparison between neurodegenerative patients with and without hallucinations: Main networks analyzed

Most of the included studies analyzed the DMN, DAN, VAN and VN as regions of interest. A summary of the FC in these areas is depicted in Fig. 2.

3.1.6.1. Connectivity within DMN. Most of the studies focusing on the DMN and comparing neurodegenerative patients with and without hallucinations found an increased FC in this network for the hallucinators (Pezzoli et al., 2021b; Bejr-kasem et al., 2019; Shine et al., 2015; Franciotti et al., 2015; Yao et al., 2016; Yao et al., 2015; Yao et al., 2014).

Specifically, using ICA, Pezzoli and colleagues (2021b) found an increased connectivity between the DMN and the inferior parietal lobule and the supramarginal gyrus in DLB patients with hallucinations compared to those without.

Another study by Franciotti and colleagues (2015), individualizing specific areas belonging to the DMN using ICA, compared PD patients with and without hallucinations. They found a higher FC in PD patients with hallucinations in all the areas except for the left and right middle frontal gyrus. These results partially contrast with the results from the study by Yao and colleagues (2014). Indeed, when comparing PD patients with and without hallucinations, they found a higher connectivity within the DMN in patients with hallucinations in the right middle frontal gyrus and in bilateral posterior cingulate precuneus (Yao et al., 2014). In 2015, Yao and colleagues found a higher ALFF in medial temporal lobe in patients with hallucinations.
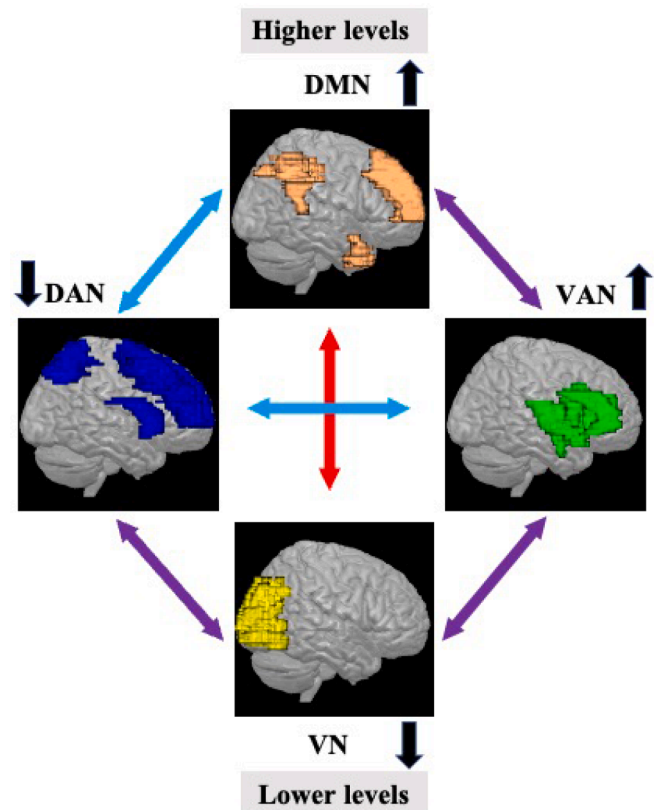

Fig. 2. Functional Connectivity (FC) within and between networks in hallucinatory neurodegenerative patients. The FC within networks is indicated by the black arrows (upwards: increased; downwards: decreased). The FC between networks is indicated by the arrows between squares (red: increased; light blue: decreased; violet: contrasting results). In the upper row (i.e., the higher level), there is the Default Mode Network (DMN). In the middle row, there are the attentional networks, that are Dorsal Attentional Network (DAN) and Ventral Attentional Network (VAN). In the lower row (i.e., the lower level), there is the Visual Network (VN). [1-column fitting image, in color]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

The study by Yao et al., 2016 investigated the role of the hippocampus in the phenomena of hallucinations, using the hippocampus as seed. In PD hallucinatory patients these authors found an increased FC in different regions of the DMN, such as the medial frontal gyrus, posterior cingulate cortex and inferior parietal lobe when compared to those without hallucinations.

The study by Bejr-kasem and colleagues (2019) is the only one focusing on minor hallucinations. Specifically, using a seed-to-whole brain analysis with the posterior cingulate cortex (PCC) selected as seed, they found a greater FC between PCC and the bilateral middle temporal gyrus in PD patients with minor hallucinations compared to those without.

However, only one study found a decreased FC in the DMN in DLB patients with hallucinations compared to those without (Zorzi et al., 2021).

3.1.6.2. Connectivity within DAN and within VAN. The study by Zorzi and colleagues (2021) found a decreased FC in the DAN and an increased FC in the VAN in DLB hallucinatory patients when compared with non-hallucinatory ones.

3.1.6.3. Connectivity between DMN-DAN. The results from the seed-based analysis carried out by Pezzoli and colleagues (2021b) showed a decreased FC between the left superior parietal lobule and the medial frontal gyrus. However, when they examined the right superior parietal lobule they found an increased FC with cerebellar regions. Using the PCC as seed, Bejr-kasem and colleagues (2019) found a great FC with the bilateral superior parietal lobes in PD patients with minor hallucinations.

3.1.6.4. Connectivity between DMN-VAN. Pezzoli et al. (2021b) found a decreased connectivity between the DMN and the left insula, which should be related to the VAN, while, another study found an increased FC between the hippocampus used as seed and the anterior cingulate cortex of PD hallucinatory patients when compared to those without (Yao et al., 2016).

3.1.6.5. Connectivity with the VN. Among the studies examining the role of the visual cortex in the hallucinations, in the study by Yao and colleagues (2015) the occipital region has been used as seed in order to analyze the connectivity with the rest of the brain. These results have shown a higher FC in different areas of the DMN, such as medial frontal gyrus and ventral medial prefrontal cortex, areas of the DAN, as the caudate, and of the VAN such as the anterior cingulate cortex. In line with these results, Bejr-kasem and colleagues (2019) found a greater FC between the PCC and visual processing areas, such as the middle occipital gyrus and the posterior middle temporal gyrus.

Using a seed-based analysis, Pezzoli and colleagues (2021b) found a decreased FC between the right primary visual cortex and temporo-parietal regions.

3.1.6.6. Whole brain analysis. Only one study investigated the whole brain resting-state fMRI networks and compared hallucinatory PD patients with a healthy control group. The results from this study have shown reduced FC in a network comprising nine distinct brain regions from the frontal cortex (i.e., superior frontal gyrus), temporal cortex (i.e., fusiform gyrus, superior temporal gyrus, middle temporal gyrus, and middle temporal pole), Rolandic operculum, occipital cortex (i.e., inferior occipital gyrus), and striatum (i.e., caudate nucleus and putamen) (Hepp et al., 2017). Thus, overall, PD patients with hallucinations were characterized by a lower whole brain FC only when compared with the control group.

3.1.6.7. Correlation fMRI, neuropsychological and behavioral results. The correlation between fMRI outcomes, neuropsychological and behavioral

results was investigated in 50 % of the studies. The study by Yao and colleagues (2016) found a lower FC between the right hippocampus with the right occipital gyrus and with the medial temporal areas, and their mean FC was associated with an impairment in the visuospatial memory performance (Yao et al., 2016). Another study found that, in PD hallucinatory patients, the reduced FC in the superior temporal gyrus was related to a worse performance in orientation, attention, praxis, perception and set shifting tests, while the reduced FC in the operculum was related to praxis and perceptual deficits (Hepp et al., 2017). One study has not found any significant results (Franciotti et al., 2015).

The study by Franciotti and colleagues (2015) also investigated the correlation between brain activity and anxiety levels. The findings showed that patients without hallucinations had higher anxiety levels and a DMN inhibition than patients with hallucinations and healthy subjects. Conversely, there was an increased DMN activity in PD patients with hallucinations compared with PD patients without hallucinations. The authors also found that DMN activity is reduced in MSA and PD patients without hallucinations, but these patients had higher levels of anxiety compared to healthy controls and PD patients with hallucinations.

Shine and colleagues (2015) examined both the connectivity within and between DMN, attentional and visual networks, but also their relations with processes like visual misperceptions and imagery. These authors found that the frequency of misperceptions on a bistable perceptual task and the strength of mental imagery predicted an increased connectivity within the VAN (i.e., bilateral anterior insula, bilateral dorsal anterior cingulate cortex) and the DMN (i.e., midline precuneus, midline medial prefrontal cortex, bilateral hippocampal formation), a decreased connectivity between the DAN (i.e., bilateral superior parietal lobule, bilateral frontal eye fields) and the VAN, between the VAN and the VN, and between the DAN and the VN (i.e., bilateral occipital cortex). Moreover, the severity in the BPP alone predicted increased connectivity within the VAN and the DMN and an impaired connectivity between the VAN and DAN. The strength of mental imagery was related to the amount of impaired connectivity between the VAN and VN.

One study investigated the association between mind-wandering and hallucinations, finding that patients with PD and hallucinations had higher levels of mind-wandering and a greater connectivity between early visual regions (i.e., fusiform gyrus/inferior temporal gyrus) and dorsal default networks (i.e., medial prefrontal cortex, posterior cingulate cortex, and left inferior parietal lobule) compared to PD patients without hallucinations (Walpola et al., 2020).

4. Discussion

This systematic review is the first work focusing uniquely on brain FC of neurodegenerative patients experiencing hallucinations. Doing so, we aim to unravel the neuronal mechanisms associated with the underlying disruptive perceptive processes. From the evidence collected so far emerges the complexity of the hallucinatory phenomena, whose pathogenesis is still not totally clear. Specifically, our work shows the heterogeneity and the limitations characterizing these studies and the overall understanding of the networks associated with the hallucinatory phenomena.

4.1. Characteristics of the included studies

The studies included in this systematic review reported clear objectives, inclusion and exclusion criteria and sociodemographic data regarding the participants. However, the overall sample size undergoing rs-fMRI was relatively small (<20 participants per group), and most of the studies lacked a clear direction in the a priori hypothesis, possibly due to the exploratory nature of these investigations. Initially, we were interested in focusing on different neurodegenerative diseases with hallucinations, including synucleinopathies (e.g., PD and DLB) and

tauopathies (e.g., AD and FTD). Nevertheless, we have not found studies on tauopathies matching our inclusion criteria. Indeed, the studies included in this systematic review focused solely on synucleinopathies, with most of the studies focusing on PD patients and only two studies focusing on DLB patients. Thus, further studies on different neurodegenerative diseases are needed in order to examine the existence of differences in brain areas between diseases.

Moreover, there were no rs-fMRI studies examining hallucinations in other sensory modalities than the visual one (e.g., auditory, gustatory, olfactory and tactile modality). However, further studies grouping different sensory modalities would be beneficial in order to better understand the possibility of an association between the presence of hallucinations in certain sensory modalities and the activation of specific brain areas.

From this review emerged the heterogeneity in the hallucination assessment and the lack of tools to differentiate between different types of hallucinations (i.e., minor vs major, simple vs complex). For instance, the NPI focuses only on complex hallucinations, providing information about their sensory modality; however, this questionnaire does not identify minor hallucinations. Conversely, the MDS-UPDRS scale (Goetz et al., 2008) used in other studies provides information on the hallucination type, but not on the sensory modality. Finally, the PPRS (Friedberg et al., 1998) is a scale ideated to investigate psychosis related to parkinsonian drug use. Thus, the assessment selected in the included studies does not characterize the hallucinatory phenomena, unless a semi-structured interview was added (Bejr-kasem et al., 2019) which was helpful to assess both the hallucination type and the related sensory modality.

However, researchers recommend, on one side, that the physician could ask specific questions about the presence of hallucinations to patients and their caregivers (Williams et al., 2008), and, on the other side, that the physician prepares the patients about the possibility of developing hallucinations as part of this specific neurodegenerative disease (Fernandez et al., 2008). Indeed, the presence of stigmas makes it difficult to accede to the description of hallucinatory experiences by the patients (Badcock et al., 2020; Badcock et al., 2017). Moreover, the fear of embarrassment, or the fact that the psychosis are not generally recognized as part of the typical set of symptoms in neurodegenerative diseases, could determine the lack of reported hallucinations (Chaudhuri et al., 2010; Goetz et al., 2006; Fénelon et al., 2000).

Furthermore, among the included study, very few described the duration of hallucinations (Yao et al., 2016; Yao et al., 2015; Yao et al., 2014). Since there are few longitudinal studies analyzing the impact of the duration of the hallucinatory experience, we cannot examine whether this factor could affect the FC.

4.2. Functional connectivity in patients with neurodegenerative diseases and hallucinations

From this systematic review emerges that only one study analyzed whole-brain FC (Hepp et al., 2017). The rest of the studies focused on specific brain regions, selecting seeds/ROI. Nevertheless, doing so, there is a risk of biasing the results, because this selection limits the possibility of developing a general model to explain the hallucinatory phenomena.

However, the neuroimaging findings from the ten studies in this systematic review tend to show an increased FC within the DMN and the VAN and a decreased FC within the DAN. Furthermore, the results suggest an increased connectivity between the DMN and the visual network and a decreased connectivity between the DMN and the DAN, and between the DAN and the VAN. Contrasting results emerge regarding the connectivity between the DMN and the VAN, and between the DAN/VAN and the visual network. An overview of the main findings from the ten rs-fMRI studies is depicted in Fig. 2.

The computational model proposed by Friston (2005) suggests a hierarchical organization of the brain functioning. That is, the previous interactions with the external world allow us to build up internal models and predictions about the causes of the sensory stimulus. These predictions act as top-down processes allowing the comparison between the expectation and the actual stimulus. In case of mismatch between the prediction and the actual stimulus ("prediction error"), the brain system updates the internal model, through bottom-up processes, in order to allow for its adjustment and save energy ("the free energy principle").

If we examine the possible origins of the visual hallucinations under the predictive umbrella, we could hypothesize that higher levels are mostly represented by the DMN (O'Callaghan et al., 2014). Thus, its disruption could determine an intrusion of the episodic memory in the perceptive system through top-down processes, as suggested by an overactivity within the DMN and by a dysregulated FC between the DMN and other networks. This disruption could influence the attentional networks, whose communication is dysregulated itself, as hinted by a decreased FC between the DAN and the VAN. This would determine a failure in evaluating the correct salience of the actual stimulus, reflected by a hypoactivity within the DAN and between the DMN and the DAN, and an attentional engagement towards the wrong perception of the stimulus, as suggested by an overactivity within the VAN. Furthermore, the attentional networks are unable to communicate with the sensory network (i.e., the lower levels), which are represented by the visual network in the case of visual hallucinations. Thus, the system is unable to update the internal model based on the comparison with the actual stimulus, as suggested by a disrupted connection between the attentional and the visual networks.

Thus, overall, our results seem to suggest that top-down (e.g., related to episodic memory intrusion) and bottom-up processes (e.g., related to the perception of the sensory stimuli) could be interrelated and both disrupted in the hallucination phenomenon. Indeed, the strong intrusion of episodic memory, and the failure in their inhibition, could result in an over-reliance on misperceived external stimuli. That is, the strong expectation of an external stimulus (e.g., a voice) could provoke the perception of that specific stimulus despite its absence, in a system which is not able to update its internal model (O'Callaghan et al., 2017a; Friston et al., 2014).

This proposed model, which we could define as the "interdependency model", could help in better identifying the mechanisms involved in the origins of the hallucinatory phenomena and in supporting the psychological rehabilitation of patients experiencing hallucinations. Indeed, if this model is correct, the analysis of the surrounding stimulus and the reinforcement of the inhibitory mechanisms could be essential to suppress the intrusive episodic memory.

Thus, our model shares with the theory proposed by Shine and colleagues (2014), Shine and colleagues (2011) the importance of the disruption of the DMN, attentional and sensory networks in the origin of the visual hallucinations. Furthermore, our hypotheses seem to be in line with previous models suggesting the involvement of memory and perceptual processes to explain the factors influencing the hallucinatory phenomenon. Among these, there are the Perception and Attention Deficit (PAD) model proposed by Collerton and colleagues (2005), which suggests perception and attention deficit as responsible of the recurrent complex visual hallucinatory phenomena (originating in frontal cortex and ventral visual stream), and the Hallucinatory Experience of Auditory Representation (HEAR) model proposed by Michie and colleagues (2005), which emphasizes memory intrusions as responsible of the auditory hallucinations in schizophrenic patients.

Finally, our FC results seem to be in line with those from a recent study on resting state effective connectivity, showing a decreased bottom-up connectivity with visual networks and increased top-down connectivity between areas of the DMN and visual networks (Thomas et al., 2022).

4.3. Limitations and future perspectives

The studies included in this systematic review are characterized by a high heterogeneity in the rs-fMRI analysis which does not facilitate a

direct comparison between findings. Furthermore, from the literature search, we noticed a lack of studies directly comparing patients with different neurodegenerative disease, but also neurodegenerative patients with psychiatric diagnoses. However, studies examining a similar set of symptoms may help in better understanding similarities and differences in the processes involved in hallucinations and whether these processes may depend on factors related to a specific disease. For instance, an fMRI study focusing on auditory hallucinations in schizophrenic patients report an hyperactivation of the sensory areas (e.g., the temporal lobe in the case of auditory verbal hallucinations) and an hypoactivation of the prefrontal lobe (Hugdahl, 2009). Notwithstanding, it is not possible to generalize these findings to populations with neurodegenerative diseases.

5. Conclusions

The present systematic review, following PRISMA guidelines, is the first one focusing solely on recent rs-fMRI studies in order to shed some light on the FC characterizing patients with neurodegenerative disease and experiencing hallucinations, and to unravel the brain processing underlying it. Moreover, our work attempts to test the predictive coding theory with regards to hallucinations in neurodegeneration (Friston, 2005) in order to identify at which level the brain system of neurodegenerative patients experiencing hallucinations could fail compared to healthy subjects.

The neuroimaging findings from rs-fMRI suggest a dysfunction in the default mode, attentional and sensory brain networks which could affect memory and perceptual processes. Thus, our work supports the idea suggesting that misperceptions could originate by a mismatch between the subjective expectation and the actual sensory stimulus.

Notwithstanding, we have found a lack of rs-fMRI studies on tauopathies and on other sensory modalities than the visual one, which hamper a better understanding of the hallucinatory phenomena. Thus, the evidence emerging from this work is limited to the characteristics of the included studies. Further studies, with a more homogenous methodology and involving different neurodegenerative diseases, are needed in order to propose a general model able to describe the brain networks related to the hallucination phenomenon in neurodegenerative diseases and to overcome the limitations currently present in literature.

CRediT authorship contribution statement

Vittoria Spinosa: Conceptualization, Validation, Methodology, Formal analysis, Resources, Investigation, Writing – original draft, Writing – review & editing. **Elvira Brattico:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Fulvia Campo:** Validation, Investigation, Writing – review & editing. **Giancarlo Logroscino:** Funding acquisition, Conceptualization, Investigation, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2022.103112.

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