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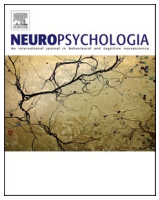

Review article

Neuroanatomical correlates and predictors of psychotic symptoms in Alzheimer's disease: A systematic review and meta-analysis

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ABSTRACT

Background: Psychotic symptoms (hallucinations and delusions) are a type of neuropsychiatric symptom found during Alzheimer's Disease (AD).
Objective: This systematic review aims to comprehensively capture, analyse, and evaluate the body of evidence that has investigated associations between brain regions/networks and psychotic symptoms in AD.
Methods: The protocol, created according to the PRISMA guidelines, was pre-registered on OSF (https://osf.io/tg8xp/). Searches were performed using PubMed, Web of Science and PsycInfo. A partial coordinate-based meta-analysis (CBMA) was performed based on data availability.
Results: Eighty-two papers were selected: delusions were found to be associated mainly with right fronto-temporal brain regions and the insula; hallucinations mainly with fronto-occipital areas; both were frequently associated with the anterior cingulate cortex. The CBMA, performed on the findings of fourteen papers on delusions, identified a cluster in the frontal lobe, one in the putamen, and a smaller one in the insula.
Conclusions: The available evidence highlights that key brain regions, predominantly in the right frontal lobe, the anterior cingulate cortex, and temporo-occipital areas, appear to underpin the different manifestations of psychotic symptoms in AD and MCI. The fronto-temporal areas identified in relation to delusions may underpin a failure to assimilate correct information and consider alternative possibilities (which might generate and maintain the delusional belief), and dysfunction within the salience network (anterior cingulate cortex and insula) may suggest a contribution for how internal and external stimuli are identified; the fronto-occipital areas linked to hallucinations may indicate diminished sensory processing and non-optimal predictive processing, that together contribute to misinterpretation of stimuli and misperceptions; the fronto-temporal and occipital areas, as well as the anterior cingulate cortex were linked to the psychotic cluster.

1. Introduction

Neuropsychiatric symptoms are psychiatric and behavioural manifestations that occur in people with Alzheimer's disease (AD) and other neurological disorders. Their cumulative prevalence in those with dementia has been estimated at 97% (Steinberg et al., 2008), and at times, they can precede cognitive decline (Gallagher et al., 2017), which has led to the proposition of the label – Mild Behavioural Impairment (Ismail et al., 2016). This can be used to characterise people with these symptoms who are in a prodromal stage of the disease (similar to how Mild Cognitive Impairment is used to describe people with cognitive problems whose symptoms do not warrant a diagnosis of dementia). Neuropsychiatric symptoms occur as an array of heterogeneous manifestations that have been identified to cluster (Lyketsos et al., 2000; Aalten et al., 2007), typically by psychosis (consisting of delusions and/or hallucinations), hyperactivity (agitation, aggression, disinhibition, irritability, aberrant motor behaviour, euphoria), affective symptoms (depression, anxiety), and apathy. Among the clusters, psychotic symptoms are highly prevalent, can be detected in about half of patients with AD during the disease course (Paulsen et al., 2000; Weamer et al., 2016), and appear to have a minimum persistence of at least a year (Vilalta-Franch et al., 2013). Notably, the presence of psychotic

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symptoms has been associated with an aggravation of the clinical picture of AD: they are associated with a more rapid cognitive (Wilson et al., 2000; Almeida et al., 2024) and functional decline (Fischer et al., 2012; Bertrand et al., 2017), and increased mortality (Almeida et al., 2024; Scarmeas et al., 2005); they cause increased distress for those people with AD and their caregivers, resulting in a higher rate of hospitalisation (Fischer et al., 2009); they are also associated with the presence of other neuropsychiatric symptoms, particularly depression and agitation (Wilkosz et al., 2007; Van der Mussele et al., 2015), which contribute to the severity of the disease; lastly, when identified at the stages of Mild Cognitive Impairment (Liew, 2019) or Mild Behavioural Impairment (Yoon et al., 2022) they have been associated with an increased risk of conversion to AD (Yokoi et al., 2019).

1.1 Phenomenology of Psychotic Symptoms in AD

Psychotic symptoms in AD have been investigated as individual symptoms or in a combined form as part of a psychotic cluster (Apostolova et al., 2014). The first approach has been most commonly employed in studies on the neuroanatomical and neurobiological correlates of each symptom (Fischer and Sweet, 2016), that attempt to shed light on whether there are different underlying mechanisms behind the two symptoms. Likewise, the symptoms are often separated in studies on clinical outcomes (e.g., with the presence of hallucinations more frequently associated with increased severity of disease and mortality (Christie et al., 2012)). Another reason to divide symptoms, is that depending on disease stage (within the AD continuum), they have different rates of prevalence, with delusions typically manifesting earlier than hallucinations (Scarmeas et al., 2005; Zhao et al., 2016). The second approach, of considering the symptoms together is, alternatively, corroborated by genetic studies (DeMichele-Sweet and Sweet, 2010; Hollingworth et al., 2012), which have highlighted the heritability and familial aggregation of psychosis in AD (Shah et al., 2017). That approach has been further supported by factor analysis investigations on the neuropsychiatric manifestations of AD (Aalten et al., 2007; Wadsworth et al., 2012) and MCI (Van der Mussele et al., 2013), which frequently identify a single psychotic factor among the patients presenting delusions and hallucinations, that is present at different stages of the disease continuum.

Delusions are defined as fixed beliefs that are not amenable to change, even in light of conflicting evidence (American Psychiatric Association, 2013). The themes they tend to present with in AD are not bizarre and complex, unlike those that occur in other syndromes such as schizophrenia; instead they are concrete and based on similar re-occurring themes (Fischer and Sweet, 2016), including theft, persecution, infidelity, jealousy, abandonment, and misidentification phenomena such as the belief that deceased individuals (typically parents or siblings) are still alive, not recognising one's home, spouse or family, Capgras syndrome, and phantom boarder syndrome (Koppel et al., 2014; Murray et al., 2014; Ballard et al., 2020).

Hallucinations are perceptions occurring in the absence of corresponding external or somatic stimuli (Arciniegas, 2015); they can reflect all senses; however, in AD, the most common type is visual, followed by auditory, with rare reports of somatic, olfactory, and tactile experiences (El Haj et al., 2017).

Recently revised criteria used to define psychotic symptoms in AD (Fischer et al., 2020; Cummings et al., 2020) propose that psychotic symptoms might manifest at the stage of Mild Cognitive Impairment (Cummings et al., 2020), including pre-clinical cases in which psychotic symptoms might manifest earlier than other symptoms of cognitive decline (Fischer et al., 2020). With respect to their phenomenology, the IPA framework (Cummings et al., 2020) proposes that delusions and hallucinations should be treated separately, while the ISTAART criteria (Fischer et al., 2020) provide evidence both in support of a shared mechanisms, and of differentiated neural correlates of delusions and hallucinations (Agü et al., 2022). Within this framework, it is further suggested that delusions should be considered with respect to their subtypes based on the themes of paranoia and misidentification, while hallucinations should be considered on the basis of their sensory modality.

Lastly, concerning their prevalence, this has proven difficult to determine, particularly due to their variability along the AD continuum (Chen et al., 2021) and the different approaches employed for their classification (Zhao et al., 2016). In a recent systematic review and meta-analysis (Zhao et al., 2016) performed across thirty-four studies for delusions, and thirty-one for hallucinations, a substantial degree of variability was found, with delusions ranging from 9 to 59% (pooled at 31%) and hallucinations ranging from 6 to 41% (pooled at 16%); this variability across studies was only partially explained by factors considered in the review, such as age of the patients and duration of disease, therefore other factors that have yet to be determined might contribute to this.

1.2 Neuroimaging Techniques in the Investigation of Psychotic Symptoms

Due to their high prevalence and detrimental impact on people with AD and other dementias, psychotic symptoms represent a worthy treatment target (Agü et al., 2022), and an increasing number of studies have been published in the last three decades to advance hypotheses on their underlying mechanisms. Notable progress has been made in identifying brain areas and networks associated with the presence of delusions and hallucinations in Alzheimer's disease and Mild Cognitive Impairment through the application of a range of different neuroimaging techniques.

Among these, magnetic resonance imaging (MRI) has been extensively used in recent years, as it allows the study of grey matter atrophy in people with psychotic symptoms. Typically, voxel-based morphometry (VBM) (Ashburner et al., 2009) or surface-based morphometric (SBM) methods (Freesurfer) are used. These techniques enable whole brain analyses (voxel or vertex-wise) to be carried out or instead allow focus to be placed upon specific brain regions using a region of interest (ROI) approach. MRI has also been used to study the role of vascular lesions, or white matter hyperintensities (WMH), in association with the clinical manifestations of AD (e.g., Hirono et al., 2000).

In addition to the results derived from a structural investigation of the brain, functional imaging techniques have been used to study neuropsychiatric symptoms. These techniques allow individual brain regions to be assessed, in addition to the mapping of neural networks. They can be applied during rest (e.g., to reveal intrinsic connectivity networks) or while participants are engaged in tasks requiring higher mental functions. Among these, those most typically used are single photon emission tomography (SPECT) and [(18F)] fluorodeoxyglucose positron emission tomography (FDG-PET), which provide measures of blood flow (perfusion) and glucose metabolism, respectively, and in more recent years, functional magnetic resonance imaging (fMRI), which relies on hemodynamic changes related to underlying cellular activity.

1.3 The Need for a Systematic Review and Meta-Analysis

Given the large number of studies that have investigated the brain regions and networks associated with the manifestation of psychotic symptoms in AD, a systematic review and meta-analysis to identify the key brain regions and networks that are linked to these symptoms would be highly beneficial and timely.

To the authors' knowledge, this is the first review to systematically identify and evaluate all of the evidence provided by studies on the associations between brain regions and networks, as assessed by the different neuroimaging modalities, while breaking down the literature into the individual symptoms (delusions and hallucinations) and also considering the findings when treated as part of a psychotic cluster.

While several systematic reviews on neuroimaging and neuropsychiatric symptoms exist, they have tackled this issue from different perspectives: some of these, which focus on neuroimaging, typically consider all neuropsychiatric symptoms (Chen et al., 2021; Boublay et al., 2016; Alvez et al., 2017), consequently providing a narrower breadth of evidence and analysis specific to the psychotic phenomenology. Others have provided an overview of key findings in this particular area (Fischer and Sweet, 2016; Murray et al., 2014; Gottesman and Stern, 2019; Ismail et al., 2022), albeit without adopting a systematic approach to capture and then analyse the entire body of evidence, nor providing meta-analyses on the data derived from the studies as we aim to do. With delusions being the most studied among psychotic manifestations, likely due to their higher prevalence in AD, two informative reviews (Ismail et al., 2012; Reeves et al., 2012) focused on this symptom, but they are now over ten years old, did not cover the literature on hallucinations, or consider the symptoms as a cluster. Furthermore, only one review (Chen et al., 2021), which was focused on a large range of neuropsychiatric symptoms, included a risk of a bias assessment tool to evaluate the quality of the studies included and provide further rigour in the interpretation of the findings of the selected studies.

Given these limitations of previous systematic reviews on the brain regions/networks linked to psychosis and the growing number of studies on this topic, which has seen an exponential surge over approximately the last five years, an up-to-date and more comprehensive systematic review is much needed.

1.4 Potential Sources of Variability in Neuroimaging Studies of Psychotic Symptoms

Several methodological choices are likely to contribute to variability in the findings across studies that attempt to link brain regions to psychotic symptoms. The current review has been designed to record key methodological details of the studies, so that these may be filtered and clustered in order to identify potential sources of variation.

Heterogeneity across neuroimaging techniques and associated analysis methods may be two sources of such variation. For instance, in relation to the analytic approach, in both structural and functional modalities, adopting a region of interest (ROI) approach could yield different results compared to when analysing the whole brain through voxel-based (or vertex-based) techniques (e.g., Giuliani et al., 2005). For this reason, the neuroimaging modality and analytic approaches will be recorded.

Other factors intrinsic to the studies' designs might present sources of variation across findings. Considering the difference in prevalence rates of psychotic symptoms along the AD continuum (Weamer et al., 2016), one such aspect is the disease stage. This refers, for example, to whether the associations were investigated in a prodromal or more clinically advanced stage of the disease.

The reliability of results might be influenced by the study sample size, and larger sample sizes are desirable. Initiatives such as the Cache County Study (Steinberg et al., 2008) or the Alzheimer's Disease Neuroimaging Initiative (ADNI), which collect data from large numbers of patients with AD and cognitively healthy elderly people, allow a variety of analyses to be performed on an extended sample. An expectation might be that they will be more reliable. Still, multi-site studies can come at the cost of having different brands or models of scanners, in addition to software versions, protocols and technical staff across sites (which can introduce variance, for example, in the homogeneity of the scans, and which may, therefore influence the results). The results derived from these larger multi-site studies might, therefore, differ from the results obtained from smaller scale projects, for example, that use a single scanner. The composition of the sample(s) is also likely to play a role (i.e. whether a matched control sample was included in the analysis, and if so, how exactly were they matched).

Furthermore, the presence of psychotic symptoms in AD is commonly assessed using standardised tools, mainly the caregiver-interview Neuropsychiatric Inventory (Cummings et al., 1994) (NPI, or NPI-Q in its shorter form), the Brief Psychiatry Rating Scale (BPRS) (Overall and Gorham, 1962), and the Behavioural Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) (Reisberg et al., 1987). The ability of a study to capture the psychotic symptomology is likely to be impacted by the sensitivity and specificity of the tool used; therefore, capturing the instrument used should be beneficial for a comprehensive appraisal of results.

The assessment of psychotic symptoms is also further impacted by an understanding of their phenomenology: as mentioned above, most studies have explored these symptoms focusing either on delusions and hallucinations as individual symptoms or within a psychotic cluster, which was at times also inclusive of other neuropsychiatric symptoms, that were found by some studies to load in the same cluster as delusions and hallucinations, for example: sleep disturbances (Aalten et al., 2007; Wadsworth et al., 2012) or agitation (Banno et al., 2014). Others have investigated different aspects of the symptomology; for example, some exploring psychosis in terms of misidentification (normally inclusive of hallucinations, and delusions of misidentification, Capgras syndrome and phantom boarder) versus paranoia (normally inclusive of delusions of persecution, theft, abandonment and jealousy) as two distinctive subtypes (Cook et al., 2003) and investigating their relation to different brain areas (Bruen et al., 2008; D'Antonio et al., 2019). Similarly, the study of delusional subtypes has provided some evidence (Nomura et al., 2012; Nakano et al., 2005; Schroeter et al., 2020) to support that the different content of delusions might relate to distinct underlying processes, and consequently, different brain mechanisms. Lastly, while hallucinations in AD tend to be mostly visual, differences have been reported in terms of brain areas related to the sensorial nature of the hallucination (El Haj et al., 2017).

Given these different approaches to the study of psychotic symptoms, within this review, we plan to provide a highly comprehensive overview by capturing all the neuroimaging literature that either a) groups symptoms into a cluster, b) that separates them into separate symptoms (e.g., hallucinations vs. delusions), or c) which divides symptoms into separate subtypes (e.g., misidentification vs paranoia).

1.5 Aims of this Systematic Review and Meta-Analysis

This systematic review aims to identify the large number and diverse range of neuroimaging studies that investigate the brain regions and networks that are linked with psychotic symptoms in AD, to record and provide a synthesis of the results, evaluate the findings for a psychotic cluster, and for hallucinations and delusions separately, investigate sources of variation across the findings, and appraise study quality using a validated tool (The Joanna Briggs Institute, 2014). Furthermore, depending on the number of included studies, and the homogeneity of methods applied, the potential for meta-analyses will be explored.

2. Methods

The protocol for this systematic review has been pre-registered on the Open Science Foundation (OSF) (https://osf.io/tg8xp/).

2.1 Search Strategy and Selection of Records

This review was based on the PRISMA protocol (Page et al., 2021a, 2021b), and each step was recorded in a PRISMA flowchart [Fig. 1]. A review of the literature was performed between the 9th and the 30th of December, 2021, on the databases PubMed (PubMed), Web of Science (Web Of Science) and PsycInfo (APA PsycInfo), using the following terms:

"Psychosis" OR "Psychotic" OR "Neuropsychiatric" OR "NPS" OR "Behavioural" OR "Behavioral" OR "BPSD" OR "Delusion*" OR

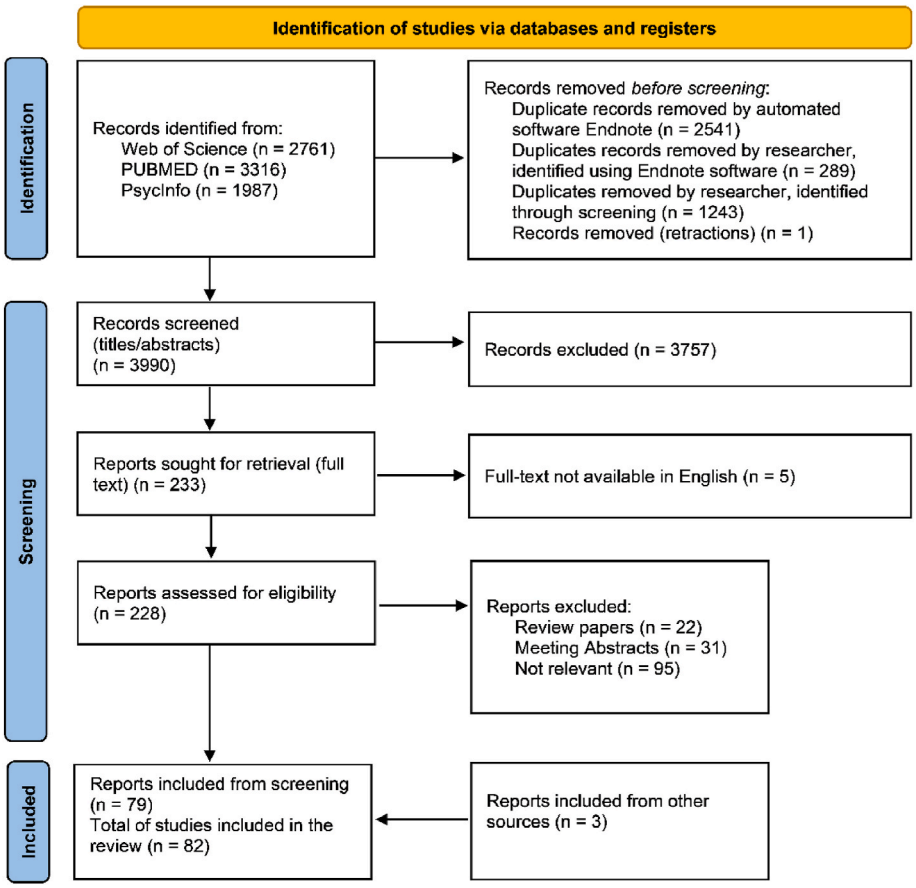

Fig. 1. Prisma Flowchart. This depicts the steps undertaken to search for the keywords on the database, the elimination of duplicates and final selection of the records analysed.

"Hallucination*" OR "Misidentification" OR "Persecut*" OR "Capgras"

AND

"Alzheimer's" OR "AD" OR "MCI" OR "Mild cognitive impairment" or "Dement*"

AND

"Neuroanat*" OR "Neuroimaging" OR "MRI" OR "Magnetic Resonance Imaging" OR "fMRI" OR "Functional Magnetic Resonance Imaging" OR "Positron Emission Tomography" OR "PET" OR "Single Photon Emission Computed Tomography" OR "SPECT" OR "Voxel-based Morphometry" OR "VBM" OR "Cortical Thickness".

All records retrieved were imported from the databases into an ad-hoc developed Endnote library; duplicates were removed both automatically (through Endnote import procedures), and manually by one of the researchers. This led to the selection of three thousand nine hundred and ninety records, which were screened for titles and abstracts by two independent reviewers [Fig. 1], according to the following eligibility criteria.

- Eligible studies were either cross-sectional studies (which investigated the association between affected brain regions/network and psychotic symptoms), or longitudinal studies (which investigated the brain regions/networks that when affected, predict future manifestation of psychotic symptoms);
- They contained samples of people with Alzheimer's disease and/or Mild Cognitive Impairment, and had a focus on delusions or hallucinations (either independently, or as part of broader analyses on psychotic symptoms or neuropsychiatric symptoms);
- Eligibility was limited to publications in English and peer-reviewed publications, but with no restrictions on publication date.

Two hundred and thirty-three records were deemed relevant from the screening: five of these were not available in English and were therefore excluded, while the remaining two hundred and twenty-eight were retrieved in full text to be assessed for eligibility by two independent reviewers; these led to the inclusion of seventy-nine records. Papers that were excluded after being assessed using the full texts were considered non-relevant for various reasons, among which the most common were: that they consisted of commentary on previous results (e.g., review articles) rather than providing original research findings; their symptoms of interest did not include psychotic symptoms; their methodology did not relate to neuroimaging techniques. A full list of excluded articles and the reasons for these is available from the authors upon request. Three additional studies were selected from the screening of reference lists of relevant papers and reviews, limited to papers published before the 30th December, 2021 [Fig. 1].

For completeness, in relation to literature capture, case studies were included in the systematic review and their findings are presented in the tables and results section. However, when performing a holistic appraisal of the regions/networks most commonly identified across the literature, only studies containing analyses with multiple participants were considered. Therefore, while the results of case studies are reported in order for the reader to have a complete representation of all studies (up to our cut-off date) which investigate these symptoms using neuroimaging, the findings from these studies were not included in the counts that provide a synthesis of the most common brain areas and networks associated with the symptoms of interest.

Agreement on the inclusion of records between the reviewers was

tested using Cohen's Kappa inter-rater reliability assessment (Cohen, 1960), after both independent selections of titles and abstracts and then full texts; this was performed on IBM SPSS Statistics (Version 28) (IBM Corp.), with moderate results (titles/abstracts: κ=.562 (95% CI, 0.614 to 0.51), $p < 0.001$; full texts: κ=.663 (95% CI, 0.759 to 0.567), $p < 0.001$). Where discrepancies arose, these were resolved through discussion of the individual papers, and full agreement was subsequently reached at both stages.

2.2 Quality Assessment of Included Papers

The papers included in the review were assessed for risk of bias, using a validated tool deemed fit for our type of data (Ma et al., 2020): the Joanna Briggs Institute Critical Appraisal Tool Checklist for Analytical Cross-Sectional Studies (The Joanna Briggs Institute, 2014).

The items of the tool were: 1. Were the criteria for inclusion in the sample clearly defined? 2. Were the study subjects and the setting described in detail? 3. Was the exposure measured in a valid and reliable way? 4. Were objective, standard criteria used for measurement of the condition? 5. Were confounding factors identified? 6. Were strategies to deal with confounding factors stated? 7. Were the outcomes measured in a valid and reliable way? 8. Was appropriate statistical analysis used?

These were applied to each study by two independent reviewers, with the purpose of assessing their methodological quality, and determining the extent to which the possibility of bias was addressed in their designs and analyses.

Any case of discrepancy between the two reviewers was resolved through discussion, and agreement on the score of all items was reached.

2.3 Data Extraction

An ad hoc protocol for data extraction was designed in order to extract the data which we considered most informative and potentially useful for synthesis. The protocol allowed details of the sample and design of the papers to be captured, along with a clear categorisation of the symptom studied; the characteristics of the neuroimaging technique employed; and clear details on the statistical analysis performed.

More specifically, the following headings were included in the protocol, which reflected elements for summarisation, and that may be potentially useful for synthesis, and/or likely to impact the findings and inform their interpretation: Author(s) and Year, Symptom(s), Participants, Diagnosis and Disease Stage, Symptom rating scale/Assessment Method for Psychosis, Design(s), Neuroimaging Technique, Type of scan, Analysis software, Neuroimaging Metrics, Aim(s) of the paper in relation to analyses relevant to this review, Confounding Factors accounted for in the Analyses, Brain Area(s) investigated, Statistical threshold and correction, Relevant Findings.

With regards to the symptomology, this was divided into the three main groups of delusions, hallucinations, and psychotic cluster, with the latter referring to the papers that used the approach of selecting a combined sample inclusive of patients presenting with delusions and/or hallucinations, and any additional symptoms considered within the cluster. The subtype of delusions and hallucinations was also further specified for those studies that reported this information.

3. Results

3.1. Descriptive Features

The data extracted from the eighty-two papers [Tables 2–4] highlighted an upward trend in the year of publication, with 61% papers published in the last decade only (n = 50), from 2011 to 2021 and the remaining 39% (n = 33, from 1991 to 2010) extending to the previous two decades.

In terms of frequency of neuroimaging technique, the most common was structural MRI (n = 47), mainly used to assess grey matter (n = 40) and white matter (n = 2) atrophy, with either regional or whole brain (voxel-wise or vertex-wise) analyses, white matter changes assessed through the Age-Related WMC Scale (Wahlund et al., 2001) (n = 2), and presence of white matter hyperintensities (n = 10); this was followed by SPECT (n = 17) and PET (n = 15), and less commonly fMRI (n = 5) and CT (n = 4).

Forty-nine papers investigated delusions and in n = 17, analyses were focused on one or more delusional subtypes (e.g., Capgras syndrome, misidentification, persecutory, etc.) [Table 2]. Twenty-five papers investigated hallucinations [Table 3]. Concerning the composition of the samples, the presence of other psychotic or neuropsychiatric symptoms was rarely reported, with few exceptions. Specifically, among the studies that investigated delusions, one study, in which the sample with delusions might also have had hallucinations, specified that the control (non-delusional) sample did not present with hallucinations, and two studies reported that other neuropsychiatric symptoms were present in their samples (who had delusions), and these were considered in the analyses; similarly, among the studies that investigated hallucinations, one considered the presence of other neuropsychiatric symptoms, and within the studies on psychotic symptoms, one considered non-psychotic neuropsychiatric symptoms in the analyses. Within the remaining studies, this information was not available. Lastly, a considerable number of papers classified participants according to a psychosis symptom cluster (n = 26) [Table 4]. In the associated analyses, participants were classified as being in a psychosis group, irrespective of what type of psychotic symptom they had (e.g., there were not separate subgroups for delusions and hallucinations). In three cases, one other neuropsychiatric symptom was also found to load on a psychosis-themed factor (in n = 2 studies this was sleep disturbances and in n = 1 disinhibition).

Supplementary Tables 1 and 2 provide a summary of the papers which reported significant and non-significant findings, reported according to the targeted symptoms and the neuroimaging technique employed (with further specification for MRI in terms of analysis method).

In terms of assessment of the symptoms, the most common standardised tool was the Neuropsychiatric Inventory (n = 44), followed by its shorter version, the NPI-Q (Cummings et al., 1994) (n = 10). Other assessment tools included the Neurobehavioural Rating Scale (Levin et al., 1987) (n = 4), and the BEHAVE-AD (Reisberg et al., 1987) (n = 3); on some occasions, no standardised tool was employed, and the symptom classification was based either on the application of DSM (American Psychiatric Association, 1987; American Psychiatric Association, 1994) (n = 5) or Jeste and Finkel (2000) (n = 2) criteria, or on observation of the clinical picture (n = 5) and unstandardised interviews (n = 2).

The sample size was commonly between 5 and 30 participants with psychotic symptoms, with few exceptions: case studies, as well as some studies with a focus on many different NPS, had only 1 or 2 patients, while the highest number of patients with psychotic symptoms (as a cluster) was 79. The studies were varied in terms of disease stage, with some studies focusing on specific levels of severity (MCI and/or specifically amnestic MCI, or mild, moderate, or severe AD dementia) and others including some or all of those.

Diagnosis of probable AD was almost always made on the basis of NINCDS-ADRDA criteria (n = 74), often supported by the Mini Mental State Examination (MMSE) (Folstein et al., 1975) (n = 20) and Clinical Dementia Rating Scale (CDR) (Morris, 1993) (n = 13). These two measures were also frequently employed to determine the severity of the disease stage.

3.2. Holistic Appraisal

An overall analysis of all regions and networks that were most commonly found across all neuroimaging techniques and symptomatologic dimensions, highlighted that some key areas appear to underpin the manifestation of psychotic phenomenology in AD: these are mainly

Table 1
Brain regions and networks identified In association with psychotic symptoms.

	Structural measures - grey and white matter atrophy, areas of white matter hyperintensities (MRI and CT)	Functional measures – hypo/hyper metabolism, hypo/hyper perfusion, haemodynamic changes (PET, SPECT, fMRI)
Delusions	Frontal Lobe Superior, Middle, Medial and Inferior Frontal Gyri (bilateral) *8* Orbitofrontal Cortex (bilateral) *2* Temporal Lobe Superior Temporal Gyrus (bilateral) *4* Parahippocampal Gyrus (bilateral) *2* Parietal Lobe Precuneus (L) *2* Occipital Lobe Inferior and Middle Occipital Gyri (bilateral) *2* Anterior Cingulate Cortex (R) *4* Posterior Cingulate Cortex (R) *3* Insula (bilateral) *3* Basal Ganglia (Putamen) (bilateral) *2* Cerebellum (bilateral) *3*	Frontal Lobe Superior, Middle, Medial and Inferior Frontal Gyri (bilateral) *11* Orbitofrontal Cortex (bilateral) *5* Prefrontal Cortex (R) *3* Temporal Lobe Superior, Middle, Medial and Inferior Temporal Gyri (bilateral) *12* Parietal Lobe Precuneus (bilateral) *3* Occipital Lobe Middle and Medial Occipital Gyri (bilateral) *2* Anterior Cingulate Cortex (bilateral) *2* Posterior Cingulate Cortex (bilateral) *3* Insula (bilateral) *2* Basal Ganglia (Putamen) (bilateral) *2*
Hallucinations	Frontal Lobe Superior and middle Frontal Gyri (bilateral) *2* Temporal Lobe Parietal Lobe Occipital Lobe Anterior Cingulate Cortex (R) *2*	Frontal Lobe Temporal Lobe Parietal Lobe Occipital Lobe
Psychotic cluster	Frontal Lobe Superior, Middle, Medial and Inferior Frontal Gyri (bilateral) *6* Orbitofrontal Cortex (bilateral) *2* Temporal Lobe Parahippocampal Gyrus (bilateral) *2* Hippocampus (R) *2* Entorhinal Cortex (bilateral) *2* Parietal Lobe Occipital Lobe Lingual Gyrus (bilateral) *3* Anterior Cingulate Cortex (bilateral) *2*	Frontal Lobe Orbitofrontal Cortex (bilateral) *2* Temporal Lobe Parietal Lobe

Notes. All reported regions were identified by at least 2 studies that contain multiple participants (case studies are excluded from the counts); *n* indicates the exact number of papers which mentioned this region. When only the category label of brain region is listed (text underlined), without a specific brain region provided beneath, it signifies that a region falling under this category was mentioned in the findings from more than two studies, however, either no further specifics were provided on location, or the studies reported different brain regions within the category label.

regions in the frontal lobe, and in the limbic system; nevertheless, associations were also found with brain regions in the temporal, parietal and occipital lobes, and in subcortical structures. There was a slight predominance of associations to the right hemisphere.

Table 1 presents an overview of the most common regions that were identified to have associations with the symptoms of interest, grouped by psychotic symptomology, and structural and functional neuroimaging technique.

3.3. Quality Appraisal: Risk of Bias Assessment

Fig. 2 depicts a visual representation of holistic appraisal performed using the risk of bias assessment tool (The Joanna Briggs Institute, 2014). This showed that the overall quality of the evidence according to the criteria of this tool was high, as more than two thirds of the studies scored positively across all items.

It also allowed reflection on the main aspects of variability revealed by this assessment: whether each study considered potential confounds, and if they adopted strategies to take their impact into account (e.g., by including these as covariates in the analyses). The severity of disease, most commonly measured with the MMSE (n = 37), CDR (n = 16), or Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-Cog) (Mohs, 1994) (n = 4) was one of the most commonly used, normally alongside age (n = 47), and at times other aspects such as gender (n = 30), years of education (n = 24), and duration of illness (n = 14).

About two thirds of the papers (n = 37) explicitly stated controlling for or considering factors in relation to the imaging technique; in the MRI, the most common was the total intracranial volume (n = 26), while a small number of PET and SPECT studies stated use of mean glucose metabolism/blood flow rate (n = 6). One potentially important aspect that was only considered in a small number of studies, was the overall neuropsychiatric picture of the sample, particularly for the studies which focused on delusions and hallucinations independently, it is mostly unclear whether the presence of the other symptom was considered. While the majority of the studies considered at least one, and more frequently combinations of those factors (most commonly disease severity, age, gender, and aspects relating to the imaging technique employed, such as total intracranial volume), in about a third of the studies whether these types of factors were included in the analyses, was not specified in the papers.

Another aspect of variability was the level of detail provided when reporting the statistical analysis methodology, in reference to the significance threshold and/or methods applied to account for multiple comparison: while the majority of the studies reported the significance threshold applied, fewer provided details either on the methods applied to correct for multiple comparisons or stated a reason why such correction was not necessary. A smaller number of studies, however, did not specify either type of information.

3.4. Results based on Psychotic Symptoms and Imaging Technique

In the following paragraphs, the findings of the papers will be synthesised based on the psychotic symptom investigated and within that, on the neuroimaging technique employed. The majority of the studies included participants presenting with AD dementia; for the studies that also included MCI participants, this will be explicitly stated. Most papers focused on the neuroanatomical features associated with the presence of the symptom of interest; on the occasions where the focus differed (e.g.,

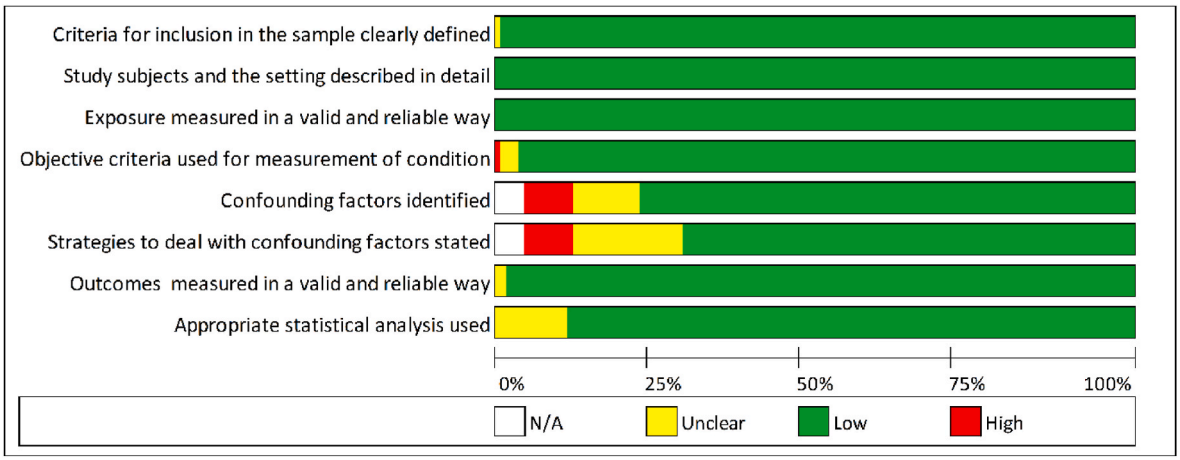

Fig. 2. Visual Depiction Of The Results Of The Joanne Briggs Institute Risk Of Bias Assessment Tool. **Notes:** The majority of papers scored positively on all items of the tool, with the exception of the items relating to confounding factors.

longitudinal studies which considered the development of the symptom, or papers which focused on the intensity or severity of the symptoms), this will be noted.

3.4.1. *Delusions*

Results are summarised in Table 2.

3.4.1.1. Grey Matter Atrophy: Results from Magnetic Resonance Imaging – Voxel Based Morphometry. The most common method to assess grey matter atrophy with MRI, was to investigate associations with delusions using voxel-based morphometry (VBM). This technique was used in nine studies, with four including a longitudinal assessment. The majority reported involvement of frontal and temporal regions, and the limbic system, more commonly with right-side predominance. Among the longitudinal investigations, one study (Boublay et al., 2020) identified an association between the future development of delusions and the right anterior cingulate cortex: this region was also identified by Nakaaki and colleagues (Nakaaki et al., 2013a), as well as the right posterior cingulate, which was also found in Fischer and colleagues' study (Fischer et al., 2016). The two aforementioned studies (Fischer et al., 2016; Nakaaki et al., 2013a) also similarly identified associations with the parahippocampal gyrus, and insula, bilaterally, however Fischer et al. (2016) identified the majority of regions to be in the left hemisphere. Qian and colleagues (Qian et al., 2019a) partially confirmed previous findings, with clusters found in the left precentral and middle frontal gyri (also in (Nakaaki et al., 2013a)) when comparing delusional and non-delusional patients; they also interestingly found differences from baseline to follow-up in those who developed delusions compared to those who did not in frontal and temporal lobes, along with single clusters in the precuneus, cerebellum (also in Fischer et al., (2016)), occipital lobe and putamen, and they showed an accelerated decrease of temporal grey matter atrophy in the group with delusions compared to the controls. In the four cross-sectional studies, Serra and colleagues (Serra et al., 2010) found an association between delusions and the right hippocampus; similarly, Tagawa and colleagues (Tagawa et al., 2014) demonstrated a link to right medial temporal atrophy, while Ting and colleagues reported greater right fronto-temporal grey matter atrophy, as well as in the right insula, right precentral gyrus, left middle occipital gyrus. Bruen and colleagues (Bruen et al., 2008) mainly found frontal involvement (right frontoparietal cortex and left frontal lobe) and the left claustrum.

Lastly, a case study (Jedidi et al., 2015) reported atrophy in the posterior cingulate cortex, and the precuneus.

3.4.1.2. Grey Matter Atrophy: Results from Magnetic Resonance Imaging – Regions Of Interest Approach. The other common technique employed with MRI to investigate associated brain areas was using a region of interest (ROI) approach: here, results are averaged within each ROI to produce single metrics (e.g., grey matter volume, or cortical thickness), and it is normally used to test predetermined hypotheses. One longitudinal study reported the case of a patient with posterior cortical atrophy who later developed Capgras syndrome (Schroeter et al., 2020): compared to a group of forty-two healthy control participants, greater involvement of the occipital and tempo-parietal regions, more in the right hemisphere, and right fusiform gyrus was reported at baseline, while the posterior cingulate gyrus, precuneus, right middle frontal gyrus, frontal eye field and left fusiform gyrus presented greater atrophy at follow-up, once the symptoms of misidentification were present. One study (Nowrangi et al., 2021), found associations between delusions and the left anterior cingulate cortex in severe and mild disease-severity groups, and the right subcallosal region in the mild subgroup only. In the last one (Whitehead et al., 2012), significant findings were found only in females, in the left medial orbitofrontal and superior temporal regions.

One study (Tetreault et al., 2020) used a new technique called 'atrophy network mapping', to identify a delusion network that included regions in the bilateral ventrolateral frontal, orbitofrontal frontal, and superior frontal cortices, which are consistent with brain regions previously identified (Schroeter et al., 2020; Boublay et al., 2020; Nakaaki et al., 2013a; Qian et al., 2019a; Ting et al., 2015; Whitehead et al., 2012; Aharon-Peretz et al., 1999).

3.4.1.3. Grey Matter Atrophy: Results from Computerised Tomography. Grey matter atrophy was also investigated in two CT studies: one a case study (Fö et al., 1991), which identified frontal lobe atrophy in relation to the presence of delusion of misidentification, and the other one found greater right involvement of the temporal lobe regions in a sample of patients presenting with paranoid and theft delusions (Geroldi et al., 2000).

3.4.1.4. Hypo and Hyper Perfusion measured with Single Positron Emission Tomography. Among the studies that investigated neuroanatomical correlates of delusions using SPECT, some explored delusions in general, while others explored the correlates of the different subtypes of delusions.

Concerning delusions in general, associated regions of hypoperfusion were the bilateral frontal gyri (Nakano et al., 2005; Kotrla et al., 1995; Staff et al., 2000), right prefrontal regions (Nakano et al., 2005; Venneri et al., 2000), right insula (Matsuoka et al., 2010), and right temporal

Table 2
Studies on delusions.

Author(s), Year	Symptom(s) Investigated in the Paper	Participants (Total and in Relation to Analyses of Interest)	Criteria for Diagnosis and Disease Stage	Symptom rating scale/ Assessment Method	Design(s)	Neuro-imaging Tech-nique	Type of scan	Analyses software	Neuro-imaging Metrics	Aim(s) of the Paper (in Relation to Analyses Relevant to this Review)	Confounding Factors accounted for in the Analyses	Brain Area(s) Investigated	Statistical Threshold and Correction	Relevant Findings
Anor et al., 2017 (Anor et al., 2017)	delusions [b]	67 AD, 9.1% delusions; 38 mixed AD/VaD, 20.8% delusions	probable AD (NINCDS-ADRDA criteria and MMSE)	NPI (presence)	cross-sectional	MRI	1.5-T, FLAIR	Osirix (5.6)	WMH	differences in incidence of NPS, in relation to frontal WMH volume	age	frontal lobe, in Atlas of the Human Brain	$\rho < 0.05$	greater WMH volume in the R frontal lobe, compared to those without delusions
Anor et al., 2021 (Anor et al., 2021)	delusions [b]	138 AD, 114 MCI-AD, from 7.1 to 20% incidence delusions	MCI and probable AD (NINCDS-ADRDA criteria, CDR and MMSE)	NPI-Q (presence and severity)	cross-sectional and longitudinal (at 1 year)	MRI	T1 weighted, FLAIR scans	MATLAB R2017b	WMH	relationship between NPS, and WMH burden in MCI-AD or AD patients; relationship between WMH volume and future development of NPS	use of psychotropic medications; total volumes of MRI scans normalised for head size	load of WMH on whole brain	FDR to correct for multiple comparison	whole brain WHM load (future delusions severity sub-scores)
Berlow et al., 2010 (Berlow et al., 2010)	delusions [b]	37 AD, 12 delusions	probable AD (NINCDS-ADRDA criteria and MMSE)	NPI (presence)	cross-sectional	MRI	GE Signa LX, 1.5-T, T-1 weighted, FLAIR scans	MRIcro and SIENAX	WMH, VBM	association between NPS in AD and: volumetric reduction of grey matter (of whole brain and hippocampus) and increase in white matter changes (WMH)	age, MMSE; skull size	whole brain and hippocampus	$\rho < 0.10$	trend (did not reach significance) with WMH load
Boublay et al., 2020[a] (Boublay et al., 2020)	delusions [b]	53 AD, 7 delusions; 40 healthy controls	probable AD (NINCDS-ADRDA criteria, MMSE, CDR) prodromal or mild dementia; MRI biomarkers	NPI-Q	longitudinal	MRI	1.5-T scans	SPM12b in MATLAB R2014b	VBM	regional brain volumes of the whole brain and behavioural changes (mild stages of AD)	sex, age; type of MRI	whole brain, in MNI space	$\rho \leq 0.001$	smaller brain volume in R anterior cingulate cortex
Bruen et al., 2008 (Bruen et al., 2008)	delusions (misidentification) [c]	31 mild AD, 16% delusions	probable AD (NINCDS-ADRDA criteria and MMSE) mild dementia	NPI (frequency and severity)	cross-sectional	MRI	1.5-T, T1-W	SPM5	VBM	decreased grey matter volume in association with NPS in patients with mild AD	age, number, education, MMSE; correction for global differences in brain shape	whole brain	$\rho < 0.01$	low GM density values in R inferior frontal gyrus, R inferior parietal lobule, L inferior and medial frontal gyri, and in the claustrum
Fischer et al., 2016[a] (Fischer et al., 2016)	delusions	24 AD delusions	MCI and probable AD (NINCDS-	NPI-Q (presence)	cross-sectional and longitudinal	MRI	1.5-T scans	SPM8	VBM	grey matter changes pre and post delusion onset	not specified	not specified, in Talairach and Tournoux Atlas	$p < 0.05$ with no masking, corrected by FDR	grey matter decreases in R and L insular, L precuneus, R and L

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Table 2 (*continued*)

Author(s), Year	Symptom(s) Investigated in the Paper	Participants (Total and in Relation to Analyses of Interest)	Criteria for Diagnosis and Disease Stage	Symptom rating scale/ Assessment Method	Design(s)	Neuro-imaging Tech-nique	Type of scan	Analyses software	Neuro-imaging Metrics	Aim(s) of the Paper (in Relation to Analyses Relevant to this Review)	Confounding Factors accounted for in the Analyses	Brain Area(s) Investigated	Statistical Threshold and Correction	Relevant Findings
			ADRDA criteria), severity with MMSE and CDR											cerebellar culmen, L superior temporal gyrus, R posterior cingulate, R thalamus, L parahippocampal gyrus
Förstl et al., 1991 (Fö et al., 1991)	delusions (Capgras, misidentification)	130 AD, 2 Capgras syndrome, 40 misidentification syndrome, 88 without delusions	possible or probable AD (NINCDS-ADRDA criteria)	not specified	case-study	CT	not specified	not specified	ROI	relationship between CT measurements in AD patients and the forms of misidentification	cognitive impairment, duration of disease and age; differences in skull size, global brain atrophy	third, R and L anterior horn ventricles, R and L anterior and posterior brain (quadrants)	not specified	R frontal atrophy, significantly larger L frontal lobes (L anterior quadrant) and larger R anterior horns
Fukuhara et al., 2001[a] (Fukuhara et al., 2001)	delusions (theft)	18 AD, 9 delusions of theft and 9 without delusions	probable AD (NINCDS-ADRDA criteria)	NPI	cross-sectional	SPECT	2000H, HITACHI	SPM	VB	delusions of theft in relation to regional cerebral blood flow	age, years of education and neuro-psychological tests	whole brain	$p < 0.01$ uncorrected (considered only clusters with $p < 0.05$ probability)	hypoperfusion in R medial posterior parietal region
García-Alberca et al., 2019 (Garcí et al., 2019)	delusions [b]	46 AD, 9 delusions	probable AD (NINCDS-ADRDA criteria), mild to severe	NPI (Spanish version)	cross-sectional	MRI	1.5-T General ElectricSignal scanner	not specified	MTA, WMH	relationship between WMH and MTA observed on MRI and specific NPS in patients with AD	age, gender, education, duration of disease, diabetes mellitus, hypertension, hyperlipidaemia, heart disease, MMSE, CFT, LFT	WMH in frontal, occipital, lateral periventricular, frontal parietal, temporal and occipital deep subcortical, basal ganglia, infratentorial lesions; L and R MTA volumes	$p < 0.05$	no significant results
Geroldi et al., 2000 (Geroldi et al., 2000)	delusions (theft and paranoid)	19 AD patients with delusions and 22 without	probable AD (NINCDS-ADRDA criteria), mild dementia, severity with MMSE,	NPI (presence)	cross-sectional	CT	spiral scanner Prospeed S (General Electrics)	not specified	WTH	delusions in association with asymmetric involvement of the temporal lobe regions in AD	sociodemographic and clinical features	temporal lobe	not specified	greater R than L temporal horns
Hirono et al., 1998 (Hirono et al., 1998)	delusions (persecutory, misidentification, jealousy) [c]	65 AD patients, 26 delusions	probable AD (NINCDS-ADRDA criteria), severity with CDR and MMSE	DSM-IV criteria, BEHAVE-AD, NPI	cross-sectional	FDG-PET	Headtome IV, Shimadzu Corp. Kyoto, Japan	Dr. View ver. 4.0, Asahikasei Joho System, Tokyo	ROI	AD patients with delusions present distinct features in regional cerebral metabolism	mean value of all cortical metabolic rates for glucose	dorsolateral and basal prefrontal, anterior cingulate, superior, medial, middle inferior temporal, medial and lateral occipital, inferior parietal; in Talairach and Tournoux atlas	$\rho < 0.05$ corrected for multiple comparison (Bonferroni)	hypometabolism in the L medial occipital region and hypermetabolism in the inferior temporal gyrus

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Table 2 (*continued*)

Author(s), Year	Symptom(s) Investigated in the Paper	Participants (Total and in Relation to Analyses of Interest)	Criteria for Diagnosis and Disease Stage	Symptom rating scale/ Assessment Method	Design(s)	Neuro-imaging Tech-nique	Type of scan	Analyses software	Neuro-imaging Metrics	Aim(s) of the Paper (in Relation to Analyses Relevant to this Review)	Confounding Factors accounted for in the Analyses	Brain Area(s) Investigated	Statistical Threshold and Correction	Relevant Findings
Hořínek et al., 2006 (Aharon-Peretz et al., 1999)	delusions [b]	30 AD, 11% delusions	probable AD (NINCDS-ADRDA criteria)	NPI	cross-sectional	MRI	Phillips, 1.5-T scans	in-house developed	ROI	association between the reduction of amygdala volume in AD and psychiatric symptoms	age, sex, and level of education; intracranial and total brain volumes	amygdala and hippocampus	$\rho < 0.05$	no significant results
Jaramillo-Jimenez et al., 2021 (Xia et al., 2020)	delusions [b]	55 AD, 34 dementia Lewy Body (DLB), delusions 13.7%, 15.5% and 18.2% (Y3 to 5)	AD (NINCDS-ADRDA criteria), mild (severity with CDR or MMSE)	NPI (severity and frequency)	longitudinal (baseline, Years 1,2,3,4,5)	MRI	Philips 1.5-T scans	Freesurfer 6.0	ROI	association between amygdala volumes and longitudinal development of NPS in AD and DLB	gender, diagnosis, MMSE tot score, time in study; intracranial volume (head size and gender differences), MRI acquisition centre	amygdala	$\rho < 0.05$ corrected for multiple testing (FDR)	no significant results
Jedidi et al., 2015 (Jedidi et al., 2015)	delusions (Capgras)	51 AD, 1 delusions, 26 without; 24 healthy controls	probable AD (NINCDS-ADRDA criteria), mild; PET biomarkers	clinical pre-sentation	case-study	MRI and FDG-PET	Siemens 3-T, T-1 weighted scan; CTI ECAT HRþ Siemens scan	SPM8 in MATLAB	VBM	functional cerebral correlates of Capgras delusion	age and sex	not specified, in MNI space	$p < 0.01$ uncorrected	atrophy in posterior cingulate cortex (PCC) and precuneus cortex, and hypometabolic cluster in L dorsal and posterior medial prefrontal cortex (MPFC) and L upper precuneus/ PCC (case study compared to healthy controls); hypometabolism of L dorsal posterior MPFC and upper L precuneus/PCC (case study and AD group);
Kotrla et al., 1995 (Kotrla et al., 1995)	delusions [c]	46 AD, 29 delusions, 16 non-psychotic	probable AD (NINCDS-ADRDA criteria)	DMS-III criteria, symptoms for more than 3 months	cross-sectional	SPECT	Siemens 7500 ZLC, Tc-99m Ceretec	in-house image analysis program	ROI	delusions and hallucinations in patients with AD associated with cerebral dysfunction in the frontal and parietal lobes	age, education and MMSE	frontal and parietal lobes, six regions of interest per hemisphere; standard atlas to determine anatomic location of each ROI and midventricular slice	not specified	hypoperfusion of the L lateral frontal lobe in the upper and lower slices (compared to R)
Lee et al., 2006 (Lee et al., 2006)	delusions[b]	55 AD, 10 with psychosis (% delusions not specified)	probable AD (NINCDS-ADRDA criteria), very mild, mild, moderate,	CERAD (BRSD, frequency and severity)	cross-sectional	MRI	General Electronics 1.5-T, T-2 weighted scans	not specified	White Matter Changes (Age-Related WMC scale)	relationship between white matter changes seen on MRI and neuropsychiatric symptoms in probable AD patients	age, education, sex, and duration of illness	L and R frontal areas, L and R parieto-occipital areas, L and R temporal areas, L and R basal ganglia	$\rho < 0.05$ uncorrected	misidentification: overall white matter changes, L frontal white matter changes, bilateral frontal and parieto-occipital white matter changes,

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Author(s), Year	Symptom(s) Investigated in the Paper	Participants (Total and in Relation to Analyses of Interest)	Criteria for Diagnosis and Disease Stage	Symptom rating scale/ Assessment Method	Design(s)	Neuro-imaging Tech-nique	Type of scan	Analyses software	Neuro-imaging Metrics	Aim(s) of the Paper (in Relation to Analyses Relevant to this Review)	Confounding Factors accounted for in the Analyses	Brain Area(s) Investigated	Statistical Threshold and Correction	Relevant Findings
			and severe (CDR)											bilateral frontal, bilateral parieto-occipital, and R basal ganglia, bilateral frontal, L parietooccipital and L basal ganglia
Lee et al., 2009 (Jedidi et al., 2015)	delusions (also confabulations)	22 AD, 13 delusions; 12 healthy controls	probable AD (NINCDS-ADRDA criteria)	BEHAVE-AD	cross-sectional	SPECT	SIGNA 1.0-T, T-1 weighted scan; Millennium MG scanner 2-head rotating gamma camera	SPM2 in MATLAB	VBM	neurologic backgrounds of delusions in relation to confabulations	individual variations	not specified, in MNI space	$p < 0.05$, corrected by FDR rate	hypoperfusion of R prefrontal cortex
Lopez et al., 2001 (Lopez et al., 2001)	hallucinations [c]	9 AD, 2 hallucinations, 2 delusions, 5 no psychotic symptoms; 9 elderly controls	probable AD (NINCDS-ADRDA criteria)	DSM-IV criteria	cross-sectional	PET	Siemens 951R/31	not specified	ROI	critical brain region that serves as common denominator for the development of psychotic phenomenon in AD	not specified	orbitofrontal, frontal dorsolateral, anterior cingulate, medial temporal, superior temporal, parietal and occipital cortices, and basal ganglia and thalami	not specified	rel-CBF in R and L thalamus
Matsuoka et al., 2010[a] (Matsuoka et al., 2010)	delusions	35 AD, 14 delusions (of which 12 females) 11 without; 7 healthy controls	probable AD (NINCDS-ADRDA criteria and MMSE)	NPI (frequency and severity)	cross-sectional	SPECT	triple-head gamma camera, low-energy, high-res.parallel collimator	SPM5 in MATLAB 7.5	not specified	brain regions associated with severity of delusions in AD	other NPI subscale scores and MMSE scores, mean cerebral global blood flow	not specified	$p < 0.01$, uncorrected, cluster size>50	hypoperfusion of R anterior insula hypoperfusion (with exacerbation of delusions)
Mentis et al., 1995 (Mentis et al., 1995; Lee et al., 2009)	delusions (misidentification)	23 AD, 9 delusions, 14 without delusions, and 17 healthy controls	probable AD (NINCDS-ADRDA criteria)	observation-based diagnosis	cross-sectional	PET	Scanditronix PC-1024-7B tomograph	SPM	ROI (absolute rCMRglc values)	rCMRglc of AD patients, with delusional misidentification syndromes	inter-subject glucose metabolism (whole brain CMRglc), in the SPM analysis	not specified	$p < 0.05$, post hoc Neuman-Keuls	ROI: hypometabolism in bilateral cingulate and basal ganglia (compared to healthy controls); hypometabolism in lateral orbitofrontal, L posterior medial temporal, L anterior and bilateral posterior cingulate, L caudate nucleus, L lentiform nucleus, L calcarine; SPM: hypometabolism in orbitofrontal and anterior cingulate regions, bilaterally, and hypermetabolism in a superior

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Table 2 (*continued*)

Author(s), Year	Symptom(s) Investigated in the Paper	Participants (Total and in Relation to Analyses of Interest)	Criteria for Diagnosis and Disease Stage	Symptom rating scale/ Assessment Method	Design(s)	Neuro-imaging Tech-nique	Type of scan	Analyses software	Neuro-imaging Metrics	Aim(s) of the Paper (in Relation to Analyses Relevant to this Review)	Confounding Factors accounted for in the Analyses	Brain Area(s) Investigated	Statistical Threshold and Correction	Relevant Findings
														temporal, inferior parietal, and precuneus cortex, bilaterally
Moon et al., 2014 (Moon et al., 2014)	delusions [b]	40 AD, 14 delusions	probable AD (DMS IV and NINCDS-ADRDA criteria)	NPI (presence and severity)	cross-sectional	MRI	Signa HDx 3.0-T, T-1 and T-2 weighted scans	SPM8 in MATLAB and MRIcro package	ROI	association between the volume ratio of the insular cortex and neuropsychiatric symptoms in patients with AD	age, CDR score, vascular risk factor and other NPS; WMH, tot GM volume divided by other NPS, intracranial volume	insular cortex, subdivided into four subregions by the CIS and bilaterally: the R anterior insular cortex, R posterior insular cortex, L anterior insular cortex and L posterior insular cortex	not specified	no significant results
Nakaaki et al., 2013 (A)[a] (Nakaaki et al., 2013a)	delusions (persecutory and misidentification)	53 AD, 18 delusions	probable AD (NINCDS-ADRDA criteria)	Japanese NPI	longitudinal	MRI	Gyoro Scan Intera; Philips MedicalSystems, 1.5-T, T-1 weighted scan	SPM5 in MATLAB 7.5	VBM	compared the baseline structural brain abnormalities of patients who developed delusions with those who did not	age, gender, education, duration (in years), and MMSE; total brain volume	whole brain	$p < 0.05$, corrected for multiple comparisons (FDR)	smaller grey matter volumes on both sides of the parahippocampal gyrus, the R posterior cingulate gyrus, the R orbitofrontal cortex, both sides of the inferior frontal cortex, the R anterior cingulate, the L claustrum, and the L insula
Nakaaki et al., 2013 (B) (Nakaaki et al., 2013b)	delusions	25 AD, 15 delusions, 10 without	probable AD (NINCDS-ADRDA criteria)	NPI	longitudinal	MRI	Gyoroscan Intera; Royal Philips Electronics, 1.5-T, T-1 weighted scan	FSL Ver 4.1	VBM, Diffusion Tensor Imaging for WM abnormality	existence of baseline abnormalities in WM integrity in AD patients who developed delusions and AD patients who did not develop delusions	age, gender, and MMSE score; eddy currents and head movements	whole brain, in MNI space	$p < 0.05$, corrected for multiple comparisons (threshold-free cluster enhancement)	one (maximum cluster) of reduced fractional anisotropy (FA) in the L parieto-occipital region; one (large cluster) in the body of the corpus callosum; one (minimum cluster) on the R superior temporal gyrus white matter
Nakano et al., 2005[a] (Nakano et al., 2005)	delusions (persecutory, misidentification, jealousy)	64 AD, 25 delusions, 39 without	probable AD (NINCDS-ADRDA criteria), MMSE for severity	NPI	cross-sectional	SPECT	triple-headed gamma camera, MULTISPECT3, Siemens	SPM99 in MATLAB	VB	association between delusions and cerebral deficits in patients with probable AD in a relatively large number of subjects	gender, age at onset, disease duration, and MMSE score; global differences in cerebral blood flow among scans	whole brain, in Talairach and Tournoux atlas	$p < 0.01$ uncorrected	bilateral frontal lobe hypoperfusion, (R prefrontal cortex, R middle frontal gyrus, R superior frontal gyrus, R inferior to middle temporal cortices,

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Table 2 (*continued*)

Author(s), Year	Symptom(s) Investigated in the Paper	Participants (Total and in Relation to Analyses of Interest)	Criteria for Diagnosis and Disease Stage	Symptom rating scale/ Assessment Method	Design(s)	Neuro-imaging Tech-nique	Type of scan	Analyses software	Neuro-imaging Metrics	Aim(s) of the Paper (in Relation to Analyses Relevant to this Review)	Confounding Factors accounted for in the Analyses	Brain Area(s) Investigated	Statistical Threshold and Correction	Relevant Findings
														R parietal cortex); persecutory (stealing) vs misidentification: bilateral anterior cingulate gyrus; misidentification: L lingual gyrus and R middle occipital gyrus
Nakatsuka et al., 2013[a] (Nakatsuka et al., 2013)	delusions (paranoid, abandonment, Capgras)	54 AD, 27 delusions and 27 without	probable AD (NINCDS-ADRDA criteria)	BEHAVE-AD-FW (presence, severity, frequency, and type)	cross-sectional	SPECT	Millennium, 2-head rotating gamma camera with low-energy high-resolution collimator	SPM5	CBF	clarify delusional subtypes, with the content of delusional ideas corresponding to category-specific sets of neural substrates	age, gender, and MMSE	whole brain	overall delusions: $p < 0.05$, corrected for FWE; cluster size>50 voxels; individual delusional type: $p < 0.001$, uncorrected	theft: decreased CBF in the bilateral temporal poles (TPs) with R-side dominancy and in the R inferior temporal gyrus; delusion of "not home": decreased CBF in the R amygdala; abandonment: decreased CBF in the R parahippocampal gyrus and R posterior insula; suspiciousness/ paranoia: decreased CBF in the bilateral TPs with R-side dominancy
Nomura et al., 2012[a] (Nomura et al., 2012)	delusions (misidentification, persecution, abandonment/ jealousy, theft)	25 AD delusions	probable AD (NINCDS-ADRDA criteria), CDR for severity	NPI	cross-sectional and longitudinal	I-MP SPECT	Gamma View SPECT 2000H with a low-energy, medium-resolution parallel-hole collimator	SPM5 in MATLAB	not specified	classified AD delusions and investigated their neural correlates by using single-photon emission computed tomography data	age, MMSE; mean of the tracer uptake in the white matter	whole brain	$p < 0.01$, uncorrected (normalization to the white matter)	misidentification/ abandonment: hypoperfusion R middle temporal gyrus (temporal pole) and hyperperfusion L medial frontal gyrus, L precentral gyrus; persecution: hypoperfusion R precuneus, L precuneus and hyperperfusion L insula, R extra-nuclear, R thalamus, R frontal sub-gyral;

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Table 2 (*continued*)

Author(s), Year	Symptom(s) Investigated in the Paper	Participants (Total and in Relation to Analyses of Interest)	Criteria for Diagnosis and Disease Stage	Symptom rating scale/ Assessment Method	Design(s)	Neuro-imaging Tech-nique	Type of scan	Analyses software	Neuro-imaging Metrics	Aim(s) of the Paper (in Relation to Analyses Relevant to this Review)	Confounding Factors accounted for in the Analyses	Brain Area(s) Investigated	Statistical Threshold and Correction	Relevant Findings
														abandonment/ jealousy: hypoperfusion R inferior temporal gyrus, and hyperperfusion L middle frontal gyrus, L insula, L putamen (lentiform nucleus), L posterior cingulate gyrus; theft: hypoperfusion L thalamus, R thalamus, L posterior cingulate gyrus and hyperperfusion L inferior frontal gyrus and L anterior cingulate gyrus
Nowrangi et al., 2021 (Nowrangi et al., 2021)	delusions [b]	72 AD (% of delusions not specified)	not specified, MMSE for severity	NPI-Q (presence)	cross-sectional	MRI	Siemens 3.0-T scans	not specified	ROI	decreased volumes of cingulate cortex, frontal and prefrontal lobe structures (including DLPFC), and amygdala associated with delusions	age, years of education and sex	DLPFC, anterior and posterior cingulate cortex, orbitofrontal cortex, anterior insula, hippocampus, and parahippocampal gyrus	$p < 0.05$; multiple comparisons (FEW, Bonferroni and Holm)	smaller volume in L ACC including the rostral regions (in severe and mild groups) and the R subcallosal region in the mild subgroup; R dorsomedial prefrontal cortex inverse association (moderate subgroup)
Ogawa et al., 2013 (Ogawa et al., 2013)	delusions [b]	163 AD, 39 delusions	probable AD (NINCDS-ADRDA criteria)	NPI (Japanese version) (severity, frequency)	cross-sectional	MRI	3.0-T, 2-T weighted scans	not specified	WMH (severity on axial FLAIR images, Fazekas scale)	relationship of cerebral SVD observed on MRI with NPS	age, sex, years of education, disease duration, CDR, cholinesterase inhibitor usage	whole brain	$p < 0.05$ uncorrected	greater SVD (compared to non-delusional)
Palmqvist et al., 2011 (Palmqvist et al., 2011)	delusions [b]	259 AD, 15% delusions	probable AD (NINCDS-ADRDA criteria and MMSE), mild to moderate	NPI (presence)	cross-sectional	CT or MRI	Somatom Plus 4 scanner, Siemens	not specified	White Matter Changes (Age-Related WMC scale)	independent association between regional subcortical lesions and NPS	cognitive ability; atrophy	frontal lobe anterior to the central sulcus, the parietooccipitalarea and the basal ganglia (striatum, globus pallidus, thalamus, internal and external capsules), and insula	entry limit was $p = 0.05$, limit of removal $p = 0.051$ (collinearity reduced by L and R regions entered separately)	lesions in the basal ganglia (increased risk of delusions)

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Table 2 (*continued*)

Author(s), Year	Symptom(s) Investigated in the Paper	Participants (Total and in Relation to Analyses of Interest)	Criteria for Diagnosis and Disease Stage	Symptom rating scale/ Assessment Method	Design(s)	Neuro-imaging Tech-nique	Type of scan	Analyses software	Neuro-imaging Metrics	Aim(s) of the Paper (in Relation to Analyses Relevant to this Review)	Confounding Factors accounted for in the Analyses	Brain Area(s) Investigated	Statistical Threshold and Correction	Relevant Findings
Pontón et al., 1995 (Pontón et al., 1995)	delusions (including Capgras)	15 AD, 6 delusions and 9 without	probable AD (NINCDS-ADRDA criteria and DSM-III)	not specified	longitudinal (at 1 year)	SPECT	Headtome device	not specified	ROI	AD patients with delusions will have lower R hemispheric rCBF; difference in rCBF of temporoparietal areas	not specified	inferior temporal gyrus, superior temporal gyrus, prefrontal area, posterior inferior frontal (Broca's) area, temporoparietal area, Brodmann's area 19, cerebellum	alpha set at 0.05, Bonferroni correction for multiple comparisons	higher perfusion in superior temporal gyrus (bilateral), R inferior temporal gyrus. R area 19; uncorrected R inferior temporal gyrus, superior temporal gyrus, area 19, temporoparietal area, posterior inferior frontal area, the prefrontal region, primary visual cortex region; L inferior temporal gyrus, superior temporal gyrus, posterior inferior frontal, prefrontal region, primary visual cortex region
Qian et al., 2019 (A)[a] (delusions Qian et al., 2019a)		59 AD, 23 delusions, 36 AD without	probable AD (NINCDS-ADRDA criteria)	NPI-Q (presence)	cross-sectional and longitudinal	MRI	1.5-T, T-1 weighted	FMRIB Software Library VBM protocol and in-house developed software	VBM	grey matter differences associated with delusions in AD, testing the effect of group (delusions against control), time, and interaction between time and group	MMSE, CDR, age, gender, education, and handedness	whole brain	$p < 0.005$, voxel-wise followed by cluster size thresholding, minimum cluster size at an adjusted $p = 0.05$, corrected for multiple comparisons	L precentral and middle frontal gyri, and R supplementary motor area (group); bilateral superior frontal, R inferior orbitofrontal, R prefrontal, bilateral middle temporal, R superior temporal and L inferior temporal, L precuneus, R inferior occipital, R cerebellum, and R putamen (time); bilateral middle temporal, R inferior frontal and R postcentral (group-time interaction)

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Table 2 (*continued*)

Author(s), Year	Symptom(s) Investigated in the Paper	Participants (Total and in Relation to Analyses of Interest)	Criteria for Diagnosis and Disease Stage	Symptom rating scale/ Assessment Method	Design(s)	Neuro-imaging Tech-nique	Type of scan	Analyses software	Neuro-imaging Metrics	Aim(s) of the Paper (in Relation to Analyses Relevant to this Review)	Confounding Factors accounted for in the Analyses	Brain Area(s) Investigated	Statistical Threshold and Correction	Relevant Findings
Qian et al., 2019 (B)[a] (Qian et al., 2019b)	delusions	30 AD, 15 delusions and 15 without	probable AD (NINCDS-ADRDA criteria)	NPI (severity)	cross-sectional	fMRI	Magnetom Syngo Skyra, Siemens 3.0-T, T-1 weighted; rs-fMRI, approx. 8 mins, T2-weighted echo-planar imaging	PRONTO software, AFNI, FMRIB, and in-house developed software	not specified	functional resting-state network differences between Alzheimer's disease (AD) patients with and without delusions	presence of hallucinations in non-delusional sample	DMN, clusters in MNI space	$p = 0.005$, voxel-wise followed by cluster size thresholding, minimum cluster size at an adjusted $p = 0.05$, corrected for multiple comparisons	reduced connectivity within the DMN, significant cluster corresponded to the L IPL (including the angular gyrus); L superior temporal, L inferior orbitofrontal and R medial orbitofrontal (with higher delusion severity)
Ramusino et al., 2021 (Ramusino et al., 2021)	delusions (also psychotic cluster) [b]	48 AD, 7 FTD, 4 LBD, 9 VD, 6 Dem NOS, 26 MCI (% not specified)	both MCI and probable AD (NINCDS-ADRDA criteria); CSF biomarkers	NPI (frequency and severity)	cross-sectional	CT and MRI	Somatome Persp. CT Siemens, and Magnetom SkyraSiemens 3T, T-1 weighted scans	not specified	ROI	biological correlates of NPS; their impact in different forms of cognitive impairment (MCI, AD, FTD, LBD, and VD); correlations between NPS and CSF biomarkers and cortical visual rating scales	age, gender, education, MMSE, diagnosis	MTA, PA, and GCA-F	$p < 0.05$ 2-sided, (p-values between 0.05 and 0.1 were also reported)	higher GCA-F scores and positive correlation with R GCA-F scores
Reeves et al., 2009 (Reeves et al., 2009)	delusions	23 late onset AD (LOAD), 7 delusions	probable AD (NINCDS-ADRDA criteria, MMSE and/or CAMCOG)	NPI (frequency and severity)	cross-sectional	[11C] RAC PET	962-S/CTI PET camera	not specified	ROI	symptom domains delusions and apathy would be associated with striatal dopamine (D2) receptor function in AD	age, sex and MMSE	ventral striatum, caudate and putamen subdivided along rostro-caudal axis and sensorimotor striatum	multiple comparison	striatal dopamine (D2/D3) receptor availability increased
Schroeter et al., 2020 (Schroeter et al., 2020)	delusions (Capgras)	1 AD Capgras; 42 healthy controls (MRI analysis)	probable AD (NINCDS-ADRDA criteria); CSF biomarkers	not specified	case study over time	MRI and FDG-PET	not specified	SPM12 (CAT12 toolbox)	VBM and ROI (MRI)	report a case of Capgras delusions in a patient with PCA	age; total intracranial volume	occipital and temporoparietal cortex, posterior cingulate gyrus, precuneus, middle frontal gyrus, frontal eye field	$p < 0.005$ uncorrected voxel, (FWE)$p < 0.05$ corrected cluster	brain atrophy in occipital and temporoparietal regions, more in the R hemisphere, R fusiform gyrus (baseline), and posterior cingulate gyrus, precuneus, R middle frontal gyrus, frontal eye field, L fusiform gyrus (follow-up); glucose hypometabolism bilaterally in parietooccipital

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Table 2 (*continued*)

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														cortex and in the R frontotemporal cortex at baseline lower GM volume R hippocampus; uncorrected level R middle frontal gyrus, parietal operculum cortex and precuneus
Serra et al., 2010[a] (Serra et al., 2010)	delusions [b]	27 AD, 20 % delusions (early AD), <20% (moderate AD); 19 a-MCI (5% delusions); 23 healthy controls	probable AD (NINCDS-ADRDA criteria, severity with MMSE and CDR) early/ moderate stage	NPI (frequency and severity)	cross-sectional	MRI	Siemens 3.0-T, T-1 weighted scans	SPM8	VBM	associations between regional GM volumes and clinical impact of NPS	MMSE, age, years of formal education, gender; intracranial volume	no hypothesis	$p < 0.05$, correction for multiple comparisons at voxel level (FWE) also reported uncorrected level ($p < 0.001$, min cluster size of 10 voxels)	
Shanks and Venneri, 2002 (Shanks and Venneri, 2002)	delusions (misidentification)	3 AD with delusions	probable AD (NINCDS-ADRDA criteria), MMSE for severity	NPI	case studies	SPECT	not specified	not specified	not specified	association between misidentifications with R sided brain dysfunction	not specified	not specified	not specified	perfusion deficit in R temporoparietal region, R parietal region and R frontoparietal region
Staekenborg et al., 2008 (Staekenborg et al., 2008)	delusions [b]	111 AD, 5% delusions	probable AD (NINCDS-ADRDA criteria and MMSE)	NPI (frequency and severity)	cross-sectional	MRI	Siemens 1.0-T, T-1 weighted scans	not specified	MTA atrophy and WMH (axial FLAIR images, Fazekas scale)	associations of NPS with MTA and WMH	age, sex, MMSE	MTA, and whole brain (for WMH)	not specified	no significant results
Staff et al., 1999[a] (Staff et al., 1999)	delusions	33 AD, 18 delusions, 15 without	probable AD (NINCDS-ADRDA criteria)	DSM-IV criteria	cross-sectional	SPECT	Vision DST-XL dual headed gamma camera	SPM96	ROI	consistent SPECT perfusion pattern characterising AD patient with single content specific delusions (compared to non-delusional AD patients)	not specified	R and L frontal, parietal, occipital, limbic, temporal lobes, and the cerebellum in addition to no a priori hypothesis	not specified	significant asymmetry (reduced uptake on the right compared to the left) in frontal and limbic regions
Staff et al., 2000 (Staff et al., 2000)	delusions (autobiographic)	45 AD, 10 delusions, 35 without	probable AD (NINCDS-ADRDA criteria), MMSE for severity	not specified	cross-sectional	SPECT	DST-XL dual-head gamma camera	SPM96	VB	compare AD patients with similar content-specific delusions and AD patients with no clinical history of delusions	MMSE	whole brain	$p < 0.01$ uncorrected (considered only clusters normally produced at $p < 0.05$ prob.)	hypoperfusion R frontal lobe
Starkstein et al., 1994 (Starkstein et al., 1994)	delusions (paranoid, hypochondrial, grandeur, Capgras, infidelity, Cotard)	45 AD, 16 delusions, 29 patients without delusions	probable AD (NINCDS-ADRDA criteria)	DSM-III-R criteria	cross-sectional	SPECT	General Electric 400 AC/T rotating gamma camera	Starcam software	ROI	differences in rCBF between AD patients with and without delusions	not specified	R and L frontal inferior (orbital) and superior (dorsal), temporal inferior and superior, parietal; basal ganglia,	not specified	lower CBF in both L and R, inferior, and superior temporal lobes

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Author(s), Year	Symptom(s) Investigated in the Paper	Participants (Total and in Relation to Analyses of Interest)	Criteria for Diagnosis and Disease Stage	Symptom rating scale/ Assessment Method	Design(s)	Neuro-imaging Tech-nique	Type of scan	Analyses software	Neuro-imaging Metrics	Aim(s) of the Paper (in Relation to Analyses Relevant to this Review)	Confounding Factors accounted for in the Analyses	Brain Area(s) Investigated	Statistical Threshold and Correction	Relevant Findings
												thalamus, and cerebellum, in Matsui and Hirano atlas		
Sultzer et al., 2003 (Sultzer et al., 2003)	delusions	25 AD, 13 delusions	probable AD (NINCDS-ADRDA criteria); CSF biomarkers	semi-structured interview, NRS	cross-sectional	PET	Siemens 953/31 tomographic scanner	not specified	ROI	relationship between delusional thoughts and regional cortical metabolism in patients with AD	age, age at onset of dementia, duration of dementia, and overall cognition; agitation; mean global cerebral metabolic rate	precentral, premotor, superior medial prefrontal, superior dorsolateral, middle, and frontal gyrus, operculum, superior and inferior frontal pole, anterior cingulate, lateral orbitofrontal, central and medial orbitofrontal, superior, middle and inferior temporal gyrus, fusiform gyrus, temporal pole, parahippocampal gyrus, amygdala, hippocampus, and posterior hippocampal formation	$p = 0.05$, corrected for multiple comparisons (Bonferroni)	hypometabolism in R prefrontal cortex, superior dorsolateral area and inferior frontal pole, and hypermetabolism in the lateral orbitofrontal region; hypometabolism in R prefrontal regions, L prefrontal regions, and the bilateral anterior cingulate (with severity of delusions); hypermetabolism in the L middle temporal gyrus
Sultzer et al., 2014[a] (Sultzer et al., 2014)	delusions (paranoid and/or misidentification)	88 patients with AD (28 with delusions and 60 without)	probable AD (NINCDS-ADRDA and NIA-AA criteria)	NPI (frequency and severity) and NRS	cross-sectional	FDG-PET	Siemens 953/31, GE Advance PET-CT, and Phillips Gemini TF PET-CT, all in-plane and axial resolution	SPM2	VB	clinical associations among delusions, memory deficits, and poor insight, explore neurobiological correlates for these symptoms, and identify shared mechanisms	DRS total, DRS memory subscale, MMSE, and NRS inaccurate insight scores	not specified, MNI space	$p < 0.01$, voxel-level (voxel clusters at the $p < 0.05$ level), corrected for the search volume in each analysis	lower cortical metabolic activity R lateral frontal (middle and inferior frontal gyrus), orbitofrontal cortex, and bilateral temporal cortex (majority of middle and inferior temporal gyri and mid-portion of parahippocampal gyrus), bilaterally; R temporal cortex at corrected cluster level (with DRS as covariate); L inferior parietal lobule (patients with combined delusions compared to only paranoid)

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Author(s), Year	Symptom(s) Investigated in the Paper	Participants (Total and in Relation to Analyses of Interest)	Criteria for Diagnosis and Disease Stage	Symptom rating scale/ Assessment Method	Design(s)	Neuro-imaging Tech-nique	Type of scan	Analyses software	Neuro-imaging Metrics	Aim(s) of the Paper (in Relation to Analyses Relevant to this Review)	Confounding Factors accounted for in the Analyses	Brain Area(s) Investigated	Statistical Threshold and Correction	Relevant Findings
Tagawa et al., 2014 (Tagawa et al., 2014)	delusions (persecutory)	31 AD patients (13 with delusions)	DSM-IV criteria	caregiver observation	cross-sectional	MRI	Siemens 1.5-T, T-1 weighted scans	VSRAD software, SPM8	VBM	relationship between MTA and persecutory delusions in patients with AD	total scores of the HDS-R and MMSE	MTA of the entire region of the entorhinal cortex, hippocampus, and amygdala	$p < 0.05$ (2-tailed)	R MTA is associated with persecutory delusions in patients with DAT
Tascone et al., 2017 (Tascone et al., 2017)	delusions [b]	19 AD, 6 delusions; 13 healthy controls	probable AD (NINCDS-ADRDA criteria, and DSM-IV, CDR for severity), mild to moderate	NPI	cross-sectional	MRI	General Electric 1.5-T, T-1 weighted scans	SPM8 in MATLAB R2010a	VBM and ROI	association between NPS and volume loss in brain regions involved in memory, emotional processing, and salience brain networks	total intracranial volume	whole brain, and prefrontal, lateral temporal and parietal cortices, anterior cingulate gyrus, temporo-limbic structures, and insula	$p < 0.001$, uncorrected for multiple comparisons (cluster size 25 contiguous voxels)	no significant results
Tetreault et al., 2020 (Tetreault et al., 2020)	delusions [b]	39 AD patients with delusions and 121 without	probable AD (NINCDS-ADRDA criteria)	NPI	cross-sectional	MRI	1.5 and 3-T scans	Freesurfer 6.0 and SnPM13	atrophy network mapping	test if NPS in AD patients map onto specific brain networks	atrophy threshold, spatial extent of atrophy across subjects, hippocampal volume	atrophy network mapping in MNI space	$p < 0.05$ (uncorrected $p < 10^{-6}$) for each patient's atrophy network map, at a voxel-wise FEW	network identified in bilateral ventrolateral frontal, orbitofrontal frontal, and superior frontal cortices
Ting et al., 2015[a] (Ting et al., 2015)	delusions	58 AD, 29 with delusions and 29 without	probable AD (NINCDS-ADRDA criteria)	NPI-Q	cross-sectional	MRI	1.5-T, T-1 weighted scans	SPM8 in MATLAB R2010b	VBM	more pronounced grey matter atrophy in the R frontal lobe compared with matched patients without delusions, in a-MCI or AD patients	age; total intracranial volume	not specified, Talairach space	threshold $p < 0.001$ uncorrected (one-tailed); thresholding with FEW correction (Random Field Theory), and FDR correction at $p < 0.05$	greater R fronto-temporal grey matter atrophy in R insula, R precentral gyrus, L middle occipital gyrus (biggest); L middle frontal gyrus, R middle frontal gyrus, R inferior frontal gyrus, L cingulate gyrus, R middle frontal gyrus, R interior and superior frontal gyrus, R cerebellar decline, L postcentral gyrus, L middle frontal gyrus
Tissot et al., 2021 (Tissot et al., 2021)	delusions [b]	26 AD, 52 MCI (% of delusions not specified); 143 CU	both MCI and probable AD (NINCDS-ADRDA criteria);	NPI-Q	cross-sectional	amyloid-PET	Siemens HRRT	not specified	VB	increase of NPS emergence and severity and biomarkers of Aβ, tau, and in vivo neurodegeneration	sex, age, years of education and diagnosis	not specified	RFT correction	[18F]MK6240 uptake in the occipital/cuneus region (lower glucose metabolism)

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Author(s), Year	Symptom(s) Investigated in the Paper	Participants (Total and in Relation to Analyses of Interest)	Criteria for Diagnosis and Disease Stage	Symptom rating scale/ Assessment Method	Design(s)	Neuro-imaging Tech-nique	Type of scan	Analyses software	Neuro-imaging Metrics	Aim(s) of the Paper (in Relation to Analyses Relevant to this Review)	Confounding Factors accounted for in the Analyses	Brain Area(s) Investigated	Statistical Threshold and Correction	Relevant Findings
Venneri et al., 2000 (Venneri et al., 2000)	delusions	12 AD, 2 delusions, 10 without	PET biomarkers probable AD (NINCDS-ADRDA criteria)	NPI	case study over time	SPECT	Siemens at 0.95-T, T-1 weighted scans and Vision DST-XL dual headed gamma camera	not specified	ROI	neuroimaging profile of two patients with probable AD dementia	MMSE	R and L frontal, the R and L parietal and the occipital regions, cerebellum	not specified	blood flow reduction in the R prefrontal regions; lesions of the frontal lobes and of the R hemisphere
Whitehead et al., 2012 (Whitehead et al., 2012)	delusions (paranoid)	113 AD, 23 delusions (17 females) and 90 without (59 females)	probable AD (NINCDS-ADRDA criteria, DSM-IV and MMSE)	NPI (type, severity, and frequency)	cross-sectional	MRI	General Electric 1.5-T, T-1 and 2 weighted scans	not specified	ROI	association of paranoid delusions, with regional cortical thickness and subcortical volume in AD	age, sex, education, age of onset or disease duration and ADAS-Cog; total intracranial volume	frontal pole, lateral and medial orbitofrontal, superior, and rostral middle frontal, superior, middle, and inferior temporal, and subcortical regions (caudate, putamen, nucleus accumbens and pallidum)	corrected for multiple comparisons; significant at the $p < 0.001$	whole sample: thinner L medial orbitofrontal and superior temporal cortex (not significant after controlling for cognitive status); in females only: L medial orbitofrontal and superior temporal regions

NOTES: in the participants' column, the first sample size provided is the total number of AD and/or MCI patients (inclusive of non-delusional controls; if healthy controls are also included, these are reported at the end of the cell); where the symptom of interest was present in a smaller ratio of this, this is specified consequently (as numbers or percentages, as available in the paper); assessment tools such as MMSE and CDR are only reported in the diagnosis column where these supported the diagnostic process or the severity of dementia, or in the confounding factors where these were specifically included in the analyses, while complete neuropsychological assessment was not reported in this table; unless differently stated, the full neuropsychiatric profile of the sample was not available (e.g., unknown if the participants presenting with delusions also presented with other symptoms); findings of the studies are only reported in relation to the symptoms investigated (i.e. delusions); all groups (sample with symptom of interest and control group) were used in the analyses which resulted in reported findings, unless differently stated; findings are only reported for the symptom of interest, therefore no significant findings only refers to that (i.e. the paper might have other significant findings with respect to other NPS that are not reported here).

ABBREVIATIONS: CIS = central insular sulcus, CFT = category fluency test, DLPFC = dorsolateral prefrontal cortex, FDR = false discovery rate, FWE = family wise error, FTD = frontotemporal dementia, GCA-F = global cortical atrophy-frontal, LBD = Lewy body dementia, LFT = letter fluency test, MTA = medial temporal lobe atrophy, NOS = not otherwise specified (dementia), PA = posterior atrophy, PCA = posterior cortical atrophy, rCBF = regional blood flow, rel-CBF = relative regional cerebral blood flow, rCMRglc = regional cerebral metabolic rate of glucose, SVD = small vessel disease, VaD/VD = vascular dementia, WTH = width temporal horn.

[a] These papers were included in the meta-analysis.

[b] These papers performed investigations on the other neuropsychiatric symptoms as well.

[c] These papers included investigations on hallucinations, and/or psychotic cluster.

areas (Nakano et al., 2005; Shanks and Venneri, 2002), as well as an overall asymmetry implicating the right hemisphere (Staff et al., 1999). One study (Pontón et al., 1995) also identified hyperperfusion in the superior (bilateral) and inferior (right) temporal gyri, and Brodmann's area 19 of the occipital lobe.

Delusions of theft were associated with hypoperfusion in the right medial posterior parietal region (Fukuhara et al., 2001), right inferior temporal gyrus (Nakatsuka et al., 2013), bilateral anterior cingulate cortex (Nakano et al., 2005), left and right thalamus and left posterior cingulate gyrus, in addition to hyperperfusion in the left inferior frontal gyrus and left anterior cingulate gyrus (Nomura et al., 2012).

Persecutory delusions were linked to hypoperfusion in the right and left precuneus, and hyperperfusion in the left insula and right thalamus (Nomura et al., 2012).

In association with delusions of abandonment, hypoperfusion was identified in the right parahippocampal gyrus, right posterior insula (Nakatsuka et al., 2013), right inferior temporal gyrus, left insula, left middle frontal gyrus, left putamen and left posterior cingulate gyrus (Nomura et al., 2012).

Lastly, misidentification was associated with hypoperfusion in the right amygdala (Nakatsuka et al., 2013), left lingual gyrus, right middle occipital gyrus (Nakano et al., 2005) and right middle temporal gyrus, and hyperperfusion in the left medial frontal gyrus and left precentral gyrus (Nomura et al., 2012).

3.4.1.5. Hypo and Hyper Metabolism measured with Positron Emission Tomography. 18F-FDG PET imaging was most commonly employed to study regional cortical metabolism in association with delusions. Three studies assessed their hypotheses using ROIs, and despite having comparable designs, they reported some similar, along with some contrasting findings, when analysing patterns of hypo and hyper metabolism. Focusing first on hypometabolism, this was linked to the presence of delusions as identified by Hirono and colleagues (Hirono et al., 1998) in the left medial occipital region, whereas Sultzer and colleagues (Sultzer et al., 2003) noted associations in the right prefrontal cortex, the superior dorsolateral area and inferior frontal pole, in addition to severity of delusions with prefrontal regions and the anterior cingulate cortex. Hypometabolism in this last region was also found by Mentis and colleagues (Mentis et al., 1995), as well as orbitofrontal areas (bilaterally), and the left posterior medial temporal area. Conversely, there were also temporal and orbitofrontal areas that were identified as hypermetabolic: the first by all three studies (inferior (Moon et al., 2014), mid (Nakaaki et al., 2013a) and superior (Nakaaki et al., 2013b) temporal gyri), while the second was found only by Sultzer et al. (2003) .

In 2014, Sultzer et al. (2014), instead applied voxel-based (VB) whole-brain analyses, and somewhat similarly to previously mentioned studies, they found hypometabolism, in the right middle and inferior frontal gyrus, orbitofrontal cortex, and bilateral temporal cortex (which included the majority of the middle and inferior temporal gyri and the mid-portion of the parahippocampal gyrus).

Two case studies of patients with Capgras syndrome reported different regions of hypometabolism: the first implicating the right frontotemporal cortex and parietooccipital cortex (Schroeter et al., 2020), while the second highlighted the left dorsal posterior medial prefrontal cortex (MPFC), upper left precuneus, posterior cingulate cortex and inferior temporal lobe (Jedidi et al., 2015).

Lastly, one study used which used [18F]MK6240-tau-PET (Tissot et al., 2021), found that those with delusions showed higher cuneus and occipital uptake, and another (Reeves et al., 2009) found an association between delusions and an increase in striatal dopamine (D2/D3) receptor availability, using [11C]raclopride (RAC) PET.

3.4.1.6. Use of Magnetic Resonance Imaging to Study Changes in the White Matter, and the Presence of White Matter Hyperintensities. Three studies investigated changes in the white matter, in association with delusions (Lee et al., 2006; Nakaaki et al., 2013b; Ogawa et al., 2013; Palmqvist et al., 2011). Employing diffusion tensor imaging to investigate white matter abnormalities, Nakaaki and colleagues (Nakaaki et al., 2013b) identified abnormalities in white matter integrity, localised mainly in the parieto-occipital region, and to a lesser extent in the body of the corpus callosum and superior temporal gyrus white matter.

Lee et al. (2006) and Palmqvist et al. (2011) employed the Age-Related White Matter Changes scale in association with delusions: they both identified a relationship with the left basal ganglia (however in Lee and colleagues' analysis this was associated only with delusions of misidentification), alongside changes in the bilateral frontal and left parietooccipital white matter. Lee et al. (2006) also found left frontal white matter changes in association with Capgras syndrome, bilateral frontal and parieto-occipital white matter changes with phantom boarder, and right basal ganglia in association with the belief that a dead person is still alive.

Magnetic resonance imaging has also been employed to identify the presence of lesions in the white matter, or white matter hyperintensities (WMH), which show up as areas of increased brightness when visualised by T2-weighted MRI. In relation to delusions, Anor and colleagues found significant associations with delusions in the right frontal lobe (Anor et al., 2017), and for the summative whole brain measure (Anor et al., 2021). In Ogawa and colleagues (Ogawa et al., 2013), who investigated cerebral small vessel disease (the progression of which is directly associated with the presence of WMH (Xia et al., 2020)) an association was found between this and the presence of delusions.

3.4.1.7. Recent Applications of Functional Magnetic Resonance Imaging. A recent study identified differences in resting state fMRI functional connectivity in delusional compared to non-delusional patients (Qian et al., 2019b), with a significant cluster of lower functional connectivity corresponding to the left inferior parietal lobule within the default mode network. Higher delusion severity was also found to be linked to significantly weaker connectivity in the left superior temporal, left inferior orbitofrontal and right medial orbitofrontal cortex.

3.4.2. Hallucinations

Results are summarised in Table 3.

3.4.2.1. Grey Matter Atrophy: Results from Magnetic Resonance Imaging. Grey matter atrophy in association with hallucinations was reported by four studies. A longitudinal, ROI study (Donovan et al., 2014) identified an association with lower baseline supramarginal cortical thickness of the lateral parietal cortex and the future development of hallucinations.

Two studies employed voxel-based morphometry, and reported similarities in the impairment of temporal and frontal areas; specifically: Blanc and colleagues (Blanc et al.) found atrophy in the anterior part of the right insular cortex and a discrete part of the left superior frontal gyrus in association with the presence of hallucinations, and in the right anterior part of the insula, right precentral gyrus and right superior temporal gyrus in association with hallucination intensity; Boublay and colleagues (Boublay et al., 2020) found associations with the middle and inferior frontal gyri bilaterally, the right anterior cingulate cortex, right orbitofrontal cortex, left superior medial gyrus, left middle temporal gyrus, right thalamus, and right caudate nucleus.

Lastly, Holroyd, Shepherd and Downs (Holroyd et al., 2000) found a decreased ratio of measured occipital volume to whole brain volume.

3.4.2.2. Hypo and Hyper Perfusion through Single Positron Emission Tomography. Mori and colleagues (Mori et al., 2006) presented a case study of musical hallucinations, highlighting lower blood flow in the left superior temporal gyrus, and left angular gyrus.

3.4.2.3. Hypo and Hyper Metabolism measured with Positron Emission Tomography. One key study on the presence and intensity of

Table 3
Studies on hallucinations.

Author(s), Year	Symptom(s) Investigated in the Paper	Participants (Total and in Relation to Analyses of Interest)	Criteria for Diagnosis and Disease Stage	Symptom rating scale/ Assessment Method	Design(s)	Neuro-imaging Tech-nique	Type of scan	Analyses software	Neuro-imaging Metrics	Aim(s) of the Paper (in Relation to Analyses Relevant to this Review)	Confounding Factors accounted for in the Analyses	Brain Area(s) Investigated	Statistical Threshold and Correction	Relevant Findings
Anor et al., 2017 (Anor et al., 2017)	hallucinations [a]	67 AD, 10.3% hallucinations, 38 mixed AD/VaD 18.8% hallucinations	probable AD (NINCDS-ADRDA criteria and MMSE)	NPI (presence)	cross-sectional	MRI	1.5-T, FLAIR	Osirix (5.6)	WMH	differences in incidence of NPS, in relation to frontal WMH volume	age	frontal lobe, in Atlas of the Human Brain	$\rho < 0.05$	no significant results
Anor et al., 2021 (Anor et al., 2021)	hallucinations [a]	138 AD, 114 MCI-AD, from 2 to 8.5% incidence hallucinations	MCI and probable AD (NINCDS-ADRDA criteria, CDR and MMSE)	NPI-Q (presence and severity)	cross-sectional and longitudinal (at 1 year)	MRI	T1 weighted, FLAIR scans	not specified, in MATLAB (R2017b)	WMH	relationship between NPS, and WMH burden in MCI-AD or AD patients; relationship between WMH volume and future development of NPS	use of psychotropic medications; total volumes of MRI scans normalised for head size	load of WMH on whole brain	FDR to correct for multiple comparison	whole brain WHM load (future hallucinations severity sub-scores)
Berlow et al., 2010 (Berlow et al., 2010)	hallucinations [a]	37 AD, 10 hallucinations	probable AD (NINCDS-ADRDA criteria and MMSE)	NPI (presence)	cross-sectional	MRI	GE Signa LX, 1.5-T, T-1 weighted, FLAIR scans	MRIcro and SIENAX	WMH, VBM	association between NPS and volumetric reduction of grey matter (of the whole brain and hippocampus) and increase of WMH	age and MMSE, skull size	whole brain and hippocampus	$\rho < 0.10$	no significant results
Blanc et al., 2014 (Blanc et al.)	hallucinations	39 AD hallucinations, 39 without; 39 healthy elderly controls (MRI); 19 AD with hallucinations, 20 without; 20 healthy elderly controls (PET)	probable AD (NINCDS-ADRDA criteria, MMSE and CDR); CSF biomarkers	NPI-Q	cross-sectional	MRI and FDG-PET	1.5-T, T1-W scans (MRI)	SPM12b, in MATLAB R2010a	VBM (MRI), VB (PET)	posterior (occipital) and anterior (frontal) atrophy and hypometabolism in association with hallucinations (presence and intensity)	age: total amount of grey matter (MRI), mean brain metabolism	occipital and frontal lobe, in MNI space	$\rho < 0.001$ uncorrected, minimum cluster size of 25 voxels	WM atrophy in lingual gyri of the occipital lobe, GM atrophy in anterior R insular cortex, L superior frontal gyrus (presence); WM atrophy in L precuneus and GM atrophy in R anterior insula, R precentral gyrus and R superior temporal gyrus (intensity); hypometabolism in R frontal lobe and hypermetabolism L superior frontal gyrus, fusiform gyrus, post-central gyrus, super marginal gyrus and precuneus (presence); hypometabolism in L limbic lobe, cingulate gyrus and R pre-central gyrus (intensity); hypermetabolism in L superior frontal gyrus, L fusiform gyrus, L post-central gyrus, L supramarginal gyrus

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Table 3 (*continued*)

Author(s), Year	Symptom(s) Investigated in the Paper	Participants (Total and in Relation to Analyses of Interest)	Criteria for Diagnosis and Disease Stage	Symptom rating scale/ Assessment Method	Design(s)	Neuro-imaging Tech-nique	Type of scan	Analyses software	Neuro-imaging Metrics	Aim(s) of the Paper (in Relation to Analyses Relevant to this Review)	Confounding Factors accounted for in the Analyses	Brain Area(s) Investigated	Statistical Threshold and Correction	Relevant Findings
														and L precuneus (presence)
Boublay et al., 2020 (Boublay et al., 2020)	hallucinations [a]	53 AD, 2 hallucinations; 40 healthy controls	probable AD (NINCDS-ADRDA criteria, MMSE and CDR), prodromal or mild dementia; MRI biomarkers	NPI-Q	longitudinal	MRI	1.5-T scans	SPM12b in MATLAB R2014b	VBM	regional brain volumes of the whole brain in association with behavioural changes at the mild stages of AD	sex, age; type of MRI	whole brain, transformed to Montreal Neurological Institute (MNI) space	$\rho \leq 0.001$	R middle frontal gyrus, R anterior cingulate cortex, R orbitofrontal cortex, L superior medial gyrus, L middle temporal gyrus, R thalamus, R caudate nucleus and L inferior frontal gyrus
Donovan et al., 2014 (Donovan et al., 2014)	hallucinations (also apathy)	188 AD dementia (5.3% hallucinations), 395 MCI (0.3 % hallucinations), 229 CN (0.4 % hallucinations)	probable AD (NINCDS-ADRDA criteria), all stages of dementia; CSF biomarkers	NPI-Q (frequency and severity)	longitudinal	MRI	T-1 weighted scan	FreeSurfer	ROI	relations of MRI cortical thickness, with apathy and hallucinations	diagnosis, gender, age Apo-E genotype, premorbid intelligence, memory performance, processing speed, antidepressant use, AD duration, baseline dependent variable	bilateral rostral anterior cingulate, inferior temporal, medial orbitofrontal and supramarginal cortices, bilateral lingual, rostral middle frontal and superior parietal cortices	$\rho < 0.01$ corrected for multiple comparison (Bonferroni)	supramarginal cortical thickness (baseline, with greater rate of increase over time)
García-Alberca et al., 2019 (Garcí et al., 2019)	hallucinations [a]	46 AD, 7 hallucinations	probable AD (NINCDS-ADRDA criteria), mild to severe	NPI (Spanish version)	cross-sectional	MRI	1.5-T General Electric Signal scanner	not specified	atrophy and WMH	relationship between WMH and medial temporal lobe atrophy (MTA) observed on MRI and specific NPS in patients with AD	age, gender, education, duration of disease, diabetes mellitus, hypertension, hyperlipidaemia, heart disease, MMSE, CFT, LFT	WMH in frontal, occipital, lateral periventricular, frontal parietal, temporal and occipital deep subcortical, basal ganglia, infratentorial lesions; L and R MTA volumes	$p < 0.05$	no significant results
Hirono et al., 1998 (Hirono et al., 1998)	hallucinations (mainly visual) [b]	26 AD, 7 hallucinations, 39 without	probable AD (NINCDS-ADRDA criteria), severity with CDR and MMSE	DSM-IV criteria, BEHAVE-AD, NPI	cross-sectional	FDG-PET	Headtome IV, Shimadzu IBM Corp., Kyoto, Japan	Dr. View ver. 4.0, Asahikasei Joho System, Tokyo	ROI	AD patients with delusions present distinct features in regional cerebral metabolism	mean value of all cortical metabolic rates for glucose	dorsolateral and basal prefrontal, anterior cingulate, superior, medial, middle inferior temporal, medial and lateral occipital, inferior parietal; in Talairach and Tournoux atlas	$\rho < 0.05$ corrected for multiple comparison (Bonferroni)	no significant results
Holroyd et al., 2000 (Holroyd et al., 2000)	hallucinations (visual)	14 AD, 7 with hallucinations and 7 without	probable AD (NINCDS-ADRDA criteria)	interview	cross-sectional	MRI	Siemens Magnetom and Vision 1.5-T, 1-T weighted scans		voxels	more neuropathology of occipital cortex in AD patients with visual hallucinations	MMSE (match controls at same cognitive score); participants brain sizes	whole brain and regions	not specified	decreased ratio of measured occipital volume to whole brain volume

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Table 3 (*continued*)

Author(s), Year	Symptom(s) Investigated in the Paper	Participants (Total and in Relation to Analyses of Interest)	Criteria for Diagnosis and Disease Stage	Symptom rating scale/ Assessment Method	Design(s)	Neuro-imaging Tech-nique	Type of scan	Analyses software	Neuro-imaging Metrics	Aim(s) of the Paper (in Relation to Analyses Relevant to this Review)	Confounding Factors accounted for in the Analyses	Brain Area(s) Investigated	Statistical Threshold and Correction	Relevant Findings
Hořínek et al., 2006 (Hoří et al., 2006)	hallucinations [a]	30 AD, 7% hallucinations	probable AD (NINCDS-ADRDA criteria)	NPI	cross-sectional	MRI	Phillips, 1.5-T scans	in-house developed	ROI	association between the reduction of amygdala volume in AD and psychiatric symptoms	age, sex, and level of education; intracranial and total brain volumes	amygdala and hippocampus	$\rho < 0.05$	no significant results
Jaramillo-Jimenez et al., 2021 (Jaramillo-Jimenez et al., 2021)	hallucinations [a]	55 AD patients, 34 dementia Lewy Body, 12.2% hallucinations (Year 2)	AD (NINCDS-ADRDA criteria), mild (CDR or MMSE)	NPI (severity and frequency)	longitudinal (baseline, Years 1,2,3,4,5)	MRI	Philips 1.5-T scans	Freesurfer 6.0	not specified	association between amygdala volumes and the longitudinal development of NPS in AD and DLB	gender, diagnosis and MMSE total score, time in study; intracranial volume (head size and gender differences), centre of MRI acquisition	amygdala	$\rho < 0.05$ corrected for multiple testing (FDR)	no significant results
Lee et al., 2006 (Lee et al., 2006)	hallucinations [a]	55 AD, 10 with psychosis (% hallucinations not specified)	probable AD (NINCDS-ADRDA criteria), very mild, mild, moderate, and severe (CDR)	CERAD (BRSD, frequency and severity)	cross-sectional	MRI	General Electronics 1.5-T, T-2 weighted scans	not specified	White Matter Changes (Age-Related WMC scale)	relationship between white matter changes seen on MRI and neuropsychiatric symptoms in probable AD patients	age, education, sex, and duration of illness	L and R frontal areas, L and R parieto-occipital areas, L and R temporal areas, L and R basal ganglia	$\rho < 0.05$ uncorrected	no significant results
Lin et al., 2006 (Lin et al., 2006)	hallucinations (visual)	10 AD, 5 hallucinations, 5 without	probable AD (NINCDS-ADRDA criteria)	observation-based diagnosis	cross-sectional	MRI	1.5-T GE Signa scans	not specified	WMH	relationship between occipital white matter lesions (PVHs and DWHs), and visual hallucinations	not specified	not specified	$p < 0.05$	increased occipital PVHs and an absence of occipital DWHs
Lopez et al., 2001 (Lopez et al., 2001)	hallucinations [b]	9 AD, 2 hallucinations, 2 delusions, 5 no psychotic symptoms; 9 elderly controls	probable AD (NINCDS-ADRDA criteria)	DSM-IV criteria	cross-sectional	PET	Siemens 951R/31	not specified	ROI	critical brain region that serves as a common denominator for the development of psychotic phenomenon in AD	not specified	orbitofrontal, frontal dorsolateral, anterior cingulate, medial temporal, superior temporal, parietal and occipital cortices, and basal ganglia and thalami	not specified	lower rel-CBF in R parietal cortex
Moon et al., 2014 (Moon et al., 2014)	hallucinations [a]	40 AD, 4 with hallucinations	probable AD (DMS IV and NINCDS-ADRDA criteria)	NPI (presence and severity)	cross-sectional	MRI	Signa HDx 3.0-T, T-1 and T-2 weighted scans	SPM8 in MATLAB and MRIcro package	ROI	association between the volume ratio of the insular cortex and neuropsychiatric symptoms in patients with AD	age, CDR score, vascular risk factor and other NPS; WMH, total grey matter volume divided by other NPS, intracranial volume	insular cortex, subdivided into four subregions by the CIS and bilaterally: the R anterior insular cortex, R posterior insular cortex, L anterior insular cortex and L posterior insular cortex	not specified	no significant results
Mori et al., 2006 (Mori	hallucinations (musical)	747 AD, 1 hallucinations	probable AD (NINCDS-	observation-based diagnosis	case-study	SPECT	not specified	SPM99 in MATLAB 6.5	not specified	regions related to musical hallucinations	not specified	not specified, in Talairach and Tournoux atlas	$p < 0.001$ uncorrected	increased rCBF in the L superior temporal

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Table 3 (*continued*)

Author(s), Year	Symptom(s) Investigated in the Paper	Participants (Total and in Relation to Analyses of Interest)	Criteria for Diagnosis and Disease Stage	Symptom rating scale/ Assessment Method	Design(s)	Neuro-imaging Tech-nique	Type of scan	Analyses software	Neuro-imaging Metrics	Aim(s) of the Paper (in Relation to Analyses Relevant to this Review)	Confounding Factors accounted for in the Analyses	Brain Area(s) Investigated	Statistical Threshold and Correction	Relevant Findings
et al., 2006)			ADRDA criteria)											gyrus, and L angular gyrus
Ogawa et al., 2013 (Ogawa et al., 2013)	hallucinations [a]	163 AD % hallucinations not specified	probable AD (NINCDS-ADRDA criteria)	NPI (Japanese version) (severity and frequency)	cross-sectional	MRI	3.0-T, 2-T weighted scans	not specified	WMH (Fazekas scale)	relationship of cerebral SVD observed on MRI with NPS	age, sex, years of education, duration of disease, cholinesterase inhibitor usage and CDR	not specified	$p < 0.05$ uncorrected	no significant results
Palmqvist et al., 2011 (Palmqvist et al., 2011)	hallucinations [a]	258 AD, 10% hallucinations	probable AD (NINCDS-ADRDA criteria), mild to moderate	NPI (presence)	cross-sectional	CT or MRI	Somatom Plus 4 scanner, Siemens	not specified	White Matter Changes (Age-Related WMC scale)	independent association between regional subcortical lesions and NPS	cognitive ability, atrophy	frontal lobe anterior to the central sulcus, the parietooccipital area and the basal ganglia (striatum, globus pallidus, thalamus, internal and external capsules), and insula	entry limit was $p = 0.05$, limit of removal $p = 0.051$ (collinearity reduced by L and R regions entered separately)	lesions in the basal ganglia (increased risk of hallucinations)
Ramusino et al., 2021 (Ramusino et al., 2021)	hallucinations [b]	48 AD, 7 FTD, 4 LBD, 9 VD, 6 Dem NOS, 26 MCI (% not specified)	both MCI and probable AD (NINCDS-ADRDA criteria); CSF biomarkers	NPI (frequency and severity)	cross-sectional	CT and MRI	Somatome Persp. CT Siemens, Magnetom Skyra Siemens 3T, T-1 weighted scans	not specified	ROI	biological correlates of NPS, evaluating their impact in different forms of cognitive impairment (MCI, AD, FTD, LBD, and VD), and correlations between NPS and CSF biomarkers and cortical visual rating scales	age, gender, education, MMSE, diagnosis	MTA, PA, and GCA-F	$p < 0.05$ 2-sided, (p-values between 0.05 and 0.1 were also reported)	higher GCA-F scores
Serra et al., 2010 (Serra et al., 2010)	hallucinations [a]	27 AD, 10% hallucinations); 23 healthy controls	probable AD (NINCDS-ADRDA criteria) moderate stage	NPI (frequency and severity)	cross-sectional	MRI	Siemens 3.0-T, T-1 weighted scans	SPM8	VBM	associations between regional GM volumes and clinical impact of NPS	MMSE, age, years of formal education, gender; intracranial volume	no hypothesis	$p < 0.05$, correction for multiple comparisons at voxel level (FWE)	no significant results
Staekenborg et al., 2008 (Staeken borg et al., 2008)	hallucinations [a]	111 AD, 5% hallucinations	probable AD (NINCDS-ADRDA criteria)	NPI (frequency, severity)	cross-sectional	MRI	Siemens 1.0-T, T-1 weighted scans	not specified	MTA atrophy and WMH (Fazekas scale)	associations of NPS with MTA and WMH	age, sex, MMSE	MTA, and whole brain (for WMH)	not specified	no significant results
Tascone et al., 2017 (Tascone et al., 2017)	hallucinations [a]	19 AD, 4 hallucinations; 13 controls	probable AD (NINCDS-ADRDA criteria, and DSM-IV, CDR for severity), mild to moderate	NPI	cross-sectional	MRI	General Electric 1.5-T, T-1 weighted scans	SPM8 in MATLAB R2010a	VBM and ROI	association between NPS and volume loss in brain regions involved in memory, emotional processing, and salience brain networks	total intracranial volume	whole brain, and prefrontal, lateral temporal and parietal cortices, anterior cingulate gyrus, temporo-limbic structures, and insula	$p < 0.001$, uncorrected for multiple comparisons (cluster size 25 contiguous voxels)	no significant results

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Table 3 (*continued*)

Author(s), Year	Symptom(s) Investigated in the Paper	Participants (Total and in Relation to Analyses of Interest)	Criteria for Diagnosis and Disease Stage	Symptom rating scale/ Assessment Method	Design(s)	Neuro-imaging Tech-nique	Type of scan	Analyses software	Neuro-imaging Metrics	Aim(s) of the Paper (in Relation to Analyses Relevant to this Review)	Confounding Factors accounted for in the Analyses	Brain Area(s) Investigated	Statistical Threshold and Correction	Relevant Findings
Tetreault et al., 2020 (Tetreault et al., 2020)	hallucinations [a]	39 AD patients with delusions and 121 without	probable AD (NINCDS-ADRDA criteria)	NPI	cross-sectional	MRI	1.5 and 3-T scans	Freesurfer 6.0 and SnPM13	atrophy network mapping	test if NPS in AD patients map onto specific brain networks	atrophy threshold, spatial extent of atrophy across subjects, hippocampal volume	atrophy network mapping in MNI space	$p < 0.05$ ($p < 10^{-6}$ uncorrected), voxel-wise FEW	no significant results
Tissot et al., 2021 (Tissot et al., 2021)	hallucinations [a]	26 AD, 52 MCI and 143 CN (% hallucinations not specified)	both MCI and probable AD (NINCDS-ADRDA criteria); PET biomarkers	NPI-Q	cross-sectional	amyloid-PET	Siemens HRRT	not specified	VB	relationship between increase of NPS, and in vivo neurodegeneration	sex, age, years of education and diagnosis	not specified	RFT correction	[18F]MK6240 uptake in the medial occipital cortex (lower glucose metabolism)
Wang et al., 2021 (Wang et al., 2021)	hallucinations [a]	22 AD, 3 hallucinations)	probable AD (NINCDS-ADRDA criteria. MMSE and CDR), mild to severe	NPI	cross-sectional	MRI	T-1 weighted scan	not specified	regions	correlation between amygdala atrophy and clinical features of AD	not specified	amygdala	$p < 0.05$	more serious amygdala atrophy (however no significant correlation)

NOTES: in the participants' column, the first sample size provided is the total number of AD and/or MCI patients (inclusive of non-hallucinations controls; if healthy controls are also included, these are reported at the end of the cell); where the symptom of interest was present in a smaller ratio of this, this is specified consequently (as numbers or percentages, as available in the paper); assessment tools such as MMSE and CDR are only reported in the diagnosis column where these supported the diagnostic process or the severity of dementia, or in the confounding factors where these were specifically included in the analyses, while complete neuropsychological assessment was not reported in this table; unless differently stated, the neuropsychiatric picture for the sample of interest was not available (e.g., unknown if the participants presenting with delusions also presented with other symptoms); findings of the studies are only reported in relation to the symptoms investigated (i.e. hallucinations); all groups (sample with symptom of interest and control group) were used in the analyses which resulted in reported findings, unless differently stated; findings are only reported for the symptom of interest, therefore no significant findings only refers to that (i.e. the paper might have other significant findings with respect to other NPS that are not reported here).

ABBREVIATIONS: CIS = central insular sulcus, CFT = category fluency test, DLPFC = dorsolateral prefrontal cortex, CN = cognitively normal, FDR = false discovery rate, FWE = family wise error, FTD = frontotemporal dementia, GCA-F = global cortical atrophy-frontal, LBD = Lewy body dementia, LFT = letter fluency test, MTA = medial temporal lobe atrophy, NOS = not otherwise specified (dementia), PA = posterior atrophy, PCA = posterior cortical atrophy, rCBF = regional blood flow, rel-CBF = relative regional cerebral blood flow, rCMRglc = regional cerebral metabolic rate of glucose, VaD/VD = vascular dementia.

[a] These papers performed investigations on other neuropsychiatric symptoms as well.

[b] These papers included investigations on delusions, and/or psychotic cluster.

hallucinations that was mentioned above (Blanc et al., 2014) also made use of the corresponding FDG-PET data from a subset of the patients, and identified: hypometabolism in the right frontal lobe with the presence, and in the left limbic lobe, cingulate gyrus and right pre-central gyrus with the intensity. Hypermetabolism was instead associated with the presence of hallucinations in the left hemisphere, particularly in the superior frontal gyrus, fusiform gyrus, post-central gyrus, supramarginal gyrus and precuneus. Lopez and colleagues (Lopez et al., 2001) found frontal, temporal, and right parietal cortex hypoperfusion in association with the presence of hallucinations in their AD patient sample. Lastly, with the use of [18F]MK6240-tau-PET, Tissot and colleagues (Tissot et al., 2021) identified uptake in the medial occipital cortex in association with severity of hallucinations.

3.4.2.4. Use of Magnetic Resonance Imaging to Study White Matter Atrophy and Presence of White Matter Hyperintensities. WM atrophy was identified by Blanc and colleagues (Blanc et al., 2014) in the lingual gyri of the occipital lobe, in association with the presence of hallucinations, and in the left precuneus with hallucination intensity. An alternative study that investigated the presence of WMH in association with hallucination severity (Anor et al., 2021) found a significant correlation with WMH load in the entire brain.

Lin, Yu and Pai (Lin et al., 2006) found an association between the presence of visual hallucinations and increased occipital periventricular hyperintensities, and an absence of occipital deep white matter hyperintensities.

3.4.3. Psychotic Cluster

Results are summarised in Table 4.

3.4.3.1. Grey Matter Atrophy: Results from Magnetic Resonance Imaging. Ten studies investigated psychosis as a cluster using MRI, of which eight used the ROI technique to study regional differences in grey matter. Two of these found bilateral hippocampal atrophy (Lee et al., 2019, 2021); the second one (Lee et al., 2021) also highlighted general temporal (also found in (Misquitta et al., 2020)), and bilateral entorhinal and parahippocampal atrophy (with the last brain region also reported in (McLachlan et al., 2018)), particularly in relation to the misidentification subtype). One study (Ramusino et al., 2021) identified right global cortical atrophy of the frontal lobe in association with psychosis, while another (Siafarikas et al., 2021) highlighted an association with the post-central gyrus of the lateral parietal lobe. Lower volume in the anterior cingulate, lateral frontal, lateral occipital, lateral parietal, and medial orbitofrontal was found by Raffi and colleagues (Rafii et al., 2014) in MCI and AD patients with psychotic symptoms compared to those without. At 1-year post-baseline, lower volume was found in the lateral frontal and lateral parietal cortex after controlling for baseline ADAS-cog performance. Lastly, another longitudinal study (Jeong et al., 2021) found that reduced cortical thickness in the right and left caudal anterior cingulate cortex was associated with a higher risk of incident psychosis after transition from amnestic MCI (a-MCI) to AD dementia, also when adjusted for hippocampal volume.

Voxel-based morphometry was used in three studies, two on the general psychotic cluster, which found atrophy in the right anterior-inferior temporal lobe, extending to the fusiform gyrus (D'Antonio et al., 2019) and fronto-orbital cortex, anterior cingulate cortex, and the thalamus (Makovac et al., 2016), and one (Lee et al., 2016) which found lower volume in association with the misidentification subtype (misidentification delusions and/or hallucinations), mainly in the right middle frontal gyrus, middle temporal gyrus, inferior parietal lobule and the occipital lobe.

Lastly, D'Antonio and colleagues (D'Antonio et al., 2021) performed a region-based morphometry analysis by extracting cortical complexity values and found reduced cortical complexity in the right ventromedial visual cortex in association with psychosis; in addition, they found the misidentification subtype associated with decreased cortical complexity in the right entorhinal cortex.

3.4.3.2. Hypo and Hyper Perfusion measured with Single Positron Emission Tomography. Four studies investigated hypoperfusion in association with psychosis, with different findings: Kotrla and colleagues (Kotrla et al., 1995) identified hypoperfusion in the parietal lobe. Mega et al. (2000) highlighted associations with several regions: left medial orbital frontal, anterior cingulate, dorsolateral frontal and parietal, pulvinar, ventral striatum, cerebellum, right dorsolateral and medial frontal. A study by Moran et al. (2008) identified gender differences: hypoperfusion in the right inferior-lateral prefrontal cortex and right mid-temporal cortex among female patients, while links to the right striatal cortex were found among male patients. Lastly, Banno et al. (2014) identified the right angular gyrus and the right occipital lobe in association with a psychotic cluster which included agitation.

3.4.3.3. Hypo and Hyper Metabolism measured with Positron Emission Tomography. The findings of the three studies which employed FDG-PET to analyse psychosis as a cluster highlight key areas of hypometabolism in the temporal cortex (Lopez et al., 2001; Cappelletto et al., 2021), and frontal cortex (Koppel et al., 2014; Sultzer et al., 1995); another using PET identified the dorsolateral cortex (Lopez et al., 2001).

3.4.3.4. Use of Magnetic Resonance Imaging to Study White Matter Hyperintensities. Misquitta and colleagues (Misquitta et al., 2020) highlighted significant associations between psychotic symptoms and increased WMH load. Another study (Barber et al., 1999) focusing on AD and other types of dementia, conversely, found an association with the absence of occipital WMH and the presence of delusions and visual hallucinations.

3.4.3.5. Recent Applications of Functional Magnetic Resonance Imaging. In one study (Serra et al., 2020) a psychosis factor was identified that included the symptoms of delusions, hallucinations and disinhibition. By using fMRI, the authors noted regions of reduced connectivity in relation to this cluster that included the right cingulum, hippocampus, and insula, and bilateral supramarginal gyrus.

3.5. Meta-Analysis on Delusions

As part of our aims, we explored the possibility of performing a coordinate-based meta-analysis (CBMA) (Turkeltaub et al., 2002; Wager et al., 2003), aiming to localise the brain regions that were consistently associated with the presence of delusions, hallucinations, and psychosis. CBMA is a common approach to estimate how frequently the same brain areas or networks are found across independent studies that share comparable hypotheses (Tench et al., 2020), and which makes use of the statistical peak location(s) within clusters that are reported by the studies as x,y,z coordinates (Mü et al., 2018); these are referred to as peak coordinates (Wager et al., 2007), and have been commonly reported either in the Talairach and Tournoux atlas (Talairach et al., 1990), or in Montreal Neurological Institute (MNI) space (Evans et al., 1993).

Therefore, for each study included in the systematic analysis, the peak coordinates of the significant clusters that were identified were extracted when these were made available in the paper. We divided the papers according to the symptoms of interest, finding that data was available in a suitable number of studies ($n = 14$) only in the set of papers that focused on delusions. Only $n = 1$ and $n = 5$ papers reported suitable data in the hallucination and psychotic cluster papers, respectively, and these small numbers of studies were not deemed suitable for performing meta-analyses.

We therefore included in the meta-analysis, studies which provided information on significant peaks in association with the symptom of

Table 4
Studies on psychotic cluster.

Author(s), Year	Symptom(s) Investigated in the Paper	Participants (Total and in Relation to Analyses of Interest)	Criteria for Diagnosis and Disease Stage	Symptom rating scale/ Assessment Method	Design(s)	Neuro-imaging Technique	Type of scan	Analyses software	Neuro-imaging Metrics	Aim(s) of the Paper (in Relation to Analyses Relevant to this Review)	Confounding Factors accounted for in the Analyses	Brain Area(s) Investigated	Statistical Threshold and Correction	Relevant Findings
Balthazar et al., 2014 (Balthazar et al., 2014)	psychosis [a]	20 AD, 10% with delusions and 10% hallucinations; 17 healthy controls	probable AD (NINCDS-ADRDA criteria, MMSE and CDR), mild to moderate	NPI (frequency and severity)	cross-sectional	fMRI	Phillips, 3-T, T2* weighted scans	Phillips scanner and AFNI	functional ROIs	alterations in functional networks (default-mode and salience) in relation to NPS clusters	grey matter atrophy	dorsal and ventral DMN and anterior and posterior SN	$\rho < 0.01$, FDR correction	no significant results
Banno et al., 2014 (Banno et al., 2014)	psychosis	32 AD, % of psychosis not specified	probable AD (NINCDS-ADRDA criteria, CDR and MMSE), very mild to moderate	Japanese version of ABID (3rd factor identifies psychosis)	cross-sectional	SPECT	e.cam; Siemens AG	SPM8, in MATLAB (7.5)	voxel-by-voxel	relationship between rCBF and presence of psychosis (as one dimension of agitated behaviour)	age, sex, years of education, duration of illness, MMSE scores	not specified	$\rho < 0.05$, FDR correction, cluster extent thresholds at 100 voxels to reduce noise	lower rCBF values in the R angular gyrus and the R occipital lobe
Barber et al., 1999 (Barber et al., 1999)	psychosis (delusions and visual hallucinations)	28 AD, 25 VaD, 27 LBD, 34 delusions, 29 hallucinations; 26 controls	possible, probable, and definite AD (NINCDS-ADRDA criteria and MMSE)	CUSPAD	cross-sectional	MRI	Tesla Siemens, 1.0-T, T2 weighted scans	not specified	WMH	relation of white matter changes on MRI in patients with AD (and also vascular dementia, and dementia with Lewy bodies), with non-cognitive features	not specified	WMH rated in frontal, temporal, parietal, occipital, and basal ganglia regions	$\rho < 0.01$ and $\rho < 0.05$	absence of occipital WMHs (analyses carried out on overall sample: all types of dementia together)
Cappelletto et al., 2021 (Cappelletto et al., 2021)	psychotic symptoms [a]	17 AD with NPS, 14 NPS developers % of psychosis not specified, 29 without	probable AD (NINCDS-ADRDA criteria)	NPI (frequency and severity)	longitudinal	FDG-PET	Philips Gemini TF16 (image acquisition 30 min after FDG injection)	SPM12	VB	common metabolic pattern of positive NPS and to explore whether such a pattern could have a role in predicting their onset	age and MMSE	not specified; in Talairach and Tournoux atlas	$\rho < 0.001$ uncorrected	association between brain hypometabolism in the temporal cortex and positive NPS
D'Antonio et al., 2019 (D'Antonio et al., 2019)	psychosis (mis-identification and paranoia)	17 AD with psychosis and 15 without	probable AD (NIA-AA criteria)	NPI (frequency and severity)	longitudinal, 2-year interval	MRI	Philips Gyroscan MRI scanner at 1.5-T; T-1 weighted scans	SPM12	VBM	detecting what grey matter alterations, their location, and the rate of atrophy are associated with psychosis of AD	time from AD onset; total intracranial volume	whole brain	$\rho < 0.05$, pFWE corrected at cluster level; $\rho < 0.001$ uncorrected at peak level	smaller volume in R anterior-inferior temporal lobe, extending to fusiform gyrus; trend towards significance for the Group-by-Time interaction in R anterior insula; greater atrophy in ventral-anterior temporal lobe (misidentification subtype)
D'Antonio et al., 2021 (D'Antonio et al., 2021)	psychosis (mis-identification and paranoia)	17 AD with psychosis, 15	probable AD (NIA-AA criteria)	NPI (psychosis index for	cross-sectional	MRI	Philips Gyroscan MRI scanner	SPM12 and CAT12	ROI, RBM	regional FD in association with psychosis;	general cognitive decline (ADAS-	primary and early visual cortex, dorsal and ventral visual	$\rho = 0.001$, Bonferroni	reduced cortical complexity in the R ventromedial visual

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Table 4 (*continued*)

Author(s), Year	Symptom(s) Investigated in the Paper	Participants (Total and in Relation to Analyses of Interest)	Criteria for Diagnosis and Disease Stage	Symptom rating scale/ Assessment Method	Design(s)	Neuro-imaging Technique	Type of scan	Analyses software	Neuro-imaging Metrics	Aim(s) of the Paper (in Relation to Analyses Relevant to this Review)	Confounding Factors accounted for in the Analyses	Brain Area(s) Investigated	Statistical Threshold and Correction	Relevant Findings
		without psychosis		each participant and domain to measure severity)			at 1.5-T; T-1 weighted scans			misidentification associated with alterations in ventral visual stream regions, and paranoia with frontal and temporal regions	Cog score) and time elapsed between NPI administration; MRI acquisition	stream, middle temporal area, medial temporal cortex, anterior cingulate and medial prefrontal cortex, orbital and polar frontal cortex, and dorsolateral prefrontal cortex	multiple comparisons	cortex (psychosis compared to control); decreased cortical complexity in the R entorhinal cortex (misidentification)
Hayata et al., 2015 (Hayata et al., 2015)	psychosis, including sleep disturbances [a]	33 AD, % of psychosis not specified; 29 controls	probable AD (NINCDS-ADRDA criteria and CDR), mild or moderate	NPI	cross-sectional	MRI	Phillips 3-T, T-2 weighted scans	Freesurfer	not specified	correlations between neuroanatomical structures with NPS	age, gender, and education level	not specified, in Talairach and Tournoux atlas	FDR corrected	no significant results
Jeong et al., 2021 (Jeong et al., 2021)	psychosis	172 a-MCI, of which 94 progressed to AD and 18 to AD + P, at follow-up	a-MCI (Petersen criteria) and probable AD (NINCDS-ADRDA criteria); PET biomarkers	NPI (Korean version); psychosis in AD by Jeste and Finkel	longitudinal	MRI	Siemens 3.0-T, T-1 weighted scans	Freesurfer 5.1	ROI	effect of sub-regional thickness in the frontal lobe on the risk of AD + P conversion in patients with aMCI, association independent of hippocampal atrophy	age, sex, education level, follow-up period; total brain volume, hippocampal volume	frontal lobe, specifically anterior cingulate cortex (rostral and caudal ACC)	$\rho < 0.05$; Bonferroni multiple comparisons (continuous variables), chi-square (discrete variables)	thinner L caudal anterior cingulate cortex (cACC) compared (psychosis converters compared to aMCI stable or AD converters); decreasing trend in both biltaeral rostral ACC and R cACC (did not reach significance)
Koppel et al., 2014 (Koppel et al., 2014)	psychosis	21 AD with psychosis and 21 without (trait analysis), 39 AD patients with psychosis and 39 without (state analysis)	both MCI and probable AD (NINCDS-ADRDA criteria), CDR as proxy of progression	NPI-Q (presence)	longitudinal	FDG-PET	not specified	SPM5	CMRgl by sROI	perturbations in frontal brain glucose metabolism associated with psychosis either preceding it (genetic or neuro-developmental "trait" effect) or coincide with the psychotic "state"	trait and state psychosis definition, age-matched controls	L and R angular gyrus, bilateral posterior cingulate gyrus, L and R inferior temporal gyrus, orbitofrontal region, in MNI space	$\rho < 0.05$ uncorrected	decrement in mean brain CMRgl for each ROI in the AD + P compared with AD-P; only orbitofrontal impairment robust enough to achieve statistical significance (focal frontal vulnerability as a mediator of progression)
Lee et al., 2019 (Lee et al., 2019)	psychosis	26 AD with psychosis, 48 AD without psychosis	probable AD (NINCDS-ADRDA criteria)	Jeste and Finkel criteria	cross-sectional	MRI	3-T Trio TIM, T-1 weighted scans	Freesurfer 5.1	ROI	regionally distributed MTC thickness (or hippocampal volume) and frontal lobe volume are independently associated with the	age, gender, years of education, CDR-SOB score, MMSE (K-version), duration of AD; total intracranial	total frontal cortex, total temporal cortex, and subregions of the medial temporal cortex (HC, entorhinal, and parahippocampus),	$\rho < 0.05$	R hippocampal atrophy (adjusted for frontal volume)

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										onset of AD with psychosis	volume and total frontal volume	in the Desikan-Killiany Atlas		
Lee et al., 2021 (Lee et al., 2021)	psychosis	27 AD with psychosis	probable AD (NINCDS-ADRDA criteria)	Jeste and Finkel criteria,	longitudinal (3-months intervals)	MRI	Siemens 3-T Trio TIM, T-1 weighted scans	Freesurfer 5.1	ROI	effect of decreased cortical thickness or volume of medial temporal lobe structures on the risk of incident psychosis in AD patients	age, sex, education level, CDR-SOB score, follow up period; total intracranial volume	regions of interest were structures of the medial temporal cortex (the hippocampus, entorhinal, and parahippocampus) included in the Desikan-Killiany Atlas	$\rho < 0.05$	L and R hippocampal volume, L and R entorhinal cortical thickness, L and R parahippocampal volume
Lee et al., 2016 (Lee et al., 2016)	psychosis (mis-identification and paranoid)	40 AD with psychosis, 25 without	probable AD (NINCDS-ADRDA criteria)	NPI (Korean version)	cross-sectional	MRI	Siemens Trio TIM 3.0-T, T-1 weighted scans	SPM8 (VBM8 toolbox)	VBM	association between brain regional grey matter volume and two subtypes of psychotic symptoms, paranoid and misidentification, in antipsychotic-naïve mild or moderate AD patients	age, gender, education, CDR score and K-NPI non-psychotic scores; total intracranial volume	not specified, in MNI template	$\rho < 0.001$ uncorrected at voxel level, threshold of contiguous 100 voxels	R inferior parietal lobule, R lingual gyrus, L cuneus, R middle frontal gyrus, R superior occipital gyrus R middle temporal gyrus (misidentification); R middle frontal gyrus, R medial frontal gyrus, L middle frontal gyrus, L medial frontal gyrus, L superior frontal gyrus, L inferior frontal gyrus, R middle occipital gyrus, R superior frontal gyrus, R middle temporal gyrus (misidentification vs paranoia); R medial frontal gyrus, L inferior frontal gyrus, L middle temporal gyrus, L medial frontal gyrus, R middle frontal gyrus, L cuneus, L middle frontal gyrus, R superior frontal gyrus, L lingual gyrus (paranoia)
Lee et al., 2020 (Lee et al., 2020)	psychosis [a]	70 AD, % psychosis not specified	probable AD (NINCDS-ADRDA criteria),	NPI (Korean version)	cross-sectional	fMRI	Phillips 3.0-T, T-2 weighted scans	SPM12 (iRSFC toolbox)	DMN	relationship between NPS subsyndromes and resting functional connectivity	not specified	anterior and posterior DMN	clusters based on FWE corrected $\rho <$ 0.05, cluster-	no significant results

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			cognitive status with K-MMSE, CDR							(DMN) in patients with Alzheimer's disease			determining threshold at uncorrected $\rho < 0.001$	
Lopez et al., 2001 (Lopez et al., 2001)	psychosis	9 AD, 2 delusions, 2 hallucinations and 5 without; 9 elderly controls	probable AD (NINCDS-ADRDA criteria)	DSM-IV criteria	cross-sectional	PET	Siemens 951R/31	not specified	ROI	critical brain region that serves as a common denominator for the development of psychotic phenomenon in AD	not specified	orbitofrontal, frontal dorsolateral, anterior cingulate, medial temporal, superior temporal, parietal and occipital cortices, and basal ganglia and thalami	not specified	lower rel-CBF in the L medial temporal and dorsolateral frontal cortices
Makovac et al., 2016 (Makovac et al., 2016)	psychosis [a]	58 AD, % of psychosis not specified	probable AD (NINCDS-ADRDA criteria)	NPI (frequency and severity)	cross-sectional	MRI	Siemens 3.0-T, T-1 weighted scans	not specified	VBM	correlations between regional GM atrophy and WM abnormalities in the corpus callosum (CC) of AD patients with NPS	individual brain size	corpus callosum, in MNI standard space	$\rho < 0.05$	MD and FA in the genu of the CC, and GM atrophy in the fronto-orbital cortex, R anterior cingulate cortex (paracingulate) and R thalamus
McLachlan et al., 2018 (McLachlan et al., 2018)	psychosis (misidentification and paranoia)	104 AD patients (47 with psychosis and 57 without)	probable AD (DMS-IV criteria and MMSE)	NPI (frequency and severity)	cross-sectional	MRI	not specified	not specified	ROI	psychosis associated with visuo-perceptual/ frontal networks, and regional brain volume differences in relation with paranoia (persecutory delusions) or misidentification (misidentification delusions and/or hallucinations)	age, duration of illness, ADAS-Cog; total intracranial volume	entorhinal cortex, parahippocampal gyrus, lateral occipital cortex, fusiform gyrus, lingual gyrus, rostral and caudal anterior cingulate cortex, rostral middle frontal gyrus and medial orbitofrontal cortex	$\rho < 0.05$	L parahippocampal gyrus and L lingual gyrus; L and R parahippocampal gyri and post-hoc pairwise comparisons showed significantly lower L parahippocampal volume in (misidentification and mixed groups); R parahippocampal volume (mixed group)
Mega et al., 2000 (Mega et al., 2000)	psychosis	20 AD patients (10 with psychosis, 10 without)	probable AD (NINCDS-ADRDA criteria)	NPI	cross-sectional	SPECT	Picker 3000XP scanner	not specified	6 mm voxels (FWHM of the scanner) within ROI	functional imaging profile of patients with psychosis in AD	demographic profile and MMSE	not specified, in Talairach and Tournoux atlas	Bonferroni correction	L medial orbital frontal, L anterior cingulate, L dorsolateral frontal, L dorsolateral frontal, L dorsolateral parietal, L pulvinar, L ventral striatum, L cerebellum, R dorsolateral frontal, R dorsolateral frontal, R medial frontal

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Misquitta et al., 2020 (Misquitta et al., 2020)	psychosis [a]	121 AD, 315 MCI, % of psychosis not specified; 225 healthy controls	both MCI and probable AD (NINCDS-ADRDA criteria)	NPI (frequency and severity)	longitudinal	MRI	1.5 and 3-T, 1 and 2-T weighted and FLAIR scans	MATLAB R2017b	WMH and ROI	WMH burden and regional GM atrophy contribution to NPS (over time)	age, gender, cohort (control, MCI, or AD); mean GM in each ROI, WMH segmenting sequences modality	not specified, in MNI atlas	$\rho < 0.05$, corrected for multiple comparisons (FDR)	lower GM mean deformation-based morphometry values in the R middle temporal gyrus and L Heschl's gyrus, and R and L cerebellum; WMH load
Moran et al., 2008 (Moran et al., 2008)	psychosis	157 AD, 79 with psychosis and 78 without	probable AD (NINCDS-ADRDA criteria), moderate to severe	BEHAVE-AD (presence)	cross-sectional	SPECT	Ceraspect brain camera	SPM2 in MATLAB	VB	determine if the presence of psychotic symptoms in patients with Alzheimer's disease is associated with abnormal regional cerebral function	age, MMSE	not specified	$\rho < 0.05$, corrected for multiple comparisons (FDR) at voxel level	hypoperfusion in R inferior-lateral prefrontal cortex and R mid-temporal cortex was observed among female AD patients with psychotic symptoms, but not among male patients; R striatal hyperperfusion among male AD patients with psychotic symptoms, but not among females (peak of this cluster centred at the border of the R posterior putamen and the globus pallidus)
Rafii et al., 2014 (Rafii et al., 2014)	psychosis	389 MCI and AD, 47 with psychosis and 342 without	both MCI and probable AD (NINCDS-ADRDA criteria)	NPI (severity and frequency)	cross-sectional and longitudinal	MRI	1.5-T, T-1 weighted scans	Freesurfer	ROI	relationship between regional neocortical atrophy and psychotic symptoms in adults MCI and AD	age, education, MMSE and ADAS-Cog	anterior cingulate, entorhinal, lateral frontal, lateral occipital, lateral parietal, medial orbitofrontal, and posterior cingulate	$\rho < 0.05$	volume loss in anterior cingulate, lateral frontal, lateral occipital, lateral parietal, medial orbitofrontal; greater lateral frontal, and lateral parietal atrophy at 1-year postbaseline in patients with psychotic symptoms and/or antipsychotic medication use (controlling for baseline ADAS-cog performance)
Ramusino et al., 2021 (Ramusino et al., 2021)	psychosis [b]	48 AD, 7 FTD, 4 LBD, 9 VD, 6 Dem NOS, 26 MCI (% not specified)	both MCI and probable AD (NINCDS-	NPI (frequency and severity)	cross-sectional	CT and MRI	Somatome Perspective CT Siemens, and Magnetom	not specified	ROI	biological correlates of NPS, impact in different forms of cognitive impairment (MCI,	age, gender, education, MMSE, diagnosis	MTA, PA, and GCA-F	$p < 0.05$ 2-sided, (p-values between 0.05 and 0.1 were	positive correlations with R GCA-F scores

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Author(s), Year	Symptom(s) Investigated in the Paper	Participants (Total and in Relation to Analyses of Interest)	Criteria for Diagnosis and Disease Stage	Symptom rating scale/ Assessment Method	Design(s)	Neuro-imaging Tech-nique	Type of scan	Analyses software	Neuro-imaging Metrics	Aim(s) of the Paper (in Relation to Analyses Relevant to this Review)	Confounding Factors accounted for in the Analyses	Brain Area(s) Investigated	Statistical Threshold and Correction	Relevant Findings
			ADRDA criteria)				Skyra Siemens 3T, T-1 weighted scans			AD, FTD, LBD, and VD), and correlations NPS with CSF biomarkers and cortical visual rating scales			also reported)	
Santhosh et al., 2009 (Santhosh et al., 2009)	psychosis	9 AD, 4 with psychosis and 5 without)	probable AD (NINCDS-ADRDA criteria)	NPI and subscales of BPRS	cross-sectional	[18F] deuteroaltanserinPET	HR + Siemens camera	not specified	ROI	correlations between regional 5-HT2A receptor binding and psychosis/ depression in AD patients	age, gender	anterior cingulate, frontal, medial frontal, temporal, parietal, occipital, cerebellum, putamen, and thalamus	not specified	no significant results
Serra et al., 2018 (Serra et al., 2018)	psychosis [a]	84 AD, 48 a-MCI, 22 with psychosis; 37 healthy elderly controls	both a-MCI and probable AD (NINCDS-ADRDA and NIA-AA criteria)	NPI (frequency and severity)	cross-sectional	fMRI	Siemens 3.0-T, T-1 and -2 weighted scans	SPM8 in MATLAB	ROI	changes in VTA and LC connectivity (used as a proxy of neuronal loss) in relation with higher level of dysfunctions in AD	years of formal education; whole-brain GM volumes, MTA	PCC, right and left angular gyrus and whole brain (VTA connectivity)	$\rho < 0.05$ FWE corrected at cluster level	no significant results
Serra et al., 2020 (Serra et al., 2020)	psychosis (including dis-inhibition) [a]	101 AD, 56 a-MCI, 31 with psychosis; 35 healthy elderly controls	both a-MCI and probable AD (NINCDS-ADRDA and NIA-AA criteria, with CDR for MCI)	NPI (frequency and severity)	cross-sectional	fMRI	3.0-T, T-2 weighted scans	SPM8 in MATLAB and in-house developed	ROI	alterations of functional brain connectivity at different clinical stages of AD patients, with NPS	MMSE score, age, gender, education, psychoactive medications; motion, clinical status, GM volumes, MTA	not specified	$\rho < 0.05$ Bonferroni correction	reduced connectivity in the R cingulum, hippocampus and insula, and in the bilateral supramarginal gyrus
Siafarikas et al., 2021 (Siafarikas et al., 2021)	psychosis [a]	133 AD, 102 MCI, % of psychosis not specified	ICD-10 (AD dementia) and ICD-10, MMSE for severity	NPI-Q (severity)	cross-sectional	MRI	GE 3T T-1 weighted FSPGR; GE 3T T-1 weighted BRAVO; Siemens 1.5 sagittal MPRAGE	Freesurfer 5.3	Regions	hypothesized NPS to be associated with the thickness and volume of frontotemporal regions, including the anterior cingulate cortex (ACC)	age, sex, and diagnosis	not specified	$\rho < 0.005$ FDR correction	L post-central gyrus
Sultzer et al., 1995 (Sultzer et al., 1995)	psychosis [a]	21 AD, % psychosis not specified	probable AD (NINCDS-ADRDA criteria)	NRS	cross-sectional	FDG-PET	ECAT III tomograph		ROI	psychiatric symptomatology associated with the extent of global cortical hypometabolism and relationships between specific symptoms and hypometabolism in	age, MMSE, NRS total score, duration of dementia	medial and lateral orbitofrontal, dorsomedial frontal, dorsolateral convexity, precentral gyrus, post-central gyrus, superior and inferior lobule, primary and secondary visual,	not specified	frontal cortex hypometabolism

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										individual cortical lobes		superior, and inferior temporal, septal region, cingulate, hippocampus, para-hippocampal gyrus, temporal pole, insula		
Sultzer et al., 2002 (Sultzer, 2002)	psychosis [a]	18 AD patients (males), % with delusions not specified	probable AD (NINCDS-ADRDA criteria); CSF biomarkers	NRS (presence and severity)	cross-sectional	MRI	MTS.35 MRI System, 0.35-T, 1T weighted scans	not specified	WMH	extent of subcortical WMH (SH) related to the degree of regional cortical hypometabolism and severity of NPS	MMSE rank	not specified	not specified	trends of positive correlation between hyperintensities in the R and the anterior halves of the subcortex (non-significant after covarying for MMSE)
Yasuno et al., 2020 (Yasuno et al., 2020)	psychosis (including sleep disturbances) [a]	21 AD, 29 MCI, % of psychosis not specified; 49 cognitively normal controls	both MCI and probable AD (NINCDS-ADRDA criteria, MMSE and CDR)	NPI	cross-sectional	PET	AV-45 scans	not specified	ROI	relationship between Aβ- and tau-based AD pathologies and NPS	not specified	bilateral frontal, anterior and posterior cingulate, lateral parietal and lateral temporal cortices and whole cerebellum; entorhinal cortex and hippocampus, medial temporal and limbic region, neocortical region, and uptake of inferior cerebellum	$\rho < 0.05$, Bonferroni multiple comparisons	no significant results

NOTES: in the participants' column, the first sample size provided is the total number of AD and/or MCI patients (inclusive of non-psychosis controls; if healthy controls are also included, these are reported at the end of the cell); where the symptom of interest was present in a smaller ratio of this, this is specified consequently (as numbers or percentages, as available in the paper); assessment tools such as MMSE and CDR are only reported in the diagnosis column where these supported the diagnostic process or the severity of dementia, or in the confounding factors where these were specifically included in the analyses, while complete neuropsychological assessment was not reported in this table; unless differently stated, the neuropsychiatric picture for the sample of interest was not available (e.g., unknown if the participants presenting with delusions also presented with other symptoms); findings of the studies are only reported in relation to the symptoms investigated (i.e. psychosis); all groups (sample with symptom of interest and control group) were used in the analyses which resulted in reported findings, unless differently stated; findings are only reported for the symptom of interest, therefore no significant findings only refers to that (i.e. the paper might have other significant findings with respect to other NPS that are not reported here).

Abbreviations: CMRgl = cerebral metabolic rate for glucose, FD = fractal dimension, DMN = default mode network, GCA-F = global cortical atrophy-frontal, LBD = Lewy body dementia, MTA = medial temporal lobe atrophy, NOS = not otherwise specified (dementia), PA = posterior atrophy, FDR = false discovery rate, FWE = family wise error, iRSFC = intuitive resting-state functional connectivity, SN = salience network.

[a] These papers performed investigations on other neuropsychiatric symptoms/clusters of symptoms as well.

[b] These papers included investigations on delusions, and/or hallucinations as individual symptoms.

delusions (n = 14) [Table 2], with no restrictions in terms of neuroimaging technique employed, analytic method, sample size (excepting case studies), and number of reported peak clusters. Two studies performed analyses on the severity of delusions in association with brain atrophy (Nomura et al., 2012; Fischer et al., 2016) (no control sample), while the remaining twelve compared AD patients with delusions to AD patients without delusions (Nakano et al., 2005; Schroeter et al., 2020; Fukuhara et al., 2001; Nakaaki et al., 2013a, 2013b; Nakatsuka et al., 2013; Qian et al., 2019a, 2019b; Serra et al., 2010; Staff et al., 1999; Sultzer et al., 2014; Ting et al., 2015) and/or healthy controls (Boublay et al., 2020; Jedidi et al., 2015; Matsuoka et al., 2010); the total sample size ranged from eighteen to ninety-three, and the number of significant peaks for coordinates ranged from one to twenty-three.

Among the different CBMA meta-analysis methods, we decided to perform a multi-level kernel density analysis (MKDA) (Kober et al., 2008; Kober and Wager, 2010), as this was deemed the most appropriate for the features of the studies included in our analysis. Compared to other common methods such as kernel density analysis (KDA) (Wager et al., 2003) and activation likelihood estimate (ALE) (Turkeltaub et al., 2002), the MKDA has the advantage of considering each set of peaks at the study level, rather than by only considering each independent peak as the unit of analysis (Wager et al., 2007; Kober and Wager, 2010). In this way, it accounts for differences in the number of clusters reported by each paper (it accounts for the multilevel characteristics of the data), thus preventing studies with a higher number of coordinates from weighting disproportionately in the meta-analysis (Salimi-Khorshidi et al., 2009): for this reason it is advised when the studies present with a heterogeneous number of clusters, such as those found in our extraction.

Information concerning the peak coordinates and sample sizes of the fourteen studies were analysed using an MKDA algorithm, made available on NiMARE (Salo et al., 2022), a Python package developed to perform meta-analyses on coordinate-based neuroimaging data. As the algorithm requires MNI coordinates, the coordinates that were reported in the Talairach and Tournoux atlas space in the papers were transformed, using the validated converter tool included in GingerALE (GingerALE; Lancaster et al., 2007; Laird et al., 2010). The algorithm was run on Spyder (Version 5.3.3) (Raybaut, 2022), and False Discovery Rate correction (FDR) was applied (Salo et al., 2022), with a threshold of $z \geq 1.64$ (equivalent to $p < 0.05$). This produced three clusters, that are reported in Table 5 and visualised in Fig. 3. The uncorrected clusters (thresholded at $z \geq 1.64$, equivalent to $p < 0.05$) are reported in Supplementary Fig. 1 and Supplementary Table 3.

Lastly, the brain locations of the peak coordinates [Table 5] were estimated using the mni2atlas function (Mascali, 2021) in MATLAB (Version R2022b) (MATLAB (2022)), which translates coordinates into labels from different atlases, and the MNI structural atlas (Collins et al., 1995; Mazziotta et al., 2001) was selected among these. Use of this atlas identified the following brain regions that were in closest proximity to the three peaks; all were in the right hemisphere: a cluster in the frontal lobe, one in the putamen and one smaller cluster in the insula.

4. Discussion

To our knowledge, this is the first systematic review which synthesises the findings of all papers published up to the recent past (to December 30, 2021) that investigate the neuroanatomical correlates of psychotic symptoms in AD and MCI, while also capturing and comparing the different neuroimaging approaches and methodologies.

The results derived from this systematic review and meta-analysis have highlighted a number of key brain areas and networks that appear to be linked to the occurrence and severity of psychotic manifestations in Alzheimer's disease, when these are considered together as a cluster, as well as separately in the form of delusions and hallucinations. Confirming the findings derived from previous reviews (Gallagher et al., 2017; Murray et al., 2014; Ballard et al., 2020; Ismail et al., 2012; Reeves et al., 2012), common areas of atrophy and change (e.g., in metabolism) were again identified predominantly in the frontal lobe, tending towards a right asymmetry. As expected, though, a greater number of regions was identified, which spanned all four lobes, most likely due to comprehensive capture of the wide variety of studies that report on various psychotic phenomena, and to factors intrinsic to the methodology of the studies, such as the severity of the samples included and neuroimaging technique that was adopted. The combination of findings has allowed us to consider potential underlying mechanisms, which other factors may contribute to the results, as well as to propose directions for future studies in this area.

4.1 Observations Derived from the Systematic Review and Meta-Analysis on Delusions and Delusional Subtypes

As delusions were the most commonly studied symptom within our symptomology of interest, unsurprisingly a substantial number of brain regions were identified across the numerous studies. Our synthesis of these studies confirmed the findings of earlier previous reviews on delusions (e.g., Ismail et al., 2012; Reeves et al., 2012) in that some common areas could be identified, which may help explain the origin of delusional formation from a neuroanatomical point of view. Variation across studies was also noted that seemed to reflect the delusional subtype that was most prevalent within a particular study, the neuroimaging approach that was adopted, in addition to the size and stratification of the sample along the AD continuum.

Summing up the brain regions that were identified, across the majority of the studies there was predominant involvement of frontal regions; this was evidenced both from the findings of the systematic review and the results of the meta-analysis (in which the right frontal lobe contained the largest cluster, as seen in the results using FDR correction [Table 5, Fig. 3], and extensive frontal associations were detected when the uncorrected statistical threshold was applied [Supplementary Table 3, Supplementary Fig. 1]). Subcortical structures such as the insula and the putamen appeared also to be of importance both from an analysis of the systematic review and the output of the meta-analysis. On the other hand, areas which were frequently identified by analysing the results of the systematic review, but not from the meta-analysis were temporal regions, as well as the anterior and posterior cingulate cortex. Concerning laterality, while the meta-analysis identified all three regions in the right hemisphere, in the systematic review there was also a predominance of right hemisphere brain regions, but this was not unequivocal.

Considering the links between delusions and the fronto-temporal regions, these areas are generally responsible for regulation of executive function and working memory, and for storage and retrieval of biographic memory, respectively (Uysal, 2023). This might suggest that greater atrophy in these areas could be associated with an inability to correctly remember and process information about self and others,

Table 5
Peak clusters of coordinates derived from the meta-analysis on fourteen studies on delusions.

Cluster ID	X	Y	Z	Peak Statistic (z)	Cluster Size (mm^3)	Label (MNI structural atlas)
1	44.0	8.0	44.0	1.859	608	R Frontal Lobe (74%)
2	28.0	12.0	−10.0	1.859	408	R Putamen (27%)
3	32.0	22.0	−10.0	1.859	40	R Insula (60%)

Notes. Coordinates are expressed in MNI space. FDR correction was applied; clusters are significant at $z \geq 1.64$ (equivalent to $\rho < 0.05$).

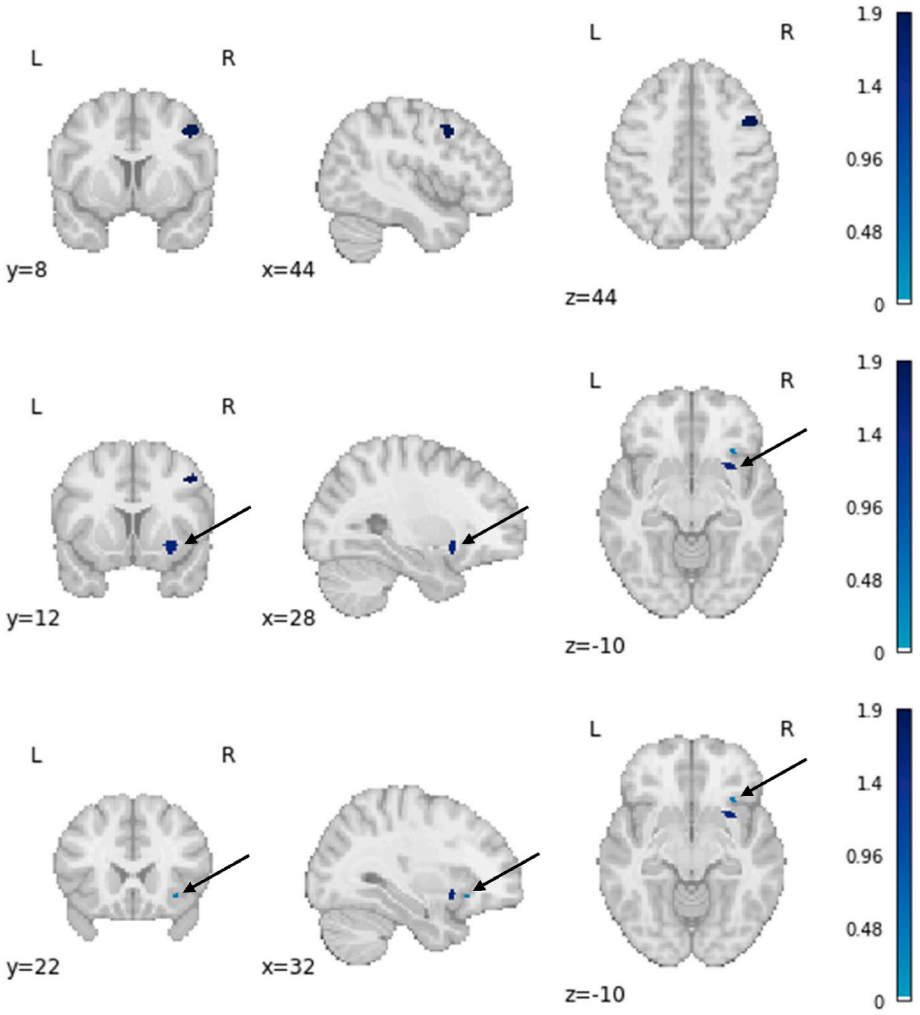

Fig. 3. Meta-Analysis Results. With reference to the MNI structural atlas, the coordinates correspond respectively to the R Frontal Lobe, the R Putamen, and the R Insula.

which contributes to the formation of delusional beliefs. More specifically, the areas which were more frequently identified across the studies within the frontal lobe were the prefrontal cortex (mainly on measures of hypo-activation), and within this, the orbitofrontal cortex; these have been linked to the regulation of intentional and motivated behaviours (Rafii et al., 2014), memory and learning processes (Stanislav et al., 2013; Rolls, 2004), and assigning values to specific emotional inputs (Dixon et al., 2017). Among temporal areas, on the other hand, the most frequently identified were the parahippocampal gyri, responsible for memory encoding and retrieval (Yoo et al., 2012), context appraisal and associative learning (Pras and ad, 2019). The combination of these processes might help explain how the failure to assimilate the correct information and to consider alternative possibilities could generate and maintain the delusional belief (Sultzer et al., 2014).

Albeit with less frequency, areas associated with delusions were also identified within the parietal lobe, mainly the precuneus, which is involved in self-centred mental imagery strategies, episodic memory retrieval (Cavanna and Trimble, 2006), and discriminating self-relevant from self-irrelevant information (Nomura et al., 2012). With regards to the occipital lobe, this brain region was mainly identified within studies with participants that had a greater prevalence of misidentification phenomena.

One limbic structure that was identified by a large number of the studies on delusions was the cingulate cortex, anterior and posterior. The anterior cingulate cortex is commonly subdivided into a dorsal and ventral portion; the dorsal anterior cingulate cortex is related to high-level cognition, such as executive functioning and error detection, as well as the processing of visual stimuli, while the ventral anterior cingulate cortex is mainly involved with emotional processing, such as regulation of overall affect, and assigning emotion to internal and external stimuli, and pain perception (Boublay et al., 2020; Jeong et al., 2021; Rolls, 2019): one interpretation might be that the impaired monitoring of reality functions, associated with abnormal perceptual and emotional experiences, might contribute to the development of delusions. The posterior cingulate cortex, on the other hand, is mainly related to memory and visual processes, self-reflection and imagery (Rolls, 2019), and this was mostly identified in studies on delusions of misidentification, including Capgras syndrome.

It might be possible to explain further key processes through the involvement of the subcortical structures that were most frequently identified, such as the insula and parts of the basal ganglia, (particularly the putamen). These brain regions are involved respectively in the perception of self-generated stimuli, awareness of external stimuli, and maintaining rigidly held beliefs (Ting et al., 2015), and in the facilitation of different types of learning, particularly emotional (Luo et al., 2019), which might explain their involvement in the perpetuation of delusions.

The insula and the anterior cingulate cortex are part of the salience network (Uddin and Uddin, 2017). Their involvement might therefore explain the difficulty that patients with delusions have in discriminating, processing, and filtering relevant stimuli. The salience network

has been highlighted in previous models on delusional formation, such as the 'aberrant salience' hypothesis (Kapur, 2003): this refers to the attribution of motivational salience to irrelevant stimuli, generating distorted interpretations, and it appears to be linked to dysfunction in dopamine regulation, which might lead to the unfounded associations that are characteristic of delusional beliefs, as it causes irrelevant stimuli to receive excessive salience. Support for this model has been provided by functional neuroimaging studies on delusions in other studies, such as those on people at risk of psychosis, or those experiencing first episode psychosis (e.g., Panula et al., 2022; Roiser et al., 2012), as well within a review on the origins of delusions in AD (Reeves et al., 2012), which seems to indicate disruption of this network across different syndromes, and its contribution to the generation mechanism of delusional beliefs. Furthermore, there similarly appears to be some evidence that dysfunction within this network precedes delusional formation in both AD patients (Jeong et al., 2021) and other psychiatric disorders (Raij et al., 2016), again pointing toward its importance as a target for further investigation.

Concerning laterality, as expected, the majority of areas of atrophy and hypoperfusion/hypometabolism were identified in the right hemisphere (Ismail et al., 2012), albeit not exclusively. Potentially of equal interest, areas of hyperactivation were on the other hand identified within the left hemisphere. It has been hypothesized in different models of delusional formation (Gurin and Blum, 2017; Devinsky, 2009), that this might be linked to the fact that while less activity in the right hemisphere might be linked to deficits in the interpretation of external and internal data, as well as social cues, regions in the left hemisphere could be involved in creating alternative explanations, as well as excessive and false explanations on the self, memory and reality (Cotta Ramusino et al., 2024).

With respect to the thematic aspects of delusional content, contrary to our expectations, clear trends were not identified with respect to each individual delusional subtypes; this is likely due to the fact that, to date, this approach has been taken by so few studies, and these were methodologically different. Thus, it appears preliminary to draw conclusions, and we suggest further investigations of delusional subtypes are likely to be worthwhile. However, some correspondence between studies appeared clearer when considering delusions that relate to paranoid aspects (such as theft, persecution, abandonment) versus those that relate to misidentification phenomena such as Capgras syndrome (with this investigated in a few papers, particularly case-studies). Specifically, fronto-temporal involvement was particularly evident in association with paranoia, while regions across the four lobes and a greater involvement of the cingulate cortex (particularly the posterior portion, as mentioned above) were identified in association with misidentification. Therefore, the evidence seems to suggest that a more fine-grained classification of the delusional subtype might constitute an interesting approach to undertake (see below).

4.2 Observations on Hallucinations

Although fewer studies focused on the neuroimaging correlates of hallucinations, some interpretation of the findings is possible. While associations were identified with multiple regions across the brain, the occipital lobe was consistently mentioned in most studies in relation to visual hallucinations, (but not in the single study that investigated musical hallucinations), suggesting a modality specific neuroanatomical impairment that underpins specific types of hallucinations. An association with the anterior cingulate cortex was frequently identified, and in one key study (Blanc et al., 2014), the insula, suggesting a disruption of the salience network in the formation of hallucinations, as well as delusions, and offering a potential explanation for why these symptoms can tend to co-occur.

Furthermore, involvement of frontal brain regions was identified in two studies (Boublay et al., 2020; Blanc et al., 2014); a combined impairment of frontal and occipital areas may indicate diminished sensory processing of visual stimuli (Zhang et al., 2023) and deficits in predictive coding, the ability to correctly implement generative models in the brain to interpret sensory inputs (Kocagoncu et al., 2021). Previous studies have suggested an association between non-optimal predictive processing and the presence of hallucinations (Horga et al., 2014; Sterzer et al., 2018), underpinned by prediction errors. Combined, these processes might explain the misinterpretation of stimuli and misperceptions which underlie visual hallucinations; further investigations into these processes might be warranted to increase the understanding of hallucinations in AD.

There were also a number of studies that did not identify any brain regions in association with hallucinations, although this was mainly found in those that investigated the associations of all neuropsychiatric symptoms, with the potential consequence that the participant samples did not exhibit hallucinations to a sufficient prevalence, and were therefore, not optimal for the study of this symptom. More studies are needed that focus specifically on the neuroanatomical underpinnings of hallucinations at different stages of the AD continuum, so that variability in the incidence of hallucinations may be accounted for (as hallucinations tend to be less common at earlier stages of the disease (Linszen et al., 2018)).

4.3 Psychotic Clustering and an Alternative Approach to Classification: Misidentification and Paranoia

Considered that the studies that investigated psychosis as a cluster were predominantly inclusive of symptoms of delusions and/or hallucinations, as might be expected, they showed a vast degree of overlap with areas identified above when approaching the symptoms separately: reporting involvement mainly of frontal, temporal and occipital areas, as well as the anterior cingulate cortex.

Analysing the key findings of the studies that specified the content of psychotic symptoms, a pattern emerged that seems to confirm that two distinct phenotypes can be identified (Ismail et al., 2012; D'Antonio et al., 2019): misidentification and paranoia. The neuroanatomical correspondences of these two manifestations could support the identification of new criteria to reflect this (Cook et al., 2003; Perez-Madriñ et al., 2004), recently revisited in an international effort to revisit criteria for psychosis (Fischer et al., 2020).

According to this proposed means of classification (Cook et al., 2003), in order to identify the brain areas in relation to misidentification, we considered all the papers which included in their sample, patients presenting delusions of misidentification, such as Capgras syndrome and phantom boarder, as well as their similarities with the findings of the studies on hallucinations; within the paranoia subtype, we considered delusions of persecution, theft, abandonment, and jealousy.

This revealed that the misidentification subtype was the most frequently studied, and it was quite consistently found in association with a more severe overall clinical picture compared to the paranoid one (e.g., Lee et al., 2016). The misidentification subtype frequently showed associations with frontal, occipital and temporal lobe regions, while within the paranoid subtype, associations with temporal lobe regions were found much more often, with a smaller contribution of frontal areas.

Specifically, within the misidentification subtype, the posterior cingulate, prefrontal and orbitofrontal cortices were frequently identified, as well as the lingual gyrus of the occipital lobe, and impairments in the ventral visual stream: this might suggest that misidentification phenomena in AD are, at least partially, related to misperception and misinterpretation of stimuli (D'Antonio et al., 2019).

Concerning the involvement of temporal areas, while these were found in both subtypes, two recent studies identified the entorhinal cortex in relation to misidentification; the entorhinal cortex is involved in the perceptual processing of stimuli, in novelty detection, associative learning, and processing episodic, recognition, and autobiographical

memory, which might contribute to explaining its involvement within phenomena of misidentification (Prasad et al., 2004). Importantly, this appears to be the case also when statistically controlling for disease severity, as both studies included measures of cognitive impairment as covariates in their analyses. Therefore, while both the entorhinal cortex (Braak et al., 1993) and misidentification phenomena are associated with a more severe clinical picture, their association appears to be found irrespective of this, suggesting an interesting route to further investigate in the future.

With regard to the delusional subtypes that had an underlying paranoid component, the most commonly identified regions were fronto-temporal areas and the anterior cingulate cortex, which might indicate a shared mechanism explaining this category of delusional content. Atrophy in the temporal cortex in relation to different aspects of paranoia might be linked to a misinterpretation of stimuli and failure to accurately encode new memories, as well as an increased sensitivity to perceive emotional pain and emotions that have a negative connotation (Nakatsuka et al., 2013). However, very few studies focused on particular types of paranoid delusions (e.g., theft, jealousy, abandonment), and attempted an interpretation of different mechanisms underpinning each thematic component; not enough to enable the differences and similarities of associated brain regions to be assessed more clearly.

Comparisons between studies such as those mentioned above that link neuroanatomy to each type of delusional phenomena may be informative in shedding light on why one category of delusions may occur over another, as well as informing on the potential shared mechanisms between certain subtypes of delusions and hallucinations. Nevertheless, it remains that the summaries of brain regions that are linked to each subtype need to be interpreted with caution, as substantial methodological differences were present across the studies that treated the symptoms separately, and further investigations in this area will help to clarify these mechanisms.

4.4 Other Neuropsychiatric Symptoms within the Psychotic Cluster

When approaching psychosis as a cluster, studies normally included participants who presented with delusions and/or hallucinations, while on three occasions another symptom was included in the cluster.

In one study this symptom was disinhibition, which in a preliminary analysis was factored within the same cluster (Wang et al., 2021): as predicted, they found the cingulate cortex to be involved, likely due to the role of this brain region in regulating higher-order behaviours, which might explain its association with a psychotic cluster which includes disinhibition as well.

On the other hand, the two studies in which sleep disturbances were clustered within psychosis did not yield any significant results in relation to associations with neuroanatomy. While it appears that sleep dysfunction and psychosis are related phenomena, and many theoretical models have been proposed to explain their relationship (Reeve et al., 2015), clear mechanisms in relation to brain regions or networks, particularly within the context of AD, are yet to be understood. Therefore, should this clustering be seen regularly, exploring the reasons for it, whether neuroanatomical or due to other factors, might be something worth doing in future investigations.

While on some occasions the grouping of delusions and hallucinations was guided by a factor analysis on the sample, this was not always the case. It would be interesting through additional investigations to explore delusions and hallucinations consistently factor together, whether other neuropsychiatric symptoms are identified within the cluster, and what the correspondent neuroanatomical correlates are in relation to these.

4.5 Observations on the Methodological Differences among the Studies and Considerations from the Risk of Bias Assessment

A range of data was extracted in our review with the objective of attempting to explain potential sources of variance that may affect the findings for the neuroanatomical regions that link to psychosis in AD. Analysing the methodological differences among the studies, we found that some of the features that we had considered to be of potential importance seemed to contribute to this. One such aspect was in relation to sample size and composition. While unexpectedly the results of studies with very large sample sizes (e.g., Moran et al., 2008)) were found to be mostly comparable to the majority of the papers that had smaller numbers of participants, when interpreting the studies that did not find any significant results, on many occasions this seemed to be related to the small percentage of patients presenting with the symptoms of interest within the overall sample. Future studies should ensure that the sample size is sufficient for those with the symptom(s) of interest to be adequately represented.

Furthermore, variability was found in relation to the choice of a control sample: while some studies did not employ one, focusing on aspects such as the correlation of neuroanatomical regions with the severity of symptoms, the majority of studies performed group comparisons, either with an AD sample that did not exhibit psychotic symptoms, or cognitively healthy controls. While the approach to matching the controls was normally identified, mainly through similarities in terms of age, level of education, and within AD patient controls, severity of the cognitive impairment, this was not always the case; furthermore, control for the presence of other neuropsychiatric symptoms was normally not performed, which might be a factor to consider in future studies, in order to identify regions that are more certainly specifically linked to psychotic symptomology. If group comparisons are used to isolate neuroanatomy specific to the symptoms of interest, we suggest an appropriate control group is one matched to the group of interest, on factors such as sample size, diagnosis, age, sex, and other neuropsychiatric symptoms. Often it is desirable for the control group to differ from the other group on the symptom of interest only, but of course in practice this is unachievable. In the case of correlation/multiple regression, similar factors, for example, age, sex, diagnosis, and other neuropsychiatric symptoms, might be considered as covariates. In both types of statistical modelling, we would recommend that analyses are performed and reported fully, with and without the covariate options that have been selected, such as indicators of disease severity (which may take the form of cognitive or neuroanatomical markers), so that the differences between the results may be assessed, as these may be informative when attempting to understand the brain regions and networks that link to the psychotic symptom of interest).

One element that was particularly evident from the results of the risk of bias assessment analysis, was the variability in terms of what covariates were included in the analyses, or more generally, what potentially impactful aspects were considered. One important example of this was the lack of consideration for disease stage, which appeared to be linked to non-significant findings in some studies, indicating that sample selection is an important aspect to consider in future study designs and subsequent analyses (and in addition to clinical and neuropsychological indicators of disease severity the integration and consideration of biomarkers could be advantageous). Taking into account how the prevalence may change as the disease progresses (Ballard et al., 2020; Ismail et al., 2022), it appears clear that careful consideration of disease stage in sample selection is likely to be important. With regards to neuroimaging methodological aspects, a minority of studies did not specifically state whether they controlled for factors such as total intracranial volume for MRI and mean metabolic rate for PET. However, no clear and consistent differences were identified between studies that did adopt these procedures compared to those that did not, which was contrary to our expectations. However, as further investigation on the methodology was not pursued beyond what was reported in the papers, it is possible that even when not clearly stated, strategies to account for these factors

were taken into account (and it is reporting standards that has been the issue rather than inclusion of covariates).

Studies which employed ROI and VB approaches to analyse structural and functional data, overall provided comparable findings. However, in the cases where the pre-selected brain areas in ROI studies were limited to one or two specific regions, which did not result in significant associations, they might have overlooked the importance of other relevant regions, appearing to suggest that focused ROI analyses should also be accompanied by whole-brain voxel (or vertex)-wise analyses (and these other analyses could be very useful for future meta-analyses).

Furthermore, other discrepancies across studies may potentially relate to the procedural and statistical approaches taken (including, for example, the means of correction for multiple comparisons), as well as the type of information (reporting standards) which was made available within the papers to allow for clear synthesis and comparisons.

In confirmation of recent evidence on the prevalence of psychotic manifestations at earlier stages of AD pathology (Fischer et al., 2020; Ismail et al., 2022), studies that included MCI in their sample tended to find comparable results to those who did not, with involvement of frontal and orbitofrontal areas, anterior cingulate cortex and insula appearing to be evident in associations with these symptoms at this earlier stage (Koppel et al., 2014; Fischer et al., 2016; Ramusino et al., 2021; Jeong et al., 2021; Misquitta et al., 2020; Rafii et al., 2014; Serra et al., 2020). However, these were typically investigated within a larger sample comprised of both MCI and AD patients, therefore, to further clarify this, investigations focusing only on preclinical or prodromal stages, where symptoms might be more likely to be observed in isolation, could constitute a useful future approach. Similarly, studies that had a longitudinal design tended to consistently identify similar areas as those with a cross-sectional design.

Although the most common tool used by some margin was the Neuropsychiatric Inventory (Cummings et al., 1994), studies that employed different standardised questionnaires or interviews, those that based their diagnosis on the set of criteria, and those that approached it with unstandardised methods (e.g. clinical observation or interviews) did not have any clear and consistent comparable differences on their overall results.

At the same time, though, clarity over the classifications of psychotic symptoms is a key area to address in future studies: few studies have focused their analyses on specific psychotic symptoms that can be detected by the tools in order to pinpoint the precise areas related to that particular type of manifestation, and this might be an interesting approach to consider in the future (in order to consider the unique associations that might be observed between certain symptoms and brain regions, as well to understand the commonalities that can be found across delusional subtypes). Similarly, more accurate depiction of the frequency and severity of the symptoms within the sample of psychotic patients, which was not always adequately captured or described within the papers studied, might also help to clarify their neuroanatomical underpinnings, with respect to their course within the AD continuum. We suggest that future studies will benefit from providing a clear phenomenological profile of the psychotic symptomology present in their samples, from detailing symptom subtypes, by adequately capturing the frequency, severity and persistence of the symptoms, as well as providing clear information on the presence of other neuropsychiatric symptoms.

4.6 Limitations

Some methodological limitations to our review should be considered. First of all, in relation to the included studies, we did not contact the authors to enquire about potential missing data or aspects of their methods that may have been missing or ambiguous within the published reports, nor did we adopt strategies to address the potential risk of publication bias (e.g., by trying to capture the findings from non-published data), therefore this may have affected the results of both the systematic review and meta-analysis. Had the authors had been contacted, in some cases it may have been possible to obtain additional information for the tables of results produced by the systematic review (whereby some cells which currently state “not specified” might have been otherwise filled), and having more detailed data might have enabled an opportunity to perform meta-analyses inclusive of all the papers. As it was, only the peak coordinates that were readily available from the papers were considered which meant that we were only able to perform a meta-analysis on a subset of papers that focused on delusions only and we could not proceed with one on hallucinations or on the psychotic cluster. Other limitations of the meta-analysis should also be taken into account, mainly the fact that the subset of papers, which while homogeneous in terms of focusing on delusions, were heterogeneous with respect to other aspects, such as the neuroimaging techniques employed and the stratification (disease staging) of the samples. As the literature develops in these areas, further opportunities for meta-analyses should be explored, and analysis of raw data or, for example, contrast images, would minimise any bias relating to using the cluster peaks only.

One limitation related to our methods, in that only publications that were available in English were considered, which led to an a-priori exclusion of five papers which were published in other languages.

Furthermore, while the quality of the papers was assessed using a validated tool, this only revealed the overall quality of papers with respect to certain aspects. This meant that certain key features of the studies may not have been captured. This meant that when presenting the results of the tool, studies that may appear similar in quality may actually have had different methodological strengths and weaknesses in terms of sample sizes and accuracy in control matching, as well as different approaches to the analytic and statistical methods, and level of details provided on the significance threshold and correction methods employed. The lack of consideration of some of these other factors through using the chosen instrument might mean that certain studies have been classified as being of high quality, using the available criteria, while they have some quite significant shortcomings. Future systematic reviews in this area should consider these other factors (e.g., by customising or creating a new quality control or weight of evidence tool so that it is able to capture these additional methodological features).

With respect to the psychotic symptom cluster category, some studies were specific in terms of sample composition (e.g., within the sample, how many participants presented with only delusions, how many presented with only hallucinations, and how many presented with both types of symptoms), while in others this was not clearly specified. This might constitute a limitation of our grouping for this category, as the prevalence in the symptoms manifested might therefore be variable across the studies. Similarly, within the studies that focused either on delusions or hallucinations only, it was not always specified whether people with the other symptom were excluded (or included) the sample with few exceptions (there was one, for example, in which the presence of other neuropsychiatric symptoms was included as a covariate in the analysis). Going forward, authors should report the full characteristics of their samples to assist future synthesis and comparisons between studies, and investigators might also consider study designs where samples are recruited on the basis of one key symptom and who are excluded on the basis of another, or by accounting for other types of symptoms as covariates in the analyses.

Lastly, while the criteria employed for the diagnosis of AD and MCI were overall provided by the vast majority of studies, few reported specific information on which biomarkers, if any, were used within the diagnostic process: we suggest that this type of information should be reported by future studies.

4.7 Conclusions and Future Directions

The aim of this review was to systematically analyse and synthesise the findings of the neuroimaging studies that have investigated the brain

regions and networks linked with psychosis in AD, in an effort to clarify the neuroanatomical underpinnings of these symptoms. To the authors' knowledge this is the first comprehensive review, performed with a specific focus on neuroimaging and psychotic symptoms, that has used a detailed protocol for article discovery and data extraction. We have also attempted to include all articles on these topics from when neuroimaging was first adopted to only the recent past (Dec 2021) and has been inclusive of a range of different imaging modalities (e.g., MRI, PET, SPECT). Analysing the findings both from a holistic perspective, and an individual focus through thematic grouping of studies has allowed for a synthesis of the main neuroanatomical correlates of psychosis as a cluster of manifestations, as well as with respect to individual symptom types (e.g., delusions vs. hallucinations) and subtypes (e.g., misidentification vs paranoia).

While some brain regions/networks could be identified that relate to psychotic manifestations as viewed broadly, for example the key role of the anterior cingulate cortex, clearer distinctions appeared evident when considering thematic differences, with regions localised in fronto-temporal areas in the case of delusions, and fronto-occipital areas in relation to hallucinations. Further distinctions could also be made between misidentification phenomena, that were mainly related to fronto-occipital areas, and paranoid delusions, that were mostly associated with temporal areas. While this line of research is not without its challenges, being able to study the correlates of distinct symptom types has the advantage of offering a more precise understanding of the different clinical profiles. Considering the value of precision medicine and how this has been recently proposed as an avenue to assess and treat psychotic symptoms in other non-degenerative disorders such as schizophrenia through the use of biomarkers (e.g., Hill et al., 2024), the clinical implications that can be derived from this review on the brain areas and networks identified in relation to specific manifestations of the psychotic phenomenology can support future studies that aim to develop more specialised and customised treatment strategies within the context of AD. For example, the neuroimaging biomarkers identified within this review could help to assist in the early detection and more personalised treatment for psychotic phenomena in AD (Mirzakhanian et al., 2014). Within the context of exploring new treatment strategies, given the relevance identified within this review of brain areas, such as those that comprise the Salience Network, future research could build on current strategies employed in other psychotic disorders, such as the brain network modulation used to address Salience Network dysfunction (Palaniyappan et al., 2012), in order to explore new therapeutic approaches. Additional future directions might be, that given findings, for example, of associations between biofluid measures and psychiatric conditions (Huang et al., 2006), and also recently of associations between CSF measures and psychotic symptoms in MCI/AD (Gomar and Koppel, 2024; Koppel et al., 2013), future studies may consider additionally incorporating biofluid assays (e.g., CSF, blood), to investigate how these relate to neuroanatomical/neurobiological changes and symptom presentation, as understanding these relationships may present additional novel treatment opportunities.

The key findings of our review provide clarification on this topic, and provide support to the most recent directions that have been undertaken with respect to the need for new criteria for the classification of psychosis in AD (Fischer et al., 2020), and they include: 1) the identification of neuroanatomical associations with regards to psychotic symptoms, and particularly when considered with regards to their content-related differences; 2) information on the associations that can be found with specific brain regions in those at earlier stages of disease, however it is highlighted that there is a need for further investigations of this kind, in an effort to clarify neuroanatomical underpinnings when symptoms may be most discrete; 2) there is a need for carefully considered and thorough measurement of psychotic phenomenology in future studies, to ensure that unique and shared associations with brain regions and networks can be identified, 3) further thought should be given to sample selection in the study design stages (e.g., which diagnostic/research criteria will be applied, will neuropsychological assessments, and/or biomarkers be used for classification of the sample, and if controls are to be used, how will these be matched), and 4) there should be systematic inclusion and full reporting of important covariates within the analyses, such as disease severity (which could be, for example, via clinical scales or biomarkers), 5) there is a necessity for clear and accurate reporting of analytic approaches in scientific articles, and wherever possible study data should be open access to enable larger and more thorough meta-analyses.

CRediT authorship contribution statement

Sara Scarfo: Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Antonella M.A. Marsella:** Investigation, Data curation, Conceptualization. **Loulouda Grigoriadou:** Investigation, Data curation, Conceptualization. **Yashar Moshfeghi:** Writing – review & editing. **William J. McGeown:** Writing – review & editing, Visualization, Supervision, Methodology, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare no potential conflicts of interest with respect to the research, authorship, or publication of this article.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuropsychologia.2024.109006.

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