

Paranoid and Misidentification Subtypes of Psychosis in Dementia

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Abstract

This study aimed to review the neurobiological and neuropsychological correlates of paranoid (persecutory delusions) and misidentification (misidentification delusions and/or hallucinations) subtypes of psychosis in dementia, to establish if they represent distinct subphenotypes. Nine studies were eligible, all included patients with Alzheimer's disease. Greater global cognitive deficits and an accelerated global cognitive decline were observed in the misidentification subtype. Neuroimaging studies showed more marked volume loss in multiple regions in patients with the misidentification subtype, including those involved in object recognition and the processing of information on spatial and temporal context. A single study found greater impairment in visual sustained attention and object recognition in

the misidentification subtype. The small number of studies and methodological heterogeneity limit interpretation of the findings. Nevertheless, these findings would tentatively suggest that there may be additional or accelerated pathological change in functional networks involved in visuo-perceptual processing in the misidentification subtype. This should be further explored in prospective studies and the investigation extended to other forms of dementia, to gain a transdiagnostic perspective.

Keywords: dementia, delusions, misidentification, persecutory, paranoid, neurobiology, neuropsychology

Introduction

1.1 Background

Psychosis symptoms (delusions, hallucinations) are common in neurodegenerative disorders (Aarsland, 2020a), and can be highly distressing for people with dementia and their families (Aarsland, 2020b). They predict polypharmacy (Cadogan et al., 2016; Parsons, 2017), and are associated with a faster speed of cognitive and functional decline (Wilkosz et al., 2006) and earlier care home placement (Connors et al., 2018). Antipsychotic drugs are associated with significant side effects (falls, sedation, postural hypotension, stroke) and an increased risk of death, and it is imperative that safer effective drug treatments are identified (Ballard and Howard, 2006; Schneider et al., 2006; Weintraub et al., 2016). Alongside research which aims to improve the safety of existing antipsychotic drug treatments (Reeves et al., 2020), increasing our understanding of the pathophysiology of psychosis symptoms could help to effectively target novel treatment strategies.

A previously published narrative review of research into the neurobiological and neuropsychological correlates of delusions in Alzheimer's disease described two emerging

themes (Reeves et al., 2012). Firstly, they found evidence of a shared aetiology for delusions in AD and schizophrenia, including disruption of mesocorticolimbic networks involved in salience attribution, belief evaluation, and cognitive control. Secondly, they described emerging literature to support the existence of discrete sub-phenotypes of psychosis in AD: A paranoid subtype, characterised by persecutory delusions of theft, harm, morbid jealousy or abandonment; and a misidentification subtype, characterised by delusional misidentification with or without hallucinations. The two subtypes were identified through use of factor and cluster analyses of behavioural data from people with psychosis in AD (Cook et al., 2003), and corresponded to the classification used by early studies of the phenomenology of psychosis in AD, which described misidentification delusions as perceptual in nature and grouped them with hallucinations (Burns et al., 1990a; Burns et al., 1990b; Reisberg et al., 1987).

Preliminary evidence presented in the review suggested that persecutory delusions occurred earlier in the disease course and were associated with neurochemical and neuropathological changes in corticostriatal networks, whereas the misidentification subtype was associated with more global deficits in cognition and AD pathology in the hippocampal and parahippocampal areas (Reeves et al., 2012). There were however inconsistencies in the literature, which may have been explained by the wide heterogeneity in study design, including the criteria used to define subtype symptoms, incomplete data on the presence or absence of hallucinations, and inconsistent treatment of potential confounding factors (Mini Mental State Examination [MMSE], age, educational level, psychotropic medication and affective symptoms). They concluded that prospective studies would be required to investigate whether paranoid and misidentification subtypes are part of the same endophenotype (AD psychosis) (Sweet et al., 2010) or represent distinct subphenotypes, towards which interventions could be targeted.

1.2 Objectives

This study aimed to systematically review the neurobiological and neuropsychological correlates of paranoid and misidentification subtypes of psychosis in AD and other forms of dementia, to establish if they represent distinct subphenotypes.

2. Methods

2.1 Protocol and registration

No ethical approval was required. PRISMA guidelines (Moher et al., 2009) were adhered to for reporting the findings of the systematic review, as shown in Figure 1.

2.2 Electronic databases and literature search

A systematic search was conducted on 1st February 2017 and repeated on 3rd March 2020 using the following online databases: PubMed, PsychInfo, Embase, and Web of Science. References of included studies and relevant reviews were manually searched for additional studies. Search terms were constructed based on definitions from previous research (Reeves et al., 2012). The following terms were used: (delusion* OR belief* OR misidentification* OR Capgras OR Fregoli OR "reduplicative paramnesia" OR "mirror sign" OR "phantom boarder" OR "TV sign" OR paranoi* OR persecut* OR theft OR jealous* OR abandon*) AND (AD OR Alzheimer* OR dement* OR Pick*) AND (associat* OR correlat*). No limits were applied and all years were searched.

One author (DP) screened every title and abstract for relevance using the eligibility criteria, whilst four other authors (GR, EW, RB, MR) independently and blindly screened all of the studies between them. Full-text manuscripts were obtained for the selected studies, which

were then screened against the eligibility criteria. Any disagreements were resolved through discussion, and any unresolved discrepancies were discussed with a fifth author (SR).

2.2 Eligibility criteria

Studies were eligible for inclusion if they met the following criteria: 1) Peer-reviewed cohort studies (cross-sectional and longitudinal), case-control studies, or case series written in English; 2) Included participants with any form of dementia (including AD, frontotemporal dementia, vascular dementia, Lewy Body dementia, Parkinson's disease dementia, and early onset); 3) Psychosis symptoms of a 'paranoid' or 'misidentification' content: Based on previous research (Cook et al., 2003), persecutory delusions were deemed to include paranoid, theft, jealousy, and abandonment delusions. The misidentification syndrome included hallucinations (visual or auditory) and/or the following delusions: Capgras (carer is an imposter), Fregoli (a loved one is disguised as a stranger), reduplicative paramnesia (delusion of doubles), mirror sign (failure to recognise oneself in the mirror), phantom boarder (intruder in the house), and TV sign (inability to distinguish between the television screen and reality) delusions subtypes; 4) Comparison between subtypes or with non-psychotic patients; 5) Reported neurobiological or neuropsychological outcomes: Neurobiological outcomes included neuroimaging, neuropathological, neurochemical or genetic; and neuropsychological outcomes included measures of global cognitive function or specific cognitive domains. Studies were excluded if they were: 1) Non-peer-reviewed studies, case studies, case reports, meeting abstracts/conference presentations, protocols, and unpublished dissertations and theses; 2) Symptoms were not separated on the basis of subtypes; 3) Data were only available on those with mixed symptoms; 4) Delusional content was not of a persecutory or misidentification content (such as erotomania or grandiose).

2.3 Data extraction process

DP extracted data to a pre-defined template for all included studies, while other authors (GR, EW, RB, MR) independently and blindly extracted data for all included studies between them. Any disagreements were resolved through discussion. Percentages were calculated for demographic data (sex, ethnicity, medication status) where available and overall (pooled) mean and standard deviations (SD) of demographic data (e.g., age, duration of illness) or results were calculated by DP according to Cochrane guidelines (Higgins, 2008). Data were extracted regarding all relevant outcomes (neuropsychological, neuroimaging, genetic, neuropathological, neurophysiological, neurochemical), study characteristics (setting, inclusion/exclusion criteria), and participant demographics and clinical characteristics (dementia subtype, sample size, diagnostic criteria, age, sex, and ethnicity). Where possible and appropriate, data were extracted after controlling for potential confounders (sex, age, education, medication) and/or adjusting for multiple comparisons. Results were reported as significant if $p < .05$.

2.4 Risk of bias assessment

Bias was assessed using the Quality Assessment Tool for Quantitative Studies developed by the Effective Public Health Practice Project (EPHPP) (Project, 1998a), which is designed for assessing multiple study types. The EPHPP tool evaluates selection bias, study design, confounders, blinding, data collection methods, withdrawals and dropouts, intervention integrity, and analysis. The scores in each subsection were used to provide an overall rating of ‘strong’, ‘moderate’, or ‘weak’, using the EPHPP guidance (Project, 1998b). Sections I and J were excluded as they focus on randomised controlled trials and so were not relevant to this review.

3. Results

3.1 Study inclusion

The initial database search in February 2017 identified 7643 records, and updating the search in March 2020 identified an additional 1714 records. 3588 records were duplicates and were removed. 5769 articles were screened, 111 of these were retained for full text review and an additional 11 articles were identified from manual reference searching. Upon full text review, 113 articles were excluded; the most common reasons being they did not separate symptoms on the basis of paranoid or misidentification subtypes/groups (n = 64), or there was potential confounding of the paranoid subtype by the presence of hallucinations (n = 27). A total of 9 studies were included in this systematic review, all of which were carried out in patients with AD.

3.2 Study and demographic characteristics

As shown in Table 1, this review identified six cross-sectional studies (Geroldi et al., 2000; Geroldi et al., 2002; Lee et al., 2016; Perez-Madrinan et al., 2004; Reeves et al., 2015; Tagawa et al., 2014), two longitudinal studies (D'Antonio et al., 2019; Wilkosz et al., 2006), and one longitudinal study which was treated as cross sectional as only baseline imaging data were included in the analysis (McLachlan et al., 2018). Two studies reported outcomes based on the same sample of participants (Geroldi et al., 2000; Geroldi et al., 2002). Studies were published from 2000 to 2019. Five were conducted in Europe, three in East Asia and three in the USA. Seven studies recruited participants from a hospital setting and four from community settings. All studies included a non-psychotic dementia comparator group. Sample size across the studies ranged from 31 (Tagawa et al., 2014) to 528 (D'Antonio et al., 2019). Mean (SD) participant age in the studies ranged from 75 (6.0) years (Geroldi et al., 2000; Geroldi et al., 2002; McLachlan et al., 2018; Wilkosz et al., 2006) to 81 (5.6) years (Reeves et al., 2015). The proportion of female participants in the studies ranged from 40% (D'Antonio et al., 2019) to 90% (Tagawa et al., 2014). The ethnicity of the study population was only reported by one study (Perez-Madrinan et al., 2004).

3.3 Clinical characteristics

All studies included participants with AD. National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRADA) and Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV were the most commonly used diagnostic criteria for AD. All studies utilised the MMSE as a screening tool and the mean scores ranged from 13.4 (5.4) (Perez-Madrinan et al., 2004) to 25.7 (3.9) (D'Antonio et al., 2019). The mean duration of dementia ranged from 1.8 (1.3) (Reeves et al., 2015) to 4.2 (1.4) (Perez-Madrinan et al., 2004) years. Seven studies used the carer-rated Neuropsychiatric Inventory (NPI) (Cummings et al., 1994) to rate psychotic symptoms, one used an unstructured carer report (Tagawa et al., 2014), and one (Lee et al., 2016) used the 46-item version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Behavioral Rating Scale (CBRS) (Tariot et al., 1995).

Studies determined the presence of psychosis using varying time frames of reported symptoms. One study included patients who were described as having 'currently or ever experienced' symptoms in the psychosis group (Reeves et al., 2015), others included patients who had experienced symptoms at any point during follow up (D'Antonio et al., 2019; McLachlan et al., 2018; Wilkosz et al., 2006), whereas others specified that patients had experienced persistent symptoms for one month (Geroldi et al., 2000; Geroldi et al., 2002; Lee et al., 2016; Tagawa et al., 2014). Eight studies included participants who were prescribed cognitive enhancers or antipsychotic medication, and one (Lee et al., 2016) specified that patients were antipsychotic naïve but did not report other prescribed medication.

Six studies included both psychosis subtypes and categorised them using previously suggested criteria (Cook et al., 2003): Paranoid (persecutory delusions, no hallucinations), and misidentification subtype (misidentification delusions and/or hallucinations) (D'Antonio

et al., 2019; Lee et al., 2016; McLachlan et al., 2018; Perez-Madrinan et al., 2004; Reeves et al., 2015; Wilkosz et al., 2006). Of these, one study excluded patients with mixed symptoms (presence of both subtypes) from the analysis (Lee et al., 2016). Three studies focused their investigation solely on patients with persecutory delusions (Geroldi et al., 2000; Geroldi et al., 2002; Tagawa et al., 2014). Five studies reported both neuropsychological and neuroimaging results (Geroldi et al., 2000; Geroldi et al., 2002; Lee et al., 2016; McLachlan et al., 2018; Tagawa et al., 2014) and four reported neuropsychological outcomes only (D'Antonio et al., 2019; Perez-Madrinan et al., 2004; Reeves et al., 2015; Wilkosz et al., 2006).

3.4 Narrative synthesis of the results

3.4.1 Global cognitive function

All studies described baseline MMSE (or Korean language equivalent, K-MMSE) scores for participants in the different delusional subtypes or groups. Significant group differences were reported in 2/9 studies comparing patients with the paranoid subtype with non-psychotic patients (D'Antonio et al., 2019; Wilkosz et al., 2006), 3/6 studies comparing patients with the misidentification subtype with non-psychotic patients (D'Antonio et al., 2019; Perez-Madrinan et al., 2004; Wilkosz et al., 2006), and 2/6 studies comparing paranoid and misidentification subtypes (D'Antonio et al., 2019; Wilkosz et al., 2006).

Of the four cross-sectional studies that compared MMSE across subtypes (paranoid, misidentification, mixed and non-psychotic), one reported lower MMSE scores (indicating greater cognitive deficits) in patients with misidentification or mixed compared to non-psychotic patients (Perez-Madrinan et al., 2004), and three reported no differences (Lee et al., 2016; McLachlan et al., 2018; Reeves et al., 2015).

One prospective longitudinal study, which used Cox proportional hazards regression to investigate the emergence of psychosis in 288 patients who were non-psychotic at baseline

(Wilkosz et al., 2006), found that lower baseline MMSE scores were associated with the onset of the misidentification (parameter estimate -0.087, $p < 0.0001$) and mixed (parameter estimate -0.438, $p < 0.0001$), but not paranoid (parameter estimate -0.043, $p = .22$) subtypes over an average follow up period of 22 months.

One study (D'Antonio et al., 2019) which used a mixed effects based approach to analyse longitudinal data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) 2 dataset, investigated subtype specific differences in the trajectory of cognitive decline in 528 participants with late mild cognitive impairment (MCI) or AD. The analysis, which accounted for drop out using a time to event model, found that the rate of decline in global cognition in the mixed AD and MCI group, indexed by the rate of increase in Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-cog) total scores, was doubled in patients with misidentification ($\beta_{r,misid_subtype} = 0.63$, $p = .030$) and mixed ($\beta_{r,mixed_subtype} = 0.70$, $p = .003$) subtypes compared to nonpsychotic or paranoid patients, after accounting for baseline MMSE score, age, gender, education, medications, and Apolipoprotein E epsilon 4 carrier status. Findings are summarised in Table 3.

3.4.2 Specific cognitive domains

Four studies assessed specific cognitive domains, either as a primary outcome (Perez-Madrinan et al., 2004; Reeves et al., 2015) or as a complement to neuroimaging (Geroldi et al., 2000; Lee et al., 2016), and all apart from one (Lee et al., 2016) controlled for the potential confounding effects of MMSE in their analysis.

Three studies examined visuoperceptual/visuospatial/praxis performance (Lee et al., 2016; Perez-Madrinan et al., 2004; Reeves et al., 2015). One study reported poorer performance on the Rey-Osterrieth Complex Figure Copy in patients with misidentification compared to paranoid subtype (Perez-Madrinan et al., 2004). However, this was no longer significant after adjusting for baseline differences in MMSE.

One study reported significant group differences between patients with the misidentification subtype and both the paranoid subtype and non-psychotic patients (Reeves et al., 2015). This study tested the primary hypothesis that performance on the Rapid Visual Information Processing (RVP) test of sustained visual attention would be more impaired in AD patients with the paranoid subtype compared to non-psychotic patients and those with misidentification symptoms. This hypothesis was based on a previous imaging study which reported higher striatal dopamine D2/3 receptor availability and poorer RVP performance in AD patients with mild, fleeting (largely paranoid) delusions compared to non-psychotic patients. However, they found that poorer performance on the RVP test in patients with psychotic symptoms was largely accounted for by the misidentification subtype (Reeves et al., 2015). In an exploratory analysis which included (and corrected for) tests of multiple cognitive domains that were administered as part of a standardised test battery, poorer performance on the object recognition subtest of the Visual Object and Space Perception (VOSP) battery in psychotic than non-psychotic patients was similarly accounted for by the misidentification subtype.

Two studies examined performance on memory tests (Lee et al., 2016; Perez-Madrinan et al., 2004). One study reported poorer word list delayed recall in patients with the misidentification subtype compared to non-psychotic patients (Lee et al., 2016). Another study reported poorer performance on the Rey-Osterrieth Complex Figure Immediate Memory test in patients with the misidentification subtype compared to non-psychotic patients (Perez-Madrinan et al., 2004). However, this was no longer significant after adjusting for baseline differences in MMSE.

Two studies examined performance on executive function tests, finding no evidence of any subtype differences in relation to tests of executive function (Lee et al., 2016; Perez-Madrinan et al., 2004). Finally, three studies examined performance on language tests

(Geroldi et al., 2000; Lee et al., 2016; Reeves et al., 2015), with only one (Lee et al., 2016) reporting poorer Boston Naming Test (BNT) performance in the paranoid and misidentification subtypes compared to non-psychotic patients, but no difference between subtypes. However, these authors did not adjust for MMSE and so these findings may have simply reflected greater global cognitive deficits in these groups. Findings are summarised in Table 3.

3.4.3 Neuroimaging outcomes

Five studies reported neuroimaging outcomes, but only two examined group differences between patients with the misidentification subtype and those with the paranoid subtype or without psychosis symptoms. Two studies used brain computerised tomography (CT) (Geroldi et al., 2000; Geroldi et al., 2002) and three studies structural brain magnetic resonance imaging (MRI) (Lee et al., 2016; McLachlan et al., 2018; Tagawa et al., 2014). None of the identified studies examined function or perfusion. Imaging outcomes of interest included frontal (Geroldi et al., 2002; Lee et al., 2016), temporal (Geroldi et al., 2000; Geroldi et al., 2002; Lee et al., 2016; McLachlan et al., 2018; Tagawa et al., 2014), parietal (Lee et al., 2016) and occipital (Lee et al., 2016; McLachlan et al., 2018) lobes. Two studies included a measure of global impairment as a covariate in the analysis, indexed by the Clinical Dementia Rating (CDR) Scale (Lee et al., 2016) or ADAS-cog scores (McLachlan et al., 2018).

One study used brain CT to test the hypothesis that persecutory delusions in AD would be associated with asymmetrical temporal lobe volume loss in 41 patients (19 with, 22 without delusions). Although their findings of reduced width of right compared to left temporal horn, and greater right to left asymmetry in temporal lobe volume in paranoid than non-delusional participants were consistent with their hypothesis, the authors acknowledged that they could not exclude a more generalised right side brain atrophy (Geroldi et al., 2000). In a subsequent

study, which included the same participants but used a different analytic approach, they found region specific asymmetry, such that the paranoid group had greater right temporal and left frontal horn size than the non-delusional group (Geroldi et al., 2002).

Using 1.5 tesla brain MRI, one study investigated the relationship between medial temporal lobe atrophy and persecutory delusions in AD (13 with, 18 without), using voxel-based specific regional analysis system for AD software. Volumes of interest included the entire region of the entorhinal cortex, hippocampus, and amygdala. There was significant right-sided atrophy in the group with persecutory delusions compared to those without ($p < 0.05$) (Tagawa et al., 2014).

Two studies separated patients on the basis of subtypes (Lee et al., 2016; McLachlan et al., 2018) One study (Lee et al., 2016), which included 65 patients (23 paranoid, 17 misidentification and 25 non-psychotic), tested the hypothesis that grey matter volume would be reduced in both subtypes compared to non-psychotic patients, and would be most marked in patients with the misidentification subtype. Associations between regional grey matter volume and subgroups were explored using factorial analysis of covariance (ANCOVA), within statistical parametric mapping. Their finding of lower grey matter volume predominantly in right sided regions (middle frontal gyrus, middle temporal gyrus, inferior parietal lobule, lingual gyrus, superior occipital gyrus) in patients with the misidentification subtype was consistent with their primary hypothesis. However, conversely, patients with the paranoid subtype had *greater* grey matter volume in frontal (right medial, right middle, left inferior, and right superior), left middle temporal gyrus, and left occipital lobe (cuneus and lingual gyrus) than non-psychotic patients.

One study (McLachlan et al., 2018) assessed cortical volume and thickness measures of brain regions that are functionally connected to the ventral visual pathway, and corticostriatal regions, using baseline structural brain imaging data from 104 AD participants (15 paranoid,

10 misidentification, 22 mixed subtype) from the AddNeuroMed cohort; a cross-European study, funded by the European Union and members of the European Federation for Pharmaceutical Industries and Associations (EFPIA), designed to find biomarkers, or tests, for Alzheimer's disease. In line with their primary hypothesis, multivariate analysis of covariance (MANCOVA) of the grouped regions showed a significant main effect between psychotic and non-psychotic patients in relation to cortical volume but not thickness of the ventral visual stream (right and left entorhinal cortex, parahippocampal gyrus, fusiform gyrus, lingual gyrus, lateral occipital cortex). ANCOVAs of individual regions of interest showed that this was explained by reduced volume in the left and right parahippocampal gyri, with post hoc comparisons showing a significantly lower left parahippocampal volume in the misidentification and mixed groups only. Findings are summarised in Table 4.

3.4.5 Genetic, neuropathological, neurophysiological and neurochemical outcomes

No studies examined genetic, neuropathological, neurophysiological or neurochemical outcomes in patients with dementia on the basis of subtypes.

3.4.6 Risk of bias within studies

A summary of the risk of potential bias is provided in the Supplementary Table. All of the nine included studies clearly stated their aims and all were rated as having a moderate risk of selection bias on EHPP. All study designs were rated as weak apart from the two cohort studies (D'Antonio et al., 2019; Wilkosz et al., 2006). All nine studies had adequate control groups. Validated diagnostic tools for dementia were used in all apart from two studies (Geroldi et al., 2000; Geroldi et al., 2002). Four studies did not provide adequate information on the inclusion of patients with probable versus possible dementia (D'Antonio et al., 2019; McLachlan et al., 2018; Tagawa et al., 2014; Wilkosz et al., 2006). Cognitive examination was undertaken on all participants in all studies. All studies used validated tools to assess for delusions apart from one (Tagawa et al., 2014) which relied on unstructured carer-report

only. Risk of confounding from other types of delusions was low for all studies. Five studies both described and controlled for cognitive enhancer use (D'Antonio et al., 2019; McLachlan et al., 2018; Reeves et al., 2015; Tagawa et al., 2014; Wilkosz et al., 2006). All studies used appropriate statistical methods for their study design, although none provided power calculations to guide sample size. Two studies did not adjust for any potential confounders in their design or analysis (Geroldi et al., 2000; Geroldi et al., 2002). Six studies used means to statistically control for confounding by MMSE (or other cognitive assessment) (D'Antonio et al., 2019; McLachlan et al., 2018; Perez-Madrinan et al., 2004; Reeves et al., 2015; Tagawa et al., 2014; Wilkosz et al., 2006).

4. Discussion

4.1 Main findings

This review aimed to investigate the neurobiological and neuropsychological correlates of paranoid and misidentification subtypes of psychosis in different forms of dementia. The inclusion criteria were however met solely by studies of patients with AD.

Longitudinal studies, which were rated as having the least risk of bias, found evidence of emergent misidentification symptoms in those with greater global impairment at baseline and an accelerated rate of global cognitive decline in patients with the misidentification subtype, including those with mixed symptoms.

With respect to neuroimaging data, only one study (Geroldi et al., 2002) reported a decrease in volume in one brain region in patients with the paranoid subtype compared to non-psychotic patients. In contrast, numerous changes in brain structure and function were reported in patients with the misidentification subtype compared to those with and without persecutory delusions. (Lee et al., 2016; McLachlan et al., 2018). This included regions (right lingual gyrus, right middle occipital gyrus, left cuneus and left parahippocampal gyrus) that form part of the ventral (temporo-occipital) visual pathway, that is involved in object

recognition (Goodale and Milner, 1992; Goodale, 2013). Greater volume loss was also observed in regions (inferior parietal lobule, middle frontal gyrus) (Lee et al., 2016) that are functionally connected to the ventral and dorsal (parieto-occipital) visual pathway (Bray et al., 2013; Greenberg et al., 2010).

Volume loss in the ventral visual pathway in patients with the misidentification symptoms was largely accounted for by reduced volume in the parahippocampal gyrus (McLachlan et al., 2018), which plays a key role in processing the spatial and temporal context of visual information ('where' and 'when' was the object seen) (Eichenbaum and Lipton, 2008). This warrants further discussion, as post-mortem studies have previously reported greater pathology in hippocampal/parahippocampal regions in patients with the misidentification subtype (Ferman et al., 2013; Forstl et al., 1994; Mukaetova-Ladinska et al., 1993). Our findings would therefore tentatively suggest that earlier or additional pathological change in the parahippocampal region may contribute to emergent misidentification symptoms

Studies that investigated specific cognitive domains showed little evidence of a distinct neuropsychological profile in paranoid and misidentification subtypes, after controlling for MMSE scores. This may have been partly due to the small number and methodological heterogeneity of included studies, or may reflect the use of neuropsychological measures lacking the sensitivity required to detect any subtle cognitive changes in patients with the paranoid subtype. It could also be argued that the MMSE is a screening tool and may not provide the desired control effect for global cognition.

The exception to this was a single study (Reeves et al., 2015) which showed poorer performance on the RVP test of visual sustained attention and the VOSP object recognition task in those with the misidentification subtype. These tests localise to functional networks involved in visual processing, particularly the lateral occipital cortex, which contributes to figural completion and is recruited during RVP performance (Coull et al., 1996; Ffytche and

Zeki, 1996). Although preliminary, these findings support shared theories regarding the origins of delusions and hallucinations: Reduced accuracy of RVP performance has been similarly observed in patients with schizophrenia spectrum disorders and their non-affected first degree relatives compared to healthy adults (Cattapan-Ludewig et al., 2005; Hilti et al., 2010a; Hilti et al., 2010b); and poorer performance on the VOSP has been observed in patients with Lewy Body dementia, who present with hallucinations early in the illness course (Cagnin et al., 2013).

4.2 Limitations

Interpretation of the findings of this review is limited by the small number of included studies and their methodological heterogeneity, including the criteria used to define psychosis (trait versus state, duration of symptoms, symptom severity) in AD and use of concomitant medication. Furthermore, the absence of a threshold cut off to denote the presence of delusions or hallucinations in several studies increased the risk of a type I error. In addition, the exclusion of unpublished ‘grey’ literature and non-English papers may give an unrepresentative view of the literature.

The fact that the inclusion criteria were met solely by studies of patients with AD disease meant that it was not possible to describe and compare subtype specific correlates in patients with other forms of dementia, such as Lewy Body dementia (DLB) and posterior cortical atrophy (PCA), which are associated the early emergence of hallucinations and misperceptions, and widespread deficits in visual attention and/or visuoperceptual function (Cagnin et al., 2013; Ferman et al., 2013; Yerstein et al., 2021).

The relatively small sample sizes of most of the included studies meant that it was not possible to establish to what extent the presence of hallucinations accounted for the greater global cognitive impairment, or more marked volume loss in patients with the misidentification subtype. There is certainly post-mortem evidence of greater pathology

(reduction in acetyl cholinesterase activity) in the visual pathways (lingual gyrus, cuneus, and lateral occipital gyrus), in AD patients with a history of visual hallucinations compared to those without (Sinclair et al., 2019).

Several studies acknowledged that they could not completely rule out the possibility that a proportion of patients with the misidentification subtype may have had undiagnosed Lewy Body dementia, as they did not examine neuropathology. However, the fact that neuropathological studies which excluded brains with alpha synuclein deposition, reported a history of hallucinations in 9% of patients with Braak III/IV and 35% of patients with V/VI AD pathology (Ehrenberg et al., 2018) would argue against the suggestion that the misidentification subtype in AD reflects ‘misdiagnosis’. Furthermore, in contrast to DLB patients, a recent postmortem study found no evidence of increased α -synuclein deposition in BA19 in AD patients with a history of visual hallucinations (Sinclair et al., 2019).

The possibility of undiagnosed PCA (Yerstein et al., 2021) also warrants further consideration, as AD (tau) pathology in posterior cortical networks, and the involvement of fronto-parietal networks, is a common finding (Crutch et al., 2017; Schott and Crutch, 2019). Against this is the fact that PCA typically occurs in those who present with an early (under 65 years) onset of AD-related dementia, whereas the included studies focused on patients with late onset disease.

5. Conclusion

Despite the small number of included studies and their methodological heterogeneity, it is possible to draw tentative conclusions and provide recommendations for future research in this area. A consistent pattern emerged of greater global neurocognitive dysfunction specifically in relation to the misidentification subtype. The finding of an accelerated decline in global cognitive function in those with misidentification or mixed subtypes needs further

investigation in samples large enough to differentiate between misidentification delusions and hallucinations.

Combined evidence from studies of structural brain imaging and neuropsychology implicate disruption of functional networks involved in visual processing in the misidentification subtype, particularly the ventral visual pathway. Although these findings need to be replicated in larger samples, they support contemporary theories which suggest that visuo-perceptual deficits, combined with impaired belief evaluation, play a key role in the emergence of misidentification delusions (Coltheart et al., 2011). They are also in line with integrative theories suggesting both perceptual and attentional dysfunction are necessary for the emergence of misperceptions and hallucinations in neurodegenerative disorders (Collerton et al., 2005; Collerton and Taylor, 2013; Diederich et al., 2009; Shine et al., 2011). Prospective studies would allow a more detailed exploration of the trajectory of volume loss in ventral and dorsal visual pathways, and how this relates to emergent symptoms. Studies that combine imaging with neuropsychological tests such as RVP and VOSP, could help to determine the extent to which global versus localised network dysfunction contributes to the misidentification subtype. It will also be important to explore existing longitudinal data from large cohort studies such as ADNI. One of the included studies showed subtype specific differences in the rate of global cognitive decline (D'Antonio et al., 2019) and this investigation should be extended to include specific cognitive domains, and imaging markers. For example, the latest iteration, ADNI3, includes information on a number of potential biomarkers, including serial imaging of tau pathology, and 3-dimensional arterial spin labelling (ASL) perfusion imaging to map the effects of AD on brain connectivity.

Perhaps most importantly, a transdiagnostic approach should be adopted in future studies, to explore common mechanisms, and more effectively target interventions across neurodegenerative disorders (O'Brien et al., 2020). Careful consideration should thus be

given to the nature of the outcome measures that are included in cohort studies, and studies of novel interventions, to allow for a meaningful transdiagnostic comparison.

Conflict of interest

Nil

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Table 1: Study Characteristics

Author, Year	Country	Type of study	Referral setting	Sample size (n)	Outcome(s)	Type of statistical analysis
D'Antonio et al., 2019	USA	Longitudinal	Community	528 (P: 38, M: 29, Mixed: 29, ND: 432)	Neuropsychological – trajectory of cognitive decline	Nonlinear mixed effects modelling, linear regression
Geroldi et al., 2000	Italy	Cross-sectional	Hospital outpatient	41 AD (P:19, ND: 22)	Neuroimaging (CT) - temporal lobe atrophy Neuropsychological - general cognitive abilities, and language abilities	Chi-square; t-test
Geroldi et al., 2002	Italy	Cross-sectional	Hospital outpatient	41 dementia (P: 19, ND: 22), 29 controls	Neuroimaging (CT) - regional brain atrophy	ANOVA; independent sample t-test; and chi-square test
Lee et al., 2016	Korea	Cross-sectional	Hospital outpatient	65 (P:23, M:17, ND:25)	Neuroimaging (MRI) - grey matter loss Neuropsychological	ANCOVA integrated in SPM
McLachlan et al., 2018	Europe (multisite)	Longitudinal (cross-sectional analysis)	Hospital outpatient	104 (ND: 57, P:15, M:10, Mixed: 22)	Neuroimaging (MRI) – volume and cortical thickness measures in visoperceptual and frontal networks	MANCOVA, ANCOVA
Perez-Madrinan et al., 2004	USA	Cross-sectional	Community	119 (P: 24, M: 32, Mixed: 14, ND: 49)	Neuropsychological - general cognitive ability, executive function, memory, and visuospatial abilities	Kruskal-Wallis test; chi-square test; Fisher's exact test; general linear model; and Tukey-Kramer post hoc test
Reeves et al., 2015	UK	Cross-sectional	Community	70 (P: 14, M: 12, Mixed: 8, ND: 36)	Neuropsychological - processing speed, sensorimotor, executive function, memory, language abilities, and visuo-perceptual function	ANCOVA; MANCOVA; Bonferroni correction; post-hoc pairwise comparisons; Fisher's least sig diff test
Tagawa et al., 2014	Japan	Cross-sectional	Hospital outpatient	31 (P: 13, ND: 18)	Neuroimaging (MRI) - medial temporal lobe atrophy	Mann Whitney U test; and ANCOVA
Wilkosz et al., 2006	USA	Longitudinal	Community	288 (P: 25, M: 46, Mixed: 11, ND: 206)	Neuropsychological - global cognitive functioning	Cox proportional hazard models with time-dependent covariates
<p>Country: UK = United Kingdom; USA = United States of America; EU = Europe Subtypes: P = Paranoid; M = Misidentification; Mixed = P and M; ND = non-delusional. Outcome(s): MRI = magnetic resonance imaging; SPM = Statistical Parametric Mapping analysis; CT = computerised tomography Statistical analysis: ANOVA = analysis of variance; ANCOVA = analysis of covariance; MANCOVA = multivariate analysis of covariance</p>						

Table 2: Demographics and Clinical Characteristics

Author, Year	Dementia subtype	Diagnostic criteria for dementia	Psychosis subtype	Cognitive screening: Mean \pm SD	Mean \pm SD duration (years) of dementia	Psychosis rating tool	Mean \pm SD age (years)	Mean \pm SD years of education	% female	% white ethnicity	Medication status
D'Antonio et al., 2019	MCI or Mild AD	NINCDS-ADRDA + standardized criteria for MCI	M, P and Mixed	MMSE: ND 25.7 \pm 3.9, P 24.6 \pm 3.2, M 24.1 \pm 5.6, Mixed 22.7 \pm 4.3	NR	NPI (baseline or any follow-up)	ND 75.9 \pm 7.9, P 76 \pm 7.2, M 74.3 \pm 8.3, Mixed 74.3 \pm 8.3	All groups between 15-16 years	ND 38%, P 39%, M 62%, Mixed 52%	NR	Cognitive enhancer not prescribed: ND 88%, P 82%, M 72%, Mixed 83%
Geroldi et al., 2000	Mild probable AD (MMSE \geq 18)	Standardised clinical, neuropsychological, and instrumental evaluation	P only	MMSE: 21.5 \pm 3.0 [†] (del: 22 \pm 3.0, ND: 21 \pm 3.0)	NR	NPI (presence during last month)	74.9 \pm 8.0 [†] (del: 76 \pm 8.0, ND: 74 \pm 8.0,	6 \pm 3.0 [†] (P: 6 \pm 3.0; ND: 6 \pm 3.0)	75.6% [†] (P: 90%; ND: 64%)	NR	Antipsychotic prescribed - P: 21.1% [†] , ND: 0%
Geroldi et al., 2002	Mild probable AD (MMSE \geq 18; CDR 0.5 or 1)	Standardised clinical, neuropsychological, and instrumental evaluation	P only	MMSE: 21.5 \pm 3.0 [†] (P: 22 \pm 3.0, ND: 21 \pm 3.0, controls: 27 \pm 1.0)	NR	NPI (presence during last month)	74.9 \pm 8.0 [†] (P: 76 \pm 8.0, ND: 74 \pm 8.0, controls: 69 \pm 9.0)	6 \pm 3.0 [†] (P: 6 \pm 3.0, ND 6 (\pm 3.0, controls: 9 \pm 5.0)	75.6% [†] (P: 90%, ND: 64%, controls: 65%)	NR	Antipsychotic prescribed - P: 21%, ND: 0% Benzodiazepine prescribed - P: 37%, ND: 14% Antidepressants - P: 37%, ND: 27%
Lee et al., 2016	Mild to moderate probable AD	NINCDS-ADRDA	M and P	K-MMSE: 17.3 \pm 4.0 [†] (P: 16.6 \pm 3.5, M: 16.1 \pm 3.6, ND: 18.7 \pm 4.5)	NR	K-NPI (presence during last month),	74.7 \pm 8.4 [†] (P: 77.6 \pm 7.4, M: 74.3 \pm 7.3, ND: 72.4 \pm 9.4)	6.5 \pm 6.3 [†] (P: 6.0 \pm 5.1, M: 5.5 \pm 4.7, ND: 7.7 \pm 8.1)	73.4% [†] (P: 68.4%, M: 75%, ND: 76.9%)	NR	Excluded for lifetime antipsychotic use. No information on medications.
McLachlan et al., 2018	Possible or probable AD	DSM-IV	M, P and Mixed	MMSE: 20.8 \pm 4.7 (ND: 21.3 \pm 4.8, P: 19.9 \pm 4.2, M: 21.9 \pm 4.0, Mixed 19.7 \pm 5.1)	ND 3.4 \pm 2.5 (P 2.6 \pm 1.8, M 2.8 \pm 2.6, Mixed 4.0 \pm 2.9)	NPI (baseline or any follow-up)	74.9 \pm 5.9 (ND 73.4 \pm 5.8, P 77.5 \pm 4.8, M 74.8 \pm 6.1, Mixed 76.9 \pm 5.7)	NR	67.3% (ND 63.2%, P 73.3%, M 80%, Mixed 68.2%)	NR	Cholinesterase inhibitor and/or memantine prescribed: ND 77.2%, P 66.7%, M, 90.0%, Mixed 95.5% Antipsychotic prescribed: ND 3.5%, P 0%, M 10%, Mixed 9.1%

Perez-Madrinan et al., 2004	Possible or probable AD	NINCDS-ADRDA	M, P and Mixed	MMSE: 16.6 ± 4.1† (M: 13.4 ± 5.4, P: 16.9 ± 4.9, Mixed: 15.8 ± 4.7, ND: 18.7 ± 5.0)	3.8 ± 1.1† (M: 4.2 ± 1.5, P: 3.6 ± 1.3, Mixed: 3.8 ± 1.4, ND: 3.6 ± 1.6)	CBRS at baseline (occurring >3 times in the last month)	77.2 ± 5.3† (M: 78.4 ± 5.5, P: 78.0 ± 4.6, Mixed: 78.7 ± 5.5, ND: 75.5 ± 4.7)	12.1 ± 2.5† (M: 12.1 ± 2.6, P: 11.5 ± 2.8, Mixed: 10.1 ± 3.8, ND: 13.0 ± 3.4)	64.7%† (M: 75%, P: 62.5%, Mixed: 64.3%, ND: 59.2%)	89.1%† (M: 87.5%, P: 83.3%, Mixed: 78.6%, ND: 95.9%)	NR
Reeves et al., 2015	Probable AD	NINCDS-ADRDA	M, P and Mixed	MMSE: 22.2 ± 4.9 (P: 22.1 ± 5.3, M: 20.1 ± 6.0, Mixed: 20.0 ± 6.2, ND: 23.5 ± 3.7)	1.9 ± 1.5† (M, P and Mixed: 2.0 ± 1.7, ND: 1.8 ± 1.3)	Modified NPI (timeframe changed to 'ever' + 8% assessed for having experienced in the last 6 months) +	81.0 ± 5.6 (M, P and Mixed: 82.8 ± 4.8, ND: 79.5 ± 5.5)	10.0 ± 1.6† (M, P and Mixed: 9.9 ± 1.4, ND: 10.0 ± 1.8)	54.3%	NR	Cholinesterase inhibitors and/or memantine prescribed - M, P and Mixed: 79.4%, ND: 88.9%
Tagawa et al., 2014	AD	DSM-IV	P only	MMSE: 19.3 (P: 17.9 ± 5.0, ND: 20.2 ± 4.2)	3.0 (P: 3.96, ND: 2.35)	Caregivers asked if experienced P in last month, excluding other delusions	78.2 (P: 80.8 ± 8.2, ND: 76.3 ± 8.6)	NR	90.3% (P: 100%, ND: 84%)	NR	Donepezil prescribed - P: 15.4%, ND: 5.6%
Wilkosz et al., 2006	Possible or probable AD	NINCDS-ADRDA + standardized criteria for MCI + DSM-IV	M and P	MMSE: 19.6 ± 5.95 (P: 18.6 ± 6.3, M: 15.9 ± 6.7, ND: 20.8 ± 5.3)	3.51 ± 2.28	CBRS (CERAD) at baseline and follow-ups. (occurring >3 times in the last month)	74.58 ± 8.65	13.23 ± 3.04	59.0%	NR	Medication prescribed at baseline: Cognitive enhancers 49.3% Antipsychotics 2.4% Antidepressants 31.9% Sedatives 9.7%

NR = not reported; SD = standard deviation

Subtypes: P = Paranoid; M = Misidentification; Mixed = P and M; ND = non-delusional.

Dementia subtype: AD = Alzheimer's disease; MCI = Mild Cognitive Impairment

Diagnostic criteria for dementia: DSM = Diagnostic and Statistical Manual of Mental Disorders; ICD = International Classification of Diseases; NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; NIA-AA = National Institute on Aging and the Alzheimer's Association; CDR = Clinical Dementia Rating

Diagnostic criteria for delusions: NPI = Neuropsychiatric Inventory; K-NPI = Korean Neuropsychiatric Inventory; CBRS = CERAD behavioral rating scale

Cognitive screening tools: MMSE = Mini-Mental State Examination; K-MMSE = Korean Mini-Mental State Examination;

Table 3. Summary of Findings: Neuropsychology

	Geroldi et al., 2000	Geroldi et al., 2002	Lee et al., 2016	Perez-Madrinan et al., 2004	Reeves et al., 2015	Tagawa et al., 2014	Wilkosz et al 2006	D'Antonio et al., 2018	McLachlan et al., 2018
Global cognitive function									
MMSE / K-MMSE	P=ND	P=ND	P=ND M=ND M=P	P=ND M<ND M=P	P=ND M=ND M=P	P=ND	P<ND M<ND M<P	P<ND M<ND M<P	P=ND M=ND M=P
HDS-R						P=ND			
ADAS-Cog								P<ND M<ND M<P	
Executive function									
FAB-K			P=ND M=ND M=P						
Digit span forwards				P=ND M=ND M=P					
Digit span backwards				P=ND M=ND M=P					
Word fluency				P=ND M=ND M=P					
Language									
BNT	P=ND		P<ND M<ND M=P		P=ND M=ND M=P				
Token test	P=ND								

COWA	P=ND								
Memory									
Verbal immediate recall				P=ND M=ND M=P					
Verbal delayed recall				P=ND M=ND M=P					
Word list delayed recall			P=ND M<ND M=P						
ROCF: copy (recognition)				P=ND M=ND M<P					
ROCF: immediate memory				P=ND M=ND M<P					
ROCF: delayed recall				P=ND M=ND M=P					
Visuoperceptual/visuospatial/ praxis									
Constructional apraxia			P=ND M=ND M=P		P=ND M=ND M=P				
Visual discrimination				P=ND M=ND M=P					
CANTAB: RVP					P=ND M<ND * M=P				
VOSP: incomplete letters					P=ND M<NP * M<P *				
VOSP: object decision					P=ND M=ND M=P				

VOSP: number location					P=ND M=ND M=P				
VOSP: cube analysis					P=ND M=ND M=P				
<p>Differences in performance between groups ($p < 0.05$) before controlling for differences in MMSE are indicated in bold using < (less than) and > (greater than) ($p < 0.05$).</p> <p>Differences that remained significance ($p < 0.05$) after controlling for the confounding effects of MMSE are shown as *</p> <p>P=Paranoid, M=Misidentification, ND=Non-delusional</p> <p>Neuropsychological measures: ADAS-Cog = Alzheimer's Disease Assessment Scale-Cognitive; BNT = Boston Naming Test; CAMCOG = Cambridge Cognitive Examination; CANTAB: RVP = Cambridge Neuropsychological Test Automated Battery: Rapid Visual Information Processing subtest; COWA = Controlled Oral Word Association Test; FAB-K = Korean version of the Frontal Assessment Battery; HDS-R = Hierarchic Dementia Scale-Revised; HVLTL = Hopkins Verbal Learning Test; MFTC = Multiple Features Target Cancellation; MMSE = Mini-Mental State Examination; RAVLT = Rey Auditory Verbal Learning Test; ROCF = Rey-Osterrieth complex figure test; RPM = Raven's Progressive Matrices; ToM = Theory of Mind; VOSP = The Visual Object and Space Perception Battery</p>									

Table 4. Summary of Findings: Structural Imaging

	Geroldi et al., 2000	Geroldi et al., 2002	Lee et al., 2016	Tagawa et al., 2014	McLachlan et al., 2018
R frontal		P=ND	P>ND † M<ND † M<P †		
R temporal	P>ND ±	P<ND #	P=ND M<ND † M<P †	P<ND d	P=ND M=ND a M=P
R parietal			P=ND M<ND † M=P		
R occipital			P=ND M<ND † M<P †		P=ND M=ND c M=P
L frontal		P<ND #	P>ND † M=ND M<P †		
L temporal		P=ND	P>ND † M=ND M=P	P=ND d	P=ND a M<ND b M=P a
L parietal			P=ND M=ND M=P		
L occipital			P>ND † M<ND † M=P		P=ND M=ND c M=P

Differences between groups are indicated in bold (p<0.05).
P=Paranoid, M=Misidentification, ND=Non-delusional; L = left; R = right
± = lower R:L ratio of the radial width of the temporal horn in delusional patients, indicating less marked volume loss
= asymmetrical atrophy, with greater relative volume loss in the regions shown
† = multiple regions, see text for full details; a = entorhinal cortex, parahippocampal gyrus, fusiform gyrus;
b = parahippocampal gyrus; c = lateral occipital cortex, lingual gyrus; d = medial temporal lobe
Neuroimaging: CT = Computed tomography; MRI = Magnetic resonance imaging

Supplementary Table: Summary Risk of Potential Bias

Potential sources of heterogeneity between delusional subtypes and/or non-delusional described, matched or controlled for							Factors that may confound or influence the interpretation or generalizability of results				Factors that may affect the statistical significance of results	
Author, Year	Age	Gender	Ethnicity	Cognition (MMSE / other)	Illness duration	Education	Psychotropic use (described, controlled or excluded)	Cognitive enhancers (described, controlled or excluded)	Validated diagnostic tool use for delusions	Sample size (n>30) and subtype frequency described	Correction for multiple comparisons	Accounted for confounding effects of cognition (MMSE / other)
D'Antonio <i>et al.</i> , 2019	YES	YES	NO	YES	YES	YES	NO	YES	YES	YES	NA	YES
Geroldi <i>et al.</i> , 2000	YES	YES	NO	YES	NO	YES	NO	NO	YES	YES	NO	NA
Geroldi <i>et al.</i> , 2002	YES	YES	NO	YES	YES	YES	YES	NO	YES	YES	NO	NA
Lee <i>et al.</i> , 2016	YES	YES	NO	YES	NO	YES	YES	NO	YES	YES	NO	NO
McLachlan <i>et al.</i> , 2018	YES	YES	NO	YES	YES	NO	YES	YES	YES	YES	NO	YES
Perez-Madrinan <i>et al.</i> , 2004	YES	YES	NO	YES	YES	YES	NO	NO	YES	YES	YES	YES
Reeves <i>et al.</i> , 2015	YES	YES	NO	YES	YES	YES	YES	YES	YES	YES	YES	YES
Tagawa <i>et al.</i> , 2014	YES	YES	NO	YES	YES	NO	NO	YES	NO	YES	NO	YES
Wilkosz <i>et al.</i> , 2006	YES	YES	NO	YES	NO	YES	YES	YES	YES	YES	NA	YES