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Review

Neuropsychological deficits in Posterior Cortical Atrophy and typical Alzheimer's disease: A meta-analytic review

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ABSTRACT

Aims: To identify cognitive tests that best differentiate between Posterior Cortical Atrophy (PCA) and typical Alzheimer's Disease (tAD), as well as PCA and healthy control (HC) participants.

Method: Medline, PsycInfo and Web of Science were systematically searched using terms related to PCA, tAD, and cognitive testing. Seventeen studies were identified, including 441 PCA, 391 tAD, and 284 HC participants. Standardised effect sizes of mean scores were calculated to measure performance differences on cognitive tests for PCA versus tAD and PCA versus HC groups. Meta-analyses used a random effects model.

Results: The most discriminating cognitive tests for PCA and tAD presentations were measures of visuospatial function and verbal memory. Large, significant effect sizes were produced for all measures of visuospatial function, most notably for Rey–Osterrieth Copy (Hedges' $g = -2.79$), VOSP Fragmented letters (Hedges' $g = -1.73$), VOSP Dot Counting (Hedges' $g = -1.74$), and VOSP Cube Analysis (Hedges' $g = -1.98$). For measures of verbal memory, the RAVLT delay and Digit Span Backwards produced significant medium effects (Hedges' $g = .62$ and $-.56$, respectively).

Conclusion: Establishing a common framework for testing individuals with PCA has important implications for diagnosis and treatment, and forms a practical objective for future research. Findings from this meta-analysis suggest that measures of visuospatial function and verbal memory would form an important part of this framework.

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1. Introduction

PCA is a rare neurodegenerative syndrome characterised by early and progressive decline in high-order visual processing functions in the absence of visual acuity deficits (Benson, Davis, & Synder, Bruce, 1988). The majority of PCA cases are due to underlying Alzheimer's disease pathology (Tang-Wai et al., 2004), though PCA usually presents with a younger age at onset (between 50 and 60) than typical Alzheimer's disease (tAD) (Mendez, Ghajarania, & Perryman, 2002). Alternative underlying pathologies for PCA include Lewy body disease, corticobasal degeneration, and Prion disease (Tang-Wai et al., 2004). Notably, in PCA, the pattern of brain atrophy involves the parietal, occipital and occipitotemporal cortex (Crutch et al., 2012; Suárez-gonzález, Henley, Crutch, & Walton, 2015) whereas in tAD, the pattern of brain atrophy involves the frontotemporal association cortex and atrophy in the precuneus (Perl, 2010).

In contrast to tAD, episodic memory and insight are relatively preserved in the initial stages of PCA, whilst other functions relying on posterior cortices of the brain are affected early on. Impairment in these functions may give rise to difficulties with reading, spatial navigation and orientation, object recognition, and praxis, leading to difficulties with daily living tasks including cooking, using electronic devices, and getting dressed. In addition, elements of Balint (simultanagnosia, optic ataxia, and ocular apraxia) and Gerstmann syndromes (acalculia, agraphia, finger agnosia, and left-right disorientation) are frequent and widely reported (McMonagle, Deering, Berliner, & Kertesz, 2006; Suárez-González, Crutch, Franco-Macias, & Gil-Négica, 2016; Tang-Wai et al., 2004).

Dementia diagnosis is a multidisciplinary effort involving various specialists. Understanding of pathophysiology is informed by multiple lines of evidence, including images of brain structure, blood tests, plus the findings of neurological examinations and neuropsychological tests. Differential diagnosis is informed by the results of tests and compared against diagnostic criteria for each dementia syndrome (Table 1).

It is important to make timely and correct diagnosis of PCA so that patients can access support and treatment (Shaji, Sivakumar, Rao, & Paul, 2018). Individuals with PCA are more likely to experience a delay in receiving a diagnosis as they often present with unusual visual symptoms, of which they are aware, when they are experiencing mild cognitive impairment (MCI). Unusual visual symptoms often prompt health-care professionals to consult an optometrist for primary investigation of the problem (Crutch et al., 2012; Shakespeare, Ryan, Petrushkin, & Crutch, 2012). PCA patients are thus more likely to be diagnosed at a later stage of disease progression (Holden, Bettcher, & Pelak, 2020). This may delay referral to cognitive specialists and contribute significantly to the stress experienced by individuals living with PCA (Harding et al., 2018).

Diagnosis of PCA in the early stages requires neuropsychological tests that are sensitive enough to detect subtle impairments in visuospatial functioning. Diagnosis of PCA at more advanced stages requires visuospatial functioning tests for which validity is not affected by general cognitive

impairment. Thus, it is important to both differentiate between PCA and healthy controls (HC) in the early stages of the disease and between PCA and tAD at later stages of the disease.

Neuropsychological assessment is a key element of dementia differential diagnoses. Neuropsychological testing can be used to complement the findings of neuroimaging and neurological examinations (Hutchinson & Mathias, 2007; Looi & Sachdev, 1999). In addition, results from neuropsychological tests can be used to inform the functional, occupational, and cognitive rehabilitation needs assessments of individuals and thereby also contribute to disease management (Jacova, Kertesz, Blair, Fisk, & Feldman, 2007). Whilst there are assessment tools available for tAD and other rare phenotypes of AD, there are currently no test batteries particularly recommended for the assessment of PCA. Collating findings from neuropsychological testing is therefore an important step towards establishing a common framework for neuropsychological examination (Li et al., 2018).

The aim of this review is to identify cognitive tests that best discriminate between PCA and tAD, as well as PCA and HC, based on the results of published studies. Studies reporting scores of standardised measures for PCA, AD and HC were systematically searched in order to answer the following question: Which neuropsychological tests show performance differences between PCA and AD, and PCA and HC?

2. Method

The protocol for the systematic review was registered with PROSPERO (CRD42020171897).

2.1. Data sources and study inclusion

A systematic search of Medline, PsycINFO and Web of Science electronic databases, from 1st January 1985 (Medline), 1st January 1991 (PsycINFO) and 1st January 1985 (Web of Science) up to and including 12th November 2019, was undertaken to identify all published studies that assessed cognitive functioning of PCA and AD/HC samples.

Search terms related to PCA were combined with terms associated with typical Alzheimer's Dementia (tAD) and cognitive testing (Fig. 1). Search terms were based on a highly cited meta-analysis of neuropsychological deficits in Frontotemporal dementia and tAD (Hutchinson & Mathias, 2007) but with adaptation for PCA and inclusion of a control group through discussion among authors and other PCA experts. All potentially relevant studies were screened against the following inclusion criteria:

- (i) The study examined one PCA group and at least one control group, which consisted of individuals with tAD and/or HC with no objective cognitive impairment.
- (ii) Diagnoses of PCA and tAD were specifically mentioned and performed in accordance with the established criteria for PCA (Crutch et al., 2017; Mendez et al., 2002; Tang-Wai et al., 2004) and AD (McKhann et al., 1984; McKhann et al., 2011) (see Table 1 for a summary of diagnostic criteria).

Table 1 – Diagnostic Criteria for PCA and tAD – Summary of defining features included in diagnostic criteria.

	tAD (based on McKhann et al., 2011 ; and McKhann et al., 1984)	PCA based on Tang-Wai et al. (2004) , Mendez et al. (2002) and Crutch et al. (2017)
Core features (course and presentation)	Cognitive or behavioural: (neuropsychiatric) symptoms that: 1. Interfere with the ability to function socially or occupationally and represent a decline from previous levels of functioning 2. Are not explained by delirium or psychiatric disorder 3. Impairments in two or more of the following areas; ability to acquire and remember new information, reasoning and judgement, visuospatial abilities, language function 4. Changes in personality or behaviour	Clinical features: 1. Insidious onset 2. Gradual progression 3. Prominent early disturbance of visual $\pm$ other posterior cognitive functions
Supportive features	Probable AD is diagnosed when the patient meets criteria described above and has the following characteristics: 1. Insidious onset but clear-cut history of worsening of cognition 2. Non-amnesic presentations, the most prominent deficits are in; language (word-finding), visuospatial (object agnosia, simultagnosia and alexia), executive dysfunction (reasoning, problem solving)	Cognitive features: All of the following must be evident; relatively spared anterograde memory function, speech and nonvisual language functions, executive functions, behaviour and personality Cognitive features: At least three of the following must be present as early or presenting features $\pm$ evidence of their impact on activities of daily living; space perception deficit, simultanagnosia, object perception deficit, constructional dyspraxia, environmental agnosia, oculomotor apraxia, dressing apraxia, optic ataxia, alexia, left/right disorientation, acalculia, limb apraxia, apperceptive prosopagnosia, agraphia, homonymous visual field defect, finger agnosia. Neuroimaging: Predominant occipito-parietal or occipito-temporal atrophy/hypometabolism/hypoperfusion
Investigations (supportive)	Cognitive impairment is diagnosed through: 1. History taking from the patient and an informant 2. Objective cognitive assessment using “bedside” examination or neuropsychological testing	
Considerations	The clinical criteria include Possible, Probable, and Definite Alzheimer's disease	Classification into subtypes of PCA can be made using Crutch et al.'s (2017) three level classification framework.

- (iii) Cognitive tests were administered to PCA and tAD and/or HC groups and quantitative data necessary to calculate Hedges' g effect sizes ([Rosenthal, Cooper, & Hedges, 1994](#)) were provided (e.g., means and standard deviations (SD)).
- (iv) The cognitive tests used for diagnosis and classification of participants into the PCA and tAD groups were not the same cognitive tests used as the dependent variable.
- (v) The cognitive tests used were standardized measures (as defined by having population-based normative data that allow the examiner to compare an individual's performance with an appropriate comparison group) ([Committee on Psychological Testing, 2005](#)).
- (vi) The study used a cross-sectional or longitudinal design.
- (vii) Studies were published in English and in a peer-reviewed journal.

There were several studies with overlapping samples, where one or more paper had been published using the same participant group. A two-step strategy was used to select which studies to include in such cases. The first step was to prioritise the number of studies that could be included in the analysis so that data was preserved for as broader number of cognitive tests as possible. Secondly, the study with the largest sample size of the overlapping studies was included.

2.2. Risk of bias

Risk of bias for individual studies was assessed using the AXIS critical appraisal tool for cross-sectional studies ([Downes, Brennan, Williams, & Dean, 2016](#)), a 20-item scale developed using a Delphi panel consensus. Abstracts and full articles were reviewed for inclusion criteria by the reviewer, and double-rated by an independent second rater (GH), with discrepancies resolved through discussion.

2.3. Data collection and analytic strategy

For each study included in the analysis, the number of participants per group, as well as the mean and SDs for each of the cognitive measures, was extracted for all comparisons of performance between PCA and tAD/HC groups. All tests were broadly grouped into cognitive categories and sub-categories, as guided by Spreen and Strauss ([Spreen & Strauss, 2006](#)) and Lezak et al. ([Lezak, Howieson, Loring, & Fischer, 2004](#)), in order to organise the findings of the meta-analysis. These categories were: Global cognitive functioning, verbal memory (immediate, working and delayed); visual memory, semantic memory, verbal abilities & language (naming, category fluency and phonemic fluency), visuospatial function (visuoconstructional, object perception, space perception), and attention & orientation.

Fig. 1 – Literature search strategy.

A minimum of two studies needed to have used a particular cognitive test for that test to be considered in the analysis (Robert Rosenthal, 1995). Total scores and subscale scores for the same test could not both be used in the calculation of an effect size, in order to ensure that scores for a given test provided independent measures of performance.

2.4. Effect size calculation

Effect sizes were calculated using standardized between-group mean differences in cognitive performance (PCA vs tAD and PCA vs HC). Effect sizes were interpreted using Hedges' g values (.2 = small; .5 = medium; .8 = large). In the situation where negative values resulted these were interpreted to be indicative of the direction of the effect and the absolute value was used to gauge effect size.

2.5. Statistical procedures

Analysis was conducted in the R environment (R Core Team, 2014) using package metafor (Viechtbauer, 2010). The meta-

analyses were conducted using the random effects model (Hedges & Olkin, 1985). Effect sizes (Hedges' g) and statistical significance ($p < .05$) were considered when assessing a measure's usefulness in differentiating between PCA and tAD & PCA and HC. Measures of heterogeneity (I^2 and Q scores) were also used to examine the interpretability of the results. I^2 values of 75%, 50% and 25% indicated high, medium and low heterogeneity respectively (Cooper & Hedges, 1994).

3. Results

3.1. Corpus of studies

A database search identified 1011 records after removal of duplicates. Of these, 17 studies fulfilled all the inclusion criteria set out above (Fig. 1). The studies that were included in the final meta-analysis are summarised in Table 2. Of the 17 included studies, 16 studies compared PCA to tAD with 10 of these also comparing PCA to HC. One study compared PCA to HC only.

Table 2 – Summary of studies included in the meta-analysis.

	Posterior Cortical Atrophy				Typical Alzheimer's Disease				Healthy Controls			
	n	Age M(SD)	Years of Education M(SD)	Males %	n	Age M(SD)	Years of Education M(SD)	Males %	n	Age M(SD)	Years of Education M(SD)	Males %
Ahmed et al. (2018)	14	65 (7.7)	13.9 (2.4)	50	18	67 (8.7)	12.8 (3.4)	78	28	70 (5.7)	11.8 (3.3)	29
Aresi & Giovagnoli (2009)	17	59 (6.1)	5.5 (3.2)	18	17	63 (6.6)	6.1 (3.0)	18	17	59 (15.2)	6.4 (3.0)	18
Charles et al. (2005)	15	65 (6.6)	—	27	15	69 (11.7)	—	27	—	—	—	—
Crutch, Lehmann, Warren, & Rohrer (2013)	15	64 (8.2)	—	33	—	—	—	—	18	68 (5.4)	—	50
Firth et al. (2019)	109	64 (7.5)	—	38	58	66 (7.1)	—	62	49	63 (5.9)	—	25
Kas et al. (2011)	39	61 (7.8)	10.5 (5)	26	24	65 (12.1)	7.8 (5.1)	58	24	69 (6.9)	10.6 (4.1)	29
Li et al. (2018)	18	58 (6.1)	10.2 (3.7)	44	20	52 (7.3)	10.7 (4.5)	40	20	52 (7.7)	12.4 (4.1)	40
Magnin et al. (2013)	16	62 (5.1)	—	31	16	62 (4.5)	—	31	16	62 (5.1)	—	31
McMonagle et al. (2006)	19	—	—	47	11	—	—	36	18	67 (7.9)	—	28
Mendez et al. (2019)	14	59 (4)	17 (3.8)	29	28	59 (4.7)	15.9 (2.3)	64	—	—	—	—
Migliaccio et al. (2009)	14	61 (8.2)	15.1 (2.9)	36	16	61 (3.7)	15.9 (4.1)	63	65	61 (10)	17.6 (2.4)	42
Miller et al. (2018)	77	—	15.5 (3.1)	73	100	—	14.8 (3.5)	43	—	—	—	—
Nestor, Caine, Fryer, Clarke, & Hodges (2003)	9	64 (7.8)	13.3 (2.4)	67	14	68 (7.4)	10.7 (1.4)	72	15	61 (7.6)	11.3 (1.5)	67
Peng et al. (2016)	16	56 (6.5)	—	56	13	60 (8.2)	7.9 (2.2)	46	—	—	—	—
Suárez-González et al. (2016)	16	63 (5.3)	—	44	18	60 (1.8)	—	39	—	—	—	—
Wang et al. (2015)	7	60 (2.5)	—	14	6	61 (1.8)	9.5 (1.4)	83	—	—	—	—
Yong et al. (2014)	26	61 (7.7)	—	38	17	65 (5.1)	14.9 (2.4)	29	14	63 (5)	16.1 (2.4)	36

Note: - missing data not obtained/reported.

A total of 1116 participants were included across the studies, (males: $N_{PCA} = 190$, $N_{tAD} = 191$, $N_{HC} = 100$; females: $N_{PCA} = 251$, $N_{tAD} = 200$, $N_{HC} = 184$).

In total 19 tests were identified. All 19 were used to compare people with PCA and tAD and of these 12 were used to compare people with PCA and HC. These 19 tests spanned five cognitive domains: global cognitive functioning, verbal memory, visual memory, verbal abilities & language and visuospatial function (Table 3).

3.2. Study quality

Quality was assessed for each study (Table 4). All studies defined their target population and justified their discussion and conclusions. However, none of the studies justified their sample size or reported a method of measuring non-response to recruitment. In addition, one study did not present results for all planned analyses (Charles & Hillis, 2005) and one disclosed a conflict of interest (Firth et al., 2019).

3.3. Meta analyses

Hedges' g was calculated for all measures (mean, SD, 95% CI, Q and I^2), grouped according to test category (global functioning, verbal memory, verbal abilities and language, and visuospatial function) (Table 5: PCA vs tAD; Table 6: PCA vs HC).

For PCA and tAD comparisons, data were available from 16 studies ($N = 832$). There was variation in differences between PCA and tAD groups on cognitive tests, with Hedges' g ranging

from $-.03$ for the FAS to -2.79 for the Rey–Osterrieth Copy. For PCA and HC comparisons, data were available from 11 studies ($N = 399$). There was variation in differences between PCA and HC groups on cognitive tests, with Hedges' g ranging from -1.03 for the FAS to -10.37 for the Rey–Osterrieth Copy.

3.3.1. Cognitive tests that differentiated between PCA and tAD

3.3.1.1. GLOBAL FUNCTIONING. Two measures of global functioning, the MMSE and the MoCA, were used by two or more studies. The MMSE produced a small but significant effect size (Hedges' $g = -.23$) with more impairment in people with tAD than PCA.

3.3.1.2. VERBAL MEMORY. Five measures of verbal memory, including two measures of working memory, were used by two or more studies. Two of these tests, the RAVLT-delay and Digit Span Backwards produced significant effect sizes. The RAVLT-delay produced medium effect sizes (Hedges' $g = .62$) (more impairment in people with tAD than PCA). The Digit Span Backwards produced a small to medium effect (Hedges' $g = -.56$) (more impairment in people with PCA than tAD). The other three tests, CVLT-delay, Digit Span Forward and (verbal) Pyramids & Palm Trees did not find any significant differences between the two groups.

3.3.1.3. VISUOSPATIAL FUNCTION. Visuospatial function was one of the most commonly assessed cognitive domains. Nine measures of visuospatial function were used by two or more

Table 3 – Summary of measures used to assess cognition in the included studies organized by domain.

Cognitive Test(s)	Description of Test(s)
Global Functioning	
Montreal Cognitive Examination (MoCA) (Nasreddine et al., 2005)	The MoCA is a rapid screening instrument (battery of 30) with high sensitivity and specificity for detecting mild cognitive impairment (Nasreddine et al., 2005). It assesses attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. A clinical cut-off score of 26 is recommended (Mast & Gerstenecker, 2010).
Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975)	The MMSE is the most commonly used brief cognitive tool. It comprises a short battery of 20 individual tests covering 11 domains. The MMSE performs adequately at a screening capacity and has provided a benchmark against which all newer tools can be measured. A score of 24 is the cut off for 'normal' cognitive function (Mitchell, 2013).
Verbal Memory	
Rey's Auditory Verbal Learning Test (RAVLT) –Delayed Recall (Bean, 2011)	The RAVLT recall test requires participants to recall as many words from a list presented to them across five learning trials. It is a reliable measure for differentiating between the preclinical phase of tAD, MCI, and normal aging (Estévez-González, Kulisevsky, Boltes, Otermin, & García-Sánchez, 2003). In the delayed subtest, participants are asked to recall words from the list after 30-min of interpolated testing.
Digit Span Forwards and Backwards	The digit-span task is used to measure attention and working memory. Participants are presented with a sequence of digits and asked to recall them exactly, with increasingly longer sequences being tested in each subsequent trial.
California Verbal Learning Test (CVLT) – Delayed Recall (Elwood, 1995)	The CVLT is a widely used verbal learning and memory test. It requires the examinee to recognise a list of words after a 20-min delay. The long-delay free recall is a subtest, which reliably detects cognitive impairment (Wolf et al., 2010).
Pyramids & Palm Trees (PPT) (Howard & Patterson, 1992)	The Pyramids and Palm Trees Test (PPT) is a measure of semantic memory frequently used in aphasia, agnosia, and dementia research (Klein & Buchanan, 2009). Subjects are asked to choose one of two items that is most closely associated with the target. The stimuli are presented as either pictures or written words.
Visual Memory	
Face Recognition Tests	Tests of facial recognition are important in classifying the degree of difficulty individuals experience in the visual-memory domain as they provide information about the accuracy with which the face is represented, recognized, and distinguished from others (Faja, 2013).
Verbal Abilities & Language	
Category Fluency	Verbal fluency can be assessed in category fluency tasks. Performance on these tasks are related to indicators of vocabulary size, updating, and inhibition ability. They require participants to produce as many words as possible from a category in a given time (Shao, Janse, Visser, & Meyer, 2014).
FAS (Spreen & Benton, 1977)	Phonemic verbal fluency tests assess the production of words beginning with specific letters (F A and S). It is a sensitive test for assessing executive functioning (Machado et al., 2009).
Boston Naming Test (BNT) (Kaplan, Goodglass, & Weintraub, 2001)	The BNT and its shortened versions consist of black and white line drawings of objects. It is a measure of confrontation naming. Participants with tAD and other cognitive impairments have greater difficulties with the naming of low frequency objects (Roth, 2011).
Visual Functioning	
Rey–Osterrieth Complex Figure Copy (ROFC) (Osterrieth, 1944)	The ROFC is a brief and widely used neuropsychological test for the evaluation of visuospatial constructional abilities (Shin, Park, Park, Seol, & Kwon, 2006). In the copy condition, participants are given a stimulus card and asked to draw the same figure.
Visual Object and Space Perception (VOSP) - Fragmented Letters (Warrington & James, 1991)	Fragmented letters is an object perception test that requires participants to mentally fill in incomplete visual stimuli (i.e., incomplete letters). Such tasks are least sensitive to visual organization difficulty, except in the case of relatively severe cognitive impairment (Lezak et al., 2004).
VOSP Object Decision (Warrington & James, 1991)	Object decision is a test of object perception. Twenty boards with four stimuli are presented, with one depicting a real object and the other three acting as distractor stimuli. The participant is asked to identify and name the stimulus that represents the real shape.
VOSP Number Location (Warrington & James, 1991)	Ten boards have two squares arranged one above the other. The top square contains numbers arranged randomly and the bottom square contains only a black dot. The participant is asked to identify which number corresponds to the black dot.
VOSP Dot Counting (Warrington & James, 1991)	Dot counting is a space perception test, which requires participants to count a series of slides with various numbers of dots without pointing.
VOSP Cube Analysis (Warrington & James, 1991)	The cube analysis subtest entails identification of hidden cubes whose presence must be inferred. Amongst all VOSP subtests, failure on cube analysis best distinguished individuals with tAD pathology from those with non-AD pathology (Boyd et al., 2014).
VOSP Position Discrimination (Warrington & James, 1991)	20 cards are presented, each of which contains two adjacent squares. A dot marks the exact centre of one square; in the other, it is off-centre. The subject identifies the square containing the centred dot.
Hooper Visual Organization Test (HVOT) (Jefferson et al., 2006)	The HVOT is a common neuropsychological instrument for assessing visuospatial skills with good psychometric characteristics (Lopez, Lazar, & Oh, 2013). It consists of 30-line drawings of segmented objects that require mental integration for identification.

Table 4 – Quality appraisal of studies using the AXIS tool. Grey shading indicates potential quality concerns.

			Ahmed et al. (2018)	Aresi et al. (2009)	Charles et al. (2005)	Crutch et al. (2013)	Firth et al. (2019)	Kas et al. (2011)	Li et al. (2018)	Magnin et al. (2013)	McMonagle et al. (2006)	Mendez et al. (2019)	Migliaccio et al. (2009)	Miller et al. (2018)	Nestor et al. (2003)	Peng et al. (2016)	Suarez-Gonzalez et al. (2016)	Wang et al. (2015)	Yong et al. (2014)
Intro	1	Clear aims?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Methods	2	Appropriate study design?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	?	Y	Y
	3	Justified sample size?	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	4	Clearly defined population?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	5	Appropriate sample population?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	6	Process selects representative sample?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	7	Addresses and categorises non-responders	N	N	N	N	N	N	N	/	N	N	N	N	N	N	N	N	N
	8	Appropriate outcome variables?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	9	Valid instruments to measure outcomes?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	10	Statistical significance clear?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	11	Methods described enable to be replicated?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Results	1	Basic data described adequately?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	2	Non-response bias concern?	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
	3		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	4		N	N	N	N	N	N	N	/	N	N	N	N	N	N	N	N	N
	5	Results internally consistent?	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
	6	Results presented for all method analyses?	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Discussion	1	Conclusions justified by results?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	7	Limitations discussed?	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N
Other	1	Funding or conflict of interest concern?	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N
	2	Ethical approval or consent obtained?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

studies. In all measures of visuospatial function, people with PCA were found to be significantly more impaired than those with tAD.

The Rey–Osterrieth Figure Copy test of visuoconstruction was associated with a very large, significant effect (Hedges' $g = -2.79$). There was significant heterogeneity associated ($I^2 = 91.3\%$, $Q = 57.13$, $df = 5$, $p < .0001$) associated with this result.

Significant effect sizes were found for all measures of visuospatial function. Large effect sizes were associated with: VOSP Fragmented letters (Hedges' $g = -1.73$); VOSP Object Decision (Hedges' $g = -1.50$), VOSP Number Location (Hedges' $g = -1.03$), VOSP Dot Counting (Hedges' $g = -1.74$) (with significant heterogeneity ($I^2 = 81.2\%$, $Q = 15.99$, $df = 3$, $p < .01$), VOSP Cube Analysis (Hedges' $g = -1.98$), and VOSP Position Discrimination (Hedges' $g = -1.37$) and medium effect sizes associated with the HVOT (Hedges' $g = -.69$).

3.3.1.4. COGNITIVE TESTS THAT DID NOT DIFFERENTIATE BETWEEN PEOPLE WITH PCA AND TAD. One measure of visual memory and three measures of visual abilities and language were used by two or

more studies and none of these measures produced significant effects (Table 5).

3.3.2. Cognitive tests that differentiate between PCA and HC

3.3.2.1. GLOBAL FUNCTIONING. The MMSE was used by two or more studies and produced large, significant effect sizes (Hedges' $g = -2.84$) with more impairment in people with PCA than HC.

3.3.2.2. VERBAL MEMORY. Three measures of verbal memory were used by two or more studies, all of which produced large, significant effects: Digit Span Forward (Hedges' $g = -1.11$); Digit Span Backward (Hedges' $g = -2.46$); and (verbal) Pyramids & Palm Trees (Hedges' $g = -1.63$). In all three measures there was more impairment in people with PCA than in HC.

3.3.2.3. VERBAL ABILITIES AND LANGUAGE. Two measures of verbal ability and language, category fluency and FAS, were used by two or more studies and produced large, significant effect sizes (Hedges' $g = -1.57$ and Hedges' $g = -1.03$ respectively). In

Table 5 – Posterior Cortical Atrophy and Alzheimer's Disease: Hedge's *g* effect sizes for each test.

	K	N Participants (PCA/tAD)	Mean Hedges' <i>g</i> (95% CI)	I ²	Q (df)	Reference
Global Functioning						
MOCA	2	24/27	-.75 (-1.92, .43)	66.4%	2.98 (1)	Li et al. (2018), Wang et al. (2015)
MMSE	11	245/226	-.23 (-.42, -.05)*	0%	9.14 (10)	Charles et al. (2005), Kas et al. (2011), Li et al. (2018), Magnin et al. (2013), McMonagle et al. (2006), Miller et al. (2018), Nestor et al. (2003), Peng et al. (2016), Suárez-González et al. (2016), Wang et al. (2015), Yong et al. (2014)
Verbal Memory						
<i>Working Memory</i>						
Digit Span Forward	7	116/127	-.30 (-.66, .06)	47.9%	11.5 (6)	Aresi & Giovagnoli (2009), Li et al. (2018), Mendez et al. (2019), Nestor et al. (2003), Peng et al. (2016), Suárez-González et al. (2016), Yong et al. (2014)
Digit Span Backward	7	169/184	-.56 (-.78, -.35)***	0%	5.02 (6)	Li et al. (2018), Mendez et al. (2019), Miller et al. (2018), Nestor et al. (2003), Peng et al. (2016), Suárez-González et al. (2016), Yong et al. (2014)
<i>Delayed Memory</i>						
RAVLT	2	29/33	.62 (.11, 1.13)*	0%	.21 (1)	Ahmed et al. (2018), Charles et al. (2005)
CVLT	2	80/87	1.2 (-.03, 2.36)	84.9%	6.61 (1)	Miller et al. (2018), Peng et al. (2016)
<i>Semantic Memory</i>						
Pyramids & Palm Trees	2	22/22	-.14 (-1, .72)	48.6%	1.95 (1)	Ahmed et al. (2018), Nestor et al. (2003)
Visual Memory						
Face Recognition	2	79/50	.06 (-.3, .41)	0%	.37 (1)	Firth et al. (2019), Peng et al. (2016)
Verbal Abilities & Language						
<i>Category Fluency</i>						
Category Fluency	7	154/189	.07 (-.39, .52)	72%	21.5 (6)	Ahmed et al. (2018), Li et al. (2018), Mendez et al. (2019), Miller et al. (2018), Nestor et al. (2003), Peng et al. (2016), Suárez-González et al. (2016)
<i>Phonemic Fluency</i>						
FAS	2	22/31	-.03 (-.58, .52)	0%	.75 (1)	Ahmed et al. (2018), Nestor et al. (2003)
<i>Naming</i>						
Boston Naming Test	4	110/127	-.17 (-.55, .22)	44.6%	5.41 (3)	Charles et al. (2005), Li et al. (2018), Miller et al. (2018), Suárez-González et al. (2016)
Visuospatial Function						
<i>Visuoconstruction</i>						
Rey–Osterrieth Copy	6	74/93	-2.79 (-4.2, -1.38)***	91.3%	57.13 (5)***	Ahmed et al. (2018), Aresi & Giovagnoli (2009), Charles et al. (2005), Li et al. (2018), Migliaccio et al. (2009), Nestor et al. (2003)
<i>Object Perception</i>						
VOSP Fragmented Letters	3	51/49	-1.73 (-2.2, -1.25)***	3.8%	2.1 (2)	Nestor et al. (2003), Suárez-González et al. (2016), Yong et al. (2014)
VOSP Object Decision	2	116/70	-1.5 (-1.8, -1.12)***	0%	.31 (1)	Firth et al. (2019), Nestor et al. (2003)
<i>Space Perception</i>						
VOSP Number Location	3	56/51	-1.03 (-1.5, -.57)***	21.5%	2.55 (2)	Migliaccio et al. (2009), Suárez-González et al. (2016), Yong et al. (2014)
VOSP Dot Counting	4	65/67	-1.74 (-2.7, -.79)***	81.2%	15.99 (3)**	Ahmed et al. (2018), Nestor et al. (2003), Suárez-González et al. (2016), Yong et al. (2014)
VOSP Cube Analysis	3	36/45	-1.98 (-2.52, -1.44)***	1%	2.02 (2)	Ahmed et al. (2018), Nestor et al. (2003), Suárez-González et al. (2016)
VOSP Position Discrimination	2	25/36	-1.37 (-2.7, -.03)*	79.98%	4.99 (1)*	Ahmed et al. (2018), Suárez-González et al. (2016)
HVOT	2	17/38	-.69 (-1.28, -.1)*	0%	.76 (1)	McMonagle et al. (2006), Mendez et al. (2019)

K, number of studies; Hedges *g* effect size (negative values indicate worse performance in people with PCA); 95% CI, 95% Confidence Intervals; I², heterogeneity between studies; Q, sampling error; df, degrees of freedom; **p* < .5, ***p* < .01, ****p* < .001.

Table 6 – Posterior Cortical Atrophy and Healthy controls: Hedge's *g* effect sizes for each test.

	K	N Participants (PCA/HC)	Hedges' <i>g</i> (95% CI)	I ²	Q (df)	Reference
Global Functioning						
MMSE	6	99/151	−2.84 (−3.33, −2.35)***	37.3%	7.97 (5)	Crutch et al. (2013) , Kas et al. (2011) , Magnin et al. (2013) , McMonagle et al. (2006) , Migliaccio et al., 2009 , Nestor et al. (2003)
Verbal Memory						
Working Memory						
Digit Span Forward	3	41/66	−1.18 (−1.86, −.5)***	58.7%	4.84 (2)	Aresi & Giovagnoli (2009) , Crutch et al. (2013) , Nestor et al. (2003)
Digit Span Backward	2	76/54	−2.23 (−2.97, −1.5)***	51.6%	2.07 (1)	Firth et al. (2019) , Nestor et al. (2003)
Semantic Memory						
Pyramids & Palm Trees	2	22/32	−1.18 (−1.92–.44)**	0%	.2 (1)	Ahmed et al. (2018) , Nestor et al. (2003)
Verbal Abilities & Language						
Category Fluency						
Category Fluency	3	37/77	−1.57 (−2.25, −.9)***	53.5%	4.3 (2)	Ahmed et al. (2018) , Crutch et al. (2013) , Nestor et al. (2003)
Phonemic Fluency						
FAS	3	37/77	−1.03 (−1.77, −.3)**	65.5%	5.8 (2)	Ahmed et al. (2018) , Crutch et al. (2013) , Nestor et al. (2003)
Visuospatial Function						
Visuoconstruction						
Rey–Osterrieth Copy	3	27/75	−10.37 (−17.15, −3.6)**	96.1%	51.8 (2)***	Ahmed et al., 2018 , Aresi & Giovagnoli (2009) , Nestor et al. (2003)
Object Perception						
VOSP Fragmented Letters	2	88/53	−2.89 (−3.4, −2.37)***	0%	.02 (1)	Firth et al. (2019) , Nestor et al. (2003)
VOSP Object Decision	2	116/62	−1.82 (−2.21, −1.42)***	0%	.13 (1)	Firth et al. (2019) , Nestor et al. (2003)
Space Perception						
VOSP Dot Counting	3	111/72	−2.75 (−4.31, −1.2)***	90.1%	20.3 (2)	Ahmed et al. (2018) , Firth et al. (2019) , Nestor et al. (2003)
VOSP Cube Analysis	3	30/68	−4.01 (−4.72, −3.3)***	0%	1.14 (2)	Ahmed et al. (2018) , Ahmed et al. (2016) , Nestor et al. (2003)
VOSP Position Discrimination	3	103/53	−2.25 (−3.31, −1.2)***	75.1%	8 (2)*	Ahmed et al. (2018) , Firth et al. (2019) , Nestor et al. (2003)

K, number of studies; Hedges' *g* effect size (negative values indicate worse performance in people with PCA); 95% CI, 95% Confidence Intervals; I², heterogeneity between studies; Q, sampling error; df, degrees of freedom; ****p* < .001, ***p* < .01, **p* < .5.

both measures there was more impairment in people with PCA than in HC.

3.3.2.4. VISUOSPATIAL FUNCTION. The Rey–Osterrieth Figure Copy test of visuoconstruction produced a very large, significant effect (Hedges' $g = -10.37$), which was associated with significant levels of heterogeneity.

Large, significant effect sizes were produced for all measures of visuospatial function: VOSP Fragmented letters (Hedges' $g = -2.89$); and VOSP Object Decision (Hedges' $g = -1.82$); VOSP Dot Counting (Hedges' $g = -2.75$); VOSP Cube Analysis (Hedges' $g = -4.01$); and VOSP Position Discrimination (Hedges' $g = -2.25$). In all cases there was more impairment in people with PCA than in HC.

4. Discussion

4.1. Summary of findings

This is the first systematic review and meta-analysis to examine the utility of specific neuropsychological tests to support the differential diagnosis of PCA from tAD. The findings of this review are of key importance given the need for timely and accurate diagnosis and subtyping of dementia (Shaji et al., 2018). The neuropsychological tests that best differentiated between PCA and tAD were: (i) four tests of visuospatial function: the Rey–Osterrieth Copy, and the VOSP (fragmented letters, dot counting, cube analysis); (ii) one test of delayed memory: the RAVLT; (iii) and one test of working memory, the Digit Span Backwards. Our findings suggest that tests of language or visual memory do not differentiate between PCA and tAD, though in the case of visual memory, this may partly reflect discontinuation of tests when performance on the copy task is low, leading to a selection bias in those who can perform the test. Compared to HCs, people with PCA were found to have a global pattern of impairment with deficits particularly evident in visuospatial function but also in verbal memory, working memory, and language.

4.1.1. PCA versus tAD

The results of this study indicated that six neuropsychological tests were useful in differentiating between PCA and tAD. In line with previous literature and clinical observation, performance on tests of visuospatial function was significantly worse in people with PCA than those with tAD (Crutch et al., 2012). Significant differences were detected in all tests of visuospatial function. The four tests demonstrating some of the largest effect sizes and thus most informative for differential diagnosis were: Rey–Osterrieth Copy, VOSP Fragmented Letters, VOSP Dot Counting and VOSP Cube analysis. The Rey–Osterrieth Copy generated the largest effect size; however, it is likely that this very large effect is due to the additional praxis element of the test. This may prove to be an additional challenge to patients with PCA and thus explain the very large differences observed between people with PCA and tAD. Progressive dyspraxia, specifically limb apraxia is relatively common in people with PCA with up to 95% of people with PCA displaying some symptoms (Yong, Crutch, & Schott, 2020). Although studies indicate that aspects of visual and

memory function may be relatively spared in people with PCA and dyspraxia (Yong et al., 2020) it is important to consider the impact of dyspraxia on cognitive tests that have a praxis element.

It is of note that the tests that differentiated PCA from tAD were tasks linked to the dorsal visual processing stream as opposed to the ventral visual processing stream. The dorsal stream, which connects to the posterior parietal cortex, is implicated in processing spatial location and positioning of objects, whereas the ventral pathway, which connects to the inferior temporal cortex, is implicated in perceptual identification of objects (Goodale & Milner, 1992). Tests of object recognition such as the Boston Naming Test showed no differences compared to tAD. Therefore, it would appear that PCA is more strongly linked to ventral visual rather than dorsal visual dysfunction.

In addition to the four visuospatial function tests, the results of this study indicated that scores on the RAVLT test of delayed memory also differentiated between people with PCA and tAD. People with tAD performed more poorly compared to people with PCA, on measures of delayed verbal memory. This finding is supported by clinical consensus that the presence of less impaired delayed verbal recall is a distinguishing factor in diagnosing PCA (Charles & Hillis, 2005). However, when people with PCA are compared to HCs people with PCA were found to have worse performance in delayed memory. Taken together these findings support the finding that subtle impairments in memory are likely to be present in PCA at onset and progress as they move towards a more global profile of cognitive impairment (Trotta, Lamoureux, Bartolomeo, & Migliaccio, 2019).

The sixth test that differentiated between PCA and tAD patients with a medium effect size was Digit Span Backwards, with people with PCA performing more poorly. This test taps into an aspect of working memory and the differential findings between PCA and tAD is in line with previous literature which indicates working memory deficits in people with PCA (Frith et al., 2019; Trotta et al., 2019). Working memory difficulties in people with PCA are observed in clinical practice and deterioration in this domain can have detrimental impact on quality of life (Trotta et al., 2019). The finding from the current review of a specific difficulty with working memory concerned with numerical processing may be explained by a number of reasons. For example, this task relies on the phonological loop, numerical processing and visual imagery all of which are found to be more impaired in people with PCA (Bartolomeo, Bachoud-Lévi, Azouvi, & Chokron, 2005; Firth et al., 2019; Trotta et al., 2019). Underpinning these cognitive deficits are patterns of brain atrophy that are found in people with PCA such as the bilateral parietal lobe which is a region found to be involved in numerical processing and the posterior cortical regions which are involved in spatial mental imagery (Bartolomeo, Bourgeois, Boulon, & Migliaccio, 2013; Nieder & Dehaene, 2009).

Although there was a significant difference in MMSE score between PCA and tAD patients, brief screening tools that aggregate performances across subtests are not useful in differentiating PCA from tAD. This is because while people with PCA perform poorly on some tests (e.g., those of visuospatial function), patients with tAD will perform worse on

others tests (e.g., memory) (Ahmed, Baker, Thompson, & Christopher, 2016). Thus, when scores are aggregated they may appear more or less similar in terms of global levels depending on the stage of the disease. However, it is of clinical relevance that people with PCA will perform significantly worse on items where visuospatial function is required compared to people with tAD. In the MMSE these tasks are language (naming, reading, writing) and visuospatial (copy task).

4.1.2. PCA versus HC

The results of this study found that there were significant differences on all the tests of cognitive function between people with PCA and HC. This suggests that there are global deficits in cognitive functioning in people with PCA compared to HC, with the largest effect sizes seen in tests of visuospatial functioning. Of these tests of visuospatial functioning, the largest effect size was demonstrated in the Rey–Osterrieth Copy suggesting that this test might be useful in detecting early subtle indications of PCA. A large effect size was also present in the MMSE suggesting that utilising this test of global cognition would be a useful first step in identifying people with PCA. However, the degree of global cognitive functioning that is impacted in people with PCA depends on how far the disease has progressed. It is likely that the people with PCA captured in this study are not representative of those at the early stages of the disease. Therefore, there may be more subtle differences in PCA patients presenting early in disease course and HC on tests such as the MMSE.

4.2. Limitations

There are a number of limitations to the current review that warrant consideration. Firstly, a total of 114 tests were used to examine the cognitive profiles of people with PCA, tAD and HC. However, because tests were only eligible for inclusion in meta-analysis where two or more studies reported results, only 19 tests could be used in the current review. Therefore, there may be tests not been captured by this review that do effectively differentiate PCA from tAD.

A further limitation is the lack of reporting by studies on the duration of PCA or tAD. This is important because the main differences in neuropsychological profiles between PCA and tAD are most evident early on in disease progression. Without this contextualising information, it may be harder to identify neuropsychological tests that effectively differentiate between PCA and tAD.

We note that some tests routinely used in clinical practice and important for identification of PCA and differential diagnosis, such as the Trail Making Test (TMT) and tests of Executive Functioning (EF), were not identified in the meta-analysis. One explanation is that, in some patients with PCA, these tests may be discontinued or in some cases not even attempted, meaning that results cannot be entered into statistical analysis. Therefore, tests that are known to be clinically useful in identifying PCA, including the TMT and tests of EF, were not identified in our study. This highlights the importance of integrating insights from expert practitioners alongside meta-analytic findings when developing an assessment framework for individuals with PCA.

From a practical viewpoint, testing cognitive functions in persons with profound visuospatial deficits is a challenge, which may partly explain why so few tests were used across many of the identified studies. Differential diagnosis by expert clinicians may also draw on observations not captured in the scoring of neuropsychological tests. For example, in tests of language, total score does not differentiate between circumlocutions and perceptual errors, which may be informative for differential diagnosis. Given that such notes may often be in written qualitative form, other methodologies, such as meta-synthesis of clinical case studies or case note reviews, are needed to capture these observations to inform the developing an assessment framework. As well as neuropsychological tests, assessments of difficulties that form part of the diagnostic criteria, including oculomotor apraxia, acalculia, reading impairment, hemineglect, and limb apraxia may also be informative for assessment.

4.3. Conclusions and implications for practice

The results of this review found that six neuropsychological tests effectively differentiated between people with PCA and those with tAD. These tests were the Rey–Osterrieth Copy, VOSP Fragmented Letters, VOSP Dot Counting, VOSP Cube Analysis, RAVLT Delayed Memory and Digit Span Backwards. These tests should be considered for inclusion in clinical practice in batteries aimed at differentiating between PCA and tAD. In addition, the Rey–Osterrieth Copy test and the MMSE are indicated for differentiating between people with PCA and HC participants. Recommendations from meta-analytic data should be supplemented by narrative guidance from expert practitioners to highlight where tests may prove too challenging for people with PCA to attempt, which may discriminate them from tAD and HC participants.

Credit statement

CN: Conceptualization, methodology, investigation, formal analysis, interpretation of results, writing -original draft; RD: interpretation of results, writing -critical review and editing; RS: methodology, software, statistical plan, validation, interpretation of results; ASG: interpretation of results, writing -critical review and editing; DM: writing -critical review and editing; SGC: writing -critical review; GdH: interpretation of results, writing -critical review and editing; GH: validation, critical review and editing; JH: interpretation of results, critical writing – review and editing; EON: writing - editing; NU: writing -critical review and editing; AJ: methodology, writing-critical review and editing, Supervision; JS: conceptualization, interpretation of results, supervision, final approval.

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Declaration of competing interest

None.

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