Development and Validation of the "Addenbrooke's Cognitive Examination" as a Screening Test for Mild Cognitive Impairment in Hearing Impaired Individuals

Courtney North

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UCL Doctorate in Clinical Psychology Thesis declaration form

I confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signature: 

Name: Courtney North

Date: 19th June 2020

Overview

This thesis examined the utility of different neuropsychological tests in the detection of cognitive impairment in older adult populations. Limitations, directions for research and clinical implications have been highlighted.

Part One: Meta-Analysis - The literature review sought to identify, for the first time, the cognitive tests that best discriminate between Posterior Cortical Atrophy (PCA) and typical Alzheimer's Disease (tAD), as well as PCA and healthy controls (HC). The most discriminating cognitive tests for PCA and tAD presentations were found to be measures of perception and verbal memory.

Part Two: Empirical Paper - The objectives were to develop a hearing-impaired version of the Addenbrooke's Cognitive Examination (HI-ACE-III) and assess whether it can be used as a screening tool for mild cognitive impairment (MCI), as well as accurately distinguish cognitively impaired people from healthy controls. It was found to be a sensitive and specific screening tool, with a good ability to diagnose individuals with and without MCI in hearing-impaired populations. This was a joint project with Nattawan Utoomprurkporn, PhD student and qualified audiologist, and Mary Heatley, Trainee Clinical Psychologist

Part Three: Critical Appraisal - The critical appraisal, considers the challenges of the project, including the barriers to recruitment, the navigation of the scientist-practitioner role and the impact of conducting research during a pandemic. It offers personal reflections on the research process and considers how my personal experiences fit with the issues that are commonly cited in the literature.

Impact Statement

The present findings indicate that researchers and clinicians could benefit from updating their approach to neuropsychological testing in certain aging populations. In line with increasing recognition for the role of neuropsychology in differential diagnosis, this study highlights the need for nuanced approaches in rarer dementias and in older adults with sensory impairments.

The literature review took a meta-analytic approach to identify cognitive tests that best discriminate between Posterior Cortical Atrophy (PCA) and typical Alzheimer's Disease (tAD), as well as PCA and healthy controls (HC). When compared with other dementias, PCA is relatively under-researched, and until recently, the majority of research into PCA has concentrated around establishing the neuroimaging profile(s) of those with the diagnosis. The academic contributions of this review are therefore towards the understanding of the role of neuropsychology in the diagnosis of PCA.

Outside of academia, this review recognises the need to understand the tests that are best suited to distinguishing between dementia subtypes, and their importance in improving the accuracy of clinical classification or clinical diagnosis. At present there is no established common framework for the selection of cognitive outcome measures for trials involving individuals with PCA. Findings from this review suggest that measures of perception and delayed & immediate verbal memory should form an important part of this emerging framework.

Part 2 of this thesis addressed a recognised need for cognitive screening tests adapted to individuals with hearing loss. This is the first study to develop a hearing-impaired version of the Addenbrooke's Cognitive Examination (HI-ACE-III) and validate it as a screening tool for people with MCI and comorbid hearing loss. Whilst other tools have been adapted, no studies have yet reported the sensitivity or specificity of those tools in clinical populations. This study validates the use of the HI-ACE-III amongst populations with MCI and comorbid hearing loss and suggests that, in instances where clinicians are aware of diagnosed hearing impairments, the HI-ACE-III could be considered an appropriate tool for use in clinical settings.

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Acknowledgements

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Part 1: Literature Review

Neuropsychological Deficits in Posterior Cortical Atrophy and Alzheimer's Disease: A Meta-Analytic Review

Abstract

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

Method: Medline and PsycInfo and Web of Science were systematically searched using terms related to PCA, tAD and cognitive testing. Twenty studies were included, comprising 496 PCA participants, 457 tAD participants and 339 HC participants. Standardised effect sizes of mean scores between PCA and tAD and HC's performance on cognitive tests were calculated, and meta-analyses used a random effects model.

Results: The most discriminating cognitive tests for PCA and tAD presentations were measures of perception and verbal memory. Large and significant effect sizes were produced for all measures of object perception: Navon Figures, Views Usual, VOSP Fragmented letters and VOSP Object Decision, and for three measures of space perception: VOSP Dot Counting, VOSP Cube Analysis and VOSP Position Discrimination. For measures of verbal memory, the CVLT-Delay produced a significant large effect and the RAVLT delay and immediate produced significant medium effects. This review does not support the use of tests of global functioning, language or visual memory to distinguish between subtypes.

Conclusion: Identifying the most sensitive test to assist the differential diagnosis of PCA has important implications for diagnosis and treatment. A practical objective for future research is to establish a common framework for cognitive testing for trials involving individuals with PCA. Findings from this research suggest that measures

of perception and delayed and immediate verbal memory would form an important part of this framework.

1.0 Introduction

1.1 The Impact of Dementia

Dementia is a major public health challenge. According to Alzheimer's Disease International (2013), the incidence of dementia worldwide is rapidly increasing, with approximately 7.7 million new cases of dementia being diagnosed each year. The Alzheimer's Disease Facts and Figures (2020) reported that the number of adults aged 65 and over with Alzheimer's dementia is expected to grow to 13.8 million by mid-century. The cost and consequences of dementia for the individual, their family, and wider society is significant. With global economic cost of dementia at approximately $818 billion according to the World Alzheimer Report (2015), and nearly 85% of these costs relating to family and social, rather than medical care.

1.2 Typical Alzheimer's Disease (tAD) and Other Dementias

Dementia encompasses a range of neurological disorders characterised by deterioration in cognition, behaviour and social function. Typical Alzheimer's Disease (tAD) is the most common form of dementia. It accounts for 50-70% of cases and has a typical age of onset of 65 and above (Winblad et al., 2016). It is diagnosed when there are cognitive or neuropsychiatric symptoms which represent a decline from previous function and interfere with an individual's ability to function occupationally and/or socially (McKhann et al., 2011). The earliest and most common clinical manifestation of tAD is difficulty remembering recent events. However, as the disorder develops a wide range of neuropsychological deficits can

emerge, such as language difficulties, executive dysfunction, visuospatial deficits, more significant memory loss and behavioural changes (Burns and Iliffe, 2009)

There are many distinct forms of dementia and the pharmacological and psychosocial management of these differ. Differential diagnosis among the dementia variants currently relies upon a weighted combination of genetic biomarkers, neuroimaging, cognitive and behavioural assessment (Reilly et al., 2010). Some of the most common non-Alzheimer's dementias include frontotemporal dementia (Ratnavalli et al., 2002), vascular dementia (Wetterling et al., 1996) and dementia with lewy bodies (Zaccai et al., 2005).

1.3 Posterior Cortical Atrophy (PCA)

PCA is a rare form of degenerative dementia characterised by a progressive decline in complex visual processing which is out of proportion to other cognitive difficulties (Benson, 1998; Tang-Wai et al., 2004). PCA means 'back of the brain shrinkage' and it refers to the progressive degeneration of brain cells in the regions that process visual and sensory information, the occipital and parietal lobes. The changes in the brain that cause PCA can be triggered by different disease processes, but in the majority of cases, PCA is caused by similar changes to brain cells to those that occur in tAD. tAD is therefore the most common underlying cause of PCA (Galton et al., 2000) accounting for at least 80% of PCA cases. Alternative underlying causes include, dementia with Lewy bodies, Corticobasal Degeneration (a rare progressive neurological disorder), and Prion Disease (a disease of structurally abnormal proteins). The heterogeneity of

potential causes has led to inconsistences in terminology which has made it difficult to compare studies across different centres (Crutch et al., 2013).

The age of onset of PCA tends to be much earlier than in tAD with most studies reporting PCA symptom onset in patients age 50 – 60 (Mendez et al., 2002). Day et al. (2017) found that patient-specific factors may convey vulnerability to regional Alzheimer's Disease pathology and disease phenotype, suggesting that individuals might be predisposed to earlier age of symptom onset in PCA. However, further research attention is required to better understand the challenges in identifying the factors associated with both the selective vulnerability of posterior cortical regions and the young age of onset (Crutch et al., 2012)

The prevalence and incidence of PCA are currently unknown. However, Snowden et al. (2007) found that 5% of a large cohort of patients with tAD, who presented to a specialist centre for cognitive disorders, had a visual presentation which was later labelled as PCA.

The most common neuropsychological deficits noted in individuals with PCA are visuoperceptual and visuospatial impairments. Although higher-order visual problems are reported more frequently than basic visual disturbances, the fundamental aspects of vision associated with occipital cortical function (such as form, motion and colour processing) do become more vulnerable, and many PCA patients are known to show impairments in at least one basic visual process (Lehmann et al., 2011).

Problems with spelling, literacy (Carreiras et al., 2009) numeracy (McCaskey et al., 2018) and learned motor skills (Dayan & Cohen, 2011) have also been reported as early indicators of PCA, as these are tasks associated with occipital and parietal lobe functions.

The key distinction between PCA and tAD is the preservation of other cognitive abilities, such as memory at the early stages of illness in PCA. However, as the disease progresses, people develop the more typical symptoms of Alzheimer's disease, such as memory loss and confusion (Migliaccio et al., 2009)

1.4 The Importance of differential diagnosis

There are psychological and economic consequences for both patients and families with continued undiagnosed dementia. In any neurodegenerative illness, timely and correct diagnosis is a prerequisite for access to support services and symptomatic treatment, such as medications and cognitive stimulation programmes (Shaji et al., 2018). However, individuals with dementia and their families may have difficulty distinguishing the early signs of dementia from their perception of "normal' ageing. In these cases, family members might unsuspectingly begin to take over the patients' social roles and delay their recognition of the decline by compensating for impairments (Jacova et al., 2007). This is particularly problematic, as early identification of pathological changes in tAD and other dementias is essential in ensuring the provision of, and effectiveness of interventions (Winblad et al., 2016).

Individuals, families and healthcare providers may also have difficulty distinguishing tAD from other, more rare forms of dementia. Due to the relative rarity of PCA, it's uncommon symptom patterns and its early age of onset, these individuals can also often be misdiagnosed (Crutch et al., 2012). Unusual visual symptoms can prompt professionals to first refer individuals to optometrists to investigate ocular abnormalities and high levels of symptom-related anxiety can lead to professionals referring for mental-health assessments (Crutch et al., 2012). These frequent and tangential investigations prolong the time it takes for individuals to be referred to cognitive specialists and contribute significantly to the stress process for individuals living with PCA (Harding et al., 2018).

PCA is more than just a visual variant of tAD (Crutch et al., 2012) and as such, the difficulties that individuals encounter on a day-to-day basis are exacerbated by deficits that are specific to the PCA syndrome. In a qualitative study conducted by Harding et al. (2018), PCA patients reported that the barriers they had experienced in engaging with their hobbies were largely caused by distinct visual deficits. This was noted to be in contrast with individuals with tAD, who's difficulties seem to be caused by problems with initiation of activities rather than performance (Giebel et al,, 2014). This has important implications for the cognitive rehabilitation of PCA as interventions should be focused on introducing compensatory strategies for visual deficits and training preserved cognitive functions, such as memory (Roca et al., 2010).

In summary, healthcare providers awareness of distinct clinical syndromes, and their ability to reach a correct diagnosis, can lead to earlier identification,

appropriate treatments and more accurate prognosis for those living with PCA (Charles & Hillis. 2005) and tAD (Winblad et al., 2016).

1.5 The Role of Neuropsychology

Neuropsychological assessment is a key element of dementia diagnoses and studies have found good evidence for the utility of neuropsychological tests in differential diagnosis (Looi & Sachdev, 1999; Hutchinson & Mathias, 2007). Neuropsychology should be a part of an integrated clinical approach to the diagnosis of dementia. When applied selectively, it can address clinical issues, such as the nuances between early dementia and healthy ageing. In particular, neuropsychological testing can complement neuroimaging and clinical history in establishing the differential diagnosis (Looi & Sachdev, 1999; Hutchinson & Mathias, 2007) by shedding light on the distinguishable neuropsychological profiles of different dementia subtypes.

Previous research has found that the profile of neuropsychological test results can highlight cognitive features that differ between PCA and tAD (Li et al., 2018; Crutch et al., 2013). The collation of these findings as reported here is therefore an important step towards establishing a common framework for neuropsychological examination. This is particularly important as cognitive testing may be more readily available and less expensive than other diagnostic techniques (e.g., PET imaging) (Li et al., 2018), and to date, there is no battery of tests particularly recommended for the assessment of PCA.

1.6 Review Aims

When compared with other dementias, PCA is relatively under-researched. Whilst the majority of research into PCA is concentrated around establishing the neuroimaging profile(s) of those with the diagnosis (Tang-Wai et al., 2004; Lehman et al., 2011), growing research attention has been given to the contribution of neuropsychology in the diagnosis of PCA. Alves et al. (2013) published a meta-analytic review of neuropsychological studies looking at the difference between PCA and tAD. However, they sought to examine the neuropsychological profile of PCA by grouping tests into eleven broad cognitive domains. As such, they did not provide information on the utility of specific neuropsychological tests in differential diagnosis between PCA and tAD. In addition, there have been many studies published since and there are no recent reports summarising and collating the recent evidence for cognitive tests that best discriminate between PCA and tAD.

This review aims to identify the cognitive tests that best discriminate between Posterior Cortical Atrophy (PCA) and Alzheimer's Disease (AD), as well as PCA and healthy controls (HC). Studies reporting on scores of standardised measures for PCA, tAD and healthy control groups will be systematically searched for in order to answer the following questions:

1. Which neuropsychological tests show performance differences between PCA and tAD and what is the effect size of those differences?
2. Which neuropsychological tests show performance differences between PCA and healthy controls and what is the effect size of those differences?

2.0 Method

The protocol for the systematic review was registered with PROSPERO Prospective Register of Systematic Reviews (CRD42020171897

2.1 Data Sources and study inclusion

A systematic search of the 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 the cognitive functioning of PCA and tAD/HC samples. Search terms related to PCA were combined with terms associated with typical Alzheimer's Dementia (tAD) and cognitive testing. Specific terms used to search the databases are reported in the PRISMA diagram (see Figure 1 for details) drawn from a review by Hutchinson and Mathias (2007) who explore differences on specific tests between tAD and Frontotemporal Dementia, PCA terms were adapted from a review conducted by Crutch et al. (2012). The literature search yielded 1010 potentially relevant studies, 20 of which met all of the following inclusion and exclusion criteria:

(i) It examined one PCA group and at least one control group which consisted of individuals with tAD and/or healthy individuals with no objective cognitive impairment.

(ii) Diagnoses of PCA and tAD were specifically mentioned and performed in accordance with established criteria. (for PCA: Tang-Wai et al., 2004; McMonagle et al., 2006; Crutch et al., 2017; Crutch et al., 2013; Mendez

et al., 2002; for tAD: Mckhann et al., 1984; McKhann et al., 2011) (see Table 1 for a summary of diagnostic criteria)

(iii) Cognitive tests were administered to PCA and tAD or HC groups and quantitative data necessary to calculate Hedges g effect sizes (Rosenthal et al., 1994) were provided (e.g. means and standard deviations (SD))

(iv) The cognitive tests were not used for the diagnosis and classification of participants into the PCA and tAD groups

(v) 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, 2015)

(vi) The study followed a cross-sectional or longitudinal design

(vii) Studies were published in English and in a peer-reviewed journal

2.2 Risk of bias

Risk of bias for individual studies was assessed using the AXIS critical appraisal tool for cross-sectional studies (Downes et al., 2016), a 20-item scale developed using a Delphi panel consensus (see Appendix A). The measure prompts the assessor to consider the quality and suitability of the study to answer the hypothesised question, as well as any risk of biases which might be introduced by the study design or by the reporting of results. Instead of numerical scoring, it has areas to record a “yes”, “no” and “don’t know” answer for each question, as well as a short comment, but it does not have a published cut-off scores to categorise studies as low, medium, or high quality. Although this has implications for interpretation, as

judgements will have some degree of subjectivity, the tool acknowledges the issues with the summation of checklists for study quality and addresses previously documented concerns that the non-linear outputs from checklists can be problematic (Juni et al., 1999).

Abstracts and full articles were reviewed for inclusion criteria by the reviewer, and double-rated by an independent clinical psychology doctoral student (GH), with discrepancies being solved through discussion with the thesis supervisor.

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, were collected 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 (2006) and Lezac et al. (2004), in order to organise the findings of the meta-analysis. These categories were: Global functioning, auditory verbal memory (immediate, working and delayed); visual memory, semantic memory, verbal abilities and language (naming, category fluency and phonemic fluency), perception (visuoconstructional, object perception, space perception), and attention and orientation.

As a meta-analysis requires two or more studies in order to aggregate primary research findings, (Rosenthal, 1995) a minimum of two studies needed to have used a particular cognitive test for that test to be considered in the analysis. 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 (0.2 = small; 0.5 = medium; 0.8 = large). This is summarized in the following equation:

$$^{1}Hedge's\ g = \frac{M_1 - M_2}{SD^{*}_{pooled}}$$

Hedges g was selected as it outperforms Cohens d when sample sizes are low, it is therefore sometimes referred to as the "corrected effect size" as it uses pooled weighted standard deviations (Cohen, 1977).

2.5 Statistical procedures

Analysis was conducted in the R environment (R Core Team, 2014) using package metafor (Viechtbauer, 2010). The meta-analyses used the random effects model, which takes a more conservative approach than the fixed effects model, as it assumes variation of effect sizes across studies and balances study weights (Hedges & Olkin, 1985).

[1] $M_1 - M_2$ equals the differences in means between PCA and one of the comparison groups (tAD or HC) and SD_{pooled} indicates the weighted standard deviation for the PCA and comparison group.

The Q and I^2 statistics were used to measure homogeneity of effect sizes across studies. A significant Q statistic indicates high between-study heterogeneity, suggesting potential methodological or study population differences. The I^2 statistic, quantifies the percentage of variation across studies due to heterogeneity and is less biased by the number of studies included in the analysis. The lower the I^2 value, the less between-study heterogeneity, with values of 75%, 50% and 25% suggested as indicating high, medium and low heterogeneity respectively (Cooper & Hedges, 1994).

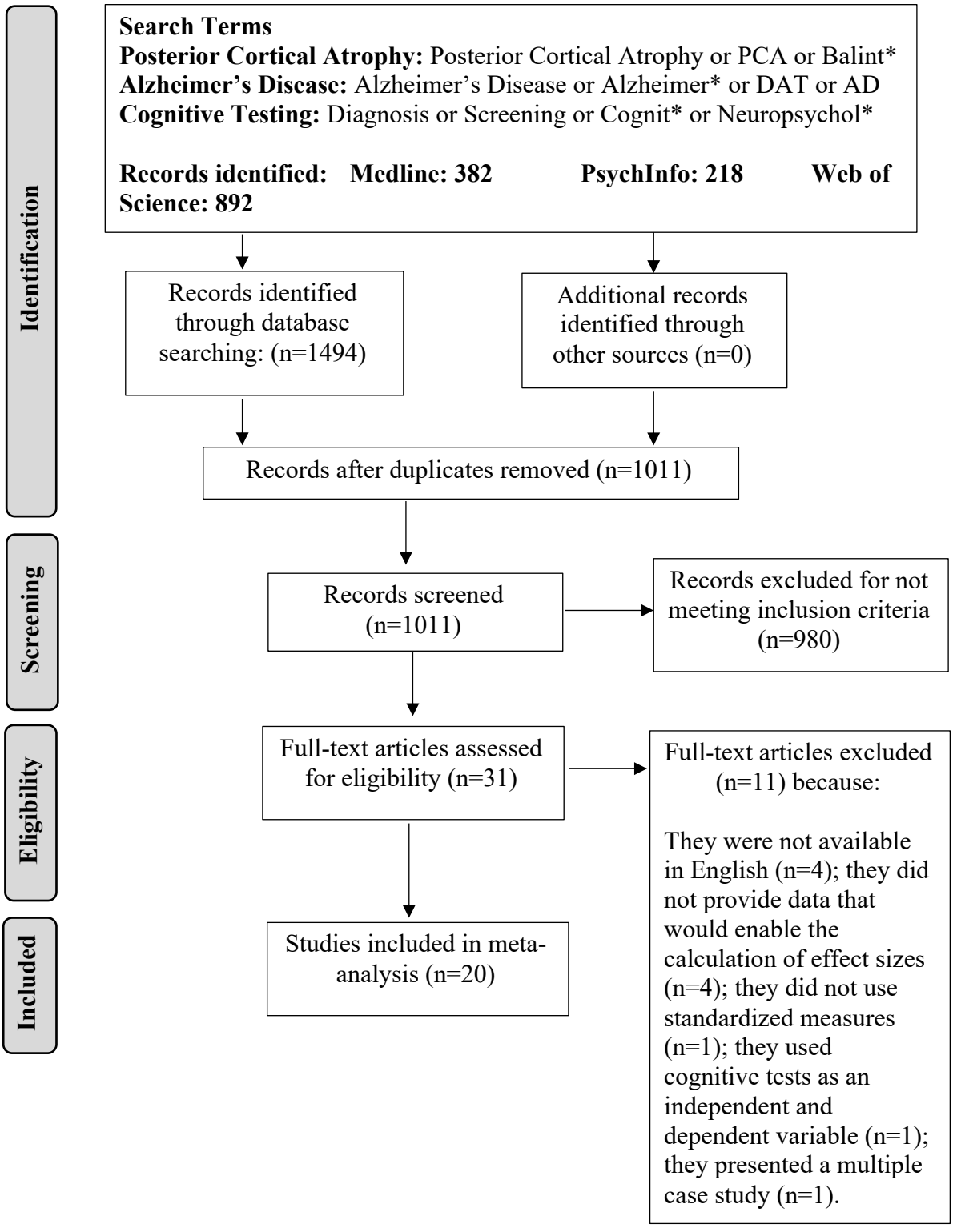
Table 1

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) and Mendez (2007)
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	1. Insidious onset and gradual progression 2. Disabling visual complaints throughout the disorder with intact primary visual functions at least on first examination 3. Relatively preserved anterograde memory and insight early in the disorder 4. Proportionately less impaired deficits in memory and verbal fluency 5. Presence of any of the following; Balint's syndrome, elements of Gerstmann's syndrome, simultagnosia and/or optic ataxia/apraxia and environmental disorientation.
Supportive features	Probable tAD 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-amnestic presentations, the most prominent deficits are in; language (word-finding), visuospatial (object agnosia, simultagnosia and alexia), executive dysfunction (reasoning, problem solving)	1. Presenile onset 2. Alexia 3. Ideomotor/dressing apraxia 4. Prosopagnosia
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	1. Predominantly impaired perceptual deficits on neuropsychological testing 2. Focal/asymmetrical deficits in the parieto-occipital regions on neuroimaging (structural and/or functional), relatively spared frontal and mesiotemporal regions
Considerations	The clinical criteria include Possible, Probable, and Definite Alzheimer's disease	

Figure 1

Literature Search Strategy



3.0. Results

3.1 Corpus of studies

A database search identified 1011 records, and of these the 20 studies fulfilled all the inclusion criteria set out above (see figure 1). The studies that were included in the final meta-analysis are summarised in Table 2. All studies included PCA participants, twelve of these compared both tAD participants and healthy controls, seven compared only tAD participants and one compared only healthy controls to PCA participants.

A total of 1292 participants were included across the studies. Gender was reported in 19 of the studies, providing data for 1261 cases (males: $N_{PCA} = 211$, $N_{tAD} = 210$, $N_{HC} = 128$; females: $N_{PCA} = 273$, $N_{tAD} = 228$, $N_{HC}=211$).

A total of 15 cognitive tests were used to compare PCA and HC participants and an additional seven were used to compare PCA and tAD participants. These 22 tests spanned five cognitive domains including; global functioning, auditory verbal memory, visual memory, verbal abilities and language and perception. A description of each test included in the analyses is detailed in Table 3.

3.2 Study quality

Table 4 summarises the study quality scores for each study. All studies defined their target population and justified their discussion and conclusions. However, none of the studies justified their sample size (where applicable) or reported a method of measuring non-response to recruitment, indicating that there

were issues with quality amongst the studies included in this review. In addition, one study did not present results for all planned analyses (Charles et al., 2005) and one disclosed a conflict of interest (Firth et al., 2019). See Appendix A for full AXIS tool.

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. (2016a)	25	-	12.3(2)	47	32	-	13.4(2.4)	47	34	-	13.7(.2.9)	50
Ahmed et al. (2016b)	12	61(6.2)	11.9(1.9)	-	19	64(8.4)	13.3(2.7)	-	-	-		-
Ahmed et al. (2018a)	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)	40
Ahmed et al. (2018b)	18	65(6.8)	13.6(2)	50	15	69(9.7)	12.6(6.5)	53	21	63(6.1)	14.4(2.1)	43
Aresi et al. (2009)	17	63(6.6)	6.12(3)	13	17	59(6.1)	5.5(3.2)	13	17	59(15.2)	6.4(2.9)	13
Charles et al. (2005)	15	65(6.6)	-	27	15	69(11.7)	-	27	-	-		-
Crutch et al. (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)	27	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 et al. (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	-	-		-
Suarez-Gonzalez (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.

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	
Addenbrooke's Cognitive Examination (ACE) (Hsieh et al., 2013)	The ACE and its Revised version (ACE-R) are screening tools composed of tests of attention, orientation, memory, language, visual perceptual and visuospatial skills, reported to have good sensitivity and specificity for identifying mild dementia and tAD at cut-off points of 88 and 82 respectively (Hsieh et al., 2013; Bruno & Schurmann-Vignaga, 2019). It is scored out of 100, with a higher score denoting better cognitive function.
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 et al., 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)
Auditory Verbal Memory	

Rey's Auditory Verbal Learning Test (RAVLT) – Immediate/Delayed Recall (Bean, 2011)	The RAVLT immediate recall test requires participants to recall as many words from a list presented to them across 5 trials. It is considered the most reliable RAVLT measure for assessing memory in tAD (Estévez-González et al., 2003). In the delayed subtest, a participant is asked to recall words from the list after 30-minutes of interpolated testing.
Digit Span Forwards & Backwards	A digit-span task is used to measure working memory's number storage capacity. Participants are tasked to recall a sequence of numerical digits correctly, with increasingly longer sequences being tested in each trial. Digit span tasks a reported to have good test-retest reliability (Waters & Caplan, 2003). Typically, a ≤7 cut-off score is utilized (Schroeder et al., 2011).
California Verbal Learning Test (CVLT) – Delay (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-minute delay. The long-delay free recall is a sensitive and specific subtest which reliably distinguishes cognitive impairment from normal ageing (Rabin et al., 2009; Wolfe et al., 2010).
Pyramids & Palm Trees (PPT) (Howard & Patterson, 1992)	The Pyramids and Palm Trees Test (PPT) is a nonverbal measure of semantic memory frequently used in aphasia, agnosia, and dementia research, though there is little psychometric information regarding the PPT available (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 et al., 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 frontal lobe functions (Machado et al., 2009). Good internal consistency has been reported (Tombaugh et al., 1999). Norms have been published for people of varying ages, levels of education, ethnic diversity, and geographical diversity (Strauss et al., 2006)
Boston Naming Test (BNT) (Kaplan & Goodglass et al., 1983)	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). Normative data for the BNT stratified on age, age and gender, and age and educational level are available (Zec et al., 2006).
Perception	
Rey-Osterrieth Complex Figure Copy (ROFC) (Osterrieth, 1994)	The ROFC is a brief and widely used neuropsychological test for the evaluation of visuospatial constructional abilities (Shin et al., 2006). In the copy condition, participants are given a stimulus card and asked to draw the same figure. Interrater, alternate form, test-retest, and internal consistency reliability have been reported as adequate to good for the ROCF (Berry et al., 1991).
Visual Object and Space Perception (VOSP) - (Warrington & James, 1991)	The VOSP is a measure designed to assess skills for which right-hemisphere-injured patients demonstrate selective deficits. Validity studies conducted have indicated that these tests reliably distinguish between controls and individuals with right hemisphere damage (Bonello et al., 1997).

VOSP Fragmented Letters (Warrington & James, 1991)	Fragmented letters is an object perception test which 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-tAD 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.
Navon Figures (Navon, 1977)	Navon figures involve visual stimulus that consist of a large character (the global level) made out of small characters (the local level). Participants are asked to identify either the large or small characters. Typically, individuals with tAD have difficulty reproducing the local forms (Jeon & Lee, 2009)

Views (Usual & Unusual) (Warrington & James, 1988)	Participants are asked to identify photographs of real objects pictured from an 'unusual', non-canonical perspective. Items not identified from the non-canonical perspective are subsequently re-presented photographed from a more 'usual', canonical perspective.
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 et al., 2003). It consists of 30-line drawings of segmented objects that require mental integration for identification. The HVOT has good psychometric characteristics, including strong test–retest reliability (Lezak et al., 2004) and good construct validity (Nadler et al.,1996),

Table 4

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

			Ahmed et al. (2016a)	Ahmed et al. (2016b)	Ahmed et al. (2018a)	Ahmed et al. (2018b)	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	Y	Y	Y
Methods	2	Appropriate study design?	Y	Y	Y	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	N	N	N
	4	Clearly defined population?	Y	Y	Y	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	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	Y	Y	Y
	7	Addresses non- responders	N	/	N	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	Y	Y	Y
	9	Valid outcome measures?	Y	Y	Y	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	Y	Y	Y
	11	Methods well described?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Results	12	Basic data described adequately?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	13	Non-response bias concern?	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y
	14	Non-responders described?	N	/	N	N	N	N	N	N	N	N	/	N	N	N	N	N	N	N	N	N
	15	Results internally consistent?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y
	16	All results analysed?	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Discussion	17	Conclusions justified by results?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	18	Limitations discussed?	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	N
Other	19	Funding/conflict of interest concern?	N	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N	N
	20	Ethical approval or consent obtained?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

3.3 Meta-Analyses

The weighted effect sizes (g_w) for all measures (mean, SD, 95% CI, Q and I^2), grouped according to test category (global functioning, auditory verbal memory, verbal abilities and language, and perception), are provided in table 5 for PCA/tAD comparisons, and in table 6 for PCA/HC comparisons. Forest plots for PCA vs tAD meta-analyses are available in Appendix B and forest plots for PCA vs HC meta-analyses are available in Appendix C.

Effect sizes (hedges g) and statistical significance ($p<0.05$) were considered when assessing a measure's usefulness in differentiating between PCA and tAD and PCA and HC. Measures of heterogeneity (I^2 and Q scores) were also used to examine the interpretability of the results.

Sensitivity analyses were performed in order to assess potential sources of heterogeneity. This involved one study being excluded at a time in order to investigate whether the summary effect and heterogeneity were heavily influenced by a particular study (Patsopoulos et al., 2008). All I^2 statistics that are above the 75% indicating high heterogeneity (Cooper & Hedges, 1994) were investigated, with other suspected incidences being examined on a case-by-case basis, as recommended by Glasziou and Sanders (2002) who provide guidance on investigating causes of heterogeneity in systematic reviews.

For the PCA and tAD comparisons, data was available for 19 studies reporting on 922 participants. There was considerable variation in the extent to which

the PCA and tAD groups differed on the cognitive tests, with hedges g_w ranging from a minimum of -0.03 for the FAS to a maximum of -2.79 for the Rey-Osterrieth Copy.

For the PCA and HC comparisons, data was available for 12 studies on 399 participants. There was considerable variation in the extent to which the PCA and HC groups differed in the cognitive tests with hedges g_w ranging from a minimum of -0.99 for the FAS and to a maximum of -9.84 for the Rey-Osterrieth Copy.

3.3.1 Cognitive domains that discriminated between PCA and tAD

Verbal Memory

Six measures of auditory verbal memory, including two measures of working memory, were used by two or more studies. Of these, the CVLT-delay, RAVLT-delay and Digit Span Backwards produced effect sizes which were statistically significant.

Medium effects were produced by the RAVLT delay (Hedges $g_w = 0.56$) and the RAVLT immediate (Hedges $g_w = 0.72$). These were both significant at $p<0.01$. Whereas the CVLT-Delay produced a large effect (Hedges $g_w = 0.86$), suggesting that persons with tAD performed more poorly than those with PCA on this measure.

Due to high heterogeneity across studies that used the CVLT-delay (I_2=74.4%), a post-hoc sensitivity analysis was conducted to explore the impact of excluding Peng et al. (2016) from the meta-analysis. This decision was based on variance that was likely introduced by their use of a slightly different scoring system. This analysis produced a smaller but still significant effect (Hedges $g_w = 0.56$) and

greatly reduced the heterogeneity across studies (I_2=0%) (see Appendix D), suggesting that that the CVLT-delay might accurately discriminate between persons with PCA and tAD.

The Digit Span Backwards produced a small/medium effect (Hedges g_w = -0.46) indicating that persons with PCA performed more poorly than those with tAD on this measure.

Perception

Perception was one of the most commonly assessed cognitive domains. Eleven measures of perception were used by two or more studies. Of these, all measures produced a significant effect, suggesting that persons with PCA performed more poorly than those with tAD on all measures of perception and visuoconstruction.

The Rey-Osterrieth Figure Copy test of visuoconstruction produced a very large and significant effect (Hedges g_w = -2.79). A post-hoc sensitivity analysis (see Appendix D), was conducted due to evidence of significant heterogeneity between studies (I^2=91.3%, Q =57.13, df =5, p <.0001). Nestor et al. (2003) was excluded from the analysis, based on their use of visuospatial deficits, rather than clinical criteria, to diagnose PCA participants resulting in lowered (though still high) heterogeneity (I^2=85.9%, Q =28.43, df =4, p <.0001) but consistent results.

Large and significant effect sizes were also produced for all measures of object perception: Navon Figure (Hedges g_w = -1.36); Views Unusual (Hedges g_w = -

0.97); Views Usual (Hedges g_w = -1.27); VOSP Fragmented letters (Hedges g_w = -1.65); and VOSP Object Decision (Hedges g_w = -1.5). However, there was evidence of significant and very large heterogeneity between the studies that used the Views Unusual test (I^2=79.3%, Q=4.83, df=3, p=0.02. As it was not possible to conduct a sensitivity analysis due to sample size (k=2), results for this test should be considered with caution.

In tests of space perception, two measures produced medium, significant effects: the HVOT (Hedges g_w = -0.69) and VOSP Number Location (Hedges g_w = -0.69), and the remaining three measures produced large, significant effects: VOSP Number Location (VOSP Dot Counting (Hedges g_w = -1.53), VOSP Cube Analysis (Hedges g_w = -1.98), and VOSP Position Discrimination (Hedges g_w = -1.12).

The VOSP Dot Counting also had problems regarding high heterogeneity (I^2=77.9%, Q=18.1, *df*=4, p<0.01), though a post-hoc sensitivity analysis excluding Nestor et al. (2003) produced lower heterogeneity (I^2=59.3%, Q=7.37, *df*=3, p=0.06) and consistent results (see Appendix D).

3.3.2 Cognitive domains that did not discriminate between PCA and tAD

Three measures of global functioning (ACE, MMSE and MoCA) and three measures of visual abilities and language (Category Fluency, FAS and Boston Naming test) were used by two or more studies and none of these measures produced significant effects.

From the memory domain, Face Recognition, Digit Span Forward and Pyramids & Palm Trees also produced non-significant effects (see Table 5).

3.3.3 Cognitive domains that discriminated between PCA and HC

Global Functioning

Two measures of global functioning, the ACE and MMSE, were used by two or more studies and produced large, significant effect sizes (Hedges g_w = -3.68 and Hedges g_w = -2.67 respectively). Suggesting that people with PCA performed worse than HC.

Auditory Verbal Memory

Five measures of auditory verbal memory were used by two or more studies, all of which produced large, significant effects: RAVLT Immediate (Hedges g_w = -1.61); Digit Span Forward (Hedges g_w = -1.11); Digit Span Backward (Hedges g_w = -2.46); RAVLT Delay (Hedges g_w = -1.67); and Pyramids & Palm Trees (Hedges g_w = -1.63). This suggests that persons with PCA performed more poorly than those with HC on these measures

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_w = -1.73 and Hedges g_w = -0.99 respectively). This suggests that persons with PCA performed more poorly than those with HC on these measures.

Perception

The Rey-Osterrieth Figure Copy test of visuoconstruction produced a very large and significant effect (Hedges g_w = -2.79). A post-hoc sensitivity analysis conducted due to evidence of significant heterogeneity between studies (I^2=94.6%, Q =55, df =3, p <.0001), produced consistent results (see Appendix D). This was after Nestor et al. (2003) was excluded from the analysis.

Large and significant effect sizes were produced for all measures of object and space perception: VOSP Fragmented letters (Hedges g_w = -3.15); and VOSP Object Decision (Hedges g_w = -1.76); VOSP Dot Counting (Hedges g_w = -2.55); VOSP Cube Analysis (Hedges g_w = -4.01); and VOSP Position Discrimination (Hedges g_w = -2.29).

Table 5

Posterior Cortical Atrophy and typical Alzheimer's Disease: Weighted Hedge's *g* effect sizes for each test

	K	N Participants (PCA/tAD)	Mean Hedges g_w (95% CI)	I^2	Q(df)	Reference
Global Functioning						
ACE †	3	45/75	-0.13(-0.55, 0.29)	17.7%	2.43(2)	*Ahmed et al. (2016a), Ahmed et al. (2016b), Ahmed et al. (2018a)*
MoCA	2	24/27	-0.75(-1.92, 0.43)	66.4%	2.98(1)	*Li et al. (2018), Wang et al. (2015)*
MMSE	13	363/326	-0.12(-0.33, 0.09)	34.6%	18.36(12)	*Charles et al. (2005), Firth et al. (2019), Kas et al. (2011), Li et al. (2018), Magnin et al. (2013), McMonagle et al. (2006), 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)*
Verbal Memory						
Immediate Memory						
RAVLT Immediate	2	32/33	0.72(0.22, 1.22)	0%	0.01(1)	*Ahmed et al. (2018a), Ahmed et al. (2018b)*
Working Memory						
Digit Span Forward	8	193/183	-0.25(-0.54, 0.04)	43%	12.27(7)	*Aresi et al. (2009), Firth et al. (2019), Li et al. (2018), Mendez et al. (2019), Nestor et al. (2003), Peng et al. (2016), Suarez-Gonzalez et al. (2016), Yong et al. (2014)*
Digit Span Backward	9	250/257	-0.46(-0.64, -0.27)***	5.6%	8.47(8)	*Firth et al. (2019), Li et al. (2018), Mendez et al. (2019), Migliaccio et al. (2009), Miller et al. (2018), Nestor et al. (2003), Peng et al. (2016), Suarez-Gonzalez et al.*
Delayed Memory						
RAVLT Delay	3	47/48	0.56(0.15, 0.98)*	0%	0.034(2)	*Ahmed et al. (2018a), Ahmed et al. (2018b), Charles et al. (2005)*
CVLT Delay †	3	94/103	0.86(0.14, 1.58)*	74.4%	7.81(2)	*Migliaccio et al. (2009), Miller et al. (2018), Peng et al. (2016)*
Semantic Memory						
Pyramids & Palm Trees	2	22/22	-0.14(-1, 0.72)	48.6%	1.95(1)	*Ahmed et al. (2018b), Nestor et al. (2003)*
Visual Memory						

Face Recognition	3	105/67	0.11(-0.2, 0.42)	0%	0.71(2)	*Firth et al. (2019), Peng et al. (2016), Yong et al. (2014)*
Verbal Abilities and Language						
Category Fluency						
Category Fluency †	8	168/205	-0.031(-0.46, 0.40)	72.6%	25.56(7)**	*Ahmed et al. (2018b), Li et al. (2018), Mendez et al. (2019), Migliaccio et al. (2009), Miller et al. (2018), Nestor et al. (2003), Peng et al. (2016), Suarez-Gonzalez*
Phonemic Fluency						
FAS	2	22/31	-0.03(-0.58, 0.52)	0%	0.75(1)	*Ahmed et al. (2018), Nestor et al. (2003)*
Naming						
Boston Naming Test	5	124/143	-0.19(-0.51, 0.12)	31.1%	5.81(4)	*Charles et al. (2005), Li et al. (2018), Migliaccio et al. (2009), Miller et al. (2018), Suarez-Gonzalez et al. (2016)*
Perception						
Visuoconstruction						
Rey-Osterrieth Copy	6	74/93	-2.79(-4.2, -1.38)***	91.3%	57.13(5)***	*Ahmed et al. (2018b), Aresi et al. (2009), Charles et al. (2005), Li et al. (2018), Migliaccio et al. (2009), Nestor et al. (2003)*
Object Perception						
Navon Figures	2	22/30	-1.36(-1.98, -0.74)***	0%	0.79(1)	*Li et a (2018), McMonagle et al. (2006)*
Views (Unusual)	2	94/68	-0.97(-1.78, -0.16)*	79.3%	4.83(1)*	*Firth et al. (2019), Yong et al. (2014)*
Views (Usual)	2	94/68	-1.27(-1.69, -0.85)***	24.1%	1.31(1)	*Firth et al. (2019), Yong et al. (2014)*
VOSP Fragmented Letters	4	130/104	-1.65(-1.95, -1.35)***	0%	2.25(3)	*Firth et al. (2019), Nestor et al. (2003), Suarez-Gonzalez et al. (2016), Yong et al. (2014)*
VOSP Object Decision	3	142/87	-1.5(-1.8, -1.19)***	0%	0.51(2)	*Firth et al. (2019), Nestor et al. (2003), Yong et al. (2014)*
Space Perception						
VOSP Number Location	4	159/106	-0.89(-1.2, -0.58)***	19.7%	3.74(3)	*Firth et al. (2019), Migliaccio et al. (2009), Suarez-Gonzalez et al. (2016), Yong et al. (2014)*
VOSP Dot Counting	5	153/121	-1.53(-2.2, -0.87)***	77.9%	18.1(4)**	*Ahmed et al. (2018b), Firth et al. (2019), Nestor e al (2003), Suarez-Gonzalez 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. (2018b), Nestor et al. (2003), Suarez-Gonzalez et al. (2016)*

VOSP Position Discrimination	3	110/91	-1.12(-1.75, -0.5)**	65%	5.7(2)	*Ahmed et al. (2018b), Firth et al. (2019), Suarez-Gonzalez et al. (2016)*
HVOT	2	17/38	-0.69(-1.28, -0.1)*	0%	0.76(1)	*McMonagle et al. (2006), Mendez et al. (2019)*

Hedges g_w, weighted effect size; 95% Cl, 95% Confidence Intervals; I^2, heterogeneity between studies; Q, sampling error; df, degrees of freedom; *p<0.5, ** p<0.01, ***p<0.001; † Different test editions

Table 6

Posterior Cortical Atrophy and Healthy controls: weighted Hedge's *g* effect sizes for each test

	K	N Participants (PCA/HC)	Hedges g_w (95% CI)	I^2	Q(df)	Reference
Global Functioning						
ACE †	2	33/55	-3.68(-4.37, -2.98)***	0%	0.06(1)	*Ahmed et al. (2016), Ahmed et al. (2018)*
MMSE	7	203/199	-2.67(-3.21, -2.14)***	66.5%	17.93(6)	*Crutch et al. (2013), Firth et al. (2019), Kas et al. (2011), Magnin et al. (2013), McMonagle et al. (2006), Migliaccio et al. (2009), Nestor et al. (2003)*
Verbal Memory						
Immediate Memory						
RAVLT Immediate	2	32/49	-1.61(-2.12, -1.1)***	0%	0.03(1)	*Ahmed et al. (2018a), Ahmed et al. (2018b)*
Working Memory						
Digit Span Forward	4	118/89	-1.11(-1.55, -0.68)***	40%	5(3)	*Aresi et al. (2009), Crutch et al. (2013), Firth et al. (2019), Nestor et al. (2003)*
Digit Span Backward	3	91/72	-2.46(-3.12, -1.8)***	51.4%	4.11(2)	*Crutch et al. (2013), Firth et al. (2019), Nestor et al. (2003)*
Delayed Memory						
RAVLT Delay	2	32/49	-1.67(-2.18, -1.14)***	0%	0.04(1)	*Ahmed et al. (2018a), Ahmed et al. (2018b)*
Semantic Memory						
Pyramids & Palm Trees	3	39/53	-1.63(-2.57, -0.70)**	56.4%	4.6(2)	*Ahmed et al. (2018a), Ahmed et al. (2018b), Nestor et al. (2003)*
Verbal Abilities & Language						
Category Fluency						
Category Fluency †	4	54/98	-1.73(-2.31, -1.15)***	52.3%	6.3(3)	*Ahmed et al. (2018a), Ahmed et al. (2018b), Crutch et al. (2013), Nestor et al. (2003)*

Phonemic Fluency						
FAS	4	54/98	-0.99(-1.5, -0.48)***	48.7%	5.85(3)	*Ahmed et al. (2018a), Ahmed et al. (2018b), Crutch et al. (2013), Nestor et al. (2003)*
Perception						
Visuoconstruction						
Rey-Osterrieth Copy	4	36/96	-9.84(-14.64, -5.04)***	94.6%	55(3)***	*Ahmed et al. (2018a), Ahmed et al. (2018b), Aresi et al. (2009), Nestor et al. (2003)*
Object Perception						
VOSP Fragmented Letters	3	103/71	-3.15(-3.8, -2.5)***	37.8%	3.21(2)	*Crutch et al. (2013), Firth et al. (2019), Nestor et al. (2003)*
VOSP Object Decision	3	131/80	-1.76(-2.11, -1.4)***	0%	0.54(2)	*Crutch et al. (3023), Firth et al. (2019), Nestor et al. (2003)*
Space Perception						
VOSP Dot Counting	5	144/111	-2.55(-3.4, -1.7)***	80.9%	21(4)	*Ahmed et al. (2018a), Ahmed et al. (2018b), Crutch et al. (2013), 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. (2018a), Ahmed et al. (2018b), Nestor et al. (2003)*
VOSP Position Discrimination	4	114/74	-2.29(-3.09, -1.49)***	68.5%	9.53(3)	*Ahmed et al. (2018a), Ahmed et al. (2018b), Firth et al. (2019), Nestor et al. (2003)*

Hedges $g_{w,}$ weighted effect size; 95% Cl, 95% Confidence Intervals; I^2, heterogeneity between studies; Q, sampling error; df, degrees of freedom; ***p<0.001, ** p<0.01, *p<0.5; † Different test editions

4.0 Discussion

4.1 Summary of findings

The neuropsychological tests that best discriminate between PCA and tAD are Rey Osterrieth-Copy, Navon Figures, Views (unusual and usual), VOSP (Fragmented Letters, Object Decision, Dot Counting, Cube Analysis, Position Discrimination), RAVLT Delay and Immediate, and CVLT delay (more impaired in tAD). Tests of language or visual memory did not distinguish between PCA and tAD. Compared to HC, PCA shows a global pattern of impairment with impairments in perception, auditory/verbal memory, working memory and language.

This is the first meta-analysis to examine the utility of specific neuropsychological tests to support the differential diagnosis of PCA and tAD something which is of key import given the need for timely and accurate diagnosis and subtyping of dementia (Shaji et al., 2018).

4.1.1. PCA vs tAD

The finding that all eleven measures of perception were useful for differentiating between PCA and tAD, is consistent with research and clinical observations (Crutch et al., 2012) that the most common neuropsychological deficits noted in individuals with PCA are visuoperceptual and visuospatial impairments (Lehman et al., 2011), whilst tAD patients are more likely to show marked deficits in verbal memory (Alves et al., 2013).

Relatively preserved memory in the early stages of illness is a well-documented neuropsychological feature of PCA (Crutch et al., 2012). The finding that the RAVLT-immediate test of verbal memory was useful in differentiating PCA from tAD groups, was therefore an expected finding. Poorer performance from tAD patients, compared to PCA patients, on two analysed measures of delayed verbal memory, also support clinical consensus that the presence of less impaired delayed verbal recall is a distinguishing factor in diagnosing PCA (Charles et al., 2005). Their ability to distinguish PCA patients from HCs, however, support our understanding that subtle impairments in memory are likely to develop in PCA participants at onset, and progress as they move towards a more global profile of cognitive impairment (Trotta et al., 2019).

PCA patients also had more difficulty on working memory tasks, and particularly in tasks that involved numbers (e.g. digit span), with noticeably more impaired performances on the backwards digit span, when compared to tAD patients. The finding that verbal working memory in PCA was particularly impaired in backward modalities is consistent with other recent research findings (Firth et al., 2019; Trotta et al., 2019). It might be explained by previously explored issues with the phonological loop in PCA, which supports working memory (Buchsbaum & D'Esposito, 2009). It could also be explained by impaired bilateral parietal lobe involvement, which is important in numerical processing (Nieder & Dahaena, 2009), or by well described dyscalculia in the PCA syndrome (Mendez et al., 2007; Tang Wai et al., 2004). In addition, while digit span backwards taps on working memory, it is also a complex cognitive task which requires the activation of spatial mental

imagery (Bartolomeo et al., 2005) which is a function effected by the pattern of atrophy involving posterior cortical regions (Bartolomeo et al., 2013).

At present, the relationship between visual memory and visuoperceptive abilities is still relatively unknown (Alves et al., 2013). The lack of tests selected to assess visual memory, therefore, seem consistent with clinical consensus that memory tests with explicit visual demands in encoding and/or retrieval are not be suitable for testing memory in individuals with PCA (Crutch et al., 2012). Across the 20 studies, only three used a short facial recognition test to assess visual memory, which yielded non-significant results when it's utility in differentiating PCA from tAD patients was examined. Impaired facial recognition has been documented in both tAD (Flicker et al., 1990) and PCA (McKhann et al., 2011) research. Though studies have found that PCA patients perform differently on tasks that require them to recognise facial identity versus facial emotions, with PCA patients performing more poorly on facial identity tasks, when compared to tAD (Pressman et al., 2019). Other research has also noted differences in performance between PCA and tAD participants on tasks that use famous vs (un)familiar faces (Werheid & Clare, 2007). Information beyond generic explanations of "short face recognition tasks" is therefore required to better understand this finding.

The finding that none of the three measures of verbal abilities and language were useful in differentiating between PCA and tAD run contrary to some research findings that language abilities are likely to be better preserved in PCA than tAD patients (Charles & Hillis, 2005; Rogers et al., 2006). However, a recent review conducted by Crutch et al. (2014) suggested that there is additional complexity to

consider when examining the language profile of PCA as language problems appeared to be a presenting complaint in five out of 14 PCA patients compared with four out of 16 early onset tAD patients (Mendez et al., 2001). Magnin et al. (2013) have also recently described a “logopenic syndrome” in a case series of PCA patients, who had prominent impairments in naming and fluency tasks.

Finally, given our understanding of prominent visuospatial impairments in PCA and marked verbal memory difficulties in tAD, it is understandable that brief screening tools, that aggregate performances on subtests testing both visuoperception and memory abilities to gage global cognitive function, will not be able to distinguish PCA from tAD participants. This is because, despite PCA patients performing more poorly on visuospatial subtests, and tAD patients performing more poorly on memory subtests (Ahmed et al., 2016b), collated scores would be similar and would not reflect these differences.

4.1.2 PCA vs HC

All PCA patients performed more poorly on all measures of cognition, when compared to HC, suggesting that all analysed measures could be considered useful in differentiating PCA from HC.

Our findings of large effect sizes suggest that visuoperception measures, such as the VOSP subtests and the Rey-Osterrieth Copy, would be specifically useful in a test battery, the finding of large differences in memory scores, and language,

between PCA vs HC suggest these should also be used. Our results also support the use of two global function measures, the ACE and MMSE, in differentiating PCA participants from healthy controls.

4.2 Limitations and Research Implications

There are a number of limitations to the current meta-analysis that warrant consideration. Firstly, a total of 114 tests were used across 20 studies to examine the cognitive profiles of individuals with PCA, tAD and HC and of these, only 23 tests could be used to aggregate primary research findings as they were used by two or more studies (Rosenthal, 1995). The effect sizes derived from the remaining 91 measures, which were used only by single studies were therefore not included in this analysis. The consequence of this is that there might be measures available, that have not been captured by this review, that do effectively differentiate PCA from tAD presentations.

Another limitation of this study is the lack of information available regarding disease duration in PCA and tAD groups. Given our understanding that the main differences between the neuropsychological presentations of the two illness, are most stark at disease onset, data on disease progression would have helped to contextualise differences in test performance. For example, PCA patients performing similarly on measures of immediate verbal memory when compared to tAD, is understandable in the context of advanced stage of illness, but less understandable at onset (Crutch et al., 2012)

In this meta-analysis, 20 studies that assessed the value of neuropsychological tests to differentiate PCA from tAD and HC were found. Studies were based on strict inclusion and exclusion criteria and therefore, studies that contained critical methodological flaws, such as failing to use clinical criteria to identify PCA and tAD, were excluded. Quality was nevertheless assessed and based on the AXIS quality criteria used here, most studies had a relatively low risk of bias. All studies relied on similar clinical criteria to identify their PCA and AD participants and presented their methodology in a clear enough way to allow replication. Yet, all of the 20 studies showed a high risk of selection bias, in that no information was offered to characterise non-responders, i.e. those approached to take part in the research but refused. This limitation might have a negative impact on the generalizability of the results from these studies.

4.3 Conclusions

Clarifying the boundaries between typical Alzheimer's disease and PCA has important implications for diagnosis, treatment and future research. Understanding the presence and extent of performance differences on neuropsychological tests between different dementia subtypes can improve diagnostic accuracy, reduce clinician testing time and enhance patient experience. It can also contribute to management decisions in dementia, including the functional and occupational impact and determination of opportunities for cognitive rehabilitation (Jacova et al., 2007). It can also contribute to the development of new, evidence informed, neuropsychological tests.

A practical objective for future research is to establish a common framework for cognitive screening, neuropsychological examination, and selection of cognitive outcome measures for trials involving individuals with PCA. This study recommends that the Rey Osterrieth-Copy, Navon Figures, Views (unusual and usual), VOSP (Fragmented Letters, Object Decision, Dot Counting, Cube Analysis, Position Discrimination), should all be systematically used in practice.

5. 0 References

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Part 2: Empirical Paper

Development and Validation of the "Addenbrooke's Cognitive Examination" as a Screening Test for Mild Cognitive Impairment in Hearing Impaired Individuals

Abstract

Background: Despite high comorbidity of age-related hearing loss in individuals with mild cognitive impairment (MCI), current tests are inadequate to screen for MCI in hearing-impaired populations.

Objectives: To develop a hearing-impaired version of the Addenbrooke's Cognitive Examination (HI-ACE-III) and assess whether it can be used as a screening tool for mild cognitive impairment (MCI), and accurately distinguish cognitively impaired people from healthy controls.

Method: In consultation with specialist neuropsychologists and older adults, the HI-ACE-III was developed by converting verbal instructions into a timed, visual PowerPoint (Microsoft Corp.) presentation. Two groups of subjects over the age of 60 were recruited; 29 had MCI and 30 were healthy controls. The HI-ACE-III was administered to both groups in order to establish diagnostic accuracy. the Rey-Osterrieth Complex Figure (ROFC), Spatial Span (SS) and Graded Naming Test (GNT), which are established non-hearing dependent measures, were also administered to assess convergent and divergent validity,

Results: A Receiver Operating Characteristic (ROC) analysis revealed an Area Under the Curve (AUC) of 0.856, achieving reasonable sensitivity (75.9%) and good specificity (86.7%) at an optimum cut-off of <92. All HI-ACE-III subtests shared statistically significant correlations with the other measures of cognitive functioning. Internal consistency of the HI-ACE-III was verified with Cronbach's alpha ($\alpha = .819$).

Conclusions: The results indicate that the HI-ACE-III is a sensitive and specific screening tool, with a good ability to diagnose patients with and without MCI. It is an

easy to use adaptation of an already familiar tool, which clinicians who screen for MCI in hearing impaired groups, could use to promptly identify individuals who might benefit from more extensive neuropsychological investigation.

1.0 Introduction

1.1 Mild Cognitive Impairment

Mild Cognitive Impairment (MCI) describes a state of cognitive functioning which falls below defined norms (Petersen, 2011). MCI is a known risk factor for dementia, with 29% of individuals with known MCI estimated to progress to develop the disorder (Roberts et al., 2014). There are currently four criteria associated with this clinical syndrome. Firstly, individuals present with an objective impairment in one or more cognitive domains that is greater than what is expected given their educational background or their age. Secondly, there is evidence of the impairment causing concern for either the individual, their family, or clinicians (especially when compared to premorbid functioning). Thirdly, their level of impairment is not severe enough to interfere with their instrumental activities of daily living (ADL). Finally, there is an absence of dementia (Petersen et al., 2013)

Roberts and Knopman (2013) collated the results from studies with large sample sizes of participants aged 60 and above and found prevalence estimates for MCI (according to the above criteria) ranged from 16% to 20%. Individuals with MCI are more likely to develop dementia than people without a recognised neurocognitive impairment and many studies have found them to experience greater mortality (Gale et al., 1996). Given the gravity and prevalence of the syndrome, continued research attention plays a vital role in contributing to the development of therapeutic interventions and better diagnostic processes and tools.

1.2 Hearing impairment

Age-related hearing impairment is the most common hearing disorder and a major cause of chronic disability in older age (Panza et al., 2015). Self-report questionnaires and audiometric measures are commonly used in the assessment of hearing impairment (Gates et al., 2003), though objective measures are considered to be more effective (Kamil et al., 2015). Pure-tone audiometry is considered the gold standard for assessment of hearing and with recent advances in technology, valid diagnostic pure-tone audiometry has been evidenced in natural environments in with portable devices (MacLennan-Smith et al., 2013).

Disabling hearing loss refers to hearing loss greater than 40 decibels Hearing Level (dB HL) in the better hearing ear in adults (World Health Organisation, 2020), though hearing loss more generally can be considered from an average hearing threshold of 26 dB or higher (World Health Organisation, 1991).

1.3 MCI and Hearing Impairment

There are many known risk factors for MCI including vascular and cardiovascular disease, neuropsychiatric conditions and systemic inflammations (Roberts & Knopman, 2013). Hearing impairment is also a known MCI risk factor. Numerous prospective studies have provided evidence for an independent relationship between central and peripheral hearing loss and cognitive decline (Lin et al., 2011). Whilst Meta-analyses have indicated that there is a significantly higher

risk of developing MCI among subjects with hearing impairments (Wei et al., 2017), the exact basis of this relationship is unclear.

Several tentative hypotheses regarding the relationship of hearing impairment to MCI have been explored in the literature. Firstly, due to its suspected involvement in accelerating cognitive decline, the possibility of hearing loss as a causal factor for MCI is being examined. Secondly, some authors have suggested that hearing loss may be a symptom of cognitive decline, as cognitive decline may reduce the cognitive resources that are available for auditory perception, increasing the effects of hearing loss. This is often referred to as the "cognitive load on perception hypothesis" (Martini et al., 2014). Thirdly, researchers have suggested that an underlying mechanism exists; one that is a common but unknown cause to both problems. This is known as the “common cause hypothesis” and it argues that cognition and sensory modalities appear to decline concurrently in older adults as a result of a common underlying factor (Lin & Albert, 2014). At present, there seems to be comparable evidence for each one of these hypothesise within the literature.

Nearly two-thirds of adults over 70 suffer from some degree of hearing loss, and many of these are unrecognized or undertreated (Chien & Lin, 2012). In an older population, the prevalence of both hearing loss and MCI is high with some studies finding risk ratios (RR) of 6.6 for people with MCI and hearing complaints (Da Costa Lopes et al., 2007).

1.4 Hearing impaired screening measures

Despite high comorbidity of hearing impairment and MCI and the recognised need to identify MCI (Petersen, 2004), current tests are inadequate to screen for MCI in a hearing-impaired population. At present, screening tools for cognitive impairment have a strong auditory component and require clients to follow oral instructions. Normal auditory processing and hearing thresholds are therefore assumed of the individuals being assessed and there is good evidence that common screening tools are impacted by hearing impairment (Utoomprurkporn et al., 2020). At present adaptations are seldom made in practice to accommodate these individuals (Pye et al., 2017). Misinterpretation of test instructions due to hearing loss could lead to poor scores that are unrepresentative of a person's true cognitive ability.

Hill-Briggs et al. (2007) found that older adults with hearing impairment perform more poorly on cognitive tests, even if the hearing impairment is not severe enough to prohibit standard verbal administration, making overdiagnosis a significant concern. Alternatively, wrongly attributing poor scores to hearing difficulties (when in reality they are the product of cognitive decline) could lead to an under-diagnosis of MCI (or increased reports of false negatives) and deprive people of proper treatment. It is therefore vital that suitable screening tools, whereby a person's performance is not affected by their hearing ability, continue to be developed.

Given the high comorbidity, and lack of currently available measures, the development of new measures is important. Screening measures appropriate for

hearing-impaired individuals would allow for more accurate diagnosis and earlier intervention for those who present with MCI. This could in turn, benefit treatment by improving an individual's self-motivation, self-esteem and confidence in their rehabilitation (Castiglione et al., 2016). Furthermore, adapted screening tools for this population would help researchers who are attempting to ascertain the etiological link between hearing loss and MCI.

While there has been a long-recognized clinical need for tests to reliably identify cognitive impairment, no studies have yet reported the sensitivity or specificity of adapted tests in detecting MCI among those with hearing impairments (Pye et al., 2017). However, there has been recent progress made in research focusing on tool development.

Lin et al (2017) adapted the Montreal Cognitive Assessment (MoCA), a short screening tool for MCI (Nasreddine et al., 2005), for the severely hearing impaired. The test was converted into a timed PowerPoint (Microsoft Corp.) presentation which displayed visual, rather than verbal instructions. 103 subjects, aged 60 and over, were recruited and screened for undiagnosed MCI. Findings showed that the HI-MOCA was easy to administer and worked as a reliable screening tool for the hearing impaired. However, the homogenous subject group of cognitively intact individuals did not allow for generalisability of findings. Further research is therefore required to validate the HI-MOCA for use on people with varying cognitive function.

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), originally developed by Randolph et al (1998), has also been adjusted to test hearing impaired subjects. Claes et al (2016) proposes to use the RBANS-H to explore the cognitive profile of hearing-impaired subjects before and after cochlear implantation. In a similar fashion to the HI-MOCA, the test will be accompanied by the use of a PowerPoint (Microsoft Corp.) presentation and oral instructions will be supported by written explanations.

Whilst this research outlines promising steps towards tool development, neither the HI-MoCA or the RBANS-H have yet been validated as screening tools for people with MCI and comorbid hearing loss. There is certainly a rationale for continued research attention focusing on adapting measures that give more in-depth analysis through provision of subscale scores (Mioshi et al., 2006) and that correspond with tools that clinicians are already familiar with.

1.5 Addenbrooke's Cognitive Examination

Formal neuropsychological assessment involving the standardized administration of a broad battery of measures by a trained professional remains the gold standard to identify cognitive changes that may be indicative of MCI (McLennan et al., 2010). However, in order to identify which individuals might benefit from more formal testing, there is a continued need for general practitioners to screen for MCI in high-risk groups (Langa & Levine, 2014). The brevity of the Mini-Mental State Examination (MMSE) has historically made it a popular tool for

cognitive screening amongst general practitioners (Pezzotti et al., 2008). However, multiple studies have demonstrated the MMSE's low sensitivity in the screening of cognitive impairment, especially in those with MCI (Arevalo-Rodriquez et al., 2015).

The Addenbrooke's cognitive examination (ACE) was developed as an extended cognitive screening tool (Hsieh et al., 2013) designed to detect cognitive impairment, and to overcome the neuropsychological omissions present in the MMSE (Folstein et al., 1975). It is composed of tests of attention, memory, language, fluency and visuospatial skills. It therefore offers a global cognitive overview of the individual as well as specifying their ability at each evaluated domain. This allows for a more comprehensive assessment view of the cognitive profile of the individual, helping to provide a differential diagnosis (Dudas et al., 2005; Rotomskis et al., 2015). Its ability to discriminate between controls and clients with amnestic MCI, and between controls and clients with mild Alzheimer's disease has also been previously demonstrated (Matias-Guiu et al., 2017).

The ACE-III has proven to be easy to use, acceptable to patients, and has shown excellent diagnostic utility in identifying cognitive impairment in a variety of clinical situations (Hsieh et al., 2013). It is familiar amongst clinicians and offers the opportunity to examine an individual's pattern of performance across the 5 subtests (Rotomskis et al., 2015). In addition, it has been found to have higher diagnostic accuracy than other common screening measures (Matias-Guiu et al., 2017).

1.6 Research aims

1. To develop a hearing-impaired version of the Addenbrooke's Cognitive Examination (ACE-III) (Hsieh et al., 2013): the HI-ACE-III, by converting verbal instructions into visual instructions displayed on a timed PowerPoint (Microsoft Corp.) presentation. To place emphasis on making the HI-ACE-III as internally consistent with the original ACE-III as possible.
2. To assess whether the HI-ACE-III (Hsieh et al., 2013) can be used as a screening tool for MCI for individuals with hearing impairment, and accurately distinguish cognitively intact from cognitively impaired people.
3. To ascertain cut-off points for the HI-ACE-III in order to aid diagnoses of MCI in a hearing-impaired population
4. To examine convergent and divergent validity of the HI-ACE-III by measuring correlations between subtests and established non-hearing dependent measures of visuospatial functioning, memory, spatial working memory and expressive language.

2.0 Method

2.1 Joint working

This was a joint project with Nattawan Utoomprurkporn, PhD student and qualified audiologist, and Mary Heatley, Trainee Clinical Psychologist. Three groups were recruited for the wider study to examine the validity of HI adapted versions of the MoCA and the ACE-III. The first group consisted of people living with dementia

and a hearing impairment. The second group, consisted of people with MCI and a hearing impairment and the final group, consisted of people with a hearing impairment but without a measurable cognitive impairment.

The current study considers the adaption and validation of the HI-ACE-III for individuals with MCI. Mary Heatley's thesis focuses on validating the HI-ACE-III for individuals with dementia and Nattawan Utoomprukporn's project focuses on validating the HI-MoCA for individuals with Mild Cognitive Impairment. Further information regarding individual contributions to the joint project can be found in Appendix E.

2.2 Ethics

Ethical approval for the study was obtained from NHS Research Ethics Committees (RECs). REC reference: 18/LO/1225. Participants were given information about the study at least 24-hours prior to participating (Appendix F) and were required to give informed consent prior to taking part (Appendix G).

2.3 Power calculation

Sample size was determined using the EasyROC tool developed by Goksuluk et al (2016). Power was calculated for using Receiver Operating Curve (ROC) analysis to address the main aims of the study. Alpha was set at 0.05 and beta was set at 0.8. The effect size for both tests was set at 0.7 based on the figure obtained from the predicted area under the curve (AUC) for the MoCA, which was 0.89 (Roalf et

al., 2013). A lower figure was used in order to ensure a conservative sample size estimate given the adaptation of the measure to an HI population. From this calculation, an appropriate sample size of 30 hearing impaired without cognitive impairment participants and 30 hearing impaired with MCI participants was determined.

2.4 Participants

Participants in the hearing-impaired without cognitive impairment group (HI group), were recruited from the Adult Audiology Hearing Aids Clinic at the Royal National Throat Nose Ear Hospital (RNTNEH) (see Figure 1). Participants in the hearing-impaired with MCI group (MCI-HI group), were recruited from the Camden and Islington Memory Clinics (see Figure 2), with MCI being diagnosed in accordance with the Petersen Criteria (Petersen et al., 2013). All participants were referred to take part in the study by a clinician involved in their care.

The presence of hearing loss in all participants was determined by a portable hearing screening device, which is a valid audiometry measure (MacLennan-Smith et al., 2013). Hearing loss was considered as an average threshold of 30dB or more. In the HI group, normal cognition was verified by using the General Practitioner Assessment of Cognition (CPCOG), a valid instrument for detecting cognitive impairment with good sensitivity (0.85) and specificity (0.86) (Brodaty et al., 2002). A GPCOG-patient score of 9 indicates no cognitive impairment. If the GPCOG-patient score lies between 5 and 8 the GPCOG-informant should be administered. To ensure participants in the study had normal cognition, GPCOG-patient scores and

GPCOG-informant scores needed to be higher or equal to 4 and 3 respectively (Brodaty et al., 2002).

Exclusion criteria for both groups

1. Uncorrected visual impairment and/or a physical disability which might inhibit performance on the written elements of the test.
2. Severe or profound hearing loss, which would be determined by a Pure Tone Audiometry (PTA) result of > 70dBHL.
3. Congenital or childhood-onset hearing loss.

Figure 1

Flowchart outlining the recruitment process for the HI Group

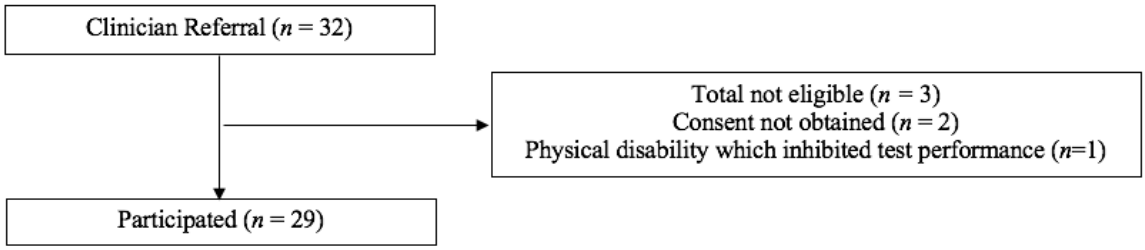
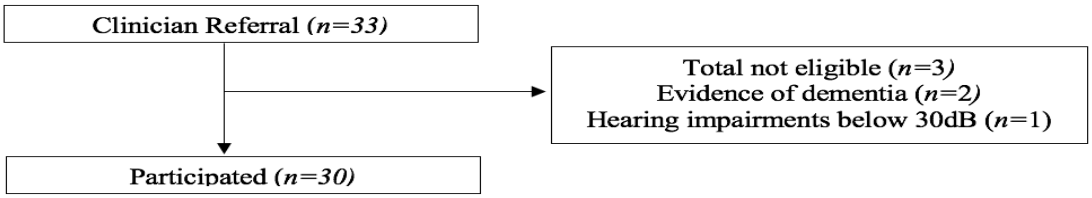


Figure 2

Flowchart outlining the recruitment process for the MCI-HI Group



2.5 Measures

All participants were examined using the Hearing Impaired Addenbrooke's Cognitive Examination III (HI-ACE-III) as well as the Rey-Osterrieth Figure Copy, Spatial Span and Graded Naming Tests – which were used to assess the construct validity of the HI-ACE-III. Tests selected either had minimal verbal instructions or were commonly presented in a non-verbal format. Adaptions made for non-verbal instructions for these measures were therefore not too dissimilar from the standardized version. Where there was a need to give brief instructions, short visual PowerPoint (Microsoft Corp.) presentations were developed to deliver instructions in a non-verbal manner.

Whilst there are not specific examples available in the literature for using written instructions for these measures, some incidences of researchers making pragmatic adaptations for hearing-impairment by creating written versions for hearing-dependent items have been cited (Pye et al., 2017).

2.5.1 Hearing Impaired Addenbrookes Cognitive Examination (HI-ACE-III)

The ACE-III is a validated and widely used cognitive screening tool, favoured for its brevity and ease of administration. It is a useful neuropsychological test for assessing the cognitive domain of attention, language, memory and visuospatial function (Hsieh et al., 2013). The ACE-III has good internal reliability, measured by Cronbach's α coefficient of 0.88 (Noone, 2015). Studies have demonstrated good sensitivity (93% to 100%) and specificity (96% to 100%) at the

common cut-offs for dementia and mild dementia, which are considered at scores lower than 82 and 88, respectively (Hsieh 2013; Velayudhan et al., 2014).

The original ACE-III was adapted for the purpose as described below in the procedure. The final version of the HI-ACE-III was presented on a visual PowerPoint (Microsoft Corp.) presentation on a computer screen. The contrast and colour of the characters (white) and background (blue) were selected to enhance the readability of the computer screen (Mills & Weldon, 1987). A manual was also developed to ensure standardization of administration across researchers. The manual, which is complete with screengrabs of the HI-ACE-III can be found in Appendix H.

2.5.2 Rey Osterrieth Complex Figure Test (ROCF)

Originally standardized by Osterrieth (1944), the ROCF is a brief and widely used neuropsychological test for the evaluation of executive function, visual memory and visuospatial constructional abilities (Shin et al., 2006). It has been found to have good interrater, test-retest and internal consistency reliability and validity procedures have confirmed the sensitivity of the ROFC to cognitive impairment (Berry et al., 1991).

There are three test conditions: Copy, Immediate Recall and Delayed Recall. All subjects are given a stimulus card (for copy condition) and asked to draw the same figure within each of the conditions. This study used all three test conditions to assess visuoconstructional abilities and visual episodic memory.

2.5.3 Spatial Span from the Weschler Memory Scale, 3rd edition

The Spatial Span (SS) test is a brief, standardized and widely used tool, which can be effectively used in the assessment of visuospatial short-term memory (Kessels et al., 2000; Chlebowski, 2011) and is frequently viewed as a non-verbal counterpart to the Digit Span test (Mammarella & Cornoldi, 2005). Research has found that it is a reliable and valid measure of attention, working memory and executive function (Vandierendonck et al., 2004; Ylioja et al., 2009). It involves remembering the order in which the examiner taps a set of blocks and takes approximately 5 minutes to complete.

2.5.4 The Graded Naming Test

Developed by McKenna and Warrington (1980), the Graded Naming Test (GNT) has been used extensively in cognitive neuropsychology to assess object naming ability. The psychometric properties of the GNT indicate that it is a valid and reliable tool for monitoring cognitive change (Bird et al., 2004). The test includes participants naming objects, grading in difficulty, presented to the participant by the tester. Reduced efficiency in retrieving the names of an object is indicative of impaired language functioning.

2.6 Procedure

2.6.1 Development of the HI-ACE-III

With permission from John Hodges (the copyright owner), the verbal instructions from the ACE-III were transformed into written format and transcribed onto a timed PowerPoint (Microsoft Corp.) presentation for seamless administration. After a preliminary presentation was developed, the adapted test was piloted on a small group of clinicians, specialist neuropsychologists, older adults and carers of people living with dementia. The presentation was then adapted based on commentary from 5 experts (neuropsychologists, psychiatrists and researchers working with people with dementia) and suggestions from the listed groups were incorporated to form the final HI-ACE-III. Following this, visual presentations were made for the administration of the Rey-Osterrieth, GNT and Corsi-block tapping tests.

2.6.2 Administration of measures for this study

Potential participants for both groups were approached by a clinician known to them in order to get their permission to be contacted by a researcher about the study (See Figure 1 and 2). Once identified, participants were scheduled to be seen at a place of their choosing, either in the clinic or at home, to complete research screening and give informed consent to participate. Participants were given the choice to complete the screening tests and the test battery (HI-ACE-III, ROFC, GNT and SS DSF and DSB) in one sitting or in two separate visits (if assessed as fitting inclusion and exclusion criteria).

2.7 Statistical Analysis

Statistical analysis was carried out with IBM Statistical Package for the Social Sciences (SPSS), Version 25.0

Demographic data was analysed using descriptive statistics and frequency analysis, as well as independent samples t-tests. Significance levels were considered as $p < 0.05$. A Welch two-samples t-test, used to adjust for unequal variances, was also conducted to examine the differences in performance on the HI-ACE-III scores between the HI and MCI-HI groups. A chi-square test of independence was performed to examine the relation between gender and cognitive status.

2.7.1 Hierarchical Multiple Regression

A hierarchical multiple regression was used to examine the unique contribution of cognitive status to variation in total HI-ACE-III score over and above participant age and years of education. Outliers for each regression model were investigated and removed if undue influence on coefficients was demonstrated. Assumptions of multivariate normality, no multicollinearity and homoscedasticity were all also tested and met.

2.7.2 Diagnostic accuracy of the HI-ACE-III

An empirical Receiver Operating Characteristics (ROC) analysis was conducted to establish the area under the curve (AUC). The AUC is a combined

measure that can offer a graphical illustration of the relationship between sensitivity and specificity. It is a measurement reflecting the overall performance of a screening tool in discriminating individuals with and without a diagnosis. Specific to this study, the AUC was used to determine the diagnostic ability of the HI-ACE-III for correctly classifying participants with and without MCI. An empirical ROC curve is non-parametric and as such, there are no assumptions about the underlying distributions of the data.

The closer the AUC is to 1.0, the better the overall diagnostic performance of the test (with an AUC value of 1.0 representing a perfect test). The practical lower limit for the AUC of a diagnostic test is 0.5. Values smaller than this are believed to constitute chance findings. According to established guidelines for interpreting AUC values, an AUC value of 0.7–0.8 is considered acceptable, 0.8–0.9 is considered excellent and higher than 0.9 is outstanding (Hosmer & Lemeshow, 2000).

2.7.3 Convergent and divergent validity of the HI-ACE-III

A correlation coefficient was used to investigate the association between the subtests of the HI-ACE-III and the outlined, non-verbal tests of cognitive function. Either the Pearson's product-moment correlation coefficient or the Spearman's rank correlation coefficient will be used, depending on whether assumptions for a Pearson’s correlation are met. These include level of measurement, related pairs, absence of outliers, normality of variables, linearity, and homoscedasticity.

2.7.4 Internal consistency reliability of the HI-ACE-III

In order to check reliability, Cronbach's alpha correlation coefficient was confirmed for each HI-ACE-III item. A value of .70 is considered the minimum acceptable value (Nunnally & Bernstein, 1994).

3.0 Results

3.1 Participant demographics

Descriptive statistics, including the mean (M) and standard deviation (SD) were used to explore the demographic characteristics of participants in the HI and MCI-HI groups (see Table 1). Shapiro-Wilk tests of normality and Levene's test of equal variance were conducted to ensure that demographic data met the assumptions for parametric testing.

Table 1

Participant Demographics

	n	Males (%)	Years of Education M(SD)	Age M(SD)
Healthy Controls	30	60	16.1(3.7)	75.3(5.9)
Mild Cognitive Impairment	29	48	13.2(4.2)	84.1(6.3)

Note: M = Mean; *SD* = Standard Deviation

An independent samples t-test was conducted to compare years of education and age between HI and MCI-HI groups. Participants in the MCI-HI group were found to be significantly older ($t(57) = -5.61$, $p < .001$), with fewer years of education ($t(57) = 2.78$, $p = .008$). A chi-square test of independence showed that there was no significant association between gender and cognitive status, $X^2 (1, N = 60) = .606$, $p = .44$.

3.2 HI-ACE-III scores

A Welch two-samples t-test was used to adjust for unequal variance. As expected, participants in the MCI-HI group had significantly lower HI-ACE-III total scores than their cognitively intact counterparts $t(38.2) = 25.4$, $p < .001$. Further Welch two-samples t-tests revealed a significant mean difference between the HI and MCI-HI groups across all cognitive domain composite scale scores (see Table 2). The MCI-HI group performed more poorly on tests of Attention $t(34.8) = 10.9$, $p = .002$; Memory $t(34.4) = 21.3$, $p < .001$; Fluency $t(51.3) = 7.9$, $p = .007$; Language $t(51.3) = 6.1$, $p = 0.17$ and Visuospatial abilities $t(34.6) = 20.1$, $p < .001$.

Table 2

HI-ACE-III scores

	Total M(SD)	Attention M(SD)	Memory M(SD)	Fluency M(SD)	Language M(SD)	Visuospatial M(SD)
HI	94.4(4.9)***	17.5(.7)**	24.4(1.8)***	12.1(1.9)**	24.9(2.4)*	15.4(.7)***
MCI-HI	83(11.2)***	16.2(2)**	19.7(5.2)***	10.4(2.6)**	23.1(3.3)*	13.6(2.1)***

Note: HI group $n = 30$, MCI-HI group $n = 29$; M = Mean; SD = Standard Deviation; *p<0.5, ** p<0.01, ***p<0.001

3.3 Hierarchical Multiple Regression

Given that groups differed in age and years of education, and both of these are possibly correlated with cognitive performance (Jubb & Evans, 2015), an exploratory hierarchical regression was conducted to determine the unique contribution of cognitive status over and above these variables in HI-ACE-III scores (see Table 3) and whether age and years of education might also be associated with between group differences in cognition. Assumptions of multivariate normality, no multicollinearity and homoscedasticity were all tested and met.

Cognitive status was included as a variable in the first block (Step 1) and contributed significantly to the regression model, $F(1,57) = 26.016$, $p < .001$. The adjusted R^2 was .301, indicating that cognitive status accounted for approximately 30% of the variation in total HI-ACE-III score.

In the second and final block (Step 2) participant age and years of education (YoE) were added to the analysis and the collective three variables contributed significantly to the regression model, $F(3,55) = 10.451$, p=<.001. The adjusted R^2 was .328 suggesting that the age and YoE explained an additional 2.8% of the variation in total HI-ACE-III score, which is not a statistically significant increase. Cognitive status was therefore the only significant predictor of the total HI-ACE-III score $t(55) = -5.101$, $p < .001$.

Table 3

Hierarchical Regression Analysis predicting total HI-ACE-III score

Predictor	Step 1			Step 2		
	b	*SE (b)*	β	*b*	*SE (b)*	β
Constant	94.40	1.572		121.947	16.555	
Cognitive Status	-11.434***	2.242	-.560	-8.013**	2.761	-.392
Age				-.374	.191	-.272
YoE				.037	.294	.015
Adjusted R^2	.301				.328	
F	26.016***				10.451***	
ΔR^2	.313				.050	
ΔF	26.016***				2.146	

Note. $n = 59$; $\Delta R^2 = R^2$ Change; $\Delta F = F$ Change * $p < .05$, ** $p < .01$ *** $p < .001$

3.4 Diagnostic accuracy

A Receiver Operating Characteristic (ROC) was calculated to evaluate the diagnostic accuracy of the HI-ACE-III in correctly identifying cognitively impaired from cognitively intact participants. The curve was constructed by plotting the proportion of true positives (sensitivity) vs the proportion of false positives (1-specificity). Figure 3 depicts the corresponding ROC curve. The AUC value was 0.856, 95% CI [0.756, 0.957] indicating that the HI-ACE-III has excellent diagnostic accuracy when identifying cognitively impaired subjects (Hosmer & Lemeshow, 2000) (see Table 4).

At an optimum cut-off score of <91.5, the largest Youden index of 0.626 was achieved, with sensitivity of 75.9% and specificity value 86.7%. At this cut-off, the

HI-ACE-III correctly classifies 84.6% of MCI cases or 22 individuals with MCI and 78.8% of cases without MCI or 26 individuals without MCI. As it is not possible to receive half marks in the ACE-III, clinical cut off should be considered as scores of 92 or less.

Table 4

ROC curve analysis of the HI-ACE-III

AUC	SE	95% CI	Cut-off Scores	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	YI
0.856	0.051	0.756 – 0.957	<90 <91.5* <92.5	72.4% 75.9%* 79.3%	86.7% 86.7%* 80%	84% 84.6%* 79.3%	76.4% 78.8%* 80%	0.591 0.626* 0.593

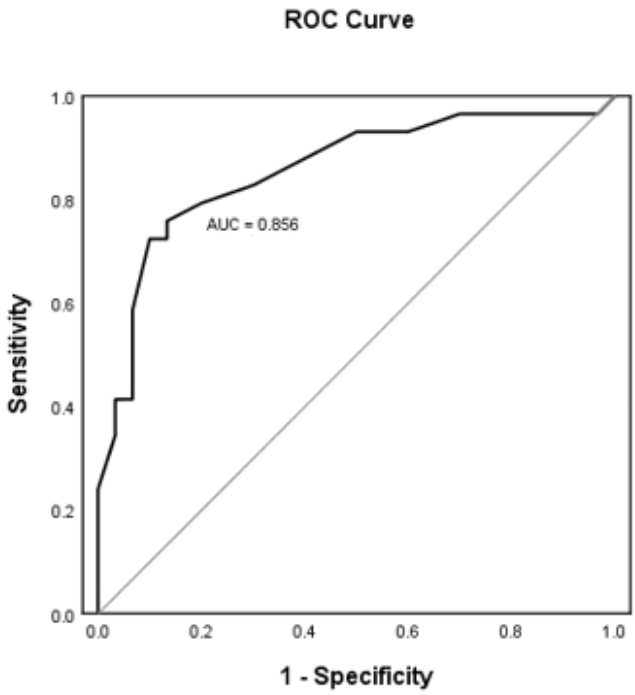


Figure 3. ROC curve for discriminating hearing-impaired individuals with MCI from hearing-impaired individuals who are cognitively intact using the HI-ACE-III

3.5 *Convergent and divergent validity*

This section will focus on responses from the MCI-HI group. Data from the HI group will be analysed separately in Mary Heatley's thesis.

Initial screening of the neuropsychological data was undertaken using Kolmogorov-Smirnov tests of normality for the MCI-HI group. Results revealed that only three variables were normally distributed: the DSF, Rey 3 mins and Rey 30 mins. Spearman rank-order correlations were therefore used as a non-parametric measure of association between the HI-ACE-III subtests and other measures of cognitive functioning. The correlation matrix for the MCI-HI group is provided in Table 5.

All HI-ACE-III subtests shared statistically significant correlations with the other measures of cognitive functioning. For attentional abilities, there was one significant correlation (ACE Attention and GNT, r_s = -.387). For memory, there were four significant correlations (ACE Memory and DSB, r_s = .481), (ACE Memory and Rey 3 mins, r_s = .537), (ACE Memory and Rey 30 mins, r_s = .516), and (ACE Memory and GNT, r_s = .502). For fluency there were two significant correlations (ACE Fluency and Rey Copy, r_s = .526) and (ACE Fluency and GNT, r_s = .376). For language abilities there was one significant correlation (ACE Language and GNT, r_s = .627). Finally, for visuospatial abilities there were four significant correlations (ACE Visuospatial and DSF, r_s = .473), (ACE Visuospatial and DSB, r_s

= .409), (ACE Visuospatial and Rey Copy r_s = .515) and (ACE Visuospatial and Rey 30 mins, r_s = .385).

Table 5

Correlation Matrix

	DSF	DSB	Rey Copy	Rey 3 mins	Rey 30 mins	GNT
ACE Attention	-.124	.407*	.070	-.069	-.007	**.387***
ACE Memory	.136	**.481****	.281	**.537****	**.516****	**.502****
ACE Fluency	.286	.336	**.526****	.345	.368	**.376***
ACE Language	.168	**.417***	.327	.102	.270	**.627*****
ACE Visuospatial	**.473***	**.409***	**.515****	.367	**.385***	.245

Data are presented as Spearman correlation coefficients
DSF = Digit span forward; DSB = Digit span backward; GNT = Graded Naming Test; ACE = Addenbrookes Cognitive Examination; *p<0.5, ** p<0.01, ***p<0.001
Significant correlations are in **bold**

3.6 *Internal reliability of the HI-ACE-III*

The internal reliability of HI-ACE-III for the MCI-HI group, as measured by Cronbach's coefficient, was high (α = .819).

4.0 Discussion

This study sought to address the recognised need for cognitive screening tests adapted to individuals with hearing loss (Hill-Briggs & Joyce, 2007; Pye et al, 2017) by developing a visual version of the ACE-III. The results indicate that the HI-ACE-III is a sensitive and specific screening tool, with a good ability to distinguish

between those with and without a mild cognitive impairment (AUC=0.86) (Mandrekar et al, 2010). According to the ROC analysis, the optimal cut-off for detecting MCI using the HI-ACE-III is 92/100, with scores higher than 92 indicating MCI, with a sensitivity of 75.9% and a specificity of 86.7%.

There are several studies available that have focused on the validity of the ACE and its associated versions, such as the ACE revised (ACE-R), in detecting MCI. Many of which have produced similar results, highlighting the ACE's overall ability to distinguish MCI from other groups, using cut-offs that fall between 92 and 94, which has also been supported here. Although content modifications were made for the ACE-R, specifically in the naming and visuospatial domains, the modifications were relatively minor. In addition, the cut-off points of ACE-III show strong correlations with the cut-off points of the ACE-R, the two versions are therefore highly comparable (Hsieh et al., 2013; Mioshi et al, 2006).

Pendlebury et al (2019) found that sensitivity and specificity for an ACE-R cut-off point of 94 were optimal (sensitivity = 83%, specificity = 73%) in MCI samples. Also using the ACE-R, Noone (2015) and Velayudhan et al (2014) published cut-off scores for detecting mild dementia at scores below 88, with a sensitivity of 100% and specificity of 96%. However, mild dementia is separate to MCI in that it is characterised by impairments that causes substantial interference with daily life (Knopman & Peterson, 2014). Individuals with MCI would therefore be expected to perform better on the ACE-III, which justifies the higher established cut-off point of <92.

Other studies that have evaluated the utility of the ACE-III for diagnosing MCI (Crawford et al, 2012) have done so with a slightly different approach to this study, highlighting the usefulness of the tool in detecting MCI in a wide range of populations. Matias-Guiu et al (2017) focused specifically on an amnestic presentation of MCI and calculated a good sensitivity of the ACE-III in distinguishing these individuals from controls who reported subjective cognitive impairment. In addition, Matias-Guiu et al. (2017), Takenoshita et al. (2019) and Wang et al (2017) all sought to validate ACE-III for diagnosing MCI in non-English speaking populations, all of which generally reported excellent diagnostic accuracy of the ACE-III or ACE-R, across and within different languages. These studies highlight the adaptability of the ACE and are consistent with our findings that modified versions of the ACE, are as good at detecting cognitive impairment as their original counterparts (Habib & Stott, 2019).

Measures of concurrent validity used in the current study show that the new HI-ACE-III correlates in expected ways with established tests of cognitive functioning. The HI-ACE-III memory subtest correlated with the DSB and ROFC recall, which are established measures of working memory (Kessels et al, 2000) and visual memory respectively (Berry et al, 2017). It also correlated highly with the validated test of naming (GNT), which is an association supported by previous findings (Martin et al, 2017; Mungus et al, 1985) and understandable given that the HI-ACE-III is a language-based memory test, albeit visually presented. The fluency sub-scale of the HI-ACE-III correlated highly with the ROFC and GNT, which is consistent with research evidence that phonemic and semantic fluency are related to

language abilities and executive functioning (Whiteside et al, 2016). Finally, as anticipated there were also significant associations between the separate ROFC conditions and the HI-ACE-III visuospatial subtest (Shin et al, 2006).

To the best of our knowledge, this is the first study to look at the concurrent validity of the ACE subscales, for any of its adapted versions, in an MCI population. However, results are consistent with findings that the subtests of the ACE-III have significant correlations with neuropsychological tests in corresponding domains in dementia populations (Bruno & Vignaga, 2019).

4.1 Limitations

A limitation of the current study is that the HI and MCI-HI groups differed considerably in terms of age and years of education. This is important, given that previous research has showed a strong connection between sensory and cognitive performance in old age (Anstey et al, 2003) and both age and education are linked to differences in performance on cognitive tests (Jubb and Evans, 2015). While an exploratory hierarchical regression found that adding age and education on top of group status did not result in a significant increase in variance in total HI-ACE-III scores. This potentially indicates that they were relatively unimportant variables in the current research, but future research attention might be directed towards conducting studies with matched controls, in order to control for confounding (Rose and Vanderleen, 2009).

Another recognised limitation is the different neural pathways that would be mapped on to in the processing of auditory versus visual instructions (Jaques et al, 2011). Previous research has tentatively suggested that visual instruction coding might be weaker in memory tasks due to a greater reliance on rehearsal processes that accompany verbal codes (Muhle-Karbe et al, 2017), whilst other studies have highlighted the likely dual role of visual and auditory processing in cognitive functions such as memory (Botzung et al, 2010). Whilst continued debate amongst neuroscientists make it difficult to fully evaluate this limitation, the construct validity of the use of this approach in the current study largely supported by the correlational findings. The study has also been careful to make only minimal modifications, necessary to achieving the study objectives.

Additionally, since the ACE-III is primarily a diagnostic screening tool, and not intended for the purposes of curating in-depth neuropsychological information, its most important quality is arguably it's sensitivity and specificity as opposed to construct validity of subscales.

4.2 Clinical implications

This study validates the use of the HI-ACE-III amongst populations with MCI and comorbid hearing loss. Therefore, in instances where clinicians are aware of diagnosed hearing impairments, the HI-ACE-III should be considered a specific and sensitive tool, appropriate for use in clinical settings.

However, as highlighted in the review of the literature, hearing impairments in older adults are commonly under-diagnosed and frequently unrecognized (Chien

& Lin, 2012). Therefore, in instances where clinicians do not have any information regarding sensory impairments, brief vision and hearing screening tests, might be considered in conjunction with cognitive tests. In general, this would allow for a greater understanding of how sensory impairments might impact cognitive evaluation (Pye et al, 2017). More specifically, it would allow for identification of individuals who might benefit from use of the HI-ACE-III, as well as recognise those who might not be able to cope with the increased visual demands of written instructions e.g. due to uncorrected visual impairments.

If there is evidence of multi-sensory difficulties, greater emphasis could be given to other methods of assessment, such as informant-reported functional and cognitive changes and patient history (Pye et al, 2017).

4.3 Directions for future research

To the best of our knowledge, this is one of the first studies to seek validation for any screening tool that has been adapted for individuals with age-related hearing loss. There are therefore several directions for future research to consider.

Firstly, more extensive exploration of the psychometric properties of the HI-ACE-III might strengthen the evidence which supports its use in populations with MCI and comorbid hearing loss. This might include testing the sensitivity and specificity of the tool in larger sample sizes; using controls matched for age and education; as well as expanding upon the battery of neuropsychological assessments used for assessing the concurrent validity of the HI-ACE-III. It might also involve conducting research in conditions which are more applicable to the types of settings

that screening tests are likely to be administered in, for instance, in memory clinics rather than participant homes.

Secondly, future research attention might be given to the validation of HI-ACE-III in individuals with cognitive difficulties that might not be conceptualised as MCI. For example, in the differential diagnosis of individuals with other common dementia's, such as Vascular Dementia (VD) or Frontotemporal Dementia (FTD). This is could be considered a realistic objective as the original ACE-III has already been objectively validated as a screening tool for cognitive deficits in FTD and AD (Hsieh et al, 2013).

Thirdly, whilst the research already outlines some promising steps towards tool development for other widely used screening instruments, such as the HI-MoCA or the RBANS-H, continued research attention is needed to validate these as screening tools for individuals with cognitive impairment. This would allow for more options for practitioners to choose from, allowing for factors such as tool familiarity, length and ease of administration to contribute to clinical decision making (Ahmed et al, 2018).

Finally, as commented upon in this study, there is very little research available on hearing-impaired adaptations on neuropsychological measures that might already be considered to have minimal verbal instructions. As the literature reveals that adaptations for these measures are already fairly common practice (Pye et al, 2017), research attention might be focused on providing objective evidence to this anecdotal understanding.

4.4 Conclusions

The HI-ACE-III has been found to be an accurate screening instrument in the detection of MCI in individuals with hearing impairment. It is an easy to use adaptation of an already familiar tool, which might aid clinicians, who screen for MCI in hearing impaired groups, to promptly identify individuals who might benefit from more formal testing.

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Part 3: Critical Appraisal

1.0 Introduction

This project gave me the opportunity to consider how clinicians might update their approach to neuropsychological testing in aging populations, by highlighting the need for nuanced measures in rarer dementias and in older adults with sensory impairments. I was able to do this in two parts. Firstly, by conducting a detailed literature review of neuropsychological testing in PCA and secondly by conducting empirical research into the use of screening tests in adults with MCI and comorbid hearing loss.

This critical appraisal will begin with some consideration of my professional context, and what drew me towards a research project in the field of neuropsychology. It will then reflect upon the challenges of the project, including the barriers to recruitment, dilemmas when selecting measures, and the navigation of the scientist-practitioner role. Within this it will consider how my personal experiences fit with the issues that are commonly cited in the literature. It will then give consideration to the conception and development of a new screening tool (the Hearing Impaired Addenbrookes Cognitive Examination (HI-ACE-III)) before discussing the impact of conducting research during a global pandemic.

1.1 Professional context

Prior to training I worked as an Assistant Psychologist in a forensic service, and my primary role was to complete new patient assessments under the supervision of the clinical neuropsychologist. This was my first introduction to cognitive testing

in clinical settings. Since starting training, I have been able to complete neuropsychological assessments in every clinical placement. This has included a Community Mental Health Team (CMHT), a Child and Adolescent Mental Health Service (CAMHS) a Looked After Children (LAC) service and importantly, a Regional Neurological Rehabilitation Unit (RNRU) which treated individuals with acquired brain injuries.

These experiences have highlighted to me the importance of neuropsychological evaluation in understanding the nature and origin of a wide range of difficulties. It has also supported my understanding of how in-depth analysis of an individual's cognitive strengths and weaknesses aids diagnosis and allows for specific and practical recommendations to be made for multi-disciplinary interventions (Silver et al., 2006). In my experience, it has helped clients to conceptualise their difficulties in a meaningful way and to understand the rationale behind their tailored rehabilitation plans (Yi & Belkonen, 2011). It has also prompted some meaningful interactions whereby screening tests have led to the removal of neuropsychological considerations in clinical formulations and have resulted in important investigations into psychosocial stressors (Schaefer et al., 2020). In addition, I have had the opportunity to work with individuals with rarer difficulties, such as PCA, and have witnessed how a diagnosis has led to relief and hope in patients and families (Harding et al., 2018).

2.0 Choosing a research topic

"I have posterior cortical atrophy or PCA. They say, rather ingenuously, that if you have Alzheimer's it's the best form of Alzheimer's to have. This is a moot point, but what it does do, while gradually robbing you of memory, visual acuity and other things you didn't know you had until you miss them, is leave you more or less as fluent and coherent as you always have been"

(Sir Terry Pratchett, Journal of Mental Health, 2010)

When the time came to choose a focus for Part 1 of this project, the literature review, I had some understanding that I wanted to concentrate on a rarer form of dementia. Dementia is an umbrella term for over 400 syndromes, the most common of which are Alzheimer's Dementia (AD), Vascular Dementia (VaD), Frontotemporal Dementia (FTD) and Dementia with Lewy bodies (DLB) (Ratnavelli et al, 2012). Of these, AD is the most studied (Karantzoullis & Galvin, 2011), attracts the most media coverage (Kirkman, 2006) and is the most focused upon by charities. Though this leads to increased funding for research, it has also contributed to public fear and a social construction of people with dementia that is potentially both prejudicial and dehumanising. Early-onset dementia's are some of the most commonly stigmatised and least understood of the dementia syndromes (Philipson et al, 2012). As echoed in the experiences of Terry Pratchett, written in the above quote, PCA unfortunately suffers from being misunderstood, and underestimated.

The dilemma I had when choosing a rare dementia, was that it had to have enough published research to collate and review. Though dementia costs the health and social care sector more than cancer and heart disease combined, it receives a disproportionately low amount of research investment. The majority of which goes to

studying AD (Luengo-Fernandez et al., 2015). Research available therefore, for the rarer dementia subtypes, was expectedly sparse. Interestingly, a study that took a very similar approach to understanding which cognitive tests best discriminate between AD and FTD, had the privilege of sorting through 2785 potentially suitable papers, the 93 selected of which looked at over 136 different cognitive tests yielding 1019 different test scores (Hutchinson & Mathias, 2007). In comparison, our database search identified 1011 potentially suitable records for PCA, of these only 20 studies fit the inclusion criteria.

This study therefore felt like an important step towards shining a light on PCA. Through our intention to prepare the paper for publication, we have had the opportunity to raise awareness of the disease, promote collaboration and hopefully stimulate more research. My draw towards PCA in particular was the apparent amount of anecdotal understanding that seemingly accompanied present day clinical decision making (for example, that visuospatial tests would best discriminate PCA from AD). This observation was echoed by leading researchers in the field, who upon reading the review, offered their view that evidence for testing in PCA was long-overdue. I had also personally experienced the need to rely on anecdotal information in my own clinical work, with a client with PCA. This research project therefore felt like a worthwhile opportunity to add evidence to practice.

Another draw towards PCA was its unique constellation of symptoms, that continue to demonstrate the important link between cognitive decline and sensory impairments, in older populations. This significant aspect of the syndrome supported

me to keep in my thinking, the wider-related issues commonly associated when splitting my time across the two papers.

3.0 Concurrent validity measures

Part 2 of this project, the empirical review, highlighted the challenges faced when choosing measures to assess convergent and divergent validity for the HI-ACE-III in a hearing-impaired population. This was because adapted measures, though commonly used (Pye et al., 2017), seldom had empirical support. This is in spite of even slight hearing impairments being found to cause barriers to the administration of verbal measures (Hills-Briggs et al., 2017). Options for validated neuropsychological measures, that were suitable for assessing convergent and divergent validity, were therefore sparse.

Whilst only measures that would require minimal adaptations on already minimal instructions were selected, this did somewhat prevent us from using potentially more suitable measures. For instance, the digit span test from the Wechsler Adult Intelligence Scale (WAIS) is a much more widely used and well researched alternative to the spatial span task (Maupin & Hunter, 1966; Orsini et al., 1988). It has also been used in other studies that have sought to validate the ACE in dementia populations (Hsieh et al., 2013). Additionally, measures of verbal learning such as the Rey Auditory Verbal Learning Test (RAVLT) and Free and Cued Selective Remining Tests (FSRT) have previously been found to correlate highly with the memory domain of the ACE-III (Hsieh et al., 2013; Mathias-Guiu et al., 2017). They have also demonstrated a greater association than other memory tests, including screening measures that are comparable to the ACE, such as the MoCA

(Lam et al., 2013). In addition, such verbal learning tests have previously been found to have a high sensitivity for diagnosis MCI and for stratifying the risk of progression to dementia (Sarazin et al., 2007). Our inability to use such measures was therefore not ideal.

Though our choosing of neuropsychological measures were somewhat constrained by practicalities, I think that our choice to use visual measures was preferable to other common approaches, such as the omission or substitution of verbal items from wider tests (Pye et al., 2017). Despite these being widely adopted methods (Dupius et al., 2015; Wittich et al., 2010) designed to navigate issues caused by sensory impairments, they have been found to introduce numerous confounds. One potential source of bias might be the under or over-estimation of cognitive ability depending on the level of challenge posed by the deleted items, which is something we have been able to avoid.

4.0 Challenges to recruitment

Recruiting older adult participants, with hearing impairments and evidence of cognitive decline, for the empirical study, was a difficult task. Whilst recruitment for individuals with MCI was somewhat more straightforward (as it relied primarily on clinician referrals), the recruitment of dementia participants posed marked challenges.

On many occasions, where clinician referrals were sparse, we were compelled to scope through the Camden and Islington clinical databases, for potentially eligible participants. Though this was a lengthy task, it was interesting to observe how our

experiences fit with the literature. Quite apparent to us was, that despite hearing impairment being a known risk factor for MCI and dementia (Wei et al, 2017), and nearly two-thirds of adults over 70 suffering from some degree of hearing loss (Chien & Lin, 2012), information on sensory impairments were rarely available in participant notes. Of the 706 individuals we assessed for eligibility, 161 did not have any information available on age-related hearing loss.

In addition, of these 706 individuals, 238 were not asked by clinicians in their care whether or not they would be interested in participating in research. This was in spite of prompts for "research consent" to be sought for each new referral and updated at each review. This fits with the information outlined in the World Alzheimer Report (2015), that highlights the disproportionately low amount of research time and financial investment received by dementia and associated illnesses.

5.0 Managing the scientist-practitioner role

Throughout data collection for the empirical project, I encountered a number of challenging interactions that felt difficult to manage as a scientist practitioner. As written in the information sheet presented to our participants, any concerns raised by performance of the tests used in our study, should be directed towards their GP. This prevented me from sharing any observation, reassurance or concern that I might have had regarding performance or barriers to performance on cognitive tests. This contradicted some of the neuropsychological supervision that I have received on placement which had emphasised the value of occasionally deviating from standardized procedures, in order to open the patient's experiential world and test

alternative responses or reactions to the assessment (Gorske, 2007). Thus, it felt like a move away from a preferred, more humanistic approach to testing.

Another trepidation was the occasional frustration observed in the participants, for example at the length of testing, or at their efforts to do well. At these times, consideration had to be given to the wellbeing of the participants as well as the standardized administration of the tests. Again, this was made difficult by our constraints as researchers, as it was not possible to give direct feedback in order to foster therapeutic relationships, in the same way that we might do in practice (Finn, 2003). More often than not, participant frustration therefore led to testing being terminated and rearranged for another occasion. Whilst this was the most sensible and compassionate response for our participants, it put increased demands on our time. Especially as any recruitment in the first place was found to be quite logistically difficult. With participants often needing a friend or family member to facilitate the meetings, due to difficulties with hearing telephone conversations, and/or with keeping appointments independently.

Frustration was also often met in part, with apprehensions about a diagnosis of dementia or MCI. In my experience of testing, many participants had some understanding that their difficulties had attracted a diagnosis, however they were less able take the severity or the functional impairment of their illness into consideration. Therefore, when tests revealed holes in their ability, distractions or compensatory explanations for performance, were often sought after.

The presence of a family member was experienced to be extremely helpful, but also on occasion, quite challenging. On the one hand, they were imperative to the

success of our study, and to the comfort of our participants who were gracious enough to invite us into their homes. Family members often helped with logistical problems, such as mobility of participants, set-up of furniture and readying the room for testing e.g. by minimising noise and sources of distraction. However, it was understandably difficult for family members to witness their loved ones perform poorly on tests, showcase their impairments and / or display sadness or anxiety related to their performance. When this happened, family members. often felt inclined to help, for instance, by offering clues that weren't part of the standardised instructions. Whilst this was not assessed to have made any significant impact on any participants performance, it was a difficult situation to manage in the moment.

6.0 COVID-19

> *"COVID-19 poses a risk not only to the health of older adults who contract the disease but also to those without the health care resources and social structures that contribute to overall wellness"*
>
> (John Hopkins University, 2020)

Dementia has emerged as a pandemic in an ageing society, with approximately 7.7 million new cases of dementia being diagnosed each year (Alzheimer's Disease International, 2019). The COVID-19 pandemic has raised great concerns for people living with dementia and their families, due to their vulnerability to the virus and their increased likelihood of exposure through supported living arrangements (Wang et al., 2013). In addition, it has highlighted great concern for the emotional welfare of these populations, due to countless and stark examples of older people being

misrepresented and undervalued in the public discourse surrounding the pandemic (Fraser et al., 2020). Ageism, expressed through age segregation, discrimination, prejudice, and stereotyping (Palmore et al., 2016), unfortunately, is not a new problem for adults living with cognitive impairments (George, 2010).

With these prejudices' in mind, and my already established concerns about the lack of research attention dedicated to dementia (as referenced above), ceasing recruitment prior to the lockdown on March 31st, was a disappointing decision. With Mary and I both working in clinical settings, we were at an increased risk of spreading the virus and thus were not willing to move between participant homes. This mostly effected our recruitment of dementia participants. Unfortunately, the uncertainty of the COVID-19 crisis is likely to have lasting effects, and concerns surrounding our ability to test more individuals with dementia (for the published paper) within the remaining time frame of our training, are also growing. Thus, we find ourselves in the uncomfortable position whereby the representation in our validation project is likely to be skewed towards the normal controls and the less impaired.

In addition to the challenges outlined above, and on a more personal note, completing a thesis in the context of lock-down did have its own had its own complications. My clinical and academic work had quite quickly become something that needed to be completed almost entirely from home. Along with the practical barriers, of being short of space in a full household, were also more emotive struggles. These included not being able to so easily check-in with fellow trainees for

support; finding it more difficult to divide time between work and rest; grappling with the coronavirus infection myself and the associated isolation – whilst trying to hold an emotional space for vulnerable clients on a new and unfamiliar placement.

7.0 Conclusion

This space for reflection has given me the opportunity to reflect on my position as a scientist-practitioner and the process of conducting research, from its conception to its dissemination. Within this I feel that I have built upon valuable skills from collaboration, to problem-solving and critical thinking. Despite some of the challenges that have been reflected upon is this appraisal, I have found working with older adults with cognitive impairments an invaluable and rewarding experience.

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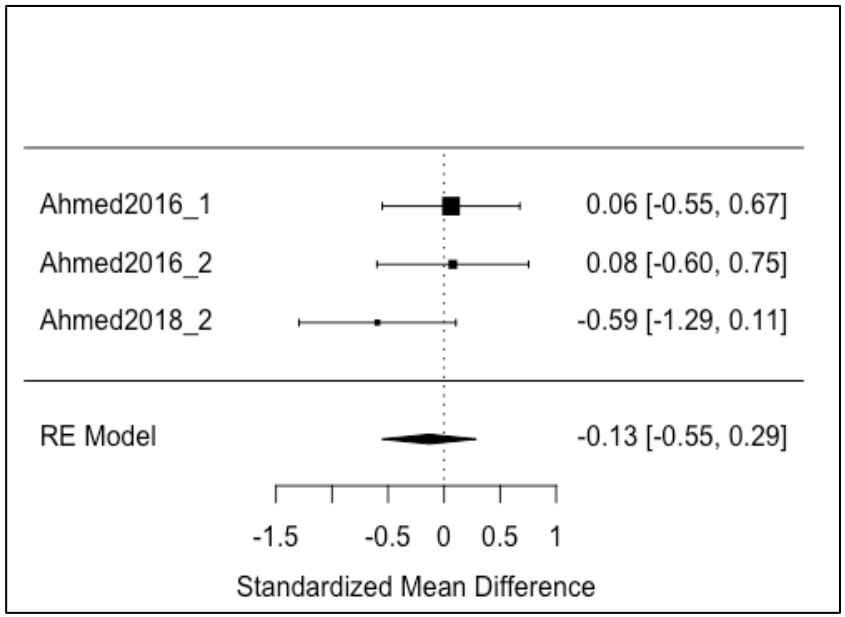
Appendices

Appendix A: Appraisal Tool for Cross-Sectional Studies (AXIS)

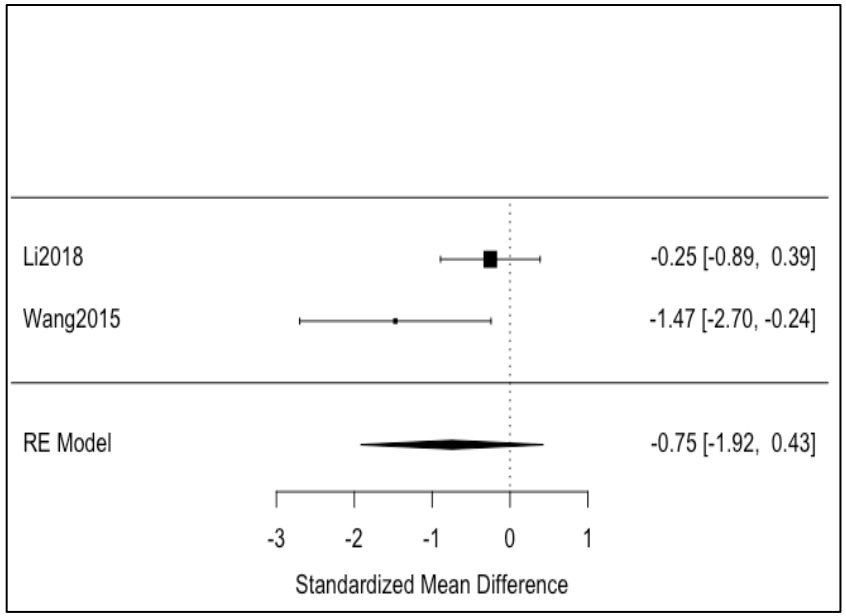
	Question	Yes	No	Don't know / comment
Introduction				
1	Were the aim/objectives of the study clear?			
Methods				
2	Was the study design appropriate for the stated aim(s)?			
3	Was the sample size justified?			
4	Was the target/reference population clearly defined? (Is it clear who the research was about?)			
5	Was the sample frame taken from an appropriate population base so that it closely represented the target/reference population under investigation?			
6	Was the selection process likely to select subjects/participants that were representative of the target/reference population under investigation?			
7	Were measures undertaken to address and categorise non-responders?			
8	Were the risk factor and outcome variables measured appropriate to the aims of the study?			
9	Were the risk factor and outcome variables measured correctly using instruments/measurements that had been trialled, piloted or published previously?			
10	Is it clear what was used to determine statistical significance and/or precision estimates? (e.g. p-values, confidence intervals)			
11	Were the methods (including statistical methods) sufficiently described to enable them to be repeated?			
Results				
12	Were the basic data adequately described?			
13	Does the response rate raise concerns about non-response bias			
14	If appropriate, was information about non-responders described			
15	Were the results internally consistent?			
16	Were the results presented for all the analyses described in the methods?			
Discussion				
17	Were the authors discussions and conclusions justified by the results?			
18	Were the limitations of the study discussed?			
Other				
19	Were there any funding sources or conflicts of interest that may affect the authors' interpretation of the results?			
20	Was the ethical approval or consent of participants attained?			

Appendix B: Forest Plots: PCA and AD

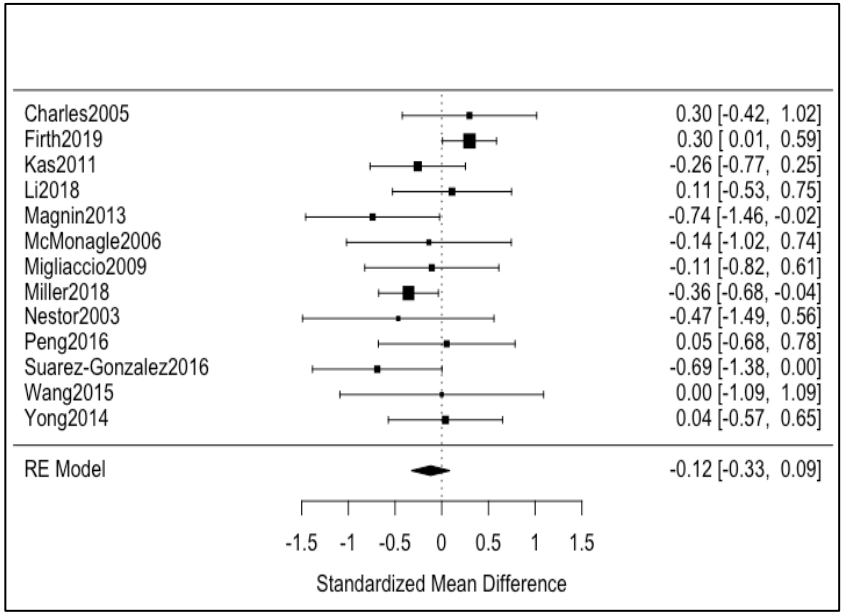
(A) ACE



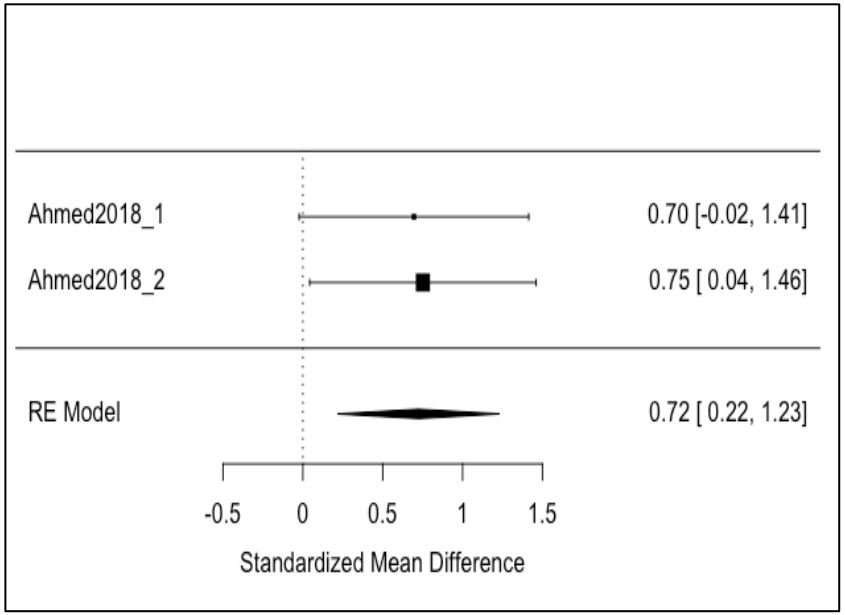
(B) MOCA



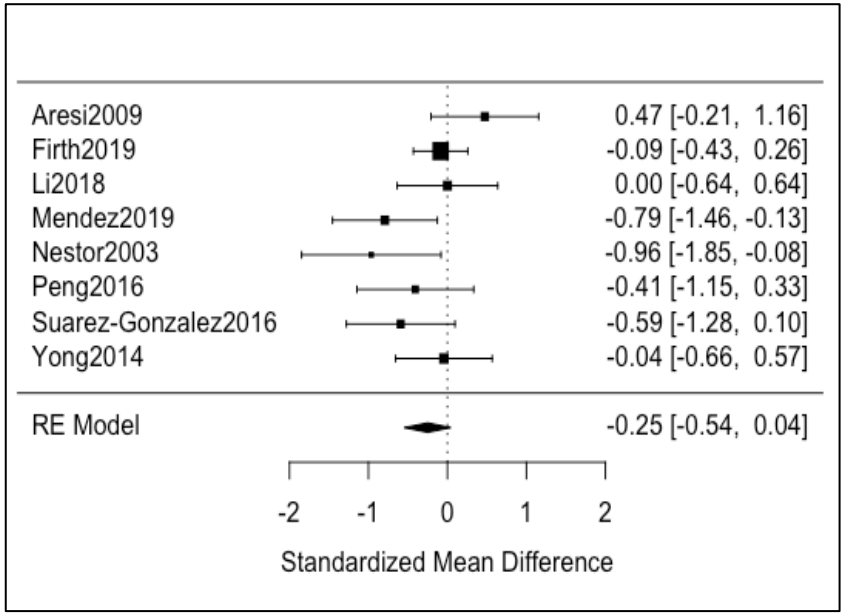
(C) MMSE



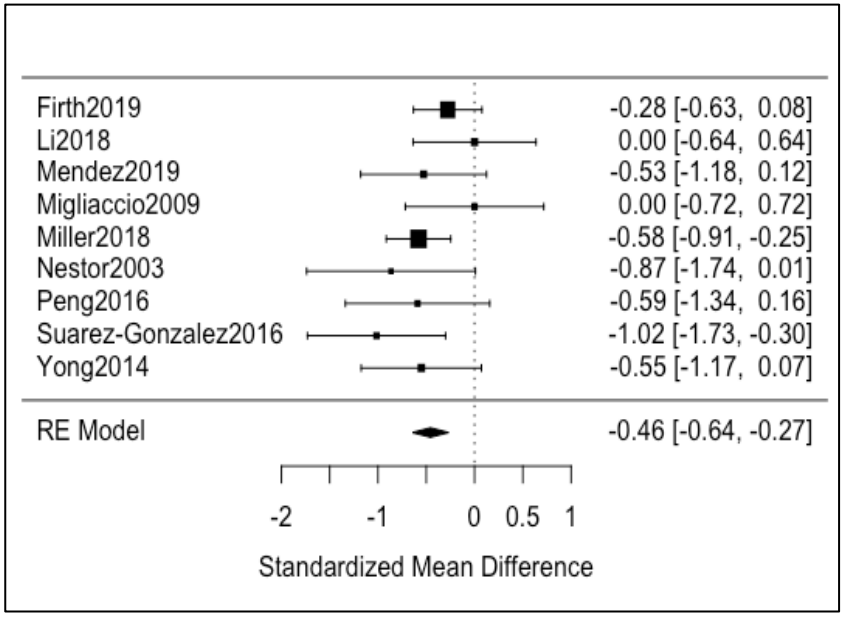
(D) RAVLT Immediate



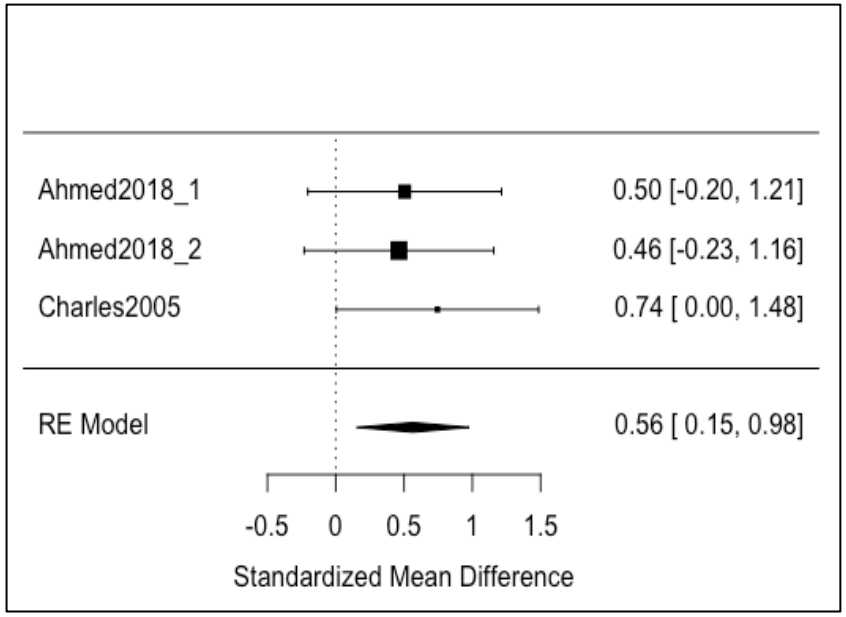
(E) Digit Span Forward



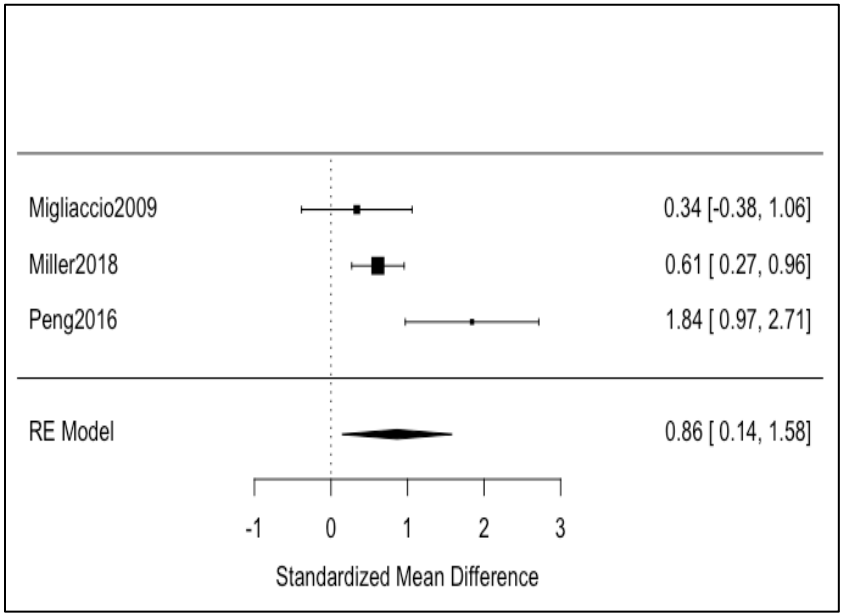
(F) Digit Span Backward



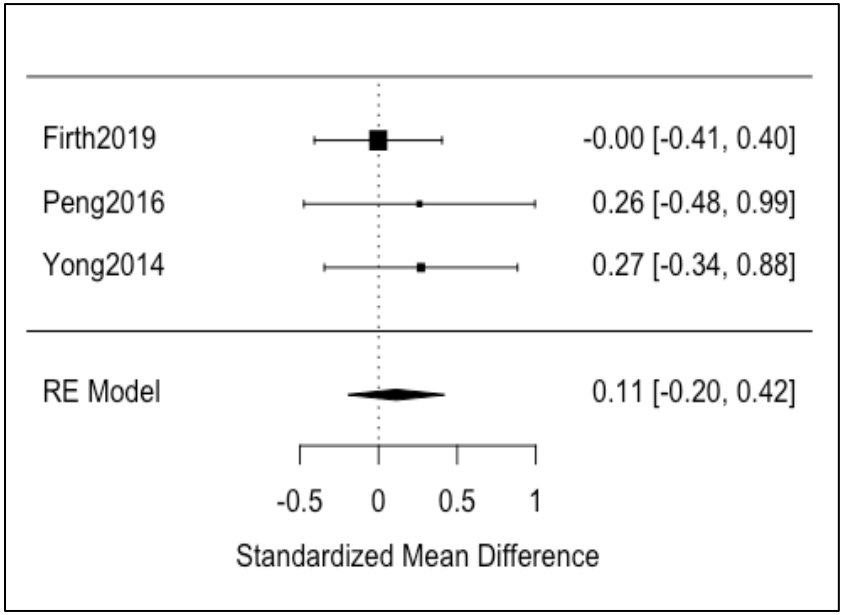
(G) RAVL Delay



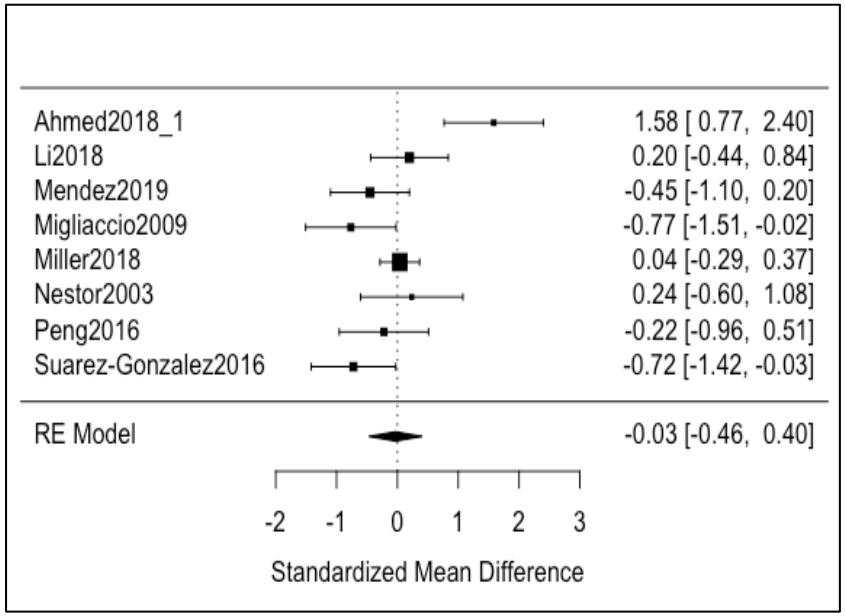
(H) CVLT Delay



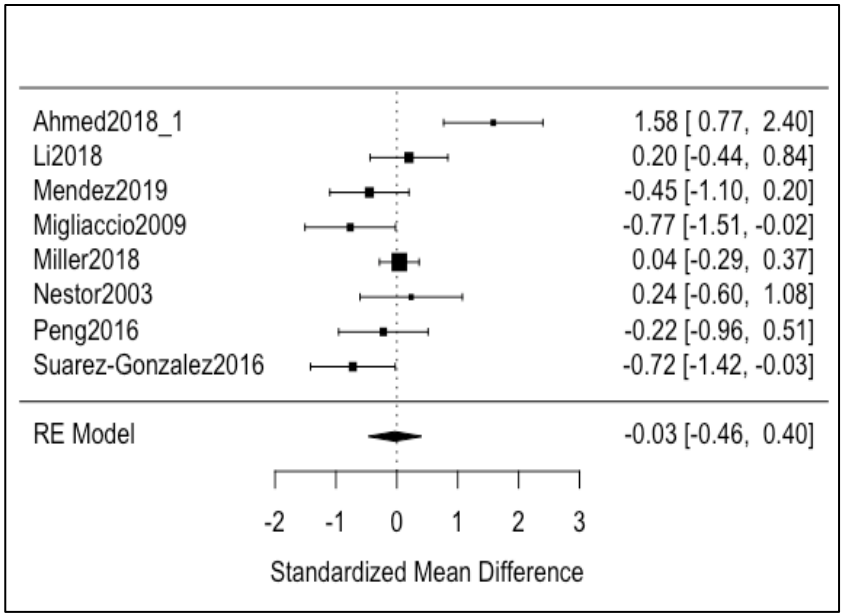
(I) Face Recognition



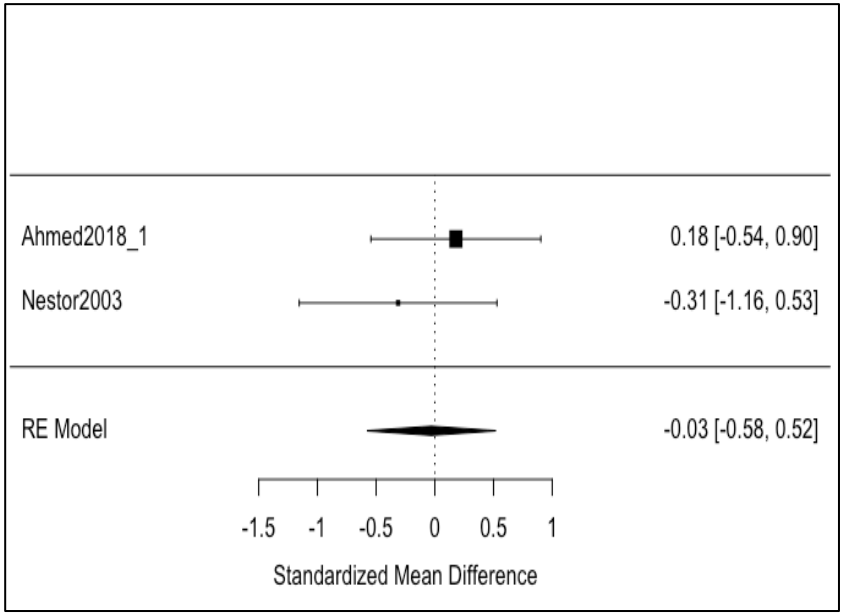
(J) Pyramids and Palm Trees



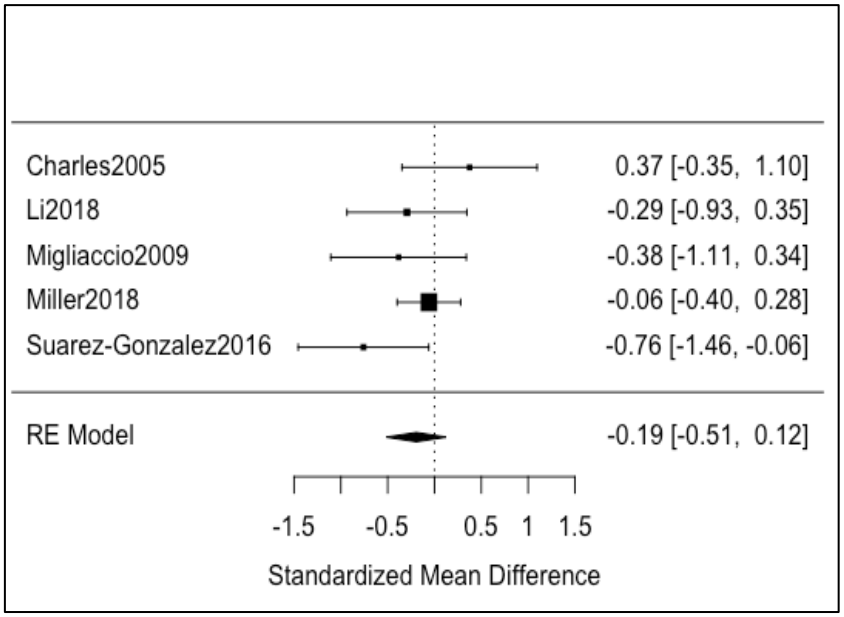
(K) Category Fluency



(L) FAS



(M) Boston Naming Test



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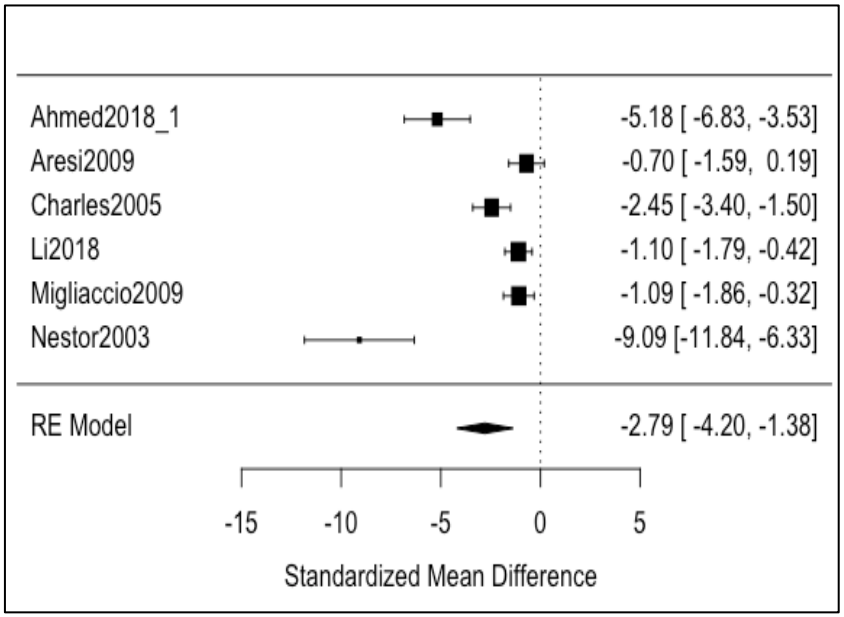
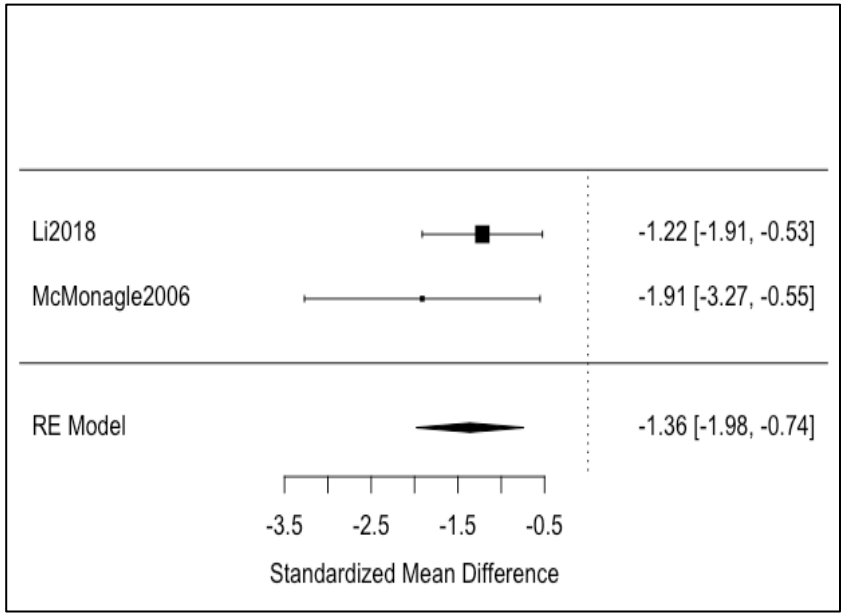
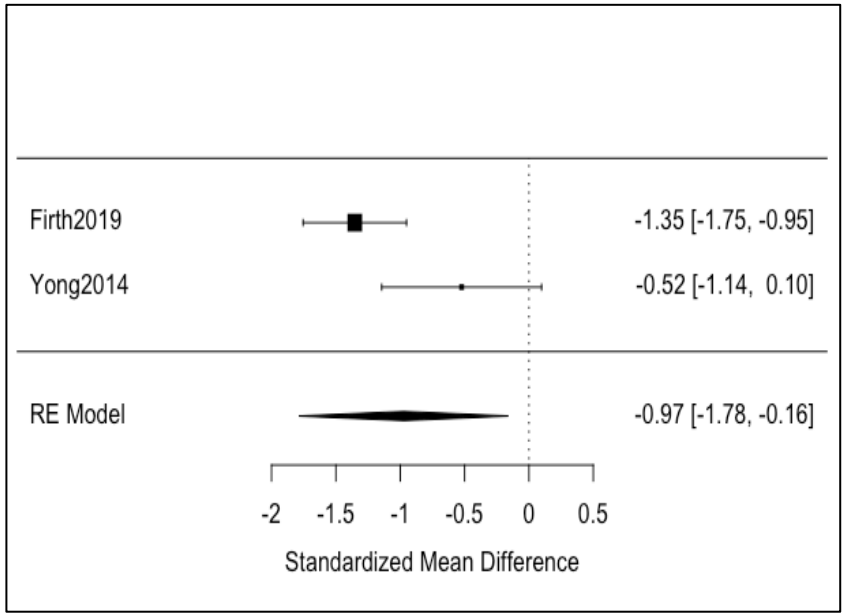


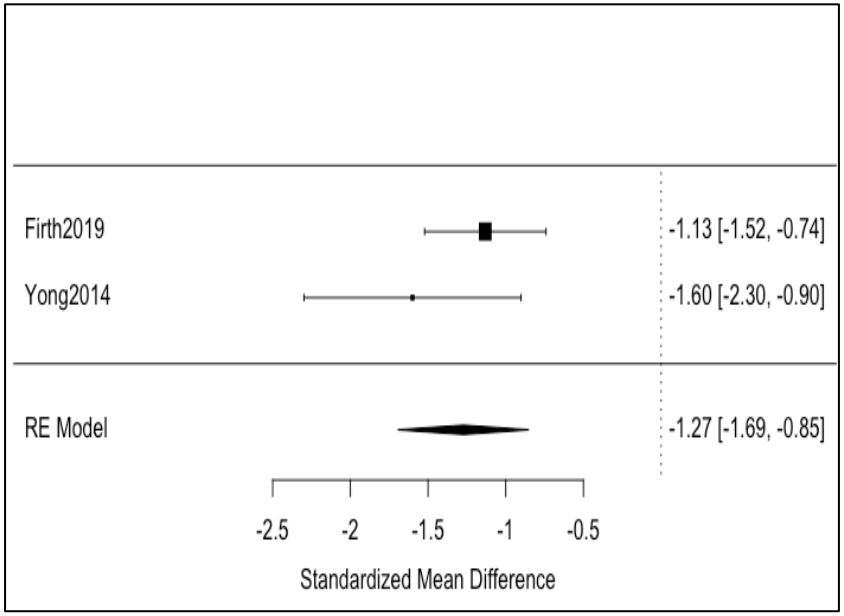
(O) Navon Figures



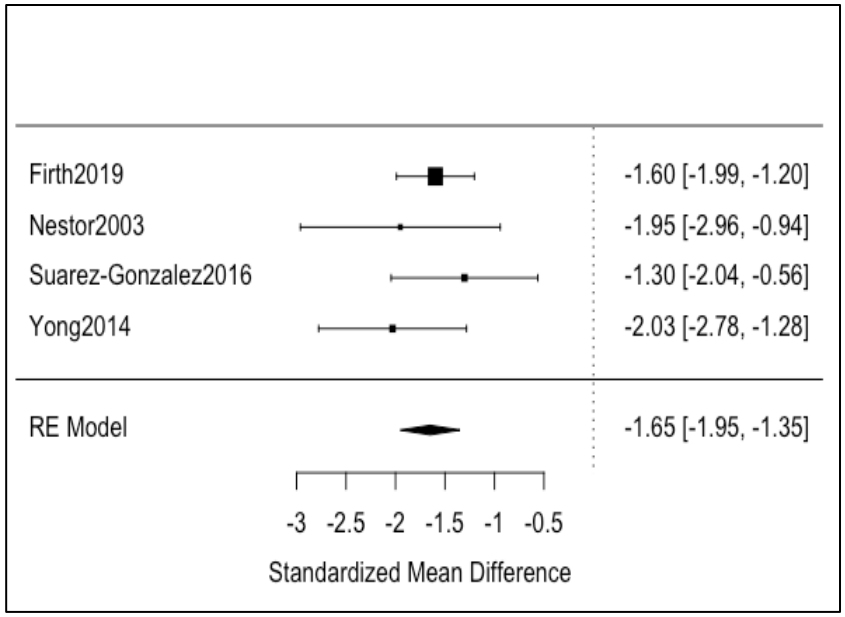
(P) Views (Unusual)



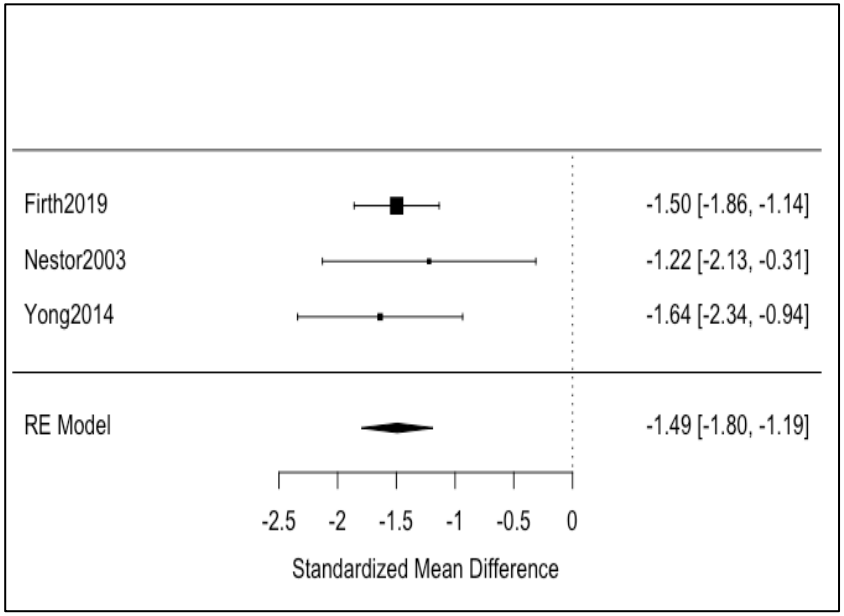
(Q) Views (Usual)



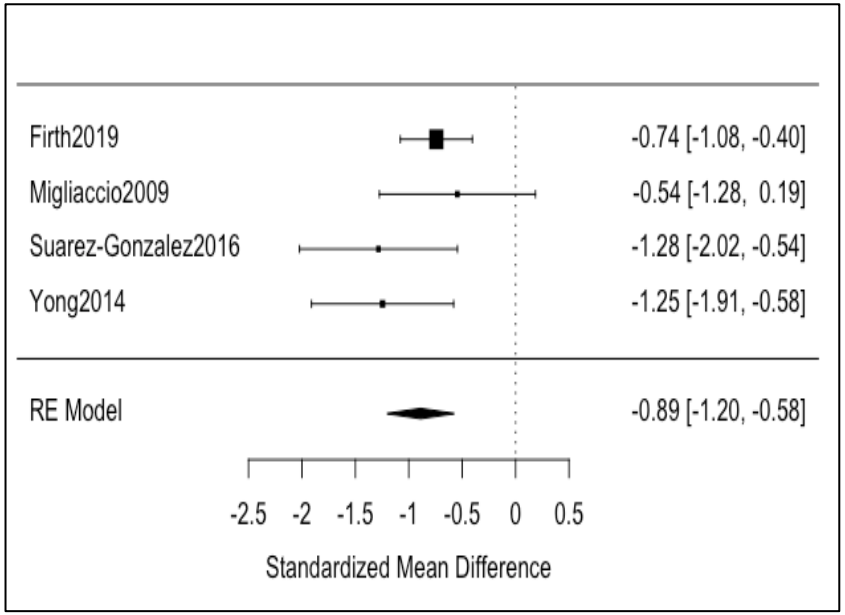
(R) VOSP Fragmented Letters



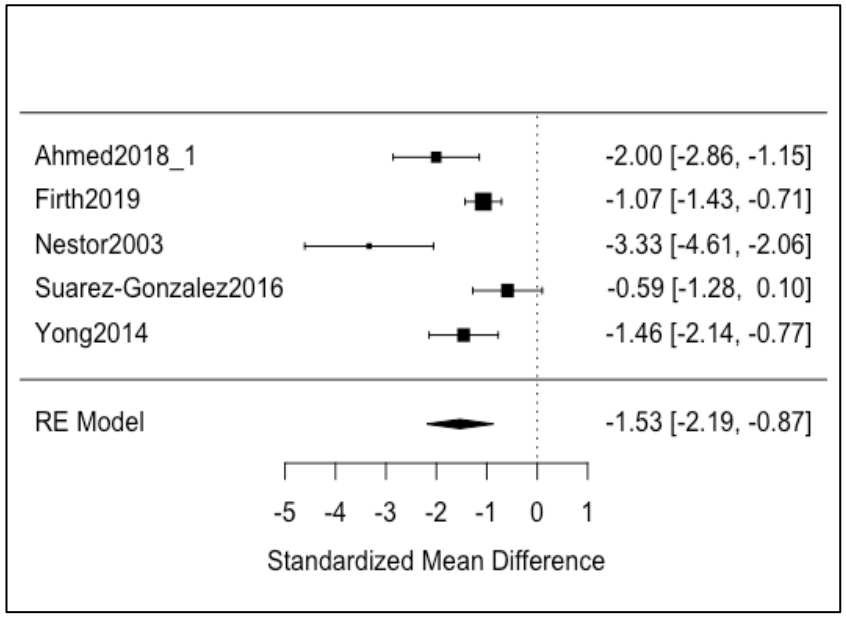
(S) VOSP Object Decision



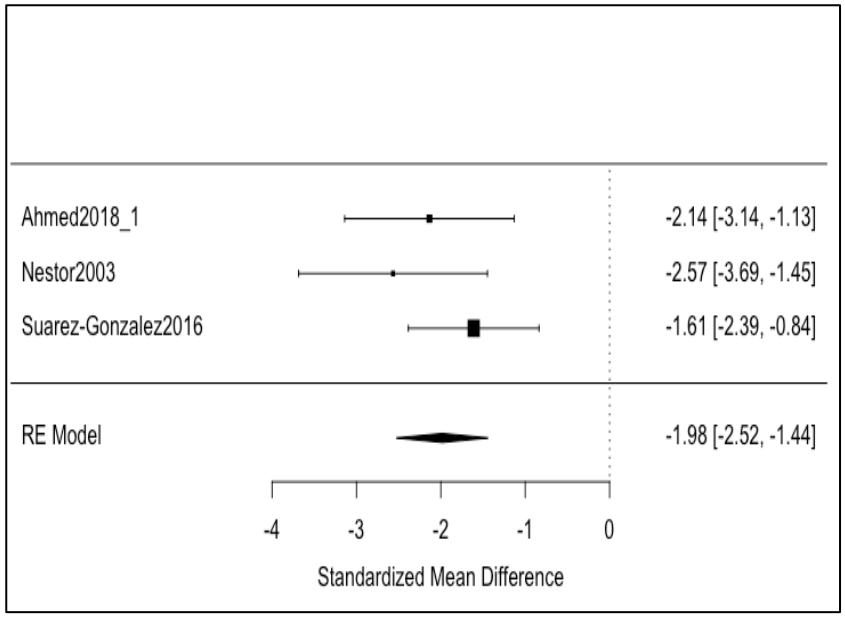
(T) VOSP Number Location



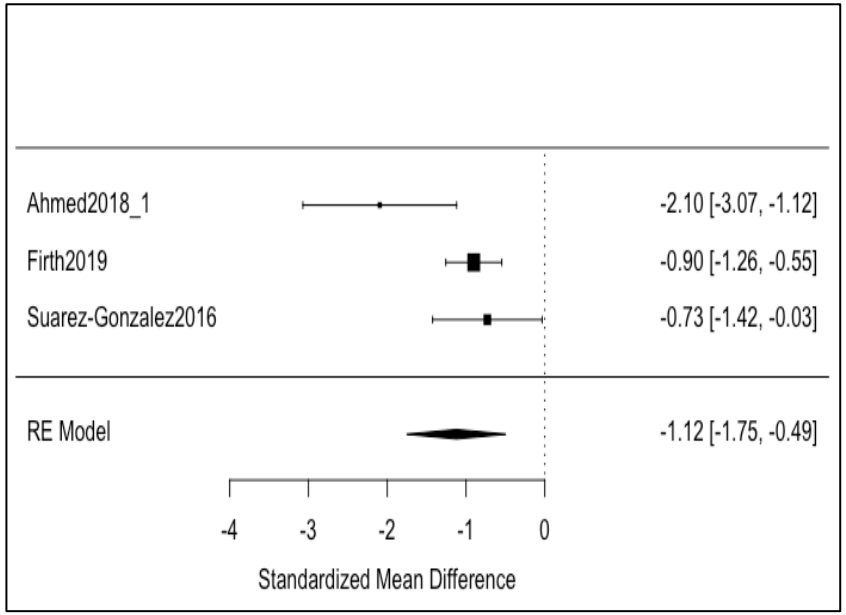
(U) VOSP Dot Counting



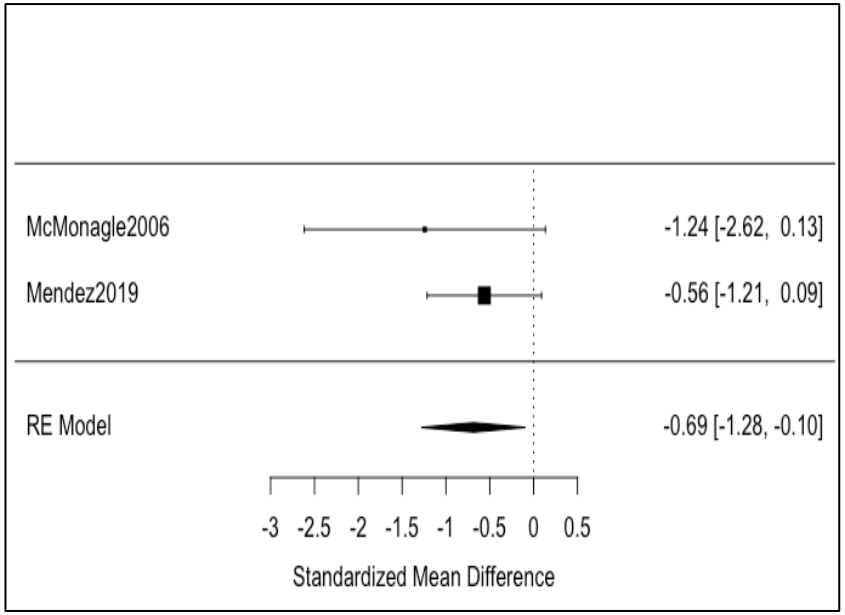
(V) VOSP Cube Analysis



(W) Position Discrimination

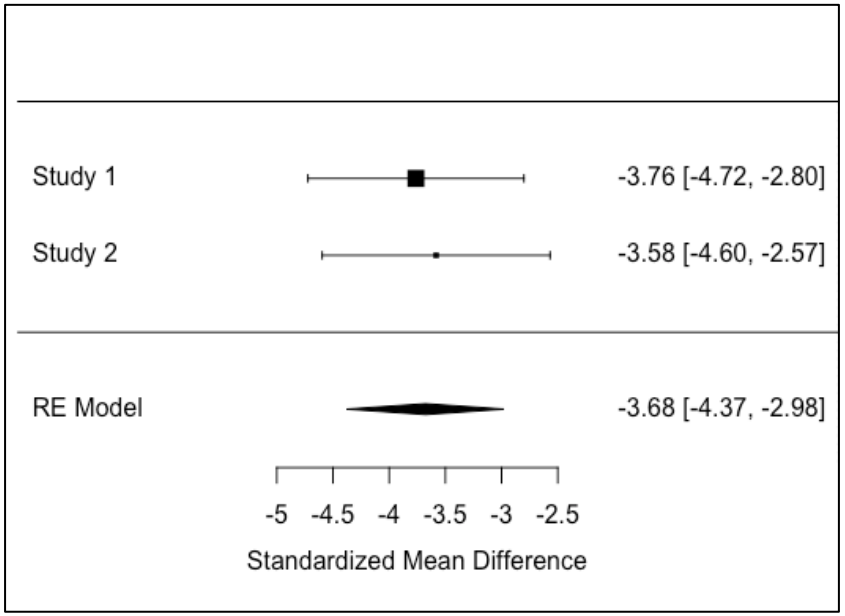


(X) HVOT

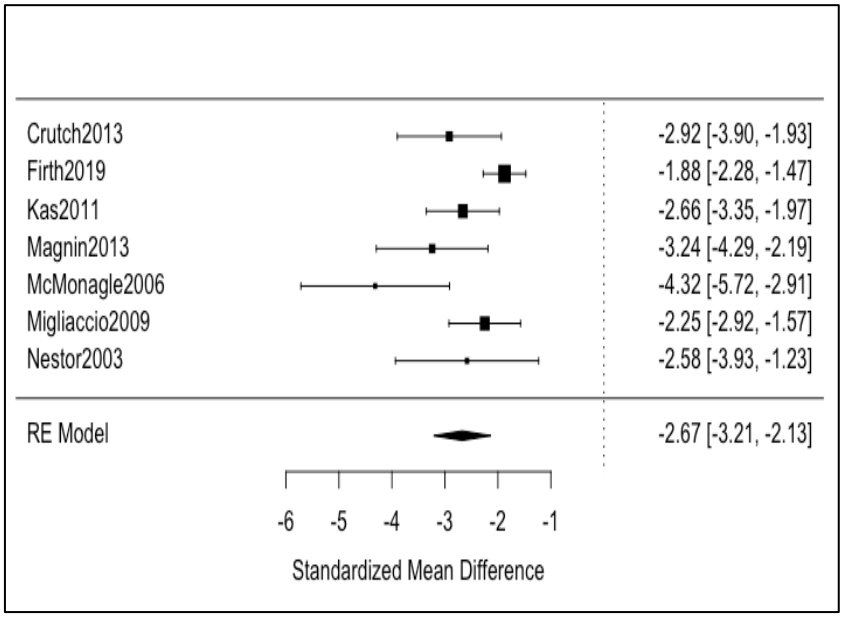


Appendix C: Forest Plots: PCA and HC

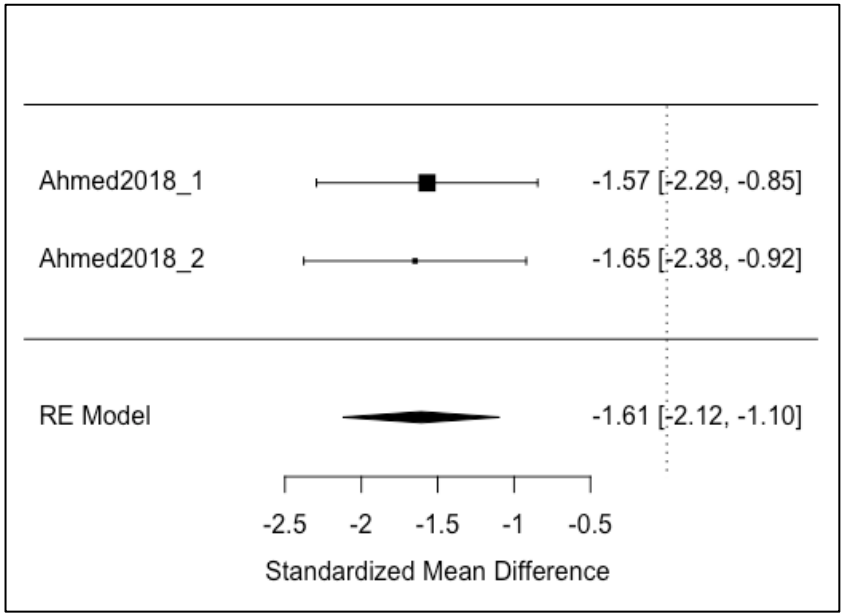
(A) ACE



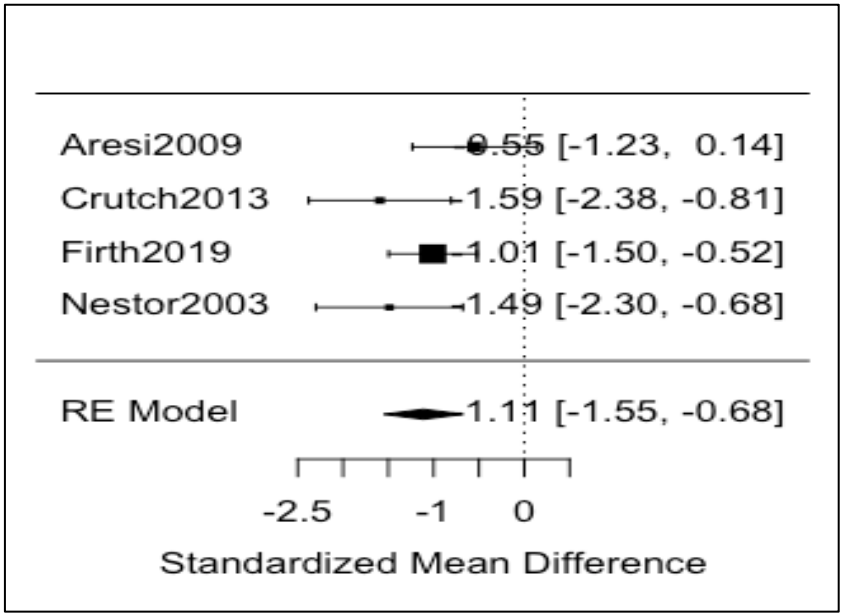
(B) MMSE



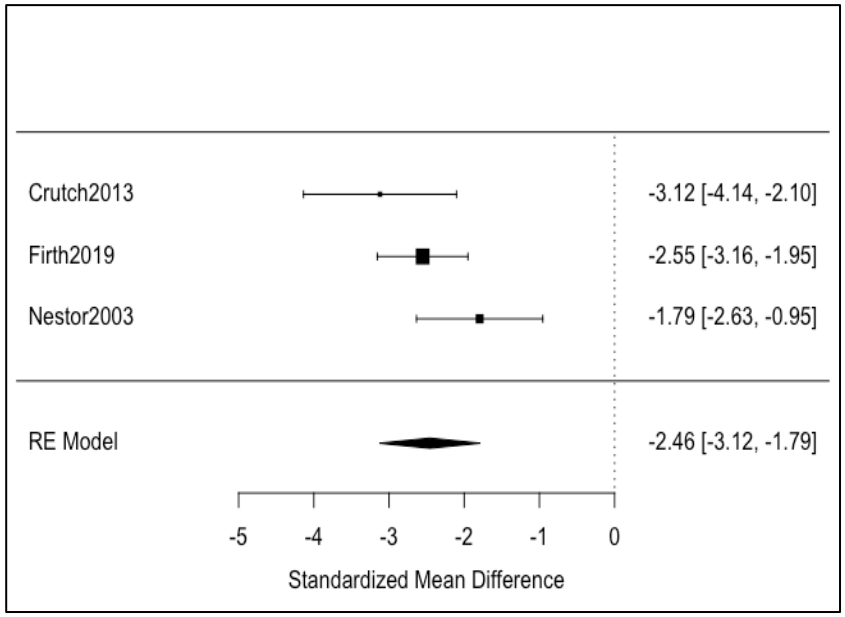
(C) RAVLT Immediate



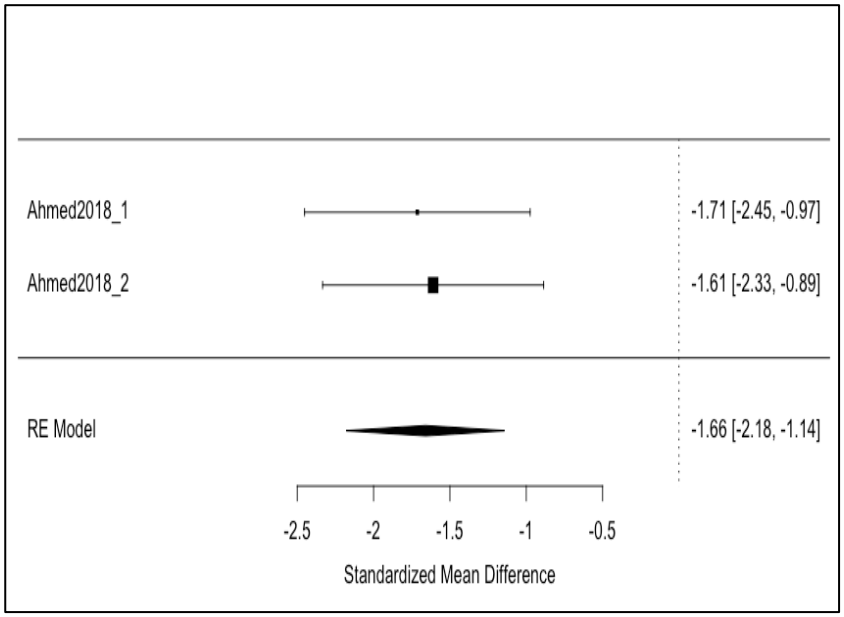
(D) Digit Span Forward



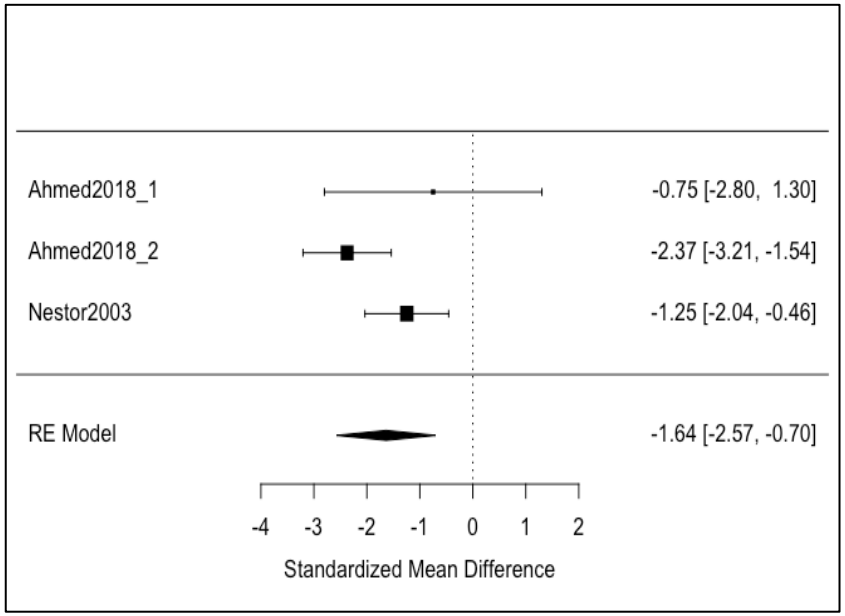
(E) Digit Span Backwards



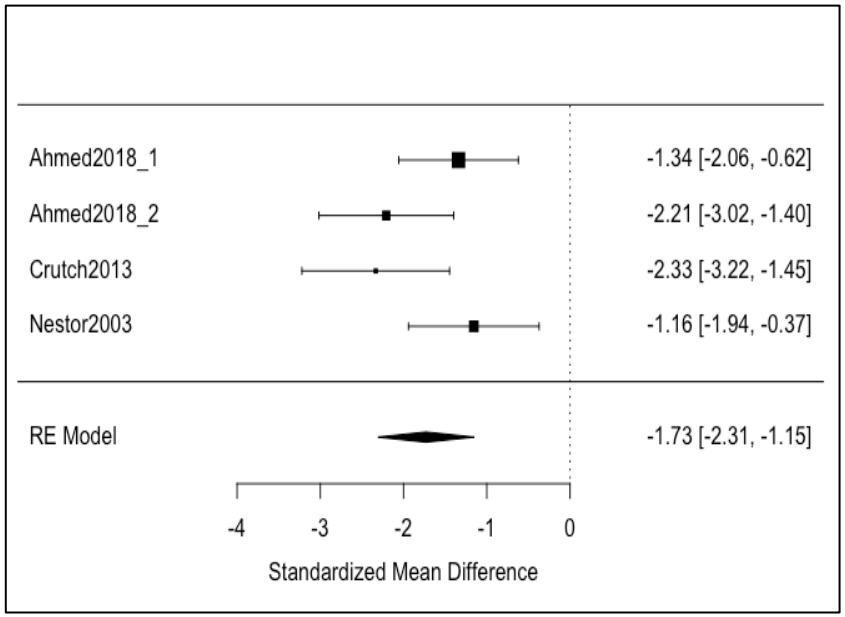
(F) RAVLT Delay



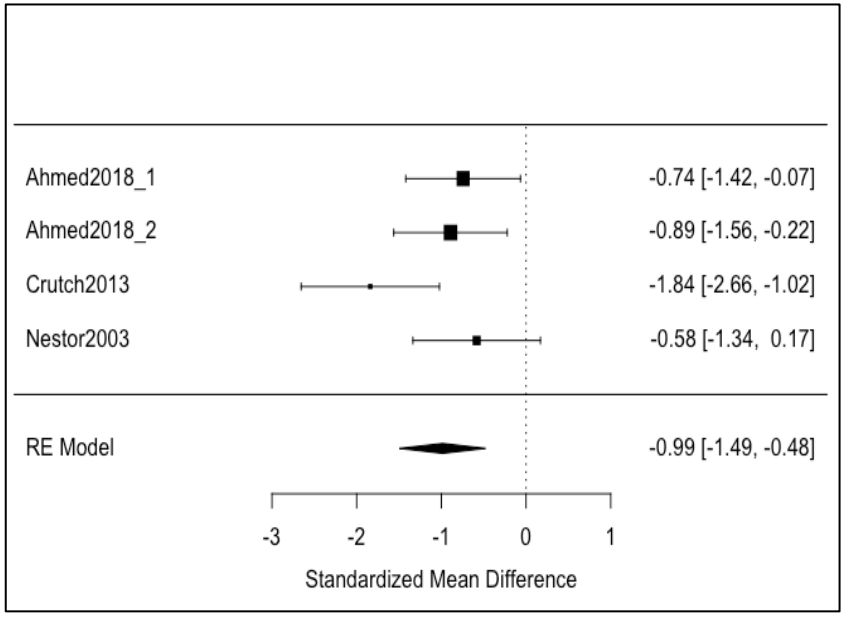
(G) Pyramid's and Palm Trees



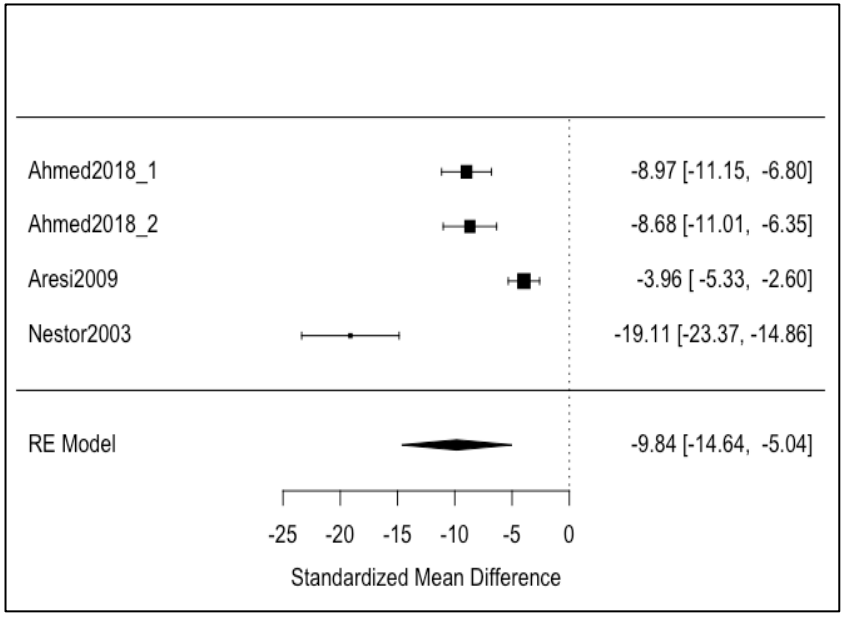
(H) Category Fluency



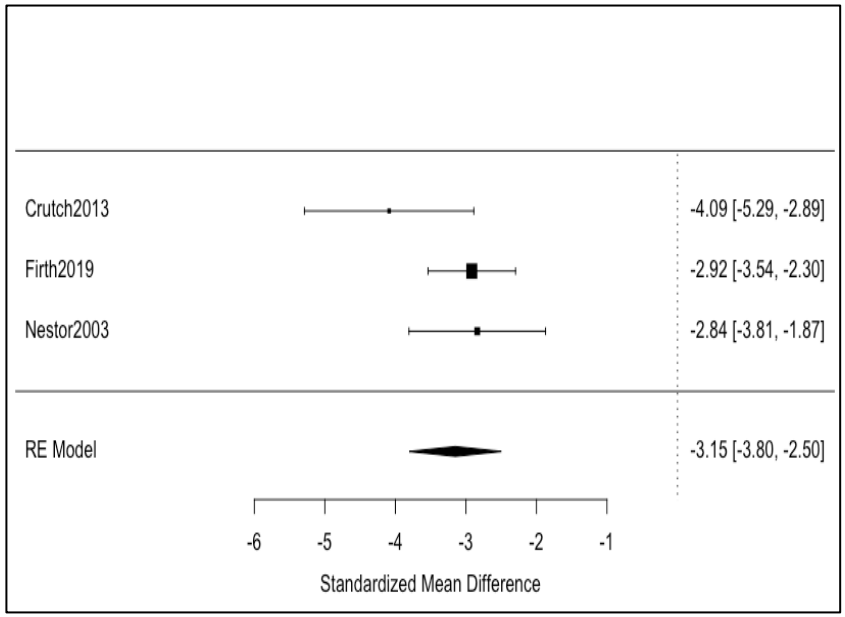
(I) FAS



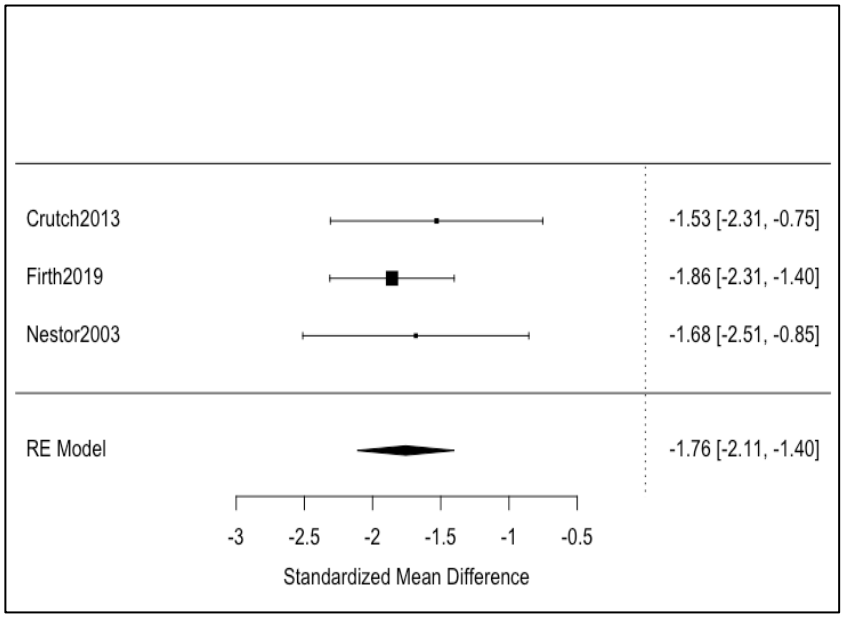
(J) Rey Osterrieth Copy



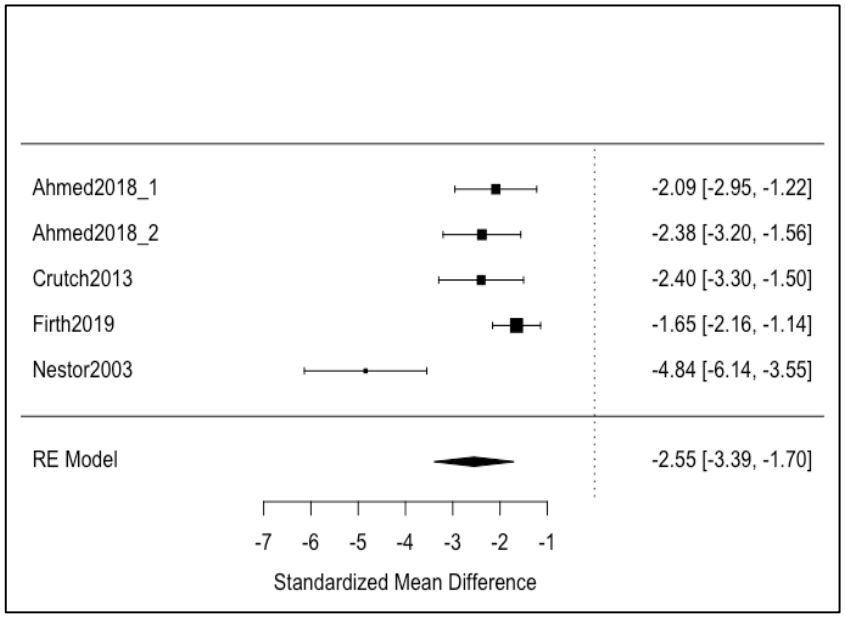
(K) VOSP Fragmented Letters



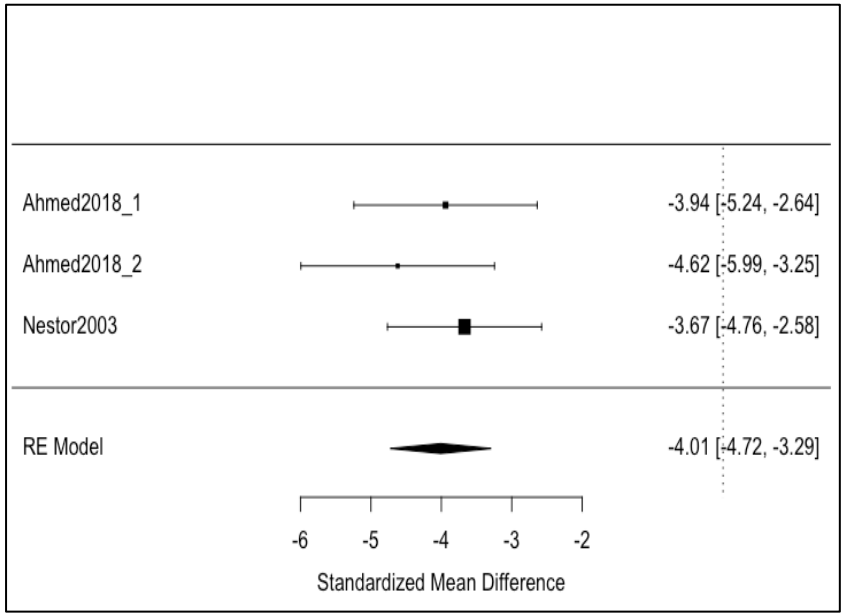
(L) VOSP Object Decision



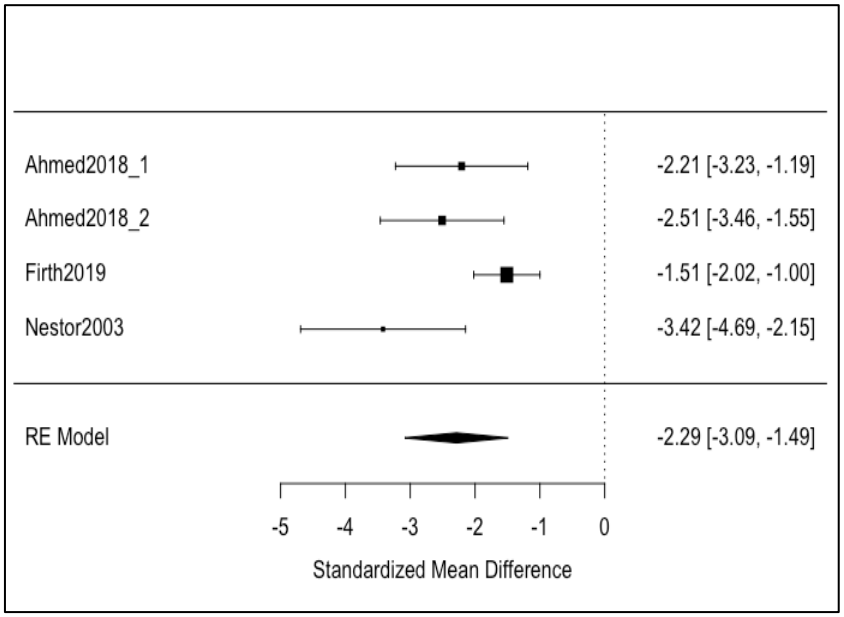
(M) VOSP Dot Counting



(N) VOSP Cube Analysis



(O) VOSP Position Discrimination



Appendix D: Sensitivity Analyses

Posterior Cortical Atrophy and Alzheimer's Disease: Weighted Hedge's g effect sizes for each test

	K	N Participants (PCA/AD)	Mean Hedges g_w (95% CI)	I^2	Q(df)	References
CVLT Delay	2	78/90	0.56(0.25-0.87)***	0%	0.46(1)	*Migliaccio et al (2009), Miller et al (2018),*
Rey Osterrieth Copy	5	65/79	-1.92(-3-0.83)***	85.9%	28.43(4)***	*Ahmed et al (2018), Aresi et al (2009), Charles et al (2005), Li et al (2018), Migliaccio et al (2009)*
VOSP Dot Counting	4	144/107	-1.22(-1.7-0.7)***	59.3%	7.37(3)	*Ahmed et al (2018), Firth et al (2019),), Suarez-Gonzalez et al (2016), Yong et al (2014)*

Posterior Cortical Atrophy and Healthy Controls: Weighted Hedge's g effect sizes for each test

	K	N Participants (PCA/HC)	Mean Hedges g_w (95% CI)	I^2	Q(df)	References
Rey Osterrieth Copy	5	27/65	-7.12(-10.71-3.51)***	90.3%	20.73(2)***	*Ahmed et al (2018, Ahmed et al (2018), Aresi et al (2009), Nestor et al (2003)*

Appendix E: Contributions to the Joint Research Project

The design of the research study and ethics application had begun when the trainees, Courtney North and Mary Heatley, joined the project, and they were able to make contributions to this process. The development of the HI-ACE-III and its administration manual was undertaken jointly between the trainees, whilst Nattawaan Utoomprukrporn took a lead in the piloting of the tools and collating feedback from various professionals and older adults.

Nattawan Utoomprurkporn was responsible for training Courtney North and Mary Heatley in the administration of the portable audiogram. Courtney North and Mary Heatley supported Nattawan Utoomprurkporn in the administration of the cognitive screening and assessments, particularly within MCI populations. Recruitment and testing of cognitively intact individuals in the HI group was undertaken by Nattawan Utoomprurkporn, including liaising with informants. Recruitment and testing of participants with MCI were undertaken jointly by all three researchers, and recruitment of the Dementia group was undertaken primarily by the two trainees. Scoring and inputting of data from all three groups was shared equally. Analysis of the results, as well as writing up the final theses was carried out individually.

Appendix F: Participant Information Sheet

Participant Information Sheet
YOU WILL BE GIVEN A COPY OF THIS INFORMATION SHEET

Title of trial: Validation of "Montreal Cognitive Assessment (MoCA) and Addenbrooke's Cognitive Examination III (ACE-III) " as cognitive screening tools for the hearing impaired.

Name and contact details of the Trial Manager: Nattawan Utoomprurkporn
Email: n.utoomprurkporn.12@ucl.ac.uk
Tel: 020 3456 7870
Department: Ear institute, Faculty of Brain science, University College London

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We would like to invite you to take part in a research project

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- Before you decide whether to take part, it is important for you to understand why the research is being done and what it will involve for you.
- Please take the time to read the following information carefully. Discuss it with friends and relatives if you wish. Take time to decide whether or not you wish to take part.
- Ask us if there is anything that is not clear or if you would like more information.
- Thank you for reading this information sheet.

---

1. Why are we doing this trial?

Hearing problems are very common in older adults, but we don't have good quality pencil and paper tests to identify whether people with hearing loss might have dementia or not. The purpose of this trial is to develop such tests.
Early and appropriate detection of dementia among older adult with hearing loss is very important. Early detection of dementia can help these older adults, who are at risk, to get timely intervention needed for them.

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2. Why am I being asked to take part?

We have invited you to take part in this trial because you have a diagnosis of hearing loss and are aged 65 or over. 30 participants of hearing loss with dementia will be recruited from total of 90 participants in this trial.
We need people with dementia to take part in this trial because we need to know how easy they find our new tests in comparison to people without dementia.

3. Do I have to take part?

No, it is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. You can withdraw at any time without giving a reason and without it affecting any benefits that you are entitled to.
If you do withdraw, any identifiable/personal information we have collected about you will be destroyed. Data which is not identifiable may be retained.

4. What will happen to me if I take part?

If you decide you would like to take part in the trial, a researcher will arrange a convenient time to meet with you to carry out a 'screening' visit. This initial visit will assess whether you are eligible to take part in the study. This assessment will involve doing a hearing test and answering some questions.
If the tests show that you are eligible to take part in the study then there will ask you to fill in some questionnaires and short tests of your memory, language and thinking abilities.
If you have a communication partner (someone you see on a near daily basis) they will also be invited to take part if you are happy for them to do so. If they do not formally want to take part, they do not have to.
The whole session will last about 2 hours, but you can take a break or do this over several visits if that suits you.
Then we will ask for your permission to contact your key worker in the memory clinic about your results at your next routine annual follow up. This is to examine whether there has been any change in your memory, intellectual or language abilities over the course of the year.

5. What are the possible benefits of taking part?

We believe participants could potentially benefit from the dementia tests and hearing tests, since they may pick up issues which were not previously known about and, which we may then be able to help.
More broadly, the information we get may lead good quality dementia tests for people with hearing loss, which could help to improve things for people with hearing loss in the future.

6. What are the possible disadvantages and risks of taking part?

We do not feel there are significant risks associated with this project.
You will spend about 2 hours completing the assessment. As mentioned, previously if you are tired, or wish to take a break for any reason you can do that before completing the rest of the study.
All the tests and questionnaires are routinely used in the NHS and are not known to cause upset or harm. However, if you feel upset or distressed by the assessments you can speak to the researcher. You can also withdraw from the trial at any point, without giving a reason.

7. What if something goes wrong?

If you have a concern about any aspect of this trial you should ask to speak to the researcher or you can contact the Chief Investigator, Nattawan Utoomprurkprurkporn (email n.utoomprurkporn.12@ucl.ac.uk).
If you feel your complaint has not been handled satisfactorily, please contact the Patient and Liaison Service (PALS) at your NHS Trust. PALS can provide information on Trust policies and put you in touch with the relevant people to help your resolve your concerns. PALS can also assist people in making formal complaints if necessary. You can find your nearest PALS office on the NHS choices website, or ask your GP surgery or hospital for the details (or phone NHS on 111).

8. Will my taking part in this project be kept confidential?

A copy of this information sheet and your signed consent form will be placed in your medical notes so that any health care professionals involved in your care are aware of your participation in the trial.

All the information that we collect about you during the course of the research will be stored at University College London and kept strictly confidential and only accessed by authorised members of the research team. All data collected about you will be anonymised by using participant ID numbers which will uniquely identify each individual and be stored in a locked filing cabinet. The anonymised data will also be stored electronically on password protected computers. Identifiable information is only kept for a short period where it is necessary for the conduct of the trial. You will not be able to be identified in any ensuing reports or publications. The research team will occasionally need to allow monitors from Regulatory Authorities to inspect the study paperwork, in order to meet legal, ethical and safety requirements. All individuals who have access to data will be bound by strict data protection and confidentiality rules.

Limits to confidentiality

If during the interview or assessments you tell the researcher something that makes them concerned for your safety, or the safety of others, they will have to share this information as appropriate with the safeguarding team.

9. What will happen to the results of this trial?

We intend to publish the results of this study in scientific journals and public platform. All results will have your personal information removed so you cannot be identified in any published articles.

10. Data Protection Privacy Notice

As a university (UCL), we use personally identifiable information to conduct research to improve health, care and services. As a publicly funded organisation, we have to ensure that it is in the public interest when we use personally-identifiable information from people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use your data in the ways needed to conduct and analyse the research study. Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

Health and care research should serve the public interest, which means that we have to demonstrate that our research serves the interests of society as a whole. We do this by following the UK Policy Framework for Health and Social Care Research.

If you wish to raise a complaint on how we have handled your personal data, you can contact our Data Protection Officer who will investigate the matter. If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO).

The data controller for this project will be University College London (UCL). The UCL Data Protection Office provides oversight of UCL activities involving the processing of personal data and can be contacted at data-protection@ucl.ac.uk. UCL's Data Protection Officer is Lee Shailer and he can also be contacted at data-protection@ucl.ac.uk.

Your personal data will be processed so long as it is required for the research project. If we are able to anonymise or pseudonymise the personal data you provide we will undertake this and will endeavour to minimise the processing of personal data wherever possible.

University College London (UCL) is the sponsor for this study based in the United Kingdom. We will be using information from you and/or your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. UCL will destroy all identifiable information about you immediately after the study has finished (The duration of this study is 3 years; your identifiable data will be kept only until 2021).

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally identifiable information possible.

You can find out more about how we use your information, if you are concerned about how your personal data is being processed, please contact UCL in the first instance at data-protection@ucl.ac.uk. If you remain unsatisfied, you may wish to contact the Information Commissioner's Office (ICO). Contact details, and details of data subject rights, are available on the ICO website at: https://ico.org.uk/for-organisations/data-protection-reform/overview-of-the-gdpr/individuals-rights

UCLH/Camden and Islington NHS foundation trust will collect information from you and/or your medical records for this research study in accordance with our instructions. UCLH/Camden and Islington NHS foundation trust will keep your name, NHS number and contact details confidential and will not pass this information to our sponsor UCL.

UCLH/Camden and Islington NHS foundation trust will use this information as needed, to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Certain individuals from UCL and regulatory organisations may look at your medical and research records to check the accuracy of the research study. UCL will only receive information without any identifying information. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details.
UCLH/Camden and Islington NHS foundation trust will destroy identifiable information about you from this study immediately after the study has finished (This study is intended to be for 3 years until 2021].

When you agree to take part in a research study, the information about your health and care may be provided to researchers running other research studies in this organisation and in other organisations. These organisations may be universities, NHS organisations or companies involved in health and care research in this country or abroad. Your information will only be used by organisations and researchers to conduct research in accordance with the UK Policy Framework for Health and Social Care Research.

This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance.

11. Who is organising and funding the trial?

This trial is sponsor and organised by University College London (UCL).
The funding of the trial is from “The national Brain Appeal” (Funding advances in neurology and neurology).

12. Who has reviewed the trial?

This trial has been reviewed by an independent group of people, called the Research Ethics Committee, to protect your safety, rights, well-being and dignity. The trial has been given a favourable opinion by (London - Surrey Borders Research Ethics Committee) Research Ethics Committee.

13. Contact for further information

Email: n.utoomprurkporn.12@ucl.ac.uk
Tel: 020 3456 7870

Appendix G: Consent Form

IRAS ID:247176

Participant Identification Number for this trial:

CONSENT FORM

Title of Project: Validation of "Montreal Cognitive Assessment (MoCA) and the Addenbrooke's Cognitive Examination III (ACE-III)" as a cognitive screening tool for the hearing impaired.

Name of Researcher:

1. I confirm that I have read the information sheet dated..... (version.....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.

3. (If appropriate) I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from [company name], from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.

4. (If appropriate) I understand that the information collected about me will be used to support other research in the future and may be shared anonymously with other researchers.

5. (If appropriate) I agree to my General Practitioner being informed of my participation in the study. / I agree to my General Practitioner being involved in the study, including any necessary exchange of information about me between my GP and the research team.

6. (If appropriate) I understand that the information held and maintained by the Health and Social Care Information Centre (or amend as appropriate) and other central UK NHS bodies may be used to help contact me or provide information about my health status.

7. I agree to take part in the above study.

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

Appendix H: HI-ACE-III Administration Instructions

HI-ACE-III Administration Instructions

Materials needed for administration: answer / score sheet, pen, pencil with eraser, blank sheet of paper and timer

The PowerPoint works when it is viewed as a slideshow. Please ensure that you are viewing the PowerPoint on a device that is big enough, in particular when displaying the pictures. Before administering the HI-ACE-III, the tester should be trained in administration and read the administration instructions.

Please read all instructions on the screen and complete the task. I will tell you if you need to write or draw, otherwise just say your answer.

When you have finished reading each screen and are ready to move on, please tell the test administrator

Instruction Screen

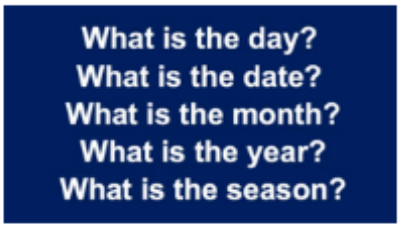
The participant should read the displayed instructions. They appear in two parts. Blank slides will appear between most test slides. Once the participant has informed you that they are ready to begin, move to the blank slide. This is to prevent the participant from referring back to instructions several times.

Please let us know if you would like to take a break at any time

Attention - Orientation

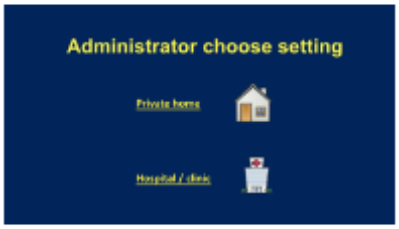
The questions on the next slide will appear one at a time with a blank screen in between. Please press the enter key to continue once the client has given their answer and record the answer on the answer sheet.

If the participant says the month in numbers e.g. 14th of the 8th then prompt for the name of the month. When the season is changing (e.g., at the end of August) and the participant says, "Autumn" then ask, "could it be another season?" If the answer is "Summer", give 1 point since the two seasons are in transition. Do not give 1 point if the answer is "Winter" or "Spring".?

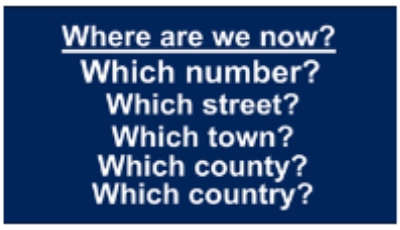


Please use the key to view a prompt. If no prompt is needed, then press the key

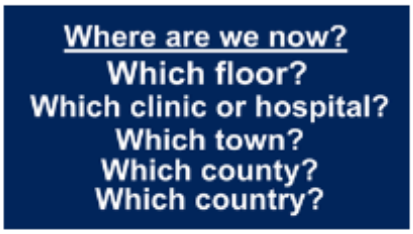
The next slide will ask you to select the hyperlink corresponding to the appropriate setting. Please select the option that will take you to the appropriate set of questions



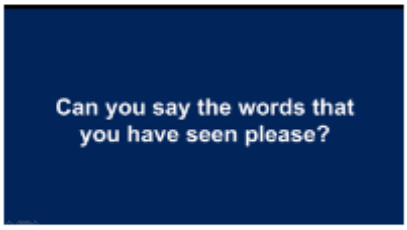
Option 1: In the private home. Please press the enter key to continue through each element of the address once the client has given their answer and record the answer on the answer sheet. After the last question another hyperlink will appear (*'proceed to the next task'*). Click on this to proceed to the next set of questions.



Option 2: In a hospital setting: Please press the enter key to continue through each element of the address once the client has given their answer and record the answer on the answer sheet.



Attention - Registration of 3 items This slide is timed, once lemon has appeared the words will each be displayed for 2 seconds to represent the length of time the word would be presented verbally. Please press enter key after the last word disappears to give instructions to repeat and remember the words. You can repeat this slide up to 3 times if they are unable to remember all three on the first trial. You do this by pressing backspace and enter. Only the first trial is scored, record the number of trials it takes to learn all 3 words and record any incorrect items.



Attention - Serial 7 Subtraction

The instructions are shown in 2 parts. Only show the second part of the instruction (by clicking the mouse) once the client has provided their answer to 'Could you take 7 away from 100?'. The blank screen should be displayed while the client provides their answers. Record all responses and do not stop the client if they make a mistake. Stop the client after 5 subtractions by clicking from the blank screen to the 'stop' screen.

Could you take 7 away from 100?

I would like you to keep taking away 7 from each new number until you see the word STOP on the screen

Memory – Recall of 3 Items

Show the screen below until the participant has had time to take in the instruction. Then click to the blank screen. This should be presented while the participant provides their answers. Record responses verbatim and score 1 point for each correct item. Do not prompt the participants for the items.

Which 3 words did I ask you to repeat and remember earlier?

Verbal Fluency – Letter and Category

I am going to give you a letter of the alphabet and I would like you to generate as many words as you can beginning with that letter
but not names of people or places

For example, if I give you the letter C you could give me words like

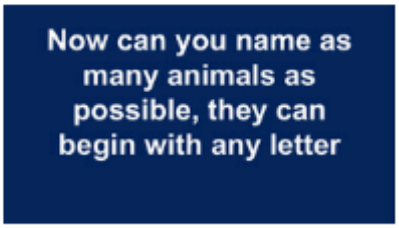
✓ Cat
✓ Cry
✓ Clock

But you can't give me words like

✗ Catherine
✗ Canada

Do you understand?
Are you ready?

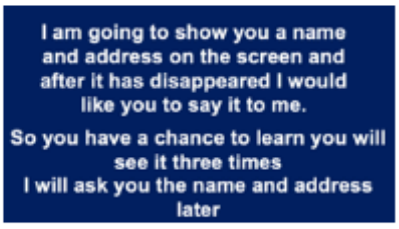
The slide below is timed, the P will appear for 3 seconds before a blank screen will be displayed. It will automatically move to the stop screen after a minute has passed. Any answers given after the minute has passed should not be counted. Record each word that the participant generates on the answer sheet in 15 second intervals. Do not include any answers given after stop has appeared.



This slide is also timed, the blank slide will appear for 1 minute after you have one minute has appeared for 3 seconds. If the participant misunderstands the instructions and perseverates by naming animals beginning with "p" then reiterate to the participant that they should name animals beginning with any letter. Address this issue by stopping clock, going back to previous instructions, let participant read, then restart). Record each word the participant generates on the answer sheet in 15 second intervals. Do not include any answers given after stop has appeared.

Memory – Anterograde Memory – Name and Address

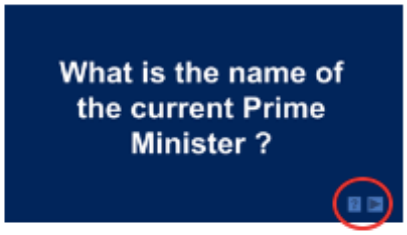
The address slide is timed (8 seconds) and will appear 3 times in order to represent the 3 learning trials. *If the participant starts reciting it before it has disappeared, ask them to wait until it has disappeared.* Record responses for each trial but only responses in the third trial contribute to the ACE-III score.

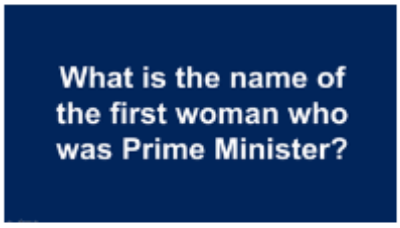


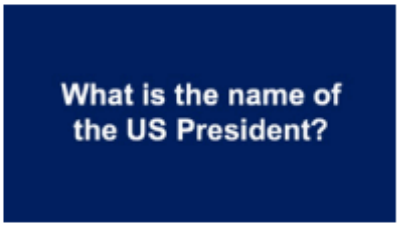
Memory – Retrograde Memory – Famous People

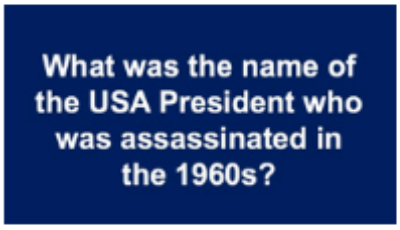
Record responses to these slides verbatim. You may need to prompt by (i) asking for a surname if only the first name is given, (ii) if there has been a recent change in leaders, you may need to prompt for the name of the outgoing politician.

You can use the key to show a prompt, If no prompt needed then press the key



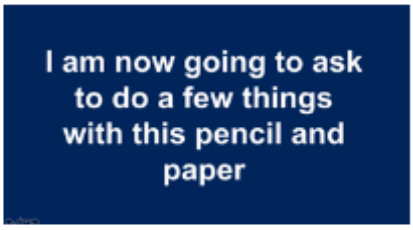






Language – Comprehension

Please place a pencil and piece of paper side by side in front of the client before presenting these slides.



This is a practice trial. If this is incorrectly performed, score 0 and do not continue any further with this item by pressing return 8 times.

Pick up the pencil and then the paper

If correctly performed go onto the next 3 slides. The slides with instructions are timed (8 seconds). When they have completed a task then click to the next instruction slide. Before beginning each trial, always place the pencil and piece of paper side by side in front of the participant.

Place the paper on top of the pencil

Pick up the pencil but not the paper

Pass me the pencil after touching the paper

Language – Sentence Writing

For the next slide, please provide the participant with the answer sheet and a pen once they have read the instructions. The blank screen should be displayed while the participant completes the task.

Please write two (or more) complete sentences about your last weekend.
Write on the paper provided, in complete sentences and do not use abbreviations.

Language – Single Word Repetition

All these slides are timed with each word appearing for 2.5 seconds with 2.5 seconds for the participant to say the word. There is no need to press enter until the blank screen appears after statistician. If the participant tries to say the word before it has disappeared, please prompt them to wait for it to disappear.

Language – Proverb Repetition

These slides are timed once the proverb has appeared (3 seconds). The blank screen during which the participant provides their response is not timed and you will need to manually press enter to move to the next proverb.

Language – Object Naming

These slides are not timed. The participant should be allowed enough time to name or attempt to name all the pictures in any order. Record responses verbatim

Please name the following pictures

.

Language – Comprehension

These slides are not timed, and you should proceed to the pictures once the client has read the question. The client should point to the picture on the screen. Please do not provide any feedback regarding the word meaning. Self-corrections are allowed.

Point to the one which is associated with the monarchy

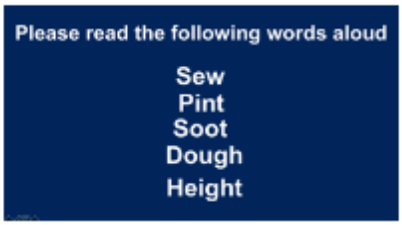
Point to the one which is a marsupial

Point to the one which is found in the Antarctic

Point to the one which has a nautical connection

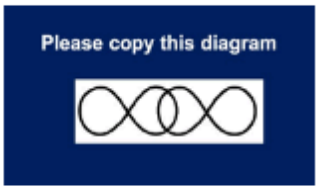
Language – Reading

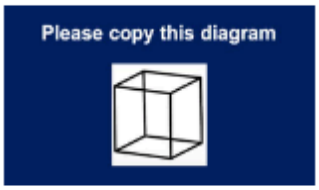
These words will appear one at a time as you press the return key. Keep the words on the screen while the client reads them. If possible, record the mistakes using the phonetic alphabet.



Visuospatial Ability – Intersecting Infinity Loops

Please give the client the answer sheet in order for them to complete the next three items. Please ensure that the answer sheet is folded so that the participant cannot see the perceptual abilities or memory recall sections.



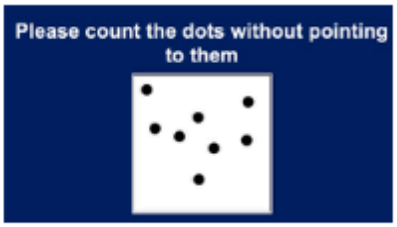


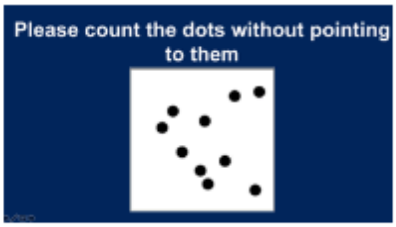
For the clock draw, switch to the blank slide once the client has begun drawing the clock. If the client does not like their first drawing and would like to do it again, you can allow for that and score the second clock. Clients may correct their mistakes by erasing it while drawing.

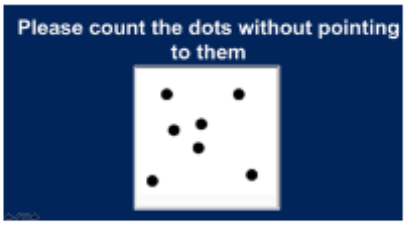
Please take the answer sheet back from the client.

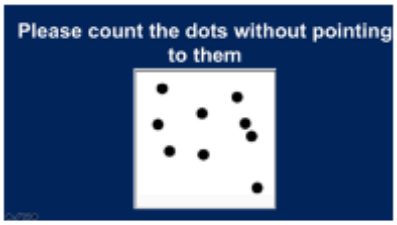
Perceptual Abilities – Counting Dots

The instructions will disappear before the dots are presented. Please ensure that the clients are not pointing to the dots on the screen in order to count them. The dot counting slides are not timed.

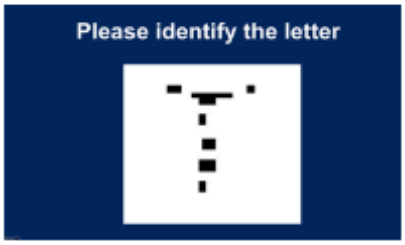








Perceptual Abilities – Identifying Letters
The instructions will disappear before the letters are presented. The participant is allowed to point. These slides are also not timed.



Memory – Recall of Name and Address

Now tell me what you remember about that name and address you were repeating at the beginning

Only proceed from the slide above if subject has not been able to recall one or more details from the name or address, otherwise administration of the test is complete. The blank screen should be displayed while the participant provides their answer. This is not timed.

Let me give you some hints	**Hint: Was the name** John Simons John Marshall Joseph Marshall	**Hint: Was the number** 42 28 24
Hint: Was the road name Market Street High Street Market Square	**Hint: Was the town** Spilsby Horncastle Sleaford	**Hint: Was the town** Spilsby Horncastle Sleaford

This gives the participant a chance to recognise items they could not recall. First, tick the correctly remembered items on the shaded column and then proceed with the prompts. The hints will appear one category at a time.

The End