THE UNIVERSITY
of EDINBURGH

Understanding functional cognitive disorder phenotypes in the differential diagnosis of neurodegenerative disease

Laura McWhirter BA(Hons) MBChB

Thesis and published work submitted for degree of Doctor of Philosophy

University of Edinburgh

Year of presentation 2021

Declaration

This thesis is my own work. Where indicated published work has been produced in collaboration with colleagues included in authorship. My contribution is described in an introduction to each paper and in the introduction to the appendix. Due references have been provided for all supporting literature. This work has not been submitted for any other degree or professional qualification in this, or any other university.

Abstract

Increasing numbers of people seek medical help for worrying cognitive symptoms. However, many patients attending services designed to detect neurodegenerative disease (such as memory clinics) do not have evidence of neurodegenerative disease, nor do their symptoms progress as such. In some, alternative causes are identified, such as medication or systemic illness. Others have been described as 'worried well', as having symptoms driven by anxiety and depression, or else reassured that they have no disease. These patients, many of whom have functional cognitive disorders, have been poorly served by research and as a result there is little evidence to guide effective treatment.

Functional cognitive disorders are an important group of overlapping conditions in which cognitive symptoms are experienced as the result of reversible and inconsistent disturbances of attention and abnormal metacognitive interpretation. They have been neglected in functional disorder research and in neurodegenerative disease research, where they are an important differential diagnosis.

The aims of this PhD were to build a firm definition of functional cognitive disorders, and to justify and explain how this definition might relate to previous and current diagnostic terminologies; to examine prevalence; to understand clinical associations; and to develop clinical methods to support accurate clinical diagnosis.

This thesis investigates the terminologies and theoretical models that have previously been used to describe and explain functional cognitive disorders; systematically reviews prevalence and clinical features; describes comparative studies of healthy adults and simulators, and systematically reviews diagnostic performance of traditional psychometric tests of inconsistency (validity tests) in order to develop understanding of functional cognitive disorder mechanism and potential diagnostic methods. Finally, the thesis includes a clinical study of adults with cognitive symptoms, describing novel diagnostic techniques with wide potential utility.

Lay Summary

What is a functional cognitive disorder?

In functional cognitive disorders (FCD), memory and thinking problems are caused by a problem with the functioning of the brain, and are not due to brain diseases like Alzheimer's Disease. Although the cause of symptoms is different, people with FCD may be just as troubled and disabled by their memory problems as people with dementia.

What were the aims of this research?

The aims of my research were to help improve our understanding of what FCDs are, what sort of other health problems and difficulties they tend to go along with, and how they can be accurately diagnosed in clinics.

What methods were used to try and meet these aims?

I did two large systematic (structured and repeatable) reviews: one of all the available scientific papers about FCD and related conditions; and another of a type of memory test sometimes used by psychologists to detect unusual patterns of performance (performance validity tests, or PVTs, sometimes called effort tests). With two enthusiastic medical students I examined the ideas that healthy people have about memory problems like dementia. With another two medical students I asked healthy people how often they experienced memory lapses, to see how common these experiences were. Finally, I met with 49 people who had been seen in clinics with memory problems (but not found to have dementia) for a detailed interview and set of memory tests.

What were the conclusions of these research projects?

FCD is a common cause of memory problems, present in around 1 in 4 people attending memory clinics. People with FCD are more likely to have symptoms of depression or anxiety, poor quality of life, and poor sleep. Healthy people (who view dementia as a state of severe rather than gradually progressive memory problems) also commonly experience memory lapses, but in contrast do not experience these as problematic or disabling. PVTs, sometimes called effort tests, are not very helpful in diagnosing FCD. However, younger age and ability to speak for a longer time about experienced memory problems is suggestive of FCD. Further research will help to understand why FCD develops and what treatments might be helpful.

Acknowledgements

I would like to thank the study participants who generously gave up their time to take part in the clinical study which formed part of this PhD. I also would like to thank the medical and nursing staff of the City of Edinburgh Memory Assessment and Treatment Service and the Neurology and Neuropsychiatry Departments of the Edinburgh Department of Clinical Neurosciences for their help with recruitment.

Thanks to my supervisors, Alan Carson, Jon Stone, and Craig Ritchie, for their ongoing support and mentorship, to the members of Edinburgh FNDRG for encouragement, and to officemate and now friend Lucy Stirland for helping me to learn to use R for my statistical analyses. Thanks to Marshall Dozier at the University Library for literature searching advice at the very beginning, and to Laura Doull at CCBS for help and understanding about financial and HR matters.

Biggest thanks to my family: Chloe, Phoebe, George, and Brodie, for all the fun (and because nothing is difficult after three under three); and to our nanny Emma and my parents for all the help with the children that has made the work possible.

Finally, I would like to thank my funders, Baillie Gifford, for the opportunity to do this research and for their support and interest in the results along the way.

Thesis contents

Introduction

Part 1 - Understanding the problem

McWhirter L, Ritchie C, Stone J, Carson A. Functional cognitive disorders: a systematic review. The Lancet Psychiatry. 2020 Feb 1;7(2):191-207.

Part 2 - Investigating phenotypes

McWhirter L, Sargent B, Ritchie C, Stone J, Carson A. I think, therefore I forget–using experimental simulation of dementia to understand functional cognitive disorders. CNS spectrums. 2020 Aug;25(4):511-8.

McWhirter L, King K, McClure E, Ritchie C, Stone J, Carson A. The frequency and framing of cognitive lapses in healthy adults. CNS spectrums. 2021 Jan 22:1-8

Part 3 - Investigating methods of diagnosis

McWhirter L, Ritchie C, Stone J, Carson A. Performance validity test failure in clinical populations—a systematic review. Journal of Neurology, Neurosurgery & Psychiatry. 2020 Sep 1;91(9):945-52.

McWhirter L, Ritchie C, Stone J, Carson A. Identifying functional cognitive disorder: a proposed diagnostic risk model. (prepared for submission for publication)

Conclusion

Appendix - other relevant publications from this period of study

Ball H, McWhirter L, Ballard C, Bhome R, Blackburn D, Edwards M, Fleming S, Fox N, Howard R, Huntley J, Isaacs JD, Larner AJ, Nicholson TR, Pennington CM, Poole N, Price G, Price JP, Reuber M, Ritchie C, Rossor MN, Schott JM, Teodoro T, Venneri A, Stone J, Carson A. Functional cognitive disorder: dementia's blind spot. Brain. 2020 October; 142(10):2895-2903

McWhirter L, Miller N, Campbell C, Hoeritzauer I, Lawton A, Carson A, Stone J. Understanding foreign accent syndrome. Journal of Neurology, Neurosurgery & Psychiatry. 2019 Nov 1;90(11):1265-9.

Baker J, Barnett C, Cavalli L, Dixon L, Dietrich M, Duffy JR, Elias A, Fraser DE, Freeburn JL, Gregory C, McKenzie K, Miller N, Patterson J, Roth C, Roy N, Short J, Utianski RL, van Mersbergen M, Vertigan A, Carson A, Stone J, McWhirter L. Management of Functional Communication, Swallowing, Cough, and Related Disorders: Consensus Recommendations for Speech and Language Therapy. (Prepared for submission for publication)

McWhirter L, Hoeritzauer I, Carson A, Stone J. (2020). Functional neurological disorder and personal injury. Journal of Personal Injury Law, Vol. 2, pp. 115-126

van Gils A, Stone J, Welch K, Davidson LR, Kerslake D, Caesar D, McWhirter L, Carson A. Management of mild traumatic brain injury. Practical neurology. 2020 May 1;20(3):213-21.

List of abbreviations

AAMI	Age Associated Memory Impairment
AD	Alzheimer's Disease
APOE	Apolipoprotein E
ARBD	Alcohol Related Brain Damage
ASVT	Amsterdam Symptom Validity Test
BDI	Beck Depression inventory
CAMCOG	Cambridge Cognitive Examination
CAMDEX	Cambridge Mental Disorders of the Elderly Examination
CC	Cognitive Complaints
CCI	Cognitive Change Index
CES-D	Center for Epidemiological Studies Depression Scale
CVLT	California Verbal Learning Test
FCD	Functional Cognitive Disorder
FMD	Functional Memory Disorder
FND	Functional Neurological Disorder
GDS	Geriatric Depression Scale
HADS	Hospital Anxiety and Depression Scale
HC	Healthy Controls
MAC-Q	Memory Assessment Clinic - Q
MC	Memory Complaints
MCI	Mild Cognitive Impairment
MFQ	Memory Functioning Questionnaire
MINI	MINI-International Neuropsychiatric Interview
MMQ	Multifactorial Memory Questionnaire
MoCA	Montreal Cognitive Assessment
MSVT	Medical Symptom Validity Test
mTBI	mild Traumatic Brain Injury
NEO	NEO [Neuroticism-Extraversion-Openness] personality inventory
PET	Positron Emission Tomography
PHQ-15	Patient Health Questionnaire 15
PNES	Psychogenic Non Epileptic Seizures
PVT	Performance Validity Test
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RDS	Reliable Digit Span
REM	Rapid Eye Movement [sleep]
SCC	Subjective Cognitive Complaints
SCD	Subjective Cognitive Decline
SCI	Subjective Cognitive Impairment
SCID	Structured Clinical Interview for DSM Disorders
SMC	Subjective Memory Complaints
SMC	Subjective Memory Complaints
SMI	Subjective Memory Impairment
STAI	State-Trait Anxiety Inventory
TMS	Transcranial Magnetic Stimulation
TOMM	Test of Memory Malingering
VD	Vascular Dementia
VSVT	Victoria Symptom Validity Test
WAIS	Wechsler Adult Intelligence Scale
WMS	Wechsler Memory Scale
WMT	Word Memory Test
ZDRS	Zung Depression Rating Scale

Introduction

Background

Cognitive symptoms, and specifically problems with memory and concentration, are commonly reported by patients with functional neurological disorders. During my clinical neuropsychiatric training I have often been struck by the disproportionate impact that these cognitive symptoms have on the daily lives of patients in whom physical symptoms would appear to predominate: seizures, weakness, movement disorders, or chronic pain. And yet we have little to say to these people about the causes of their cognitive symptoms, or about what they, or we, might do to address them.

As a psychiatrist working in the memory clinic, I have seen another area in which our incomplete attention to the nature of cognitive symptoms can do our patients a disservice: that is, in those patients who present with memory difficulties in whom no evidence of neurodegenerative disease is identified. As the opening paper of this thesis demonstrates, the terms used to describe this group are many and varied. Some of these terms (e.g., 'subjective cognitive decline', and 'mild cognitive impairment') are aetiologically neutral if taken at face value. However, the drive to detect and potentially treat neurodegenerative disease at earlier and earlier stages has led to a common perception that these may sometimes, or even often, be prodromal states. But while this may be true for an individual when we look back retrospectively at the point of dementia diagnosis, our personal and clinical experiences tell us that not all cognitive lapses or complaints of poor memory progress to dementia.

I started this body of work shortly after completing specialist psychiatry training, during which I had a broad exposure to a range of cognitive disorders and functional neurological disorders. My research background was primarily in functional neurological disorders, having led clinical studies examining attentional processes and trialling TMS treatments in functional neurological disorder. It became clear to me that during this time that research into FND over the preceding 10-20 years (much of which was led by my supervisors, Professor Stone and Carson) had made a huge positive impact on understanding and acceptance of these disorders as a core part of neurological practice. The elements underpinning these accomplishments, and which had opened the stage for a growing international research field were, to my view, simple ones: a) clear and transparent definitions and language; b) a rejection and continual challenging of dualist concepts of the body and mind being entirely separate and therefore of 'organic' and 'functional' disorders being mutually exclusive; c) testing and validation of accessible positive clinical features to enable accurate diagnosis; and d) a collaborative approach.

At the outset of this project, I found functional cognitive disorder research in a position many years behind that of functional neurological disorder research in general, and the concept was almost completely overlooked in the neurodegenerative disease field. In approaching this 'new' area I have tried to base the aims and execution of my research around the same elements: a) aiming to use clear definitions and transparent language; b) moving away from 'either/or' thinking and embracing notions of comorbidity; c) identifying positive clinical features to enable accurate diagnosis rather than diagnosis based on exclusion; d) finding opportunities for collaboration, including across disciplines.

Aims

The specific aims of this study were as follows:

1. To define FCD, estimate prevalence, and understand clinical associations.
2. To consider the relationship between cognitive symptoms experienced by healthy people and those experienced by people with FCD.
3. To examine beliefs about dementia in healthy people, and to consider whether these may have a role in the mechanism of FCD.
4. To investigate methods of diagnosis, with the aim of identifying positive clinical profiles which might accurately identify FCD in people presenting with cognitive symptoms.

Method

It was always my intention that the core of this PhD would be a clinical study undertaking detailed assessments of patients with cognitive symptoms, including due to FCD; because I enjoy seeing patients, and because it was immediately clear that this would be necessary in order to identify good clinical diagnostic methods. However, it became apparent early on that the FCD literature was at an embryonic stage in terms of diagnostic criteria and separation from other, syndromic, definitions (MCI, SCD etc.). Therefore, what initially set out as a brief systematic review became a very large investigation into the terminology, prevalence, and clinical associations of FCD; the result is the first paper in this thesis: 'Functional cognitive disorders – a systematic review'.

The systematic review helped me to identify the most appropriate clinical measures to include in the clinical study ('Improving Diagnosis in Cognitive Disorders'). It also raised questions about the high prevalence of cognitive symptoms in healthy populations, which led us to two studies examining beliefs about dementia (using a simulation paradigm) and the frequency of cognitive lapses in healthy adults.

A further question arising from the initial systematic review, and from discussion with other clinicians, concerned the utility of performance validity tests (PVTs) in FCD diagnosis. Finding this question inadequately answered in the literature, I identified a broader relevant question: how do clinical populations (i.e., not healthy, not feigning, not litigating) perform in PVTs? This led to a second systematic review; and also to inclusion of a validity test in our clinical study (the Medical Symptom Validity Test (MSVT)). In combination, these studies found PVTS unhelpful in diagnosing FCD.

Finally, our clinical study, unfortunately cut short by COVID-19, examined a clinical, cognitive, and interactional features in 49 participants with cognitive symptoms (but not dementia) recruited from memory, neurology, and neuropsychiatry clinics. Despite a small sample size, the rich data in this study and relatively high proportion of expert consensus FCD diagnoses has provided helpful information which, if replicated, is likely to aid accurate diagnosis of FCD.

Understanding the problem – paper 1

Functional cognitive disorders: a systematic review.

McWhirter L, Ritchie C, Stone J, Carson A.

The Lancet Psychiatry. 2020 Feb 1;7(2):191-207.

Introduction to the paper:

This paper introduces the functional cognitive disorder concept by reviewing the various terminology that has been used for these disorders, prevalence, clinical associations, and potential diagnostic features.

I designed and carried out the search, screened the results, collated, and analysed the data, and wrote the initial manuscript. CR, JS, and AC contributed to review and revision of the final manuscript.

The process of undertaking this large systematic review generated a series of questions addressed in the other papers contained in this thesis.

Word count:	5976 (excluding text boxes (243))
Abstract word count:	250
Tables:	8 (including 1 supplementary table)
Figures:	5
References:	277

Abstract

Background

Many who seek help for cognitive symptoms do not have, nor develop, dementia, and many described as having mild cognitive impairment do not progress to dementia. Nevertheless, subjective cognitive decline and mild cognitive impairment continue to be conceptualised as steps in the progression of degenerative brain disease towards dementia. Functional cognitive disorders (FCD), in which real and distressing symptoms result from potentially reversible changes in brain function unrelated to pathophysiologically-defined disease, account for a proportion of those who do not follow this trajectory.

Methods

We searched MEDLINE, EMBASE, and PsycINFO for observational studies of subjective cognitive symptoms that included data on ≥10 people with possible FCD published until 14th March 2019. We conducted a narrative review describing terminology, prevalence, and associations.

Findings

Our review identified 249 studies. Symptom assessment methods were heterogeneous. Cognitive symptoms were common in the general population (30%, n=245,654). 24% of 12,003 individuals presenting to clinical services for cognitive disorders were defined as having subjective cognitive impairment, pseudodementia, or FCD. These diagnoses were associated with affective symptoms, neuroticism, negative self-evaluation, and negative illness perceptions. Communication behaviours during clinical interactions discriminated functional from structural disorders. The risk of false positive biomarker profiles was noted.

Interpretation

Cognitive symptoms are common. Around 24% of people presenting to memory clinics may have functional cognitive disorders. They are not 'worried well' but have psychiatric comorbidity and poor wellbeing. Research into markers of functional cognitive disorders is needed: to enable research into treatment, and to increase specificity of prodromal degenerative brain disease diagnoses.

Introduction

Increasing numbers of people seek help for memory problems, and yet many symptomatic patients attending memory clinics do not have degenerative brain disease, and do not progress to dementia[1,2]. Cognitive symptoms or impairment may be caused by other medical and neurological disorders, or by prescribed or non-prescribed drugs, but the experience of cognitive failure can also arise through purely functional disturbances to cognitive and introspective processes.

Functional cognitive disorders are a group of overlapping conditions in which cognitive symptoms are present which are genuine, distressing and often disabling, but experienced inconsistently and not related to systemic or brain disease (**Box 1**)[3]. They can be included under the umbrella of functional neurological disorders, one of the commonest causes of neurological disability[4,5]. Although historically defined in terms of psychological stress and absence of disease, functional neurological disorders are now also understood in neurobiological terms, with evidence of dysregulated attention, sensorimotor prediction, self-agency, and emotional processing[6,7]. Psychological stressors are no longer required for the diagnosis of functional neurological disorder, which, crucially, is only made on the basis of positive clinical features demonstrating characteristic internal inconsistency; misdiagnosis is rare[8].

Functional cognitive symptoms have received less research attention than other functional symptoms, although interest is developing. Teodoro et al. systematically reviewed the literature on "brain fog", and cognitive symptoms in functional neurological disorders, fibromyalgia, and chronic fatigue syndrome, with the Teodoro paper suggesting a unifying theory in which excessive attention towards physical symptoms and cognitive processes generate symptoms[9]. Bailey et al. systematically reviewed patterns of communication in memory clinics, identifying features with potential to discriminate between functional and neurodegenerative disorders: individuals with functional disorders were more likely to attend alone, to be worried about their memory, and to provide a detailed account of personal history and memory failures[10]. However, despite increasing interest in identifying early prodromes of degenerative brain diseases, there has been no detailed examination of the prevalence and clinical associations of functional cognitive disorders (an important differential diagnosis) in the cognitive disorder literature.

One reason for this may be that the scientific literature concerning functional cognitive disorders is a tangled landscape of overlapping terminology. Early 20th century physicians used the term 'pseudodementia' to describe a wide range of clinical syndromes with the appearance of dementia but rather caused by depression, conversion disorders (hysteria), dissociative states (including 'Ganser

states'), or disordered personality[11–13]. The broader 'pseudodementia' concept has been superseded by 'depressive pseudodementia' – cognitive impairment associated with severe depression – although with better recognition of the frequency of depression and anxiety in prodromal degenerative brain disease, this clinical group remains aetiologically heterogenous.

In recent years, researchers investigating subjective cognitive decline (SCD) have been strongly invested in identifying early clinical markers of neurodegenerative disease, rarely focusing on alternative causes of symptoms. People with subjective cognitive complaints but normal cognitive examination are sometimes described, unhelpfully, as 'worried well' (describing worry about experiences which fall within the range of normal, and which are not due to disease). Of equal concern, people with both subjective cognitive complaints and impairment on testing (therefore defined as having mild cognitive impairment (MCI)), or with subjective cognitive complaints and biomarkers suggestive of an underlying disease process, may receive life-changing predictions or diagnoses of dementia which are retained even when inconsistent symptom experience and subsequent cognitive trajectory are more consistent with a functional disorder[14].

There is an almost universal tendency in dementia research to view subjective cognitive symptoms as a preliminary to mild cognitive impairment and later dementia. However, an as-yet undefined proportion of those individuals with symptoms described in terms of subjective cognitive decline, subjective memory impairment, pseudodementia, or as the 'worried well', may be better described in positive terms as having the inclusively generated diagnosis of functional cognitive disorders; challenging the prevailing SCD → MCI → dementia model. We aimed to systematically search and review the literature incorporating these diverse terms in order to assess the usage, prevalence, and clinical associations of functional cognitive disorders in people with cognitive symptoms.

Box 1: Functional cognitive disorders: definition and subtypes

Definition

- One or more symptoms of impaired cognitive function are present
- Clinical findings show evidence of internal inconsistency: with observed or measured function, or between different situations
- Symptoms or impairment are not better explained by another medical disorder, although may be comorbid with another medical disorder
- Symptoms or impairment cause clinically significant distress or impairment in social, occupational, or other important areas of function, or warrant medical evaluation

Proposed overlapping subtypes (after Stone et al 2015):

- Excessive attentional focus on 'normal' cognitive symptoms
- Health anxiety about dementia, with perceived cognitive deficit
- Isolated functional cognitive symptoms with or without impairment on cognitive tests
- Cognitive symptoms as part of anxiety or depression
- *Cognitive symptoms in other functional disorders, e.g. functional neurological disorders (dissociative seizures, functional movement disorders), chronic fatigue syndrome and fibromyalgia ('brain fog')**
- Dissociative cognitive states (e.g. dissociative amnesia, fugue, Ganser syndrome)

* not included in this review – see (Teodoro et al. 2018[s9])

Method

Search strategy and selection criteria

We conducted two simultaneous searches (A and B) of the published peer-reviewed English-language literature in MEDLINE, EMBASE, and PsycINFO databases to 14th March 2019, using the terms shown in **Box 2**. We included observational studies describing the cross-sectional diagnoses of those assessed for possible dementia in memory clinics or similar services; and observational studies, excluding treatment studies, which included (albeit not necessarily as a primary focus) original data on at least 10 adults (>18 years old) with subjective cognitive symptoms, arising de novo, who did not receive a diagnosis of dementia, delirium, or other medical or neurological causes of symptoms. Exclusion

criteria (not applied to cross-sectional studies of memory clinics) were; primary diagnosis of (non-cognitive) functional neurological disorder, chronic fatigue syndrome, fibromyalgia, major psychiatric disorder other than depressive or anxiety disorders, or cognitive symptoms after physical illness or injury. The search, screening, and data extraction was performed by one author (LM). Data were synthesised into a narrative review.

Box 2:

Search strategy

EMBASE, PsycINFO, MEDLINE

Search A: (((functional or dissociative or psychogenic or hysterical or conversion or medically unexplained or subjective) ADJ (memory or cognit* or cogniform) ADJ (impairment or disorder or decline or complain* or symptom*)) OR pseudodementia) AND (((memory or cognit* or cogniform) adj1 (symptom or complain* or subjective))

AND

Search B: ((memory or cognit* or neurology or dementia) adj1 (clinic or outpatient)). Restricted to human, English language, NOT brain injury)

AND

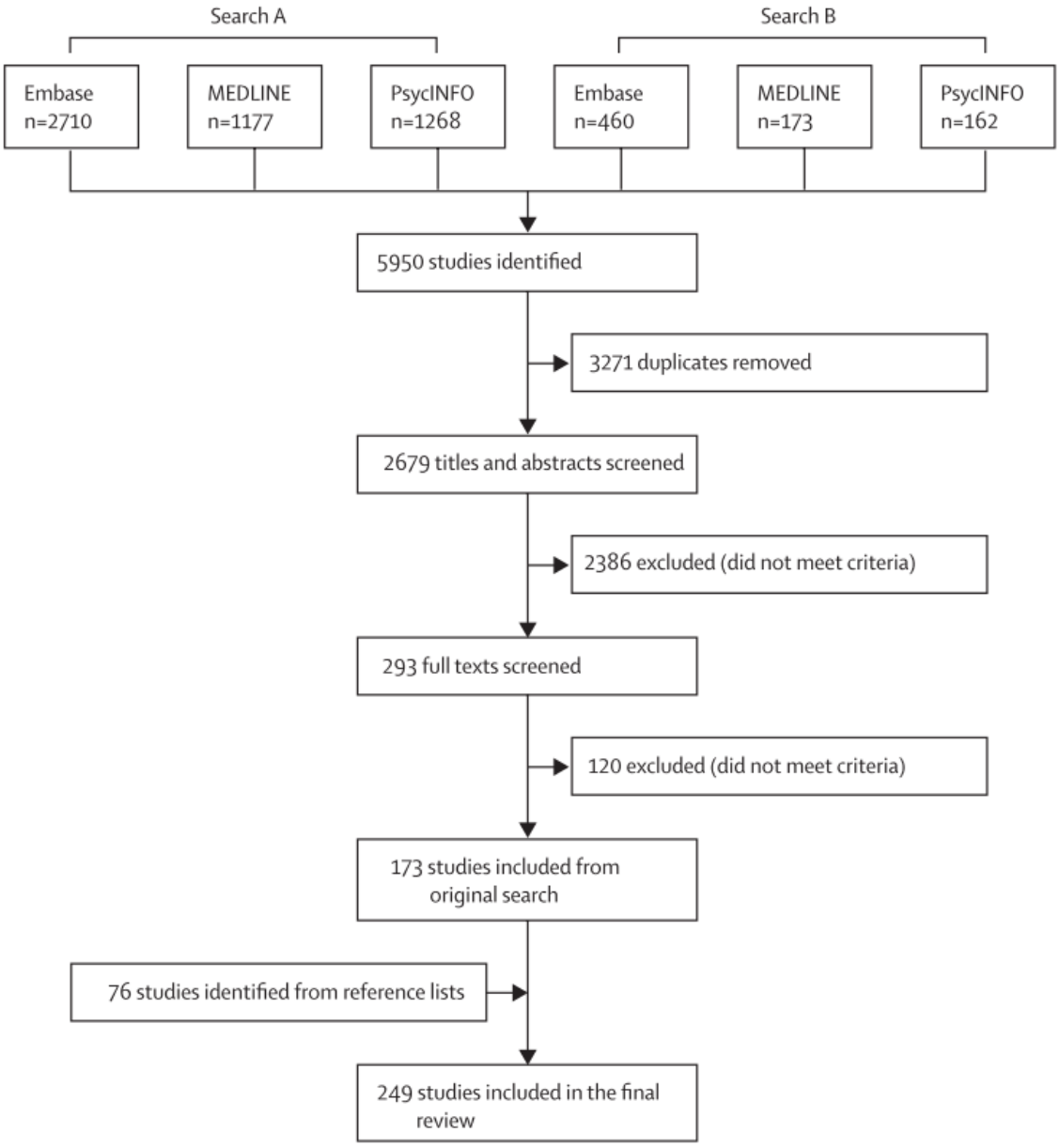
Review of reference lists of included papers.

Results

Search results

Of the 249 included studies (**Figure 1** and **Supplementary Table A**), 185 had a cross-sectional design, 59 longitudinal, and five described case series (≥ 10 people); 59 included at least one control group.

Figure 1 : Selection of included studies



Terminology

A wide range of terms were used to describe non-dementia cognitive symptom profiles and diagnoses (**Table 1**).

Table 1 – Main terminology used in included studies

Number of included studies	Main term used
66	Subjective memory complaints
25	Pseudodementia
(13)	- pseudodementia due to an affective disorder / depressive pseudodementia / pseudodementia of depression / dementia syndrome of depression
(1)	- Conversion pseudodementia
23	Memory complaints
22	Subjective cognitive decline
15	Subjective memory impairment
14	Subjective cognitive impairment
12	Subjective cognitive complaints
10	Description of primary psychiatric diagnosis
10	Functional memory disorder
7	Clinically / cognitively normal / no cognitive deficits/disturbance
6	Cognitive complaints
5	Not dementia / illness / (neuro)psychiatric illness / disease
5	Functional cognitive disorder
4	Subjective complaints
3	Memory self-report / self-rating / self-rated decline
3	Subjective memory loss
3	Subjective memory decline
2	Benign senescent forgetfulness
2	Worried well
1 each (12)	Cognitive symptoms, subjective cognitive symptoms, subjective memory symptoms, subjective forgetfulness, anticipatory dementia, memory problems, subjective worsening of memory, symptoms of memory impairment, psychoactive brain dysfunction, Ganser syndrome, non-deteriorated (longitudinal), reversible dementia.
Total: 249	

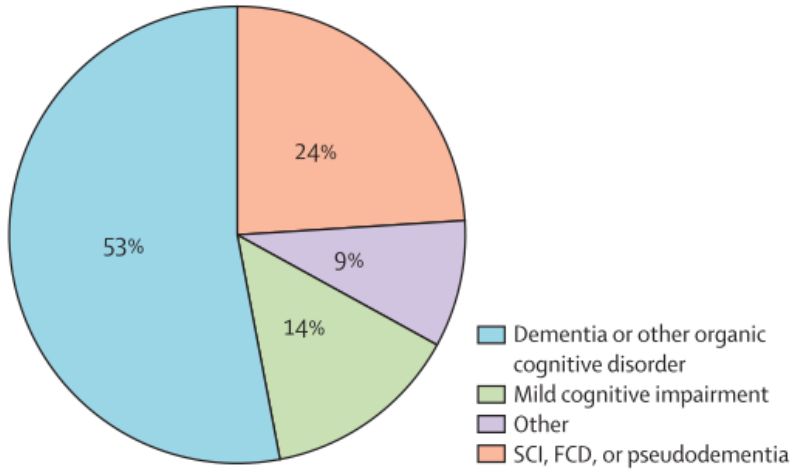
Population prevalence and outcomes

Prevalence of functional cognitive disorders in clinical settings

Thirty-nine studies (described in **Table 2**) described diagnoses in 40 clinical populations attending cognitive assessment services: all were in memory clinic (or similar) settings except for the earliest three: studies of in-patients investigated for suspected dementia, reflecting clinical practice at the time[15–18]. The 39 studies included 13,637 people (57% female)), excluding Wright and Lindesay's survey (N not reported)[2,15–50]. Studies used varying terminologies and reported varying degrees of descriptive detail. Of these 39 studies, 35 studies (n=13,353) reported dementia diagnoses in 54%, 32 studies (n=12,003) reported presence of clinical syndromes of subjective cognitive impairment, pseudodementia, or functional cognitive disorders in 24%, 30 studies (n=11,807) reported both

functional cognitive disorder prevalence (24%) and dementia prevalence (53%) **(Figure 2),** and five studies (n=1,324) reported 'no cognitive disorder' in 47%.

Figure 2: Diagnoses in 11,807 people attending memory clinics



Cognitive disorders may also come to light during treatment of medical illness: of 166 medical in-patients with severe acquired cognitive deficits suggestive of dementia (mean age 82·9), 8 (5%) were ultimately diagnosed with depressive pseudodementia[51].

Longitudinal outcomes in clinical populations

If cognitive symptoms always represent steps on a trajectory towards dementia, every person with subjective cognitive impairment would be expected to progress to MCI, then dementia, with ongoing decline from the point of dementia diagnosis. Atypical trajectories (non-progressive, remitting, or fluctuating) are a potential marker of functional cognitive disorders. Although complete meta-analysis of the longitudinal outcome of subjective cognitive symptoms was outside of the scope of this review, we examined the included studies in order to consider whether, in broad terms, non-progressive cognitive problems were common or rare in those presenting for clinical assessment.

Three pre-1980 studies examined stability of dementia diagnoses. In Kendell's study of the temporal stability of psychiatric diagnoses in 2000 patients first admitted to a psychiatric bed in 1964, dementia was the most stable of all psychiatric diagnoses at 77%; indicating, however, that 23% of those diagnosed with dementia severe enough to lead to hospital admission were ultimately re-diagnosed with something else[52]. In another 10-year case-note review of 35 inpatients diagnosed with pre-senile (<65) dementia, 15 deteriorated as expected and 10 died, but 20 (57%) did not deteriorate but improved (n=18) or remained unchanged (n=2); revised diagnoses including depression (n=3), anxiety

state (n=3), somatic symptoms without organic basis (n=6), and hysterical reaction (n=1), the authors stating that the non-progressors consisted mainly of 'people with marked personality difficulties and neurotic symptoms or affective disorder'[53].

Ten studies followed up clinical populations assessed at baseline as having subjective cognitive symptoms of uncertain or benign cause: none reported rates of progression to dementia greater than 10% during 2-4 year follow-up[54–64]. If subjective cognitive decline was most often due to degenerative brain disease, it would be expected to be associated consequently with early death. However, two included studies reported no reduction in life expectancy in individuals with SCD over mean follow-up periods of 3·5 - 4 years[65,66].

Poorer outcomes were reported in pseudodementia cohorts, both in terms of incident dementia and non-neurodegenerative mortality, although progression to dementia varied from 0-89%. Bulbena & Berrios followed up 22 individuals with pseudodementia (unipolar depression (n=10), bipolar disorder (n=5), psychosis (n=5), personality disorder (n=2), mean age 73·3) after 15-47 months; eight (36%) died, and of 14 survivors six (27%) developed dementia[67]. Sachdev followed up 19 individuals with pseudodementia, (depression (n=8), bipolar depression (n=3) ,schizophrenia (n=5), mania (n=2), and schizophreniform disorder (n=1), mean age 53), over 12 years; eight (42%) died but none of the 11 (58%) survivors developed dementia[16,68]. Kral & Emery, however, reported onset of dementia within eight years in 89% of 44 individuals with pseudodementia (mean age 76·5), despite initial resolution of affective and cognitive symptoms[69]. Similarly, of 182 with depressive pseudodementia (mean age 78) followed up over 5-7 years, 71% developed dementia[70].

Schmidtke et al reported outcome in 46 of 73 individuals diagnosed with functional memory disorder (FMD) (mean age 55·2); 39 (85%) had persistent symptoms at mean follow-up of 20·1 months; symptoms had resolved in six (13%); one (2·1%) had dementia[71]. Risk of incident dementia therefore was low (nonetheless present) but symptom persistence was the notable finding here, suggesting FMD is not a benign condition.

Cognitive symptoms in the general population

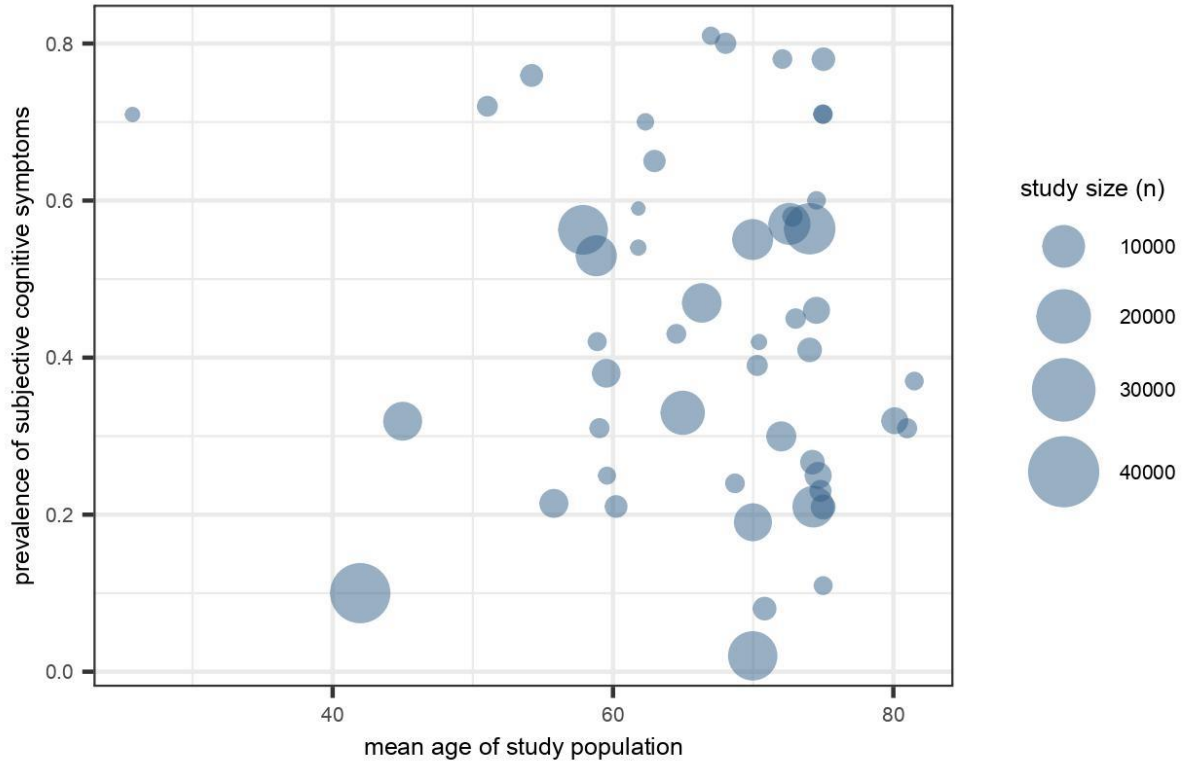
To understand who presents for clinical assessment, and why, it is important as a first step to estimate the general prevalence of cognitive symptoms.

Fifty-six studies described prevalence of cognitive symptoms in community populations (**Table 3**), using a variety of assessment methods, finding symptoms in between 8% and 80%, with overall 30% of the 245,654 individuals included reported to have cognitive symptoms[72–127].

Of those cross-sectional studies including objective measures of cognitive function; 18 found a positive association between symptoms and objective impairment;[72–77,79,82,84,88,89,93,95,97,98,100,113,121] though 14 did not[86,87,90,96,105,110,112,117,120,122,123,125,127,128]. Some reported symptom association with impairment in subgroups: specific rather than global cognitive symptoms[124], SCD-plus (SCD with additional clinical or bio-markers suggesting neurodegenerative disease) but not SCD alone[94], and only in male participants[81]. There was no correlation between prevalence of reported cognitive symptoms and mean study population age, although this must be interpreted with caution given the different measures used (**Figure 3**).

Figure 3 – Cognitive symptom prevalence vs mean sample age

Subjective cognitive symptom prevalence in 49 included studies of community populations (not including 7 studies in which sample age was not reported)



Factors associated with help-seeking for cognitive symptoms

Having established in our first step that cognitive symptoms are common, in our second step towards understanding why people present with cognitive symptoms we identified seven studies reporting factors associated with seeking help for cognitive symptoms.

Comparing self-referred with physician-referred memory clinic patients, self-referrers reported greater decline, had more depressive symptoms, more trait anxiety, higher estimated premorbid IQ, and were more likely to have had previous depression requiring treatment[129,130]. Four other studies reported that help-seekers had poorer memory self-efficacy, quality of life, and were more often worried because of a family history of dementia[131], were more likely to perceive a biological or medical (rather than social) cause of memory problems[132], and had more depressive symptoms and hippocampal atrophy than symptomatic non-help-seekers despite similar cognitive scores, anxiety scores, and cerebral amyloid deposition[133]. Haussman found that intrinsic motivation – attending because of self rather than others – reduced likelihood of dementia diagnosis[134]. In Tsoi's Ganser

syndrome study, every presentation was assessed to be motivated by external circumstances, including avoidance of murder trial, head injury compensation, and 'dissatisfaction with army life'[135].

In summary, those seeking help for subjective cognitive symptoms are more likely to be distressed, depressed, anxious, and to be more concerned than others about their memory; they cannot be considered 'worried well'. It is possible that a significant proportion have functional cognitive disorders (**Box 1**).

Longitudinal outcome of cognitive symptoms in the general population

Comprehensive meta-analysis of longitudinal outcomes was outside of the scope of this review, but we aimed to summarise the range of outcomes in included studies in order to consider broadly whether cognitive symptoms, in those who do not necessarily seek help, frequently or infrequently progress to dementia.

Twenty-six studies reported outcomes in non-clinical populations with subjective cognitive symptoms after between one and ten years. In 13 elderly cohorts, baseline subjective cognitive symptoms were associated with increased risk of future cognitive decline, although in studies reporting incident dementia rather than decline on cognitive tests, numbers progressing to dementia were small: at most 11% (over 7 years, in Reisberg et al.) of any individual study population[77,84,88,89,95,108,121,136–140]. Two studies, in 453 individuals (mean age 80·5) and 1990 (mean age 80·1), reported increased risk of progression in stable but not unstable (relapsing and remitting) SCD[82,114]. Amariglio et al. found symptoms predictive of decline only in individuals with amyloid positive profiles on PiB-PET in a cohort of 279 (mean age 73·7)[141]. In a cohort of 1416 (mean age 75·3), SCD no longer predicted decline after adjusting for baseline cognitive performance[121]. Six studies (all mean age >65) reported that symptoms did not predict future decline[57,98,112,142–144]. Three studies described predictors of future increases in cognitive symptoms: low control beliefs (corresponding to low or external locus of control)[145], female sex, fear of falling, anxiety and depression[146], and longitudinal change in cognitive performance[147].

In summary, and in keeping with systematic reviews assessing this specific question[148], while some individuals with subjective cognitive symptoms progress to dementia, the majority (around 90%) do not.

Reported associations between clinical variables and functional cognitive disorders

We hypothesise that a significant proportion of those with subjective cognitive symptoms in clinical populations have functional cognitive disorders, and summarise below reported clinical associations. In including biomarker studies, we intended not to assess the predictive value of these biomarkers *per se*, but rather to consider the clinically important question of what patterns of results might be found in those with functional cognitive disorders.

Structural Neuroimaging

As cerebral atrophy is a key marker of degenerative brain disease, and medial temporal lobe atrophy a marker of AD, functional cognitive disorders (assumed here to represent many of those with subjective cognitive symptoms) might be expected to be associated with an absence or relatively small degree of atrophy. Several included studies confirmed this: finding degree of global atrophy unrelated to measures of cognitive function in individuals complaining of memory loss[41] or to symptom severity[149], and three studies reported no difference in brain volume between groups with subjective memory complaints and healthy controls[150–152]. Two studies reported greater medial temporal volumes in depressive pseudodementia than AD, and one reported greater hippocampal volumes in subjective cognitive impairment than AD or MCI[153–155]. One study defined a 'non-neurodegenerative' subjective memory impairment subtype with minimal atrophy[156].

Five studies, however, reported smaller hippocampal volumes in subjective memory impairment compared with healthy controls, reporting smaller hippocampi in less-depressed SMI[157], in SMI with AD family history[158], and, in Perrotin et al., in association with help-seeking[150,154,159,160]. A study of 'dementia syndrome of depression' reported atrophy intermediate between unimpaired depressed individuals and those with AD[161]. In 60 memory clinic patients (mean age 72·6) white matter lesion severity correlated with subjective memory symptoms and depression severity[162]. Superior temporal gyrus atrophy correlated with depressive symptoms in unaccompanied memory-clinic attenders, the authors proposing that depression was the cause of atrophy, rather than the result[163].

Just as the absence of atrophy cannot exclude degenerative disease, the presence of atrophy is not specific: a study describing an 'AD-like' atrophy pattern present in 13% of those with SMD reported that 27% symptomatic individuals with this pattern did not progress within 90 months[164].

Functional Neuroimaging

Functional MRI

Rodda et al. reported increased fMRI activation in the left medial temporal lobe, bilateral thalamus, posterior cingulate and caudate in patients with subjective cognitive impairment compared with healthy controls[165]. Kawagoe et al. described increased resting-state functional connectivity, related to symptom severity, in the lingual gyrus, anterior insula, and superior parietal lobe[149]. The authors of both studies suggest the observations might reflect compensatory activity in early neurodegenerative disease. In contrast, Hu et al. described absent hippocampal activation during a choice-making task in people with SCD compared with controls[166].

Cerebral blood flow

A PET study of regional cerebral blood flow reported decreased flow in left anterior medial prefrontal cortex and increased flow in the cerebellar vermis in patients with major depression and significant cognitive impairment compared to depressed patients without cognitive impairment[167]. Gucuyener et al. reported no differences in cerebral blood velocities as measured by transcranial doppler ultrasound between patients with depressive pseudodementia and AD controls, but impaired vasoneural reactivity to visual stimuli only in AD[168].

Metabolic Imaging

Amyloid Positron Emission Tomography (PET)

If subjective cognitive symptoms often represented an AD prodrome, an association with increased cerebral amyloid deposition would be expected, although amyloid is not specific to AD[169]. Five studies examined cerebral amyloid burden in subjective cognitive impairment or decline, using Pittsburgh B (PiB) or (18) F-florbetapir ligands. Results were mixed. One study reported no difference in amyloid between community SCI participants and healthy controls[151]. Another reported more amyloid in clinical and community SCD participants than in healthy controls[170]. Three studies examined amyloid in relation to cognitive symptoms, finding no association with global cognitive symptom scores, although Amariglio et al. reported a specific association with impaired memory and Perrotin et al. reported, somewhat tenuously, that although those with higher PiB uptake did not report inferior memory, they were less likely to report superior memory than others[146,171,172]. Overall, therefore, of the five included amyloid PET studies, only Perrotin et al. reported a clear association with presence of subjective cognitive symptoms, reporting amyloid-positivity in 9% controls, 29% clinical and 34% community SCD participants[159].

Neurophysiological measures

The authors of two pre-1990 papers on pseudodementia and mixed depression and dementia described diagnostic use of electroencephalography (EEG): more often abnormal in AD[12,173]. Hutton reported worse eye tracking in AD compared with pseudodementia and healthy controls[174]. Examining the P300 late-evoked potential in passive listening and 'oddball' tasks, Gottlieb reported no difference between individuals with pseudodementia and healthy controls[175]. Cespon et al. reported greater medial frontal negativity (a correlate of conflict monitoring) in those with higher levels of SMC[176].

Genetic variables

Prodromal (indeed, preclinical) AD would be expected to be associated with an increased risk of carrying the APOE ε4 allele, the most penetrant genetic risk factor for sporadic AD; but in keeping with systematic reviews of this specific question, five included studies of people with subjective memory symptoms found no increase in APOE ε4 allele prevalence[123,152,155,172,177,178].

Cerebrospinal fluid (CSF) 'biomarkers'

One study found an 'AD profile' of CSF (pathological $A\beta_{42}$:T-tau ratio) more frequent in SCI (52%) than in healthy controls (31%)[58]. Eckerstrom and Garcia-Ptacek found CSF biomarkers more frequently normal in SCI than in MCI or AD[155,179]. Overall, therefore, those with subjective cognitive symptoms appear more likely to have pathological biomarkers than controls, but less likely than those with objective impairment; many described as having SCI do not have markers of degenerative brain disease.

Six included studies reported outcomes of subjective cognitive symptoms in relation to CSF AD biomarkers. Visser reported that no SCI subjects progressed to dementia (including those with a pathological $A\beta_{42}$:T-tau ratio) by 2·3 years[58]. Van Harten reported that low $A\beta_{42}$ alone (without abnormal tau) predicted progression in a clinical population with subjective complaints, but numbers were small: of 132 people with subjective complaints, ten had low $A\beta_{42}$, of whom two (18%) declined over two years; in another cohort described by the same authors, 12 of 115 with subjective complaints had low $A\beta_{42}$, of whom eight (62%) declined[61,62]. Sierra-Rio reported that pathological $A\beta_{42}$:p-tau ratio was associated with progression in SCD; but of 55, 11 had this profile of whom only three (27%) declined[180].

Overall, although CSF AD profiles may be slightly more common in SCD than in normal controls, the predictive value for any individual is uncertain; as eloquently demonstrated by a longitudinal study in

which CSF biomarkers did not improve clinicians' diagnostic or prognostic accuracy in suspected cognitive disorder; sensitivity was the same but specificity lower when CSF biomarker status was available, with most resulting false positive predictions, importantly, in those with subjective complaints only[181].

Neuropsychological test performance

Neuropsychological tests are a pre-requisite in all dementia diagnostic criteria. It is important to consider how those with functional cognitive disorders perform in such tests in order to understand when and how to use them in diagnosis.

Thirteen studies examined neuropsychological test performance in subjective symptoms (a proportion of whom are likely to have functional disorders) in comparison with healthy, MCI, or dementia controls (**Table 4**):[131,152,153,166,182–191] participants generally performed similarly to or worse than healthy controls, but better than MCI or dementia controls.

Nineteen studies examined the relationship between subjective cognitive symptoms and objective cognitive performance (**Table 5**),[149,162,172,185,192–208] ten reporting a relationship between symptom report and measured cognition in at least a subset of participants and nine finding no relationship. Where there was discord, memory complaint exceeded impairment.

Three studies reported that neuropsychological tests had predictive value in subjective cognitive symptoms, reporting associations with decline at one, two, and seven years[55,209,210]. However, while analysis of specific tests and 'forgetting index' in one study identified 79% of those with cognitive complaints converting to dementia within 5-6 years, this model therefore incorrectly predicted dementia in a significant 21%[211]. Jansen et al. did not find that neuropsychological assessment improved dementia classification in 221 memory clinic attenders, increasing false positive predictions of decline in those with SCI[212]. Overall, although mild baseline impairment seems more likely in those with degenerative brain disease, the predictive value of neuropsychological testing for any individual is inaccurate.

Specific cognitive features were described in ten patients with Ganser syndrome: amnesia, approximate answers ('vorbeigehen' – incorrect answers which demonstrate knowledge of the correct answer), fugue or trance-like state and hallucinations[135]. The approximate answer demonstrates internal inconsistency, and can be considered a (rarely described) positive sign of functional cognitive disorder.

Validity tests also demonstrate internal inconsistency, although the utility of validity test failure in discriminating prodromal degenerative brain disease from functional disorders remains unclear. One study reported that 7% of 170 (13% of those under 65) memory clinic patients with MCI, 'uncertain diagnosis', or 'worried well' scored in a 'noncredible' range on the Word Memory Test and/or Test of Memory Malingering[213].

Interactional and linguistic features

Some groups have examined interactional and linguistic features during the consultation. As clinical consensus was used as the 'gold standard' diagnosis in most studies, we note risk of diagnostic suspicion bias, in which clinicians may use the assessed features consciously or subconsciously to make the diagnosis.

Eleven studies described observable differences in behaviour or language during the clinical assessment which discriminated functional cognitive symptoms to those due to degenerative brain disease (**Table 6**)[13,24,35,163,214–221]. Those with functional symptoms were reported to be more likely to attend independently, offer detailed descriptions of complaints and personal history, to produce a written list of complaints; they were less likely to exhibit the 'head turning sign' or otherwise rely on an accompanying adult[13,24,35,215–221].

Cognitive symptom profile

We considered whether any specific cognitive symptoms increased the likelihood of a functional cognitive disorder. Wells reported that patients with pseudodementia reported memory loss for both recent and remote events (vs. relative remote memory preservation in early AD); memory gaps for specific periods or events; dated symptom onset precisely; and had symptoms of short duration and rapid progression[13]. Ahmed et al. reported, in a two-year longitudinal study, that baseline complaints did not differ between 'worried well', amnestic MCI and semantic dementia[222]. Haussman et al. found initial symptoms of attention deficit or word finding impairment more likely in those with SMI and normal objective cognition, compared with those with dementia, in whom first symptoms were more likely 'unspecified', memory impairment, or orientation deficit[134].

The use of symptom 'checklists' was described in two studies of cognitive impairment in depression: Reynolds et al. correctly classifying 90·5% (anxiety, delayed insomnia and loss of libido supporting pseudodementia diagnosis); Yousef et al correctly classified 98% of those with dementia and 95% of those with depression[223,224].

Metacognition

As described, the included studies reported poor concordance between cognitive symptoms and measured performance. Metacognition can be defined as the process of or ability to monitor and evaluate one's own thinking; discordance between memory self-report and performance representing metacognitive error.

A small number of studies examined metacognitions in those with functional or subjective cognitive symptoms. Two studies of functional memory disorders found poorer memory self-efficacy (evaluation of one's own ability) in patients compared with healthy controls[225,226]. Larner found memory self-rating of 'poor' or 'fair' 0·87 sensitive but < 0·5 specific for functional cognitive disorder in memory clinic[36]. Elsey et al. reported that those with functional memory disorder were more concerned about memory symptoms than their companions[218]. Mogle et al. found higher memory ratings compared with others the same age associated with better psychological wellbeing[227]. Chin et al. reported that, in those with normal cognitive testing, subjective memory symptom severity was associated with increased self-focused attention[208].

Illness perceptions

Three studies suggested that illness perceptions influence symptom severity. Negative ageing stereotypes were associated with more subjective memory complaints (and depressive symptoms), whereas factors contributing to 'meaning in life' were associated with fewer complaints[128,207]. The impact of knowledge of genetic risk was explored by Lineweaver et al: participants informed of their APOE ε4 positive status rated their memory worse and performed worse than those who remained unaware that they were APOE ε4 positive[228]. Hurt et al. reported that helplessness, illness identity, serious perceived consequences, emotional representation, and negative comparison with peers were strong determinants of distress and anxiety in adults with SMC[132].

Non-cognitive symptom profile

We examined reported associations between functional cognitive disorders and non-cognitive symptoms in order to consider whether a distinct phenotype could be defined in those with primary cognitive symptoms, having excluded studies of those with primary (non-cognitive) functional neurological disorder, chronic fatigue syndrome, fibromyalgia, major psychiatric disorder other than depressive or anxiety disorders, or cognitive symptoms after physical illness or injury.

The most striking association was between depressive symptoms and cognitive symptom severity, in both clinical and community populations; anxiety symptoms and personality traits (particularly neuroticism) were also frequent associations (**Table 7**)[12,13,67,116,128,129,131,132,159,162,163,172,179,185,187,189,192,196–198,201,202,205,206,208,225,226,229–251]. Depressive symptoms were in some studies associated with objective cognitive impairment[198,206,233,241,252]. Kawagoe et al. reported higher apathy scores in association with cognitive symptom severity[149]. Cognitive symptoms were also reported to be associated with self-reported multimorbidity[253], physical health complaints[234], more pain and analgesia use[107,254], and psychosomatic complaints as measured by SCL-90[225,226]. Five studies reported an association between functional or subjective cognitive symptoms and reported stress[179,207,225,226,255]. Three studies reported an association between SMC severity and more general measures of poor psychological wellbeing[109,189,227,253], two with poorer quality of life[191,195], and one qualitative study reported that presence of subjective memory symptoms had a variable impact on wellbeing[256].

Nine studies described sleep disturbance in association with functional cognitive symptoms. Reynolds et al. described more delayed insomnia, longer recording periods, early-morning waking and higher REM intensity in those with depressive pseudodementia compared to those with dementia[223,245]. Self-report of poor-quality sleep was associated with symptoms in FCD, SMC without objective impairment or AD biomarkers, memory clinic 'complainers' without dementia, and in population cohorts with SMC or perceived decline[33,252,255,257–259]. However, in 181 adults (mean age 74), sleep actigraphy showed less sleep disruption in those with higher, compared with lower, complaint of subjective memory decline; the authors suggesting a 'non-linear trajectory between sleep and memory decline in aging'[260]. An alternative explanation supported by the other studies identified would be that while sleep is more measurably disordered in degenerative brain disease, greater experience of disturbed sleep in those with functional cognitive disorders reflects differences in self-monitoring and expectation.

Age

Age is the most important risk factor for degenerative brain disease. If subjective cognitive symptoms were most often prodromal, a close relationship between symptom prevalence and advancing age would be expected, but this was not confirmed by the included studies. Rowell et al. reported that prevalence of SMC was similar across all age groups in 3,798 18-99 year olds, Derouesne et al. reported that of those self-referring to a memory clinic younger patients rated their symptoms as major and of longer duration, and Apolinario et al. similarly reported that younger patients (from an elderly cohort)

reported a higher number of complaints[235,240,243]. Sinforiani and Gallassi both reported that symptomatic patients without impairment tended to be younger, whereas Arbabi found no difference in age between impaired and unimpaired SMC[237,241,261].

Family history

Family history is a risk factor for degenerative brain disease; but experience of dementia in the family may also influence self-evaluation and help-seeking. Four studies examined memory symptoms in relation to family history of dementia: in McPherson et al. symptom report was similar overall, but relatives of people with early-onset AD reported worse memory than controls, correlating with impairment; in Rue et al. relatives had more memory complaints and depressive symptoms, explained as a possible mediator of slightly poorer performance; Cutler et al. found that although relatives were more concerned about developing AD, this concern was not reflected by memory self-ratings[262–264]. Arbabi found no difference in family history between impaired and unimpaired patients with SMC[241]. Bharambe et al. found higher rates of family history of dementia in memory clinic patients with functional cognitive disorder[37]. Haussman et al. reported more subjective impairment in healthy adults with family history compared to without, an association not present in the MCI group[158], and Hill reported equivalent levels of SMI had a greater impact on emotional wellbeing in those with personal experience with dementia[256].

Discussion

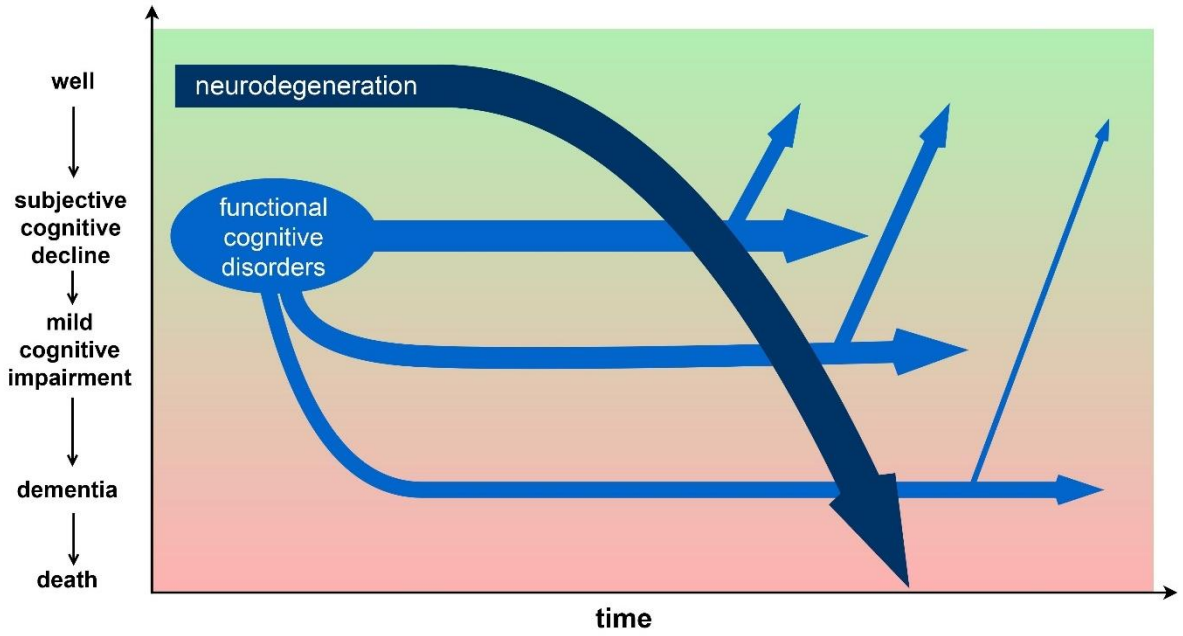
Cognitive symptoms are common: according to this review present in around a third of the population, with no clear relation to age. This alone confirms that that not all cognitive symptoms are caused by degenerative brain disease. In studies of people presenting to memory clinics, we found that only 55% received dementia diagnoses, and in studies including adequate description of diagnoses, 24% were described as having subjective cognitive impairment (with, or without primary psychiatric disorder), pseudodementia, functional cognitive disorder, or a primary psychiatric disorder, and not degenerative brain disease or other medical cause. We consider it likely that many of these individuals could be described as having functional cognitive disorders (FCD).

A striking number of terms used to denote cognitive symptoms in the studies included here denoted only a few concepts: cognitive complaints without aetiological presumption (e.g. ‘subjective memory complaints’); perceived cognitive impairment in the absence of measured impairment or disease (‘worried well’, or ‘clinically/cognitively normal’); progressive symptoms (‘subjective cognitive decline’); and symptoms with positive evidence of non-degenerative cause (‘functional cognitive

disorder', 'depressive pseudodementia'). As terminology varies, so do methods use to ascertain presence and severity of subjective cognitive symptoms: a significant limitation of this body of research is that even of those studies (see **Table 3**) using the same terminology, few used the same measure, and even those using a single question address such various aspects – for example, perceived memory decline, poor memory compared with others, worry about memory, having a poor memory –that it seems unlikely that different studies are describing similar subjective experiences. Historical use of terms such as 'pseudodementia' introduces even more confusion, having been used to describe a wide range of clinical syndromes and aetiologies.

The concepts implied by these terms are important. Authors of SCD and MCI studies tend to view these states as steps on a trajectory towards dementia, paying less attention to possible alternative causes. A dominant linear SCD → MCI → dementia trajectory is not supported by this review or by other, more comprehensive analyses of outcome, which instead suggest multiple overlapping symptom trajectories (**Figure 4**). In Jonker's review of the relationship between memory complaints and dementia, complaints in the 'young-old' were most often related to 'depression, anxiety, or personality factors', predicting dementia only in a small subset[265]. Reisberg et al's description of a 'robustly identifiable clinical entity' lasting 15 years before progressing to MCI is at odds with the observed frequency of cognitive complaints in the general population and lack of excess mortality[56,66,266]. While a systematic review reported increased risk of incident dementia in subjective cognitive impairment, 86% followed up beyond four years did not progress to dementia[148]. Although not explored here, the prevalence of FCD in individuals meeting MCI criteria will be an interesting toping for future research: meta-analysis of MCI progression in 41 cohort studies found that most with MCI did not progress to dementia even after 10 years[267].

Figure 4 – Degenerative brain disease and functional cognitive disorder trajectories



With the ongoing dominance of the SCD → MCI → dementia model, aetiological assumptions have become attached to descriptive terms, limiting the range of interpretation of research findings. As examples: researchers finding an inverse relation between measured sleep quality and SCD severity suggest 'a non-linear trajectory between sleep and memory decline', and researchers finding opposite patterns of resting state fMRI in SCD to those seen in AD hypothesise that these are compensatory responses to neurodegeneration: neither group considering that their findings might indicate functional, rather than AD, pathology[149,165,260]. Although MCI is outside of the scope of this review, efforts to make results fit with the SCD → MCI → dementia model can be seen in studies of AD biomarkers in individuals with MCI, where profiles associated with mildly increased risk (for example, 11% vs 6% over seven years)[142] are described as predictive, with little discussion of the frequency or clinical significance of false positives, when meta-analyses of the same biomarkers report poor accuracy[169,268–271]. For example, review of ^{11}C-PIB-PET as a predictor of MCI conversion to dementia reported test specificity of between 46% and 88%, estimating that for every 100 PIB scans in people with MCI, 28 people with a positive scan would not progress to Alzheimer's dementia.

This is not only a theoretical problem. Reliance on biomarker investigations without a keen awareness of the significant false positive rate risks iatrogenic harm through misdiagnoses; a possibility demonstrated by an included study in which CSF biomarkers did not improve clinicians' prognostic

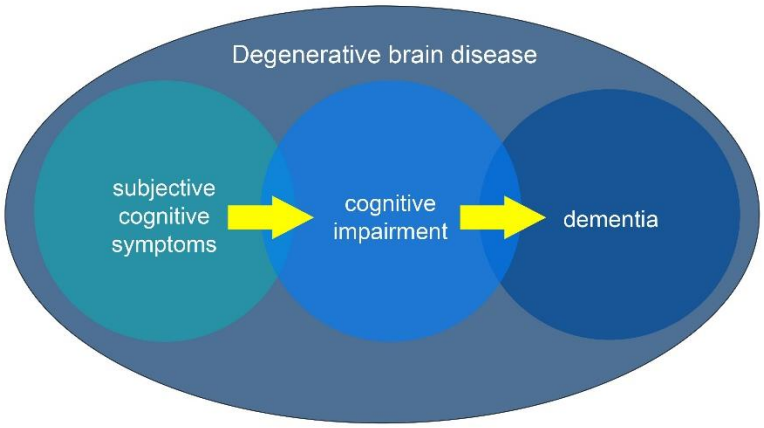
accuracy but resulted in false positive predictions of future decline in patients with subjective complaints[181].

A small proportion of those with subjective cognitive symptoms progress to dementia; more likely where symptoms are new, progressive, where there is cognitive impairment (particularly of an amnestic nature), a degenerative brain disease biomarker profile, or a depressive pseudodementia picture.[s24] For some individuals with dementia it is possible, looking retrospectively, to identify a period of prodromal subjective symptoms, and (particularly in non-AD syndromes) this period may last several years before onset of dementia. Moreover, demonstrably functional cognitive symptoms may result from metacognitive impairment or psychiatric disorder occurring in prodromal Parkinson's Disease, Lewy Body dementia, or frontotemporal dementia, just as functional motor symptoms have been reported in the prodrome of Parkinson's Disease[272]. This area of overlap and comorbidity will be an important area for future research. However, overall, only a minority of subjective cognitive symptoms progress to dementia, and we suggest that this is in part because many of those with subjective cognitive symptoms have functional cognitive disorders (**Figure 5**).

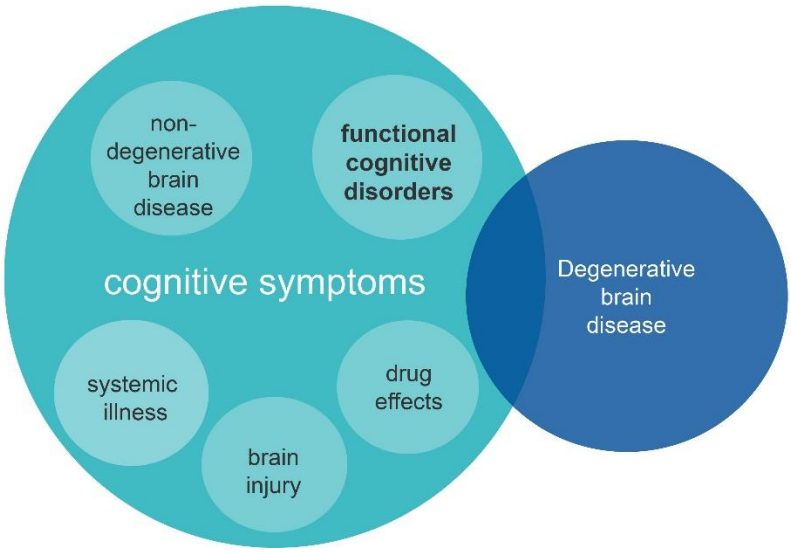
Figure 5 – an alternative model of the cognitive symptoms / degenerative brain disease relationship

The current dominant model (A) places subjective cognitive symptoms within the realm of degenerative brain disease and at the start of a linear trajectory towards dementia. An alternative model (B) acknowledges that cognitive symptoms have multiple aetiologies, including functional cognitive disorders, and only a minority are the result of degenerative brain disease (moreove, many with degenerative brain disease do not complain of symptoms).

A - current dominant model



B - alternative model



Clinically, functional cognitive disorders are, if not exactly under-recognised, considered not to be the primary business of the memory clinic. Functional cognitive disorders are infrequently discussed and

rarely investigated in dementia research despite likely ubiquity in midlife and preclinical cohorts, and there is little evidence to guide diagnosis and treatment. The harm associated with an incorrect clinical prediction of dementia cannot be underestimated. Importantly, though, identifying positive diagnostic profiles for functional cognitive disorders will improve accuracy of early degenerative brain disease diagnoses, so that only those most likely to be on a trajectory towards dementia are included in trials where aetiologically relevant levels of degenerative brain disease are a pre-requisite for target engagement and amelioration of the disease course.

The diverse studies included identified in this review paint a picture of a broad functional cognitive disorder phenotype. Depressive symptoms are the commonest clinical association, in alignment with other reviews of subjective memory symptoms[273,274].[s26,s27] Metacognitive error, present in most populations, was most marked in those with functional cognitive disorders, who significantly overestimated their deficits. Anxiety, neuroticism, negative self-beliefs, increased self-focused attention, and negative views of ageing are associated with more frequent and severe cognitive complaints. Distinctive patterns of behaviour and language during the clinical assessment (**Table 6)**[10,275] are strong candidate positive diagnostic signs for functional cognitive disorders.

Our findings are consistent with the aetiological framework proposed in Teodoro et al's review of cognitive symptoms in functional neurological disorders, fibromyalgia, and chronic fatigue syndrome, which excluded 'pure' cognitive presentations: excessive self-attention and metacognitive error (supported by negative illness beliefs) lead to heightened experience of cognitive failure, effort, and illness (exacerbated by depressive symptoms, anxiety, and neuroticism), resulting inattention and cognitive failures maintaining the cycle[9].

An inevitable limitation of this review results from difficulty in aligning results of studies using widely varying terminology and symptom assessment methods: our analyses of prevalence rates can be considered broadly indicative rather than precise. Our attempt to define and identify FCD from within the wider cognitive disorder is a necessary preliminary to future research. From here, prospective studies will be important to provide evidence for the utility of specific clinical features in making a positive (rather than by-exclusion) diagnosis, in order to define populations for much-needed trials of treatment, reduce iatrogenic harm, and improve accuracy of early degenerative brain disease diagnoses.

Tables

Table 2 – Cross sectional studies of diagnosis following assessment for suspected cognitive disorder, ordered by year of publication (n=39)

(studies in italics are excluded from summary statistics)

Studies	Clinical Setting	Population	N	Mean age (range); *% female*	n (%) dementia or another 'organic' cognitive disorder	n (%) MCI or equivalent	n (%) not dementia or another 'organic' cognitive disorder	n (%) subjective cognitive impairment +/- psychiatric disorder / pseudodementia*	n (%) specifically defined as functional cognitive disorders (FCD)	Descriptive terminology used to denote FCD, SCI (+/- psychiatric disorder), or pseudodementia diagnosis	Factors associated with FCD , SCI (+/- psychiatric disorder), or pseudodementia diagnosis
Marsden & Harrison 1972	Neurological hospital	patients admitted with a presumptive diagnosis of dementia	106	'pre-senile'; *not stated*	83 (78)			10 (9.4)		8 (7.5%) depression, 1 hysteria, 1 mania	
Smith & Kiloh 1981	Neuropsychiatric institute	patients admitted with provisional diagnoses of dementia	200	57.7; *49%*	90 (45)			20 (10)		pseudodementia (10 (5%) depressive illness, 7 (3.5%) schizophrenia, 2 (1%) hypomania, 1 (0.5%) depression and thyrotoxicosis)	Abrupt onset, short duration, depressive features, normal Ix.
Rabins 1981	Psychiatric hospital	patients admitted with diagnosis of dementia or >60 with depression	57	not stated; not stated	37 (65)			13 (23)		cognitive impairment resolved with treatment of depression	
Reifler et al. 1982	Geriatric and Family Services Clinic	cognitively impaired geriatric outpatients	88	78; 71%				3 (3.4)		depression only accounting for cognitive symptoms	

Studies	Clinical Setting	Population	N	Mean age (range); *% female*	n (%) dementia or another 'organic' cognitive disorder	n (%) MCI or equivalent	n (%) not dementia or another 'organic' cognitive disorder	n (%) subjective cognitive impairment +/- psychiatric disorder / pseudodementia*	n (%) specifically defined as functional cognitive disorders (FCD)	Descriptive terminology used to denote FCD, SCI (+/- psychiatric disorder), or pseudodementia diagnosis	Factors associated with FCD , SCI (+/- psychiatric disorder), or pseudodementia diagnosis
Yerby et al. 1985	Geriatric and Family Services Clinic	patients presenting with complaints of memory loss	117	75.81; 72%	87 (74)			19 (16)		13% primarily depressed, 2.5% psychiatric or functional (postconcussion syndrome, paranoia, psychosis)	
Bayer et al. 1987	Memory clinic	patients referred for assessment	100	74.2; 47%	67 (67)			12 (12)		9 depression, 3 'no significant problem'	
Van der Cammen et al. 1987	Memory clinic	patients referred for assessment	50	75.2; 64%	28 (56)			10 (20)		10% affective disorder, 10% no memory deficit and no diagnosis	
Erkinjuntti et al. 1987	Neurology outpatient clinic	patients evaluated because of suspected dementia	323	50.4; 55%	184 (57)			58 (18)		14% psychiatric disorder, 4.2% normal	Younger age
Derouesne et al. 1989	Memory clinic	subjects who attended a Memory clinic	367	62.9; 69%	26 (7)			62 (17)		'psychoactive brain dysfunction'	
Brodaty et al. 1990	Memory disorders clinic	patients attending the Memory Disorders Clinic	144	69.5; 61%	106 (74)			27 (19)		12 (8.3%) psychiatric, 9 (6.3%) 'normal / anxious personality', 6 (4.2%) benign senescent forgetfulness (confirmed by no decline at 22 month follow-up)	Younger age

Studies	Clinical Setting	Population	N	Mean age (range); *% female*	n (%) dementia or another 'organic' cognitive disorder	n (%) MCI or equivalent	n (%) not dementia or another 'organic' cognitive disorder	n (%) subjective cognitive impairment +/- psychiatric disorder / pseudodementia*	n (%) specifically defined as functional cognitive disorders (FCD)	Descriptive terminology used to denote FCD, SCI (+/- psychiatric disorder), or pseudodementia diagnosis	Factors associated with FCD , SCI (+/- psychiatric disorder), or pseudodementia diagnosis
Weiner et al. 1991	Clinic for Alzheimer's and Related Diseases	individuals with subjective complaint or cognitive impairment	317	not stated (all ages); not stated	295 (93)	6 (2)		11 (3.4)		2.5% depression, 1% somatization disorder	
Ames et al. 1992	Memory clinic	patients referred	100	75.5; 75%	74 (74)			11 (11)		6% functional psychiatric disorder, 3 of 4 'other' ('marital problem', malingering, unspecified mental disorder'), 2 'nil' diagnosis	
Verhey et al. 1993	Multidisciplinary memory clinic	patients referred to and evaluated at the clinic	430	61.7; 44%	150 (35)			155 (36)		45 (10%) depression, 18 (4.2%) another psychiatric disorder	
Almeida et al. 1993	Memory clinic	patients assessed	418	66.7; 57%	288 (69)			125 (30)		non-organic cause - 24% 'memory complainers, no diagnosis', 6% mood or neurotic disorders	Family history of dementia, unmarried, self-referred, younger, female
Wright and Lindesay 1995	20 memory clinics in the British Isles	Patients assessed during previous year	Not reported		Not reported (74.9)						
Swanwick et al. 1996	Specialist memory clinic	patients attending	200	74.3; 71.5%	187 (94)	8 (4)	5 (6.5)				

Studies	Clinical Setting	Population	N	Mean age (range); *% female*	n (%) dementia or another 'organic' cognitive disorder	n (%) MCI or equivalent	n (%) not dementia or another 'organic' cognitive disorder	n (%) subjective cognitive impairment +/- psychiatric disorder / pseudodementia*	n (%) specifically defined as functional cognitive disorders (FCD)	Descriptive terminology used to denote FCD, SCI (+/- psychiatric disorder), or pseudodementia diagnosis	Factors associated with FCD , SCI (+/- psychiatric disorder), or pseudodementia diagnosis
Lehmann et al.1996	Memory center' (outpatient clinic)	patients who sought help at the memory center	406	62.9; 54%	48 (24)	142 (35)		154 (38)		'no cognitive disturbance' (of whom 69 (17%) other psychotic symptoms, 46 (11.3%) depressive or neurotic symptoms, 7 (1.7%) neurasthenia, 3 personality disorder, 1 schizophrenia)	Self-referral, psychiatric disorders
Kopelman & Crawford 1996	Neuropsychiatry and memory disorders clinic	clinic attenders	200	43.7; 37%	26 (13) [114 (57) 'organic cognitive impairment]			86 (43)		Include: 37 (18.5%) depression, 10.5% psychogenic amnesia, 9% PTSD, 1.5% 'worried well', 2 (1%) severe bereavement reaction	
Hogh et al. 1999	Multidisciplinary memory clinic	patients referred with symptoms & possible dementia	400	63.6; 48%	288 (72)			104 (26)		45 (11%) 'no psychiatric disease', 34 (8.5%) depression, 10 (2.5%) personality disorder, 5 (1.3%) schizophrenia, 3 0.7%) psychotic disorder, 2 (0.5%) anxiety disorder	
Luce et al. 2001	Memory clinic	patients referred	100	68.9; 56%	57 (57)			17 (17)		9% depression, 7% subjective memory impairment, 1% anxiety	

Studies	Clinical Setting	Population	N	Mean age (range); *% female*	n (%) dementia or another 'organic' cognitive disorder	n (%) MCI or equivalent	n (%) not dementia or another 'organic' cognitive disorder	n (%) subjective cognitive impairment +/- psychiatric disorder / pseudodementia*	n (%) specifically defined as functional cognitive disorders (FCD)	Descriptive terminology used to denote FCD, SCI (+/- psychiatric disorder), or pseudodementia diagnosis	Factors associated with FCD , SCI (+/- psychiatric disorder), or pseudodementia diagnosis
	Old age psychiatry catchment area service	patients referred	100	80.9; 65%	78 (78)			15 (15)		8% depression, 6 neurotic disorders, 1 schizophrenia	
Hejl et al. 2002	Multidisciplinary memory clinic	patients referred for diagnostic evaluation	1000	66.1; 53%	580 (58)	170 (17)		240 (24)		14% 'no neuropsychiatric disease', 10% depression	
Elberling et al. 2002 - subset of population studied in Hejl 2002	*Multidisciplinary memory clinic*	*patients referred age <60*	*314*	*47.6; 44%*	*15%*					'no cognitive deficits': of whom 29% no neuropsychiatric disease, 14.6% depression, 4.5% personality disorder, 1% each schizophrenia, anxiety disorder, PTSD, persistent mood disorder, 2.2% miscellaneous. Note: of those described as having neurologic disease 0.6% (2) had 'whiplash sequelae'	Family history of old-age dementia
Hejl et al. 2003	Memory clinic	patients referred for diagnostic evaluation	100	74.2; 59%	55 (55)	11 (11)		20 (20)		24 (12%) affective disorder, 5 (2.5%) other psychiatric disorder, 10 (5%) no neuropsychiatric disorder	
Larner 2005	cognitive function clinic (neurology-led)	new referrals seen	247	not stated; not stated	121 (49)		126 (51)			Functional cognitive disorder	Attending alone

Studies	Clinical Setting	Population	N	Mean age (range); *% female*	n (%) dementia or another 'organic' cognitive disorder	n (%) MCI or equivalent	n (%) not dementia or another 'organic' cognitive disorder	n (%) subjective cognitive impairment +/- psychiatric disorder / pseudodementia*	n (%) specifically defined as functional cognitive disorders (FCD)	Descriptive terminology used to denote FCD, SCI (+/- psychiatric disorder), or pseudodementia diagnosis	Factors associated with FCD , SCI (+/- psychiatric disorder), or pseudodementia diagnosis
Banerjee et al. 2007	Memory service	referrals assessed by the Memory Service	247	not stated; 64%	156 (63)			74 (30)		'no illness'	
Hancock and Larner 2009	Cognitive disorders clinic	Patients evaluated (2006-2008)	310	66.9; 49%	155 (50)						
Kenfield et al. 2010	Neurobehaviour clinic	patients seen at the clinic	342	(60.6 for the 109 with nonneurologic conditions - overall age not stated); 54% of 'nonneurologic	218 (62)	21 (6)		92 (27)		20% psychiatric disorder, 7% no neuropsychiatric disorder (not including 5% medical	Family history most common in non-neuropsychiatric group (56%), intermediate in psych (45.6%), lowest in medical (35%)
Wang et al. 2011	Memory clinic	patients who attended the clinic	2789	not stated (58% >70); 58%	1459 (52)	635(23)		695 (25)		21.7% subjective cognitive impairment, 3.3% neurosis	
Menon & Larner 2011	Cognitive disorders clinic	patients evaluated - 2004-2006	231	not stated; not stated	118 (51)		58 (49)				
		- 2008-2009	225	not stated; not stated	74 (33)		151 (67)				
		- 2009-2010	252	not stated; not stated	76 (30)		176 (70.0)				
Mascherek et al. 2011	Memory clinic	patients assessed at the clinic	169	76; 59%	66 (39)	40 (24)		63 (37)		Subjective cognitive complaints	Lower education and depressive affect

Studies	Clinical Setting	Population	N	Mean age (range); *% female*	n (%) dementia or another 'organic' cognitive disorder	n (%) MCI or equivalent	n (%) not dementia or another 'organic' cognitive disorder	n (%) subjective cognitive impairment +/- psychiatric disorder / pseudodementia*	n (%) specifically defined as functional cognitive disorders (FCD)	Descriptive terminology used to denote FCD, SCI (+/- psychiatric disorder), or pseudodementia diagnosis	Factors associated with FCD , SCI (+/- psychiatric disorder), or pseudodementia diagnosis
Pennington et al. 2015	Cognitive clinic	patients on research database after cognitive clinic assessment	196	not stated; not stated					24 (12)	Functional cognitive disorder	
Claus et al. 2016	Memory clinic	patients with cognitive complaints	2000	78.2; 60%	1063 (53)	492 (25)		445 (22)		Subjective cognitive impairment	Higher education, younger age, white matter lesions.
Sheng et al. 2018	Memory clinic	patients referred	454	76.1; 60.4%	386 (85)	27 (6)		14 (3)		18 (4%) 'normal cognition', 15 (3.3%) psychiatric causes of reversible dementia (9 (2%) depression, 3 (0.7%) anxiety disorder, 2 (0.4%) psychosis, 1 (2.2%) adjustment disorder)	
Verity et al. 2018	Memory clinic	patients seen	375	70.76; 57%	247 (78)			83 (22)		Worried well	Higher education, previous psychiatric diagnosis, higher alcohol intake, sleep problems.
Elhadd et al. 2018 and ***Bharambe & Larner 2018***	Cognitive disorders clinic	new outpatients	89	median 62 (22-88); 48%	9 (10) dementia	26 (29)			51 (57)	Functional cognitive disorder	Disturbed sleep on dichotomised Jenkins Sleep Scale (83% vs 50%); SMC likert (poor or fair), attending alone, 'la maladie du petit papier', family history.

Studies	Clinical Setting	Population	N	Mean age (range); *% female*	n (%) dementia or another 'organic' cognitive disorder	n (%) MCI or equivalent	n (%) not dementia or another 'organic' cognitive disorder	n (%) subjective cognitive impairment +/- psychiatric disorder / pseudodementia*	n (%) specifically defined as functional cognitive disorders (FCD)	Descriptive terminology used to denote FCD, SCI (+/- psychiatric disorder), or pseudodementia diagnosis	Factors associated with FCD , SCI (+/- psychiatric disorder), or pseudodementia diagnosis
Randall et al. 2018	Cognitive disorders clinic	new outpatients	169	median 60; 47.6%	69 (41) 'cognitive disorders'		100 (59)			No cognitive impairment	
Bharambe & Larner 2018	Cognitive disorders clinic	new outpatients	169	60; 53%	30 (18)	41 (24)			95 (56)	Functional cognitive disorder	
Larner 2018	Cognitive disorders clinic	new outpatients	50	60.5 median (26-84); 52%	4 (8)	20 (40)		26 (52)		Subjective memory complaints	
Total: 39 studies			**13637**	**69 (of N=8628); 57% female (of N=11664)**	**7173 (54% of N=13353), including other 'organic' cognitive disorders**	**1686 (20% of N=8460)**	**616 (47% of N=1324)**	**2662 (22% of N=11549)**	**170 (37% of N=11549)**		

*** a proportion of cases defined as such may be alternatively described as having functional cognitive disorders (FCD)**

Table 3 – Studies reporting prevalence of cognitive symptoms in non-clinical populations (n=38)

(studies in bold also reported longitudinal data)

Name	Population	N	Mean age (range); % female	% symptoms	Terminology	Symptom prevalence assessment method; other measures of cognitive symptoms
Grut et al. 1993	all inhabitants of an area in Sweden	614	(>75); not reported	30%	memory complaints	Single item from Comprehensive Psychopathological Rating Scale (CPRS) (Perris et al 1984): '1. No memory complaints, 2. Occasional memory disturbances, 3. Disturbance embarrassing or almost total memory loss'
Spear-Bassett et al. 1993	Eastern Baltimore Mental Health Survey	810	(18-92); 65%	22%	memory complaint	Single question: 'Do you find that you have trouble with your memory?'
Jorm et al. 1994	electoral roll sample of elderly people	744	(>70); 49%	62%	memory complaints	Single question (part of study-specific questionnaire): 'Overall, do you feel you can remember things as well as you used to? That is, is your memory the same as it was earlier in life?'
Tobiansky 1995	Gospel Oak Study (electoral ward sample)	705	74.6; 63%	25%	subjective memory impairment	≥3 on short-CARE SMI scale
Collins et al. 1996	recruited through advertisement to Michigan State University Psychological Clinic Aging Research Project	90	70.4; 74%	42%	subjective memory complaints	MAC-S score ≤19
Smith et al. 1996	population-based older americans normative study	394	72.1; 56%	78%	subjective memory complaints	Single item from MFQ (Gilewski et al. 1990): 'How would you rate your memory in terms of the kinds of problems you have?'
Blazer et al. 1997	Duke Established Populations for Epidemiologic Studies of the Elderly	3080	72; 67%	56%	memory complaint	Single question: 'Is your memory getting worse?'
Braekhus et al. 1998	Norwegian population cohort ≥ 75	285	81.5; 78%	37%	subjective worsening of memory	Single question 'Is it more difficult to remember things than it used to be?'
St John et al. 2002	Manitoba Study of Health and Aging	1416	75.3; 60%	21%	subjective memory loss	Single question: 'Please tell me if you have had memory loss in the past year.'

Name	Population	N	Mean age (range); % female	% symptoms	Terminology	Symptom prevalence assessment method; other measures of cognitive symptoms
Jungwirth et al. 2004	75 year-olds from population register	302	75; 63%	11%	subjective memory complaints	Single question: 'Do you have complaints about your memory in the last 2.5 years?'
Wolf et al. 2005	research clinic volunteers	46	61.8; 54%	59%	subjective memory complaints	2 on Global Deterioration Scale: 'Subjective complaints of memory deficit, most frequently in following areas: (a) forgetting where one has placed familiar objects; (b) forgetting names one formerly knew well'; MAC-Q
Lautenschlager et al. 2005	community-dwelling women >70 recruited via advertisement	264	74.5; 100%	60%	subjective memory complaints	Single question: 'Do you have any difficulty with your memory?'
Glodzig-Sobanska et al. 2007	volunteers ('normal subjects' to a study of aging	230	67; 66%	81%	subjective memory complaints	GDS = 2: 'awareness and complaint of memory change in comparison with prior adult capacity, in the absence of objective evidence of memory or functional problems'
Park et al. 2007	Ajou-Bundang Study for the Elderly cohort	9477	72.6; 61%	57%	subjective memory complaints	'Do you think you are suffering from memory impairment in comparison to a year ago?'
Van Oijen 2007	Rotterdam Study (population-based cohort)	6927	69.5; 60%	19%	subjective memory complaints	Single question: 'Do you have memory complaints?'
Brucki and Nitrini 2009	Adults with low education, rural amazon rainforest	163	62.3; 50%	70%	subjective memory impairment	Single question: 'Do you have memory problems?'
Westoby et al. 2009	Population from 3 GP practice registers	7878	66.3; 56%	47%	cognitive complaint	>0 on Alertness Behaviour Subscale of Sickness Inventory Profile
Gino et al. 2010	volunteers attending health screening unit, blood donors, leisure centre, senior citizens college or university in Lisbon	946	54.2; 60%	76%	Subjective memory complaints	Item 1 of SMC scale: 'Do you have any complaints concerning your memory?'; SMC Scale (Schmand et al 1996)
Slavin et al. 2010	electoral roll	827	63; 68%	65%	subjective cognitive complaints	Single question: 'Have you noticed difficulties with your memory?'; MAC-Q
Amariglio et al. 2011	women participating in the Nurses' Health Study	16964	74; 100%	56%	subjective memory complaints	Study-specific questionnaire

Name	Population	N	Mean age (range); % female	% symptoms	Terminology	Symptom prevalence assessment method; other measures of cognitive symptoms
Aarts et al. 2011	population postal survey	15188	70; 33%	2%	Subjective memory complaints	'Do you consider yourself forgetful?' **AND** 'Have your memory complaints increased in the past year?'
Cooper et al. 2011	Adult Psychiatric Morbidity Survey	7461	45; 57%	32%	subjective forgetfulness	Single question: 'Have you noticed problems with forgetting in the last month?'; MFQ
Paradise et al. 2011	45 and Up Study (Australia cohort) between 45 and 64 years	45532	(>45); 55%	12%	subjective memory complaints	Subjective Memory Complaints (SMC) Likert: 'In general, how would you rate your memory?' 1 poor, fair, good, very good, 5 excellent
Bartley et al. 2012	healthy subjects recruited through public awareness meetings in retirement clubs and from relatives of impaired subjects	96	61.8; 73%	54%	subjective memory complaints	Single question and 4 questions from SMC scale (Schmand et al 1996)
Caracciolo et al. 2012	population based sample of twins	11926	(≥65); 55%	39%	subjective cognitive impairment	Single question: 'Have you noticed any change in your memory during the last three years?'
Balash et al. 2013	volunteer or self-referral	636	68; 61%	80%	subjective memory complaints	Single question: Do you feel like your memory or thinking is becoming worse? (1=no, 2=yes but not worried, 3=yes and worried)
Genziani et al. 2013	Population survey (French community surveys)	9294	74.3; 21%	21%	subjective memory impairment	3C study-specific questionnaire
Ito et al. 2013	Population survey	2034	74.6; 60%	46%	subjective memory complaints	'Do you feel that your memory has worsened in the last 6 months?'
Rijs et al. 2013	Longitudinal Aging Study Amsterdam	910	60.2; 52%	21%	memory complaints	'Do you have complaints about your memory?'
Siersma et al. 2013	People attending GP (any reason)	758	74.8; 61%	23%	subjective memory complaints	'less good', 'poor', or 'miserable' for 'How would you judge your memory?'

Name	Population	N	Mean age (range); % female	% symptoms	Terminology	Symptom prevalence assessment method; other measures of cognitive symptoms
Acikgoz et al. 2014	Patients attending neurology, cardiology, and physical therapy clinics but NOT for cognitive complaints	405	64.5; 63%	43%	subjective memory complaints	Single question: 'Do you have forgetfulness which affects your daily life?'; SMC scale
Begum et al. 2014	Population sample (English Psychiatric Morbidity surveys 1993, 2000, 2007)	26091	42; 51%	9.6%	subjective memory complaints	Single question: 'Have you noticed any problems with forgetting things in past month?' + problem noticed ≥ 1 day / past week
Caselli et al. 2014	healthy members of Arizona Apolipoprotein E cohort	447	59; 69%	31%	subjective cognitive decline	Score >0 on Multidimensional Assessment of Neurodegenerative Symptoms questionnaire (MANS)
Chen et al. 2014	telephone survey of representative community population	4423	(18-39); not reported	14%	subjective memory impairment	'a single question about the presence of perceived memory problems'
		6365	(40-59); not reported	22%		
		6365	(60-99); not reported	26%		
Mewton et al. 2014	NSMHWB sample - population survey	1905	(65-85); not reported	34%	subjective memory complaints	Study-specific questionnaire: 'Compared with others your age, how would you rate your memory?' and 'Compared with 5 years ago, how would you rate your memory?'
Singh-Manoux et al. 2014	French GAZEL study	15510	57.9; 26%	56%	subjective cognitive complaints	Single question (part of study-specific questionnaire): 'Have you experienced memory problems?'
Tomita et al. 2014	volunteers >60 participating in 'Iwaki Health Promotion Project' (2011)	394	68.7; 65%	24%	subjective memory complaints	Single question: 'Have you been distressed by your forgetfulness?'
Kaup et al. 2015	community-dwelling older women in a study of ageing	1107	70.8; 100%	8%	subjective memory complaints	Single question: 'Do you feel you have more problems with memory than most?'
Montejo et al. 2011 (also described in Montejo et al 2012, and Montejo et al 2016)	Madrid Health Survey	1637	74.7; 60%	32%	subjective memory complaints	Single question: 'Do you have memory problems?'

Name	Population	N	Mean age (range); % female	% symptoms	Terminology	Symptom prevalence assessment method; other measures of cognitive symptoms
Roehr et al 2016	Leipzig longitudinal study of the aged (LEILA75+)	453	80.5; 73%	31%	subjective cognitive decline	'assumed if unimpaired and stated to have memory problems unrelated to an event or condition explaining the memory problems according to recent research criteria.'
Tanaka et al. 2016	twins age ≥ 20 years	556	51; 70%	72%	subjective memory complaints	Single question: 'Do you consider yourself as being forgetful?' during past week (0 not at all to 4 extremely)
Wolfsgruber et al. 2016 (smaller subset of this cohort also described in Jessen et al. 2007)	cognitively normal participants AgeCoDe study	1990	80.1; 66%	32%	subjective memory complaints	Single question: 'Do you feel like your memory is becoming worse?'
Kuiper et al. 2017	older adults in LifeLine cohort study	8762	70; 52%	55%	subjective memory complaints	Single question: 'Do you have complaints about your memory?'
Markova et al. 2017	cognitively healthy volunteers	340	75; 55%	71%	subjective cognitive complaints	≥ 1/10 complaints on QPC questionnaire
Sakurai et al. 2017	'local resident registration' - >65, no cognitive impairment (MMSE>24)	496	72.7; 57%	45%	subjective memory complaints	Single question: 'Do you have problems with your memory?'
Yates et al. 2017	older people in MRC-CFAS population-based study	1344	74; 64%	41%	subjective memory complaints	'Yes' to any of: 'Have you ever had difficulty with your memory', 'Have you tended to forget things recently?' and 'Have you had any difficulty with your memory'
Avila-Villanueva et al. 2018	Vallecas Project cohort	1091	74.7; 64%	78%	Subjective cognitive decline	Study-specific questionnaire
Cosentino and Devanand 2018	Participants in North Manhattan Aging Project (NMAP)	471	72.8; 67%	58%	subjective memory complaints	Endorses least one symptom 10-item subjective memory complaint scale from Comprehensive Assessment and Referral Interview (CARE)

Name	Population	N	Mean age (range); % female	% symptoms	Terminology	Symptom prevalence assessment method; other measures of cognitive symptoms
Nunes et al. 2018	Brazil final year medical students	59	25.7; 46%	71%	self-perceived memory difficulties, memory complaints	SMC scale score ≥3 (Schmand et al 1996)
Flatt et al. 2018	older (>50) LGBT adults from LGBT community centre	210	59.6; 24%	25%	subjective cognitive decline	Memory problems AND problems in one other cognitive domain; as part of Medical Outcomes Study (MOS) HIV health survey
Hall et al. 2018	cognitively normal Mexican-American elderly people in a cohort study (HABLE)	319	58.91; 80%	42%	cognitive complaints	Single question: 'each participant was asked if they were concerned about changes in memory and thinking. Those responding in the positive were classified as having subjective cognitive complaints.'
Sanchez-Benzvides et al. 2018	cohort of cognitively healthy middle-aged first-degree descendents of AD patients (47.4% onset <75)	2670	55.8; 63%	21%	subjective cognitive decline-plus	Single question: 'Do you perceive memory or cognitive difficulties?'; SCD-Q
Schweizer et al. 2018	Cam-CAN cohort of adults free of neuropsychiatric disorders	2544	59.5; 56%	38%	subjective memory complaints	Single question: 'Do you feel you have problems with your memory?'
Luck et al. 2018	40-79 general population - LIFE adult cohort	8834	58.8; 52%	53%	subjective cognitive symptoms	Single question (part of study-specific questionnaire): 'Do you feel as if your memory is becoming worse?'
Meyer et al. 2018	stratified sample adults ≥ 55	600	70.3; 50%	39%	subjective memory complaints	Study-specific questionnaire: memory poor AND interferes with life
Brailean 2019	English Longitudinal Study of Ageing	11092	65.3	57%	subjective memory complaints	'poor' or 'fair' on SMC Likert
Total:		**245654**		**30%**		

Table 4 – Neuropsychological test performance in comparison with controls

Observation Study name	Description of participants (cases)	Measure
No impairment compared with asymptomatic healthy controls		
Benito Leon et al. 2010	subjective memory complaints (community sample)	MMSE et al.
Wakefield et al. 2018	functional memory disorder	MMSE et al.
Jenkins et al. 2019	healthy volunteers with and without SCI	Similar multi-item localization (MILO) task performance
Smart et al. 2015	subjective cognitive decline (community sample)	Iowa gambling task
Impaired compared with asymptomatic healthy controls		
Archer et al. 2006	MCI and SNCI (symptoms no cognitive impairment)	SCNI impaired on immediate and delayed recall (MMSE) and TRAILSB
Gainotti et al. 2008	depressive pseudodementia	Rey's Auditory Verbal Learning Test
Benito Leon et al. 2010	subjective memory complaints (community sample)	Verbal fluency and recall (MMSE)
Puetz et al. 2011	functional memory disorder	Similar declarative memory consolidation before but impaired after a night of sleep
Svendsen et al. 2012	patients with affective disorders	Impaired on cognitive screening tests
De Paula et al. 2013	patients with depressive pseudodementia	Impaired immediate and delayed recall but preserved recognition memory (RAVLT)
Lehrner et al. 2014	patients with cognitive complaints	Impaired compared with controls
Hu et al. 2017	subjective cognitive decline (clinical sample)	increased delay-discounting on an intertemporal decision-making task
Jenkins et al. 2019	healthy volunteers with and without SCI	Some with SCI had disproportional slowing and greater intra-individual reaction time variability
Similar performance to non-help-seekers with SMC		
Ramakers et al. 2009	subjective memory complaints (clinical sample)	Similar MMSE performance to non-help-seekers
Less impaired than MCI controls		
Archer et al. 2006	MCI and SNCI (symptoms no cognitive impairment)	MMSE et al.
Wakefield et al. 2018	functional memory disorder	MMSE et al.
Less impaired than dementia controls		
Gainotti et al. 2008	depressive pseudodementia	RAVLT
Sahin et al. 2017	depressive pseudodementia	Wechsler Memory Scale (WMS) subtests et al.
Wallert et al. 2018	subjective cognitive impairment (clinical sample)	Simple reaction time faster than in dementia or MCI

Table 5 – Relationship between cognitive symptoms and measured performance

Study	Cognitive symptoms associated with objective cognitive impairment?	Setting	Participants	
Larrabee and Levin 1986	Yes	community	volunteers	self-rated remote memory associated with objective measures of recent and remote memory.
Sunderland et al. 1986	Yes	community	healthy adults	subjective memory correlated weakly with test performance.
McGlone et al. 1990	No	clinical	patients with and without dementia; HC	symptom scores did not differ between patients with and without dementia.
Rabbitt and Abson 1990	No	community	volunteers	
Bolla et al. 1991	No	community	volunteers	
Christensen et al. 1991	Yes	community	volunteers with 'memory problems'; dementia; HC	objective performance and complaint associated in subgroup; no relationship between specific everyday failures and objective performance
Crook and Larrabee 1992	Yes	clinical	AAMI	self-rated memory correlated with memory test scores
Lucas et al. 2003	Yes	clinical	medically unexplained cognitive difficulties	50% had objective cognitive impairment, which was associated with depressed mood.
Jungwirth et al. 2004	No	community	75 year olds	
Zandi 2004	Yes	clinical	memory clinic patients	
Minett et al.2005	No	clinical	memory clinic patients	subjective memory complaints no longer correlated with cognitive performance when white matter lesion severity and depressive symptoms were controlled for
Pearman et al. 2005	No	community	volunteers	
Jessen et al. 2007	No	community	volunteers without dementia or MCI	SMI were only associated with impaired delayed recall in a non-depressed subset
Gallassi et al. 2008	Yes	clinical	memory clinic patients with SCC	49/92 had objective deficits
Mendes et al. 2008	No	community	healthy volunteers	
Svendsen et al. 2012	No	clinical	outpatients with bipolar and unipolar depression; HC	
Buckley et al.2013	No	community	elderly volunteers	
Rijs et al. 2013	Yes	community	aging study cohort participants 55-64	SMC associated with poorer delayed recall and decline in learning ability
Steinberg et al. 2013	Yes	community	volunteers ≥ 65 without cognitive impairment	SMC associated with poorer executive function and delayed recall
Lehrner et al. 2014	Yes	clinical	patients with cognitive complaints; HC	
Chin et al. 2014	No	clinical	memory complaints but normal cognitive testing	

Tomita et al. 2014	Only in men	community	healthy volunteers	SMC associated with objective impairment on MMSE only in men, not women
Zlatar et al. 2014	Yes	community	participants in study of ageing	weak association between cognitive symptoms and cognitive function; moderate association between cognitive symptoms and depressive symptoms
Chu et al. 2017	Yes	clinical	>60 + history of depression; HC	SMC associated with worse recall only in those with depression history.
Kang et al. 2017	No	community	Population-based cohort	
Schweizer et al. 2018	No	community	Healthy volunteers	
Schwert et al. 2018	No	clinical	depressed outpatients; HC	Cognitive complaints exceeded measured deficits in depressed outpatients. HC overestimated own cognitive function
Slot et al. 2018	Yes	clinical	memory clinic patients with SCD; HC	
Kawagoe et al. 2019	No	clinical	individuals with SMC	

Table 6 – Interactional, linguistic, and behavioural variables

Study	n cases (controls)	Description of participants	Comparitors	Measure	Relationship
Linguistic / conversation analysis of clinical assessment					
Wells 1979	10	pseudodementia		clinical assessment	pseudodementia: detailed description of complaints, 'don't know' answers, complain of memory loss 'with vigour and feelings'
Elsey et al. 2015	15 (15)	functional memory disorder	neurodegenerative disease	conversation analysis	those with functional memory disorder interacted more confidently, provided extended and detailed accounts of difficulties
Jones et al. 2016	16 (9)	functional memory disorder	neurodegenerative disease	conversation analysis	functional memory disorder: more detailed account of memory failures, able to answer personal questions, display working memory in interaction, respond to compound questions, more time taken to respond
Mirheidari et al. 2017	15 (15)	functional memory disorder	neurodegenerative disease	conversation analysis with machine learning techniques (manual transcripts)	automated analysis using Elsey et al. 2015 features, number of unique words & 'accompanying person' turns correctly classified 93-97%
Alexander et al. 2018	17	functional memory disorder		communication features	functional memory disorder: draw attention to how symptoms differ from normal, report 3rd-party observations and 3rd-party speech
Lundholm Fors et al. 2018	54 (36)	subjective cognitive impairment and MCI	healthy controls	syntactic analysis of 'Cookie-Theft' transcriptions	no difference in syntactic complexity between groups
Reuber et al. 2018	20 (20)	functional memory disorder	neurodegenerative disease	conversation analysis	linguistic and interactional features predict diagnoses of neurodegenerative disease or functional memory disorder
Attending alone					
Larner 2005	247	cognitive clinic attenders		attending alone despite written instruction to bring relative, friend, or carer	'attending with' 100% sensitive and 35% specific for dementia
Larner 2014	726	cognitive clinic attenders		attending alone despite instruction to bring a relative, friend, or carer	attending alone was 100% sensitive and 40% specific for **absence** of dementia
Elsey et al. 2015	15 (15)	functional memory disorder	neurodegenerative disease	conversation analysis of transcripted consultations	functional memory disorder: more likely to attend alone, rarely sought assistance from companion.
Soysal et al. 2017	529	memory clinic attenders	cognitive impairment	'attended with' accompanying adult	'attended with': 90% sensitive and 37% specific for cognitive impairment
Kambe et al. 2018	21 (75)	unaccompanied older adults with memory complaints	accompanied	MRI	unaccompanied had more depressive symptoms
Behaviours observed during clinical assessment					

Soysal et al. 2017	529	memory clinic attenders		head-turning to a relative seated behind patient and at 45 degrees during questions about complaints	Head turning 80% sensitive and 64% specific for cognitive impairment; attended with 90% sensitive and 37% specific for cognitive impairment
Randall et al. 2018	169	cognitive disorders clinic attenders		La maladie du petit papier (presentation of written or typed symptom list patient at consultation)	producing a written list of complaints: high specificity (0.94) but low sensitivity (0.03) for diagnosis of functional cognitive disorder

Table 7 – Depressive symptoms, anxiety symptoms, and personality factors in individuals with subjective or functional cognitive symptoms

Variable / study name	Source	Description of participants (cases)	Measure	Associated with symptoms / symptom severity?
Depressive symptoms (studies of *depressive* pseudodementia excluded)				
Kiloh 1961	clinical	Pseudodementia	clinical assessment	Yes
Kahn et al. 1975	clinical	psychiatry inpatients and outpatients; HC	Do you have any trouble with your memory?' rated/5, HDRS	Yes
Wells 1979	clinical	Pseudodementia	clinical assessment	Yes
Caine 1981	clinical	Pseudodementia	clinical assessment, including neuropsychological assessment	Yes
Bulbena and Berrios 1986	clinical	pseudodementia	clinical assessment	Yes
Larrabee and Levin 1986	community	volunteers	Squire et al. (1979) memory rating scale; ZDRS; memory tests	Yes
Minett et al. 2005	clinical	memory clinic patients	MAC-Q, GDS	Yes
Crook and Larrabee 1990	community	volunteers	MAC-S, GDS	Yes
O'Connor et al. 1990	community	sample of adults >75 from GP registers	CAMDEX, clinical assessment	Yes
Rabbitt and Abson 1990	community	volunteers	CFQ, MFQ, 'Lost and Found' questionnaire, BDI	Some questionnaires only
Bolla et al. 1991	community	volunteers	MMQ, GDS, memory tests	Yes
Crook and Larrabee 1992	clinical	Age-Associated Memory Impairment (AAMI)	MAC-S, HDRS, elements of WMS + others	No
Barker et al. 1994	clinical	individuals with memory symptoms; HC	MAC-Q, GDS	Yes
Barker and Prior 1995	clinical	self-referral memory clinic attenders; HC	MAC-Q, GDS	Yes
Levy-Cushraan and Abeles 1998	community	older adults	MAC-S, BDI, GDS	Yes
Derouesne et al. 1999	clinical	self-referrers to memory clinic; HC	SMS scale, Zung depression scales	Yes

Variable / study name	Source	Description of participants (cases)	Measure	Associated with symptoms / symptom severity?
Clarnette et al. 2001	community	volunteers	'volunteers with memory complaints', CAMDEX	Yes
Small et al. 2001	community	volunteers with mild age-related memory complaints	MFQ, HAM-D, APOE4 status	Only in those without APOE4 allele
Lucas et al. 2003	clinical	medically unexplained cognitive difficulties	BDI, elements of WMS	-
Jungwirth et al. 2004	community	75 year olds	HAMD, GDS	Yes
Zandi 2004	clinical	memory clinic patients	CAMDEX, CAMCOG	Yes
Jessen et al. 2007	community	sample of adults from GP registers	SIDAM, elements of CERAD, GDS	Yes
Sinforiani et al. 2007	clinical	memory symptoms not impairing activities	BDI, STAI X-1, STAI X-2	Yes
Gallassi et al. 2008	clinical	outpatients with cognitive complaints	BDI	SCI less depressed than MCI
Mendes et al. 2008	community	healthy volunteers	SMC scale, CERAD depression scale / GDS	Yes
Metternich et al. 2009	clinical	FMD, HC	MIA, BDI	Yes
Ramakers et al. 2009	clinical	SMC	MIA, SCL-90	-
Schmidtke et al. 2009	clinical	FMD, HC	SCID (DSM-IV) Axis 1 and BDI	Yes
Benito Leon et al. 2010	community	SMC (including some with MCI); HC	Do you suffer from forgetfulness since the last interview?'; 'Do you suffer from depression?'; antidepressant use	Yes
Svendsen et al. 2012	clinical	affective disorders; HC	MGH Cognitive and Physical Fx Questionnaire and Screen for Cognitive Impairment in Psychiatry, HDRS	Yes
Sindi et al. 2012	community	older adults (58-85)	study-specific aging perceptions questionnaire; EMQ (Everyday memory questionnaire), GDS	Yes
Genziani et al. 2013	community	older adults >65	CES-D, study-specific questionnaires	Yes
Merema et al. 2013	community	older adult volunteers	General Frequency of Forgetting scale, Depression Anxiety Stress Scale, Neo Five Factor	Not when neuroticism included
Buckley et al. 2013	community	elderly volunteers	MAC-Q, GDS, HADS	Yes
Apolinario et al. 2013	clinical	older adults with subjective cognitive symptoms	Novel classification system (type of complaints); Memory Complaint Questionnaire (MAC-Q); GDS-15	Yes

Variable / study name	Source	Description of participants (cases)	Measure	Associated with symptoms / symptom severity?
Chin et al. 2014	clinical	memory complaints & normal testing	MMQ, GDS short form (S-GDS)	Yes
Lehrner et al. 2014	clinical	patients with cognitive complaints; HC	Forgetfulness Assessment Inventory (FAI), BDI	Yes
Zlatar et al. 2014	community	participants in study of aging	CFQ, PHQ-9	Yes
Arbabi et al. 2015	clinical	memory clinic patients with SMC	WMS, HADS	-
Tomita et al. 2015	community	volunteers >60	CES-D, SMC scale	Yes, especially with 'inability to think' on SMC scale
Eckerstrom et al. 2016*	clinical	SCI	clinical interview	No
Kinzer and Suhr 2016	community	volunteers	Dementia worry scale, GDS, Penn State Worry Questionnaire	Yes
Rowell et al. 2016	community	healthy adults	MFQ, MAC-S, CES-D	Yes
Tanaka et al. 2016	community	MZ and DZ twins from research register	Depression-dejection scale from POMS-brief; study-specific question	Yes
Vogel et al. 2016	clinical	patients with mild cognitive symptoms	SMC scale and MAC-Q scale, MDI	Yes
Markova et al. 2017	community	cognitively healthy volunteers	QPC, GDS	Yes
Perrotin et al. 2017	clinical	patients with SCD; non-help-seeking SCD	cognitive difficulties scale, MADRAS	More depressive symptoms in help-seekers
Kambe et al. 2018	clinical	unaccompanied memory clinic attenders; accompanied attenders	MRI, MMSE, CES-D	More depressive symptoms in unaccompanied patients
Schweizer et al. 2018	community	Cam-CAN cohort – adults free of neuropsychiatric disorder	HADS, WMS	Yesa
Slot et al. 2018	clinical	memory clinic patients with SCD; HC	Cognitive Change Index, HADS-D	Yes
Zlatar et al. 2018	clinical	older adults referred for screening of cognitive complaints	study-specific 5-item SCD scale, GDS	Yes
Jenkins et al. 2019	community	healthy volunteers	Cognitive Change Index (CCI), HADS	Yes
Kawagoe et al. 2019	clinical	individuals with SMC	SMS questionnaire (Osada 1997), Zung SDS	Yes
Anxiety				

Variable / study name	Source	Description of participants (cases)	Measure	Associated with symptoms / symptom severity?
Reynolds et al. 1988	clinical	Depressive pseudodementia; dementia with depressive features	HRSD	Yes
Barker and Prior 1995	clinical	individuals attending a self-referral memory clinic; HC	STAI-T	Yes – trait anxiety
Derouesne et al. 1999	clinical	self-referrers to memory clinic; HC	SMS questionnaire Zung anxiety scale	Yes
Clarnette et al. 2001	community	volunteers	'volunteers with memory complaints', CAMDEX	Yes
Jungwirth et al. 2004	community	75 year olds	HAMD, STAI	Yes
Sinforiani et al. 2007	clinical	memory symptoms not impairing activities	STAI X-1, STAI X-2	Yes
Ramakers et al. 2009	clinical	SMC; non-help-seeking SMC	MIA, SCL-90	Similar anxiety in help-seekers and non-help-seekers
Hurt et al. 2011	clinical	adults with SMC attending memory clinic; non-help-seeking SMC	Illness Perception Questionnaire for Memory Problems (IPQ-M), Beck Anxiety Inventory	Yes – anxiety determined by negative beliefs about symptoms
Buckley et al. 2013	community	elderly volunteers	MAC-Q, HADS	Yes
Arbabi et al. 2015	clinical	SMC with and without impairment	HADS, WMS, MMPI	Yes
Rowell et al. 2016	community	healthy adults	MFQ, MAC-S, STAI-T	Yes
Tandetnik et al. 2017	community	volunteers without cognitive impairment	trait-STAI-Y, HADS-A	Yes – trait anxiety
Slot et al. 2018	clinical	memory clinic patients with SCD; HC	Cognitive Change Index, HADS-A	Yes
Jenkins et al. 2019	community	healthy volunteers	Cognitive Change Index (CCI), HADS	Yes
Personality factors				
Hanninen et al. 1994	community	memory complainers; noncomplainers	MMPI	Yes – hypochondriasis and psychaesthenia scales
Hepple et al. 2004	clinical	conversion pseudodementia	clinical assessment	'predisposing personality traits'

Variable / study name	Source	Description of participants (cases)	Measure	Associated with symptoms / symptom severity?
Pearman et al. 2005	community	SMC	NEO PI-R, self-esteem scale	self-discipline and self-consciousness
Ramakers et al. 2009	clinical	SMC; non-help-seeking SMC	Eysenck Personality Questionnaire (EPQ-BV)	similar extraversion and neuroticism in help seekers and non-help-seekers
Schmitdke et al. 2009	clinical	FMD outpatients; HC	NEO-Five Factor Inventory	Yes - neuroticism
Metternich et al. 2009	clinical	FMD; HC	NEO-Five Factor Inventory	Yes - neuroticism
Merema et al. 2013	community	older adult volunteers	General Frequency of Forgetting scale, Neo Five Factor	Yes - neuroticism
Steinberg et al. 2013	community	volunteers ≥ 65 without cognitive impairment	Prospective Retrospective Memory Questionnaire (PRMQ), Neo Five Factor Inventory	Yes - neuroticism
Studer et al. 2014	clinical	MCI; HC	QPC (French cognitive complaint quesitonnaire), NEO-PI-R	Negative association between SCD (in MCI) and agreeableness
Arbabi et al. 2015	clinical	SMC with and without impairment	MMPI	Yes – hysteria
Rowell et al. 2016	community	healthy adults	MFQ, MAC-S, Emotional Stability subscale from IPIP questionnaire	Yes – emotional instability
Tandetnik et al. 2017	community	volunteers without cognitive impairment	McNair and Kahn self-rated cognitive questionnaire, Young's Early Maladaptive schemas (YSQ-short form)	Yes – maladaptive schemas ('dependence/incompetence', 'failure to achieve', and 'vulnerability to harm or illness')
Bessi et al. 2018	clinical	SCD or MCI	Big Five Factors Questionnaire	Lower emotional stability in stable SCD compared with progressive SCD
Jenkins et al. 2019	community	healthy volunteers	Cognitive Change Index, Big Five Inventory	Yes – neuroticism
Slot et al. 2018	clinical	memory clinic patients with SCD; HC	Cognitive Change Index - Self, and subjective cognitive function self-report (compared 1 year ago) , NPV neuroticism subscale, Pearline Mastery scale	Yes – neuroticism and low mastery

Supplementary table A – all included studies, ordered by date of publication

(*,**, *5 etc = studies of same or overlapping group)

Author and year	Design	Source	Terminology	n	Population	Controls	Age, mean / [median]
Kiloh 1961	case series	clinical	pseudo-dementia	10	patients with pseudodementia		51.4
Marsden and Harrison 1972	cross sectional	clinical	primary psychiatric diagnoses	106	neurology inpatients diagnosed with presenile dementia		not stated
Tsoi 1973	case series	clinical	other - Ganser syndrome	10	patients diagnosed with Ganser syndrome in Singapore		35.4
Kendell 1974	longitudinal	clinical	primary psychiatric diagnoses	98	psychiatry inpatients with dementia diagnosis, readmitted at least once		not stated for subgroup
Kahn et al. 1975	cross sectional	clinical	cognitive complaints	82	gerontology psychiatry outpatients and inpatients	40 HC	65.1
Nott and Fleminger 1975	longitudinal	clinical	other - 'non deteriorated group'	35	inpatients diagnosed with presenile dementia		53.2
Wells 1979	case series	clinical	pseudodementia	10	psychiatry and neurology patients with pseudodementia		not stated
Caine 1981	case series	clinical	pseudodementia	11	inpatients with a descriptive label of pseudodementia		49.9
Rabins 1981	cross sectional	clinical	other - reversible dementia	41	patients with dementia and elderly patients with depression admitted to a psychiatric hospital		not stated
Smith and Kiloh 1981*	cross sectional	clinical	pseudodementing illness	200	patients admitted to neuropsychiatry with presumed dementia		57.7
Reifler et al. 1982	cross sectional	clinical	cognitive symptoms	88	cognitively impaired geriatric outpatients		78
Hutton et al. 1984	cross sectional	clinical	pseudodementia of depression	17	outpatients with 'pseudodementia of depression'	19 presumed AD, 17 HC	69.1 (69.2 (73 AD, 65 DPD); 69 controls)
Yerby et al. 1985	cross sectional	clinical	depression, psychiatric or functional disorders	117	geriatric clinic outpatients with complaints of memory loss		75.81
Bulbena and Berrios 1986	longitudinal	clinical	pseudodementia	22	inpatients with diagnosis of pseudodementia		73.3
Sunderland et al. 1986	cross sectional	community	memory complaints	60	residents of housing for elderly adults		68.6
Larrabee and Levin 1986	cross sectional	community	self-rated decline	88	volunteers from retirement apartments and organizations		73.2
Bayer et al. 1987	cross sectional	clinical	depressive pseudodementia	100	memory clinic		74.2

Author and year	Design	Source	Terminology	n	Population	Controls	Age, mean / [median]
Erkinjuntti et al. 1987	Cross sectional	clinical	psychiatric disorders / pseudodementia	323	neurology outpatients with suspected dementia		50.4
Van der Cammen et al. 1987	cross sectional	clinical	pseudodementia due to an affective disorder	50	memory clinic		75.2
Reynolds et al. 1988 a *2	cross sectional	clinical	depressive pseudodementia	14	patients with pseudodementia in MDD	28 dementia with depressive features	72.6 (75.1 DPD, 71.4 D)
Reynolds et al. 1988 b *2	cross sectional	clinical	dementia syndrome of depression	14	patients with pseudodementia	28 dementia with depressive features	70.9 (depressed 70.3, dementia 72.8, mixed 72.6, controls 69.3)
Brenner and Reynolds 1989	longitudinal	clinical	depressive pseudodementia	33	patients with mixed symptoms of depression and dementia	35 AD without depression, 61 HC	73.2 (controls 67.6)
Derouesne et al. 1989	cross sectional	clinical	'psychoactive brain dysfunction'	367	memory clinic		62.9
Kral and Emery 1989	longitudinal	clinical	depressive pseudodementia	44	patients diagnosed with depressive pseudodementia		76.5
Pearlson et al. 1989	cross sectional	clinical	dementia syndrome of depression; 'pseudodementia'	26	patients with dementia syndrome of depression	13 AD, 31 HC	69.8 (71.9 DOD, 70 depressed cognitively normal, 70.6 AD, 68.3 HC)
McGlone et al. 1990	cross sectional	clinical	memory complaints	57	patients referred by neurologists for neuropsychological assessment during screening for early dementia	35 HC	66.05 (65.6 patients (69.6 dementia, 61.5 non), 66.5 controls)
Brodaty 1990	cross sectional	clinical	psychiatric or 'normal / anxious personality'	144	memory clinic		69.5
Crook and Larrabee 1990	cross sectional	community	memory problems	1103	volunteers recruited through the print and electronic media		56
O'Connor et al. 1990	cross sectional	community	memory complaints	384	>75 year olds from GP practice registers		60.2
Rabbitt and Abson 1990	cross sectional	community	memory self-report	442	volunteers		63
Sachdev et al. 1990*	longitudinal	clinical	pseudodementia (includes all psychiatric but depressive disorders most likely)	200	inpatients assessed in Smith 1981 who were diagnosed with pseudodementia		53
Bolla et al. 1991	cross sectional	community	memory complaints	199	volunteers through newspaper advertisements		62
Christensen et al. 1991	cross sectional	community	memory complaints	20	elderly volunteers to advertisement for subjects with 'memory problems'	11 HC	64.9
Gottlieb et al. 1991	cross sectional	clinical	pseudodementia	14	patients diagnosed with pseudodementia	24 HC	69
Weiner et al. 1991	cross sectional	clinical	depression, somatization disorder, dysthmic disorder	317	memory clinic		not stated

Author and year	Design	Source	Terminology	n	Population	Controls	Age, mean / [median]
Ames et al. 1992	cross sectional	clinical	functional psychiatric disorders and 'other'	100	memory clinic		75.5
Crook et al. 1992	cross sectional	clinical	memory complaints	232	individuals participating in a trial of experimental medication for AAMI		59.2
Dolan et al. 1992	cross sectional	clinical	primary psychiatric diagnoses	10	outpatients and inpatients with moderate to severe depression	10 depression without cognitive impairment	57.05 (60.9 impaired, 53.2 unimpaired)
O'Brien et al. 1992	longitudinal	clinical	benign senescent forgetfulness	64	memory clinic patients with 'benign senescent forgetfulness'		67.2
Taylor 1992	longitudinal	community	subjective memory disorder	30	older adults with subjective memory decline (previous participants in short-term drug trial)		67.5
Almeida et al. 1993	cross sectional	clinical	memory complainers / no diagnosis (24%)	418	memory clinic		66.7
Flicker et al. 1993	longitudinal	community	SMI	59	dementia clinic patient family members and advertisement responders		68.7
Grut te al. 1993	cross sectional	community	memory complaints	614	all inhabitants of an area in Sweden		not stated
Spear-Bassett and Folstein 1993	cross sectional	community	memory complaints	810	Eastern Baltimore Mental Health Survey		not stated
Verhey 1993	cross sectional	clinical	not specified, depression, other psychiatric disorder	430	memory clinic		61.7
Barker et al. 1994	cross sectional	clinical	memory complaints	49	memory clinic - GP and self-referred	41 HC	69
Hanninen et al. 1994	cross sectional	community	SMC	10	population-based dementia screening study	10 HC	72 (71.7 complainers, 71.5 non-complainers)
Jorm et al. 1994 *3	cross sectional	community	memory complaints	744	electoral roll sample of elderly people		range >70
Barker and Prior 1995	cross sectional	clinical	memory complaints	24	patients self-referring to a memory clinic and non-presenting controls	24 HC	not stated
Mcpherson et al. 1995	cross sectional	community	memory problems	25	first-degree relatives of patients with diagnosis of probable or definite AD enrolled in a study	26 HC without family history	60.4 (59.9 relatives, 61 controls)
Tobiansky et al. 1995	longitudinal	community	SMI	705	electoral ward sample		74.6
Wright and Lindesay 1995	cross sectional	clinical	not dementia	not stated	20 memory clinics across UK year prior to survey in 1993		not stated
Collins and Abeles 1996	cross sectional	community	SMC	90	volunteers to advertisement to University Psychological Clinic Aging Research Project		70.4
Kopelman and Crawford 1996	cross sectional	clinical	dx - psychiatric disorders, WW, psychogenic amnesia	200	memory clinic		43.7
Lehmann et al. 1996	cross sectional	clinical	no cognitive disturbance	406	memory clinic		62.9

Author and year	Design	Source	Terminology	n	Population	Controls	Age, mean / [median]
Rue et al. 1996	cross sectional	community	subjective memory loss	61	1st degree relatives of AD	41 HC without family history	61.3 (60.9 relatives, 61.9 controls)
Schmand et al. 1996	longitudinal	community	SMC	357	population-based group without dementia or other psychiatric disorders at baseline		75.3
Smith et al. 1996	longitudinal	community	SMC	394	population-based older americans normative study		72.1
Swanwick et al. 1996	cross sectional	clinical	WW / not dementia	200	memory clinic		74.3
Blazer et al. 1997	longitudinal	community	memory complaints	3080	Duke Established Populations for Epidemiologic Studies of the Elderly		72
Schmand et al. 1997 *4	longitudinal	community	SMC	3590	Amsterdam Study of the Elderly (AMSTEL)		74.9
Schofield et al. 1997	cross sectional	clinical	SMC	233	individuals from a register of individuals with possible cognitive impairment	131 no cognitive impairment	75.9 (74.2 no cognitive impairment, 77 cognitive impairment)
Braekhus et al. 1998	longitudinal	community	subjective worsening of memory	285	random sample older people		81.5
Levy-Cushraan and Abeles 1998	cross sectional	community	SMC	132	older adults - advertisement responders		67.6
Yousef et al. 1998	cross sectional	clinical	depressive pseudodementia	63	patients referred for psychogeriatric assessment with differential diagnosis of depressive pseudodementia	44 dementia, 19 dementia and depression	75.5
Derouesne et al. 1999	cross sectional	clinical	memory complaints	260	self-referral memory clinic		54.6
Geerlings et al. 1999 *4	longitudinal	community	memory complaints	3778	Amsterdam Study of the Elderly (AMSTEL) - 'nondemented persons 65-84 years old'		range 65-84
Hogh et al. 1999	cross sectional	clinical	no psychiatric disease, depression, other psychiatric disease	400	memory clinic		63.6
Clarnette et al. 2001	cross sectional	community	SMC	108	volunteers	38 HC	63
Cutler and Hodgson 2001	cross sectional	community	anticipatory dementia	108	adult children with living parent diagnosed with AD	150 HC without family history	49.7 (50.0 adult children, 49.4 comparitors)
Jorm et al. 2001 *3	longitudinal	community	memory complaints	331	electoral roll sample of elderly people		74.82
Small et al. 2001	cross sectional	community	SMC	66	participants in longitudinal study, recruited through advertisements and physician referral		63.7
Luce et al. 2001	cross sectional	clinical	SMI	200	memory clinic vs old age psychiatry clinic		68.9 vs 80.9

Author and year	Design	Source	Terminology	n	Population	Controls	Age, mean / [median]
Elberling et al. 2002 *5 - subset of Hejl 2002	cross sectional	clinical	no cognitive deficits (including no neuropsychiatric disease, psychiatric disease)	314	memory clinic		47.6
Hejl et al. 2002 *5	cross sectional	clinical	no cognitive deficits, no neuropsychiatric disease	1000	memory clinic		66.1
St John and Montgomery 2002	longitudinal	community	subjective memory loss	1416	Manitoba Study of Health and Aging		75.3
Hejl et al. 2003	cross sectional	clinical	no cognitive deficits, no neuropsychiatric disease	100	memory clinic		74.2
Lucas 2003	cross sectional	clinical	subjetive cognitive complaints	20	neurology outpatients		49.8
Zimprich et al. 2003	longitudinal	community	subjective cognitive complaints	427	participants in Interdisciplinary Study on Adult Development (ILSE)		62.9
Hepple 2004	case series	clinical	conversion pseudodementia	10	psychiatry inpatients with 'conversion pseudodementia'		66.6
Jungwirth et al. 2004	cross sectional	community	SMC	302	75 year olds from population register		75
van der Flier et al 2004	cross sectional	clinical	SMC / memory complainers	28	self-referred memory complainers at memory clinic	20 HC	73.5 (72 complainers, 75 controls)
Larner 2005	cross sectional	clinical	absence of dementia	247	memory clinic		not stated
Lautenschlager et al. 2005	cross sectional	community	SMC	264	community-dwelling women >70 recruited via advertisement		74.5 (HCG 74.3, SMC 74.7, 74.2 MCI)
Lehrner et al. 2005	longitudinal	clinical	subjective complaints and MCI	114	memory clinic patients with memory complaints NOT receiving dementia diagnosis and not <50		66.9
Minett et al. 2005	cross sectional	clinical	SMC	60	memory clinic patients without dementia		72.6
Pearman et al. 2005	cross sectional	community	SMC	85	volunteers		73.2
Wolf et al. 2005	cross sectional	community	SMC	46	research clinic volunteers		61.8
Zandi 2004	cross sectional	community	SCC	603	memory clinic patients		77.6
Archer et al. 2006	cross sectional	clinical	symptoms of memory impairment	58	subjects with symptoms of memory loss without obvious or treatable cause of impairment	33 HC	63.7 (controls 62.6, altogether 63.3)
Prichep et al. 2006	longitudinal	community	subjective cognitive complaints	44	elderly volunteers with subjective cognitive complaints but no objective impairment (GDS stage 2)		72.14

Author and year	Design	Source	Terminology	n	Population	Controls	Age, mean / [median]
Banerjee et al. 2007	cross sectional	clinical	no illness	247	memory clinic		not stated
Glodzik-Sobanska et al. 2007	longitudinal	community	SMC	230	volunteers to study of ageing		67
Jessen et al. 2007	cross sectional	community	SMI	2389	volunteers without cognitive impairment recruited randomly from GP registers		80.2
Park et al. 2007	cross sectional	community	SMC	9477	population cohort recruited at flu vaccination		72.61
Saez-Fonseca et al. 2007	longitudinal	clinical	depressive pseudodementia	182	inpatients and day hospital patients with depressive pseudodementia		77.6
Sinforiani et al. 2007	cross sectional	clinical	SMC	74	memory clinic - all presenting with memory disturbances, not dementia		71.6
van Oijen et al. 2007	longitudinal	community	SMC	6927	Rotterdam Study		69.5
Ahmed et al. 2008	longitudinal	clinical	SMC, 'worried well'	22	memory clinic	85 aMCI, 40 semantic dementia	67.44
Gainotti et al. 2008	cross sectional	clinical	depressive pseudo-dementia	26	patients with depressive pseudodementia	42 AD, 35 HC	65.8 (68.6 DPD, 67.8 AD, 61.3 HC)
Gallassi et al. 2008	cross sectional	clinical	SCC / SCI	92	outpatient with subjective cognitive complaints		67.4
Mendes et al. 2008	cross sectional	community	memory complaints	292	blood donors, unpaid helpers and relatives of patients at a hospital in Lisbon, volunteers attending universities.		50.5
Schmitdke et al. 2008	longitudinal	clinical	functional memory disorder	73	probable non-organic cognitive impairment from memory clinic		55.2
Brucki and Nitrini 2009	cross sectional	community	SMI	163	rural population with low education in Amazon rainforest		62.3
Hancock and Larner 2009	cross sectional	clinical	memory complainers without dementia	310	memory clinic patients		66.9
Metternich et al. 2009	cross sectional	clinical	functional memory disorder	39	memory clinic - patients with FMD	38 HC	55
Ramakers et al. 2009	cross sectional	clinical	SMC	33	memory clinic patients with SMC	83 non-help seeking SMC in population study	64.2 (62 help-seekers, 65.1 non)
Schmitdke et al. 2009	cross sectional	clinical	functional memory disorder	86	patients with FMD	88 HC	52.9 (55.8 FMD, 50.1 controls)
Visser et al. 2009	longitudinal	clinical	SCI, naMCI, MCI	168	memory clinics (20 across europe) - patients with SCI, naMCI, aMCI	89 HC	68
Westoby et al. 2009	cross sectional	community	CC	7878	population from GP registers		66.3
Benito Leon et al. 2010	longitudinal	community	SMC	1073	population-based - SMC without dementia	1073 HC	75.4

Author and year	Design	Source	Terminology	n	Population	Controls	Age, mean / [median]
Che telat et al. 2010	cross sectional	community	SCI	49	SCI and MCI from Australian Imaging Biomarkers and Lifestyle Study of ageing	34 MCI, 35 AD, 45 HC	74.7
Elfgren et al. 2010 *6	longitudinal	clinical	SMC	59	memory clinic		59.6
Gino et al. 2010	cross sectional	community	SMC	946	volunteers attending health screening unit, blood donors, leisure centre, senior citizens college or university in Lisbon		54.2
Gucuyener et al. 2010	cross sectional	clinical	depressive pseudodementia	13	patients with depressive pseudodementia	11 AD, 10 HC	65.9 (66.2 AD, 65.4 DPD) and 63.9 HC
Kenfield et al. 2010	cross sectional	clinical	psychiatric disorders (most depression and anxiety), no neuropsychiatric disorder	109	behavioural neurology clinic patients		not stated (60.6 for the 109 with nonneurologic conditions)
Reisberg et al. 2010	longitudinal	community	SCI	166		47 no cognitive impairment	67.2
Slavin et al. 2010	cross sectional	community	SCC	827	electoral roll		63
Striepens et al. 2010	cross sectional	clinical	SMI	21	memory clinic patients with both subjective and informant-reported memory complaint, performing in normal ranges on tests	48 HC	65.9 (66.3 SMI, 65.8 controls)
Vestberg 2010 *6	longidutinal	clinical	subjective memory symptoms	52	memory clinic		57.5
Amariglio et al. 2011	cross sectional	community	SMC	16964	women from the Nurses' Health Study		74
Aarts et al. 2011	cross sectional	community	SMC	15188	postal survey of residents of Netherland province		70
Cooper et al. 2011	cross sectional	community	subjective forgetfulness	7461	Adult Psychiatric Morbidity Survey		45
Hurt et al. 2011 *7	cross sectional	clinical	SMC	60	memory clinic patients subjective memory symptoms	38 non-help-seeking SMC	73.4
Mascherek et al. 2011	cross sectional	clinical	SCC	169	memory clinic patients referred by physician or relatives		76
Menon and Larner 2011	cross sectional	clinical	not dementia	708	memory clinic		not stated
Montejo et al. 2011 *8	cross sectional	community	SMC	1637	Madrid Health Survey		74.7
Paradise et al. 2011	cross sectional	community	SMC	45532	45 and Up Study (Australia cohort)		range 45-64
Puetz et al. 2011	cross sectional	clinical	FMD	12	center for geriatric medicine and gerontology outpatients	12 HC	52.05
Rodda et al. 2011	cross sectional	clinical	subjective cognitive impairment	11	memory clinic patients with SCI	12 HC	68.5 (64.0 SCI, 73.5 control)

Author and year	Design	Source	Terminology	n	Population	Controls	Age, mean / [median]
Wang et al. 2011	cross sectional	clinical	SCI, neurosis	2789	memory clinic		58% >70
Amariglio et al. 2012	cross sectional	community	clinically normal	131	Harvard Aging Brain Study		73.5
Bartley et al. 2012	cross sectional	community	SMC	96	healthy subjects recruited through public awareness meetings and from relatives		61.8
Caracciolo et al. 2012	cross sectional	community	SCI	11926	Swedish twin register		not stated
Dolek et al. 2012	cross sectional	clinical	pseudodementia, AD, VD, MCI	16	patients presenting with memory loss to behavioural neurology clinic with pseudodementia	14VaD, 22 ATD, 12 MCI, 11 HC	69.4 (68.6 pseudodementia, 70.3 AD, 70.8 VD, 72.6 MCI, 63.9 HC)
Hurt et al. 2012 *7	cross sectional	clinical	SMC	60	memory clinic	38 non-help-seeking SMC	73.4 (71.6 clinical, 76.1 community)
Montejo et al. 2012 *8	cross sectional	community	SMC	1937	Madrid Health Survey		74.67
Perrotin et al. 2012	cross sectional	community	subjective cognition	48	cognitively normal elderly subjects		73.5
Sindi et al. 2012	cross sectional	community	SMC	40	Douglas Hospital Longitudinal Study of Normal and Pathological Ageing		71.25
Svendsen et al. 2012	cross sectional	clinical	subjective complaints, MCI	30	psychiatry outpatients: 15 bipolar disorer, 15 unipolar depression	15 HC	36.7 (34 BPAD, unipolar 41.0, control 35.1)
Apolinario et al. 2013	cross sectional	clinical	SCC	180	older patients attending memory clinic with subjective cognitive symptoms, exluding moderate dementia		74
Balash et al. 2013	cross sectional	community	SMC	636	volunteer or self-referral		68
Buckley et al. 2013	cross sectional	community	SMC	740	MCI and healthy adults from Australian Imaging Biomarkers and Lifestyle Study of Aging cohort		73.1
de Paula et al. 2013	cross sectional	clinical	depressive pseudodementia	34	patients with MDD, subjective and functional cognitive complaints and specific impairment but spared global function	62 HC	71.5 (70.21 DPD, 73.94 controls)
Genziani et al. 2013	cross sectional	community	SMI	9294	French community surveys ≥65		74.3
Ito et al. 2013	cross sectional	community	SMC	2034	community residents of Chiyoda ward, Tokyo		74.6
Kim et al. 2013	cross sectional	clinical	SMI	90	self-referrers to memory disorder clinic	28 HC	68.1 (65.8 patients, 70.7 controls)
Merema et al. 2013	cross sectional	community	MC	177	older adults - volunteers for memory study via newspaper advertisement		73.62

Author and year	Design	Source	Terminology	n	Population	Controls	Age, mean / [median]
Rienstra et al. 2013	cross sectional	clinical	MCI	170	patients with MCI		60.5
Rijs et al. 2013	longitudinal	community	SMC	962	Longitudinal Aging Study Amsterdam cohort		60.2
Siersma et al. 2013	longitudinal	community	SMC	758	Community dwellers attending primary care		74.8
Silva et al. 2013	longitudinal	clinical	cognitive complaints	250	Cognitive Complaints Cohort, Lisbon		69.1
Steinberg et al. 2013	cross sectional	community	SMC	125	U Penn AD centre 'normal control' cohort and outreach to residential independent living and other community-dwelling individuals		77
van Harten et al. 2013 'CSF AB42'	longitudinal	clinical	SC	127	memory clinic 'nondemented patients with cognitive complaints'		60
van Harten et al. 2013 'preclinical AD'	longitudinal	clinical	SC	132	memory clinic patients with subjective complaints		61
Acikgoz et al. 2014	cross sectional	clinical	SMC	405	other outpatients		64.64
Begum et al. 2014	cross sectional	community	SMC and subjective concentration complaints	26091	English Psychiatric Morbidity population surveys 1993, 2000, 2007		42
Caselli et al. 2014	longitudinal	community	SCD	447	healthy members of Alizona APOE cohort		59
Chen et al. 2014	cross sectional	community	SMI	18614	representative community sample via telephone survey		range 18-99
Chin et al. 2014	cross sectional	clinical	SMI	108	memory disorder clinic patients with complaints of memory decline but normal neuropsychological assessment		63.35
Garcia-Ptacek et al. 2014	cross sectional	clinical	SCI	993	memory clinic		62.5
Larner 2014 *9	cross sectional	clinical	absence of dementia / 'cognitively healthy'	726	memory clinic		61
Lehrner et al. 2014	cross sectional	clinical	SMC	581	memory clinic patients with subjective memory complaints	248 HC	66.3 (66.4 SMC, 66.3 controls)
Lineweaver et al. 2014	longitudinal	community	self-rated memory function	74	neurologically intact adults informed of APOE4 status	70 not informed	73.4
Mewton et al. 2014	cross sectional	community	SMC	1905	NSMHWB sample - population survey		range 65-85
Singh-Manoux et al. 2014	cross sectional	community	SCC	15510	French GAZEL study		57.9
Studer et al. 2014	cross sectional	clinical	SCD	55	patients with diagnosis of MCI	84 HC	67.8 (70.5 MCI, 66.3 controls)

Author and year	Design	Source	Terminology	n	Population	Controls	Age, mean / [median]
Tomita et al. 2014	cross sectional	community	SMC	394	volunteers >60		68.7
Zlatar et al. 2014	cross sectional	community	cognitive complaints	1000	randomly selected adults from SAGE study of aging without diagnosis of dementia		77.3
Arbabi et al. 2015	cross sectional	clinical	SMC	90	memory clinic		52.31
Djukic et al. 2015	longitudinal	clinical	Depressive pseudodementia	166	geriatric medical inpatients		82.9
Elsey et al. 2015	cross sectional	clinical	FMD	15	memory clinic	15 neurodegenerative disease	63 (60 FMD, 66 ND)
Hessen et al. 2015 *10	cross sectional	clinical	SCD	122	patients with SCD from 2 memory clinics (10% self-referrals)		62.5
Kaup et al. 2015	longitudinal	community	SMC	1107	population cohort		70.8
Pennington et al. 2015	cross sectional	clinical	FCD	196	memory clinic		not stated
Smart et al. 2015	cross sectional	community	SCD	17	community participants reporting SCD	25 HC	69.7 (69.47 SCD, 69.88 HC)
Tomita et al. 2015	cross sectional	community	SMC	289	volunteers participating in the 'Iwaki Health Promotion Project' in 2013		68.4
Cavuoto 2016	cross sectional	community	SMD	181			74
Claus et al. 2016	cross sectional	clinical	SCI + MCI	2000	memory clinic		78.2
Eckerstrom et al. 2016 *11	cross sectional	clinical	SCI + MCI	90	memory clinic patients without dementia	160 MCI	62.3 (59.8 SCI, 63.7 MCI)
Handels et al. 2016	longitudinal	clinical	SMC + MCI	114	patients referred from 4 dutch university memory clinics with suspected cognitive disorder		67.3
Jones et al. 2016	cross sectional	clinical	FMD	16	memory clinic	9 neurodegenerative disease	[61 dementia, 60 FMD]
Jung et al. 2016	cross sectional	clinical	SMI	613	memory clinic attenders with subjective memory impairment	613 HC	64.9
Kinzer et al. 2016	cross sectional	community	SMC	100	volunteers responding to memory screening advertisements		69
Lee et al. 2016	longitudinal	community	SMC	3272	Midlife in the US Study surveys		56.48
Pedro et al. 2016 *8	cross sectional	community	SMC	1342	Madrid Health Survey		74.25
Roehr et al. 2016	longitudinal	community	SCD	453	Leipzig longitudinal study of the aged (LEILA75+)		80.5

Author and year	Design	Source	Terminology	n	Population	Controls	Age, mean / [median]
Rowell et al. 2016	cross sectional	community	SMC	3798	healthy adults recruited from newspaper advertisements, excluded if cognitive impairment		51.16
Sierra-Rio et al. 2016	longitudinal	clinical	SCD + MCI	149	outpatients with memory complaints not dementia		67.5
Tanaka et al. 2016	cross sectional	community	SMC	556	twins ≥ 20 years		51
Vogel et al. 2016	cross sectional	clinical	SCD	121	memory clinic patients with mild cognitive symptoms		69
Wolfsgruber et al. 2016	longitudinal	community	SCD	1990	cognitively normal participants in AgeCoDe study		80.1
Chu et al. 2017	cross sectional	clinical	SMC	113	older people >60 with a history of depression but not current depression		66.7
Eckerstrom et al. 2017 *11	longitudinal	clinical	SCD, SCD plus, MCI	122	memory clinic patients without dementia	113 MCI	64
Ferreira et al. 2017	longitudinal	clinical and community	SMD	134	Australian Imaging Biomarkers and Lifestyle study of ageing: AD, MCI, healthy		73.4
Hessen et al. 2017 *10	longitudinal	clinical	SCD	81	2 memory clinics - patients with SCD		61
Hu et al. 2017	cross sectional	clinical	SCD	20	memory clinic patients with subjective cognitive decline	24 HC	67.3 (68.3 SCD, 66.49 control)
Jansen et al. 2017	longitudinal	clinical	SCI	221	patients from 4 Dutch memory clinics		66.6
Kang et al. 2017	cross sectional	community	SMC	459	population-based cohort		68.2
Kuiper et al. 2017	longitudinal	community	SMC	8762	population-based sample (LifeLines cohort)		70
Markova et al. 2017	cross sectional	community	SCC	340	cognitively healthy volunteers		75
Mirheidari et al. 2017	cross sectional	clinical	FMD	15	memory clinic patients with FMD	15 neurodegenerative disease	60.79 (63.78 ND, 57.8 FMD)
Mogle et al. 2017	cross sectional	community	subjective memory	3434	Midlife in the United States Study		56.1
Perrotin et al. 2017	cross sectional	clinical	SCD	28	memory clinic patients with SCD	25 non-presenting SCD, 35 HC	68 (67.6 SCD clinic, 70.8 SCD community, 65.6 controls)
Sahin et al. 2017	cross sectional	clinical	depressive pseudodementia	35	patients with depressive pseudodementia	20 AD	72.2
Sakurai et al. 2017	longitudinal	community	SMC	496	local resident registration sample with no cognitive impairment >65		72.7
Soysal et al. 2017	cross sectional	clinical	benign senescent forgetfulness	529	geriatrics outpatient clinic for memory complaints		75.7

Author and year	Design	Source	Terminology	n	Population	Controls	Age, mean / [median]
Tandetnik et al. 2017	cross sectional	community	cognitive complaints	76	subjects with intact cognitive fx recruited through advertisment offering free participation in an SCD intervention		69.2
Yates et al. 2017	longitudinal	community	SMC	1344	older people in MRC-CFAS population-based study		74
Alexander et al. 2018	cross sectional	clinical	FMD	17	outpatients at 'young onset' dementia service with FMD (excluding active depression)		not stated
Amariglio et al. 2018	longitudinal	community	SCC	279	population cohort		73.7
Avila-Villanueva 2018	longitudinal	community	SCD	1091	population cohort		74.71
Bessi et al. 2018	longitudinal	clinical	SCD	212	memory clinic patients determined as having SCD or MCI		66.7
Bharambe et al. 2018 *12	cross sectional	clinical	FCD	89	memory clinic		62
Bharambe et al. 2018 *9	cross sectional	clinical	FCD	169	memory clinic		60
Binnekade et al. 2018	cross sectional	clinical	SCI, MCI, dementia subtypes	759	memory clinic		79
Cespon et al. 2018	cross sectional	community	SMC	34	population sample		64.9
Cosentino et al. 2018	cross sectional	community	SCD	471	population-based cohort 'North Manhattan Aging Project' (medicare beneficiaries aged 65 years and older)		72.8
Elhadd et al. 2018 *12	cross sectional	clinical	FCD	89	memory clinic		[62]
Flatt et al. 2018	cross sectional	community	SCD	210	older (>50) LGBT adults from community centre		59.6
Haussman et al. 2018 a	cross sectional	clinical	SMI, normal objective cognition	171	memory clinic		not stated
Haussmann et al. 2018 b	cross sectional	clinical	SMI and MCI	35	memory clinic	40 HC	68.1 (70.3 MCI, 66.2 controls)
Hall et al. 2018	longitudinal	community	cognitive complaints	319	cognitively normal Mexican-American elderly people in HABLE cohort study		58.91
Hill 2018 14m	cross sectional	community	SMI	19	>60 with memory complaints		80.7
Kambe et al. 2018	cross sectional	clinical	MC	21	unaccompanied memory clinic patients	75 accompanied memory clinic attenders	80 (76.1 unaccompanied, 81.2 accompanied)
Larner 2018	cross sectional	clinical	SMC	50	memory clinic		[60.5]

Author and year	Design	Source	Terminology	n	Population	Controls	Age, mean / [median]
Luck et al. 2018	cross sectional	community	SCS	8834	LIFE adult cohort		58.8
Lundholm Fors et al. 2018	cross sectional	clinical	SCI and MCI	54	patients with mild and subjective cognitive impairment	36 HC	68.2 (SCI 66.3, MCI 70.1, HC 67.9)
Meyer et al. 2018	cross sectional	community	SMC	600	stratified sample adults ≥ 55		70.3
Miley-Akerstedt et al. 2018	cross sectional	clinical	SMC	209	memory clinic		58
Nunes et al. 2018	cross sectional	community	MC	59	final year medical students		25.7
Randall et al. 2018	cross sectional	clinical	FCD	169	cognitive function clinic		[60]
Reuber et al. 2018	cross sectional	clinical	FMD	20	memory clinic - patients with FMD	20 neurodegenerative disease	60.7 (57.25 FMD, 64.2 ND)
Sanchez-Benzvides et al. 2018	cross sectional	community	SCD	2670	cognitively healthy middle-aged first-degree descendents of AD patients		55.8
Schweizer et al. 2018	cross sectional	community	SCD	2544	Cam-CAN cohort		59.8
Schwert et al. 2018	cross sectional	clinical	SCC + cognitive deficits in major depressive disorder	102	outpatients with major depressive disorder	88 HC	42.8 (42.6 MDD, 43.1 HC)
Sheng et al. 2018	cross sectional	clinical	normal cognition, 'reversible dementia'	454	memory clinic		76.1
Slot 2018 14m	cross sectional	clinical	SCD	151	patients with SCD		64
Sorhabi 2018 14m	longitudinal	community	SMC	209	population cohort		64.6
Strand et al. 2018	longitudinal	clinical	SCD	4682	norwegian register of persons assessed for cognitive symptoms (norcog)		77.1
Verity et al. 2018	cross sectional	clinical	worried well, cognitively normal	375	memory clinic		70.76
Wakefield et al. 2018	cross sectional	clinical	FMD	20	patients with a clinical diagnosis of FMD	20 aMCI, 20 HC	63.4 (FMD 60.5, aMCI 66.3, controls 63.4)
Wallert et al. 2018	cross sectional	clinical	SCI + MCI	120	patients referred for full neuropsychological assessment to memory clinic		76.9
Zlatar et al. 2018	cross sectional	clinical	SCD	145	memory clinic referred with cognitive complaints with MMSE >24		74
Brailean et al. 2019	longitudinal	community	SMC	11092	population cohort > 50		65.3
Gamaldo et al. 2019	cross sectional	community	SMC	351	African American older adults		72
Jenkins et al. 2019	cross sectional	community	SCI	99	memory clinic		60.43

Author and year	Design	Source	Terminology	n	Population	Controls	Age, mean / [median]
Kawagoe et al. 2019	cross sectional	clinical	SMC	322	older adults (60-94) who had undergone resting state fMRI		69.5
Slot et al. 2019	longitudinal	clinical and community	SCD	2978	individuals with SCD (community and memory clinic)	1391 HC	73 (71 SCD,77 controls)

Investigating phenotypes – paper 2

I think, therefore I forget - using experimental simulation of dementia to understand functional cognitive disorders.

McWhirter L, Sargent B, Ritchie C, Stone J, Carson A.

CNS spectrums. 2020 Aug;25(4):511-8.

Introduction to the paper:

In this paper, I used an experimental simulation paradigm to explore the beliefs that healthy adults have about the nature and severity of the behavioural effects of dementia. We asked healthy adults a series of questions about dementia and asked them to complete a brief cognitive assessment while simulating “mild dementia”.

I designed the study and the cognitive assessment. Medical student Brendan Sargent collected the data. I analysed and interpreted the data for publication. CR, JS, and AC contributed to review and revision of the final manuscript.

We found that adults simulating dementia perform in the severely impaired range, performing particularly poorly on short digit span repetition, and we identified patterns of inconsistency for further investigation as a potential feature of functional cognitive disorder.

Word count:	3478 (including abstract)
Abstract word count:	250
Tables:	2
Figures:	2
References:	38

Abstract

Background

Symptoms of functional neurological disorder have traditionally been thought to depend, in part, on patients' ideas about symptoms rather than on the rules of pathophysiology. The possibility that functional cognitive symptoms might similarly reflect ideas of dementia has not been explored. We aimed to assess beliefs, through performance, about symptoms of dementia in healthy non-medical adults with the intention of identifying potential markers of functional cognitive disorders.

Methods

Healthy volunteers were asked to simulate symptoms of mild dementia during testing with the MoCA, coin-in-hand forced-choice test, short digit span trials, Luria 3-step test and interlocking finger test. Family history of dementia was recorded.

Results

In 50 participants aged 18-27, simulating dementia, mean MoCA score was 16 (SD 5.5, range 5 – 26). Delayed recall was the most frequently failed item (100%) and cube drawing least frequently failed (42%). 26% failed forward three-digit span and 36% failed reverse two-digit span. On the coin-in-hand test, 32% scored at or below chance level. Inconsistent response patterns were common.

Conclusions

Cognitively healthy young adults simulating mild dementia perform similarly to older adults with mild dementia, demonstrating beliefs that dementia is associated with significant global impairment, including attention, motor function, and letter vigilance, but preservation of cube drawing. Inconsistent response patterns were common. Contrary to expectation, family history of dementia did not influence performance. Two and three digit span showed particular promise as a bedside test for simulation. Further investigation will establish whether similar patterns of results are produced in individuals with functional cognitive symptoms.

Introduction

The last 10 years has seen a drive to diagnose diseases causing dementia at the earliest clinical and even preclinical stages. However, in those presenting to memory clinics with mild complaints or mild impairment, biomarker specificity is low and aetiologies heterogeneous [56,180,181,267,276]. It is likely that a significant proportion who do not ultimately receive a diagnosis of dementia have Functional Cognitive Disorders: that is, conditions where cognitive symptoms are present and associated with distress and disability, but which are caused by functional disturbances of attention, abnormal metacognitive beliefs, alongside other functional neurological symptoms, or as a result of psychiatric illness [3,277].

Subjective report of memory impairment generally correlates poorly with performance on cognitive tests, and performance on cognitive screening tests is unpredictable in those with functional disorders: some patients achieve normal scores, but some score very poorly, especially in tests of memory, attention and executive function[9]. Although cognitive screening tests are now heavily used in the diagnosis of dementia and in defining mild cognitive impairment (MCI), the specificity remains unacceptably low. A 2009 review of 41 robust longitudinal cohort studies found that fewer than half of those receiving a description of MCI (described on the basis of memory symptoms and mild impairment on screening tests) progress to dementia even after 10 years of follow up [267]. Over-reliance on cognitive screening tests brings a risk of misdiagnoses and associated iatrogenic harm, and we expect misdiagnoses to become a more pressing problem as preclinical Alzheimer disease profiles are increasingly identified in younger people.

It has been traditionally taught that the symptoms of functional neurological disorders are, in part, dependent on the patient's ideas about the symptoms rather than anatomical and pathophysiological rules [278]. Similarities have been observed between simulated and functional paralysis, for example, suggesting to us not that patients with functional disorder are feigning but rather that symptoms in both cases may depend on 'top-down' predictions that the brain makes about motor and sensory experience, which in the case of a functional disorder are involuntary.

Experimental simulation – asking a healthy subject to mimic the symptoms of a disease – can give a more detailed insight into that subject's ideas and beliefs about those symptoms than is possible through interview or questionnaire. Ideas and beliefs about symptoms of dementia may be similar in healthy individuals to in those with functional cognitive disorders; or they may be different. Experimental simulation may be a useful route in which to access these beliefs in order to further investigate how different belief profiles might relate to the experience of cognitive symptoms, and

may also suggest avenues for investigation in developing more accurate diagnostic profiles for functional cognitive disorders.

This study therefore aimed to compare performance in easily available cognitive screening tests in young adults simulating mild dementia with normative data, in order to better understand what young adults believe the symptoms of dementia to look like. We hypothesised that simulating individuals would perform as if impaired, but less severely than those with dementia, and that they would present with different patterns of impairment.

Methods

Participants were recruited via peer networks and social media. Inclusion criteria were: age over 16 and able to speak and read English. Individuals were excluded if they had a pre-existing neurological disorder or had received any education or training in medicine, healthcare, or clinical neuroscience at college or university level. Educational level and family history of neurological disease was recorded.

Participants were asked to complete a panel of cognitive tests 'as if you have mild dementia due to Alzheimer's disease'; a script was used to standardise examiner suggestion (**Appendix 1**). The assessment included a brief interview and the Montreal Cognitive Assessment (MoCA), with response times for each item measured using a stopwatch. The Luria 3-step test, interlocking fingers test, and examination of gait and tandem (heel-to-toe) gait were included due to increasing recognition of the diagnostic utility of motor symptoms in dementia [279–283]. The coin-in-hand tests and short digit span trials were included in an attempt to quantify effort or intention to fail [284]. The following procedure was used for the coin-in-hand test: the examiner showed the participant a two-pence coin in the palm of one hand, closed both hands into fists and asked the participant to close their eyes and count aloud backwards from 10; the participant was then asked to open their eyes and indicate which hand the coin was in; 10 trials were completed, the coin appearing in each hand an equal number of times. Any unusual behaviours during testing were noted.

Data were analysed using R (version 3.5.2), and with group comparisons performed using independent 2-group t-test for continuous and Pearson's chi-square for dichotomous data; distribution was assessed for normality (Shapiro Wilks). The study received University of Edinburgh ethical approval.

Results

50 subjects were recruited: 25 female and 25 male, mean age 22 (range 18-27). 78% were current university students (66% undergraduate and 12% postgraduate), 18% university graduates, and 4% neither students nor graduates.

In response to the question 'Please could you tell me what you think someone with mild or early stage dementia might experience? What symptoms might they have?' **(Table 1)**: 49/50 participants listed memory problems, of whom 25 specified preferential impairment of 'short-term' memory and 12 impairment of both 'short-term' and 'long-term' memory. Failure to recognise familiar people or faces was the most commonly reported specific memory symptom (20), followed by losing things (7), repetitive conversation (5), forgetting items like keys and shopping lists (5), forgetting tasks whilst undertaking them (4) (for example, going into a room and forgetting what you went in for), and lack of awareness of current affairs (2). Two described relative preservation of memories with emotional content. 17/50 listed 'confusion', 14 listed disorientation to place, getting lost, problems with spatial awareness or navigation and three disorientation in time. Ten participants listed distress or agitation: including 'fear', irritation and frustration', 'frustration', 'feeling insecure' and 'anxiety'. Eight listed motor impairment: including 'loss of dexterity', 'slow movement and bad imbalance', 'lacking co-ordination', 'balance problems, falling', 'slower motor skills', and 'slightly restricted mobility'; in contrast, three specifically stated they would expect no motor impairment or physical symptoms. Six described changes in behaviour: 'angry', 'strange behaviour', 'short and irritable', 'expressionless', 'slight personality change', 'saying things that are out of character or socially unacceptable', 'reduced social interaction'; six listed speech changes, including 'difficulty speaking / difficulty forming sentences', 'disorganised speech', 'mixing words up', 'slurred words' and 'slow speech'. Five listed affective symptoms including 'sadness', 'negative mood', 'not a full range of emotions', and another 'absence of drive and motivation'. Five listed problems performing simple tasks, one of whom stated that a person with dementia might sustain a greater number of accidental injuries such as burns or cuts from cooking. Three included higher-order problems: 'loss of critical reasoning', 'problems with decision making', 'difficulty problem solving'. Two listed 'short attention span'. Symptoms mentioned once only included: confabulation ('constructing false memories'); 'paranoia' and auditory and visual hallucinations ('speaking to self / seeing things'); slow processing speed; lack of insight ('denial of symptoms'); neglect of self, household and pets; 'reminiscing'; 'removal from reality'; 'tiredness'; and 'headaches'.

Table 1 – Responses of 50 healthy adults questioned about expected symptoms in mild dementia

Symptom	**Examples stated**	**Number reporting symptom**
Memory problems	'forgetful', 'memory loss', 'forgetting little things – appointments and jobs', 'forgetting if taken their pills', 'phone numbers', 'birthdays and pin numbers'	**49**
- short term > long term		***25***
- short term = long term	'gradual disintegration of long-term memories'	***12***
- failure to recognise familiar people		***20***
- Losing things	'keys, shopping lists', 'keys', 'forgetting where they put their keys', 'prone to misplacing things'	***11***
- Repetitive conversation	'identical conversation on repeat', 'repeating the same stories', 'asking the same question over and over'	***5***
- Forgetting tasks whilst undertaking them	'walking into a room and forgetting what you went in there for', 'why they went to the shop', 'that they'd put the oven on', 'leaving things on stove'	***4***
- Unaware of current affairs / news events		***2***
- Relative preservation of emotional memories		***2***
Confusion		**17**
Distress or agitation	'fear', irritation and frustration', 'frustration', 'feeling insecure' and 'anxiety'	**10**
Disorientation to place / getting lost / impaired spatial awareness / navigation		**14**
Motor symptoms	including 'loss of dexterity', 'slow movement and bad imbalance', 'lacking co-ordination', 'balance problems, falling', 'slower motor skills', and 'slightly restricted mobility'	**8**
No motor or physical symptoms	(specifically stated)	**2**
Changes in personality or behaviour	'angry', 'strange behaviour', 'short and irritable', 'expressionless', 'slight personality change', 'saying things that are out of character or socially unacceptable', 'reduced social interaction'	**6**
Speech or communication changes	'difficulty speaking / difficulty forming sentences', 'disorganised speech', 'mixing words up', 'slurred words' and 'slow speech', 'forget where they are in a sentence'	**6**
Changes in mood	'sadness', 'negative mood', 'not a full range of emotions', and another listed 'absence of drive and motivation'	**5**

Problems performing simple tasks	'forgetting how microwaves and toasters work', 'greater number of accidental injuries such as burns or cuts from cooking'	**5**
Problems with problem-solving, reasoning, decision-making		**3**
Disorientation to time		**3**
Short attention span		**3**
Confabulation ('constructing false memories'); 'paranoia' and auditory and visual hallucinations ('speaking to self / seeing things'); slow processing speed; lack of insight ('denial of symptoms'); neglect of self, household and pets; 'reminiscing'; 'removal from reality'; 'tiredness'; and 'headaches'.		**1 each**

Mean MOCA score was 16 (±5.5, range 5 – 26, maximum potential score 30) **(Table 2)**. The items with most errors were: delayed recall of five items (100%, with 72% recalling two or fewer items), letter vigilance (86%), digit span (5 digits) (82%), clock-drawing (82%), and sentence repetition (80%). The items with fewest errors were cube drawing (42%) and serial sevens (54%). 16 (32%) made at least one perseveration in verbal fluency. We also noted some perseverative responses during delayed recall: 'feet' (when previously produced in letter fluency) and 'clock'; and some semantic errors such as 'rose' for daisy. Median total summed response time for the whole MocA was 7 minutes 57 seconds with an unusually wide range (5 minutes 13 seconds - 14 minutes 12 seconds, IQR 2 minutes 4 seconds.)

Table 2 - MoCA and additional digit span results

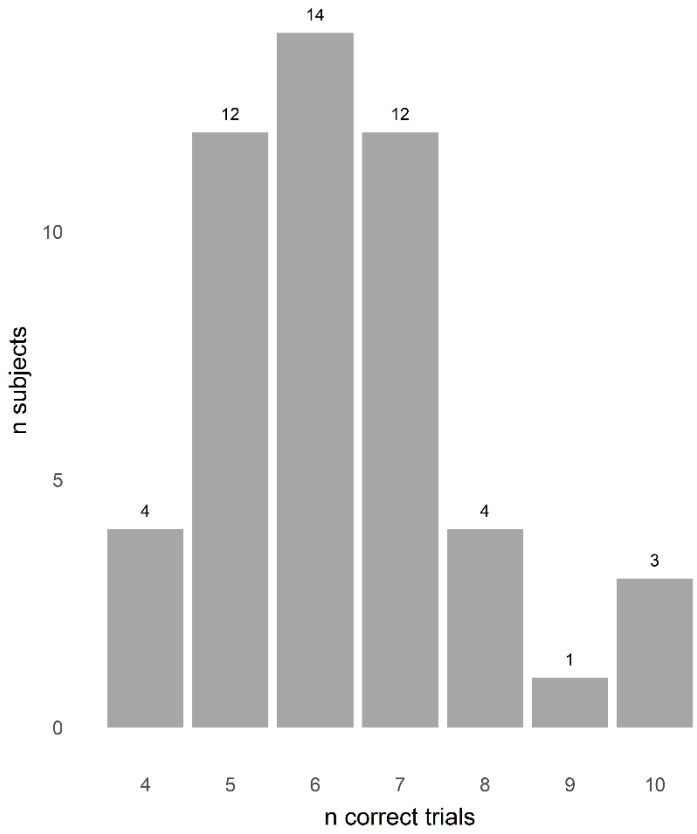
Item	Available points	n (%) achieving fewer than all available marks	Mean score ± SD / median (IQR)
Trail-making	1	36 (72%)	
Cube	1	21 (42%)	
Clock drawing	3	41 (82%)	1.78 ± 0.81
- contour	1	5 (10%)	
- numbers	1	23 (46%)	
- hands	1	33 (66%)	
Object naming	3	28 (56%)	2.12 ± 0.98
Digit span 5	1	41 (82%)	
*Digit span 4**		*29 (58%)*	
*Digit span 3**		*13 (26%)*	
Reverse digit span 3	1	30 (60%)	
*Reverse digit span 2**		*18 (36%)*	
Letter vigilance	1	43 (86%)	
Serial sevens	3	27 (54%)	2.1 ± 0.99
Repetition	2	40 (80%)	0.64 ± 0 .80
Fluency	1	39 (78%)	score 0.22 ± 0.41 valid words 7 (4.5)
Abstraction	2	30 (60%)	1.24 ± 0.71
Delayed recall	5	50 (100%) *5 correctly recalled – 0* *4 correctly recalled – 1 (0.5%)* *3 correctly recalled – 13 (26%)* *2 correctly recalled – 14 (28%)* *1 correctly recalled – 12 (24%)* *0 correctly recalled – 10 (20%)*	2 (2)
Orientation	6	37 (74%) *6 correct – 13 (26%)* *5 correct – 10 (20%)* *4 correct – 16 (32%)* *3 correct – 5 (10%)* *2 correct – 4 (8%)* *1 correct – 2 (4%* *0 correct – 0*	4 (1.75)
Total MoCA score	30	50 (100%)	15.68 ± 5.53
* additional digit span trials not part of MoCA			

Data from digit span testing was particularly interesting in relation to what might be expected in mild dementia. 58% of subjects failed a forward digit span of four digits, and 26% a forward digit span of three digits.

On the coin-in-hand test, 12 (24%) scored at and four (8%) below, the level expected by chance **(Figure 1)**. Three subjects (6%) including two of those scoring 10/10 were observed to circumvent the requirement to recall the coin's location during the test by pointing to the correct hand whilst they had their eyes closed. Four struggled or failed to count backwards from ten.

Figure 1 – Coin-in-hand test

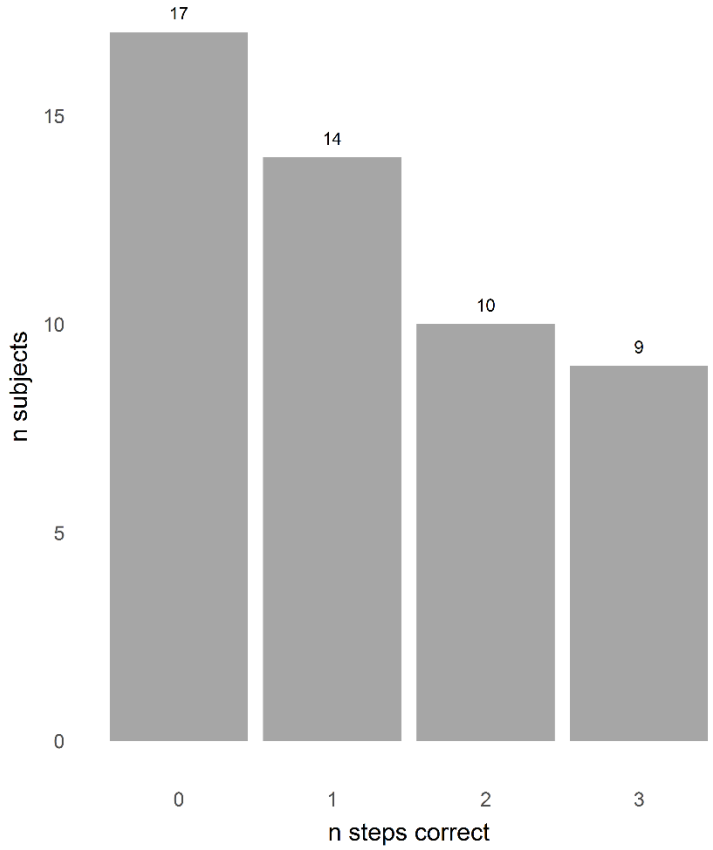
X axis – number of trials in which side of coin (L or R) correctly identified. Y axis – number of subjects. 16 subjects scored at (12) or below (4) the level which would be expected by chance.



9 (18%) achieved all three steps of the Luria three-step test and 17 (34%) did not manage the first step, the remaining 24 (48%) managing one or two steps **(Figure 2)**. 15 (30%) copied all four interlocking finger positions, 23 (46%) three, 10 (20%) two; one subject copied only one and another failed to copy any of the hand positions.

Figure 2 – Luria 3-step test

X axis – number of steps correctly completed (1 - Series copied alongside examiner, 2 – Series repeated independently, 3 – new series successfully copied independently.) Y axis – number of subjects.



We noted several inconsistent patterns of response. 15 successfully achieved 5/5 in subtraction of serial sevens from 100 but failed to repeat a digit span of five, of whom six also failed a reverse digit span of two digits. Of the 29 subjects who failed forward digit span of four digits, 16 (55%) passed cube drawing, 10 (34%) passed serial sevens and four (14%) achieved full marks for orientation. Of the 15 scoring 4/4 on Interlocking Fingers, 11 (73%) did not successfully complete the Clock Drawing task. Similarly, of the nine participants scoring 3/3 on the Clock Drawing task, five (56%) were unable to copy all four finger positions.

Gait appeared normal in 26 (52%) and abnormal in 24 (48%): five were unusually slow and one very quick, 16 appeared unsteady, and 17 failed to manage or lost their balance during tandem gait. Ten in whom gait otherwise appeared normal appeared to have difficulty remembering or following instructions during examination of gait.

There were no significant differences in total or individual item scores between the 24 participants who reported a family history of dementia (all grandparents) and in the 26 who did not. On the clock-drawing task, individuals with a family history were faster than those without (42.3 seconds vs. 54.7 seconds, p=0.02 (95%CI 1.48,23.3); there were no other significant differences in response time.

Discussion

Attention and beliefs are widely recognised as important elements in the aetiology of functional neurological disorders [7,285]. In the Bayesian paradigm described by Edwards et al, prior beliefs about movement, typically not held in awareness, exert a top-down influence on sensorimotor processing to produce and maintain symptoms of functional motor disorder [7]. Experimental simulation has previously demonstrated similarity between simulated and functional paralysis, both groups also demonstrating sensory loss, in patterns (for example, circumferential) that are less common in structural lesions [278,286]. It might therefore be similarly expected that individuals simulating dementia might demonstrate prior beliefs about dementia which are more characteristic of functional cognitive disorders than of dementia. This study aimed to access prior beliefs about dementia in healthy individuals by asking them to simulate symptoms of mild dementia, with the purpose of clarifying those ideas and identifying behaviours with potential utility in the diagnosis of functional cognitive disorders.

This cognitively healthy and highly educated group of young adults, asked to simulate mild dementia, scored similarly to individuals with mild Alzheimer's disease in the original normative data, with a mean score of 16 and 90% falling below the 23/30 cutoff [279,287–290]. We were surprised by the severity of apparent impairment displayed, expecting more subtle deficits. In previous studies of simulated 'mental disorder' and of cognitive impairment due to brain injury, simulators (particularly student simulators) have produced milder impairments than disease controls [291,292]. However, the overall level and scope of impairment demonstrated by this cohort of simulating subjects reflected the overall impression suggested by their verbal descriptions of mild dementia. Although most identified memory impairment as a key symptom, more often dementia was described as a syndrome of global impairments even at an early stage; motor, speech, emotional and behavioural symptoms were relatively over-represented in our subjects' reports of expected symptoms, whereas lack of insight – prevalent in dementia – was only included in the report of one subject, suggesting either that lack of insight is not recognised to be important or that it is assumed to be so common as to not be worthy of mention [293]. In those with functional cognitive disorder, the former seems more likely, given the frequent observation of memory catastrophisation, in which the patient is acutely aware of their

deficits whereas others are not. Our first observation, therefore, is that healthy young adults perceive even mild dementia as a condition of significant rather than subtle impairment.

Although total scores were similar, patterns of apparent impairment differed in several important ways from norms for both dementia and cognitively healthy populations. In normative data, individuals with Alzheimer's Dementia and MCI have been reported to perform worst on trail-making, clock drawing, naming, delayed recall, phonemic fluency, abstraction, and orientation [279]. This group of adults simulating dementia performed worst on delayed recall (100%), letter vigilance (86%), clock-drawing (82%), forward digit span (82%), repetition (80%), fluency (78%) and trail-making (72%); letter vigilance (a task involving sustained attention and response inhibition) therefore being more impaired than might be expected in mild dementia. A cognitively healthy cohort of 73 year olds lost most points for delayed recall (mean score 3.1±1.3), fluency (0.7±0.5), and abstraction (1.7±0.6) [289]. Our simulating subjects scored worse than healthy controls in all of these measures: delayed recall (2, IQR 2), fluency (0.22±0.41) and abstraction (1.24±0.71). In another population-based sample the items with the most frequent errors were cube drawing (59%) and delayed recall (56%) [294]. Cube drawing was comparatively preserved in our simulating group, 44% making errors, whereas 100% failed delayed recall. It seems that these simulating adults do not perform with an exaggerated pattern of normal failures, nor do they perform similarly to those of individuals with mild dementia.

The degree of effort applied during cognitive testing significantly influences performance but is notoriously difficult to define and measure. Some validity tests are so straightforward that they should be completed without difficulty even in the presence of significant impairment. Others use a 'forced choice' paradigm, on the basis that scoring less than chance indicates intention to fail: arguably a completely different concept to that of effort by degree of intention to perform to capacity. The coin-in-hand test meets both criteria, and is easy to perform in clinic without special equipment [284]. In this study, subjects simulating dementia performed poorly on the coin-in-hand test, 84% scoring 7/10 or less, although only 8% scored below the level expected by chance. We have reservations about the utility of these tests in the memory clinic. Critically, individuals with dementia also sometimes fail effort tests. In a study of six validity tests 5/22 individuals with moderate to severe dementia failed (scoring 7/10 or less) the coin-in-hand test (although the number scoring at or less than chance is not reported); 16/22 (7/20 with mild dementia) failed the Medical Symptom Validity Test and 16/22 failed the Rey 15 item test [295]. So, although a cutoff score of 7/10 on the coin-in-hand test would correctly identify 84% of our simulating patients, this could not be relied on in a clinical context to exclude other causes of cognitive impairment. Moreover, interpretation of validity test performance in non-simulating, non-litigating patients with functional neurological disorders is complex: in some

individuals, the interference from pathologically excessive effort, and anxiety, might disrupt normally automatic cognitive processes in order to produce results suggesting, paradoxically, a lack of effort.

In normative WAIS (Wechsler Adult Intelligence Scale) digit span data, individuals with memory impairment, including due to Alzheimer's dementia or vascular dementia, traumatic brain injury, Korsakoff's syndrome, and temporal lobectomy, generally scored between five and eight on forward digit span; 4.1%, of all clinical groups and 10.5% with Alzheimer's disease scored a maximum of four and 2.6% of the Alzheimer's disease group scored a maximum of three; young adults aged 20-24 scored a mean of 6.8±1.3, reducing gradually over age to a mean of 5.7±1.0 in those aged 85-89 [296]. In a study of 18 individuals with Alzheimer's dementia, 18 with vascular dementia and 26 controls, neither Alzheimer's nor vascular dementia were associated with impaired performance on forward digit span (mean scores around 5.5 in both groups), although both dementia groups were impaired on backward digit span compared with controls [297]. Reliable digit span (summed maximum forward and backwards span measured using the WAIS) has been used in attempts to measure effort [298–300]. Although Reliable Digit Span could not be calculated here due to the simple method used to test digit span, addition of short digit span trials to those included in the MoCA enriched the examination by demonstrating exceedingly poor performance in some individuals; 26% failed a digit span of three and 36% failed reverse span of two digits, suggesting that a substantial minority of those tested believe working memory to be significantly impaired in individuals with mild dementia.

Internal inconsistency is a key feature of functional neurological disorders; for example, in Hoover's test, hip extension is weak during active movement but returns to normal with contralateral flexion against resistance. Inconsistency was also a prominent feature in these simulating young adults. Atypical performance patterns in less widely used neuropsychological tests have been described as a marker of malingering [301]. In our study, discrepant patterns such as poor performance in digit span relative to serial sevens (examining overlapping functions of sustained attention and working memory), and poor performance in construction tasks relative to performance in imitation of hand gestures were potential indicators of functional cognitive disorders which merit testing in larger cohorts of individuals with both neurodegenerative and functional disorders.

Family history of dementia did not influence performance in this study. However, our subjects were young (mean age 22), and family history of dementia related to a grandparent in all cases. They were significantly younger than the reported mean age (54.6± 13.0 years) of people with functional cognitive disorders in a series of memory clinic patients, in whom family history was associated with increased likelihood of functional cognitive disorder.[37] We predict that older individuals are more likely

to have experience of dementia in a first degree relative, and that this might impact on beliefs about symptoms, although how this might manifest is an interesting topic for further investigation

Although there may be similarities in beliefs about dementia between those with functional cognitive disorders and healthy adults, there are also likely to be differences, and these differences may be important in determining why functional cognitive symptoms develop in some people and not others. At a group level, people who develop functional neurological disorders have a greater experience of ill health and psychiatric comorbidity, and may also have different background experiences. These factors, together with general factors such as gender, educational background, and ethnicity, are likely to influence beliefs about illness. Further research using an experimental simulation paradigm in those with experiences of chronic pain or ill health, or who have experienced adverse events, might be used to further explore the relationship between beliefs and cognitive symptoms in those with functional disorders.

Describing performance patterns in simulating adults and, in future, in individuals with functional cognitive disorders is an important step in improving our understanding of functional cognitive disorder phenotypes. However, overall, we suspect that raw cognitive test results will continue to have a limited reach in discriminating between neurodegenerative disease and functional cognitive disorders as preliminary clinical studies have suggested[37]. Promising work in this area has concentrated instead on linguistic and behavioural features during the clinical consultation, finding for example that individuals with functional cognitive disorders are more likely to attend clinic alone, more likely to provide detailed accounts of forgetting events, and less likely to 'head turn' towards an accompanying adult [10,215,216,219,302].

The conclusions we can draw from this study are limited by the lack of functional cognitive disorder controls. In addition, detailed enquiry was not made into the extent to which the instruction to simulate mild (rather than moderate or severe) dementia was understood, and it is possible that some subjects aimed to simulate more severe impairment than we intended. Finally, digit span was measured on the basis of single trials and not according the method used in the WAIS (Wechsler Adult Intelligence Scale - not available for general clinical use by non-psychologists), and as a result it was not possible to calculate Reliable Digit Span in order to compare directly with normative data.

In summary, cognitively healthy individuals simulating dementia attain similar overall scores in cognitive screening tests as individuals with mild dementia, but with particularly poor performance on short digit span trials, relative preservation of cube drawing and abstraction, inconsistent patterns

of performance and higher rates of effort test failure. Experimental simulation of cognitive impairment is a novel method of accessing beliefs about dementia with potential utility in the development of diagnostic tools for functional cognitive disorders.

Investigating phenotypes – paper 3 –

The frequency and framing of cognitive lapses in healthy adults

McWhirter L, King L, McClure E, Ritchie C, Stone J, Carson A

CNS spectrums. 2021 Jan 22:1-8.

Introduction to the paper:

Analyses in the first paper in this thesis, 'Functional cognitive disorder – a systematic review', I found that cognitive symptoms are very common in all age groups, and so unlikely to be a specific marker of degenerative brain disease. In this study I aimed to establish baseline frequencies for a range of cognitive lapses of the sort also commonly reported in the memory clinic.

I designed the survey, with input from medical students Lachlan King and Eilidh McClure, who collected and collated the data and performed some initial analyses. I performed more detailed analyses and wrote up the data into the current form. CR, JS, and AC contributed to review and revision of the final manuscript.

This paper supported the hypothesis that cognitive lapses are common in healthy adults, providing us with useful data to use to help patients contextualise their experiences. This data also revealed that recognition of these cognitive failures does not preclude good health and indeed may be a part of healthy metacognition; in contrast to functional cognitive disorder, where experience of cognitive failure is a source of distress and impairment.

Word count: 3529 (including tables)
Abstract word count: 250
Tables: 2
Figures: 4
References: 17

Abstract

Objective

Many people present to health services with concern about cognitive symptoms. In a significant proportion those symptoms are not the result of pathologically-defined brain disease. In some they are part of a Functional Cognitive Disorder. We assessed the frequency of cognitive lapses in a non-clinical sample in order to consider the utility of frequency of cognitive lapses in diagnosing cognitive disorders.

Methods

Healthy adults, who had never sought help for cognitive symptoms, completed a questionnaire, distributed via social media, about self-evaluation of cognitive function, frequency of specific cognitive lapses, and use of memory aids, including Schmitdke and Metternich's Functional Memory Disorder (FMD) inventory.

Results

124 adults, aged 18-59 (median 23), most with further or higher education, responded. 31(25%) reported 'fair' or 'poor' memory. 48(39%) reported memory worse than 5 years ago, and 30(24%) reported memory worse than others the same age. Participants endorsed a mean 13/18 specific cognitive lapses at least monthly. 111 (89%) scored ≥4, the suggested cut off for the FMD inventory.

Conclusions

Cognitive lapses described in functional cognitive disorders are common in highly-educated adults. The high rate of reported lapses in this healthy population suggests that self-reported frequency of memory lapses alone cannot discriminate functional cognitive disorders from 'normal' cognitive experiences. Further research is required to clarify the role of abnormal self-evaluation of cognitive function (metacognition) in functional cognitive disorder. Better understanding of the factors moderating subjective interpretation of cognitive failures will also aid development of better clinical risk-stratification methods in people concerned about future dementia.

Introduction

The last ten years have seen increasing societal and scientific drive to detect the neurodegenerative diseases causing dementia at the earliest stage, in the hope that, as effective treatments become available (including risk factor modification), it will be possible to ameliorate progression of these diseases and therein delay or prevent dementia onset. Yet, while increasing numbers of people present to health services concerned about memory problems, the percentage leaving memory clinics with a diagnosis of neurodegenerative brain disease is falling[2,303].

Discriminating clinical presentations which are likely to be due to neurodegenerative brain disease from those which are not is, therefore, an important clinical and research priority. In clinical practice, the assessment process includes interpretation of the patient's own report of their experience of cognitive difficulties. However, the relationship between self-perceived cognitive decline or inefficiency and brain disease is not straightforward. Subjective cognitive impairment is common in a range of populations, and studies of base rates of cognitive complaints are remarkable for the heterogeneity of results, depending on the cohort and also the questions asked[74,83,304]. 'Do you have a memory problem?' is a very different question from 'Is your memory worse than five years ago?' and different again from 'Is your memory better or worse than other people the same age?'. Subjective cognitive decline (SCD) over time is associated with a slightly increased risk of future dementia over people without SCD, especially when tightly defined[305]. Yet, the majority of those with SCD do not progress to dementia, and the presence of subjective cognitive impairment does not appear to correlate with age[306].

A Subjective Memory Complaints' Likert scale has been used in a number of studies, in which a memory rating of 'fair' or 'poor' in response to the question 'In general, how would you rate your memory?' is used as an indicator of the presence of Subjective Memory Complaints(SMC) [126,307]. Of studies using this scale, Purser et al found that SMC did not predict progression of impairment in MCI, and Paradise et al found SMC in 12% of 45432 adults strongly related to psychological distress but not vascular risk factors[126,307]. Larner found the same indicator sensitive but not specific for an ultimate diagnosis of Functional Cognitive Disorder in patients attending a memory clinic[36].

Around a quarter of people attending memory clinics with cognitive complaints receive diagnoses in keeping with functional cognitive disorders (FCD)[306]. In FCDs, cognitive symptoms are present, and associated with distress and/or disability, as the result of dynamic and therefore internally

inconsistent changes in higher cognitive function, rather than progression of neurodegenerative disease[308]. Research into FCD diagnosis has concentrated on how we might discriminate cognitive symptoms due to FCD from those due to brain disease. While raw scores on cognitive screening tests seem unhelpful one promising approach has involved analysis of interaction and language in the clinical examination[215]. Another approach, employed in the FMD (functional memory disorder) inventory proposed by Schmidtke and Metternich, examines the frequency and nature of self-reported cognitive complaints[226].

In order to interpret the diagnostic relevance of self-reported cognitive complaints, it is important to understand the baseline frequency of comparable experiences in apparently healthy people. However, there have been only a few studies of base rates of specific cognitive lapses in healthy populations. In Jonsdottir et al's diary study of 'action slips' (defined as 'actions which we would normally classify as being a sign of absentmindedness') in 189 healthy adults (mean age 30.8) participants responded a mean of 6.4 'action slips' per week (range 0-30)[309]. The largest healthy population included in McCaffrey et al's review of symptom base rates is from a 1987 study including a healthy control group of 620 US college students, of whom 9.7% experienced memory gaps (a gap in memory for an undefined period of time), 23% staring spells and 27% word-finding lapses[310,311]. Another study included in the McCaffrey review was a 1995 study that included a group of 170 adults (mean age 38) of whom 32% forgot where the car is parked, 17% lost items around the house, and 27% forgot why they entered a room; although 40% of this group had an alcohol use disorder at 10 year follow-up suggesting possible confounders[312]. There is therefore a lack of up-to-date data on cognitive symptom base rates in unselected healthy adults.

Although there is a well-developed body of research which differentiates the cognitive symptom profile and clinical presentation therein between FCD and people with dementia[306] there has been little analysis of the questions of how and why cognitive symptoms in FCD differ from cognitive lapses experienced by healthy people during everyday life. These are important questions. Historically, some people within an FCD group have been described as 'worried well', in a way that has dismissed the extent of their cognitive disability and thereby seeming to justify not providing appropriate treatment. At the other end of this spectrum, a pervasive narrative in which subjective cognitive symptoms lie on a 'one-way path' to mild cognitive impairment and then dementia means that the fact that cognitive symptoms are really quite common is often lost. As a result, unwarranted prognostic significance may be placed on the presence of cognitive lapses which are a part of normal experience.

Understanding cognitive lapses in healthy adults, and how these are framed in terms of overall self-evaluation of cognitive function (metacognition), is an important preliminary step in the development of more accurate methods of clinical diagnosis and risk profiling in both degenerative brain disease and in functional cognitive disorders. In this study we therefore aimed to establish the frequency of, and interrelationships between, subjective memory complaint, specific cognitive lapses, and use of memory strategies, in healthy adults with a low risk of neurodegenerative brain disease.

Methods

An online questionnaire was advertised through a Facebook group for people living within a central area of Edinburgh (in the vicinity of Edinburgh University) with over 30,000 members, described as "a community board for those within walking distance of the Meadows to share resources, tools, skills, information etc."

The questionnaire was open from January until late March 2020. Participants between 18-60 years were eligible. Exclusion criteria were: self-report of having sought medical advice for memory symptoms or having 'ever been diagnosed with dementia or any other memory-related condition'. No incentive was provided for completing the questionnaire. Ethical approval was obtained from Edinburgh University, and no identifying information was collected.

The questionnaire asked participants about their perceptions of their own memory in general ('In general, how would you rate your memory just now?) using the SMC Likert scale as described by Paradise et al, and respondents were considered to have Subjective Memory Complaints (SMC) if they rated memory 'Poor' or 'Fair' on this scale[126]. Participants were also asked about their memory in comparison to others and to themselves 1 and 5 years ago, and compared with others the same age.

Participants were asked how frequently they experienced a range of memory lapses, and were also asked whether they experienced each lapse 'much more', 'more', 'about the same', 'less', or 'much less' than other people the same age. The questionnaire incorporated all components of the Schmidtke and Metternich (2009) short version FMD inventory[226](**Appendix 1**). Additional lapses were included following discussion and consensus between the authors. In analysis of cognitive lapses, and of components of the FMD inventory, report of experiencing a lapse 'frequently (several times a week or more)', 'occasionally (about once a week)', or 'rarely (about once a month)', but not 'never', was interpreted as equivalent to 'yes' on the FMD inventory.

Questionnaire data were collected with Google Forms, and statistical analyses were performed using Excel (version 2007) and R (v3.6.0). Data were tested for normality using the Shapiro-Wilk test, and Spearman rank correlation coefficient and Wilcoxon rank sum tests were used in analyses of nonparametric data.

Results

Demographics

The survey was completed by 124 eligible participants, with a median age of 23 (range 18-59). 74% (92) were female, 24% (30) male and 1 'other'. 97% (120) were in or had completed further or higher education. 3 people self-reported ineligibility by responding 'yes' to the question 'Have you ever visited the doctor with concerns about your memory?'

General self-evaluation of memory

Table 1. Self-evaluation of memory

	Excellent	Very Good	Good	Fair	Poor
In general, how would you rate your memory?	13% (16)	32% (40)	30% (37)	19% (23)	6% (8)
	Much better	**Better**	**Same**	**Worse**	**Much worse**
How do you think your current memory is when compared to yourself 1 year ago?	2% (2)	4% (5)	81% (101)	13% (16)	0
How do you think your current memory is when compared to yourself 5 years ago?	2% (3)	10% (13)	48% (60)	31% (38)	8% (10)
How would you rate your memory compared to others your age?	10% (13)	27% (34)	38% (47)	22% (27)	2% (3)

Subjective memory complaint (SMC) was common: 25% (31/124) rated memory in general as 'Fair' or 'Poor' (**Table 1**).

There was no correlation between general rating of memory (the SMC Likert scale) and age (r_s=-0.14,p=0.12). There was a positive association between perceived memory decline over 1 and 5 years (chi square test, df = 12, p<0.01), but there was no correlation between subjective memory decline over the last 1 or 5 years and age (r_s=0.03, p=0.71; r_s=0.11,p=0.24); and there was no correlation between memory rating compared to others, and age (r_s=-0.07,p=0.41) (**Figure 1**).

Figure 1 - Self evaluation of memory function in 124 healthy volunteers, median age 23

Memory worry and fear of developing dementia

Forty-seven (38%) participants responded 'Yes' to the statement 'Are you worried about your memory?'; of whom four were 'very worried'. Seventy (56%) were 'afraid of developing dementia', including 16 (13%) who were 'very afraid'. Neither severity of memory worry or being 'afraid of developing dementia' correlated with age (r_s=0.02, p=0.41; r_s=-0.06, p=0.49) (**Figure 1**).

Twenty (17%) endorsed the statement 'When I forget something I fear that I may have a serious memory problem'. This correlated with memory worry (r_s=0.41, p<0.001) but not SMC Likert (r_s=0.06, p=0.54) or number of cognitive lapses endorsed (r_s=0.01, p=0.99).

Twenty one (17%) responded 'yes' to 'Has another person (e.g. friends/family) ever expressed concerns about your memory?'.

Frequency of specific cognitive lapses

Table 2 shows the reported frequency of cognitive lapses. 'Absent mindedness and daydreaming during conversation' was most frequent (several times a week or more in 29% and about once a week in another 28%), followed by word-finding difficulties (at least weekly in 56%), forgetting why one had entered a room (at least weekly in 50%), and misplacing a mobile phone (at least weekly in 40%). Forgetting where one's car or bike is parked was the least frequently endorsed symptom, but was still experienced at least monthly in 33%.

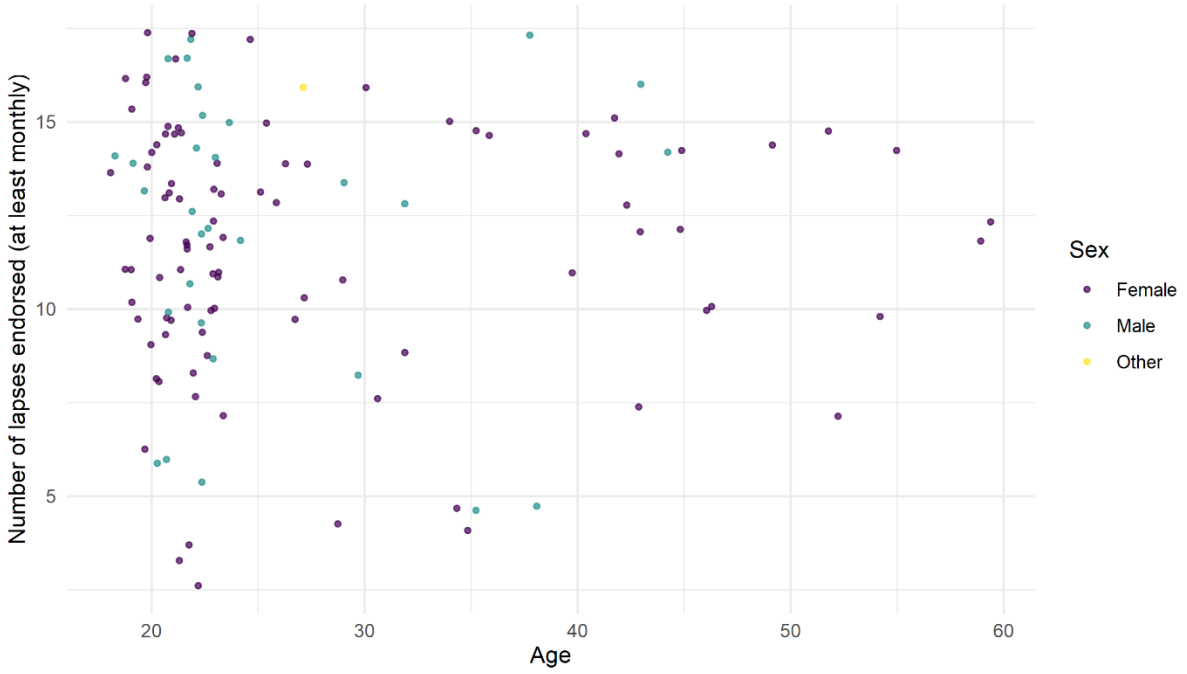
Table 2 (N=124) Frequency of cognitive lapse / symptom in 124 healthy volunteers, median age 23 (% (n))

'How often do you…'	Frequently (several times a week or more)	Occasionally (about once a week)	Rarely (about once a month)	Never
experience absent mindedness and day-dreaming during conversations?*	27% (34)	29% (36)	30% (37)	14% (17)
experience difficulties finding the right word?*	22% (27)	35% (43)	30% (38)	13% (16)
forget why you have entered a room?	19% (23)	31% (39)	31% (38)	19% (24)
forget or misplace your mobile phone?	17% (21)	23% (29)	37% (46)	23% (28)
experience disruptions in the thread of thoughts in conversations?*	15% (19)	30% (37)	44% (55)	11% (13)
forget your shopping list or forget to buy items?	15% (18)	33% (41)	41% (51)	11% (14)
forget important contents of conversations, appointments and errands?*	13% (16)	20% (25)	39% (48)	28% (35)
experience difficulties understanding and registering the contents of news, reading and lectures?*	11% (13)	26% (32)	32% (40)	31% (39)
forget activities/events that happened the day before?	10% (13)	18% (22)	36% (44)	36% (45)
forget significant dates or birthdays?	10% (12)	12% (15)	43% (53)	35% (44)
rapidly forget essential parts of a personal or telephone conversation?*	7% (9)	14% (17)	42% (52)	37% (46)
forget or misplace your keys?	8% (10)	13% (16)	51% (63)	28% (35)
forget whether you have locked a door or turned off an appliance?	6% (8)	22% (27)	45% (56)	27% (33)
experience blocks of retrieval of well-known names, phone numbers, PIN codes etc?*	3% (4)	15% (18)	43% (53)	39% (49)
commit errors, or experience "blackouts" during routine activities at work, at home, whilst driving etc?*	2% (3)	14% (17)	28% (35)	56% (69)
forget errands on the way to their execution?*	2% (3)	14% (17)	40% (49)	44% (55)
forget where you have left your car or bike?	2% (2)	2% (3)	29% (36)	67% (83)
How often is your memory performance subject to variations, namely less marked during times of relaxation?*	6% (8)	21% (26)	49% (60)	24% (30)

*** items included in the FMD short inventory (Schmidtke and Metternich)**

Number of lapses out of 17 ('subject to variation' being excluded) was counted for each participant. Participants with SMC endorsed significantly more cognitive lapses (at least monthly) – a median of 14 compared with 11 in those without SMC (Wilcoxon rank sum test W=15376, p<0.001). No participant with SMC endorsed fewer than 10/17 lapses. Number of lapses endorsed did not correlate with age (**Figure 2**).

Figure 2 – Number of memory lapses / 17 endorsed in 124 healthy adults, median age 23



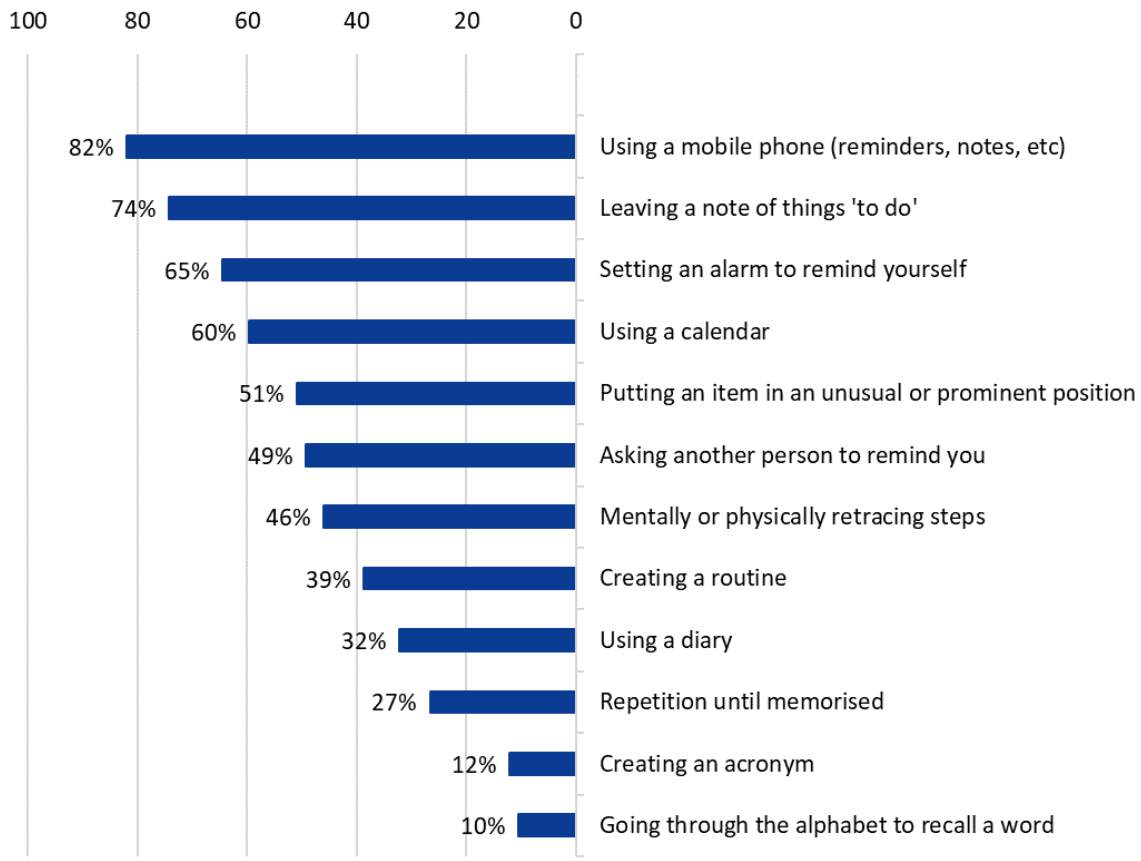
Participants generally (69-97%) reported experiencing the lapses listed in Table 2 **as often** or **less often** than others the same age; outliers were 'disruptions in the thread of thought during conversations' and word finding difficulties which 52 (42%) and 50 (40%) respectively reported experiencing more often than others the same age.

Memory aids and strategies

All participants had used at least one listed memory aid or strategy from those listed within the previous two weeks (**Figure 3**) The most frequently endorsed strategy was using a mobile phone to create electronic reminders or notes (82%). The number of memory aids or strategies used did not correlate with age (r_s=-0.15, p=0.08). Younger age was associated with greater use of repetition

(Wilcoxon rank sum test W = 2098.5, p=0.03), but there were no other age associations between specific memory strategies. There was no significant association between the number of aids used and the number of lapses endorsed (chi square test, df = 140, p = 0.51)

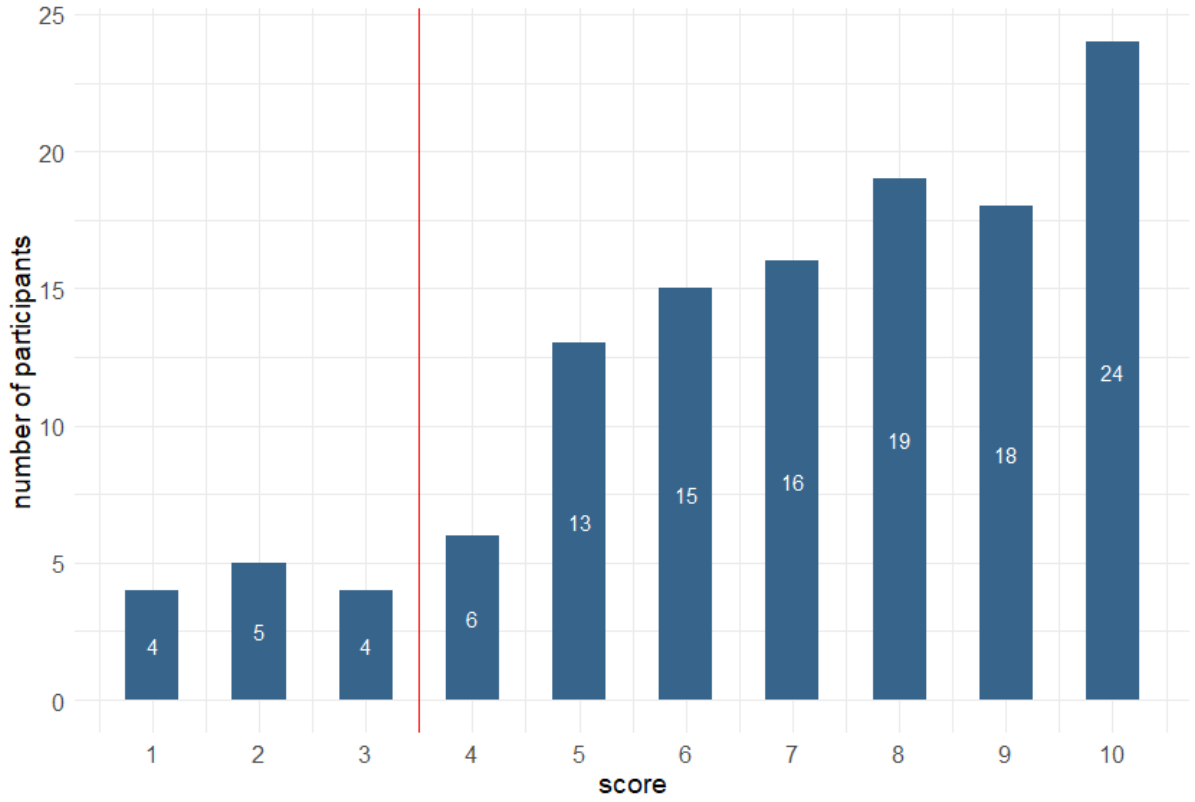
Figure 3 – Memory aids and strategies used in last 2 weeks (n=124)



Functional Memory Disorder Inventory

Mean score on the short FMD inventory (**Appendix 1**) was 7 (SD 2.5), and no participant scored zero. Using Schmidtke and Metternich's suggested cut off score of ≥ 4, 89% (110) of participants met Functional Memory Disorder criteria. **Figure 4** illustrates participants' scores on the FMD inventory. FMD score was inversely correlated with SMC Likert (r_s=-0.42, p=0.03).

Figure 4 – Scores of 124 healthy adults (median age 23) on the Schmidtke and Metternich FMD short inventory.



Given this unexpectedly high proportion of FMD profiles, results were also calculated using an alternative method whereby each symptom was registered as present only if it was experienced at least once per week, instead of at least once per month. Using this method, the mean score was 3 (SD 2.6), and 22 (%) participants scored 0, but 55 (44%) still scored above the ≥ 4 cut off.

Discussion

The subjective experience of cognitive failure or inefficiency is very common. Using a Likert scale, previously described by Paradise and colleagues, 25% of this population of healthy adults, the majority of whom were in or had completed further or higher education, can be classified as having subjective memory complaints[36,126,307].

Perceived decline was also common, with 39% reporting that their memory was 'worse' or 'much worse' than five years previously, and did not correlate with age. However, participants tended to perceive their memory as being as good or better than others the same age, particularly in relation to specific cognitive lapses. This paradoxical combination of perceived cognitive decline alongside 'illusory superiority' in comparison to others has also been observed in older adults[313].

Much of the subjective cognitive impairment and subjective cognitive decline literature is focussed on older adults, where it is more likely that degenerative brain disease and other pathophysiological processes may impact on cognitive function. However, our previous review of the wider literature found that subjective cognitive symptoms are common, present in a mean of 30% (range 8% - 80%) of non-clinical populations, and moreover that prevalence does not correlate with age, as would be expected if cognitive symptoms were primarily the result of degenerative brain disease[306]. The high rate of subjective cognitive complaint and cognitive lapses in this population with a low risk of degenerative brain disease supports a view that the majority of cognitive lapses in the general population are not caused by brain disease. But while degenerative brain disease is overall an infrequent cause of cognitive lapses, they are nevertheless a source of worry. 38% of our participants were worried about their memory; more (56%) were afraid of future dementia.

Our participants endorsed having experienced a mean of 13 of the 18 suggested cognitive lapses at least once per month, and often several times per week. This is a helpful reminder that frequent memory lapses such as day-dreaming during conversation, walking into a room and forgetting what you went in for, or misplacing your phone are all commonly experienced several times a week by healthy and highly-educated adults. That is not to say that these experiences, presenting in a clinical setting, should be dismissed, as in some they may be part of a functional cognitive disorder, associated with cognition-focussed distress and disability, requiring accurate diagnosis and appropriate treatment. Having accurate and age-related data on particular cognitive experiences may be especially helpful in the context of designing specific therapies for functional cognitive disorder. These could be used to help reframe experiences and challenge metacognitions.

In this study, a striking 89% (110) of 124 non-complaining adult participants scored highly enough (≥ 4) on the FMD short inventory to meet criteria suggested by the authors of that inventory to suggest a diagnosis of Functional Memory Disorder had they presented with impairment of function. In Schmidtke and Metternich's original 2009 validation study the FMD short inventory was administered

to 50 healthy controls (mean age 49.5, 50% female) and 45 patients with Functional Memory Disorder (mean age 55.2). The control group in the 2009 study had a mean score of 0.8 (SD1) on the FMD short inventory, compared with 7.6 (SD2.6) in the FMD group, giving a specificity of 100% using a cutoff of ≥ 4 against the gold standard of FMD diagnosis made following non-blinded clinical examination according to the authors' FMD diagnostic criteria [226]. In contrast, the participants in this younger and predominantly female 'healthy control' population scored much higher (mean score 7, SD 2.5).

Although our participants were younger and more predominantly female than Schmidtke and Metternich's healthy controls, and therefore in a group at slightly higher risk of functional neurological disorder, it would be quite wrong to assume that all of those scoring highly on the FMD inventory have Functional Cognitive Disorders. Allowing for the limitation of self-report, all denied diagnosed conditions affecting memory and none had consulted a health professional for memory problems. Moreover the 89% (or 44%) scoring above the suggested cut off on the FMD inventory study exceeds the proportion (25%) with subjective memory complaint (SMC). That is, many of our participants endorsed frequent memory lapses of different sorts, even though they overall rated their memory as good, very good, or excellent. This is at odds with our clinical experience of patients with functional cognitive disorders who are distressed by their symptoms and tend to overestimate their memory deficit.

We would argue instead that this study shows that the memory lapses included in the FMD inventory are experiences that fall within the normal range of experience. As Schmidtke and Metternich's make clear in the separate FMD diagnostic criteria used as the 'gold standard' in the FMD inventory validation study, these experiences become 'symptoms' only when they are accompanied by impaired function and distress[226].

This study supports a view that abnormalities in metacognition are key to the mechanism of FCD; cognitive lapses are not only experienced, but are experienced as problematic and distressing. In contrast, a large proportion of our population of healthy, highly educated, adults notice and acknowledge frequent cognitive lapses, without undue worry or concern, whilst also believing their memory performance to be similar to or superior to others. This normalising (or even illusory superiority) alongside acceptance of failure and inefficiency appears important for healthy cognition.

The population studied here was heavily skewed towards a higher educational background. Most participants were in or had completed further or higher education. We speculate that this group might

be expected to perform at a high level in psychometric tests, but also to be accustomed to a degree of self-scrutiny and social comparison against high internal standards. Study of more demographically diverse populations might help us to understand how educational participation and attainment influences both the experience and interpretation of common cognitive lapses.

So while evaluation of the nature and frequency of cognitive lapses has value in the evaluation of FCD in clinic, we suggest that this approach is best used in combination with a broader examination of what the person expects of their cognition, and how they interpret failures; and with other diagnostic methods such as observation and analysis of internally inconsistent patterns of performance and interaction[215,308]. Future research might usefully examine the basis of and processes through which personal and shared interpretation of experienced cognitive failure and inefficiency might influence cognitive performance; in health, in functional disorders, and in degenerative brain disease.

Investigating methods of diagnosis – Paper 4

Performance validity test failure in clinical populations—a systematic review.

McWhirter L, Ritchie CW, Stone J, Carson A.

Journal of Neurology, Neurosurgery & Psychiatry. 2020 Sep 1;91(9):945-52.

Introduction to the paper:

In presenting and discussing the early parts of my PhD research with other clinicians I was often asked about the usefulness of performance validity tests (PVTs) in identifying functional cognitive disorders. As these are essentially objectively easy tests which are designed to pick up internally inconsistent (described in the field as 'invalid') patterns of response, and with our awareness of internal inconsistency as a key feature of functional neurological disorders, this seemed like an important possibility to explore. However, on my initial reading I found that the methods used to validate PVTs made it difficult to establish 'normal' failure rates in people with illness or disease. I therefore embarked on this systematic review to establish failure rates in a range of PVTs and a range of clinical diagnoses including functional disorders. The results of this review helpfully pointed to PVTs being unlikely to be helpful in the diagnosis of functional cognitive disorder, and generated lively discussion.

I conceptualised the study, designed and carried out the search, screened the results, collated and analysed the data, and wrote the initial manuscript. CR, JS, and AC contributed to review and revision of the final manuscript.

Word count:	4300
Abstract word count:	240
Tables:	9
Figures:	2
References:	60

Abstract

Objective

Performance validity tests (PVT) are widely used in attempts to quantify effort and/or detect negative response bias during neuropsychological testing. However, it can be challenging to interpret the meaning of poor PVT performance in a clinical context. Compensation-seeking populations predominate in the PVT literature. We aimed to establish base rates of PVT failure in clinical populations without known external motivation to underperform.

Methods

We searched MEDLINE, EMBASE, and PsycINFO for studies reporting performance validity test (PVT) failure rates in adults with defined clinical diagnoses, excluding studies of active or veteran military personnel, forensic populations, or studies of participants known to be litigating or seeking disability benefits. Results were summarised by diagnostic group and implications discussed.

Results

Our review identified 69 studies, and 45 different PVTs or indices, in clinical populations with intellectual disability, degenerative brain disease, brain injury, psychiatric disorders, functional disorders, and epilepsy. Various pass/fail cut-off scores were described. PVT failure was common in all clinical groups described, with failure rates for some groups and tests exceeding 25%.

Conclusions

PVT failure is common across a range of clinical conditions, even in the absence of obvious incentive to underperform. Failure rates are no higher in functional disorders than in other clinical conditions. As PVT failure indicates invalidity of other attempted neuropsychological tests, the finding of frequent and unexpected failure in a range of clinical conditions raises important questions about the degree of objectivity afforded to neuropsychological tests in clinical practice and research.

Background

Performance validity tests, also historically called effort tests, are used by clinical psychologists to try to detect inadequate effort and exaggerated or feigned impairment. Identifying invalid performance has critical implications for how the psychologist interprets the rest of the neuropsychological examination, and may also have clinical and medicolegal implications.

As clinicians in neuropsychiatry and neurology we often read neuropsychology reports which include reference to effort and validity measures. However, it can be difficult to interpret the significance of PVT failure in our patients, where complex combinations of neuropathological, cognitive, and emotional factors, including negative prior experiences with other health professionals, can influence symptom experience and behaviour in the consultation.

Moreover, the PVT literature is difficult to assimilate in a clinically meaningful way. This is in part due to the wide range of free-standing and embedded measures described in different studies, and in part due to the range of mixed clinical and litigating populations tested. In addition, descriptions of tests and cut-offs provided are often limited, in view of concerns about the possibilities of preparation or coaching in litigants undergoing neuropsychological assessment[314].

Previous reviews have discussed the application, meaning, and interpretation of validity tests results[315–317], have reviewed specific tests, or described PVT performance in specific groups. While some describe the proportion of examinees involved in seeking compensation, it is difficult to extract from these data a clear picture of performance in individuals who are ill and/or impaired and are not seeking compensation.

We identified a clinical need for a clear summary of the rates of PVT failure in distinct clinical groups: i.e. by diagnosis. In our view, better understanding of how people with different clinical diagnoses perform in PVTs is an important preliminary to further research to understand what single or multiple factors we might be measuring when one of our patients 'fails' one or more PVTs.

Aim

Our primary aim was to summarise the available published data on performance validity test failure rates in clearly defined (by diagnosis) non-litigating, non-forensic, non-military, non-military-veteran,

clinical populations. Secondly, we aimed to consider the implications of our findings in terms of the uses of performance validity tests (PVTs) in clinical practice.

Method

Search strategy and selection criteria

We systematically searched the published peer-reviewed English language literature in MEDLINE, Embase, and PsycINFO databases from inception to July 5th 2019. The search, screening, and data extraction were done by one author (LM), and the review was conducted in line with PRISMA guidelines[318]. The search terms used were ["performance validity test*" OR "symptom validity test*" OR "effort test*"]. We included studies reporting the results of performance validity tests (not symptom validity questionnaires) in one or more individuals with a recorded clinical diagnosis of a specific medical disorder. We excluded studies of mixed clinical populations, in which performance by diagnosis was not reported. We also excluded studies of children and adolescents (<16), forensic populations, studies in which ≥ 50% of participants were known to be involved in litigation or seeking welfare benefits, studies of active military personnel or military veterans, and studies involving assessments of individuals with possible Attention Deficit Hyperactivity Disorder (ADHD) or Post-traumatic Stress Disorder (PTSD). The reason for exclusion of these groups was that they are substantially more likely to be undergoing assessment where there is a potential incentive for financial compensation or other social advantages. However, it should be noted that it is also likely that the included studies included individuals with incentives to underperform which were unknown to the investigators. Studies describing attempts to assess the validity of self-reported symptoms were excluded, as they were considered outside the scope of the paper.

Following the initial search and collation of data, additional title and keyword searches were performed on 15th January 2020, for the eight most frequently identified PVTs in the studies identified in the initial search. This search yielded an additional 11 eligible studies.

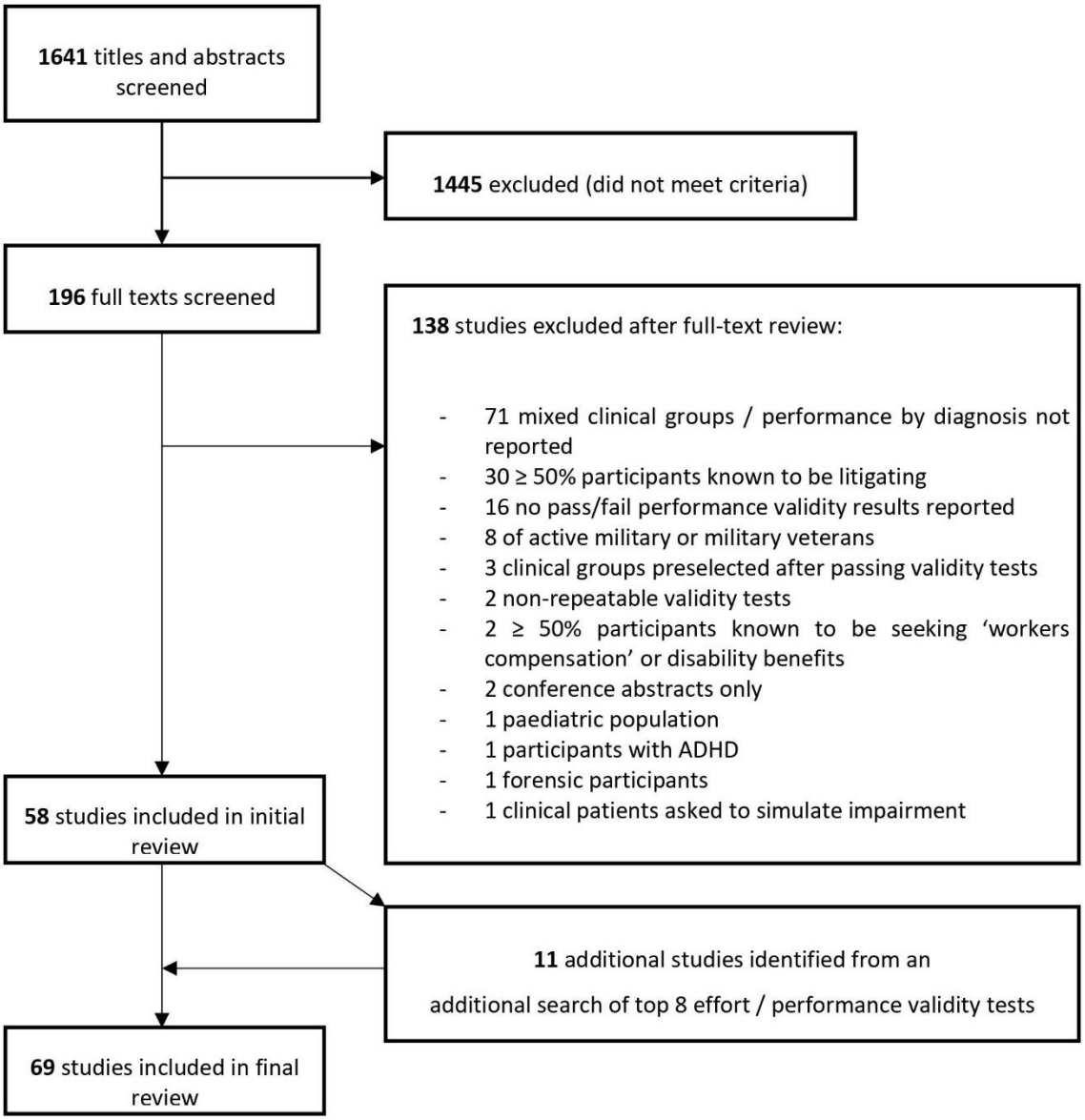
Data were extracted independently by author LM using Excel, and synthesised into tables of test failure rate by diagnosis, with the aim of examining pooled failure rates for specific disorders in the context of a narrative review.

Results

Search results and screening

45 different PVTs or indices were identified (**Figure 1** and **Table 1**), and within these indices a range of cut-off scores were reported for many tests. The majority of results identified were for free-standing validity tests.

Figure 1 – Selection of included studies



Many of the validity tests identified (including the three most frequently reported tests: the Word Memory Test (WMT), Test of Memory Malingering (TOMM), and Medical Symptom Validity Test (MSVT)) used a forced choice paradigm. In a forced choice PVT, the examinee is asked to recognise previously seen words, pictures or numbers mixed with unseen foils in a 1:1 ratio. If the examinee correctly recognises significantly fewer than half (<18/50 in the TOMM, on the basis of 90% confidence intervals), as would be expected if they were selecting answers at random, they are assumed to be preferentially selecting incorrect answers (intentionally or unintentionally). Of note, however, the cut-off scores for these tests were consistently much higher than the chance level, and the proportion of individuals scoring below the chance level was infrequently reported. The relevance of the use of a forced-choice paradigm was therefore unclear.

Other tests used the 'floor effect': a cut-off score which it seems improbable that any individual applying full effort will score below. Reliable Digit Span (the fourth most commonly reported test, consisting summed maximum forward and backward digit span) and the Rey 15-item test, are examples of 'floor effect' validity tests.

A small number of tests used an 'atypical pattern' principle. For example, in the dot counting test, examinees are expected to count grouped collections of dots more quickly than ungrouped dots and the absence of such a discrepancy (or reversed discrepancy) is taken as an indicator of invalid performance.

Twenty-seven studies stated either that no litigating or compensation-seeking examinees were included. In 40 studies, presence of litigation was not reported, but the population was recruited from a clinical or clinical research (rather than medicolegal) setting. In one study participants were informed that test results would not be made available and so could not be used to support compensation claims. Finally, one study examined adults seeking to regain custody of their children, who were presumably motivated to perform well[319].

Intellectual disability (Table 2)

Three studies described PVT performance in adults with intellectual disability. In Goldberg and Miller, 6/16 (38%) adults with mean IQ 63.9 failed (<9) the Rey 15-item test[320]. In the largest study included,

6 of 276 (2%) adults with intellectual deficits but full-scale IQ >70 seeking to regain custody of their children (and therefore expected to be motivated to pass) failed the Medical Symptom Validity Test (criterion A) and 11 of 223 (5%) failed the Word Memory Test[319]. In the same study, 14% (2) of 14 individuals in the same circumstances but with FSIQ ≤70 failed the Word Memory Test and 0 of 17 failed the Medical Symptom Validity Test[319].

Mild cognitive impairment (MCI) (Table 3)

Nine studies reported PVT performance in mild cognitive impairment (MCI) or minor neurocognitive disorder, constructs in which measurable cognitive impairment is present which is not severe enough to merit diagnosis of dementia and which is not associated with functional impairment. The highest reported failure rates were 42% (153 of 365) individuals with amnestic MCI in Loring et al.; 36% (29) of 80 with minor neurocognitive disorder failed the Rey 15-item test (cut-off <20) in Fazio et al.; 27% (1462) of 5414 with MCI failed the logical memory test (cut-off <14) and 25% (1354) of 5414 failed semantic word generation (cut-off <13) in Davis et al, and 22% (13) of 60 individuals with 'probable MCI' in Green et al.[321–324]. Of note, 11 of the 13 MCI individuals in Green et al. 2011 who failed criterion A of the Word Memory Test did not meet criterion B (easy – hard difference <30) and so had a possible dementia profile[324]. Pooled failure rates for Reliable Digit Span in MCI were 16% (83 of 533) at a cut-off of ≤7[321,325], and 1% (6/613) at a cut-off of ≤5[321,322,325].

Functional disorders (Table 4)

Eleven studies described PVT performance in people with functional disorders, including for the purposes of this review those conditions termed 'medically unexplained', somatoform or 'nonorganic'. Where possible, PVT failure rates were pooled by specific condition. In two studies of individuals with fibromyalgia, 8% (8) of 104 failed the TOMM[326,327]. In three studies of psychogenic non-epileptic seizures (PNES, also called dissociative seizures), 10% (13) of 132 failed the TOMM[328–330]. In two other studies of PNES, 44% (25) of 57 met criterion A (therefore failed) on the standard Word Memory Test[331,332]. In two studies of individuals with chronic fatigue syndrome, 25% (374) of 1526 failed the Amsterdam Short Term Memory Test (scoring <86/100)[333,334].

Failure rates higher than 25% were reported by Tyson et al in 33 individuals with psychogenic non-epileptic seizures on Reliable Digit Span (cut-off ≤7), vocabulary – digit span (≥3), forced choice recall on the CVLT (≤15), and the Boston Naming Test[330].

Epilepsy (Table 5)

Eleven studies reported PVT performance in people with epilepsy. In five studies including 246 people with epilepsy, 13% (31) failed the TOMM[328–330,335,336]. In three studies including a total of 74 people with epilepsy, 19% met criterion A of the standard version of the Word Memory Test[331,332,337]. Two studies reported Reliable Digit Span results in people with epilepsy. Maiman et al. reported a failure rate of 23% (14/63) at a ≤7 cut-off and 10% (6/63) at a ≤5 cut-off, and Tyson et al. reported a failure rate of 45% (32/72) at a ≤7 cut-off; the two studies producing a pooled RDS failure rate in epilepsy of 34% at a ≤7 cut-off.

Notably, Tyson et al. reported higher failure rates in epilepsy compared with a group with Psychogenic Non-Epileptic Seizures (see **Table 4**) in six of eight tests included (TOMM, RDS, digit span, Boston naming test, complex ideational material, logical memory recognition trial) with failure rates higher in PNES than epilepsy only in vocabulary – digit span, and the forced choice test of CVLT. Of the two other studies comparing these groups, Cragar et al. reported higher failure rates in PNES than epilepsy (14% vs 2% on TOMM), as did Drane et al. (48% vs 8%), but Hoskins reported similar failure rates on the standard Word Memory Test in epilepsy and PNES (31% and 29% respectively).

Acquired brain injury (Table 6)

The studies included in **table 6** describe PVT performance in clinical groups falling under a broad acquired brain injury definition: irreversible but non-progressive structural brain injury, including traumatic and hypoxic brain injury, stroke, and Korsakoff's syndrome.

Eight studies described PVT performance after mild Traumatic Brain Injury (TBI). Results in this group as a whole were highly variable, suggesting between-group differences. Most studies in mild TBI reported low PVT failure rates (<20%). In contrast, however, Novitski et al. reported failure rate of 52% (13/25) on RBANS digit span (cut-off <9) in 25 individuals who had sustained a mild TBI more than six months previously, and Erdodi et al. 2017 reported failure using a liberal cut-off on the TOMM in 53% of 20 adults after mTBI [335,338]. Similarly, Sherer et al. reported 25% of 118 people with mild TBI failed on criterion A of the Word Memory Test: the same failure rate (25%, or 38/150) as that reported in the severe TBI population described in the same study[339].

Grouping together moderate and severe brain injuries in what we consider a clinically relevant way (communication impairments prevent testing in those with the most severe injuries), three studies

reported Word Memory Test results after moderate and severe brain injury, resulting in a pooled failure rate of 28% (63 of 228; 95% CI 22-34%)[337,339,340]. Results of other tests studied in moderate and severe brain injury were heterogeneous. Macciochi et al. in 2006 reported 0% failures on the Victoria Symptom Validity Test in 71 adults a mean 43.4 days after severe brain injury[341]. The same group in 2017 reported poor performance on the delayed recall (failure in 5/9), and consistency (4/9) components of the Medical Symptom Validity Test during the post-traumatic amnesia phase after brain injury but lower failure rates after resolution of post-traumatic Amnesia[342]. Erdodi et al. reported high failure rates on validity indices derived from the WAIS[343].

A study reporting validity test performance after stroke with initial aphasia found low failure rates on the (standard, pictorial) TOMM measures (7% (1/15 failing trial 2 and 0 failing the retention trial, but high failure rates on the Rey 15-item, RDS (<7) and reliable spatial span (60%, 73% and 40% respectively)[344].

One study described a single case of surgical removal of medial temporal lobe structures, and another described three cases of bilateral hippocampal atrophy after anoxic brain injury; none of these four individuals failed the Word Memory Test[345,346]. Oudman et al. reported that 2 of 20 individuals (10%) with Korsakoff Amnesia failed the 2nd trial of the TOMM[347].

Neurodegenerative brain disease (Table 7)

Neurodegenerative disorders featured in 20 included studies – a greater number than any other group of conditions. The wide range of disorders, severities, tests, and test cut-off scores prevented calculation of meaningful pooled failure rates, although in general, failure rates were high (**Table 7, Figure 2**).

The Word Memory and Medical Symptom Validity Tests were most frequently described. Green et al. reported high failure rates in clinically defined 'probable, mild, and moderate' dementia on the Word Memory Test (71% of 42) and Medical Symptom Validity Test (48% of 23), but reported that all who failed met the 'dementia or severe impairment profile', a profile of results defined by the test author as typical of dementia or severe impairment rather than non-credible performance[324]. Howe et al. reported failure rates of 38% on the Medical Symptom Validity Test in 13 with mild dementia, all of whom met the 'dementia profile', and 83% (of 18) in advanced dementia of whom 15 met the 'dementia profile'[348]. 18 of 20 (90%) mild Alzheimer's dementia examinees in Merten et al's study

failed the delayed recall component of the Word Memory Test, even though a cut-off (34%) significantly lower than the standard cut-off(45%) was applied[349]. Rudman et al. and Singhal et al. both reported high failure rates (73% of 22, and 100% of 10) in advanced dementia on the Medical Symptom Validity Test[295,350].

Two studies reported validity test results in individuals with Parkinson's disease undergoing testing in the workup for possible deep brain stimulation[351,352]. Here, failure rates were reasonably low – at most 5 of 47 (10%) failed the Medical Symptom Validity Test in Wodushek et al - but this 10% might also be considered a rather higher failure rate than expected in individuals without gross cognitive impairment in whom there is an incentive (in the form of access to a potentially beneficial treatment) to perform well on neuropsychological testing[351].

Psychiatric disorders (Table 8)

Studies of schizophrenia, schizoaffective disorder, and other psychotic disorders generally reported relatively high failure rates on a range of validity tests. The highest failure rate reported was in 72% of 64 individuals with schizophrenia on the Word Memory Test[353]. In contrast, Schroeder et al's study of 104 individuals with a 'psychotic psychiatric disorder' reported low failure rates on a range of embedded tests, including 4% failure on RDS with a <=6 cut-off and 3% failure on finger-tapping[354]. Whearty et al's 2015 study of 60 individuals with schizophrenia or schizoaffective disorder reported that 28% failed Reliable Digit Span ≤6 and 36% failed finger-tapping[355].

Two studies examined performance validity in depression, Lee et al. reporting low failure rates(<=5%) on the Rey 15-item and dot counting tests and Rees et al. reporting no failures on the TOMM in 26 inpatients with depression[356,357].

Dandachi-Fitzgerald compared Amsterdam Short-Term Memory test performance in different psychiatric diagnoses: failure rates were 31% of 16 with personality disorders, 25% of 8 with psychotic disorders, 18% with substance abuse/dependence, 16% with ASD and 14% with ADHD[358]. Price et al. reported no failures on the TOMM in 71 individuals with methamphetamine dependence[359].

Other conditions (Table 9)

Heintz et al. reported 23% of 13 individuals with Gilles de la Tourette syndrome failed the ASTM[360]. Two studies reported validity results in people with HIV – in one study 15% of 111 people with HIV (stable on antiretroviral therapy) failed trial 1 of the TOMM (note, TOMM is usually scored on trial 2

or a delayed trial); and in another 17% of 30 failed the Amsterdam Short-Term Memory test [361,362]. A study of neuropsychological performance in adults with sickle cell disease reported low failure rates on the TOMM and on RDS <=6, but 33% of 43 failed Reliable Digit Span with a <=7 cut-off[363]. In Rossetti et al. 2 of 10 deep brain stimulation candidates with essential tremor failed the Word Memory Test[352].

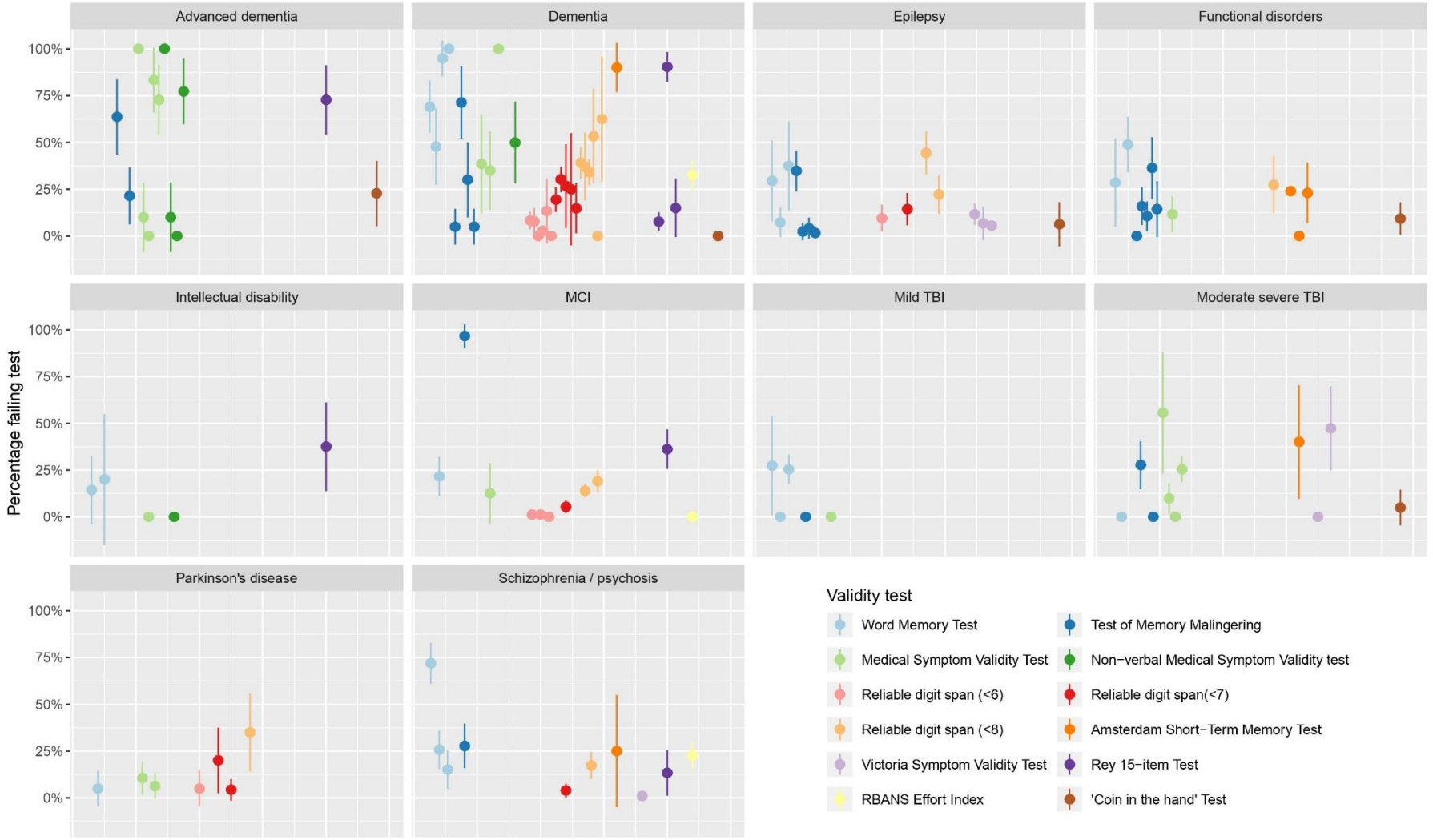
Comparative analysis of PVT results between groups

The heterogeneity of populations, tests, and in some cases cut-off scores used, makes comparisons difficult.

Failure rates (with confidence intervals), by study, in the most frequently reported validity tests are displayed graphically, by diagnostic heading, in **Figure 2**. Error margins are wide due to the small numbers in most studies. Allowing for this, however, it is clear that PVT failure is common in a range of clinical groups.

Figure 2 - failure rates in the 12 most frequently reported tests by diagnosis (next page)

Each point represents reported failure rate, in a particular test (indicated by colour), as reported by an individual study. Points are grouped along the x axis in the same test (colour) order in each plot, so as to allow visual comparison


Advanced dementia
Dementia
Epilepsy
Functional disorders
Intellectual disability
MCI
Mild TBI
Moderate severe TBI
Parkinson's disease
Schizophrenia / psychosis
Percentage failing test
100%
75%
50%
25%
0%
Validity test
Word Memory Test
Test of Memory Malingering
Medical Symptom Validity Test
Non−verbal Medical Symptom Validity test
Reliable digit span (<6)
Reliable digit span(<7)
Reliable digit span (<8)
Amsterdam Short−Term Memory Test
Victoria Symptom Validity Test
Rey 15−item Test
RBANS Effort Index
'Coin in the hand' Test

Discussion

Our review suggests that failure of performance validity tests during neuropsychological assessment is not a rare phenomenon, but is common in many clinical groups. Of note, validity test failure is particularly likely in moderate and severe traumatic brain injury, and both mild and moderate-severe dementia (where the 'severe impairment' profile on the Word Memory Test often applies). Of note, whilst some individuals with functional disorders fail PVTs, failure rates are no higher than in a range of other diverse conditions, including epilepsy, and mild cognitive impairment.

Remarkably few studies in the very large validity test literature describe performance by clinical diagnosis. Even some studies which appear to do so often group together different illness or injury severities in a way that renders the data difficult to apply to clinical practice. For example, studies of validity tests in traumatic brain injury populations mixed those with mild, moderate and severe injuries, in whom vastly different cognitive and symptom profiles would be expected. These studies were excluded from our review on this basis, but it is likely that there is still a degree of heterogeneity in the included studies.

We aimed to select studies of individuals without clear external incentives to fail. It is of course possible that these factors were present in some cases, unknown to the investigators. Indeed, we would argue that a range of external motivators and internal factors influence how people behave during the majority of conscious encounters in most areas of healthcare. One possibility to explain our results, therefore, is that many patients do not apply the degree of effort that we would like them to apply, intentionally or unintentionally, for reasons that we cannot always immediately perceive or understand.

It seems much more likely, however, that PVTs, using commonly-applied cut-offs, are in fact not only measuring deficient effort but a whole range of factors, including memory impairment, apathy, fatigue, or attention deficit due to pain or other cognitive or somatic symptoms. People who have symptoms of any sort, in any condition, are liable to divert attention towards those symptoms. If attention is conceptualised as a finite resource (more accurately, attentional processes govern use of finite processing capacity), we suggest it is possible to fail almost any 'floor-level' test if there is not enough spare attention available to allocate to the task.

Many of the tests reported by included studies are based on a 'forced choice' paradigm. Scoring comfortably below the level of chance in a forced choice validity test has been used as evidence of deliberate exaggeration of impairment – intention to fail – which most would acknowledge is qualitatively different from, rather than on a spectrum with, not applying sufficient effort. In our experience there is a widely-held view that less-than-chance performance is precisely what PVTs are used to detect. However, our review demonstrates is that this is not really the case. Without exception, the cut-off scores used in PVTs are much higher than chance (defined as 50% or ideally lower, to allow for error): most test cut-offs are between 80% and 90%. We suggest that using a forced choice paradigm with cut-off scores greatly exceeding chance makes the forced choice element redundant, and that the test instead functions as a 'floor level' test, vulnerable to functional attentional deficit in people with symptoms of any sort. We feel it is important to point out that failure at accepted cut-off levels on commonly-used forced choice tests – the TOMM, the Word Memory Test, and the Medical Symptom Validity Test – does **not** demonstrate intention to fail.

Inadequate attentional focus on a PVT might sometimes result from diversion of attention in adaptation to symptoms and associated disability. In other situations, however, excessive focus on the task may be an intrinsic feature of the disorder being tested. In functional neurological disorders, clinical experience and experimental evidence show that excessive or misdirected effort interfere with normal performance. For example, patients with functional motor disorders who are unable to walk may be able to walk backwards, or to run – essentially when engaged in tasks which divert attention away from deliberate and effortful processes so that automatic movement-control processes to take over. Similarly, people with functional cognitive disorders can struggle and underperform when trying hard on cognitive tests but demonstrate intact cognition by providing effortless and detailed descriptions of memory lapses[219,306]. We wonder if individuals with functional neurological disorders might in some cases paradoxically fail PVTs because of an excessive degree of effort, where the harder they try, the worse their performance. Hoover's sign of functional leg weakness depends on demonstrating impaired 'effort' in hip extension which returns to normal with contralateral hip flexion. Our clinical experience with patients with functional leg weakness is that the more they try the weaker their movements are.

Our experience of screening studies for this review illustrates some of the problems and difficulties that have arisen in validating performance validity tests.

The majority of excluded studies reported validity test from mixed groups of people with a wide range of different conditions attending for neuropsychological assessment, and did not report test results by diagnosis. The reason for this clumping is of course that the question investigators have been interested in is not 'How do people with different clinical conditions perform in PVTs?' but 'How can I identify a non-credible performance regardless of clinical condition?' Mixed groups are either compared with simulators, or split into 'credible' and 'noncredible' groups for the purposes of a known-groups design. Slick, Sherman and Iverson's criteria for 'probable malingered neurocognitive dysfunction', or similar definitions, are frequently used to define 'noncredible': a) motive to feign symptoms (litigation or seeking disability compensation), b) failure on two independent performance validity tests, and c) evidence of inconsistency between self-reported symptoms and observed behaviour[364].

Examination of these criteria quickly makes apparent some of the difficulties in establishing a 'gold standard' for invalid performance. Firstly, the presence of an external incentive, particularly in the form of seeking disability benefit, while it may increase the chance of invalid performance, also selects out a group of people who are 'ill' and have a range of other reasons to perform poorly. While this review did not include studies of primarily litigating or disability-benefit seeking populations in order to minimise the influence of major external influences on performance, we suggest that there are many reasons for people with 'external incentives' to fail PVTs other than inadequate effort or intention to fail.

The second 'malingered neurocognitive dysfunction' criterion[364], failure on two independent PVTs, relies on an assumption that those tests are indeed measuring something akin to effort. Alternatively, we suggest that failure on multiple PVTs indicates that 'something' is going on, but does not tell us that that 'something' is inadequate effort or wilful exaggeration. The assumption that PVTs primarily measure effort is pervasive in the PVT literature and is reinforced by reporting of sensitivity and specificity metrics, with use of the term 'false positive' to describe failure in a 'credible' participant.

Finally, inconsistency between cognitive scores and level of function in activities of daily living is in our experience common in functional neurological disorders, and also in certain psychiatric disorders.

An important question is, therefore, why is it so difficult to find a 'gold standard' here? We suggest firstly that inadequate effort – 'not trying hard enough' – is highly subjective, is not a binary variable with a single dimension, and depends on a mixture of cognitive and emotional processes. Importantly,

we consider that 'inadequate effort' is qualitatively different from deliberate exaggeration or intentional failure (as defined by Slick et al.[364]). And yet, by using these criteria to divide examinees into credible and non-credible groups, researchers use a definition for the latter (malingered dysfunction) to establish cut-offs for the former (inadequate effort).

Importantly, the manner in which we have described PVT failure rates does not necessarily reflect how they are used in practice by skilled clinical neuropsychologists, although where there is certainly expertise there is little consensus[365]. Published guidance documents for neuropsychologists are clear to point out limitations, including various reasons for test failure, and limited evidence in clinical populations[366,367]. Guidance documents recommend that multiple performance validity measures should be used, including both free-standing and embedded indicators, and emphasise that PVTs should be interpreted as part of the wider context of the assessment.

Finally, it is important to remember that 1the key purpose of validity tests should be not to assess the validity of the person being tested, but the validity of the results of other neuropsychological tests. While what we are measuring in PVTs remains unclear, what is much clearer is that poor performance on PVTs renders other neuropsychological tests invalid[368]. One analogy is of movement artefact on an MRI scan; there are many reasons that a person might move during an MRI scan, but a single common end result: degradation of the images so that they are difficult or impossible to interpret. While PVT failure tells us that there is a problem with the image drawn by the other neuropsychological tests, it is not always possible to fully understand the reasons for that interference. We suggest that future research in clinical groups with a range of symptom and impairment complexes is one possible route to better understanding of the factors influencing performance.

Tables

Table 1 - PVTs / performance validity tests in included studies

Test name (acronym)	**Free-standing / embedded**	**Type of test**	**N studies reporting test**
Word memory test (WMT)	Free-standing	Forced choice	18
Test of memory malingering (TOMM)	Free-standing	Forced choice	16
Medical Symptom Validity Test (MSVT)	Free-standing	Forced choice	11
Reliable Digit Span (RDS)	Free-standing or embedded (in WAIS)	Floor effect	10
Amsterdam Short Term Memory Test (ASTM)	Free-standing	Forced choice	5
Victoria Symptom Validity Test (VSVT)	Free-standing	Forced choice	5
Rey 15-item Test	Free-standing	Floor effect	4
RBANS Effort Index	Embedded	Floor effect	4
Coin-in-the-hand Test	Free-standing	Forced choice	3
Dot counting	Free-standing	Atypical pattern	3
Finger tapping	Free-standing	Floor effect	3
Vocabulary - digit span	Embedded (WAIS)	Atypical pattern	3
California Verbal Learning Test II forced choice	Embedded (CVLT)	Forced choice	2
Digit Symbol Coding	Embedded (WAIS)	Floor effect	2
Rey Word Recognition Test	Free-standing	Forced choice OR Atypical pattern (with RAVLT recall)	2
Visual Association Test-Extended	Free-standing	Forced choice	2
Logical Memory	Embedded(WMS)	Floor effect	2
Mental Control test	Embedded (WAIS)	Floor effect	2
Autobiographical Memory Inventory	Free-standing	Floor effect	2
Digit span	Embedded (WAIS)	Floor effect	2
Rey-Osterrieth Complex Figure Test equation: copy score + [(true positive recognition – atypical recognition errors) x 3	Embedded (ROCFT)	Atypical pattern + floor effect	2
Hiscock Digit Memory Test / Hiscock forced choice test	Free-standing	Forced choice	2
Validity Indicator Profile (VIP) verbal, Symbol Search, Portland Digit Recognition Test, b-Test, Rarely missed index, Sentence repetition, Rey Auditory Verbal Learning Test equation, Camden memory test for faces, Camden Pictorial Recognition Memory Test, Wechsler Adult Intelligence Scale (WAIS) processing speed index, Digit Memory Test (DMT), Semantic word generation raw score, Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Effort Scale, Short Test of Mental Status (STMS), Rey Complex Figure Test (RCFT), Letter Memory Test			1 each

(LMT), Trail Making Test B:A ratio, reading subtest of Wide Range Achievement Test, fourth edition (WRAT-4), elements of the Auditory Verbal Learning Test (AVLT), Reliable spatial span, Coding age-corrected scaled score, Wechsler Adult Intelligence Scale (WAIS) effort index, Warrington Words	

The remaining supplementary tables summarise reported failure rates (percentages) by diagnosis (>25% highlighted red).

Table 2 – Intellectual disability (percentages ≥25% highlighted in red)

Intellectual disability				
Study*	**Clinical definition**	**Test (cut-off)**	**N**	**% to fail test**
Goldberg and Miller 1986	"intellectually deficient individuals": IQ 40-69 (mean 63.9)	Rey 15-item test (< 9)	16	38%
Hoskins et al. 2010	learning disability	WMT (criterion A)	5	20%
		WMT oral (criterion A)	6	0%
Green and Flaro 2015	adults with intellectual deficits (full-scale IQ (FSIQ) **≤70**) seeking to regain custody of their children	WMT (criterion A)	14	14%
		MSVT (criterion A)	17	0%
		NV-MSVT (criterion A)	4	0%
	*adults with intellectual deficits (FSIQ **>70**) seeking to regain custody of their children*	*WMT (criterion A)*	*223*	*5%*
		MSVT (criterion A)	*276*	*2%*

* References for all included studies are available in the supplementary file 'List of included studies'

Table 3 - Mild cognitive impairment (MCI) (percentages ≥25% highlighted in red

Mild cognitive impairment (MCI)				
Study	**Clinical definition**	**Test (cut-off)**	**N**	**% to fail test**
Howe et al. 2007	MCI	MSVT (criterion A)	16	13%
Duff et al. 2011	amnestic MCI	RBANS Effort Index (>3)	72	0%
Green et al. 2011	possible MCI	WMT (criterion A)	60	22%*
Walter et al. 2014	MCI	TOMM trial 2 (≤45)	31	10%
Loring et al. 2016	amnestic MCI	RDS (≤5)	365	1%
		RDS (≤7)		14%
		AVLT recognition (≤9/15)		42%
Zenisek et al. 2016	MCI	RDS (≤5)	168	1%
		RDS (≤6)		5%
		RDS (≤7)		19%
Meyer et al. 2017	MCI	VAT-E (Visual Association Test-Extended) IR (≤21)	76	0%
		VAT-E DR (≤20)		1%
		VAT-E CNS (≤21)		4%
		VAT-E FR-MC - (≥7 - ≤9)		7%
Davis 2018	MCI	Digit Symbol Coding AASS (<6)	5414	3%
		Digit Span AASS (<6)		4%
		Logical memory (<14)		27%
		Semantic word generation (<13)		25%
		Trail Making Test B:A ratio (<1.5)		3%
Fazio et al. 2019	Minor neurocognitive disorder	Rey 15-Item Test (recall <20)	80	36%
		RDS (≤5)		0%
*11/13 'possible dementia profile' – profile of results suggestive of failure due to dementia rather than invalid performance				

Table 4 - Functional and somatoform disorders (percentages ≥25% highlighted in red)

Functional and somatoform disorders				
Study	**Clinical definition**	**Test (cut-off)**	**N**	**% to fail**
Bar-On Kalfon et al. 2016	fibromyalgia	TOMM (≤45, assume on trial 2 or retention)	50	16%
Cragar et al. 2006	Psychogenic non-epileptic seizures ()	LMT (<93%)	21	23%
		DMT (<90%)		5%
		PDRT-27 (<54%)		14%
		TOMM trial 2 (≤45)		14%
		TOMM retention (≤45)		14%
	both epilepsy and psychogenic non-epileptic seizures (PNES)	LMT (<93%)	18	5%
		DMT (<90%)		5%
		PDRT-27 (<54%)		0%
		TOMM trial 2 (≤45)		0%
		TOMM retention (≤45)		5%
Drane et al. 2006	Psychogenic non-epileptic seizures	WMT (criterion A)	43	48%
Heintz et al. 2013	Psychogenic movement disorder with jerk-like movements	ASTM (≤85)	26	24%
Hill et al. 2003	Psychogenic non-epileptic seizures	TOMM (≤45 trial 2 or retention trial)	57	11%
Hoskins et al. 2010	Psychogenic non-epileptic seizures	WMT oral (criterion A)	16	44%
		WMT (criterion A)	14	29%
Iverson et al. 2007	Fibromyalgia	TOMM trial 1 (not stated)	54	0%
		TOMM trial 2 (not stated)		0%
		TOMM retention (not stated)		0%
Kemp et al. 2008	patients with medically unexplained symptoms (20 psychogenic non-epileptic seizures, 14 functional movement disorder/paralysis, 4 nonorganic sensory deficit, 2 functional blindness, 1 fibromyalgia, 1 nonorganic neuropsychological complaints)	MSVT IR (≤85)	43	12%
		MSVT DR (≤85)		12%
		Coin-in-hand test (≤7/10)		9%
		Autobiographical Memory Index (≤9)		5%
		Camden Pictorial Recognition Memory Test (<5th age-related centile using upper limit sample)		19%
		Mental Control Test (<5th age-related centile using upper limit sample)		16%
Van der Werf et al. 2000	Chronic fatigue syndrome	ASTM (<86)	144	29%
Roor et al. 2018	Chronic fatigue syndrome	ASTM (≤85)	1382	24%

Tyson et al. 2018	Psychogenic non-epileptic seizures	TOMM (trial 1 ≤39 or trial 2 ≤44)	33	13%
		RDS (≤7)		27%
		Digit span age-corrected scaled score (≤6)		22%
		vocabulary – digit span (≥3)		26%
		Forced choice recall test of CVLT (≤15)		32%
		FAS and animals verbal fluency (≤33)		24%
		Boston Naming Test (≤37)		25%
		Complex Ideational Material (≤29)		10%
		Logical Memory Recognition trial (≤20)		13%

Table 5 – Epilepsy (percentages ≥25% highlighted in red)

Epilepsy				
Study	**Clinical definition**	**Test (cut-off)**	**N**	**% to fail test**
Cragar et al. 2006	epilepsy	LMT (<93%)	41	17%
		DMT (<90%)		5%
		PDRT-27 (<54%)		2%
		TOMM trial 2 (≤45)		2%
		TOMM retention (≤45)		2%
	both epilepsy and psychogenic non-epileptic seizures	LMT (<93%)	18	5%
		DMT (<90%)		5%
		PDRT-27 (<54%)		0%
		TOMM trial 2 (≤45)		0%
		TOMM retention (≤45)		5%
Drane et al. 2006	epilepsy	WMT criterion A	41	8%
Grote et al. 2000	epilepsy	VSVT(<16/24 difficult correct)	30	7%
Erdodi et al. 2017 (2)	epilepsy	TOMM trial 2 (≤48)	22	9%
Hampson et al. 2014	epilepsy	WMT-IR	16	6%
		WMT-DR		13%
		WMT-CR		38%
		WMT criterion A		38%
		Coin-in-hand test (ns)		6%
		Autobiographical memory index (ns)		0%

		digit-symbol coding (not stated)		25%
		Camden memory test for faces (ns)		6%
		Mental Control Test (ns)	15	27%
Hill et al. 2003	epilepsy (temporal lobe)	TOMM (≤45)	48	4%
Hoskins et al. 2010	epilepsy	WMT oral (criterion A)	14	14%
		WMT (criterion A)	17	31%
Keary et al. 2013	medically intractable focal epilepsy	VSVT (<18/24 hard items)	404	5%
Loring et al. 2005	epilepsy	VSVT (<18/24 hard items)	120	12%
Tyson et al. 2018	epilepsy	TOMM (<45)	72	35%
		RDS (≤7)		45%
		Digit span age-corrected scaled score (≤6)		45%
		vocabulary – digit span (≥3)		21%
		Forced choice recall test of CVLT (≤15)		12%
		FAS and animals verbal fluency (≤33)		51%
		Boston Naming Test (≤37)		68%
		Complex Ideational Material (≤29)		31%
		Logical Memory Recognition trial (≤20)		18%
Maiman et al. 2019	epilepsy or suspected seizures	RDS (≤6)	63	15%
		RDS (≤7)		23%
		RDS (≤5)		10%
		TOMM trial 1 (≤45)		35%
		TOMM trial 2 (≤45)		2%

Table 6 - Acquired brain injury (percentages ≥25% highlighted in red)

Acquired brain injury				
Study	**Clinical definition**	**Test (cut-off)**	**N**	**% to fail test**
Rees et al. 1998	mild traumatic brain injury	TOMM (<45 trial 2)	10	0%
Allen et al. 2011	mild traumatic brain injury	WMT (criterion A)	1	0%
Erdodi et al. 2017	mild traumatic brain injury	WAIS processing speed index (≤68)	52	0%
		Coding age-corrected scaled score (≤4)		6%
		Symbol Search age-corrected scaled score (≤4)		2%
		WAIS EI 5 (Digit span, CVLT-II, WMS-IV Logical memory, letter and animal fluency) (≥5)		18%
		WAIS EI 5 (FCR) (≥4)		13%
		WAIS EI 5 (PSP) (≥4)		18%
	moderate-severe traumatic brain injury	WAIS processing speed index (≤68)	10	30%
		Coding age-corrected scaled score (≤4)		30%
		Symbol Search age-corrected scaled score (≤4)		20%
		WAIS EI 5 (Digit span, CVLT-II, WMS-IV Logical memory, letter and animal fluency) (≥2)		44%
		WAIS EI 5 (FCR) (≥4)		40%
		WAIS EI 5 (PSP) (≥4)		25%
Erdodi et al. 2017 (2)	mild traumatic brain injury	TOMM (≤48 trial 2 or retention)	20	53%
Hoskins et al. 2010	mild head trauma	WMT oral (criterion A)	10	50%
		WMT (criterion A)	11	27%
Macciocchi et al. 2006	acute severe traumatic brain injury (mean 43.4 days post injury)	VSVT combined scores (<30 invalid)	71	0%
Macciocchi et al. 2017	moderate-severe traumatic brain injuryin post-traumatic amnesia (orientation log 20-24)	MSVT IR (≤85)	9	11%
		MSVT DR (≤85)		55%
		MSVT CNS (≤85)		44%
	moderate-severe traumatic brain injurynot in post-traumatic amnesia (orientation log 25-29)	MSVT IR (≤85)	51	6%
		MSVT DR (≤85)		10%
		MSVT CNS (≤85)		26%
		MSVT IR (≤85)	17	0%

	moderate-severe traumatic brain injuryunimpaired on orientation log (30/30)	MSVT DR (≤85)		0%
		MSVT CNS (≤85)		12%
Novitski et al. 2012	mild traumatic brain injury, > 6/12 post injury	RBANS digit span (<9)	25	52%
Sherer et al. 2015	mild traumatic brain injury (GCS 13-15)	WMT (criterion A)	118	25%
	moderate traumatic brain injury (9-12)	WMT (criterion A)	47	28%
	severe traumatic brain injury (GCS 3-8)	WMT (criterion A)	150	25%
Wu et al. 2010	severe traumatic brain injury (GCS 3-8)	WMT (criterion A)	2	0%
Hampson et al. 2014	brain injury (acute moderate-severe (post-traumatic amnesia >24h, GCS <12/15))	WMT-IR	11	27%
		WMT (criterion A)	10	30%
	brain injury (in community residential care, moderate / severe (post-traumatic amnesia >24h, GCS <12/15))	WMT (criterion A)	19	45%
		coin-in-hand test (ns)	20	5%
		autobiographical memory index (ns)	18	78%
		digit-symbol coding (ns)	17	20%
		mental control (ns)	19	26%
		Camden memory test for faces (<5th age-related percentile for oldest normative age group)	18	28%
Terry et al. 2015	former high school footballers with >2 concussions >15 years prior	MSVT (criterion A)	25	0%
Bodner et al. 2019	acute stroke with first manifestation of aphasia (mild to severe)	TOMM 2nd trial (≤45)	15	7%
		TOMM retention trial (≤45)		0%
		Rey 15-item test pass/fail) (<8)		60%
		RDS (<7)		73%
		Reliable spatial span (<7)		40%
Oudman et al. 2019	Korsakoff amnesia	TOMM 2nd trial (not stated)	20	10%
		VAT-E IR (not stated)		5%
		VAT-E DR (not stated)		5%
		VAT-E CNS (not stated)		0%
Goodrich-Hunsaker and Hopkins 2009	bilateral hippocampal atrophy secondary to anoxic brain injury	WMT (criterion A)	3	0%
Carone et al. 2014	surgical removal of left anterior hippocampus and parahippocampal gyrus	WMT (criterion A)	1	0%

Table 7 - Degenerative brain disease (percentages ≥25% highlighted in red)

Degenerative brain disease				
Study	**Clinical definition**	**Test (cut-off)**	**N**	**% to fail test**
Teichner et al. 2004	dementia	TOMM (<45 trial 2 or retention trial)	21	76%
Carone et al. 2014	non-specific progressive dementia	MSVT (criterion A)	1	100%*
		WMT (criterion A)		100%*
		RDS (not stated: assume ≤7)		0%
Davis 2018	dementia	Digit Symbol Coding (age-adjusted scaled score) (<6)	5761	16%
		Digit Span (age-adjusted scaled score) (<6)		11%
		Logical memory (<14)		68%
		Semantic word generation raw score (<13)		60%
		Trail Making Test B:A ratio (<1.5)		2%
Dean et al. 2009	dementia	Digit Span (age-adjusted scaled score) (≤5)	172	27%
		RDS pass/fail (≤6)		30%
		Three digits timed (>2s)	50	18%
		Four digits timed (>4s)	48	10%
		Vocabulary - digit span (>5)	149	3%
		Dot counting (escore <17)	80	50%
		TOMM trial 2 (≤45)	20	55%
		Warrington words (<33)	39	41%
		Rey 15-item test free recall (<9)	105	74%
		Rey 15-item test recognition equation (<20)	50	86%
		Logical memory RMI (≤136)	43	23%
		Finger tapping (men ≤35, women ≤28)	55	31%
		b-Test (≥160)	34	53%
		Rey word recognition (men ≤5, women ≤7)	32	22%
		Rey word recognition equation (≤9)	32	44%
		RAVLT equation (≤12)	64	87%
		Rey-Osterreith equation (≤47)	51	63%
Duff et al. 2011	probable Alzheimer's Disease	RBANS Effort Index (>3)	126	33%
Fazio et al. 2019	dementia (major neurocognitive disorder)	Rey 15-Item (<20 on recall & recognition)	52	90%
		RDS pass/fail (≤5)		9%
Green et al. 2011	dementia (probable, mild, and moderate: CDR 0.5 - 2)	WMT (criterion A)	42	71%*
		MSVT (criterion A)	23	48%*

Howe et al. 2007	dementia (early)	MSVT (criterion A)	13	38%*
	dementia (advanced)	MSVT (criterion A)	18	83%**
Loring et al. 2016	early Alzheimer's dementia (MMSE 20-26,+NINCDS/ARDRA criteria probable)	RDS (≤5)	176	3%
		RDS (≤7)		34%
		AVLT recognition		70%
Merten et al. 2007	mild Alzheimer's dementia (mean MMSE score 22.2, SD 2.9)	ASTM (<85)	20	90%
		WMT IR (<34)		90%
		WMT DR (<34)		90%
		WMT consistency (<34)		95%
		TOMM 2nd trial (<45)		30%
		TOMM delay trial (<45)		50%
Meyer et al. 2017	mild Alzheimer's dementia	VAT-E IR (≤20)	26	0%
		VAT-E DR (≤19)		0%
		VAT-E CNS (≤19)		4%
Rudman et al. 2011	mild dementia diagnosed before 65 (CAMCOG)	coin in hand (ns)	20	0%
		dot counting time (grouped > ungrouped)		0%
		dot counting errors (ns)		10%
		Rey 15-item test (ns)		15%
		TOMM (ns)		5%
		NV-MSVT (ns)		50%
		MSVT (ns)		35%
	moderate/severe dementia diagnosed before 45 (CAMCOG)	coin in hand (ns)	22	23%
		dot counting time (grouped > ungrouped)		0%
		dot counting errors (ns)		32%
		Rey 15-item test		73%
		TOMM (ns)		64%
		NV-MSVT (ns)		77%
		MSVT (ns)		73%
Sieck et al. 2013	Huntington Disease	RBANS EI (>3)	121	18%
		RBANS ES (only the 43 scoring <19 list recognition and <9 digit span) (<12)	43	70%
		TOMM (<45 on trial 2)	36	8%
Singhal et al. 2009	advanced dementia (6 AD, 4 undetermined)	MSVT (criterion A)	10	100%*
		NV-MSVT (criterion A)		100%*
Walter et al.	moderate-severe dementia	TOMM trial 2 (≤45)	28	21%
Wodushek et al.	Parkinson's disease candidates for DBS	MSVT (criterion A)	47	10%***
		MSVT (criterion A)		6%
		RDS (≤6)		5%
		vocabulary – digit span (scaled score) (>5)		4%
		CVLT-II forced choice (<14)		0%
	Alzheimer's dementia	RDS (≤7)	133	39%

Zenisek et al. 2016		RDS (≤6)		20%
		RDS (≤5)		8%
	Vascular dementia	RDS (≤7)	8	63%
		RDS (≤6)		25%
		RDS (≤5)		0%
	Dementia with Lewy Bodies	RDS (≤7)	27	37%
		RDS (≤6)		15%
		RDS (≤5)		0%
	Frontotemporal dementia	RDS (≤7)	15	53%
		RDS (≤6)		27%
		RDS (≤5)		13%
	Parkinsonian syndromes	RDS (≤7)	20	35%
		RDS (≤6)		20%
		RDS (≤5)		5%
Rossetti et al. 2018	Parkinson's disease – deep brain stimulation surgical candidates	WMT (criterion A)	20	5%
Woods et al. 2003	HIV-associated neurocognitive disorders	Hiscock Digit Memory Test (<90%)	82	2%
Van der Werf et al. 2000	Multiple sclerosis	ASTM (<86)	40	13%
* all who failed had a dementia / severe impairment profile (profile of results suggestive of failure due to dementia rather than invalid performance) **13/15 who failed had dementia / severe impairment profile *** examinees with dementia / severe impairment profile excluded				

Table 8 - Psychiatric disorders (percentages ≥25% highlighted in red)

Psychiatric disorders				
Study	**Clinical definition**	**Test (cut-off)**	**N**	**% to fail test**
Back et al. 1996	schizophrenia	Rey 15-item test (<9)	30	13%
		Rey dot-counting (mean grouped-dot counting time > 4.8x AND grouped time:ungrouped time ≤ 2:1		13%
		Hiscock Forced Choice, 18-trial version (<90%)		27%
Gorissen et al. 2005	schizophrenia	WMT (criterion A)	64	72%
Moore et al. 2013	schizophrenia or schizoaffective disorder	RBANS EI (> 3)	128	23%
Hunt et al. 2014	schizophrenia (63%) or schizoaffective disorder (37%)	Validity Indicator Profile (VIP) verbal (ns)	53	60%
		VIP non-verbal (ns)	54	83%
		TOMM trial 2		28%
		TOMM retention		17%
		STMS (short test of mental status) (≤29)		35%
		reading subtest of WRAT-4 (≤79)		22%
Stevens et al. 2014	schizophrenia	WMT (criterion A)	70	26%
Strauss et al. 2015	schizophrenia or schizoaffective disorder	VSVT	97	1%
		WMT (criterion A)	46	15%
Morra et al. 2015	schizophrenia (289), schizoaffective disorder (32) or another psychotic disorder (9)	RBANS Effort Index (>3)	330	9%
Whearty et al. 2015	schizophrenia (47) or schizoaffective disorder (13)	RDS (≤6)	60	28%
		Finger tapping (≤35 male, ≤28 female)		36%
Schroeder et al. 2011	psychotic psychiatric disorder	sentence repetition (≤10)	104	2%
		RDS (≤ 7)		17%
		RDS (≤ 6)		4%
		CVLT-II forced choice (≤14)		8%
		rarely missed index (≤ 136)		10%
		finger tapping (≤ 35 males, ≤ 28 females)		3%
		dot counting (≥ 20)		3%
		dot counting (≥ 17)		3%
		RCTF (≤3 true positive or > 4 false positive)		4%
	personality disorders	ASTM	16	31%

Dandachi-Fitzgerald et al. 2011	mood and anxiety disorders	ASTM	34	24%
	Autism spectrum disorder	ASTM	25	16%
	substance abuse/dependence	ASTM	11	18%
	Attention deficit hyperactivity disorder	ASTM (<85)	56	14%
	psychotic disorder	ASTM	8	25%
Ruocco 2016	borderline personality disorder	VSVT hard items (≤ 15/24)	50	2%
Lee et al. 2000	major depressive disorder (middle aged or elderly)	Rey 15-item test (<9 OR spatial score < 9)	64	5%
		Rey dot-counting (mean grouped counting time ≥ mean ungrouped dot counting time OR > 3 errors OR ungrouped time > 180s OR grouped time > 130s		0%
Rees et al. 2001	depression (psychiatric inpatients)	TOMM (<45 trial 2 or retention trial)	26	0%
Price et al. 2011	methamphetamine dependence	TOMM ('published cut-off score')	71	0%

Table 9 - Other conditions (percentages ≥25% highlighted in red)

Other conditions

Study	Clinical definition	Test (cut-off)	N	% to fail test
Heintz et al. 2013	Gilles de la Tourette syndrome	ASTM (<85)	13	23%
Janssen et al. 2013	HIV-1 infected patients	ASTM (<85)	30	17%
Paul et al. 2017	HIV-infected individuals on stable combination antiretroviral therapy	TOMM trial 1 (<45)	111	15%
Rossetti et al. 2018	Essential tremor – deep brain stimulation surgical candidates	WMT criterion A	10	20%*
Dorociak et al. 2018	Sickle cell disease	TOMM trial 1 (< 40)	54	4%
		TOMM trial 2 (< 45)	43	2%
		RDS (≤ 6)	43	9%
		RDS (≤ 7)	43	33%
*1/2 of those who failed had Mild Cognitive Impairment				

Investigating methods of diagnosis – Paper 5

Identifying functional cognitive disorder: a proposed diagnostic risk model

McWhirter L, Ritchie C, Stone J, Carson A

(prepared for submission for publication)

Introduction to the paper:

This paper describes a clinical study seeking distinct clinical profiles in people presenting to memory and neurology clinics with cognitive symptoms with expert consensus diagnosis of functional cognitive disorder.

I designed the study with supervisory input from AC, JS and CR. I collected the data during home visits to patients across Lothian (covering 765 km on bicycle), collated and analysed the data, interpreted the results and prepared the data for publication. CR, JS, and AC contributed to review and revision of the final manuscript.

This clinical study was unfortunately cut short by COVID-19, and recruitment stopped after 49 of the target ~100 participants. Nevertheless, this is a richly detailed dataset, and the higher-than-expected prevalence of FCD in the sample and strong effect sizes for the variables of interest have produced data of clinical utility, which will benefit from future validation.

Word count:	3991
Abstract word count:	247
Tables:	3
Figures:	4
References:	24

Abstract

Objective

Functional cognitive disorders (FCD) are an important differential diagnosis of neurodegenerative disease. The utility of suggested diagnostic features has not been prospectively explored in 'real world' clinical populations. This study aimed to identify positive clinical markers of FCD.

Methods

Adults with cognitive complaints but not dementia were recruited from memory, neurology, and neuropsychiatry clinics. Participants underwent structured interview, MINI, MoCA, Luria 3-step, interlocking fingers, digit span and MSVT, PHQ-15, HADS, MMQ, and PSQI. Potential diagnostic variables were tested against expert consensus diagnosis using logistic regression.

Results

FCD were identified in 31/49 participants. Participants with FCD were younger, spoke for longer when prompted 'Tell me about the problems you've been having', and had more anxiety and depression symptoms and psychiatric diagnoses than those without FCD. There were no significant differences in sex, education, or cognitive scores. Younger age and longer spoken response predicted FCD diagnosis in a model which explained 74% of diagnostic variability and had an AUC of 94%.

Conclusions

A detailed description of cognitive failure is a sensitive and specific positive feature of FCD, demonstrating internal inconsistency between experienced and observed function. Cognitive and performance validity tests appear less helpful in FCD diagnosis. People with FCD are not 'worried well' but often perform poorly on tests, and have more anxiety, depression, and physical symptoms than people with other cognitive disorders. Identifying diagnostic profiles is an important step towards parity of esteem for FCDs, as differential diagnoses of neurodegenerative disease and an independent target for clinical trials.

Introduction

Many people presenting to memory clinics do not ultimately receive diagnoses of the neurodegenerative diseases the clinics were established to identify and treat[1,2]. Although subjective cognitive symptoms might herald future dementia in a minority, many patients with subjective or mild cognitive impairment might alternatively be positively identified as having **functional cognitive disorders (FCD)**[308].

FCD have been described as a heterogeneous but overlapping set of clinical presentations which produce genuine cognitive symptoms which are internally inconsistent and not the direct result of brain disease; including memory symptoms in anxiety or depression; excessive attentional focus on everyday memory problems; health anxiety about dementia; and memory symptoms as part of another functional disorder[3,9]

Meta-analysis of memory clinic populations suggests that 24% of patients are likely to have FCD[306]. Our clinical experience also tells us that patients with functional neurological disorders (FND) complain bitterly of troublesome cognitive symptoms. But despite the frequency of FCD in both clinical environments, research into functional cognitive symptoms has lagged behind that of other FND domains, and has been largely absent from the neurodegenerative disease arena.

Defining positive clinical signs for functional neurological disorders (FND) has improved patient care and invigorated research into mechanisms of and treatments; these are no longer diagnoses of exclusion but can now be accurately identified and therefore studied and treated[6]. There is a pressing need for similar well-evidenced clinical signs to aid accurate diagnosis of FCD and therein improve management.

We now know that large numbers of individuals with FCD present to memory clinics; but in the absence of trials of treatment there remains almost no evidence for the best course of treatment or follow-up. More accurate diagnostic methods, along with recent proposed diagnostic criteria[308], will facilitate much-needed clinical trials of treatments for FCD. Second, there is a risk that patients with FCD are incorrectly described as having preclinical Alzheimer's disease. As researchers aim to identify, and therefore modify, disease at the earliest stages, it is important to identify not only neurodegenerative disease, but also those individuals with FCD, whose symptom trajectories may obscure trial outcomes and lead to potentially harmful interventions.

Previous studies examining potential FCD diagnostic features have reported that patients with FCD are more likely to attend clinic alone, to report 'poor' or 'fair' memory on a Likert scale, and to bring a written list of symptoms than those with neurodegenerative disease[35–37,216]. Others have pointed to impaired metacognition as a potential mechanism and marker of FCD[369]. Reuber, Blackburn and colleagues have analysed language and interaction during the clinical consultation, finding that patients with FCD provide more linguistically complex accounts of symptoms than those with established diagnoses of neurodegenerative disease[215,219]. But these interactional features have primarily been tested against a definition of FCD in which there is an absence of 'objective' cognitive impairment, and not in those who struggle with cognitive tests, or in unselected patients typically encountered in memory clinics.

This study aimed to address the question of how we might confidently and accurately diagnose FCD in an unselected sample of patients presenting with cognitive symptoms and complaints but not dementia.

Method

Participants of all ages were recruited direct from an older-adults memory clinic, neurology and neuropsychiatry clinics, and a county-wide register of people assessed in the memory clinic who had consented to be contacted about research (The Scottish Brain Health Register).

Participants had already been clinically assessed by a consultant old-age psychiatrist, neuropsychiatrist, or neurologist as a part of usual clinical care. Subjects met inclusion criteria who had presented for assessment of predominantly cognitive symptoms, but were not severely cognitively impaired or assessed as having probable Alzheimer's type dementia (according to current consensus diagnostic criteria[370]), or another dementia syndrome. Exclusion criteria, established from case notes and referrer assessment, were: non-English speakers (due to English-language validated measures), age <18, learning disability, psychotic disorder, severe personality disorder, active suicidal ideation, or suspicion of factitious disorder or malingering.

Participants were visited at home (unless they preferred to attend clinic) by a researcher (LM), who was blind to the previous clinical assessment. The research interview opened with an open question:

'Tell me about the problems you have been having?', following which the researcher used an electronic timer to measure the duration in seconds of the initial response; allowing the participant to speak without interruption and stopping the timer when the participant came to a natural stop. The researcher recorded, using a structured proforma, a summary of the response, the number of discrete cognitive complaints (word-finding difficulties and forgetting appointments would be recorded as two complaints); and the number and degree of detail of each example of cognitive failure described. The interview examined awareness and engagement with current news, television or film, reading (books, magazines or newspapers), description of typical daily activities, and a compound question: 'Where are you from, and what did you / do you do for a job?'.

The interview included questions about the duration and perception of memory and thinkin problems: 'Did your problems start after an event, injury, or illness?'; 'Do you think other people are more worried about your memory and thinking than you? Or are you more worried than other people?'; a 5-point Likert scale: 'In general, how would you rate your memory?'[36,126]; 'What did your memory used to be like?'; 'What do you think is the cause of any memory or thinking problems you have been having?'; and 'Do you think that your memory or thinking problems are most likely to: Get better/worse/stay the same/come and go.' Participants were asked about dementia in a close family member or previous 'daily contact or caring responsibility' for a person with dementia.

Brief examination of gait (short observed walk, turn, heel-to-toe walk) and coordination (finger-nose test) was followed by cognitive tests Montreal Cognitive Assessment (MoCA, with responses timed using an electronic timer), Luria 3-step test, interlocking finger test[280], digit spans, and the Medical Symptom Validity Test (MSVT)[371], and questionnaires: Patient Health Questionnaire 15 (PHQ-15), Hospital Anxiety and Depression Scale (HADS), and the Pittsburgh Sleep Quality Inventory (PSQI), and multifactorial memory questionnaire (MMQ) (consisting of three scales; MMQ-Satisfaction - overall satisfaction with memory (scale 0-72), MMA-Ability - perception of memory ability, via experience of 20 common memory mistakes (0-80), and MMQ-Strategy - use of memory strategies and aids (0-76))[372]. The assessment concluded with the Mini International Neuropsychiatric Interview (MINI) (English version 7.0.2 for DSM 5).

Ethical approval was obtained from the South East Scotland Research Ethics Committee. The protocol was pre-registered (https://dx.doi.org/10.17504/protocols.io.z97f99n).

Establishing the reference diagnoses

Reference diagnoses were established during meetings of the senior authors (a consultant neurologist (JS), consultant neuropsychiatrist (AC), and consultant of psychiatry of ageing (CR)). All information from the pre-study clinical assessment (clinical notes from the memory, neurology or neuropsychiatry clinic assessment, electronic medical records, and results of neuroimaging and other investigations), **not** including information collected during the research assessment, was presented to the panel. Panel members independently recorded their opinion on a) the most appropriate diagnosis(es) to account for the cognitive symptoms, and b) the contribution of various aetiological factors (**Figure 1)**. Consensus opinion allowed diagnostic ratings in parallel domains: FCD, neurodegenerative disease, medical or pharmacological cause of cognitive symptoms, and primary psychiatric disorder, recognising that cognitive symptoms often have overlapping aetiologies. Discrepancy in opinions triggered discussion and review of information until consensus was reached. For the purposes of identifying predictors of a functional disorder, a score of 'Probable' or 'Possible likely' for Functional cognitive symptoms indicated presence of FCD (regardless of other contributory factors), whereas 'Possible unlikely' or 'Unlikely' indicated absence of FCD.

Figure 1 – Structure of reference diagnosis

Functional cognitive symptoms	Probable	Functional
	Possible likely	
	Possible unlikely	Not functional
	Unlikely	
Neurodegenerative disease	Probable	
	Possible	
	Unlikely	
Medical or pharmacological cause of cognitive symptoms	Probable	
	Possible	
	Unlikely	
Primary psychiatric disorder	Probable	
	Possible	
	Unlikely	

Statistical Methods

Excel (v2101) and R (v3.6.0) were used for analyses.

A pre-study sample size calculation suggested that a sample size of 115 would be required for a diagnostic risk prediction accuracy of 90% sensitivity and 90% specificity in a group with a 30% prevalence of FCD.

Data were tested for normality using the Shapiro-Wilkes test. Multiple t-tests, Mann Whitney tests, chi-square and Fishers exact tests were used to compare variables between patients with a reference diagnosis of FCD ('probable' or 'possible likely' FCD) and those without ('unlikely or 'possible unlikely' FCD). Significance was adjusted for multiple comparisons using the Holm-Bonferroni method. Variables which were significantly (p<.05) different between groups were entered as covariates in a multivariable logistic regression model, and covariates removed iteratively to optimise the model.

Results

Forty-nine participants were recruited: 26 from memory clinic, 10 from neurology clinic, 6 from neuropsychiatry clinic, and 7 from the Scottish Brain Health Register). Forty-six were visited at home and 3 attended the research facility. Recruitment ended early, in March 2020, because of COVID-19.

Demographic and baseline clinical data is described in **Tables 1 and 2. Table 3** describes results of the key research measures.

Thirty-one participants received a reference diagnosis of FCD. Participants with FCD were significantly younger than those without FCD (p<.01), but there was no significant difference in sex (p=.5), or years of education (p=.9).

Table 1 – Demographic and clinical characteristics

	By study reference diagnosis:		All participants
	Functional cognitive disorder (n=31)	**Not functional cognitive disorder* (n=18)**	**All participants n=49**
Age, mean (sd)	63.2 (14.3)	81.8 (5.87)	70.0 (14.9)
Female, n (%)	18 (58.1%)	8 (44.4%)	26 (53%)
Years of education, n	13.0 (3.31)	13.1 (3.20)	13.1 (3.24)
First degree relative with dementia, n (%)	20 (65%)	5 (28%)	25 (51%)
Referral source:			
- **Memory clinic, %**	12 (40%)	14 (74%)	26 (53%)
- **Neurology/neuropsychiatry, %**	16 (52%)	0	16 (33%)
- **Research register %**	3 (10%)	4 (21%)	7 (14%)
Clinical Addenbrookes Cognitive Examination iii (ACEiii) score, mean (sd)	87.9 (10)	84 (7.72)	86.0 (9.08)
[n (%) not available]	[12 (40%)]	[0]	[12 (25%)]
Brain imaging this symptom episode	19 (61%)	9 (50%)	28 (57%)
Attended clinic alone, n (%)	15 (48%)	2 (11%)	17 (35%)
Clinical discharge plan			
- **n discharged (%)**	15 (48%)	6 (33%)	21 (43%)
- **n for further follow-up (%)**	16 (52%)	12 (67%)	28 (57%)
Research study reference diagnoses:			
- Probable/'possible likely' FCD, n(%)	30 (100%)	0	30 (61%)
- Probable neurodegenerative disease, n (%)	0	7 (39%)	7 (14%)
- Probable medical/pharmacological cause, n (%)	6 (19%)	4 (22%)	10 (20%)
- Probable primary psychiatric disorder, n (%)	17 (55%)	2 (11%)	19 (39%)

* non FCD group reference diagnoses:

Probable or possible AD (n=4), probable or possible cerebrovascular disease (n=3), probable or possible mixed AD/cerebrovascular disease (n=5), alcohol-related cognitive impairment (n=1), hearing or visual impairment (n=2), normal ageing (n=3). Psychiatric comorbidities: anxiety (n=2), depression (n=3), adjustment disorder (n=1).

Table 2 – Diagnoses as reported in clinic letter pre study recruitment

diagnostic terms – by subtype	by study reference diagnosis:	
	Functional cognitive disorder (n=30)	**Not functional cognitive disorder (n=19)**
'Functional disorder'	Functional neurological disorder x 6; Functional cognitive disorder x 4	
'Absence of disease'	no diagnosis x 1, 'no evidence of cognitive decline', 'very little if any evidence of a neurodegenerative disease'	no diagnosis, 'no neurodegenerative disease', 'normal cognitive ageing', 'cognitively healthy; hearing loss'
'Subjective cognitive impairment/ subjective cognitive decline'	'subjective cognitive decline' x 2, 'subjective cognitive impairment but no evidence of significant neurocognitive disorder', 'subjective cognitive impairment; mixed anxiety and depressive episode'	subjective cognitive decline x 2
'Mild cognitive impairment'	'very mild cognitive impairment / subjective cognitive impairment', 'very mild cognitive impairment; adjustment disorder now resolved', 'mild problems with word finding and memory which I suspect is simply age-related', 'amnestic MCI', 'MCI'	'MCI' x 7, 'mild cognitive impairment – subjective', 'amnestic MCI', 'MCI of vascular aetiology', 'MCI and mild to moderate depression'
'Depression and anxiety'	'anxiety', 'depression', 'depression and anxiety/mood instability', 'pain; depression and anxiety; insomnia and fatigue', 'very depressed'	'post-stroke depression'
'Multifactorial'	'ARBD; anxiety/fatigue/sleep disturbance', 'anxiety and hearing impairment; previous probable transient global amnesia', 'memory impairment secondary to comorbidities; previous multi drug abuse', 'probably not neurodegenerative disease; cocodamol, low B12, alcohol maybe contributing'	

Table 3 – Research measures in FCD and non-FCD participants

	All (n=49)	FCD (n=31)	Not FCD (n=18)	univariate *p* (Holm-Bonferroni)
Age, mean (sd)	70.0 (16)	63.2 (14)	81.8 (6)	**<.01**
Duration of memory problems (years), median (IQR)	2 [1.5-3.5]	3 [1-5]	1.75 [1-2.5]	.09
"Tell me about the problems you have been having?" – duration of response (seconds), median [IQR]	75 [31-120]	124 [80-168]	42 [28-55]	**<.01**
n memory complaints, mean (sd)	2 (1.3)	3 (1.2)	1 (1.4)	**<.01**
n (%) describing ≥1 specific cognitive failure event	17 (35%)	16 (52%)	1 (6%)	**.01**
n (%) answer both parts of a compound question	37 (76%)	26 (84%)	11 (61%)	0.6
SMC Likert – 'fair' or 'poor', n (%)	39 (80%)	25 (81%)	14 (78%)	1
n (%) 'memory symptoms started after a specific event or illness?'	14 (45%)	12 (39%)	2 (11%)	0.8
n (%) think 'others are more worried about your memory than you'	25 (51%)	13 (42%)	12 (67%)	1
n (%) 'Excellent' to 'What did your memory used to be like?'	15 (31%)	11 (35%)	4 (22%)	1
n (%) think memory or thinking problems will 'get worse' over time	20 (41%)	14 (45%)	6 (33%)	1
n (%) family member or daily contact with person with dementia	27 (55%)	21 (68%)	6 (33%)	0.6
n (%) describing cognitively engaging daily activities	15 (31%)	13 (42%)	2 (11%)	0.2
n (%) demonstrate cognitive engagement with news	13 (27%)	11 (35%)	2 (11%)	1
n (%) details (not just name) of specific tv programme / film	11 (22%)	8 (26%)	3 (17%)	1
n (%) details (not just name) of book, magazine or newspaper	10 (21%)	7 (23%)	3 (17%)	1
MMQ – Satisfaction, mean (sd)	29 (11)	26 (12)	35 (10)	.08
MMQ – Ability, mean (sd)	39 (15)	34 (14)	48 (11)	**.01**
MMQ – Strategy (mean (sd)	32 (14)	35 (13)	28 (14)	1
MoCA - total score, mean (sd)	21 (4.1)	21.9 (4.6)	20.3 (3.1)	1
MoCA - total time in seconds, mean (sd)	481 (84)	467 (82)	506 (84)	1
MoCA - orientation (0-6), mean (sd)	5.3 (1.2)	5.6 (0.8)	4.8 (1.6)	1
Luria 3-step test score, median[IQR]	3 [0-3]	3 [0,3]	2.5 [0-3]	1
Interlocking fingers test (0-4), median[IQR]	4 [0-4]	4 [2-4]	3 [0-4]	1
Digit span - forward, mean (sd)	5.6 (1.2)	5.5 (1.3)	5.7 (0.8)	1
Digit span - reverse, mean (sd)	4.3 (0.9)	4.2 (0.9)	4.2 (0.9)	1
Digit span - summed forward + reverse, mean (sd)	9.9 (1.9)	9.9 (2.2)	10.1 (1.6)	1
Medical Symptom Validity Test (MSVT)	*(n=48)*	*(n=30)*		
- pass / valid profile, n (%)	23 (48%)	16 (52%)	7 (41%)	1
- invalid profile, n (%)	10 (21%)	7 (23%)	3 (18%)	1
- dementia profile, n(%)	15 (31%)	8 (26%)	7 (41%)	1
HADS-A, mean (sd)	6.4 (4.8)	8.2 (5.0)	3.3 (2.6)	**<.01**
HADS-D, mean (sd)	6.0 (4.8)	7.6 (5.1)	3.3 (2.8)	**.01**
Pittsburgh Sleep Quality Inventory	7.1 (5.3)	8.8 (5.6)	4.2 (3.1)	.11
PHQ-15 (physical symptoms), mean (sd)	3.9 (3.1)	5.2 (3.1)	1.9 (1.8)	**<.01**
MINI n (%) with ≥ 1 diagnosis	24 (49%)	19 (61%)	2 (11%)	**.01**

Abbreviations: MMQ (Multifactorial Memory Questionnaire), MoCA (Montreal Cognitive Assessment), HADS-A (Hospital Anxiety and Depression Scale – Anxiety), HADS-D (Hospital Anxiety and Depression Scale – Depression), PHQ-15 (Patient Health Questionnaire 15), MINI (Mini-International Neuropsychiatric Interview)

Memory symptom self-report

Two non-FCD participants denied memory problems; no FCD participants denied memory problems. FCD participants reported a longer duration of symptoms than patients without FCD (median 3 yrs (IQR 1-5) vs 1.75 yrs (IQR 1-2.5).

Similar proportions of FCD (25 (19%)) and non-FCD (14 (22%)) groups met criteria for Subjective Memory Complaint as ascertained by a rating of 'poor' or 'fair' on a 5-point Likert scale (SMC Likert) in response to: 'In general, how would you rate your memory?'. SMC Likert scores inversely correlated with age in the whole group (Spearman test, rho=-.54, p=<.01) and in the FCD group, but not in the non-FCD group (Spearman test, rho=.05, p=.9).

Similar proportions of FCD and non-FCD groups (11/31 (35%) vs 4/18 (22%)) reported previously having an "excellent" memory responding to: "What did your memory used to be like?".

More FCD participants related the start of symptoms to a specific event, injury, or illness (49% FCD vs 11% non-FCD). In the FCD group: adjustment to retirement, a stressful personal event, a bereavement, a fall; an anxiety disorder or another functional disorder (n=2); serious illness; medication; and elective medical/surgical treatment (n=2). In the non-FCD group: stroke; and medical illness.

More FCD than non-FCD participants reported that others were more worried than they were about their memory (45% (14/31) vs 33% (6/18)), and more FCD than non-FCD participants believed their symptoms would get worse over time (45% (14/31) vs 33% (6/18)); neither difference was statistically significant after Bonferroni-Holm correction

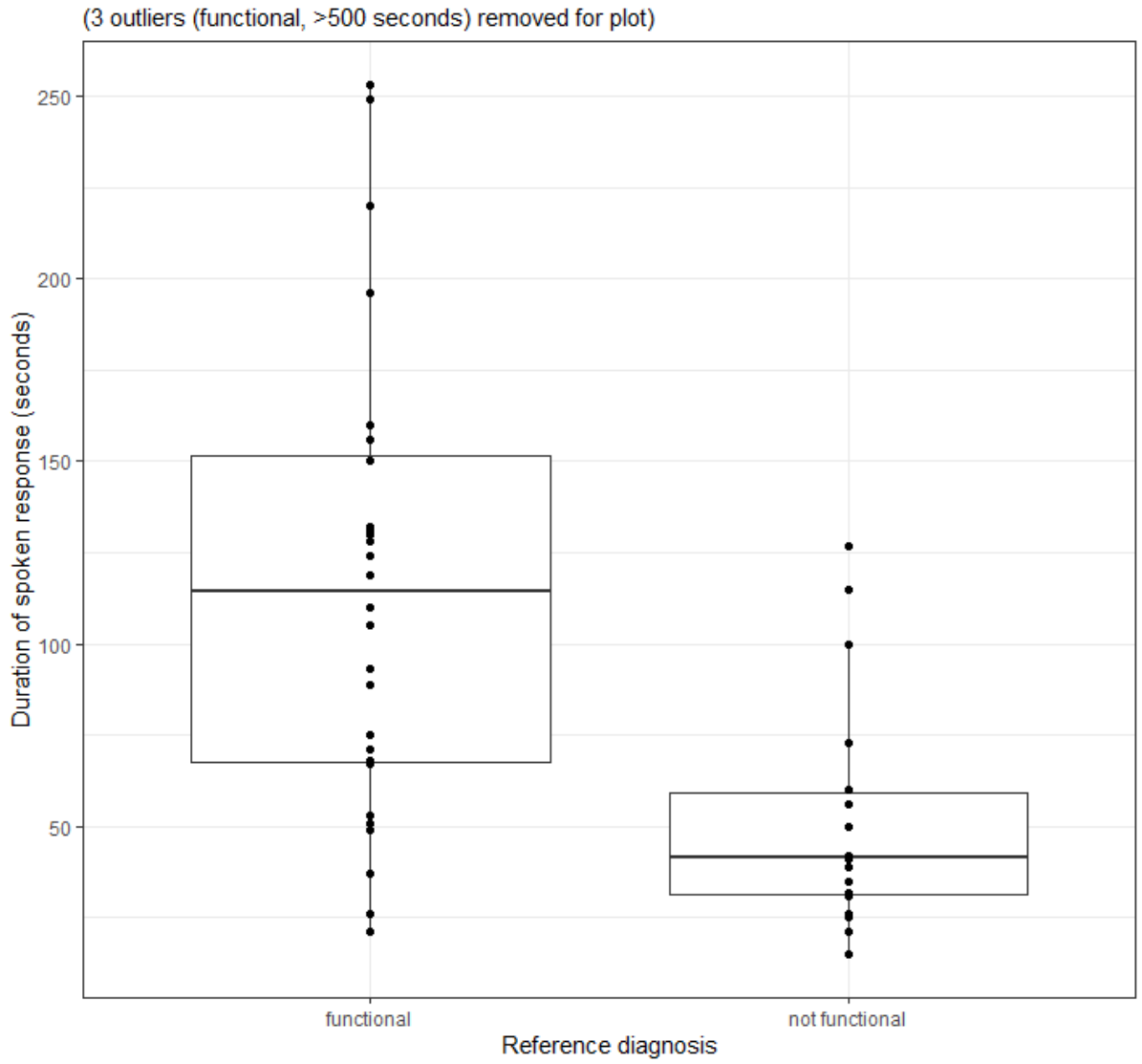
More FCD participants reported having a close family member with dementia (20 (65%) vs 5 (28%)), or previous caring responsibilities or daily contact with a person with dementia (11 (35%) vs 2 (11%); neither difference reached significance after Bonferroni-Holm correction.

Interaction and language

Only 8 participants were accompanied by another adult during the research assessment (4 FCD, 4 non-FCD), but significantly more FCD participants had attended the pre-study clinical appointment alone (15/31(48%) vs 2/18(11%) of non-FCD participants) (Chi-square p<.01).

FCD participants, when asked: “Tell me about the problems you have been having?”, spoke without interruption for a median time of 124 seconds (IQR 80 – 168), significantly longer than non-FCD participants who spoke for a median time of 42 seconds (IQR 28-55) (Mann Whitney test, corrected p <0.01) (**Figure 2**). FCD participants described a mean of three cognitive complaints/symptoms compared with one in the non-FCD group (p<.01), and were more likely to describe one or more specific examples of cognitive failure than non-FCD participants (p=.01) (**Box 1** for examples). There was no significant difference between the rate of successfully answering both parts of a compound question between FCD and non-FCD participants (26/31 (84%) vs 11/18 (61%)).

Figure 2 - Duration of response: 'Tell me about the problems you've been having?'



Box 1. "Tell me about the problems you have been having?"

Participants without FCD reference diagnoses:

"I don't know. I have a bad memory. I always check with [my husband]"

77-year-old woman

"My daughter says I don't remember her shifts. Other than that, my memory's fine."

79-year-old woman

Participants with FCD reference diagnoses:

"It's forgetfulness. For example, I forgot the name of the doctor I saw in clinic - Dr [X] - I had to check his name. It is frustrating. I will watch a film and think 'who is that actor?'. For example, I was watching a film called 'Pimpernel Smith' and I couldn't remember the actor in it – it's Lesley Howard of course! I can remember things from 40-50 years ago or even 4-5 years ago. Sometimes I struggle with finding words. The other day I went out to meet a pal - I took my jacket off and thought I had lost my wallet - but I had just put it on the side."

74-year-old man

"I wonder around the house trying to remember what I'm looking for. I'm bad on names, even with people I know well. I have difficulty calculating in recipes eg to make a recipe for 4 for 8 people. And yesterday my son asked where the nearest ATM and I couldn't remember but it came back to me later. Things often come back later on. I went to collect the Christmas tree at Christmas time and when I reached a fork in the road I couldn't visualise which way to go…"

80-year-old woman

Report of cognitively engaging activities

When asked to describe typical daily activities, 13/31 (42%) FCD participants and 2/18 (11%) non-FCD participants described cognitively engaging activities (fisher test, corrected p=.45): office work, reading, academic study, and administrative tasks in the FCD group; reading and playing piano in the non-FCD group.

There was no difference between FCD and non-FCD participants in ability to recall details from a recently-watched specific television programme or movie (8/31 (26%) vs 3/18 (17%)), or in detailed recall of books, magazines, or newspapers (7/31 (23%) vs 3/18 (17%)). Non-FCD participants were more often unable to recall the name of a book they were currently reading (10/18 (56%) vs 7/31 (23%) FCD participants) but this was not significant (fisher test, corrected p=.45).

When asked "can you tell me what has been happening in the news?", FCD participants tended to describe events with evidence of some cognitive engagement (rather than just broad naming of topics), compared with non-FCD participants, but this was not statistically significant (11/31 (35%) vs 2/18 (11%)). Similar proportions of FCD and non-FCD participants reported no awareness at all of current news (5/31 (16%) vs 5/18 (28%)).

Multifactorial memory questionnaire

FCD participants had significantly lower MMQ-Satisfaction scores and MMQ-Ability scores than non-FCD participants, and reported greater use of memory strategies, but only for MMQ-Ability was this difference significant after correction for multiple comparisons.

Cognitive tests

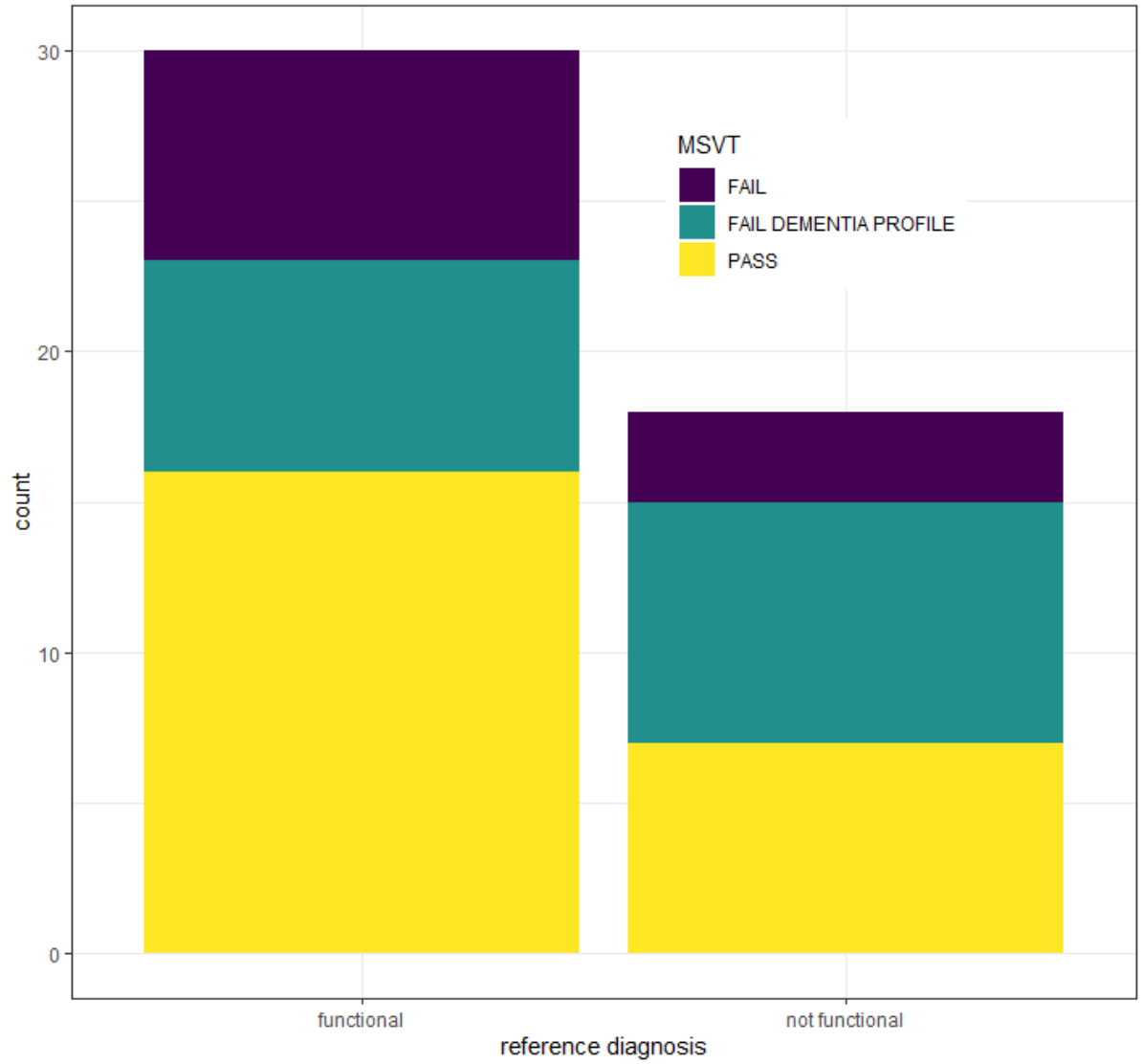
Mean MoCA score was 22 in the FCD group and 20 in the non-FCD group (t-test corrected p=1). Differences in orientation score and time taken to draw a wire cube were no longer significant after correction for multiple comparisons. FCD and non-FCD participants achieved similar scores in Luria 3-step and Interlocking fingers tests.

Exploratory analyses were performed to identify patterns of internal inconsistency within cognitive tests. Individual participants tended to score similarly across the board; i.e. those who performed well performed well in all tests; those who performed in the impaired range did so throughout, regardless of reference diagnosis. Perseverations on verbal fluency were more frequent in non-FCD participants

(7/31 and 8/18), not reaching significance. No participant scored better on delayed recall than registration.

There was no significant difference in overall failure rate or in the proportion of either 'invalid' or 'severe impairment/dementia' profiles on the Medical Symptom Validity Test (F**igure 3**). That is, participants in both FCD and non-FCD groups had invalid profiles, and participants in both groups had 'severe impairment/dementia' profiles.

Figure 3 - MSVT results by reference diagnosis



Psychiatric symptoms and diagnoses

FCD participants had significantly higher scores on both anxiety and depression subscales of the HADS. In the MINI diagnostic interview, significantly more FCD participants met criteria for at least one current psychiatric diagnosis (19 (68%) vs 1 (11%), Chi-square test, corrected $p<.01$).

In the non-FCD group, two participants met criteria for current major depressive disorder.

In the FCD group, 13 met criteria for primary diagnosis of current major depressive disorder, of whom eight also met criteria for an anxiety disorder (panic disorder, social anxiety disorder, generalised anxiety disorder). Six met criteria for primary diagnosis of an anxiety disorder (panic disorder and generalised anxiety disorder). One reported a previous episode of hypomania. Three endorsed passive suicidal thoughts, but were assessed as being at low risk of suicide.

Two FCD participants became tearful in discussion of bereavements but did not meet criteria for any psychiatric diagnosis. Of note, although no participants met DSM 5 criteria for Obsessive Compulsive Disorder (OCD), one participant described previous severe OCD and several others were noted by the researcher to describe obsessional thought structures and compulsive cognitive processes which were not detected by the study measures. Indeed, we note a lack of suitable measures to capture this clinical observation; an area for further research.

Sleep and physical symptoms

FCD participants reported poorer sleep than non-FCD participants, globally and on all subscales of the PSQI except for sleep latency, sleep disturbance, and use of sleep medication; only on the sleep efficiency subscale did this difference remain significant after Bonferroni-Holm correction (Mann Whitney, corrected $p<.01$).

FCD participants endorsed more physical symptoms than non-FCD participants on PHQ-15: noteworthy given the younger age of the FCD participants (a mean of 5 vs. 2 symptoms in the non-FCD group, t test, corrected $p<.01$).

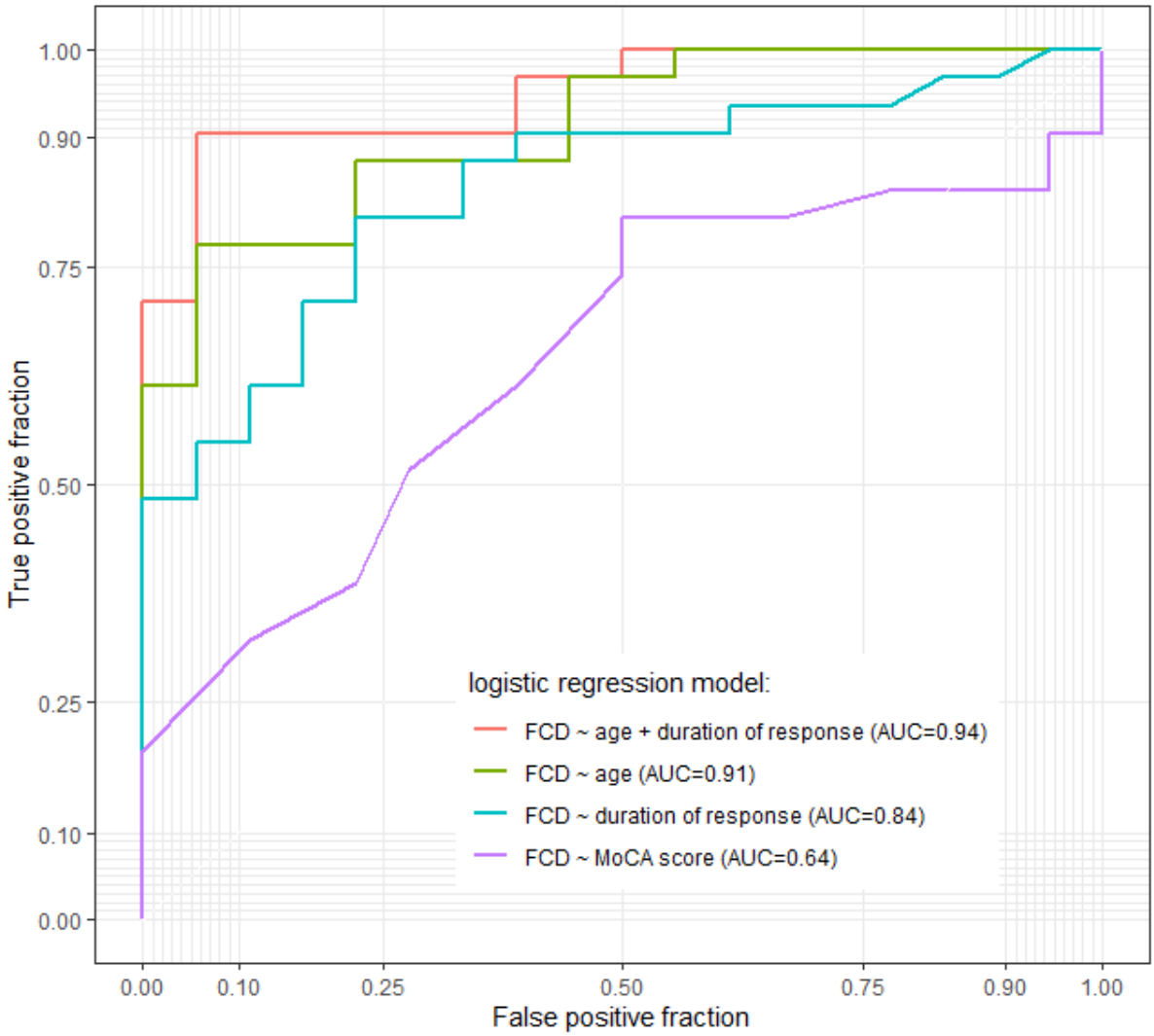
Predictive models for FCD reference diagnosis

On multiple logistic regression analysis, decreasing age and increasing duration of spoken response were both associated independently and significantly with FCD [*age in years* beta=-0.23, SE=0.09, OR=0.79 (95%CI 0.67-0.95), d*uration of response in seconds* beta=0.03, SE=0.01, OR=1.03 (95%CI 1-1.05)]. The model explained 74% of the variability in diagnosis (Nagelkerke's pseudo R^2) with a sensitivity of 90%, specificity of 83% and accuracy of 80% and an area under the ROC curve in the observed data of 0.94. HADS depression and anxiety scores and PHQ-15 scores were no longer significant in multiple regression in this small sample.

Receiver-operating curves comparing the performance of this model with predictive models based solely on age, solely on duration of response, and solely on MoCA score, are illustrated in **Figure 4**.

An alternative model was calculated with a view to clinical utility, using optimum cut points for age (<74 years) and duration of spoken response (>67 seconds). A logistic regression model using these binary classifiers explained 63% of variability in diagnosis (Nagelkerke's pseudo R2), and produced odds ratios favouring diagnosis of FCD of 34.8 for age < 74 years (95%CI 29.1-41.5) and 7.48 for duration of spoken response > 67 seconds (95%CI 7.31-7.64); this model had a sensitivity of 93%, specificity of 78%, accuracy of 88% and area under the ROC curve of 0.91 in the observed data.

Figure 4 - model performance



Discussion

In this study, a robust expert panel consensus process identified probable Functional Cognitive Disorder in 63% of the 49 patients with cognitive symptoms recruited to the study. This sample of 'borderline' cases, excluding those with dementia, may not be representative of all new cognitive presentations in the population. Nevertheless, the proportion of probable FCD diagnoses was consistent with prevalence figures identified in our previous meta-analysis of memory clinic patients (in which, of the 47% of 12 000 patients who **did not** receive diagnoses of dementia, 51% received

diagnoses in keeping with FCD and 28% descriptive diagnoses of MCI)[306]. Functional cognitive disorder appears to be a common cause of cognitive symptoms.

Despite these consistent empirical observations, functional cognitive disorders remain under-recognised, or under-reported, in real-world clinical practice. Of the 31 FCD participants in this study, only 17 (54.8%) had received a clinical diagnosis of, or descriptive diagnosis in keeping with, a functional disorder. The remaining 14 had been described in clinic letters as having 'subjective cognitive impairment' or similar, 'mild cognitive impairment', or described in terms of likely absence of disease. One could speculate on how acceptable a 'missed' diagnosis rate of 45.2% would be in other expert medical or psychiatric clinics. We suggest that the wide and varied range of diagnostic descriptions used by clinicians for this group of patients with cognitive symptoms but not dementia (**Table 2**) reflects the inadequacy of research terms such as MCI and SCD; clinicians quite appropriately look instead to multiaxial formulations in attempts to address issues of multiple aetiology and uncertainty.

This study suggests that not only is FCD a common cause of symptoms, but that it can be confidently identified on the basis of positive clinical features of internal inconsistency.

The most striking feature predicting FCD in the research assessment was longer duration and greater degree of detail of participants' response to an open question. Participants with an FCD reference diagnosis, when asked: "Tell me about the problems you have been having?", spoke without interruption for on average **three times longer** than those without FCD. This supports findings of conversation analysis studies[215], but crucially also demonstrates utility of these factors not only in selected patients with definite FCD but in an unselected 'real' clinical cohort. Moreover, our study suggests that these techniques do not require special technology but are accessible as part of simple clinical assessment, supported only by a clock.

'Duration of spoken response' is at core a proxy marker of internal inconsistency between perceived and observed function. While the person with FCD perceives amnestic, severe attentional difficulties and cognitive 'struggle', their detailed and linguistically intact description of their difficulties and past cognitive lapses demonstrates: preserved episodic memory function, ability to maintain attention, and, often, sophisticated use of language and information. That is not to say that people with FCD do not have genuine cognitive difficulties in these areas. Rather, we suggest that the 'automatic' nature of the task of relaying their difficulties and experiences allows them to circumvent processes (not yet

clearly understood) which cause processes akin to 'choking' during more deliberate cognitive tasks. Similar clinical signs of inconsistency are key in the diagnosis of other forms of functional neurological disorder. For example, in Hoover's sign, leg weakness resolves or improves when attention is shifted to moving the contralateral leg.

Duration of spoken response reflects additional factors likely to increase specificity to FCD. Detailed spoken response requires intact language function, contrasting with early disruption and semantically impoverished language in neurodegenerative diseases[373], and reflects the metacognitive evaluation of a cognitive problem, also reflected in FCD participants' lower memory satisfaction and ability MMQ scores.

Although internal inconsistency is key to FCD diagnosis, it is important that we look for internal inconsistency in the right places. Internal inconsistency **within** cognitive tests, including in a forced-choice performance validity test, was less helpful in predicting FCD in this study. Some participants with FCD scored consistently highly and others consistently poorly; cognitive scores did not significantly differ between FCD and non-FCD participants. Another study of neuropsychological test profiles in FCD found subtle deficits and similar performance to healthy controls: suggesting that these researchers examined patients from the former 'high-performing' FCD category[190]. FCD with 'objective' cognitive impairment (i.e., poor performance on cognitive tests) is poorly described in the FCD literature, and yet consists a group at particular risk of misdiagnosis. Our study suggests that cognitive tests, including performance validity tests, appear largely unhelpful in the diagnosis of FCD.

The other significant predictive variable for FCD in this study was younger age; advancing age being the largest risk factor for neurodegenerative disease.

Presence of symptoms of anxiety and depression, and DSM 5 psychiatric diagnoses, were associated with FCD in this study, but were not significantly predictive on multiple regression, being strongly inversely related to age. Symptoms of depression and anxiety are recognised associations with FCD and subjective cognitive decline[306], but are also common features of neurodegenerative disease[374,375]. Our findings support a recommendation that diagnosis of FCD should not rest solely on presence of anxiety or depression in the absence of crucial diagnostic features of internal inconsistency.

However, more detailed **phenomenological** inquiry into the nature of the experience of cognitive failure in FCD may be a fruitful avenue for future research. For example, we observed descriptions of

obsessive-compulsive patterns of thinking in FCD participants who did not satisfy DSM 5 criteria for diagnosis of OCD. Better description and measurement of these phenomena may help both in diagnosis and in generating accurate models of mechanism of cognitive impairment in FCD.

Some previously-suggested predictors did not emerge from this study as we might have expected. Recruitment was cut short by the COVID-19 pandemic, and it seems likely that small sample size will have led to false negative errors in some comparison variables. For example, we did not find statistically significant differences between those reporting a prior excellent memory, those reporting that others were more worried than themselves, who had previous contact with a person with dementia, reporting detail of television watching, or being able to respond to a compound question.

Strengths of the study include the rich data set, painstaking reference diagnosis process, and engagement with the 'real world' problem of how to distinguish FCD not from clear-cut dementia but from the 'grey area' of prodromal neurodegenerative disease and other causes of mild and subjective cognitive symptoms. We acknowledge the possibility that reference diagnoses may have been influenced by clinical features overlapping with research measures interrogated for diagnostic specificity, although this was avoided as far as practicable with blinding. Longitudinal follow-up and replication are important next steps.

In conclusion, we suggest that the predictive methods described in this study are an important move towards parity of esteem for FCD: an important differential diagnosis in the investigation of possible neurodegenerative disease, and a definable target for clinical trials.

Conclusion

The large number and variety of terms used to describe cognitive symptoms **not** caused by disease has contributed to such conditions being viewed as footnotes in the story of the relationship between neurodegenerative diseases and clinical dementia syndromes. Different terms come with different aetiological and prognostic implications – depressive pseudodementia, subjective memory impairment, subjective cognitive decline, 'worried well' – all of which may have some element of validity. However as demonstrated in the systematic review which opens this thesis, if we take a step back from this tangled mass of overlapping terminologies it becomes apparent that the burden of morbidity associated with functional cognitive disorders (FCD) is not a minor problem but a major one.

Functional cognitive disorders, as defined in the first paper in this thesis and later in the appended diagnostic criteria paper[308], are present in around a quarter of those patients presenting to memory clinics. Moreover, this systematic review and clinical study demonstrate that these patients are not 'well' in any sense, but have high levels of psychiatric comorbidity, physical symptoms, poor sleep, and are worried and distressed by their cognitive difficulties.

Cognitive symptoms, and experiences of brief cognitive failures, also occur frequently in healthy adults. Many of us evaluate our own memory as poor. Indeed, the sort of lapses that healthy adults endorsed in our survey are also the sorts of symptoms FCD patients describe in clinic.

Some key features differentiate normal experiences from those described by people with FCD. First, there is a problem with expectations: patients are distressed and concerned about cognitive lapses, perceive that they are of a nature and severity outwith normal experience, and predict that these experiences are a harbinger of future loss of function. Secondly, it appears that increased self-monitoring, and abnormal attentional focus during cognitive tasks becomes problematic: dialling up the perception of failure but also, importantly, leading to impaired performance. These mechanistic themes are in keeping with current predictive processing models of FND[376], and of cognitive symptoms in functional neurological disorders (including 'brain fog')[9].

And yet, while review of clinical descriptions suggests common features of abnormal expectations, self-monitoring, and attentional focus, functional cognitive disorder(s) can also be described in the plural, as a heterogeneous group of clinical conditions.

The extent to which we describe FCD(s) as one thing or many things, depends in part on context. There are certainly common themes, as just mentioned, and perhaps in many cases a 'final common pathway' of expectation and abnormal monitoring perpetuating symptoms. But perhaps most importantly, as a single entity, 'functional cognitive disorder' accounts for an epidemiologically meaningful 24% of memory clinic presentations – a disorder of this scale cannot be ignored and requires clinical and research attention. In contrast, the range of terms previously used (as listed in **Table 1** of 'Functional cognitive disorders – a systematic review', page 18 of this thesis) can be said to have contributed to this disorder or group of disorders remaining almost invisible in neurodegenerative disease research.

It is therefore generally helpful to think of FCD as a group of overlapping disorders with common features, including internal inconsistency and reversibility. However, in developing a more detailed understanding of mechanism it will be important to acknowledge and address heterogeneity. A range of subtypes can be described:

A minority of those meeting proposed FCD diagnostic criteria would previously have been described as 'worried well'; that is, individuals who either have non-pathological worry about future dementia and who may have noticed normal cognitive lapses, but who are fully reassured after assessment. At another extreme however are those who have unassuageable illness anxiety (previously hypochondriasis) about dementia or other brain disease, and who have altered their activities due to this concern.

Another group have a relatively 'pure' functional cognitive disorder. In this group, abnormal metacognition is prominent; in an inversion of the attitude generally seen in those with neurodegenerative disease, they perceive greater impairment than their observed function indicates. But as time goes on, 'cogniphobic' avoidance of cognitively challenging or risky activities contributes to withdrawal from domestic and employment responsibilities, producing disability and compounding distress. Recent research suggests that these individuals are accurate in their assessment of performance on individual small tasks (local metacognition) but perceive that they are overall more impaired than evidence suggests (global metacognition)[377]. This complements our findings in healthy adults, who reported frequent lapses and imperfect memory yet were not unduly concerned about it. Accepting that we often fail, and that this is normal and not a personal fault, may be an important

component of healthy appropriate cognitive function; and might be susceptible to manipulation via a range of psychotherapy modalities.

Others have inattentive cognitive symptoms as a 'side effect' of other symptoms (in functional neurological disorder; or after mTBI or viral illness, for example); or episodes of dissociation leading to poor registration of new information and perceived memory problems. Current experience in the 'long COVID' clinic echoes experience with those with persistent cognitive symptoms after mild head injury, and one possible interpretation is that volume of symptoms – any symptoms – might draw on our limited attentional resource so producing poor concentration and inattentive lapses.

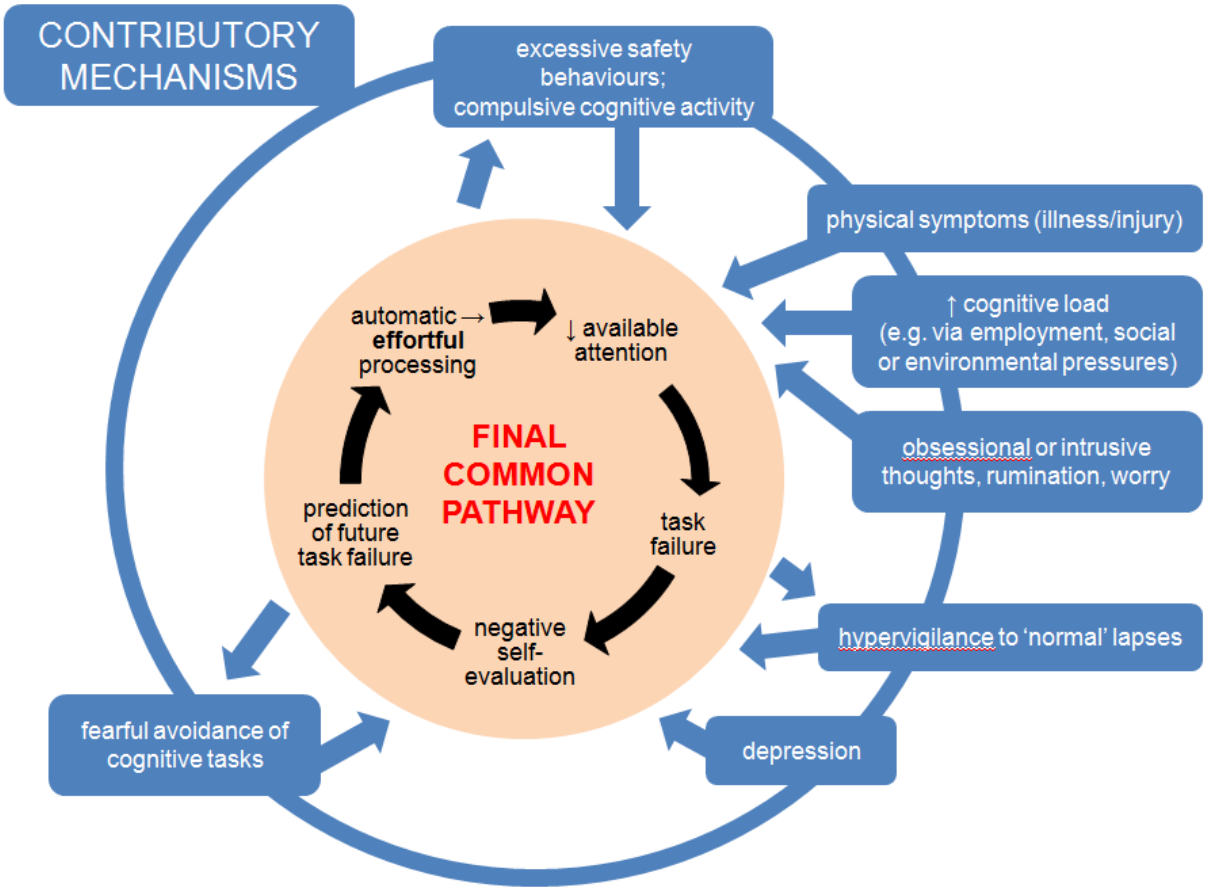
While the physical components of 'fight or flight' are well-recognised, it is relevant to note here that there is also a cognitive component to autonomic arousal and/or panic. Tearfulness and autonomic arousal, with a reported 'mind blank' or 'can't do it' experience during cognitive testing contributes to poor test performance in many people with FCD, and is the primary cause of symptoms in some.

Another presentation which is prominent in clinic but which seems poorly detected and measured in research relates to obsessional symptoms and compulsive internal cognitive processes. These can be detected by asking people in detail about their experiences and responses during and in response to perceived cognitive failures: 'Exactly what happens when you forget?'. Descriptions of prolonged internal repetition, calculations, self-testing suggest an obsessional component, as do reports of grossly excessive record-keeping or prompt-setting. It seems likely that in some individuals, these obsessional symptoms can contribute to a 'vicious cycle' of increased self-monitoring, perceived or predicted failure, and anxiety, leading in some cases to major interference with task performance.

Finally, cognitive symptoms caused by depression will often meet proposed FCD criteria. However, although as noted in the initial review paper of this thesis, older patients with profound cognitive impairment mimicking dementia (previously described as 'depressive pseudodementia') often have poor outcomes and are more likely to progress to dementia even after resolution of the mood episode. Many of such patients, with severe depression, will at presentation lack internal inconsistency and so not meet FCD criteria. Others may meet criteria, but a cautionary approach should be taken regarding prognosis, with close follow-up. This may be one group in whom demonstrably functional cognitive symptoms may be part of the early prodrome to a dementia syndrome. In the majority of those with FCD and depression, however, mild mood symptoms may be either a contributor or secondary consequence of the cognitive symptoms.

This non-exhaustive list of descriptions of FCD subtypes illustrates some of the heterogeneity in this group. A range of common features – primarily inattentive symptoms, negative self-evaluation, and frequent comorbidity – support a view that in many cases there is a 'final common pathway' through which altered self-evaluation and expectation produce altered behaviour, producing cognitive symptoms and impaired performance. A simple representation of this process can be seen in **Figure 1**. Essentially, a range of behavioural, biological, and environmental factors might reduce the available attentional resource for any specific task; resulting in failure, or a cognitive 'lapse'. A consequent prediction of future failure and decline contribute to a range of unhelpful cognitive and behavioural processes, further depleting attention, and creating a 'vicious cycle' of effortful, fatiguing, and inefficient cognitive activity. This schematic builds on previous work by Teodoro et al[9], and is informed by clinical experience as well as observations made during this research.

Figure 1 - Proposed final common pathway and multiple contributory mechanisms in the genesis of FCD



Schema like this (**Figure 1**) are helpful in that they allow for multiple aetiological contributors but also, crucially, can help in explaining the diagnosis to patients and in identifying targets for treatment – for

example, optimising management of physical symptoms, treating depression, reducing excessive note-taking or prompt-reliance, and addressing social or employment difficulties. Further, experimental, work is needed to support this model.

Recognising and disentangling multiple potential contributory mechanisms will be crucial in designing future research into mechanisms of and treatments for FCD. Multiple contributory mechanisms might best be identified not only in the neurodegenerative disease arena, but also in samples of people who have symptoms after mild head injuries, with persistent symptoms after COVID-19, and in general psychiatry and general practice samples.

The next important part of this thesis was examination of which tools may be helpful, or less helpful, in positively identifying FCD.

As evident from our clinical study of a 'real life' sample, recruited from memory and neurology clinics, people with FCD do not all score highly on cognitive tests (although some do); many score below conventional impairment thresholds. This is an important finding to emphasise, as previous studies have examined FCD only in patients who score highly on cognitive tests5,6; also a possible confounder to important observations about interaction and language. In my opinion, as we move forward with FCD research, it will be important to recognise and include this impaired group in research. People with FCD who score poorly on tests (likely a frequent cause of non-progressive MCI) are at risk of misdiagnosis, iatrogenic harm, and inappropriate inclusion in clinical trials.

An important part of this study was looking for positive clinical features of FCD; specifically, positive features of internal inconsistency. We sought a cognitive 'Hoover's sign' which might be similarly sensitive and specific to the presence of FCD even in the comorbid presence of disease. We initially suggested, including in the diagnostic recommendations1, that patterns of internal inconsistency within cognitive tests might be helpful. However, while it is possible that these sorts of inconsistencies might be detected in more in-depth cognitive testing batteries, grossly inconsistent patterns were not helpful in my clinical study. Indeed, on reflection, performance validity tests (PVTs) are specifically designed to identify internal inconsistency; and both my systematic review of failure rates in clinical populations and my clinical study suggest that these are not helpful in identifying FCD, being neither sensitive nor specific.

However, we did identify strongly predictive clinical evidence of internal inconsistency. In line with previous research in unimpaired FCD compared with neurodegenerative disease, people with FCD gave significantly longer and more detailed responses to an open question about the nature of recent difficulties. The long and detailed response demonstrates intact episodic memory, preserved drive to communicate, intact language function, and a degree of metacognitive engagement and oversight that is absent in those with neurodegenerative disease and other causes of cognitive impairment, who tend to dismiss the suggestion of a problem. A log regression model using duration of response greater than 67 seconds and age under 74 years produced similar sensitivity and specificity to Hoover's sign in the diagnosis of functional weakness.

There were limitations to this research, and particularly to the clinical study, which was terminated early because of COVID-19 and therefore had a smaller-than-anticipated sample size. I hope to test the models and measures that were helpful in this study in new clinical groups; first, in patients with cognitive symptoms in long-COVID, of whom we suspect a proportion may have FCD.

This thesis has described Functional Cognitive Disorders in the context of differential diagnosis of neurodegenerative disease. I hope that some of the work produced in collaboration with this others as part of this thesis has helped to start to put FCD on the map in clinical practice and neurodegeneration research.

However, description is only a beginning. Much more research is needed, a) to identify the key pathological mechanisms of FCD, and then to identify ways of measuring and manipulating these; and in tandem b) to develop evidence-based treatments for FCD. I am aware that colleagues have embarked on research aiming to manipulate metacognition in FCD; others are trialling Acceptance and Commitment Therapy and Cognitive Behavioural Therapy as treatments. These are exciting developments, and I look forward to future collaborations and the development of FCD research networks to help move this work forward in an efficient way.

Finally, an important priority for all undertaking research into FCD should be the question of how we might identify FCD or FCD-like profiles in big datasets. Any examination of cognitive disorders requires that we attend to and address (in planning and interpretation of results) the likelihood that cognitive symptoms and impairment are caused by FCD in a subset of participants, influencing the trajectory of symptoms and any interpretation of biomarkers.

Ultimately, I hope that further developing these diagnostic profiles, moving towards experimental research into mechanism will allow us to develop effective treatments so that we can work to lessen the considerable morbidity associated with these common conditions.

References

1 Bell S, Harkness K, Dickson JM, Blackburn D. A diagnosis for £55: what is the cost of government initiatives in dementia case finding. *Age Ageing* 2015; **44**: 344–5.

2 Menon R, Larner AJ. Use of cognitive screening instruments in primary care: the impact of national dementia directives (NICE/SCIE, National Dementia Strategy). *Fam Pract* 2011; **28**: 272–6.

3 Stone J, Pal S, Blackburn D, Reuber M, Thekkumpurath P, Carson A. Functional (Psychogenic) Cognitive Disorders: A Perspective from the Neurology Clinic. *J Alzheimer's Dis* 2015; **48**: S5–17.

4 Stone J, Carson A, Duncan R, *et al.* Symptoms 'unexplained by organic disease' in 1144 new neurology out-patients: how often does the diagnosis change at follow-up? *Brain* 2009; **132**: 2878–88.

5 Carson A, Stone J, Hibberd C, *et al.* Disability, distress and unemployment in neurology outpatients with symptoms 'unexplained by organic disease'. *J Neurol Neurosurg Psychiatry* 2011; **82**: 810–3.

6 Espay AJ, Aybek S, Carson A, *et al.* Current concepts in diagnosis and treatment of functional neurological disorders. *JAMA Neurol* 2018; **75**: 1132–41.

7 Edwards MJ, Adams RA, Brown H, Parees I, Friston KJ. A Bayesian account of 'hysteria'. *Brain* 2012; **135**: 3495–512.

8 Gelauff JM, Carson A, Ludwig L, Tijssen MAJ, Stone J. The prognosis of functional limb weakness: a 14-year case-control study. *Brain* 2019; published online June 5. DOI:10.1093/brain/awz138.

9 Teodoro T, Edwards MJ, Isaacs JD. A unifying theory for cognitive abnormalities in functional neurological disorders, fibromyalgia and chronic fatigue syndrome: systematic review. *J Neurol Neurosurg Psychiatry* 2018; **89**: 1308–19.

10 Bailey C, Poole N, Blackburn DJ. Identifying patterns of communication in patients attending memory clinics: a systematic review of observations and signs with potential diagnostic utility. *Br J Gen Pract* 2018; **68**: e123–38.

11 Bleuler E. Textbook of Psychiatry, 2nd edn. New York: MacMillan, 1934.

12 Kiloh LG. Pseudo-dementia. *Acta Psychiatr Scand* 1961; **37**: 336–51.

13 Wells CE. Pseudodementia. *Am J Psychiatry* 1979; **136**: 895.

14 Howard R. Doubts about dementia diagnoses. *The Lancet Psychiatry* 2017; **4**: 580–1.

15 Marsden CD, Harrison MJG. Outcome of Investigation of Patients with Presenile Dementia. *Br Med J* 1972; **2**: 249–242.

16 Smith JS, Kiloh LG. The investigation of dementia: results in 200 consecutive admissions. *Lancet* 1981; **1**: 824–7.

17 Rabins P V. The Prevalence of Reversible Dementia in a Psychiatric Hospital. *Psychiatr Serv* 1981; **32**: 490–2.

18 Brodaty H. Low Diagnostic Yield in a Memory Disorders Clinic. *Int Psychogeriatrics* 1990; **2**: 149–59.

19 Lehmann WM, Gottfries C, Hellstrom P. Experience from a memory center at a university hospital. *Nord J Psychiatry* 1996; **50**: 63–70.

20 Kopelman M, Crawford S. Not all Memory Clinics are Dementia Clinics. *Neuropsychol Rehabil* 1996; **6**: 187–202.

21 Hogh P, Waldemar G, Knudsen GM, *et al.* A multidisciplinary memory clinic in a neurological setting: diagnostic evaluation of 400 consecutive patients. *Eur J Neurol* 1999; **6**: 279–88.

22 Elberling TV, Stokholm J, Hogh P, Waldemar G. Diagnostic profile of young and middle-aged memory clinic patients. *Neurology* 2002; **59**: 1259.

23 Hejl A-M, Hording M, Hasselbalch E, *et al.* Psychiatric morbidity in a neurology-based memory clinic: the effect of systematic psychiatric evaluation. *J Am Geriatr Soc* 2003; **51**: 1773–8.

24 Larner AJ. 'Who came with you?' A diagnostic observation in patients with memory problems? *J Neurol Neurosurg Psychiatry* 2005; **76**: 1739.

25 Hancock P, Larner AJ. Diagnostic utility of the Pittsburgh sleep Quality Index in memory clinics. *Int J Geriatr Psychiatry* 2009; **24**: 1237–41.

26 Wang B, Guo Q-H, Chen M-R, *et al.* The clinical characteristics of 2,789 consecutive patients in a memory clinic in China. *J Clin Neurosci* 2011; **18**: 1473–7.

27 Mascherek A, Zimprich D, Rupprecht R. What do cognitive complaints in a sample of memory clinic outpatients reflect? *GeroPsych J Gerontopsychology Geriatr Psychiatry* 2011; **24**: 187–95.

28 Pennington C, Newson M, Hayre A, Coulthard E. Functional cognitive disorder: what is it and what to do about it? *Pract Neurol* 2015; **15**: 436–44.

29 Claus JJ, Staekenborg SS, Roorda JJ, *et al.* Low Prevalence of Mixed Dementia in a Cohort of 2,000 Elderly Patients in a Memory Clinic Setting. *J Alzheimer's Dis* 2016; **50**: 797–806.

30 Wright N, Lindesay J. A survey of memory clinics in the british isles. *Int J Geriatr Psychiatry* 1995; **10**: 379–85.

31 Sheng B, Bon Law C, Mo Yeung K. Characteristics and diagnostic profile of patients seeking dementia care in a memory clinic in Hong Kong. *Int Psychogeriatr Assoc* 2018; **21**: 392–400.

32 Verity R, Kirk A, O'Connell ME, Karunanayake C. The Worried Well? Characteristics of Cognitively Normal Patients Presenting to a Rural and Remote Memory Clinic. *Can J Neurol Sci* 2018; **45**: 158–67.

33 Elhadd K, Bharambe V, Larner AJ. Functional Cognitive Disorders: Can Sleep Disturbance Contribute to a Positive Diagnosis? *J Sleep Disord Ther* 2018; **07**: 1–4.

34 Bharambe V, Larner AJ. Functional cognitive disorders: memory clinic study. *Prog Neurol Psychiatry* 2018; **22**: 19–22.

35 Randall A, Larner AJ. La maladie du petit papier: A sign of functional cognitive disorder? *Int J Geriatr Psychiatry* 2018; **33**: 800.

36 Larner AJ. Dementia screening: a different proposal. *Future Neurol* 2018; **13**: 177–9.

37 Bharambe V, Larner AJ. Functional cognitive disorders: demographic and clinical features

contribute to a positive diagnosis. *Neurodegener Dis Manag* 2018; **8**: 377–83.

38 Banerjee S, Willis R, Matthews D, Contell F, Chan J, Murray J. Improving the quality of care for mild to moderate dementia: an evaluation of the Croydon Memory Service Model. *Int J Geriatr Psychiatry* 2007; **22**: 782–8.

39 Kenfield MC, Arciniegas DB, Anderson CA, Howard KL, Filley CM. When cognitive evaluation does not disclose a neurologic disorder: experience of a university behavioral neurology clinic. *Cogn Behav Neurol* 2010; **23**: 112–8.

40 Reifler B V, Larson E, Hanley R. Coexistence of Cognitive Impairment and Depression in Geriatric Outpatients. *Am J Psychiatry* 1982; **139**: 623–6.

41 Yerby MS, Sundsten JW, Larson EB, Wu SA, Sumi SM. A new method of measuring brain atrophy: the effect of aging in its application for diagnosing dementia. *Neurology* 1985; **35**: 1316–20.

42 Bayer AJ, Pathy MSJ, Twining C. The Memory Clinic. *Drugs* 1987; **33**: 84–9.

43 Van der Cammen TJM, Simpson JM, Fraser RM, Preker AS, Exton-Smith AN. The Memory Clinic: A New Approach to the Detection of Dementia. *Br J Psychiatry* 1987; **150**: 359–64.

44 Erkinjuntti T, Sulkava R, Kovanen J, Palo J. Suspected dementia: Evaluation of 323 consecutive referrals. *Acta Neurol Scand* 1987; **76**: 359–64.

45 Derouesne C, Alperovitch A, Arvay N, *et al.* Memory complaints in the elderly: a study of 367 community-dwelling individuals from 50 to 80 years old. *Arch Gerontol Geriatr Suppl* 1989; **1**: 151–63.

46 Weiner MF, Bruhn M, Svetlik D, Tintner R. Experiences with depression in a dementia clinic. *J Clin Psychiatry* 1991; **52**: 234–8.

47 Ames D, Flicker L, Helme RD. A memory clinic at a geriatric hospital: rationale, routine and results from the first 100 patients. *Med J Aust* 1992; **156**: 618–22.

48 Verhey F. Diagnosing dementia: a comparison between a monodisciplinary and a multidisciplinary approach. *J Neuropsychiatry Clin Neurosci* 1993; **5**: 78–85.

49 Almeida OP, Hill K, Howard R, O'Brien J. Demographic and clinical features of patients attending a memory clinic. *Int J Geriatr Psychiatry* 1993; **8**: 497–501.

50 Swanwick GJ, Coen RF, O'Mahony D, *et al.* A memory clinic for the assessment of mild dementia. *Ir Med J* 1996; **89**: 104–5.

51 Djukic M, Wedekind D, Franz A, Gremke M, Nau R. Frequency of dementia syndromes with a potentially treatable cause in geriatric in-patients: analysis of a 1-year interval. *Eur Arch Psychiatry Clin Neurosci* 2015; **265**: 429–38.

52 Kendell RE. The Stability of Psychiatric Diagnoses. *Br J Psychiatry* 1974; **124**: 352–6.

53 Nott PN, Fleminger JJ. Presenile dementia: the Difficulties of Early Diagnosis. *Acta Psychiatr Scand* 1975; **51**: 210–7.

54 O'Brien JT, Beats B, Hill K, *et al.* Do subjective memory complaints precede dementia? A three-year follow-up of patients with supposed 'benign senescent forgetfulness'. *Int J Geriatr Psychiatry* 1992; **7**: 481–6.

55 Lehrner J, Gufler R, Guttmann G, *et al.* Annual conversion to Alzheimer disease among patients

with memory complaints attending an outpatient memory clinic: the influence of amnestic mild cognitive impairment and the predictive value of neuropsychological testing. *Wien Klin Wochenschr* 2005; **117**: 629–35.

56 Hessen E, Eckerstrom M, Nordlund A, *et al.* Subjective cognitive impairment is a predominantly benign condition in memory clinic patients followed for 6 years: The Gothenburg-oslo MCI Study. *Dement Geriatr Cogn Dis Extra* 2017; **7**: 1–14.

57 Slot RER, Sikkes SAM, Berkhof J, *et al.* Subjective cognitive decline and rates of incident Alzheimer's disease and non-Alzheimer's disease dementia. *Alzheimer's Dement* 2019; **15**: 465–76.

58 Visser PJ, Verhey F, Knol DL, *et al.* Prevalence and prognostic value of CSF markers of Alzheimer's disease pathology in patients with subjective cognitive impairment or mild cognitive impairment in the DESCRIPA study: a prospective cohort study. *Lancet Neurol* 2009; **8**: 619–27.

59 Elfgren C, Gustafson L, Vestberg S, Passant U. Subjective memory complaints, neuropsychological performance and psychiatric variables in memory clinic attendees: a 3-year follow-up study. *Arch Gerontol Geriatr* 2010; **51**: e110–4.

60 Vestberg S, Passant U, Elfgren C. Stability in the clinical characteristics of patients with memory complaints. *Arch Gerontol Geriatr* 2010; **50**: e26-30.

61 van Harten AC, Smits LL, Teunissen CE, *et al.* Preclinical AD predicts decline in memory and executive functions in subjective complaints. *Neurology* 2013; **81**: 1409–16.

62 van Harten AC, Visser PJ, Pijnenburg YAL, *et al.* Cerebrospinal fluid Aβ42 is the best predictor of clinical progression in patients with subjective complaints. *Alzheimer's Dement* 2013; **9**: 481–7.

63 Eckerstrom M, Gothlin M, Rolstad S, *et al.* Longitudinal evaluation of criteria for subjective cognitive decline and preclinical Alzheimer's disease in a memory clinic sample. *Alzheimer's Dement Diagnosis, Assess Dis Monit* 2017; **8**: 96–107.

64 Hessen E, Nordlund A, Stalhammar J, *et al.* T-Tau is Associated with Objective Memory Decline over Two Years in Persons Seeking Help for Subjective Cognitive Decline: A Report from the Gothenburg-Oslo MCI Study. *J Alzheimer's Dis* 2015; **47**: 619–28.

65 Siersma V, Waldemar G, Waldorff FB, V. S, G. W. Subjective memory complaints in primary care patients and death from all causes: a four-year follow-up. *Scand J Prim Health Care* 2013; **31**: 7–12.

66 Strand BH, Knapskog A-B, Persson K, *et al.* Survival and years of life lost in various aetiologies of dementia, mild cognitive impairment (MCI) and subjective cognitive decline (SCD) in Norway. *PLoS One* 2018; **13**: e0204436.

67 Bulbena A, Berrios GE. Pseudodementia: facts and figures. *Br J Psychiatry* 1986; **148**: 87–94.

68 Sachdev PS, Smith JS, Angus-Lepan H, Rodriguez P. Pseudodementia twelve years on. *J Neurol Neurosurg Psychiatry* 1990; **53**: 254–9.

69 Kral VA, Emery OB. Long-term follow-up of depressive pseudodementia of the aged. *Can J Psychiatry* 1989; **34**: 445–6.

70 Sáez-Fonseca JA, Lee L, Walker Z. Long-term outcome of depressive pseudodementia in the

elderly. *J Affect Disord* 2007; **101**: 123–9.

71 Schmidtke K, Pohlmann S, Metternich B. The syndrome of functional memory disorder: definition, etiology, and natural course. *Am J Geriatr Psychiatry* 2008; **16**: 981–8.

72 Grut M, Jorm AF, Fratiglioni L, Forsell Y, Viitanen M, Winblad B. Memory complaints of elderly people in a population survey: variation according to dementia stage and depression. *J Am Geriatr Soc* 1993; **41**: 1295–300.

73 Spear-Bassett S, Folstein MF. Memory Complaint, Memory Performance, and Psychiatric Diagnosis: A Community Study. *J Geriatr Psychiatry Neurol* 1993; **6**: 105–11.

74 Balash Y, Mordechovich M, Shabtai H, Giladi N, Gurevich T, Korczyn AD. Subjective memory complaints in elders: depression, anxiety, or cognitive decline? *Acta Neurol Scand* 2013; **127**: 344–50.

75 Acikgoz M, Ozen Barut B, Emre U, Tascilar N, Atalay A. Assessment of relation between subjective memory complaints and objective cognitive performance of elderly over 55 years old age. *Noropsikiyatri Ars* 2014; **51**: 57–62.

76 Jorm AF, Christensen H, Henderson AS, Korten AE, Mackinnon AJ, Scott R. Complaints of cognitive decline in the elderly: a comparison of reports by subjects and informants in a community survey. *Psychol Med* 1994; **24**: 365.

77 Caselli RJ, Chen K, Locke DEC, *et al.* Subjective cognitive decline: Self and informant comparisons. *Alzheimer's Dement* 2014; **10**: 93–8.

78 Chen ST, Siddarth P, Ercoli LM, Merrill DA, Torres-Gil F, Small GW. Modifiable risk factors for Alzheimer disease and subjective memory impairment across age groups. *PLoS One* 2014; **9**: e98630.

79 Mewton L, Sachdev P, Anderson T, Sunderland M, Andrews G. Demographic, clinical, and lifestyle correlates of subjective memory complaints in the Australian population. *Am J Geriatr Psychiatry* 2014; **22**: 1222–32.

80 Singh-Manoux A, Dugravot A, Ankri J, *et al.* Subjective cognitive complaints and mortality: does the type of complaint matter? *J Psychiatr Res* 2014; **48**: 73–8.

81 Tomita T, Sugawara N, Kaneda A, *et al.* Sex-specific effects of subjective memory complaints with respect to cognitive impairment or depressive symptoms. *Psychiatry Clin Neurosci* 2014; **68**: 176–81.

82 Roehr S, Villringer A, Angermeyer MC, Luck T, Riedel-Heller SG. Outcomes of stable and unstable patterns of subjective cognitive decline - results from the Leipzig Longitudinal Study of the Aged (LEILA75+). *BMC Geriatr* 2016; **16**: 180.

83 Montejo P, Montenegro M, Fernandez MA, Maestu F. Subjective memory complaints in the elderly: Prevalence and influence of temporal orientation, depression and quality of life in a population-based study in the city of Madrid. *Aging Ment Health* 2011; **15**: 85–96.

84 Glodzik-Sobanska L, Reisberg B, De Santi S, *et al.* Subjective memory complaints: presence, severity and future outcome in normal older subjects. *Dement Geriatr Cogn Disord* 2007; **24**: 177–84.

85 Tanaka H, Ogata S, Omura K, *et al.* Association between subjective memory complaints and depressive symptoms after adjustment for genetic and family environmental factors in a

Japanese twin study. *Environ Health Prev Med* 2016; **21**: 92–9.

86 Sakurai R, Suzuki H, Ogawa S, *et al.* Fear of falling, but not gait impairment, predicts subjective memory complaints in cognitively intact older adults. *Geriatr Gerontol Int* 2017; **17**: 1125–31.

87 Yates JA, Clare L, Woods RT. Subjective memory complaints, mood and MCI: a follow-up study. *Aging Ment Health* 2017; **21**: 313–21.

88 Tobiansky R, Blizard R, Livingston G, Mann A. The Gospel Oak Study stage IV: the clinical relevance of subjective memory impairment in older people. *Psychol Med* 1995; **25**: 779–86.

89 Avila-Villanueva M, Maestu F, Fernandez-Blazquez MA. Internal Consistency Over Time of Subjective Cognitive Decline: Drawing Preclinical Alzheimer's Disease Trajectories. *J Alzheimers Dis* 2018; **66**: 173–83.

90 Cosentino S, Devanand D. A link between subjective perceptions of memory and physical function: Implications for subjective cognitive decline. *J Alzheimer's Dis* 2018; **61**: 1387–98.

91 Nunes TC, Hirano RS, Cruz LC, Seixas A, Jean-Louis G, Fonseca VAS. Self perceived memory difficulties in medical students as another symptom of anxiety. *Trends Neurosci Educ* 2018; **11**: 9–12.

92 Flatt JD, Johnson JK, Karpiak SE, Seidel L, Larson B. Correlates of Subjective Cognitive Decline in Lesbian, Gay, Bisexual, and Transgender Older Adults. *J Alzheimer's Dis* 2018; **64**: 91–102.

93 Hall JR, Wiechmann A, Johnson LA, Edwards M. Characteristics of cognitively normal Mexican-Americans with cognitive complaints. *J Alzheimer's Dis* 2018; **61**: 1485–92.

94 Sanchez-Benavides G, Grau-Rivera O, Suarez-Calvet M, *et al.* Brain and cognitive correlates of subjective cognitive decline-plus features in a population-based cohort. *Alzheimer's Res Ther* 2018; **10**: 123.

95 van Oijen M, de Jong FJ, Hofman A, Koudstaal PJ, Breteler MMB. Subjective memory complaints, education, and risk of Alzheimer's disease. *Alzheimer's Dement* 2007; **3**: 92–7.

96 Luck T, Roehr S, Rodriguez FS, *et al.* Memory-related subjective cognitive symptoms in the adult population: prevalence and associated factors - results of the LIFE-Adult-Study. *BMC Psychol* 2018; **6**: 23.

97 Meyer OL, Leggett A, Liu S, Nguyen NH. Prevalence and correlates of subjective memory complaints in Vietnamese adults. *Int Psychogeriatrics* 2018; **30**: 1039–48.

98 Brailean A, Steptoe A, Batty GD, Zaninotto P, Llewellyn DJ. Are subjective memory complaints indicative of objective cognitive decline or depressive symptoms? Findings from the English Longitudinal Study of Ageing. *J Psychiatr Res* 2019; **110**: 143–51.

99 Kuiper JS, Oude Voshaar RC, Zuidema SU, Stolk RP, Zuidersma M, Smidt N. The relationship between social functioning and subjective memory complaints in older persons: a population-based longitudinal cohort study. *Int J Geriatr Psychiatry* 2017; **32**: 1059–71.

100 Collins MW, Abeles N. Subjective memory complaints and depression in the able elderly. *Clin Gerontol* 1996; **16**: 29–54.

101 Begum A, Dewey M, Hassiotis A, *et al.* Subjective cognitive complaints across the adult life span: a 14-year analysis of trends and associations using the 1993, 2000 and 2007 English Psychiatric Morbidity Surveys. *Psychol Med* 2014; **44**: 1977–87.

102 B. C, M. G, W. X, *et al.* Differential distribution of subjective and objective cognitive impairment in the population: A nation-wide twin-study. *J Alzheimer's Dis* 2012; **29**: 393–403.

103 Kaup AR, Nettiksimmons J, LeBlanc ES, Yaffe K. Memory complaints and risk of cognitive impairment after nearly 2 decades among older women. *Neurology* 2015; **85**: 1852–8.

104 Genziani M, Stewart R, Béjot Y, Amieva H, Artero S, Ritchie K. Subjective memory impairment, objective cognitive functioning and social activity in French older people: Findings from the Three Cities study. *Geriatr Gerontol Int* 2013; **13**: 139–45.

105 Schweizer S, Kievit RA, Emery T, Henson RN. Symptoms of depression in a large healthy population cohort are related to subjective memory complaints and memory performance in negative contexts. *Psychol Med* 2018; **48**: 104–14.

106 Gino S, Mendes T, Maroco J, *et al.* Memory complaints are frequent but qualitatively different in young and elderly healthy people. *Gerontology* 2010; **56**: 272–7.

107 Westoby CJ, Mallen CD, Thomas E. Cognitive complaints in a general population of older adults: Prevalence, association with pain and the influence of concurrent affective disorders. *Eur J Pain* 2009; **13**: 970–6.

108 Brækhus A, Øksengård A, Engedal K. Subjective worsening of memory predicts dementia after three years. *Nor J Epidemiol* 1998; **8**: 189–94.

109 Ito K, Inagaki H, Sugiyama M, Okamura T, Shimokado K, Awata S. Association between subjective memory complaints and mental health well-being in urban community-dwelling elderly in Japan. Geriatr. Gerontol. Int. 2013; **13**: 234–5.

110 Jungwirth S, Fischer P, Weissgram S, Kirchmeyr W, Bauer P, Tragl KH. Subjective Memory Complaints and Objective Memory Impairment in the Vienna-Transdanube Aging Community. *J Am Geriatr Soc* 2004; **52**: 263–8.

111 Park MH, Min JY, Min HY, Lee HJ, Lee DH, Song MS. Subjective memory complaints and clinical characteristics in elderly Koreans: a questionnaire survey. *Int J Nurs Stud* 2007; **44**: 1400–5.

112 Blazer DG, Hays JC, Fillenbaum GG, Gold DT. Memory Complaint as a Predictor of Cognitive Decline. *J Aging Health* 1997; **9**: 171–84.

113 Rijs KJ, Comijs HC, van den Kommer TN, Deeg DJH. Do employed and not employed 55 to 64-year-olds' memory complaints relate to memory performance? A longitudinal cohort study. *Eur J Public Health* 2013; **23**: 1013–20.

114 Wolfsgruber S, Kleineidam L, Wagner M, *et al.* Differential Risk of Incident Alzheimer's Disease Dementia in Stable Versus Unstable Patterns of Subjective Cognitive Decline. *J Alzheimer's Dis* 2016; **54**: 1135–46.

115 S.M.D. B, Brucki SMD, Nitrini R. Subjective memory impairment in a rural population with low education in the Amazon rainforest: An exploratory study. *Int Psychogeriatrics* 2009; **21**: 164–71.

116 Markova H, Andel R, Stepankova H, *et al.* Subjective Cognitive Complaints in Cognitively Healthy Older Adults and Their Relationship to Cognitive Performance and Depressive Symptoms. *J Alzheimer's Dis* 2017; **59**: 871–81.

117 Slavin MJ, Brodaty H, Kochan NA, *et al.* Prevalence and Predictors of "Subjective Cognitive Complaints" in the Sydney Memory and Ageing Study. *Am J Geriatr Psychiatry* 2010; **18**: 701–

10.

118 Montejo P, Montenegro M, Fernández MA, Maestú F. Memory complaints in the elderly: Quality of life and daily living activities. A population based study. *Arch Gerontol Geriatr* 2012; **54**: 298–304.

119 Pedro MC, Mercedes M-P, Ramón L-H, Borja MR. Subjective memory complaints in elderly: relationship with health status, multimorbidity, medications, and use of services in a population-based study. *Int Psychogeriatr Assoc* 2016; **28**: 1903–16.

120 Smith GE, Petersen RC, Ivnik RJ, Malec JF, Tangalos EG. Subjective memory complaints, psychological distress, and longitudinal change in objective memory performance. *Psychol Aging* 1996; **11**: 272–9.

121 St John P, Montgomery P. Are cognitively intact seniors with subjective memory loss more likely to develop dementia? *Int J Geriatr Psychiatry* 2002; **17**: 814–20.

122 Wolf OT, Dziobek I, McHugh P, *et al.* Subjective memory complaints in aging are associated with elevated cortisol levels. *Neurobiol Aging* 2005; **26**: 1357–63.

123 Lautenschlager NT, Flicker L, Vasikaran S, Leedman P, Almeida OP. Subjective Memory Complaints With and Without Objective Memory Impairment Relationship With Risk Factors for Dementia. 2005 DOI:10.1097/00019442-200508000-00013.

124 Amariglio RE, Townsend MK, Grodstein F, Sperling RA. Specific subjective memory complaints in older persons may indicate poor cognitive function. *J Am Geriatr Soc* 2011; **59**: 1612–7.

125 Cooper C, Bebbington P, Lindesay J, *et al.* The meaning of reporting forgetfulness: a cross-sectional study of adults in the English 2007 Adult Psychiatric Morbidity Survey. *Age Ageing* 2011; **40**: 711–7.

126 Paradise MB, Glozier NS, Naismith SL, Davenport TA. Subjective memory complaints, vascular risk factors and psychological distress in the middle-aged: A cross-sectional study. *BMC Psychiatry* 2011; **11**: 108.

127 Bartley M, Bokde AL, Ewers M, *et al.* Subjective memory complaints in community dwelling healthy older people: The influence of brain and psychopathology. *Int J Geriatr Psychiatry* 2012; **27**: 836–43.

128 Sindi S, Juster RP, Wan N, Nair NP V, Ying Kin N, Lupien SJ. Depressive symptoms, cortisol, and cognition during human aging: the role of negative aging perceptions. *Stress* 2012; **15**: 130–7.

129 Barker A, Carter C, Jones R. Memory performance, self-reported memory loss and depressive symptoms in attenders at a GP-referral and a self-referral memory clinic. *Int J Geriatr Psychiatry* 1994; **9**: 305–11.

130 Barker A, Prior J. Memory complaint in attenders at a self-referral memory clinic: The role of cognitive factors, affective symptoms and personality. *Int J Geriatr Psychiatry* 1995; **10**: 777–81.

131 Ramakers IHGB, Visser PJ, Bittermann AJN, *et al.* Characteristics of help-seeking behaviour in subjects with subjective memory complaints at a memory clinic: A case-control study. *Int J Geriatr Psychiatry* 2009; **24**: 190–6.

132 Hurt CS, Burns A, Brown RG, Barrowclough C. Why don't older adults with subjective memory complaints seek help? *Int J Geriatr Psychiatry* 2012; **27**: 394–400.

133 Perrotin A, de Flores R, Lamberton F, *et al.* Hippocampal Subfield Volumetry and 3D Surface Mapping in Subjective Cognitive Decline. *J Alzheimers Dis* 2015; **48 Suppl 1**: S141-50.

134 Haussmann R, Mayer-Pelinski R, Borchardt M, *et al.* Extrinsic and Intrinsic Help-Seeking Motivation in the Assessment of Cognitive Decline. *Am J Alzheimers Dis Other Demen* 2018; **33**: 215–20.

135 Tsoi WF. The Ganser Syndrome in Singapore: A Report on Ten Cases. *Br J Psychiatry* 1973; **123**: 567–72.

136 Reisberg B, Shulman MB, Torossian C, Leng L, Zhu W. Outcome over seven years of healthy adults with and without subjective cognitive impairment. *Alzheimer's Dement* 2010; **6**: 11–24.

137 Jorm AF, Christensen H, Korten AE, Jacomb PA, Henderson AS. Memory complaints as a precursor of memory impairment in older people: a longitudinal analysis over 7-8 years. *Psychol Med* 2001; **31**: 441–9.

138 Prichep LS, John ER, Ferris SH, *et al.* Quantitative EEG correlates of cognitive deterioration in the elderly. *Neurobiol Aging* 1994; **15**: 85–90.

139 Schmand B, Jonker C, Geerlings MI, Lindeboom J. Subjective memory complaints in the elderly: depressive symptoms and future dementia. *Br J Psychiatry* 1997; **171**: 373–6.

140 Geerlings MI, Jonker C, Bouter LM, Adèr HJ, Schmand B. Association Between Memory Complaints and Incident Alzheimer's Disease in Elderly People With Normal Baseline Cognition. 1999.

141 Amariglio RE, Buckley RF, Mormino EC, *et al.* Amyloid-associated increases in longitudinal report of subjective cognitive complaints. *Alzheimer's Dement Transl Res Clin Interv* 2018; **4**: 444–9.

142 Flicker C, Ferris SH, Reisberg B. A longitudinal study of cognitive function in elderly persons with subjective memory complaints. *J Am Geriatr Soc* 1993; **41**: 1029–32.

143 Sohrabi HR, Weinborn M, Laske C, *et al.* Subjective memory complaints predict baseline but not future cognitive function over three years: Results from the Western Australia Memory Study. *Int Psychogeriatrics* 2019; **31**: 513–25.

144 Taylor JL, Miller TP, Tinklenberg JR. Correlates of memory decline: A 4-year longitudinal study of older adults with memory complaints. *Psychol Aging* 1992; **7**: 185–93.

145 Lee P-L. A Joyful Heart is Good Medicine: Positive Affect Predicts Memory Complaints. *Am J Geriatr Psychiatry* 2016; **24**: 662–70.

146 Amariglio RE, Becker JA, Carmasin J, *et al.* Subjective cognitive complaints and amyloid burden in cognitively normal older individuals. *Neuropsychologia* 2012; **50**: 2880–6.

147 Zimprich D, Martin M, Kliegel M. Subjective cognitive complaints, memory performance, and depressive affect in old age: a change-oriented approach. *Int J Aging Hum Dev* 2003; **57**: 339–66.

148 Mitchell A, Beaumont H, Ferguson D, Yadegarfar M, Stubbs B. Risk of dementia and mild cognitive impairment in older people with subjective memory complaints: Meta-analysis. *Acta Psychiatr Scand* 2014; **130**: 439–51.

149 Kawagoe T, Onoda K, Yamaguchi S. Subjective memory complaints are associated with altered resting-state functional connectivity but not structural atrophy. *NeuroImage Clin* 2019; **21**:

101675.

150 Striepens N, Scheef L, Wind A, *et al.* Volume loss of the medial temporal lobe structures in subjective memory impairment. *Dement Geriatr Cogn Disord* 2010; **29**: 75–81.

151 Ché telat G, Villemagne VL, Bourgeat P, *et al.* Relationship between Atrophy and-Amyloid Deposition in Alzheimer Disease. 2010. DOI:10.1002/ana.21955.

152 Archer HA, MacFarlane F, Price S, *et al.* Do symptoms of memory impairment correspond to cognitive impairment: a cross sectional study of a clinical cohort. *Int J Geriatr Psychiatry* 2006; **21**: 1206–12.

153 Sahin S, Okluoglu Onal T, Cinar N, Bozdemir M, Cubuk R. Distinguishing Depressive Pseudodementia from Alzheimer Disease: A Comparative Study of Hippocampal Volumetry and Cognitive Tests. *Dement Geriatr Cogn Disord* 2017; **7**: 230–9.

154 Dolek N, Saylisoy S, Ozbabalik D, Adapinar B. Comparison of hippocampal volume measured using magnetic resonance imaging in Alzheimer's disease, vascular dementia, mild cognitive impairment and pseudodementia. *J Int Med Res* 2012; **40**: 717–25.

155 Garcia-Ptacek S, Cavallin L, Kåreholt I, *et al.* Subjective cognitive impairment subjects in our clinical practice. *Dement Geriatr Cogn Dis Extra* 2014; **4**: 419–30.

156 Jung N-Y, Seo SW, Yoo H, *et al.* Classifying anatomical subtypes of subjective memory impairment. *Neurobiol Aging* 2016; **48**: 53–60.

157 Kim M-J, Seo SW, Kim GH, *et al.* Less depressive symptoms are associated with smaller hippocampus in subjective memory impairment. *Arch Gerontol Geriatr* 2013; **57**: 110–5.

158 Haussmann R, Ganske S, Gruschwitz A, *et al.* Family history of Alzheimer's disease and subjective memory performance. *Am J Alzheimers Dis Other Demen* 2018; **33**: 458–62.

159 Perrotin A, La Joie R, de La Sayette V, *et al.* Subjective cognitive decline in cognitively normal elders from the community or from a memory clinic: Differential affective and imaging correlates. *Alzheimer's Dement* 2017; **13**: 550–60.

160 Van Der Flier WM, Van Buchem MA, Weverling-Rijnsburger AWE, *et al.* Memory complaints in patients with normal cognition are associated with smaller hippocampal volumes. *J Neurol* 2004; **251**: 671–5.

161 Pearlson GD, Rabins P V, Kim WS, *et al.* Structural brain CT changes and cognitive deficits in elderly depressives with and without reversible dementia ('pseudodementia'). *Psychol Med* 1989; **19**: 573–84.

162 Minett TSC, Dean JL, Firbank M, English P, O'Brien JT. Subjective memory complaints, white-matter lesions, depressive symptoms, and cognition in elderly patients. *Am J Geriatr Psychiatry* 2005; **13**: 665–71.

163 Kambe T, Yasuda A, Kinoshita S, Shigeta M, Kinoshita T. Severity of Depressive Symptoms and Volume of Superior Temporal Gyrus in People Who Visit a Memory Clinic Unaccompanied. *Dement Geriatr Cogn Dis Extra* 2018; **8**: 207–13.

164 Ferreira D, Falahati F, Linden C, *et al.* A 'Disease Severity Index' to identify individuals with Subjective Memory Decline who will progress to mild cognitive impairment or dementia. *Sci Rep* 2017; **7**: 2–12.

165 Rodda J, Dannhauser T, Cutinha DJ, Shergill SS, Walker Z. Subjective cognitive impairment:

Functional MRI during a divided attention task. *Eur Psychiatry* 2011; **26**: 457–62.

166 Hu X, Uhle F, Fliessbach K, *et al.* Reduced future-oriented decision making in individuals with subjective cognitive decline: A functional MRI study. *Alzheimer's Dement Diagnosis, Assess Dis Monit* 2017; **6**: 222–31.

167 Dolan RJ, Bench CJ, Brown RG, Scott LC, Friston KJ, Frackowiak RS. Regional cerebral blood flow abnormalities in depressed patients with cognitive impairment. *J Neurol Neurosurg Psychiatry* 1992; **55**: 768–73.

168 Gucuyener DO, Yenilmez C, Ayranci U, *et al.* An analysis of changes in cerebral blood flood velocities in depressive pseudo-dementia and Alzheimer disease patients. *Neurologist* 2010; **16**: 358–63.

169 Ritchie C, Smailagic N, Noel-Storr AH, *et al.* Plasma and cerebrospinal fluid amyloid beta for the diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). Cochrane Database Syst. Rev. 2014; **2014**. DOI:10.1002/14651858.CD008782.pub4.

170 Perrotin A, La Joie R, de La Sayette V, *et al.* Subjective cognitive decline in cognitively normal elders from the community or from a memory clinic: Differential affective and imaging correlates. *Alzheimer's Dement* 2017; **13**: 550–60.

171 Perrotin A, Mormino EC, Madison CM, Hayenga AO, Jagust WJ. Subjective Cognition and Amyloid Deposition Imaging. *Arch Neurol* 2012; **69**: 223.

172 Buckley R, Saling MM, Ames D, *et al.* Factors affecting subjective memory complaints in the AIBL aging study: biomarkers, memory, affect, and age. *Int psychogeriatrics* 2013; **25**: 1307.

173 Brenner RP, Reynolds CF. EEG findings in depressive pseudodementia and dementia with secondary depression. *Electroencephalogr Clin Neurophysiol* 1989; **72**: 298–304.

174 Hutton JT, Nagel JA, Loewenson RB. Eye tracking dysfunction in Alzheimer-type dementia. *Neurology* 1984; **34**: 99–102.

175 Gottlieb D, Wertman E, Bentin S. Passive listening and task related P300 measurement for the evaluation of dementia and pseudodementia. *Clin Electroencephalogr* 1991; **22**: 102–7.

176 Cespon J, Galdo-Alvarez S, Diaz F. Event-related potentials reveal altered executive control activity in healthy elderly with subjective memory complaints. *Front Hum Neurosci* 2018; **12**: 445.

177 Jessen F, Wiese B, Cvetanovska G, *et al.* Patterns of subjective memory impairment in the elderly: association with memory performance. *Psychol Med* 2007; **37**: 1753–62.

178 Ali JI, Smart CM, Gawryluk JR. Subjective cognitive decline and APOE 4: A systematic review. *J Alzheimer's Dis* 2018; **65**: 303–20.

179 Eckerstrom M, Berg AI, Nordlund A, *et al.* High Prevalence of Stress and Low Prevalence of Alzheimer Disease CSF Biomarkers in a Clinical Sample with Subjective Cognitive Impairment. *Dement Geriatr Cogn Disord* 2016; **42**: 93–105.

180 Sierra-Rio A, Balasa M, Olives J, *et al.* Cerebrospinal Fluid Biomarkers Predict Clinical Evolution in Patients with Subjective Cognitive Decline and Mild Cognitive Impairment. *Neurodegener Dis* 2016; **16**: 69–76.

181 Handels RLH, Joore MA, Vos SJB, *et al.* Added Prognostic Value of Cerebrospinal Fluid

Biomarkers in Predicting Decline in Memory Clinic Patients in a Prospective Cohort. *J Alzheimer's Dis* 2016; **52**: 875–85.

182 Smart CM, Krawitz A, C.M. S. The impact of subjective cognitive decline on Iowa Gambling Task performance. *Neuropsychology* 2015; **29**: 971–87.

183 Gainotti G, Marra C. Some aspects of memory disorders clearly distinguish dementia of the Alzheimer's type from depressive pseudo-dementia. *J Clin Exp Neuropsychol* 2008; **16**: 65–78.

184 Puetz J, Grohmann S, Metternich B, *et al.* Impaired memory consolidation during sleep in patients with functional memory disorder. *Biol Psychol* 2011; **86**: 31–8.

185 Svendsen AM, Kessing L V., Munkholm K, Vinberg M, Miskowiak KW. Is there an association between subjective and objective measures of cognitive function in patients with affective disorders? *Nord J Psychiatry* 2012; **66**: 248–53.

186 de Paula JJ, Miranda DM, Nicolato R, *et al.* Verbal learning on depressive pseudodementia: Accentuate impairment of free recall, moderate on learning processes, and spared short-term and recognition memory. *Arq Neuropsiquiatr* 2013; **71**: 596–9.

187 Lehrner J, Moser D, Klug S, *et al.* Subjective memory complaints, depressive symptoms and cognition in patients attending a memory outpatient clinic. *Int Psychogeriatrics* 2014; **26**: 463–73.

188 Wallert J, Westman E, Ulinder J, Annerstedt M, Terzis B. Differentiating patients at the memory clinic with simple reaction time variables: A predictive modeling approach using support vector machines and bayesian optimization. *Front Aging Neurosci* 2018; **10**: 144.

189 Benito-Leon J, Mitchell AJ, Vega S, Bermejo-Pareja F. A population-based study of cognitive function in older people with subjective memory complaints. *J Alzheimer's Dis* 2010; **22**: 159–70.

190 Wakefield SJ, Blackburn DJ, Harkness K, Khan A, Reuber M. Distinctive neuropsychological profiles differentiate patients with functional memory disorder from patients with amnestic-mild cognitive impairment. *Acta Neuropsychiatr* 2018; **30**: 90–6.

191 Jenkins A, Tree JJ, Thornton IM, Tales A. Subjective Cognitive Impairment in 55-65-Year-Old Adults Is Associated with Negative Affective Symptoms, Neuroticism, and Poor Quality of Life. *J Alzheimer's Dis* 2019; **67**: 1367–78.

192 Zlatar ZZ, Moore RC, Palmer BW, Thompson WK, Jeste D V. Cognitive complaints correlate with depression rather than concurrent objective cognitive impairment in the successful aging evaluation baseline sample. *J Geriatr Psychiatry Neurol* 2014; **27**: 181–7.

193 Chu C-S, Sun I-W, Begum A, *et al.* The association between subjective memory complaint and objective cognitive function in older people with previous major depression. *PLoS One* 2017; **12**: e0173027.

194 Schwert C, Stohrer M, Aschenbrenner S, Weisbrod M, Schroder A. Biased neurocognitive self-perception in depressive and in healthy persons. *J Affect Disord* 2018; **232**: 96–102.

195 Slot RER, Verfaillie SCJ, Overbeek JM, *et al.* Subjective Cognitive Impairment Cohort (SCIENCe): Study design and first results. *Alzheimer's Res Ther* 2018; **10**: 76.

196 Pearman A, Storandt M. Self-discipline and self-consciousness predict subjective memory in older adults. *J Gerontol Psychol Sci* 2005; **60**: P153–7.

197 Zandi T. Relationship between subjective memory complaints, objective memory performance, and depression among older adults. *Am J Alzheimers Dis Other Demen* 2004; **19**: 353–60.

198 Larrabee GJ, Levin HS. Memory self-ratings and objective test performance in a normal elderly sample. *J Clin Exp Neuropsychol* 1986; **8**: 275–84.

199 Sunderland A, Watts K, Baddeley AD, Harris JE. Subjective Memory Assessment and Test Performance in Elderly Adults. 1986.

200 McGlone J, Gupta S, Humphrey D, Oppenheimer S, Mirsen T, Evans DR. Screening for Early Dementia Using Memory Complaints From Patients and Relatives. *Arch Neurol* 1990; **47**: 1189–93.

201 Rabbitt P, Abson V. 'Lost and Found': Some logical and methodological limitations of self-report questionnaires as tools to study cognitive ageing. *Br J Psychol* 1990; **81**: 1–16.

202 Bolla KI, Lindgren KN, Bonaccorsy C, Bleecker ML. Memory Complaints in Older Adults. *Arch Neurol* 1991; **48**: 61.

203 Lehrner J, Moser D, Klug S, *et al.* Subjective memory complaints, depressive symptoms and cognition in Parkinson's disease patients. *Eur J Neurol* 2014; **21**: 1276-e77.

204 Christensen H. The validity of memory complaints by elderly persons. *Int J Geriatr Psychiatry* 1991; **6**: 307–12.

205 Crook TH, Feher EP, Larrabee GJ. Assessment of Memory Complaint in Age-Associated Memory Impairment: The MAC-Q. *Int Psychogeriotrics* 1992; **4**: 165–76.

206 Lucas MD. Neuropsychological evidence for subjective memory complaints in the neurologically well individual. *South African J Psychiatry* 2003; **9**: 29–32.

207 Steinberg SI, Negash S, Sammel MD, *et al.* Subjective memory complaints, cognitive performance, and psychological factors in healthy older adults. *Am J Alzheimers Dis Other Demen* 2013; **28**: 776–83.

208 Chin J, Oh KJ, Seo SW, Na DL. Are depressive symptomatology and self-focused attention associated with subjective memory impairment in older adults? *Int psychogeriatrics* 2014; **26**: 573–80.

209 Schofield PW, Jacobs D, Marder K, *et al.* The validity of new memory complaints in the elderly. *Arch Neurol* 1997; **54**: 756–9.

210 Bessi V, Mazzeo S, Padiglioni S, Piccini C, Nacmias B, Sorbi S. From Subjective Cognitive Decline to Alzheimer's Disease: The Predictive Role of Neuropsychological Assessment, Personality Traits, and Cognitive Reserve. A 7-Year Follow-Up Study. *J Alzheimer's Dis* 2018; **63**: 1523–35.

211 D. S, M. G, I. S, *et al.* Prediction of long-term (5 years) conversion to dementia using neuropsychological tests in a memory clinic setting. *J Alzheimer's Dis* 2013; **34**: 681–9.

212 Jansen WJ, Handels RLH, Visser PJ, *et al.* The Diagnostic and Prognostic Value of Neuropsychological Assessment in Memory Clinic Patients. *J Alzheimer's Dis* 2017; **55**: 679–89.

213 Rienstra A, Groot PFC, Spaan PEJ, *et al.* Symptom validity testing in memory clinics: Hippocampal-memory associations and relevance for diagnosing mild cognitive impairment. *J Clin Exp Neuropsychol* 2013; **35**: 59–70.

214 Lundholm Fors K, Fraser K, Kokkinakis D, K. LF, K. F. Automated Syntactic Analysis of Language

Abilities in Persons with Mild and Subjective Cognitive Impairment. *Stud Health Technol Inform* 2018; **247**: 705–9.

215 Reuber M, Blackburn DJ, Elsey C, *et al.* An Interactional Profile to Assist the Differential Diagnosis of Neurodegenerative and Functional Memory Disorders. *Alzheimer Dis Assoc Disord* 2018; **32**: 197–206.

216 Larner AJ. Screening utility of the 'attended alone' sign for subjective memory impairment. *Alzheimer Dis Assoc Disord* 2014; **28**: 364–5.

217 Soysal P, Usarel C, Ispirli G, Isik AT. Attended with and head-turning sign can be clinical markers of cognitive impairment in older adults. *Int Psychogeriatrics* 2017; **29**: 1763–9.

218 C. E, P. D, D. J, *et al.* Towards diagnostic conversational profiles of patients presenting with dementia or functional memory disorders to memory clinics. *Patient Educ Couns* 2015; **98**: 1071–7.

219 Jones D, Drew P, Elsey C, *et al.* Conversational assessment in memory clinic encounters: interactional profiling for differentiating dementia from functional memory disorders. *Aging Ment Health* 2016; **20**: 500–9.

220 Mirheidari B, Blackburn D, Harkness K, *et al.* Toward the Automation of Diagnostic Conversation Analysis in Patients with Memory Complaints. *J Alzheimers Dis* 2017; **58**: 373–87.

221 Alexander M, Blackburn D, Reuber M. Patients' accounts of memory lapses in interactions between neurologists and patients with functional memory disorders. *Sociol Heal Illn* 2018; **20**: 1–17.

222 Ahmed S, Mitchell J, Arnold R, Dawson K, Nestor PJ, Hodges JR. Memory complaints in mild cognitive impairment, worried well, and semantic dementia patients. *Alzheimer Dis Assoc Disord* 2008; **22**: 227–35.

223 Reynolds CF, Hoch CC, Kupfer DJ, *et al.* Bedside differentiation of depressive pseudodementia from dementia. *Am J Psychiatry* 1988; **145**: 1099–103.

224 Yousef G, Ryan WJ, Lambert T, Pitt B, Kellett J. A preliminary report: a new scale to identify the pseudodementia syndrome. *Int J Geriatr Psychiatry* 1998; **13**: 389–99.

225 Metternich B, Schmidtke K, Hüll M. How are memory complaints in functional memory disorder related to measures of affect, metamemory and cognition? *J Psychosom Res* 2009; **66**: 434–44.

226 Schmidtke K, Metternich B. Validation of two inventories for the diagnosis and monitoring of functional memory disorder. *J Psychosom Res* 2009; **67**: 245–51.

227 Mogle JA, Hill N, McDermott C. Subjective Memory in a National Sample: Predicting Psychological Well-Being. *Gerontology* 2017; **63**: 460–8.

228 Lineweaver TT, Bondi MW, Galasko D, Salmon DP. Effect of Knowledge of APOE Genotype on Subjective and Objective Memory Performance in Healthy Older Adults. 2014.

229 Barker A, Prior J, Jones R, A. B, J. P, R. J. Memory complaint in attenders at a self-referral memory clinic: The role of cognitive factors, affective symptoms and personality. *Int J Geriatr Psychiatry* 1995; **10**: 777–81.

230 Kahn RI, Zarit SH, Hilbert NM, Niederehe G. Memory complaint and impairment in the aged: The effect of depression and altered brain function. *Arch Gen Psychiatry* 1975; **32**: 1569–73.

231 Caine ED. Pseudodementia. Current concepts and future directions. *Arch Gen Psychiatry* 1981; **38**: 1359.

232 Crook TH, Larrabee GJ. A self-rating scale for evaluating memory in everyday life. *Psychol Aging* 1990; **5**: 48–57.

233 O'Connor DW, Pollitt PA, Roth M, Brook CPB, Reiss BB. Memory Complaints and Impairment in Normal, Depressed, and Demented Elderly Persons Identified in a Community Survey. *Arch Gen Psychiatry* 1990; **47**: 224.

234 Levy-Cushraan J, Abeles N. Memory complaints in the able elderly. *Clin Gerontol* 1998; **19**: 3–24.

235 Derouesne C, Lacomblez L, Thibault S, *et al.* Memory complaints in young and elderly subjects. *Int J Geriatr Psychiatry* 1999; **14**: 291–301.

236 Small GW, Chen ST, Komo S, *et al.* Memory self-appraisal and depressive symptoms in people at genetic risk for Alzheimer's disease. *Int J Geriatr Psychiatry* 2001; **16**: 1071–7.

237 Sinforiani E, Zucchella C, Pasotti C. Cognitive disturbances in non-demented subjects: heterogeneity of neuropsychological pictures. *Arch Gerontol Geriatr* 2007; **44 Suppl 1**: 375–80.

238 Mendes T, Ginó S, Ribeiro F, *et al.* Memory complaints in healthy young and elderly adults: Reliability of memory reporting. *Aging Ment Heal* 2008; **12**: 177–82.

239 Merema MR, Speelman CP, Foster JK, Kaczmarek EA. Neuroticism (not depressive symptoms) predicts memory complaints in some community-dwelling older adults. *Am J Geriatr Psychiatry* 2013; **21**: 729–36.

240 Apolinario D, Miranda RB, Suemoto CK, *et al.* Characterizing spontaneously reported cognitive complaints: The development and reliability of a classification instrument. *Int Psychogeriatrics* 2013; **25**: 157–66.

241 M. A, N. Z, S. E, *et al.* Correlates of memory complaints and personality, depression, and anxiety in a memory clinic. *Acta Med Iran* 2015; **53**: 270–5.

242 Kinzer A, Suhr JA. Dementia worry and its relationship to dementia exposure, psychological factors, and subjective memory concerns. *Appl Neuropsychol Adult* 2016; **23**: 196–204.

243 Rowell SF, Green JS, Teachman BA, *et al.* Age does not matter: Memory complaints are related to negative affect throughout adulthood. *Aging Ment Health* 2016; **20**: 1255–63.

244 A. V, L.C. S, B.B. A, *et al.* Differences in quantitative methods for measuring subjective cognitive decline - Results from a prospective memory clinic study. *Int Psychogeriatrics* 2016; **28**: 1513–20.

245 Reynolds CF, Kupfer DJ, Houck PR, *et al.* Reliable Discrimination of Elderly Depressed and Demented Patients by Electroencephalographic Sleep Data. *Arch Gen Psychiatry* 1988; **45**: 258.

246 Tandetnik C, Hergueta T, Bonnet P, Dubois B, Bungener C. Influence of early maladaptive schemas, depression, and anxiety on the intensity of self-reported cognitive complaint in older adults with subjective cognitive decline. *Int Psychogeriatrics* 2017; **29**: 1657–67.

247 T. H, K.J. R, E.-L. H, *et al.* Subjective memory complaints and personality traits in normal elderly subjects. *J Am Geriatr Soc* 1994; **42**: 1–4.

248 Hepple J. Conversion pseudodementia in older people: a descriptive case series. *Int J Geriatr*

Psychiatry 2004; **19**: 961–7.

249 Studer J, Donati A, Popp J, von Gunten A. Subjective cognitive decline in patients with mild cognitive impairment and healthy older adults: association with personality traits. *Geriatr Gerontol Int* 2014; **14**: 589–95.

250 Tomita T, Yasui-Furukori N, Sugawara N, Takahashi I, Sawada K. The association between the subjective memory complaints scale and depressive state and cognitive impairment: A factor analysis. *Neuropsychiatr Dis Treat* 2015; **11**: 2935–41.

251 Zlatar ZZ, Muniz MC, Espinoza SG, *et al.* Subjective cognitive decline, objective cognition, and depression in older Hispanics screened for memory impairment. *J Alzheimer's Dis* 2018; **63**: 949–56.

252 Clarnette RM, Almeida OP, Forstl H, Paton A, Martins RN. Clinical characteristics of individuals with subjective memory loss in Western Australia: results from a cross-sectional survey. *Int J Geriatr Psychiatry* 2001; **16**: 168–74.

253 Aarts S, van den Akker M, Hajema KJ, *et al.* Multimorbidity and its relation to subjective memory complaints in a large general population of older adults. *Int psychogeriatrics* 2011; **23**: 616–24.

254 Binnekade TT, Scherder EJA, Maier AB, *et al.* Pain in patients with different dementia subtypes, mild cognitive impairment, and subjective cognitive impairment. *Pain Med* 2018; **19**: 920–7.

255 Miley-Akerstedt A, Jelic V, Marklund K, *et al.* Lifestyle Factors Are Important Contributors to Subjective Memory Complaints among Patients without Objective Memory Impairment or Positive Neurochemical Biomarkers for Alzheimer's Disease. *Dement Geriatr Cogn Dis Extra* 2018; : 439–52.

256 Hill N, Mogle J, Kitko L, *et al.* Incongruence of subjective memory impairment ratings and the experience of memory problems in older adults without dementia: A mixed methods study. *Aging Ment Health* 2018; **22**: 978–85.

257 Hancock P, Larner AJ. Diagnostic utility of the Pittsburgh Sleep Quality Index in memory clinics. *Int J Geriatr Psychiatry* 2009; **24**: 1237–41.

258 Kang S-H, Yoon I-Y, Lee SD, *et al.* Subjective memory complaints in an elderly population with poor sleep quality. *Aging Ment Health* 2017; **21**: 532–6.

259 Gamaldo AA, Wright RS, Aiken-Morgan AT, Allaire JC, Thorpe RJ, Whitfield KE. The Association between Subjective Memory Complaints and Sleep within Older African American Adults. *J Gerontol B Psychol Sci Soc Sci* 2019; **74**: 202–11.

260 Cavuoto MG, Ong B, Pike KE, Nicholas CL, Bei B, Kinsella GJ. Better Objective Sleep Quality in Older Adults with High Subjective Memory Decline. *J Alzheimer's Dis* 2016; **53**: 943–53.

261 Gallassi R, Bisulli A, Oppi F, Poda R, Di Felice C. Subjective cognitive complaints, neuropsychological performance, affective and behavioural symptoms in non-demented patients. *Int J Geriatr Psychiatry* 2008; **23**: 95–101.

262 Mcpherson S, Rue L, Fitz A, *et al.* Self-Reports of Memory Problems in Relatives of Patients With Probable Alzheimer's Disease. *Int Psychogeriarics* 1995; **7**: 367–76.

263 Rue A La, Small G, McPherson S, Komo S, Matsuyama SS, Jarvik LF. Subjective memory loss in age-associated memory impairment: Family history and neuropsychological correlates. *Ageing,*

Neuropsychol Cogn 1996; **3**: 123.

264 Cutler SJ, Hodgson LG. Correlates of personal concerns about developing Alzheimer's Disease among middle-aged persons. *Am J Alzheimers Dis Other Demen* 2001; **16**: 335–43.

265 Jonkers C, Geerlings MI, Schmand B. Are memory complaints predictive for dementia?; A review of clinical and population-based studies. *Int J Geriatr PSYCHIATRY Int[J[Geriatr[Psychiatry 04*\ 2000; **872**. https://onlinelibrary.wiley.com/doi/pdf/10.1002/1099-1166(200011)15:11%3C983::AID-GPS238%3E3.0.CO;2-5 (accessed Sept 5, 2018).

266 Reisberg B, Gauthier S, B. R. Current evidence for subjective cognitive impairment (SCI) as the pre-mild cognitive impairment (MCI) stage of subsequently manifest Alzheimer's disease. *Int Psychogeriatrics* 2008; **20**: 1–16.

267 Mitchell AJ, Shiri-Feshki M. Rate of progression of mild cognitive impairment to dementia - Meta-analysis of 41 robust inception cohort studies. *Acta Psychiatr Scand* 2009; **119**: 252–65.

268 Ritchie C, Smailagic N, Noel-Storr AH, Ukoumunne O, Ladds EC, Martin S. CSF tau and the CSF tau/ABeta ratio for the diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). Cochrane Database Syst. Rev. 2017; **2017**. DOI:10.1002/14651858.CD010803.pub2.

269 McShane R, Noel-Storr A, Ritchie C. The quality and extent of evidence for biomarkers: A cochrane systematic review. *Alzheimer's Dement* 2011; **7**: S100–1.

270 Morbelli S, Garibotto V, Van De Giessen E, *et al.* A Cochrane review on brain [18F]FDG PET in dementia: limitations and future perspectives. Eur. J. Nucl. Med. Mol. Imaging. 2015; **42**: 1487–91.

271 Zhang S, Smailagic N, Hyde C, *et al.* 11C-PIB-PET for the early diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). Cochrane Database Syst. Rev. 2014; **2014**. DOI:10.1002/14651858.CD010386.pub2.

272 Wissel BD, Dwivedi AK, Merola A, *et al.* Functional neurological disorders in Parkinson disease. *J Neurol Neurosurg Psychiatry* 2018; **89**: 566–71.

273 Reid LM, Maclullich AMJ. Subjective memory complaints and cognitive impairment in older people. *Dement Geriatr Cogn Disord* 2006; **22**: 471–85.

274 Hill NL, Mogle J, Wion R, *et al.* Subjective Cognitive Impairment and Affective Symptoms: A Systematic Review. 2016. DOI:10.1093/geront/gnw091.

275 Griem J, Stone J, Carson A, *et al.* Psychologic/functional forms of memory disorder. In: M H, J S, Carson A, eds. Functional Neurologic Disorders, Volume 139 of the Handbook of Clinical Neurology series. Amsterdam: Elsevier, 2016: 407–17.

276 Mitchell AJ. Is it time to separate subjective cognitive complaints from the diagnosis of mild cognitive impairment? *Age Ageing* 2008; **37**: 497–9.

277 Blackburn DJ, Wakefield S, Shanks MF, Harkness K, Reuber M, Venneri A. Memory difficulties are not always a sign of incipient dementia: a review of the possible causes of loss of memory efficiency. *Br Med Bull* 2014; **112**: 71–81.

278 Stone J, Mutch J, Giannokous D, Hoeritzauer I, Carson A. Hurst revisited: Are symptoms and signs of functional motor and sensory disorders "dependent on idea"? *J Neurol Sci* 2017; **381**: 188–91.

279 Nasreddine ZS, Phillips NA, Bedirian V, *et al.* The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment. *J Am Geriatr Soc* 2005; **53**: 695–9.

280 Moo LR, Slotnick SD, Tesoro MA, Zee DS, Hart J. Interlocking finger test: a bedside screen for parietal lobe dysfunction. *J Neurol Neurosurg Psychiatry* 2003; **74**: 530–2.

281 Elamin M, Bennett G, Symonds A, *et al.* Introducing a brief screening a tool for motor signs in patients with dementia. *Neurology* 2015; **84**.

282 Bak TH. Why patients with dementia need a motor examination. *J Neurol Neurosurg Psychiatry* 2016; **87**: 1157.

283 Ahmed S, Baker I, Thompson S. Utility of testing for apraxia and associated features in dementia. *J Neurol Neurosurg Psychiatry* 2016; **87**: 1158–62.

284 Kapur N. The coin-in-the-hand test: a new 'bed-side' test for the detection of malingering in patients with suspected memory disorder. *J Neurol Neurosurg Psychiatry* 1994; **57**: 385–6.

285 Van den Bergh O, Witthöft M, Petersen S, Brown RJ. Symptoms and the body: Taking the inferential leap. *Neuoscience Biobehav Rev* 2017; **74**: 185–203.

286 Hurst AF. The psychology of the special senses and their functional disorders, 1st edn. London: Frowde, Hodder & Stoughton, 1920.

287 Rossetti HC, Lacritz LH, Hynan LS, Cullum CM, Van Wright A, Weiner MF. Montreal Cognitive Assessment Performance among Community-Dwelling African Americans. *Arch Clin Neuropsychol* 2017; **32**: 238–44.

288 Malek-Ahmadi M, Powell JJ, Belden CM, Evans L, Coon DW, Nieri W. Age-and education-adjusted normative data for the Montreal Cognitive Assessment (MoCA) in older adults age 70-99. *Aging, Neuropsychol Cogn* 2015; **22**: 755–61.

289 Borland E, Nägga K, Nilsson PM, Minthon L, Nilsson ED, Palmqvist S. The Montreal Cognitive Assessment: Normative Data from a Large Swedish Population-Based Cohort. *J Alzheimer's Dis* 2017; **59**: 893–901.

290 Julayanont P, Phillips N, Chertkow H, Nasreddine ZS. Montreal Cognitive Assessment (MoCA): Concept and clinical review. In: Larner AJ, ed. Cognitive screening instruments: A practical approach. Springer, 2017: 139–95.

291 Anderson EW, Trethowan WH, Kenna JC. An experimental investigation of simulation and pseudo-dementia. *Acta Psychiatr Neurol* 1959; **34**, **Suppl.**: 42.

292 Haines ME, Norris MP. Comparing Student and Patient Simulated Malingerers Performance on Standard Neuropsychological Measures to Detect Feigned Cognitive Deficits. *Clin Neuropsychol* 2001; **15**: 171–82.

293 Wilson RS, Sytsma J, Barnes LL, Boyle PA. Anosognosia in Dementia. *Curr Neurol Neurosci Rep* 2016; **16**: 77.

294 Rossetti HC, Lacritz LH, Cullum CM, Weiner MF. Normative data for the Montreal Cognitive Assessment (MoCA) in a population-based sample. *Neurology* 2011; **77**: 1272–5.

295 Rudman N, Oyebode JR, Jones CA, Bentham P. An investigation into the validity of effort tests in a working age dementia population. *Aging Ment Health* 2011; **15**: 47–57.

296 Iverson GL, Tulsky DS. Detecting malingering on the WAIS-III: Unusual Digit Span performance

patterns in the normal population and in clinical groups. *Arch Clin Neuropsychol* 2003; **18**: 1–9.

297 Carlesimo G, Fadd L, Lorusso S, Caltagirone C. Verbal and spatial memory spans in Alzheimer's and multi-infarct dementia. *Acta Neurol Scand* 1994; **89**: 132–8.

298 Butters N, Cermak LS. Alcoholic Korsakoff's Syndrome : an Information-Processing Approach to Amnesia. New York: Academic Press, 1980.

299 Greiffenstein MF, Baker WJ, Gola T. Validation of Malingered Amnesia Measures With a Large Clinical Sample. *Psychol Assess* 1994; **6**: 218–24.

300 Mathias CW, Greve KW, Bianchini KJ, Houston RJ, Crouch JA. Dysfunction Using the Reliable Digit Span in Traumatic Brain Injury. *Assessment* 2002; **9**: 301–8.

301 Larrabee GJ. Detection of Malingering Using Atypical Performance Patterns on Standard Neuropsychological Tests. *Clin Neuropsychol* 2003; **17**: 410–25.

302 Williamson J, Larner A. Attended with and head-turning sign can be clinical markers of cognitive impairment in older adults. *Int Psychogeriatrics* 2018; **20**: 1569–1569.

303 Blackburn D, Wakefield S, Bell S, Harkness K, Venneri A, Reuber M. Functional memory disorder; review from a memory clinic. In: Journal of Neurology, Neurosurgery and Psychiatry. D. Blackburn, Sheffield Teaching Hospitals NHS Foundation Trust, United Kingdom: BMJ Publishing Group, 2014: A8.

304 Commissaris CJAM, Ponds RWHM, Jolles J. Subjective forgetfulness in a normal Dutch population: possibilities for health education and other interventions. *Patient Educ Couns* 1998; **34**: 25–32.

305 Jessen F, Amariglio RE, Buckley RF, *et al.* The characterisation of subjective cognitive decline. Lancet Neurol. 2020; **19**: 271–8.

306 McWhirter L, Ritchie C, Stone J, Carson A. Functional cognitive disorders: a systematic review. *The Lancet Psychiatry* 2020; **7**: 191–207.

307 Purser JL, Fillenbaum GG, Wallace RB. Memory complaint is not necessary for diagnosis of mild cognitive impairment and does not predict 10-year trajectories of functional disability, word recall, or short portable mental status questionnaire limitations. *J Am Geriatr Soc* 2006; **54**: 335–8.

308 Ball H, McWhirter L, Ballard C, *et al.* Functional cognitive disorder: dementia's blind spot. *Brain* 2020; **143**: 2895–903.

309 Jónsdóttir MK, Adólfsdóttir S, Cortez RD, Gunnarsdóttir M, Gústafsdóttir ÁH. A diary study of action slips in healthy individuals. *Clin Neuropsychol* 2007; **21**: 875–83.

310 McCaffrey RJ, Bauer L, O'Bryant SE, Palav AA. Practitioner's Guide to Symptom Base Rates in the General Population. New York: Springer Science & Business Media, 2006.

311 Grant I, Atkinson JH, Hesselink JR, *et al.* Evidence for early central nervous system involvement in the acquired immunodeficiency syndrome (AIDS) and other human immunodeficiency virus (HIV) infections. Studies with neuropsychologic testing and magnetic resonance imaging. *Ann Intern Med* 1987; **107**: 828–36.

312 Demallie D, Cottler L, Compton W. Alcohol abuse and dependence: consistency in reporting of symptoms over ten years. *Addiction* 1995; **90**: 615–25.

313 Schmidt IW, Berg & Betto IJ, Deelman GG. Illusory Superiority in Self-Reported Memory of Older Adults. *Neuropsychol Cogn* 1999; **6**: 288–301.

314 Bauer L, Mccaffrey RJ. Coverage of the Test of Memory Malingering, Victoria Symptom Validity Test, and Word Memory Test on the Internet: Is test security threatened? *Arch Clin Neuropsychol* 2006; **21**: 121–6.

315 Larrabee GJ. Assessment of malingering. In: Forensic neuropsychology: A scientific approach. New York: Oxford University Press, 2012: 116–59.

316 Bigler ED. Symptom validity testing, effort, and neuropsychological assessment. J. Int. Neuropsychol. Soc. 2012; **18**: 632–42.

317 Davis JJ, Millis SR. Examination of performance validity test failure in relation to number of tests administered. *Clin Neuropsychol* 2014; **28**: 199–214.

318 Moher D, Liberati A, Tetzlaff J, *et al.* Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med. 2009; **6**. DOI:10.1371/journal.pmed.1000097.

319 Green P, Flaro L. Results From Three Performance Validity Tests (PVTs) in Adults With Intellectual Deficits. *Appl Neuropsychol Adult* 2015; **22**: 293–303.

320 Goldberg JO, Miller HHR. Performance of psychiatric inpatients and intellectually deficient individuals on a task that assesses the validity of memory complaints. *J Clin Psychol* 1986; **42**: 792–5.

321 Loring DW, Goldstein FC, Chen C, *et al.* False-Positive Error Rates for Reliable Digit Span and Auditory Verbal Learning Test Performance Validity Measures in Amnestic Mild Cognitive Impairment and Early Alzheimer Disease. *Arch Clin Neuropsychol* 2016; **31**: 313–31.

322 Fazio RL, Faris AN, Yamout KZ. Use of the Rey 15-Item Test as a performance validity test in an elderly population. *Appl Neuropsychol Adult* 2019; **26**: 28–35.

323 Davis JJ. Performance validity in older adults: Observed versus predicted false positive rates in relation to number of tests administered. *J Clin Exp Neuropsychol* 2018; **40**: 1013–21.

324 Green P, Montijo J, Brockhaus R. High specificity of the Word Memory Test and Medical Symptom Validity Test in groups with severe verbal memory impairment. *Appl Neuropsychol* 2011; **18**: 86–94.

325 Zenisek R, Millis SR, Banks SJ, Miller JB. Prevalence of below-criterion Reliable Digit Span scores in a clinical sample of older adults. *Arch Clin Neuropsychol* 2016; **31**: 426–33.

326 Iverson GL, Le Page J, Koehler BE, Shojania K, Badii M. Test of Memory Malingering (TOMM) scores are not affected by chronic pain or depression in patients with fibromyalgia. *Clin Neuropsychol* 2007; **21**: 532–46.

327 Bar-On Kalfon T, Gal G, Shorer R, Ablin JN. Cognitive functioning in fibromyalgia: The central role of effort. *J Psychosom Res* 2016; **87**: 30–6.

328 Cragar DE, Berry DTR, Fakhoury TA, Cibula JE, Schmitt FA. Performance of Patients with Epilepsy or Psychogenic Non-Epileptic Seizures on Four Measures of Effort. *Clin Neuropsychol* 2006; **20**: 552–66.

329 Hill S, Ryan L, Kennedy C, Malamut B. The relationship between measures of declarative memory and the test of memory malingering in patients with and without temporal lobe dysfunction. *J Forensic Neuropsychol* 2003; **3**: 1–18.

330 Tyson B, Baker S, Greenacre M, *et al.* Differentiating epilepsy from psychogenic nonepileptic seizures using neuropsychological test data. *Epilepsy Behav* 2018; **87**: 39–45.

331 Drane DL, Williamson DJ, Stroup ES, *et al.* Cognitive impairment is not equal in patients with epileptic and psychogenic nonepileptic seizures. *Epilepsia* 2006; **47**: 1879–86.

332 Hoskins LL, Binder LM, Chaytor NS, Williamson DJ, Drane DL. Comparison of oral and computerized versions of the word memory test. *Arch Clin Neuropsychol* 2010; **25**: 591–600.

333 Van Der Werf S, Prins J, Jongen P, Van Der Meer J, Bleijenberg G. Abnormal neuropsychological findings are not necessarily a sign of cerebral impairment. A matched comparison between chronic fatigue syndrome and multiple sclerosis. *Neuropsychiatry, Neuropsychol Behav Neurol* 2000; **13**: 199–203.

334 Roor JJ, Knoop H, Dandachi-FitzGerald B, Peters MJ V, Bleijenberg G, Ponds RWHM. Feedback on underperformance in patients with chronic fatigue syndrome: The impact on subsequent neuropsychological test performance. *Appl Neuropsychol Adult* 2018; **27**: 188–96.

335 Erdodi L, Roth R. Low scores on BDAE Complex Ideational Material are associated with invalid performance in adults without aphasia. *Appl Neuropsychol Adult* 2017; **24**: 264–74.

336 Maiman M, Del Bene VA, MacAllister WS, *et al.* Reliable digit span: Does it adequately measure suboptimal effort in an adult epilepsy population? *Arch Clin Neuropsychol* 2019; **34**: 259–67.

337 Hampson NE, Kemp S, Coughlan AK, Moulin CJA, Bhakta BB. Effort test performance in clinical acute brain injury, community brain injury, and epilepsy populations. *Appl Neuropsychol Adult* 2014; **21**: 183–94.

338 Novitski J, Steele S, Karantzoulis S, Randolph C. The Repeatable Battery for the Assessment of Neuropsychological Status Effort scale. *Arch Clin Neuropsychol* 2012; **27**: 190–5.

339 Sherer M, Davis L, Sander A, *et al.* Factors Associated with Word Memory Test Performance in Persons with Medically Documented Traumatic Brain Injury. *Clin Neuropsychol* 2015; **29**: 522–41.

340 Wu TC, Allen MD, Goodrich-Hunsaker NJ, Hopkins RO, Bigler ED. Functional neuroimaging of symptom validity testing in traumatic brain injury. *Psychol Inj Law* 2010; **3**: 50–62.

341 Macciocchi SN, Seel RT, Alderson A, Godsall R. Victoria Symptom Validity Test performance in acute severe traumatic brain injury: implications for test interpretation. *Arch Clin Neuropsychol* 2006; **21**: 395–404.

342 Macciocchi SN, Seel RT, Yi A, Small S. Medical Symptom Validity Test Performance Following Moderate-Severe Traumatic Brain Injury: Expectations Based on Orientation Log Classification. *Arch Clin Neuropsychol* 2017; **32**: 339–48.

343 Erdodi LA, Abeare CA, Lichtenstein JD, *et al.* Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV) processing speed scores as measures of noncredible responding: The third generation of embedded performance validity indicators. *Psychol Assess* 2017; **29**: 148–57.

344 Bodner T, Merten T, Benke T. Performance validity measures in clinical patients with aphasia. *J Clin Exp Neuropsychol* 2019; **41**: 476–83.

345 Goodrich-Hunsaker NJ, Hopkins RO. Word memory test performance in amnesic patients with hippocampal damage. *Neuropsychology* 2009; **23**: 529–34.

346 Carone DA, Green P, Drane DL. Word memory test profiles in two cases with surgical removal

of the left anterior hippocampus and parahippocampal gyrus. *Appl Neuropsychol Adult* 2014; **21**: 155–60.

347 Oudman E, Krooshof E, van Oort R, Lloyd B, Wijnia JW, Postma A. Effects of korsakoff amnesia on performance and symptom validity testing. *Appl Neuropsychol Adult* 2019. DOI:http://dx.doi.org/10.1080/23279095.2019.1576180.

348 Howe LLS, Anderson AM, Kaufman DAS, Sachs BC, Loring DW. Characterization of the Medical Symptom Validity Test in evaluation of clinically referred memory disorders clinic patients. *Arch Clin Neuropsychol* 2007; **22**: 753–61.

349 Merten T, Bossink L, Schmand B. On the limits of effort testing: Symptom validity tests and severity of neurocognitive symptoms in nonlitigant patients. *J Clin Exp Neuropsychol* 2007; **29**: 308–18.

350 Singhal A, Green P, Shankar K, Gill D. High specificity of the Medical Symptom Validity Test in patients with very severe memory impairment. *Arch Clin Neuropsychol* 2009; **24**: 721–8.

351 Wodushek TR, Domen CH. Comparing two models of performance validity assessment in patients with parkinson's disease who are candidates for deep brain stimulation surgery. *Appl Neuropsychol Adult* 2018; **27**: 9–21.

352 Rossetti MA, Collins RL, York MK. Performance Validity in Deep Brain Stimulation Candidates. *Arch Clin Neuropsychol* 2018; **33**: 508–14.

353 Gorissen M, Sanz JC, Schmand B. Effort and cognition in schizophrenia patients. *Schizophr Res* 2005; **78**: 199–208.

354 Schroeder RW, Marshall PS. Evaluation of the appropriateness of multiple symptom validity indices in psychotic and non-psychotic psychiatric populations. *Clin Neuropsychol* 2011; **25**: 437–53.

355 Whearty K, Allen C, Lee B, Strauss G. The evaluation of insufficient cognitive effort in schizophrenia in light of low IQ scores. *J Psychiatr Res* 2015; **68**: 397–404.

356 Lee A, Boone K, Lesser I, Wohl M, Wilkins S, Parks C. Performance of older depressed patients on two cognitive malingering tests: False positive rates for the Rey 15-item memorization and Dot Counting Tests. *Clin Neuropsychol* 2000; **14**: 303–8.

357 Rees LML, Tombaugh TN, Boulay L. Depression and the Test of Memory Malingering. *Arch Clin Neuropsychol* 2001; **16**: 501–6.

358 Dandachi-FitzGerald B, Ponds RWHM, Peters MJ V, Merckelbach H. Cognitive underperformance and symptom over-reporting in a mixed psychiatric sample. *Clin Neuropsychol* 2011; **25**: 812–28.

359 Price K, Desantis S, Simpson A, *et al.* The impact of clinical and demographic variables on cognitive performance in methamphetamine-dependent individuals in rural South Carolina. *Am J Addict* 2011; **20**: 447–55.

360 Heintz CEJ, van Tricht MJ, van der Salm SMA, *et al.* Neuropsychological profile of psychogenic jerky movement disorders: importance of evaluating non-credible cognitive performance and psychopathology. *J Neurol Neurosurg Psychiatry* 2013; **84**: 862–7.

361 Janssen MAM, Bertens D, Kessels L, Kessels RPC, Koopmans PP. A case-control pilot study on cognitive functioning, symptom validity and psychological wellbeing in HIV-1-infected patients

in the Netherlands. *Int J STD AIDS* 2013; **24**: 387–91.

362 Paul R, Rhee G, Baker LM, Vaida F, Cooley SA, Ances BM. Effort and neuropsychological performance in HIV-infected individuals on stable combination antiretroviral therapy. *J Neurovirol* 2017; **23**: 725–33.

363 Dorociak K, Schulze E, Piper L, Molokie R, JK J. Performance validity testing in a clinical sample of adults with sickle cell disease. *Clin Neuropsychol* 2018; **32**: 81–97.

364 Slick DJ, Sherman EMS, Iverson GL. Diagnostic Criteria for Malingered Neurocognitive Dysfunction: Proposed Standards for Clinical Practice and Research. *Clin Neuropsychol* 1999; **13**: 545–61.

365 Dandachi-FitzGerald B, Ponds RWHM, Merten T. Symptom Validity and Neuropsychological Assessment: A Survey of Practices and Beliefs of Neuropsychologists in Six European Countries. *Arch Clin Neuropsychol* 2013; **28**: 771–83.

366 British Psychological Society. Assessment of Effort in Clinical Testing of Cognitive Functioning For Adults. Leicester, 2009 https://www.sheffield.ac.uk/polopoly_fs/1.793680!/file/ASW_11and12Jun8_BPS_EffortTestingGuidelines.pdf (accessed Sept 27, 2019).

367 Heilbronner RL, Sweet JJ, Morgan JE, *et al.* American Academy of Clinical Neuropsychology Consensus Conference Statement on the Neuropsychological Assessment of Effort, Response Bias, and Malingering. *Clin Neuropsychol (Neuropsychology, Dev Cogn Sect D)* 2009; **23**: 1093–129.

368 Green P. The Pervasive Influence of Effort on Neuropsychological Tests. Phys. Med. Rehabil. Clin. N. Am. 2007; **18**: 43–68.

369 Bhome R, McWilliams A, Huntley JD, Fleming SM, Howard RJ. Metacognition in functional cognitive disorder- a potential mechanism and treatment target. *Cogn Neuropsychiatry* 2019; **24**: 311–21.

370 McKhann GM, Knopman DS, Chertkow H, *et al.* The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* 2011; **7**: 263–9.

371 Green P. Medical Symptom Validity Test (MSVT) for microsoft windows: User's manual. 2004.

372 Troyer AK, Rich JB. Multifactorial Memory Questionnaire. Toronto: Baycrest, 2018 www.baycrest.org (accessed April 26, 2021).

373 Fraser KC, Meltzer JA, Rudzicz F. Linguistic features identify Alzheimer's disease in narrative speech. *J Alzheimer's Dis* 2015; **49**: 407–22.

374 Diniz BS, Butters MA, Albert SM, Dew MA, Reynolds CF. Late-life depression and risk of vascular dementia and Alzheimer's disease: Systematic review and meta-analysis of community-based cohort studies. Br. J. Psychiatry. 2013; **202**: 329–35.

375 Becker E, Lorena C, Rios O, *et al.* Anxiety as a risk factor of Alzheimer's disease and vascular dementia. *Br J Psychiatry* 2018; **213**: 654–60.

376 Edwards MJ, Adams RA, Brown H, Pareés I, Friston KJ. A Bayesian account of 'hysteria'. *Brain* 2012; **135**: 3495–512.

377 Bhome R, McWilliams A, Price G, *et al.* Metacognition in Functional Cognitive Disorder. *medRxiv* 2021; : 2021.06.24.21259245.

Appendix

The five appended papers were completed and published during the term of the PhD. Some are specifically relevant to functional cognitive disorders; the others to functional neurological disorders more broadly. Here I explain the relevance of each project, and my contribution:

Ball H, McWhirter L, Ballard C, Bhome R, Blackburn D, Edwards M, Fleming S, Fox N, Howard R, Huntley J, Isaacs JD, Larner AJ, Nicholson TR, Pennington CM, Poole N, Price G, Price JP, Reuber M, Ritchie C, Rossor MN, Schott JM, Teodoro T, Venneri A, Stone J, Carson A Functional cognitive disorder: dementia's blind spot. Brain. 2020 October; 142(10):2895-2903

My initial systematic review ('Functional cognitive disorder – a systematic review') identified that variation in terminology and diagnostic criteria was an important obstacle to FCD. The aim of this following multi-author paper was to bring together researchers from both functional disorder and dementia research arenas in order to establish, by consensus, a set of working diagnostic criteria for use in clinical practice and research.

I contributed equally alongside first author Harriet Ball and senior author Alan Carson in generating the concept for this paper, and collaborated on the early revisions of the manuscript. The process of working on this paper provided good opportunities for professional networking, and specifically allowed co-authors less familiar with the FCD concept to see common ground and advantages in the prospect of improved recognition of FCD.

McWhirter L, Miller N, Campbell C, Hoeritzauer I, Lawton A, Carson A, Stone J. Understanding foreign accent syndrome. Journal of Neurology, Neurosurgery & Psychiatry. 2019 Nov 1;90(11):1265-9.

This paper describes the unusual clinical presentation of Foreign Accent Syndrome (FAS) – new onset of a 'foreign' accent – which was previously largely attributed to brain injury or disease. This has a cognitive component – often including abnormalities of language – and people with this symptom commonly also have cognitive complaints. We surveyed, and in some cases collected audio samples of voice, from people who self-identified as having FAS. We analysed the data (in collaboration with Professor Nick Miller, speech pathologist at Newcastle University) and found that many of the cases in this study were most likely to represent functional disorders. We were able to outline some key positive features suggesting the internal inconsistency supporting a functional diagnosis.

I collaborated on study conceptualisation, I designed and distributed the survey, analysed the survey data, and wrote the initial drafts of the manuscript, which underwent review and revisions collaboratively with all authors. This was a great experience of collaboration with the speech language pathology profession. We were able to identify from this work that there was a lot of variation in experience and confidence in speech language therapists with regards to assessment and treatment of functional speech and communication disorders. This work encouraged us to proceed to the subsequent development of consensus recommendations in this area.

Baker J, Barnett C, Cavalli L, Dixon L, Dietrich M, Duffy JR, Elias A, Fraser DE, Freeburn JL, Gregory C, McKenzie K, Miller N, Patterson J, Roth C, Roy N, Short J, Utianski RL, van Mersbergen M, Vertigan A, Carson A, Stone J, McWhirter L. Management of Functional Communication, Swallowing, Cough, and Related Disorders: Consensus Recommendations for Speech and Language Therapy. (Prepared for submission for publication)

This is a set of consensus recommendations for the assessment and management of speech and communication disorders, which may overlap with functional cognitive symptoms. The target audience is speech and language professionals who may not have experience and confidence in managing functional neurological disorders. The 'short version' is attached; our intention is that a full version, which is comprehensive and detailed, will be available online to readers of the target journal.

As senior author, I collaborated equally with Jon Stone, Alan Carson on the concept and with Jan Baker on the initial concept, plan, and selection of co-authors. I substantially led initial and subsequent versions of the manuscript. I managed the adapted Delphi process through a system of online survey and email responses to drafts, ensuring that all co-authors views were represented. This was a positive experience of international collaboration with a large number of authors.

McWhirter L, Hoeritzauer I, Carson A, Stone J.(2020). Functional neurological disorder and personal injury. Journal of Personal Injury Law, Vol. 2, pp. 115-126

and

van Gils A, Stone J, Welch K, Davidson LR, Kerslake D, Caesar D, McWhirter L, Carson A. Management of mild traumatic brain injury. Practical neurology. 2020 May 1;20(3):213-21.

These papers are general reviews of aspects of functional neurological disorders written for readers who do not necessarily have specific interest or expertise in FND. These have all been positive experiences and open opportunities for discussion and collaboration outside of this small research field. Most importantly it is hoped that continuing to put effort into papers like this, alongside original research, might improve the quality of treatment available to the many people with FND (or mild TBI) who are unable to access specialist services.

I planned and wrote the Journal of Personal Injury Law paper, the other authors providing comments and contributing to subsequent revisions. I contributed a section on management of cognitive symptoms and later substantially revised an early draft of the Management of mild traumatic brain injury paper to enable resubmission and acceptance for publication.

doi:10.1093/brain/awaa224 BRAIN 2020: 143; 2895–2903 | 2895

BRAIN
A JOURNAL OF NEUROLOGY

UPDATE

Functional cognitive disorder: dementia's blind spot

Harriet A. Ball,[1] Laura McWhirter,[2] Clive Ballard,[3] Rohan Bhome,[4] Daniel J. Blackburn,[5] Mark J. Edwards,[6] Stephen M. Fleming,[7] Nick C. Fox,[8] Robert Howard,[4] Jonathan Huntley,[4] Jeremy D. Isaacs,[6,9] Andrew J. Larner,[10] Timothy R. Nicholson,[11] Catherine M. Pennington,[2] Norman Poole,[9] Gary Price,[12] Jason P. Price,[13] Markus Reuber,[5] Craig Ritchie,[2] Martin N. Rossor,[8] Jonathan M. Schott,[8] Tiago Teodoro,[6,14] Annalena Venneri,[5] Jon Stone[2] and Alan J. Carson[2]

An increasing proportion of cognitive difficulties are recognized to have a functional cause, the chief clinical indicator of which is internal inconsistency. When these symptoms are impairing or distressing, and not better explained by other disorders, this can be conceptualized as a cognitive variant of functional neurological disorder, termed functional cognitive disorder (FCD). FCD is likely very common in clinical practice but may be under-diagnosed. Clinicians in many settings make liberal use of the descriptive term mild cognitive impairment (MCI) for those with cognitive difficulties not impairing enough to qualify as dementia. However, MCI is an aetiology-neutral description, which therefore includes patients with a wide range of underlying causes. Consequently, a proportion of MCI cases are due to non-neurodegenerative processes, including FCD. Indeed, significant numbers of patients diagnosed with MCI do not 'convert' to dementia. The lack of diagnostic specificity for MCI 'non-progressors' is a weakness inherent in framing MCI primarily within a deterministic neurodegenerative pathway. It is recognized that depression, anxiety and behavioural changes can represent a prodrome to neurodegeneration; empirical data are required to explore whether the same might hold for subsets of individuals with FCD. Clinicians and researchers can improve study efficacy and patient outcomes by viewing MCI as a descriptive term with a wide differential diagnosis, including potentially reversible components such as FCD. We present a preliminary definition of functional neurological disorder–cognitive subtype, explain its position in relation to other cognitive diagnoses and emerging biomarkers, highlight clinical features that can lead to positive diagnosis (as opposed to a diagnosis of exclusion), and red flags that should prompt consideration of alternative diagnoses. In the research setting, positive identifiers of FCD will enhance our recognition of individuals who are not in a neurodegenerative prodrome, while greater use of this diagnosis in clinical practice will facilitate personalized interventions.

1 Population Health Sciences, University of Bristol, BS8 1QU, UK
2 Centre for Clinical Brain Sciences, The University of Edinburgh, EH16 4SB, UK
3 College of Medicine and Health, University of Exeter, EX1 2LU, UK
4 Division of Psychiatry, University College London, W1T 7NF, UK
5 Department of Neuroscience, Medical School, The University of Sheffield, S10 2TN, UK
6 Neuroscience Research Centre, St George's, University of London, SW17 0RE, UK
7 Wellcome Centre for Human Neuroimaging, University College London, WC1N 3AR, UK
8 Dementia Research Centre, Department of Neurodegenerative Diseases, UCL Queen Square Institute of Neurology, WC1E 6BT, UK
9 Department of Neurology, St George's University Hospitals NHS Foundation Trust, London, SW17 0QT, UK
10 Cognitive Function Clinic, Walton Centre for Neurology and Neurosurgery, Liverpool, L9 7LJ, UK
11 Institute of Psychiatry Psychology and Neuroscience, King's College London, SE5 8AF, UK
12 University College London Hospitals NHS Foundation Trust, NW1 2BU, UK
13 Department of Neuropsychology, South Tees Hospitals NHS Foundation Trust, TS4 3BW, UK
14 Instituto de Medicina Molecular, Universidade de Lisbon, 1649-028 Lisboa, Portugal

Received January 27, 2020. Revised May 06, 2020. Accepted May 21, 2020. Advance access publication August 13, 2020

Correspondence to: Harriet A. Ball
Learning and Research, Southmead Hospital, Bristol, BS10 5NB, UK
E-mail: harriet.ball@bristol.ac.uk

Keywords: cognition; dementia; functional cognitive disorder; functional neurological disorder; mild cognitive impairment

Abbreviations: FCD = functional cognitive disorder; FND = functional neurological disorder; MCI = mild cognitive impairment; SCD = subjective cognitive decline

Overlapping definitions

Functional cognitive disorder (FCD) refers to complaints of persistent problematic cognitive difficulties, when accompanied by positive features termed 'internal inconsistency' (Box 1), and which are not better explained by another disorder e.g. a neurodegenerative disease process (Box 2). This is relevant to all clinicians to whom such patients present, including in general practice, gerontology, neurology, psychiatry and others. FCD is likely common but is rarely diagnosed, perhaps in part because such patients usually concurrently meet descriptive criteria for either mild cognitive impairment (MCI), or subjective cognitive decline (SCD). MCI is a syndrome involving objective cognitive decline greater than expected for age that does not interfere with activities of daily life (Albert *et al.*, 2011). SCD describes subjective concern regarding decline in cognitive abilities without evidence of objective cognitive deficit (Howard, 2020; Jessen *et al.*, 2020). Conceptually, both SCD and MCI are heterogeneous concepts and include subjects with a variety of underlying causes (Blackburn *et al.*, 2014), including neurodegenerative diseases, medical or psychiatric diagnoses, medication and alcohol or other recreational drug effects, and FCD (Fig. 1A). However, in practice, the majority of research involving MCI and/or SCD has been predicated on a linear progression from SCD through MCI to dementia, which is problematic if most of these patients do not in fact have underlying neurodegenerative disease.

Box 1 Internal inconsistency

Internal inconsistency is the ability to perform a task well at certain times, but with significantly impaired ability at other times, particularly when the task is the focus of attention. Therefore, the individual components required to execute the task are intact, but there is difficulty engaging them at the appropriate intensity or duration on demand. We also considered whether a patient's tendency to give 'approximate answers' should be used as an example of internal inconsistency. This may reflect differences in automatic versus explicit processing. This is not the same as simple fluctuation over time, which can be observed in many other processes (such as delirium, Lewy body disease, etc.). Finally, internal inconsistency needs to be demonstrated within a particular cognitive domain. Do not superficially take a cognitive screen summary score in the normal or mild range, plus a patient with significant day-to-day impairment, to conclude this is FCD (rather, this should be a starting point for exploring the particular cause of the day-to-day impairment).

Positive evidence of cognitive internal inconsistency can be demonstrated through any of the following:

(i) Where subjectively-reported cognitive difficulties, and/or low standardized cognitive test scores, directly contrast with:
  (a) Conversational abilities observed during interview (Alexander *et al.*, 2019).
  (b) Reported activities, such as being involved in a cognitively demanding occupation; or difficulties only occurring in particular situations.
  (c) Collateral history suggesting concern is significantly higher in the individual than their supporter (including the 'attended alone' sign) (Bharambe and Larner, 2018*b*).

(ii) Specific patterns within neuropsychological testing that indicate cognitive processes performing better when accessed less explicitly, e.g. greater ability in delayed recall than initial registration of information.

Where examples such as the above are elicited, part of the diagnostic process should include pointing them out to the patient, and explaining that they demonstrate a temporary block to accessing memories, rather than a persistent memory defect.
Research is ongoing to investigate whether impaired meta-cognition (the ability to reflect on and monitor cognitive processes) may contribute to cognitive internal inconsistency (Bhome *et al.*, 2019*b*).
We also considered whether a patient's tendency to give 'approximate answers' should be used as an example of internal inconsistency. This tendency, the so-called Ganser syndrome, is poorly characterized in the literature, and care should be taken over what counts as an 'approximate' versus a 'wrong' answer. The key focus should be on a patient demonstrating normal and abnormal performance on the same cognitive ability, without there being other mitigating factors that intervene (e.g. fluctuations in consciousness, psychiatric state, or a significant headache).

Biomarkers that predict Alzheimer's pathology in particular, or neurodegeneration more generally (including but not limited to MRI and PET, genetics, and blood or CSF measurement of amyloid, tau and neurofilament) are already finding utility in clinical trials and are increasingly used in clinical practice. However, while biomarkers may provide evidence for or against a diagnosis of Alzheimer's disease, a positive diagnosis of FCD on clinical grounds has a number of potentially important complementary roles. First, patients with FCD are likely to benefit from distinct strategies to help with their symptoms. Second, having FCD may prove to be an important exclusion criterion for clinical trials, or may need to be taken into account when interpreting the results of trials targeting Alzheimer's pathology to reduce heterogeneity. Third, since a dual diagnosis of FCD and cognitive impairment secondary to Alzheimer's pathology is entirely possible (indeed such dual diagnoses are common in other areas of neurology), optimal treatment strategies may need to focus both on FCD and Alzheimer's pathology. And finally, as we move to diagnosing patients ever earlier, communicating biomarker results may precipitate FCD in individuals who would otherwise not have manifest symptoms for some time.

Patients with FCD are increasingly prevalent in tertiary memory clinics (comprising 12–56% of new referrals) (Elsey *et al.*, 2015; Pennington *et al.*, 2015*a*; Bharambe and Larner, 2018*a*; Wakefield *et al.*, 2018; Bhome *et al.*, 2019*a*; Pennington *et al.*, 2019). Different case definitions may explain how some FCD case series score predominantly normally on objective cognitive testing, whereas others underperform or demonstrate inconsistencies in some areas of objective testing. Note that symptoms in FCD are not feigned. Where tested, patients with functional disorders do not consistently fail tests of performance validity or 'effort', but may display impaired selective attention (Teodoro *et al.*, 2018). We encounter many patients who pass performance validity testing but score >2 standard deviations below normal on standardized cognitive testing (i.e. falling into the FCD/MCI overlap area on Fig. 1A). Population-based

Box 2 Diagnostic criteria for functional neurological disorder: cognitive subtype

(i) One or more symptoms of impaired cognitive function.

(ii) Clinical evidence of internal inconsistency[a].

(iii) Symptoms or deficit that are not better explained by another medical or psychiatric disorder[b].

(iv) Symptoms or deficit that cause clinically significant distress or impairment[c] in social, occupational, or other important areas of functioning, or warrants medical evaluation.

[a]Box 1.

[b]Patients may have co-morbid medical or psychiatric disorders as well as FCD.

[c]To aid reliability for neurodegenerative research purposes, a minimum of 6 months duration should be considered (refer to text).

Specify if: with/without a linked co-morbidity (refer to text).

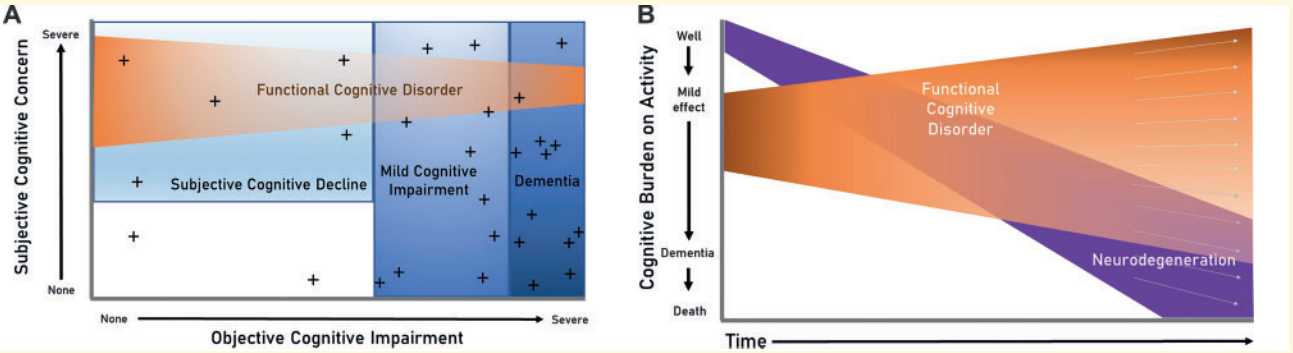


Figure 1 How FCD relates to other cognitive concepts. (**A**) Where FCD fits in relation to other key terminology used in the cognitive clinic. 'Objective cognitive impairment' denotes low scores on standardized testing. 'Subjective cognitive concern' denotes an individual's perception of their cognitive difficulties (note some patients with MCI and dementia lack insight). Patients with FCD account for a proportion of those with MCI, and a proportion of those with SCD; rarely, those with FCD can meet criteria for dementia (i.e. severe enough to interfere with daily function and independence). Crosses represent biomarkers for neurodegenerative conditions. Biomarkers are clustered most densely among patients with dementia; a small number of true positive biomarkers also exist in the healthy population with neither subjective concerns nor objective impairment (indicating neurodegenerative tendency that has not yet manifested), and some will be false positives because a biomarker with 100% specificity seems unlikely (see McWhirter *et al.*, 2020 for further discussion). (**B**) Trajectories in FCD (adapted from McWhirter *et al.*, 2020). This illustrates the wide spectrum of potential trajectories within FCD, highlighting that some patients have considerable persisting symptoms and impairment even after serial testing, whereas others return to baseline functioning. The causes of these divergent trajectories may be explicable via co-morbidities or external factors, but often no such factors are identified. Disentangling this heterogeneity is an important area for future research. The *x*-axis represents each lifetime; those who remain above the *x*-axis to the end of their lifetime have died from other causes.

identification of MCI cases may over-recruit individuals with FCD, as they may be younger, more aware of research opportunities and more open to recruitment efforts.

De-emphasizing the inevitable expectation of progression to Alzheimer's dementia

Understanding the prodromal phase of dementia is clearly of great importance for elucidation of causal mechanisms and development of novel interventions for Alzheimer's pathology. However, a substantial proportion of individuals with MCI will later return to normal cognitive function, or maintain stable cognition, rather than showing progressive deterioration. Neuropathological analyses of cohorts who met MCI criteria before death show they are intermediate between those with normal cognition and those with dementia (Stephan *et al.*, 2012). In highlighting such associations, few reports focus on the substantial proportion of individuals with MCI whose brains are histologically normal (Schneider *et al.*, 2009; Abner *et al.*, 2017). It is also difficult to define a clear boundary between age-normative neuropathological changes and the burden of neurodegeneration that is required for cognitive impairment (Ferrer, 2012). There are many reasons why autopsy studies might miss very early neurodegeneration, such as subtle or not-yet-understood pathologies, varying degrees of immunohistochemical analysis and regional brain sampling (Nelson *et al.*, 2012). Regardless, these factors do not fully explain the phenomenon of MCI in the presence of minimal or no brain pathology. In addition, many individuals with demonstrable neuropathological changes associated with Alzheimer's disease identified after death did not experience cognitive symptoms in life (Latimer *et al.*, 2017), raising the possibility that only a proportion of the cognitive symptoms experienced by those with neuropathology, might be caused by that pathology.

There is clearly a biological trajectory in Alzheimer's disease, with the clinical syndrome usually preceded by an MCI phase (Jack *et al.*, 2010). However, it is important not to extrapolate this backwards to assume that all or most subjects with MCI are on this trajectory *en route* to dementia, because this downplays the importance of other (including FCD) explanations for MCI. Many studies emphasize 'conversion' to dementia (e.g. annualized conversion rates of MCI to dementia), which implies a deterministic relationship between MCI and Alzheimer's dementia (as well as implying an abrupt step-change). Biomarkers are increasingly being used to identify risk of clinical progression on an individual basis (van Maurik *et al.*, 2019) but are, as yet, imperfect and not always available; and in general there tends to be less focus on the causes of cognitive symptoms in those who do not progress to dementia. A population-based analysis that tracked these changes over 7 years, found that 53% remained as MCI cases, while 35% reverted to normal cognition (Ganguli *et al.*, 2019). A default assumption that neurodegeneration underlies MCI may be reinforced amongst clinicians and researchers who frequently interact with subject affected by established dementia (i.e. subjects who have passed through MCI as part of a neurodegenerative trajectory). In the wider population however, and especially in older subjects, other non-neurodegenerative aetiologies and multifactorial processes are likely to contribute significantly (Petersen *et al.*, 2014). Figure 1B (adapted from McWhirter *et al.*, 2020) illustrates how heterogeneous trajectories in FCD can account for some of the abovementioned discrepancy. Assumptions of progression may also contribute to widespread public anxiety regarding the inevitability of dementia.

Diagnosis and aetiology of functional cognitive disorder

Typical clinical presentations of FCD most commonly focus around memory impairment (often alongside attention and concentration difficulties), often in the form of 'memory perfectionism' and mnestic block (Pennington *et al.*, 2015*b*). FCD less often involves non-amnestic cognitive functions such as praxis, language, or executive function. Current data suggest the typical age at onset of FCD is mid-life (therefore overlapping with early-onset neurodegeneration) (Pennington *et al.*, 2015*a*; Bharambe and Larner, 2018*a*; Wakefield *et al.*, 2018), but this may in part reflect the composition of specialist clinics, with referral patterns influenced by the increased likelihood of neurodegeneration in older ages. As with people in the prodromal stage of neurodegenerative dementia, those with FCD are often understandably anxious about their symptoms, are able to discuss their difficulties and coping strategies, and can display mild but persistent deficits (including those seen on objective standardized cognitive tests, or as observed by others in the general course of life), with few other clinical signs.

FCD definitions still lack consensus, hindering our understanding of prevalence particularly in community settings (Stone *et al.*, 2015), and hindering wider understanding and acceptance of the diagnosis. Diagnostic difficulty around FCD exists for several reasons. First, the presence of mnestic concern, and the cognitive trajectory over the short term, may look similar across FCD and early neurodegeneration. Second, there is frequently co-occurrence of functional cognitive symptoms alongside some combination of neurodegeneration, general medical, psychiatric or surgical problems, or drug toxicity. In this context, the functional symptoms may be secondary, in the form of a 'functional overlay', although in the clinic setting it is often difficult to differentiate this from the background cognitive symptoms due to identified co-morbidities (including substances used). Unfortunately, this distinction is not aided by research

studies that often exclude people with mental health conditions, despite their being very common in memory clinic. Third, FCD symptoms often persist over time (Schmidtke *et al.*, 2008), so for example will still feature in MCI studies that check for the persistence of symptoms. Longer-term outcomes of FCD have not been thoroughly studied, although the default assumption should be that affected individuals have the same chance of later developing neurodegeneration as the background population (without such an occurrence indicating a 'missed' earlier diagnosis of neurodegeneration). However, this does require empirical testing, because in certain contexts FCD could arise as a prodrome to neurodegeneration (as has been found with certain presentations of late life anxiety, depression and mild behavioural impairment) (Livingston *et al.*, 2017; Creese *et al.*, 2019). These difficulties, and the recent entry of FCD into the cognitive diagnostic lexicon, likely explain why FCD is rarely diagnosed, despite its likely frequency, given the high prevalence of other functional neurological conditions (Carson and Lehn, 2016).

In addition to under-diagnosis due to diagnostic difficulty, some clinicians will be using other terms for the same condition in different settings (Blackburn *et al.*, 2014; Bailey *et al.*, 2017). Also, some clinicians may be avoiding naming the condition at all, or fall back on classifying the patient as either SCD or MCI (which are descriptive rather than aetiological categories). Some practitioners use the term 'worried well', presumably as a means of identifying a group of individuals whose symptoms are not due to underlying neurodegeneration. This is unsatisfactory to patients, who are generally not reassured when told their symptoms have no underlying pathological basis, but aren't offered an alternative explanation. It also hinders efforts to positively identify a distinct group. The situation is improving with diagnostic systems e.g. Diagnostic and Statistical Manual, 5th edition (DSM-5) (American Psychiatric Association, 2013), recently switching to emphasize positive criteria for diagnosis rather than identifying functional neurological disorder (FND) solely by the absence of neurological, psychiatric or other general medical explanatory causes.

Here, we propose an operational definition for FCD (Box 2), which we hope will enable clearer communication in the clinical setting, and standardization for research purposes. This definition is in line with the DSM-5 definition of FND. The key to diagnosing FCD is identifying positive evidence of internal inconsistency (Box 1). However, we have also included a list of mimics (Box 3)—situations with a flavour of internal inconsistency but that should prompt consideration of alternative diagnoses. We recognize this is a changing field; these criteria represent a work in progress.

It is important to note that DSM-5 FND includes only sensory and motor (not cognitive) phenotypes. We envisage FCD as the equivalent cognitive phenotype (and we would recommend DSM to consider this in their next revision). Placing FCD within the broader FND umbrella recognizes the phenotypic overlap across functional disorders, which includes similarities in neurocognitive profiles (Teodoro *et al.*, 2018). Thus the 'cognitive fog' often described by patients with functional movement disorder or dissociative seizures can be conceptualized as part of the same broad condition. Although our mechanistic understanding of FND is incomplete, it is notable that neurobiological models of FND make no distinction between the mechanism of different symptom types. Motor, sensory, cognitive and interoceptive symptoms can all conceivably arise from the same basic malfunction proposed to occur in FND, which is entirely consistent with the common co-occurrence of multiple functional symptoms in the same individual (Edwards *et al.*, 2012; Van den Bergh *et al.*, 2017).

We also feel DSM's 'associated features supporting diagnosis' for FND generally apply to FCD in particular, namely: a history of multiple somatic symptoms; stress or trauma at onset; and dissociative symptoms (though none of these features are necessary for diagnosis, and absence should not lead to the diagnosis being withheld). Finally, we also feel it is helpful to include a specifier for presence or absence of any co-morbidity that is linked to the cognitive symptoms. A non-exhaustive list includes health anxiety, mild traumatic brain injury (mTBI), depression, fibromyalgia or Alzheimer's pathology. Such co-morbidities can influence the way people with FCD present, and the types of interventions they might respond to. As an illustration, systematic reviews have suggested that whilst mTBI is sometimes accompanied by temporary effects on attention, processing speed and memory, there is evidence of good recovery beyond the initial weeks and months (Carroll *et al.*, 2014; Cassidy *et al.*, 2014). This makes it possible that many of the self-reported symptoms outside this time frame may have a functional disorder aetiology. The situation is often clarified by the clinician's reassessment of the reported severity of the head injury and surrounding circumstances; a cognitive behavioural therapy framework is often helpful to understand how expectations may drive behavioural responses to the injury (van Gils *et al.*, 2020). An operational definition of FCD provides the opportunity for the TBI field to quantify the prevalence of a functional component to cognitive symptomatology.

In cognitive clinics, patients with FCD are typically encountered following symptom duration of at least 6 months. However, there is no clear need to wait for this duration before making an FCD diagnosis if positive indicators are present. Recent-onset cases may be harder to diagnose than persistent cases, and this would alter the differential diagnosis. It would also be important to avoid over-diagnosis of short-lived forgetting that is within the normal human experience. However, substantial clinical benefit could be gained from making and communicating an FCD diagnosis early, rather than subjecting the patient to prolonged diagnostic limbo.

Substantial heterogeneity in severity can be seen within FCD, as illustrated in Fig. 1A and B. Depending on the level of associated impairment, FCD cases may often additionally meet the definition of one of SCD, MCI or dementia. However, these purely descriptive classifications should be used with great caution (regardless of suspected underlying aetiology). This is because they have come to be associated

Box 3 Red flags to prompt consideration of diagnoses other than functional cognitive disorder (and why)

FCD is common and most clinicians who interact with patients with cognitive difficulties should be confident at identifying it. It is important not to medicalize normal human experience, for example where cognitive concerns are found in the absence of objective deficit, and where this is not associated with distress nor impairment. The following are some features that should prompt consideration of certain differential diagnoses.

(i) Internal inconsistency needs to be demonstrated within a particular cognitive domain. This is because certain other disorders of mind or brain can allow normal performance on simple testing, while disrupting daily activities that require subtly different cognitive domains.
   (a) Greater difficulty understanding single words than the superficially more complex task of whole sentence comprehension (this is a feature of semantic dementia).
   (b) Difficulties pertaining primarily to visual comprehension [posterior cortical atrophy can produce difficulties that mimic internal inconsistency, including the reverse size phenomenon, and perception of moving versus static objects (Crutch *et al.*, 2012)].
   (c) Apathy or low mood can also cause discrepancy between real-world behaviour and reported deficits (for example in depression or frontal meningioma). For example, in response to 'Where did you go on holiday' receiving a sparse response such as 'Provence' without the patient being able to move from this to spontaneously generate more specific information; yet he can, on direct questioning, recall specific events once these are mentioned by his wife.
   (d) Intact implicit memory with defective conscious memory, can occur in conditions such as Korsakoff's psychosis.
   (e) Difficulties greater on recognition than on recall, may be a consequence of damage to perirhinal or parahippocampal areas (Eichenbaum *et al.*, 2007).
   (f) Difficulty in real-world executive functioning out of proportion to superficial pencil-and-paper testing, can be a feature of dorsolateral prefrontal damage.

(ii) Long term temporal pattern: Absence of decline, or fluctuation over months or years. Such a pattern indicates incongruity with neurodegeneration, but by itself is not a positive identifier for FCD, since other processes could cause this.
   (a) Variability day-to-day should lead to consideration of conditions such as obstructive sleep apnoea, delirium or Lewy body disease (if other appropriate features are present). Typically patients with these conditions would not display normal and abnormal performance on similar tasks within a single consultation.
   (b) Sudden onset and persistence should lead to consideration of stroke syndromes. Semantic access dyslexia is a left-hemisphere stroke syndrome that typically causes inconsistency in identifying the same semantic stimulus presented multiple times (this is distinct from semantic dementia, in which the semantic concepts are consistently non-retrievable) (Mirman and Britt, 2014).

(iii) Finally, have a higher suspicion for neurodegeneration if the presentation is non-mnestic, particularly since early-onset Alzheimer's disease has relatively more non-mnestic presentations (Koedam *et al.*, 2010).

with progressive neuropathology; if, however, the cognitive presentation is being driven by a functional disorder, then greater impairment does not have the same implications regarding irreversible progression. The adoption of a definition for FCD opens the door to testing whether an 'FCD subtype of MCI' would contribute to sample stratification in biomarker or intervention studies, and also aid communication of likely outcome and potential treatment.

A diagnosis of FCD would be excluded if another condition better accounted for the symptoms, such as cognitive symptoms that occur as part of a depressive episode, sometimes termed 'depressive pseudo-dementia'. The temporal relationship, severity of depression, and the pattern of impairments can inform this distinction. Note that cognitive symptoms may not resolve on depressive episode resolution (Rock *et al.*, 2014). Of patients referred to a tertiary neuropsychiatry clinic, half of those meeting FCD criteria had comorbid depression (and therefore half did not) (Bhome *et al.*, 2019*a*). In addition, subthreshold generalized anxiety disorder, dysthymia, and obsessive-compulsive personality traits are commonly noted and appear to be aetiologically relevant in many cases. We hope that our definition can enable research to better quantify rates and relevance of comorbidities and other external factors, in FCD and in comparison to those in other groups (such as healthy controls, and those with early neurodegeneration). Patients with functional disorders often find themselves falling between different specialties, and individual clinicians often feel they are not best placed to offer management. We consider that clinicians working in all specialties that diagnose cognitive disorders should have the skills to recognize FCD, and can play an important part in its management (Carson *et al.*, 2016). Heterogeneity within FCD means that some patients may be relatively straightforward to identify, and management should begin with an explanation of the symptoms and giving a positive diagnosis; others may require referral tailored to unravelling a diagnostic challenge; and others may be best managed within a mental health model.

We also considered whether FCD could fit within DSM-5's somatic symptom disorder (SSD). However, SSD does not actually capture elements of FCD that we feel are integral (i.e. internal inconsistency), so does nothing to aetiologically disentangle FCD from prodromal Alzheimer's disease (which can involve similar levels of anxiety). SSD also does not account for those with FCD without a significant anxiety component.

Better appreciation of functional cognitive disorder would enhance outcomes across the cognitive field

Research is ongoing to identify positive features in clinical assessment that point to a functional cognitive diagnosis (for a review see McWhirter *et al.*, 2020). When found, it is usually helpful to transparently discuss these internal inconsistencies and their implications with the patient (Stone and Edwards, 2012). These features can also be used to form testable hypotheses. For example, we could predict that among individuals with cognitive symptoms, those displaying internal inconsistency would be: (i) more likely to respond to certain treatments (e.g. treatments to modify metacognition); (ii) more likely to remain stable or improve their cognitive scores, and less likely to eventually develop dementia; and (iii) less likely to have biomarkers of Alzheimer's or global neurodegeneration.

It may actually be easier to identify those who meet criteria for FCD, than those who have underlying Alzheimer's pathology, due to the limited access and imperfect precision of current Alzheimer's biomarkers. In other words, neurodegeneration clinical trial candidates should not just meet SCD or MCI criteria, but also lack the positive features of functional cognitive conditions, in order to enhance power to detect effective Alzheimer's disease modifiers. On the other hand, to understand processes and efficacy at the population level, particularly in the older age bracket, it may be more appropriate to use dimensional scales (rather than exclusions) to quantify the separate effects of co-morbidities, drug toxicity, psychological and lifestyle factors, and FCD.

Improving our identification of key characteristics of FCD, and the many often interwoven aetiologies behind MCI, should simultaneously improve identification of those who are in the prodromal stage of neurodegeneration. Doing so requires thorough assessment of other likely aetiological contributors, as well as examining patterns of 'reversion' as well as 'conversion'. This could provide greater signal relative to noise, both in understanding biological processes of neurodegeneration, and in testing interventions. Establishing FCD as an essential axis in cognitive assessment will help us to better understand, and ultimately modify, the causes of cognitive impairment, and to determine who will and who will not develop dementia.

Funding

H.A.B. is funded by a National Institute for Health Research (NIHR) Clinical Lectureship. R.B. is supported by a NIHR Academic Clinical Fellowship. D.J.B. is funded by Alzheimer's Research UK & Rosetrees. D.J.B., M.R. and A.V. acknowledge the support of the National Institute for Health Research Sheffield Biomedical Research Centre (Translational Neuroscience). M.J.E. is funded by NIHR and the Medical Research Council. S.M.F. is funded by the Wellcome Trust & the Royal Society. J.H. is funded by a Wellcome Clinical Research Career Development Fellowship. R.H., N.C.F., J.M.S. and M.N.R. acknowledge the support of the National Institute for Health Research University College London Hospitals Biomedical Research Centre. L.M. receives philanthropic funding from Baillie Gifford. T.R.N. is funded by an NIHR Clinician Scientist Award. C.P. is funded by the Innovative Medicines Initiative, BRACE, and the David Telling Charitable Trust. J.S. is supported by a National Research Scotland Career Researcher Fellowship. This publication presents independent research; the views expressed are those of the authors and not necessarily those of the specified funding bodies.

Competing interests

A.J.C. runs a not for profit website www.headinjurysymptoms.org, is a paid associate editor of JNNP, is unpaid treasurer of the functional neurological disorders society, and gives independent testimony in court on a range of topics including functional cognitive disorders. J.D.I. received an honorarium for an advisory board for Biogen on treatments for Alzheimer's disease, has received conference expenses from Roche and has been Principal Investigator on clinical trials in Alzheimer's disease funded by Roche, Merck and Lupin Pharmaceuticals. L.M. provides independent medical testimony in court cases regarding patients with functional disorders. M.R. has received speaker's fees from UCB Pharma, Eisai and LivaNova, and benefitted from an educational grant from UCB Pharma; he receives payments from Elsevier as Editor-in-Chief of Seizure, and authorship fees for book publications from Oxford University Press. J.S. reports independent expert testimony work for personal injury and medical negligence claims, royalties from UpToDate for articles on functional neurological disorder, is unpaid secretary of the Functional Neurological Disorder Society and runs a free non-profit self-help website for FND, www.neurosymptoms.org. A.V. has received consulting fees and travel support from Biogen and Merck.

References

Abner EL, Kryscio RJ, Schmitt FA, Fardo DW, Moga DC, Ighodaro ET, et al. Outcomes after diagnosis of mild cognitive impairment in a large autopsy series. Ann Neurol 2017; 81: 549–59.

Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011; 7: 270–9.

Alexander M, Blackburn D, Reuber M. Patients' accounts of memory lapses in interactions between neurologists and patients with functional memory disorders. Sociol Health Illn 2019; 41: 249–65.

American Psychiatric Association. Somatic Symptom and Related Disorders. Diagnostic and statistical manual of mental disorders (DSM-5). 5th edn. Washington, DC: American Psychiatric Publishing; 2013.

Bailey C, Bell SM, Blackburn DM. How the UK describes functional memory symptoms. Psychogeriatrics 2017; 17: 336–7.

Bharambe V, Larner AJ. Functional cognitive disorders: demographic and clinical features contribute to a positive diagnosis. Neurodegener Dis Manag 2018a; 8: 377–83.

Bharambe V, Larner AJ. Functional cognitive disorders: memory clinic study. Prog Neurol Psychiatry 2018b; 22: 19–22.

Bhome R, Huntley JD, Price G, Howard RJ. Clinical presentation and neuropsychological profiles of Functional Cognitive Disorder patients with and without co-morbid depression. Cogn Neuropsychiatry 2019a; 24: 152–64.

Bhome R, Mcwilliams A, Huntley JD, Fleming SM, Howard RJ. Metacognition in functional cognitive disorder- a potential mechanism and treatment target. Cogn Neuropsychiatry 2019b; 24: 311–21.

Bhome R, McWilliams A, Huntley JD, Fleming SM, Howard RJ. Metacognition in functional cognitive disorder- a potential mechanism and treatment target. Cogn Neuropsychiatry 2019b; 24: 311–21.

Blackburn DJ, Wakefield S, Shanks MF, Harkness K, Reuber M, Venneri A. Memory difficulties are not always a sign of incipient dementia: a review of the possible causes of loss of memory efficiency. Br Med Bull 2014; 112: 71–81.

Carroll LJ, Cassidy JD, Cancelliere C, Cote P, Hincapie CA, Kristman VL, et al. Systematic review of the prognosis after mild traumatic brain injury in adults: cognitive, psychiatric, and mortality outcomes: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. Arch Phys Med Rehabil 2014; 95 (3Suppl): S152–73.

Carson A, Hallett M, Stone J. Assessment of patients with functional neurologic disorders. Handb Clin Neurol 2016; 139: 169–88.

Carson A, Lehn A. Epidemiology Handb Clin Neurol 2016; 139: 47–60.

Cassidy JD, Cancelliere C, Carroll LJ, Cote P, Hincapie CA, Holm LW, et al. Systematic review of self-reported prognosis in adults after mild traumatic brain injury: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. Arch Phys Med Rehabil 2014; 95: Suppl): S132–51.

Creese B, Brooker H, Ismail Z, Wesnes KA, Hampshire A, Khan Z, et al. Mild Behavioral Impairment as a Marker of Cognitive Decline in Cognitively Normal Older Adults. The American journal of geriatric psychiatry: official journal of the American Association for. Geriatric Psychiatry 2019; 27: 823–34.

Crutch SJ, Lehmann M, Schott JM, Rabinovici GD, Rossor MN, Fox NC. Posterior cortical atrophy. Lancet Neurol 2012; 11: 170–8.

Edwards MJ, Adams RA, Brown H, Parees I, Friston KJ. A Bayesian account of 'hysteria'. Brain 2012; 135: 3495–512.

Eichenbaum H, Yonelinas AP, Ranganath C. The medial temporal lobe and recognition memory. Annu Rev Neurosci 2007; 30: 123–52.

Elsey C, Drew P, Jones D, Blackburn D, Wakefield S, Harkness K, et al. Towards diagnostic conversational profiles of patients presenting with dementia or functional memory disorders to memory clinics. Patient Educ Couns 2015; 98: 1071–7.

Ferrer I. Defining Alzheimer as a common age-related neurodegenerative process not inevitably leading to dementia. Prog Neurobiol 2012; 97: 38–51.

Ganguli M, Jia Y, Hughes TF, Snitz BE, Chang C-C, Berman SB, et al. Mild cognitive impairment that does not progress to dementia: a population-based study. J Am Geriatr Soc 2019; 67: 232–8.

Howard R. Subjective cognitive decline: what is it good for? Lancet Neurol 2020; 19: 203–4.

Jack CR Jr, Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 2010; 9: 119–28.

Jessen F, Amariglio RE, Buckley RF, van der Flier WM, Han Y, Molinuevo JL, et al. The characterisation of subjective cognitive decline. Lancet Neurol 2020; 19: 271–8.

Koedam EL, Lauffer V, van der Vlies AE, van der Flier WM, Scheltens P, Pijnenburg YA. Early versus late-onset Alzheimer's disease: more than age alone. J Alzheimers Dis 2010; 19: 1401–8.

Latimer CS, Keene CD, Flanagan ME, Hemmy LS, Lim KO, White LR, et al. Resistance to Alzheimer disease neuropathologic changes and apparent cognitive resilience in the nun and Honolulu-Asia aging studies. J Neuropathol Exp Neurol 2017; 76: 458–66.

Livingston G, Sommerlad A, Orgeta V, Costafreda SG, Huntley J, Ames D, et al. Dementia prevention, intervention, and care. Lancet 2017; 390: 2673–734.

McWhirter L, Ritchie C, Stone J, Carson A. Functional cognitive disorders: a systematic review. Lancet Psychiatry 2020; 7: P191–207.

Mirman D, Britt AE. What we talk about when we talk about access deficits. Phil Trans R Soc B 2014; 369: 20120388.

Nelson PT, Alafuzoff I, Bigio EH, Bouras C, Braak H, Cairns NJ, et al. Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature. J Neuropathol Exp Neurol 2012; 71: 362–81.

Pennington C, Ball H, Swirski M. Functional cognitive disorder: diagnostic challenges and future directions. Diagnostics (Basel) 2019; 9.

Pennington C, Hayre A, Newson M, Coulthard E. Functional cognitive disorder: a common cause of subjective cognitive symptoms. J Alzheimers Dis 2015a; 48: S19–S24.

Pennington C, Newson M, Hayre A, Coulthard E. Functional cognitive disorder: what is it and what to do about it? Pract Neurol 2015b; 15: 436–44.

Petersen RC, Caracciolo B, Brayne C, Gauthier S, Jelic V, Fratiglioni L. Mild cognitive impairment: a concept in evolution. J Intern Med 2014; 275: 214–28.

Rock PL, Roiser JP, Riedel WJ, Blackwell AD. Cognitive impairment in depression: a systematic review and meta-analysis. Psychol Med 2014; 44: 2029–40.

Schmidtke K, Pohlmann S, Metternich B. The syndrome of functional memory disorder: definition, etiology, and natural course. Am J Geriatr Psychiatry 2008; 16: 981–8.

Schneider JA, Arvanitakis Z, Leurgans SE, Bennett DA. The neuropathology of probable Alzheimer disease and mild cognitive impairment. Ann Neurol 2009; 66: 200–8.

Stephan BC, Hunter S, Harris D, Llewellyn DJ, Siervo M, Matthews FE, et al. The neuropathological profile of mild cognitive impairment (MCI): a systematic review. Mol Psychiatry 2012; 17: 1056–76.

Stone J, Edwards M. Trick or treat? Showing patients with functional (psychogenic) motor symptoms their physical signs. Neurology 2012; 79: 282–4.

Stone J, Pal S, Blackburn D, Reuber M, Thekkumpurath P, Carson A. Functional (Psychogenic) cognitive disorders: a perspective from the neurology clinic. J Alzheimers Dis 2015; 48: S5–S17.

Teodoro T, Edwards MJ, Isaacs JD. A unifying theory for cognitive abnormalities in functional neurological disorders, fibromyalgia and

chronic fatigue syndrome: systematic review. J Neurol Neurosurg Psychiatry 2018; 89: 1308–19.
Van den Bergh O, Witthöft M, Petersen S, Brown RJ. Symptoms and the body: taking the inferential leap. Neurosci Biobehav Rev 2017; 74: 185–203.
van Gils A, Stone J, Welch K, Davidson LR, Kerslake D, Caesar D, et al. Management of mild traumatic brain injury. Pract Neurol 2020; 1–9. doi: practneurol-2018-002087.
van Maurik IS, Vos SJ, Bos I, Bouwman FH, Teunissen CE, Scheltens P, et al. Biomarker-based prognosis for people with mild cognitive impairment (ABIDE): a modelling study. Lancet Neurol 2019; 18: 1034–44.
Wakefield SJ, Blackburn DJ, Harkness K, Khan A, Reuber M, Venneri A. Distinctive neuropsychological profiles differentiate patients with functional memory disorder from patients with amnestic-mild cognitive impairment. Acta Neuropsychiatr 2018; 30: 90–6.

SHORT REPORT

Understanding foreign accent syndrome

Laura McWhirter ,[1] Nick Miller,[2] Catriona Campbell,[3] Ingrid Hoeritzauer,[1] Andrew Lawton,[4] Alan Carson,[5] Jon Stone

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/jnnp-2018-319842).

[1]Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK
[2]Speech and Language Sciences, University of Newcastle, Newcastle upon Tyne, UK
[3]Department of Clinical Psychological Science, Maastricht University, Maastricht, Netherlands
[4]Department of Psychological Medicine, Royal Infirmary of Edinburgh, Edinburgh, UK
[5]Department of Psychiatry, University of Edinburgh, Edinburgh, UK

Correspondence to
Dr Laura McWhirter, Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh EH10 5HF, UK; laura.mcwhirter@ed.ac.uk

Received 17 October 2018
Revised 30 January 2019
Accepted 6 February 2019
Published Online First 2 March 2019

To cite: McWhirter L, Miller N, Campbell C, *et al*. *J Neurol Neurosurg Psychiatry* 2019;**90**:1265–1269.

ABSTRACT

Objective Foreign accent syndrome (FAS) is widely understood as an unusual consequence of structural neurological damage, but may sometimes represent a functional neurological disorder. This observational study aimed to assess the prevalence and utility of positive features of functional FAS in a large group of individuals reporting FAS.

Methods Participants self-reporting FAS recruited from informal unmoderated online support forums and via professional networks completed an online survey. Speech samples were analysed in a subgroup.

Results Forty-nine respondents (24 UK, 23 North America, 2 Australia) reported FAS of mean duration 3 years (range 2 months to 18 years). Common triggers were: migraine/severe headache (15), stroke (12), surgery or injury to mouth or face (6) and seizure (5, including 3 non-epileptic). High levels of comorbidity included migraine (33), irritable bowel syndrome (17), functional neurological disorder (12) and chronic pain (12). Five reported structural lesions on imaging. Author consensus on aetiology divided into, 'probably functional (n=35.71%), 'possibly structural' (n=4.8%) and 'probably structural' (n=10.20%), but positive features of functional FAS were present in all groups. Blinded analysis of speech recordings supplied by 13 respondents correctly categorised 11 (85%) on the basis of probable aetiology (functional vs structural) in agreement with case history assignment.

Conclusions This largest case series to date details the experience of individuals with self-reported FAS. Although conclusions are limited by the recruitment methods, high levels of functional disorder comorbidity, symptom variability and additional linguistic and behavioural features suggest that chronic FAS may in some cases represent a functional neurological disorder, even when a structural lesion is present.

INTRODUCTION

Foreign accent syndrome (FAS) represents a disorder of speech in which listeners perceive the affected individual as speaking with a foreign or different regional accent that is not their habitual accent. It has been reported as a result of stroke or other lesion within speech-motor networks, but there is increasing recognition of functional or psychogenic FAS.[1–4] A 2015 systematic review identified 105 published case reports of FAS between 1907 and 2014 of which 15 met criteria for 'psychogenic FAS'.[2]

Additionally, FAS could represent a functional neurological symptom even in patients with demonstrable structural lesions. Functional neurological disorder (FND) is a common reason for attendance at neurology outpatient clinics, with symptoms that are involuntary but internally inconsistent, and associated with distress and disability.[5–7] Speech and language symptoms are not uncommon in patients with FND.[8] There have been important changes over the last 20 years in approach to FND: now recognised to be not always stress related; and diagnosed on the basis of positive clinical signs rather than by exclusion, which crucially allows the diagnosis to be made in the presence of structural disease.[9 10] Suggested positive features of functional FAS include accent inconsistency, ability to mimic other accents and periods of transient recovery of normal accent, indicating a different kind of disruption to speech-motor control.[11]

This study aimed to describe characteristics of a group of individuals with self-reported FAS, to estimate the proportion representing functional FAS and to evaluate the diagnostic value of specific speech and clinical features.

METHODS

Participants were recruited from two unmoderated online FAS support groups, and survey details shared with colleagues internationally including via the Association of British Neurologists and Royal College of Speech and Language Therapists. Inclusion criteria were being over 18 and responding 'yes' to the question: 'Do you believe that you may have a condition, sometimes called 'foreign accent syndrome', as a result of which you speak, for all or part of the time, with a voice or accent not your own?'

Participants completed a secure online survey including validated questionnaires assessing somatic symptoms (Patient Health Questionnaire 15 (PHQ-15)), depression and anxiety (Hospital Anxiety and Depression Scale (HADS)), social/occupational function (Work and Social Adjustment Scale (WSAS)) and illness perceptions (modified Illness Perceptions Questionnaire - Revised (IPQ-R)). Participants were invited to submit samples of speech, recorded via computer or smartphone, consisting of reading a standardised text ('Rainbow Passage') and spontaneous description of a standardised scene ('Cookie Theft Picture').

Clinical summaries were reviewed by authors JS, AC and LM who after discussion reached consensus about likely cause of the overall clinical picture in each case: 'probably functional', 'possibly structural' or 'probably structural'. A 'probably structural' diagnosis was made where the respondent described a neurological event with investigation

Appendix 14

results in keeping with a neurological injury or illness corresponding with onset of the foreign accent. A 'probably functional' diagnosis was made where (1) no such neurological injury or illness occurred at onset and (2) other features were present which strongly suggested a functional disorder, such as marked inconsistency (but not spontaneous remission). Those where there were some features suggestive of a functional disorder but some uncertainty about a possible structural cause were classified as 'possibly functional'.

The audio recordings supplied (including one video recording) underwent auditory-perceptual analysis by author NM and, independently, by another speech and language therapy professional, blind to clinical details. Spoken output was analysed in terms of severity and nature of speech changes with regard to respiration, voice, articulation, prosody, word finding and sentence structure. Perceived changes were examined for how far they conformed to standard diagnoses of dysarthria, apraxia of speech, dysprosody and aphasia, congruency between different levels of analysis and consistency internal to the different levels. On the basis of this analysis, the audio recordings were classified as 'probably functional', 'possibly structural' or 'probably structural'.

Results

The survey, open 23.11.16–1.3.17, collected 49 responses: UK (24), North America (23) and Australia (2). Original accents were English—unspecified (25), English—American (20), Scottish (2), Australian (1) and Welsh (1).

Consensus classification was: 35 (71%) probably functional, 4 (8%) possibly structural (two stroke not visible on scan, one Parkinson's disease one mild traumatic brain injury [TBI]) and 10 (20%) probably structural (eight stroke, one TBI and one severe headache with Bell's palsy).

Clinical features

Onset was typically sudden and followed a significant event in all but one presentation. Forty-three had brain imaging (CT(33), MRI(38), Positron Emission Tomography (PET)(3)), four electroencephalography (EEG) and three lumbar puncture (table 1).

Many different accents were reported, with most participants reporting a number of different accents; some (22) indicated that their accent itself changed, and others (10) reported a consistent accent heard as different accents by different listeners. Reported accents included (1) foreign perceived accents (Italian (12), Eastern European (11), French (8), German (7), South African (6), Polish (5), Russian (4), Indian (3), Asian (3), Swedish (3), Chinese (3), French/Italian (2), Scandinavian (2), Czech/Slovak (2), European (2) and one each of Dutch, Nigerian, Japanese, Spanish, Belgian, Croatian, Norwegian and Balkans) and (2) a different accent of the native language (British (7), Irish (7), South African (6), Scottish (3), Welsh (2), Australian (2), Jamaican (1), Texas (1), North Dakota (1) and Canada (1)). In addition to one or more foreign accents, one respondent each reported 'slurred and gibberish' speech, 'a child voice', 'bad stutter or 'triple talk'

Table 1 Clinical features of patients with self-reported FAS

Measure	All	Probably functional (n=35)	Possibly structural (n=4)	Probably structural (n=10)
Features				
female:male:other	42:6:1	32:2:1	4:0:0	6:4:0
Mean age, years (SD, range)	49 (11, 24–72)	46 (10, 24–67)	50 (5, 43–54)	57 (11, 40–72)
Median symptom duration, years (range)	3.25 (0.2–18)	2.67 (0.17–18)	3.13 (2.67–4.75)	8.33 (0.50–16.67)
Structural lesion identified on investigation	5 (10%)	0	0	5 (50%)
Sudden onset	23 (67%)	21 (60%)	2 (50%)	10 (100%)
Gradual onset	16 (33%)	14 (40%)	2 (50%)	0
Event at onset n (%)*				
Migraine or severe headache	15 (30)	14 (40)	0	1 (10)
Stroke	11 (22)	1 (2)	2 (50)	8 (80)
Physical injury or surgery to mouth, face or jaw	9 (18)	8 (16)	1 (25)	0
Head injury with loss of consciousness	3 (6)	2 (4)	0	1 (10)
Seizure or non-epileptic seizure/attack	5 (10)	5 (10)	0	0
Dissociative seizure/non-epileptic attack	3 (6)	3 (6)	0	0
Epileptic seizure	1 (2)	1 (2)	0	0
Uncertain/seizures are under investigation	1 (2)	1 (2)	0	0
Stress/'mental breakdown'	3 (6)	3 (6)	0	0
Other physical injury	2 (4)	2 (4)	0	0
No obvious trigger	1 (2)	0	1 (25)	0
Other (viral infection, other surgery, spider bite, 'blinding light')	4 (8)	4 (8)	0	0
Positive features of functional FAS:				
Periods of remission	23 (47)	18 (51)	1 (25)	4 (40)
Ability to copy other accents	8 (16)	7 (20)	0	1 (10)
Behavioural features associated with a stereotype	15 (43)	12 (34)	0	3 (30)
Changes in grammar and style of writing	16 (32)	9 (26)	2 (50)	5 (50)
Speech recording provided	13	10	0	3
Functional features identified in speech analysis	8	8	0	0

*Some reported >1 simultaneous event at onset.
FAS, foreign accent syndrome.

Appendix 15

(sic), 'a tendency to pick up stronger accents' and one reported 'I tend to say words backwards. And put the first letter of first word on the front of the second word': a type of paraphasia also called a 'spoonerism' (eg, 'belly jeans' for 'jelly beans'.)

Fourteen patients reported symptoms that 'come and go', but 23 (47%) reported distinct remissions during which their normal accent returned for hours to days. Tiredness, stress and migraine were frequent exacerbating factors; rest and relaxation frequent relieving factors. Most believed that symptoms were caused by 'neurological disease like stroke' (30) or 'damage to the nervous system' (26) although several did not believe symptoms were caused by disease (9) or damage (8). A significant proportion endorsed 'stress or worry' (16) as a cause of symptoms.

Fifteen (31%) agreed that they had developed national characteristics which they associated with their accent: hand movements (9), changes in syntax ('like Pidgeon (sic) English', 'like a foreigner learning English'), vocabulary ('instead of saying yes, saying ja ja', and interpersonal behaviour ('…become loud, arrogant and sneering'). One described using appropriate slang words so as to 'fit the part'.

Comorbidities

Other symptoms included memory problems (42), limb weakness (31), daily pain in more than one part of the body (28) and tremor or abnormal limb movements (26). There were mild anxiety symptoms in the group overall, with moderate-severe anxiety in 11 and moderate-severe depressive symptoms in 8 (table 2).

Auditory-perceptual analysis

Eleven of the 13 cases for which an audio(visual) recording was provided were classified after blinded auditory-perceptual analysis in agreement with the consensus classification above. For two classification was uncertain. Both blinded independent raters were in full agreement regarding allocation to 'probably functional', 'possibly structural', 'probably structural' or 'uncertain'. Those categorised as 'probably functional' had speech and/or voice and/or language behaviours that did not fit diagnostic features for dysarthria, apraxia of speech, dysprosody or aphasia; inconsistencies were present (table 3). A selection of recorded speech samples from four participants and commentary on our analysis of these recordings are included as online supplementary files (online supplementary notes, Recording A Task A, Recording A Task B, Recording B Task A, Recording B Task B, Recording C Task A, Recording C Task B, Recording D Task A, Recording D Task B).

Table 2 Comorbidities and social and occupational function

Comorbidities	All, (%)	Probably functional n=35, (%)	Possibly structural n=4, (%)	Probably structural n=10, (%)
Migraine	33 (67)	27 (77)	4 (100)	2 (50)
Irritable bowel syndrome	17 (35)	15 (43)	2 (50)	0
Chronic pain	12 (24)	9 (26)	3 (75)	0
Functional neurological disorder	12 (24)	11 (31)	1 (25)	0
Non-epileptic attack disorder	8 (16)	8 (16)	0	0
Fibromyalgia	11 (22)	8 (16)	3 (6)	0
Autoimmune disorder (eg, rheumatoid arthritis, lupus, coeliac disease)	8 (16)	5 (10)	1 (25)	2 (20)
Diabetes	5 (10)	4 (14)	0	1 (10)
Hypothyroidism	5 (10)	4 (14)	1 (25)	0
Chronic fatigue syndrome/ ME	8 (16)	7 (20)	0	1 (10)
Anxiety	4 (8)	4 (14)	0	0
Asthma	2 (4)	2 (7)	0	0
Depression*	2 (4)	2 (7)	0	0
Diverticular disease	2 (4)	1 (3)	0	1 (10)
Hypertension	2 (4)	1 (3)	0	1 (10)
Other medical conditions	26	13 †	2‡	13§
Somatic symptom burden/anxiety and depression¶				
PHQ15 mean (SD)	13 (6) (n=44)	12 (5) (n=9)	17 (6) (n=4)	8 (6) (n=8)
HADS-A (anxiety) mean (SD)	8 (1)	8 (4)	6 (3)	9 (4)
HADS-D (depression) mean (SD)	7 (1)	8 (4)	6 (4)	6 (3)
Social and occupational function				
In employment or education	21 (48%)	14 (40%)	3 (75%)	4 (40%)
WSAS median (range)	15 (4–17)	17 (2–38)	16 (2–30)	4 (0–30)

*Self-reported diagnosis–not from HADS score.
†Arthritis, cluster headaches, hiatus hernia, oral cancer (asymptomatic), Post-traumatic Stress Disorder (PTSD), postconcussion syndrome, pulmonary hypertension, Raynaud's syndrome, syncope, somatoform disorder, tetany, trigeminal neuropathy, vitamin D deficiency.
‡Parkinson's disease, ulcerative colitis.
§Ankylosing spondylitis, atrial fibrillation, cyclothymia, diabetes, dysautonomia/orthostatic hypotension syndrome, factor V Leiden, kidney cancer, Marfan syndrome, methylenetetrahydrofolate reductase deficiency, multiple sclerosis, patent foramen ovale, skin cancer, sleep apnoea
¶PHQ15 measures somatic symptom severity: minimal 0–4, low 5–9, medium 10–14, high 15–30; HADS-A and HADS-D scores of less than 7 indicate non-cases, 8–10 mild, 11–14 moderate and 15–21 severe.
Myalgic Encephalomyelitis, ME.

Appendix 16

Table 3 Examples of language, speech, voice and prosody changes suggesting classification as functional or structural disease aetiology (link to annotated recordings)

Speech subsystems	Speech features if present supporting a functional aetiology	Features if present supporting a structural disease aetiology
Language (morphology, syntax, semantics)	Apparent difficulty with simple grammatical structure but no problems on more complex sentences Idiosyncratic expressions: 'very overfilling with water', 'stool that is getting ready to tip over', 'thinking in thoughts'. Isolated and/or inconsistent omission of—ing endings from verbs, Inappropriate addition of/s/sound to words (eg, thankyous, byes, fall overs) but not to all words; no apparent articulatory cause for this.	Semantic paraphasic slips, for example, 'kitchen cupboard' labelled 'china cabinet', 'arch' read as 'arc'. Difficulty marking past tense syntactically while present and future tense relatively spared.
Voice quality	Excessive and/ or inconsistent variability in, for example, degree of hoarseness or breathiness; changes not associated with structural neurological changes to phonation, for example, falsetto voice quality and pitch inconsistent with age and gender of speaker.	Consistent voice changes (eg, creaky voice) compatible with alterations to tone, power, coordination of laryngeal muscles.
Articulation	Incompatibility of vowel versus consonant pronunciation: for example, tendency to produce vowels at back of mouth, but production of consonants suggests this is not due to neuromuscular (eg, tongue tip weakness, velar insufficiency) difficulties Isolated change of /r/ sound to uvular 'r' sound, for example, associated with a French accent, in presence of no other related changes Inconsistent consonant production, for example, 'cookie jar' produced as 'tutty dar' but 'j', /k/, /g/, 'sh' produced effortlessly and accurately in other words.	Changes to articulation compatible with structural neurological motor speech disorder, for example, articulatorily more complex sounds/ sound sequences more susceptible to distortion than less complex sounds 'piksure' for 'picture' Changes to vowel production compatible with weakness of tip or back (or both) of tongue.
Perceived accent	Marked variability within short passage (completely unaccented to heavily accented; 'Italian' to 'Australian') 'Accent' does not match accents found in natural languages, or shows affective variation, for example, childish rather than 'foreign' tone of voice.	Perceived accent in keeping with consistent alteration to specific aspects of articulation or prosody (eg, producing /w/ as /v/, effects of hypernasality on vowels, insertion of 'uh' in consonant clusters—'suhtanding, pikuhture' for 'stand, picture').
Prosody (rate, word and sentence stress, intonation)	Excessive and inconsistent swings in pitch and intonation and/or where stress placed on word, for example, 'thuuu cooKIE juh' instead of 'the COOkie jar'.	Changes compatible with recognised structural neurological diagnoses, for example, scanning speech of cerebellar ataxia, syllabification of apraxia of speech, monopitch and monoloudness of Parkinson's disease.
Fluency (pauses, blocks, repetitions)	'Pseudo-struggle' for example, output has effortful quality but other aspects, such as rate of speech and articulatory accuracy appear intact Pauses occur in syntactically inappropriate places and/or within words without any apparent articulatory/respiratory reason for this Idiosyncratic inconsistent splitting up of words, for example, pri-sm, div-i-zhu-n.	Changes to pauses consistent and compatible with changes to, for example, respiration, speech-motor planning Pauses occur at syntactically and phonologically lawful loci Struggle/effortfulness of speech consistent and compatible with changes to tone, power, coordination and manifest in concurrent other aspects of speech and voice.

DISCUSSION

In this study of a large cohort of people self-reporting FAS, the majority (71%) were considered likely to have a functional aetiology.

Identifying features which can indicate functional FAS with more certainty would help in developing treatments and reducing iatrogenic harm. The auditory-perceptual framework employed here for classification of speech-voice-language deviations was able to highlight positive clinical features of functional FAS, showing mismatches across levels of analysis (voice, speech, etc) not compatible with expected findings for structural disorders. This framework might usefully be tested for diagnostic value in a validated clinical sample. The three speech behaviours that appeared to most strongly associated with a diagnosis of functional FAS (table 3) concerned: (1) where there was a mismatch between the apparent speech difficulties and the underlying physical assessment (eg, problems with tongue tip sounds but no evidence of tongue tip weakness, incoordination or apraxia of speech that might account for this); (2) inconsistency in occurrence of a speech change not linked to well-recognised variables such as syllable complexity ('l' sound in 'lane' vs 'explain') or phonotactic probability (likelihood of one sound following another; 'asked' vs 'axed'); (3) presence of speech changes not found in neurological motor speech disorders (eg, infantile prosody; intrusion of foreign words—'garden is bella'; 'parents' pronounced as a French word even though all surrounding words have an English accent).

However, some features suggested by Lee *et al*[1] as evidence of functional FAS did not discriminate 'probably functional' from 'probably structural' FAS in this sample, occurring at a similar frequency in both groups: periods of remission (indicating inconsistency) (51% vs 40%); characteristics in keeping with a stereotype associated with the accent (34% vs 30%) and ability to copy other accents (20% vs 10%) .

Structural FAS may occur in connection with lesions of pathways contributing to well-understood speech motor control networks (basal ganglia; cerebellum; thalamus; primary and secondary motor cortex, insula and their interconnections, eg, thalamocortical, cerebellar-cortical tracts), predominantly in the left/dominant hemisphere, though prosodic disturbance may be associated with right hemisphere lesions.[12] Structural FAS is less likely where there is no visible structural lesion; where the lesion is at a site unlikely to disrupt speech motor control; or where the speech changes are not compatible in their nature or consistency with the pattern expected from a lesion at the particular site. We propose that features of functional FAS can occur in those with structural lesions because FAS may in some cases have a functional basis even when it starts after neurological injury. This is supported by wider observations. In our clinical experience, most who develop FAS after neurological injury recover within weeks. While acoustic and physiological speech changes may persist, the period of sounding 'foreign' is typically short. It seems likely that, where FAS persists, a functional disorder is largely responsible for a chronic change in accent.

The frequency of physically or psychologically noxious events at symptom onset was striking and may have pathophysiological significance paralleling other functional disorders such as persistent postural-perceptual dizziness after vestibular

disturbance or functional limb weakness after physical injury.[13 14] Recent research has examined the role of attention in functional symptoms.[15] Here, perhaps transient changes in awareness or perception following facial injury, migraine, stroke, functional disorder presenting similarly to a stroke, or dissociative seizure produce abnormal attentional focus on the voice or mechanics of speech, disrupting normally automatic speech processes.[16]

Our analyses also help to clarify the extent to which FAS may be considered a disturbance of prosody. The perception of FAS has been associated with the presence of both segmental speech changes (ie, changes to individual sounds, eg, 'sh' sounds like 's', sheet → seat, 'i' sounds like 'ee', ship → sheep) and suprasegmental/prosodic changes (eg, alterations to speech rhythm, stress placement in words and sentences, intonation pattern). Reports of an isolated dysprosody have appeared, starting with Monrad-Krohn's classic study.[17] However, our analysis here supports a view that altered prosody is not the sole trigger for perceived foreign accent. In keeping with the majority of reports of FAS, the speakers in the present cohort evidenced features of segmental and suprasegmental alterations. There were none with a solely prosodic disturbance.

The self-reported nature of these data prevents confident conclusions about aetiology. Selection bias is also likely: some individuals with self-reported FAS may strongly identify with this diagnosis and yet not necessarily be classified by naïve listeners as having a foreign accent, though it might usually be agreed that they have a different accent to their previous habitual speech; they may be influenced by experiences shared by other support group members; all were English speaking and the online survey precluded significant cognitive difficulties.

Nevertheless, this study reporting the largest series of FAS cases to date generates an important hypothesis: that FAS may often be an FND, whether a structural neurological lesion is present or not.

Contributors LM designed the study, collected the data, analysed the data and prepared and revised the manuscript. NM designed the study, analysed and reported the audio data and revised the manuscript. CC drafted the manuscript. IH designed the study and drafted the survey. AL collected the audio recording data. AC designed the study, interpreted the data and revised the manuscript for intellectual content. JS designed the study, interpreted the data and revised the manuscript for intellectual content.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests LM is undertaking a research fellowship funded philanthropically by Baillie Gifford. IH is supported by and ABN/Patrick Berthoud Charitable Trust Research Training Fellowship. AC is a paid editor of the Journal of Neurology, Neurosurgery and Psychiatry. He is a director of a limited personal services company that provides independent medical testimony in court cases on a range of neuropsychiatric topics on a 50% pursuer 50% defender basis. JS is a Chief Scientists Office NHS Research Scotland Career Researcher. JS provides independent medical testimony in court cases regarding patients with functional disorders.

Patient consent for publication Obtained.

Ethics approval The study received NHS Ethical approval.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Laura McWhirter http://orcid.org/0000-0001-9839-6549
Jon Stone http://orcid.org/0000-0001-9829-8092

REFERENCES

1 Lee O, Ludwig L, Davenport R, *et al*. Functional foreign accent syndrome. *Pract Neurol* 2016;16:409–11.
2 Keulen S, Verhoeven J, De Witte E, *et al*. Foreign accent syndrome as a psychogenic disorder: a review. *Front Hum Neurosci* 2016;10.
3 Baizabal-Carvallo JF, Jankovic J. Speech and voice disorders in patients with psychogenic movement disorders. *J Neurol* 2015;262:2420–4.
4 Luzzi S, Viticchi G, Piccirilli M, *et al*. Foreign accent syndrome as the initial sign of primary progressive aphasia. *J Neurol Neurosurg Psychiatry* 2008;79:79–81.
5 Carson AJ, Brown R, David AS, *et al*. Functional (conversion) neurological symptoms: research since the millennium. *J Neurol Neurosurg Psychiatry* 2012;83:842–50.
6 Carson A, Stone J, Hibberd C, *et al*. Disability, distress and unemployment in neurology outpatients with symptoms 'unexplained by organic disease'. *J Neurol Neurosurg Psychiatry* 2011;82:810–3.
7 Gelauff J, Stone J, Edwards M, *et al*. The prognosis of functional (psychogenic) motor symptoms: a systematic review. *J Neurol Neurosurg Psychiatry* 2014;85:220–6.
8 Barnett C, Armes J, Smith C. Speech, language and swallowing impairments in functional neurological disorder: a scoping review. *Int J Lang Commun Disord*;50.
9 Espay AJ, Aybek S, Carson A, *et al*. Current concepts in diagnosis and treatment of functional neurological disorders. *JAMA Neurol* 2018;75.
10 Keynejad RC, Frodl T, Kanaan R, *et al*. Stress and functional neurological disorders: mechanistic insights. *J Neurol Neurosurg Psychiatry* 2019;90:813–21.
11 Duffy JR, Hallett M, Stone J, *et al*. Functional speech disorders: clinical manifestations, diagnosis, and management. In: *Handbook of Clinical Neurology series*. Elsevier, 2016: 379–88.
12 Beeldman E, Raaphorst J, Klein Twennaar M, *et al*. The cognitive profile of ALS: a systematic review and meta-analysis update. *J Neurol Neurosurg Psychiatry* 2016;87:611–9.
13 Popkirov S, Staab JP, Stone J. Persistent postural-perceptual dizziness (PPPD): a common, characteristic and treatable cause of chronic dizziness. *Pract Neurol* 2018;18:5–13.
14 Pareés I, Kojovic M, Pires C, *et al*. Physical precipitating factors in functional movement disorders. *J Neurol Sci* 2014;338:174–7.
15 Edwards MJ, Adams RA, Brown H, *et al*. A Bayesian account of 'hysteria'. *Brain* 2012;135:3495–512.
16 Gargalas S, Weeks R, Khan-Bourne N, *et al*. Incidence and outcome of functional stroke mimics admitted to a hyperacute stroke unit. *J Neurol Neurosurg Psychiatry* 2017;88:2–6.
17 Monrad-Krohn GH. Dysprosody or altered melody of language. *Brain* 1947;70:405–15.

Appendix 18

Management of Functional Communication, Swallowing, Cough, and Related Disorders: Consensus Recommendations for Speech and Language Therapy

Baker J, Barnett C, Cavalli L, Dixon L, Dietrich M, Duffy JR, Elias A, Fraser DE, Freeburn JL, Gregory C, McKenzie K, Miller N, Patterson J, Roth C, Roy N, Short J, Utianski RL, van Mersbergen M, Vertigan A, Carson A, Stone J, McWhirter L.

(Prepared for submission for publication)

Abstract word count:	244
Word count for text:	7640
Number of tables:	13
Number of text boxes:	4
Number of figures:	0

Abstract

Background

Communication problems (e.g. dysphonia, dysfluency, and language and articulation disorders), swallowing disorders (dysphagia and globus), cough and upper airway symptoms, resulting from Functional Neurological Disorder (FND), are commonly encountered by speech and language professionals. However, there are few descriptions in the literature of the most effective practical management approaches. This consensus document aims to provide recommendations for assessment and intervention that are relevant to both adults and young people.

Methods

An international panel of speech and language professionals with expertise in FND were approached to take part. Participants responded individually by email to a set of key questions regarding best practice for assessment and interventions. Next, a video conference was held in which participants discussed and debated the answers to these key questions, aiming to achieve consensus on each issue. Drafts of the collated consensus recommendations were circulated until consensus was achieved.

Results

Functional disorders should be diagnosed on the basis of positive clinical features. Speech and language therapy for functional disorders should address illness beliefs, self-directed attention and abnormal movement patterns through a process of education, symptomatic treatment and cognitive behavioural therapy within a supportive therapeutic environment. We provide specific examples of these strategies for different symptoms.

Conclusions

Speech and language professionals have a key role in the management of people with communication and related symptoms of functional neurological disorder. It is intended that these recommendations serve as both a practical toolkit and a starting point for further research into evidence-based treatments.

Introduction

The pivotal role of the speech and language professional has been long established in the management of a range of disorders of communication, swallowing, and cough.

There is a strong evidence-base for the treatment of the aforementioned disorders occurring during childhood development, in association with organic and structural anomalies, and as the result of neurological disease or injury. In contrast, there have been comparatively few intervention and outcome studies for individuals with *functional* communication, swallowing, and cough disorders; while there is some evidence for the assessment and treatment of functional dysphonia and dysphagia, other symptoms have received very little systematic research attention.

In functional neurological disorder (FND), neurological symptoms are experienced which are genuine, and usually associated with distress and disability, as a result of potentially-reversible changes in function and not as a result of disease, damage, or structural abnormality [1]. FND is a common cause of neurological symptoms, present in around 1/3 of patients presenting to neurology outpatient clinics [2]. Crucially, FND is diagnosed on the basis of positive clinical features of internal inconsistency, and not by exclusion of structural damage or disease [1]. FND is also described in children and young people [3], in whom successful outcomes have been reported by speech and language professionals.

Although many speech and language professionals will have assessed or treated people with functional dysphonia, they may also be asked to assist with differential diagnosis or provide treatment of a much wider range of functional communication, swallowing, and cough disorders. This is an area in which some and perhaps many speech and language professionals have felt unsure or underprepared when asked to provide treatment [4]. And yet these disorders are not rare: review of referrals to one large U.S.A. speech pathology department over a 3-year period found that (excluding functional dysphonia) 3% of patients with acquired communication disorders had functional disorders [5].

These consensus recommendations for assessment and intervention draw on published evidence where available. However, in areas where empirical evidence is sparse, the approaches recommended here represent those the authors have found useful in their own clinical practices.

We hope that these recommendations will assist practitioners in their practical management of these disorders, and support future research towards evidence-based treatments.

This is a shortened version of our **full recommendations** (*hyperlink please to full recommendations*) which contain more information about diagnosis and further detail of management of functional foreign accent syndrome and related disorders, globus/functional dysphagia and laryngeal hypersensitivity syndrome/functional cough. We would like to direct the reader to these **full recommendations** (*hyperlink please to full recommendations*).

Method

Consensus Process

A modified Delphi approach was used. Speech and language professionals from different countries with extensive experience with functional communication, swallowing or upper airway-related symptoms (including cough and/or breathing) were invited to respond to a series of questions relating to their recommendations for assessment and treatment. This was followed by a series of video-conference discussions, after which a draft of each subsequent document was circulated until consensus was reached. The aims and methods were similar to those used to develop published recommendations for occupational therapy and physiotherapy in FND; it is intended that this document complements these publications [6,7].

Participants

The group included 18 speech and language professionals (speech and language therapists / speech-language pathologists; 9 based in the UK, 5 in the U.S.A., 1 in Germany [German and U.S.A trained], and 3 in Australia) with clinical experience of treating patients with FND. Participants had between 6 and 46 years of post-graduate experience. The group also included UK representatives from neuropsychiatry (n=2) and neurology (n=1), supporting a multidisciplinary approach.

Terminology

Historically, functional neurological disorders have had many names including *conversion disorder, psychogenic*, *psychosomatic, somatoform, medically unexplained*, or *functional*; these terms reflect differing behavioural, physical, and psychological perspectives. There is now reasonable consensus amongst neurologists and psychiatrists that the term *functional* is the most appropriate diagnostic term, primarily to emphasise a disorder of function with aetiological neutrality, when referring to specific symptoms (e.g. *functional dystonia*, *functional tremor*, *functional blindness*). *Functional Neurological Symptom Disorder (FND)* as defined by the DSM-5 (2013) is the umbrella term for these disorders which lie at the interface between neurology and psychiatry. Diagnosis of Functional Neurological Symptom Disorder in DSM-V requires the presence of one or more symptom of altered

voluntary motor or sensory function, which is incompatible with or not better explained by other recognised neurological or medical conditions, and which causes clinically significant distress or impairment. Each symptom type may be specified, i.e. 'With swallowing symptoms' or 'With speech symptoms'."

There continues to be confusion about the most appropriate terminology for disorders of communication, swallowing, and cough in the absence of structural or neurological pathology**.** Difficulties in reconciling terms for these symptoms can undermine efforts to define clinical phenotypes, to collate data, and to develop evidence-based treatments [8–10].

This document aims to focus on the elements of effective treatment, rather than on these complex issues of terminology and definition. In the interests of consistency, therefore, the term *functional* will be used throughout this document to refer to these disorders of communication, swallowing, and cough.

Conceptual understanding

Some reviews have examined psychosocial risk factors in functional communication and related disorders [5,11–18]. However, symptoms do not always develop after adverse life events, or in the context of psychological distress or psychiatric comorbidity [12,19]. In common with FND in general, symptoms often develop instead in the context of injury or illness: for example, upper respiratory tract infection, voice overuse, injury to the face, mouth, oropharynx or larynx; traumatic head injury.

This group's consensus on the conceptual understanding of the diagnosis of communication and related FND symptoms (**Box 1**) is informed by current and widely-accepted explanatory models for FND [1,20–24].

Box 1. Functional communication, swallowing, and cough disorders – conceptual understanding

Functional communication, swallowing, and other upper airway-related (e.g. cough and breathing) disorders occur when there is a loss of voluntary control or altered sense of self-agency (the subjective experience of controlling one's own actions (Haggard, 2017)) over the initiation, inhibition, and maintenance of the functions involved in speech, voice, language, swallowing, breathing, or cough. As a result, there often is inconsistency between voluntary functions, which become inaccessible or excessively effortful, and automatic functions, which are usually preserved.

The symptoms of functional disorders are genuinely experienced and involuntary. A range of biological, psychological, and social predisposing, precipitating, and perpetuating factors (Table 1) are recognised.

The role of the speech and language professional

In the **full version** of this document we conclude that the existing skillset and practice environment of most speech and language professionals allows for a major contribution to the diagnosis and effective treatment of most functional communication, swallowing, and cough disorders. A list of additional helpful resources can be found in **Appendix 1**.

Initial assessment (Box 2)

Aims of the initial assessment include information-gathering and preliminary diagnostic formulation, and rapport building; attention to additional elements can be helpful in establishing illness beliefs and expectations which may be important in maintenance of symptoms, the conduct of therapy, and response to treatment (Box 2). Anecdotal evidence suggests that many patients with functional disorders only attend for one session, similar to findings for psychotherapy [37], so it is crucial that the first session is a positive experience [7,28,38,39].

Psychosocial assessment often provides an understanding of the life events, relationships, and personality traits that may be relevant to the symptoms. Gentle enquiry about recent stresses or significant events is appropriate, as part of an exploration of the risk factors described in **Table 1**. However, while some patients are interested and may benefit from exploring the possible relationship between their experience of psychosocial trauma or distress and their symptoms, others prefer not to do so. It is important that patients are made to feel comfortable discussing such issues, but it is also important not to probe injudiciously if a history of trauma is not forthcoming; it is possible that there has been no relevant psychological trauma or adverse life events and repeated uninvited questioning about trauma can undermine the therapeutic relationship. It is also important that speech and language professionals are aware of available local resources with appropriate levels of expertise to address suspected or certain significant psychological/psychiatric/psychosocial needs that may need to be addressed prior to or concurrently with symptomatic treatment of communication or swallowing symptoms.

Box 2 – Important elements of the history to consider during initial assessment

1. How and when did the symptom(s) begin, and what does the person understand about the possible cause of the symptoms?
2. Do symptoms come and go, or are they constant? Are there any exacerbating or relieving factors? Have there been any periods when the symptoms have disappeared completely?
3. What has the patient been told about the symptoms by other health professionals? What has been the outcome of any previous treatments for the same symptoms?
4. What is the impact of the symptoms on daily life, work, and relationships? The extended psychosocial interview developed by Butcher et al., (2007) may be helpful in this regard.

Diagnosis of a functional disorder

Functional neurological disorder should not be a diagnosis based on the exclusion of disease [1,38]. In line with FND in general, a range of **positive clinical features** of functional communication, swallowing, and cough disorders are now recognised which support a positive diagnosis of functional disorder. General features are outlined in **Table 2**; examples of specific symptom profiles are described in the relevant sections below. These features may be observed during history taking, during the standard motor speech examination, or may be observable in the person's social utterances and activities, specific speech or swallowing tasks, or conversational speech.

Although diagnosis of a functional disorder can generally be made on the basis of positive features, comorbid structural pathology should be excluded early in the diagnostic process (with appropriate investigations, when necessary), even when a functional diagnosis seems likely. Importantly, the presence of 'structural' pathology does not exclude a functional disorder diagnosis, which can be comorbid with structural or neurological disease, possibly representing 'functional overlay', and can be identified on the basis of positive clinical features. In such cases the speech and language professional plays an important role in the process of differential diagnosis and communicating to the patient and other clinicians which elements of the presentation are the result of structural damage or disease and which have a functional basis.

Treatment

In general, the broad principles of treatment of functional disorders of communication, swallowing, and cough are the same as for other functional neurological disorders [40–42]. The first and most important part of treatment involves making a positive diagnosis (i.e. based on symptoms consistent with FND and not solely based on ruling out other explanations) and clearly explaining the diagnosis and the reasons for it to the patient [39,43]. This explanation may have therapeutic value in its own right. Subsequent therapy may include symptomatic, behavioural and/or psychological interventions along with ongoing education about the diagnosis.

Explaining the diagnosis

In explaining the diagnosis, it is important to 1) take the problem seriously and acknowledge that the symptoms are real, 2) explain that this is a positive diagnosis (as defined above), and that the diagnosis is not unknown or mysterious, 3) explain the reasons for the diagnosis by demonstrating or explaining its positive clinical signs (**Box 3**), 4) provide written material and links to other resources (**Appendix 1**). Suggestions to help with effective explanations are listed in **Table 3**.

When the person referred for treatment has already had the diagnosis explained by the referring professional, it is still important for the speech and language professional to reinforce, consolidate, and, if necessary, expand the person's understanding about the functional disorder diagnosis. When there is comorbid structural pathology, the therapist may need to discuss the extent to which it may or may not be an obstacle to improvement [44–49].

Duration of treatment

Most patients referred with functional disorders of communication, swallowing, and cough can benefit from speech and language therapy, often substantially/dramatically and sometimes rapidly. Many achieve some improvement or even elimination of one or more, and sometimes all of their symptoms during the initial consultation. While this does not necessarily mean that the functional disorder has fully resolved, such early symptomatic improvement is very encouraging. Others require several therapy sessions of symptomatic/behavioural work, integrated with counselling. Clinical experience suggests that intensive therapy, with sessions several times per week, may be most successful in helping patients to regain normal function and inhibit abnormal movements or struggle behaviours, and to maintain gains in the wider social context. We recognise, however, that limited resources may limit the frequency of therapy.

For some, several weeks or months of treatment may be required for a sustained improvement that generalises beyond the clinical setting. This has sometimes been attributed to the patient 'being resistant' or 'failing to comply' with recommendations, but generally speaking, patients do want to improve – that is why they are there – and are cooperative with treatment. Habituated patterns of movement and behaviour can take time and practice to overcome, and there may also be perpetuating influences (see **Table 1**). Some therapists find it useful to develop a time-limited treatment contract which includes indications for ending therapy, a plan for self-management, and strategies for coping with possible relapse of symptoms.

Suitability for treatment

Factors important for engagement with treatment include: 1) a **reasonable** degree of understanding and agreement with of the diagnosis and 2) motivation and agreement to treatment.

Circumstances in which beginning or continuing symptomatic therapy is less likely to be successful or may be inadvisable. and which suggest a guarded or poor prognosis **in some cases** include:

- Transient, unpredictable, or highly variable symptoms across settings,.
- Resolution or improvement of symptoms will lead to a return to what may be an unsafe or 'futile' work environment or domestic situation.
- Unresolved litigation related to symptoms.
- Severe psychiatric comorbidity.

- Other severe FND symptoms are present, such as seizures, dissociative states, severe pain, or fatigue. However, early treatment of communication symptoms may enable the person to engage better with treatment of the other symptoms.
- Patient doubts the diagnosis of functional disorder, although some may accept/embrace it during successful symptomatic treatment.
- Poor confidence in therapist's ability to help them resolve symptoms.

A trial of therapy is generally appropriate despite a degree of resistance or ambivalence. However, some positive response to treatment should be expected during the first 1-2 sessions; failure to respond at all during these initial sessions suggests it would be better to pause and revisit symptomatic treatment at a later date, or with another therapist.

General principles of symptomatic treatment

The principles of symptomatic management of functional communication, swallowing, and cough disorders can be helpfully informed by both perceptual-motor learning models as they have been applied to voice training and therapy [53,54] and recommendations from physiotherapy and occupational therapy professionals with experience of treating FND [6,7]. Treatment involves learning or retraining of motor patterns, while highlighting the ways in which attention, expectations, illness beliefs, and the vulnerability of our sense of agency (the experience of controlling one's own movements) may inhibit normal movements and promote abnormal movements.

1. Identify symptomatic behaviours and explain the mechanism of the symptom

It is important to explain how the patient's symptoms differ from those associated with normal speech, voice, swallowing, or cough and then to draw attention to the inadvertent and unnecessary efforts being used in particular muscle groups, such as in the head and neck, face, upper torso and shoulders; for example, patients are often surprised to learn that even producing a hoarse whisper can reflect excessive effort. Acknowledging how tiring and distressing it can be to exert such effort may prompt a reaction of relief or gratitude when the patient senses someone understands what they have been experiencing.

2. Introduce strategies to facilitate natural automatic patterns of movement

A common key feature of symptomatic treatment involves finding ways to access natural automatic movement patterns.

3. Regain voluntary control over conscious initiation of speech, phonation, swallowing etc

In addition to facilitating natural automatic movement patterns, in some cases the aim will be to trigger highly volitional utterances that will be simply *different* from the abnormal speech pattern. It may not necessarily be normal, but it will be different, and it can then be shaped towards normal. The therapist may then invite the person to extend these different or natural automatic patterns of movement into familiar and well-learned sequences that require little conscious thought or planning. The schemas for these automatic sequences tend to be locked into our *procedural memory which are revealed when we ask a person to engage in well-learned and practised tasks which they are able to do largely without detailed awareness of what has been learned* [53,55].

4. Extend automatic activities into graded, functionally relevant and meaningful activities

When the therapist asks the patient to do these automatic and well-learned sequential tasks, many will be able to complete them successfully (even if only tentatively at first). However, if the patient is clearly reticent, the therapist may introduce a number of additional activities in order to *distract the patient's attention* from their own performance. For instance, during verbal tasks the therapist may introduce ways to momentarily mask the patient's auditory feedback of their own voice and speech which will then help to trigger a reflexive vocal response. Distraction of attention can serve to block the patient's heightened sensitivity to auditory feedback which may have prompted a self-conscious inhibition of their voice or speech [56,57].

For many patients, it can be an exciting moment to hear their speech, voice and fluency returning to normal once again, or to realise they have swallowed some fluid without choking. For some, their relief may trigger laughter or tears. For others it can be an uncomfortable experience and may even stimulate an escalation in the severity of their involuntary symptomatic behaviours. Here it is important for the therapist to confidently persist with the interventions, reassuring the patient that it is not unusual for their speech or swallowing patterns to go through different stages as it returns to normal, and that they intend to persevere with them through this transition phase if the patient wishes to continue.

5. Positive and negative practice between old and new

Distraction or diverted attention is not always necessary, and some find it helpful to guide the patient to allocate all attentional resources to **positive** (auditory, kinaesthetic, vibrotactile) changes that take place during the course of therapy. This is an essential component of positive/negative (new way/old way) practice; paying attention to how the new pattern feels compared to the old disordered pattern aids a sense of voluntary control and mastery.

6. Consolidate and generalise normalised behaviours into wider social context

The next step is to extend these improved utterances or behaviours into graded and meaningful, *task-oriented activities* that will eventually culminate in conversation, swallowing comfortably during social mealtime eating and drinking, or managing symptoms of cough in different settings. In keeping with another key principle of perceptual-motor learning, findings suggest that *conscious self-focused attention* on the minutiae of the mechanics of motor tasks affects both performance and learning negatively. In contrast, focused attention on the *target of the activity* and the *desired outcomes of the task* are generally more beneficial.

7. Help the patient to notice and challenge unhelpful thoughts

Incorporating principles from Cognitive Behavioural Therapy (CBT) can aid treatment of FND, and there have been promising results from trials of specific CBT for functional movement disorders and dissociative seizures, [42,58,59] and functional communication, swallowing, and cough disorders specifically in relation to voice [60–63]. CBT principles can inform therapy even without formal CBT training. For example, by helping the patient to notice and challenge unhelpful automatic thoughts, such as catastrophising (e.g. “If I stutter at work I’ll lose my job”; “once I start coughing I won’t be able to stop”); or ‘all or nothing’ thoughts like “If my voice isn’t perfect all the time then I’m a failure” or “swallowing is sometimes hard so it is better if I never eat in public”. Behavioural strategies might include helping the patient to plan ‘behavioural experiments’ – such as a telephone call, or coffee with a friend – to address fear and avoidance of specific activities.

8. Address psychosocial predisposing and perpetuating factors

Many patients with FND will have rapid and successful resolution of symptoms without the need to explore psychological or social risk factors, which may not be relevant. However, some patients will wish to explore the relevance of psychological or social factors as therapy progresses. From a purely practical point of view, it is easier to address those influences once functional symptoms are no longer interfering with communication. We emphasise that the therapist can helpfully and appropriately engage in supportive discussion about the role of anxiety, or about the impact that symptoms have had on relationships and everyday life, without special training in counselling or psychotherapy. These discussions might, for example, help the patient to plan for situations where symptoms may recur, and allow them to explore how best to manage future relapses.

In the more unusual situation in which a patient becomes extremely distressed or psychiatrically unwell during treatment, a plan for additional or alternative management should be made,

incorporating the patient's general practitioner/family doctor, or referral to a mental health professional or crisis services as available locally [64].

A final stage of treatment often involves encouraging the ongoing involvement of family, friends and caregivers, and re-establishing the links to and support from the patient's workplace and work colleagues.

9. Preparing strategies for dealing with setbacks or relapse

Patients should be prepared for the possibility of relapse, with the emphasis on enabling them to self-manage any relapse using the techniques used during therapy. Clear criteria should be provided to the patient and referrer about how and when future therapy should be sought; this advice should be provided on a case-by-case basis and obviously may depend on service constraints. However, in general we recommend that further treatment or support be made available in case of relapse. As emphasised in a discussion paper addressing ways to end therapy 'the therapeutic relationship once established need never be broken' [65].

Assessment, diagnosis, and treatment of specific symptoms

The following sections address specific symptoms. However, it should be noted that these specific symptoms are not mutually exclusive but often co-occur. An individual may experience a range of different symptoms at different times, including during treatment and recovery. The treatment strategies suggested here are based on available evidence and the combined clinical experience of the consensus group. They largely represent recommendations rather than high-level-evidence-based guidelines.

Specific symptoms – Functional voice disorders

Functional voice symptoms include dysphonia, aphonia, odynophonia (pain using the voice), vocal fatigue, and mutational falsetto or puberphonia (high pitched voice after puberty). Globus is common, and excessive physical effort is a hallmark feature of these disorders. There is a (usually) sudden or intermittent loss of volitional control over the initiation and maintenance of phonation despite normal structure and function as observed during laryngoscopy and clinical examination. Since the voice is often closely associated with the expression of emotion, sudden total or partial loss of voice is often presumed to be linked to psychological factors and negative emotions associated with stress. Furthermore, patterns of vocal hyperfunction related to dysregulated or imbalanced laryngeal muscle activity are often observed, both of which are consistent with current FND models that emphasise the interplay between 'top down' and 'bottom up' influences on peripheral sensorimotor processing

[52,66,67]. As a consequence, in the past these functional disorders have often been referred to as 'psychogenic', or 'conversion dysphonia', with others more recently preferring the more aetiologically neutral term of 'functional' or 'primary muscle tension dysphonia' (pMTD) [8,68].

Onset may follow acute stress or longer-term difficulties, sometimes characterised by conflict over speaking out, expressing negative emotions, a sense of powerlessness; sometimes related to personality vulnerabilities [18,69,70]. Importantly, many patients do not recall any emotionally stressful incidents, but will associate their loss of voice with a recent upper respiratory tract infection, a medical procedure involving the head and neck, or some form of blunt injury which cannot account for the nature and severity of the vocal symptoms. Therapists often comment that while some patients do not report or recall significant stresses prior to onset, once they have their voice back, they might reopen conversations about possible psychosocial triggers. Helpful assessment methods and diagnostic features are listed in **the full version.**

Treatment includes strategies to bypass problematic movement patterns by facilitating short, instinctual responses and overlearned or reflexive utterances (**Table 4**). It is advisable to inform patients that you are going to ask them to do some things differently which may entail making unusual sounds or carrying out gestures or bodily movements not associated with their usual way of talking. These activities can elicit normal phonation easily, without conscious preparation, since they are neither generally associated with use of the voice, nor are they experienced as being directly related to a conscious intent to communicate. If they were, they may trigger patterns of inhibitory muscular tension and exaggeration of the symptoms.

Specific treatment strategies may be necessary to reduce excessive musculoskeletal tension when present. They may include focal palpation of the laryngeal region, circumlaryngeal massage, and manual repositioning with gentle but firm lowering or compression of the larynx (when within professional scope and competence*[2]) [50,51]. The speech and language professional should reassure the patient that their pattern of excessive tension does not represent an irreversible muscular abnormality, but rather reflects a well-intentioned, but misdirected effort to achieve normal voice. Just prior to touching the neck, throat and larynx, it is important to explain what the clinician will do and why, and to ask permission to palpate, massage or reposition the larynx.

Use of traditional evidence-based techniques for dysphonia such as Vocal Function Exercises, Semi-Occluded Vocal Tract Exercises, and Resonant Voice Exercises may be useful for modifying voice, consolidation and generalisation.

Once normal phonation has been achieved, generalisation beyond the clinical setting is relatively straightforward, but it can be particularly challenging for some individuals in specific psychosocial contexts (i.e. a schoolteacher returning to the classroom after developing functional aphonia following significant difficulties in managing rebellious student behaviours and lack of support from school leaders). Under these circumstances, sustained improvement may be difficult to achieve, especially if there is evidence of long-standing anxiety, co-morbid depression, or ongoing medicolegal or workers' compensation issues [57]. Outcomes are more likely to be positive if the patient understands the relationship between the voice problem and any ongoing psychosocial issues and has strategies in place to deal with them. Basic supportive counselling (and use of additional psychological approaches within individual scope) by the speech and language professional is often sufficient, but referral for additional support from a mental health professional is sometimes essential [62,63,71–73].

Systematic reviews of randomised controlled trials exploring the efficacy of symptomatic voice therapy for 'functional dysphonia' report moderate-to-good evidence for the direct symptomatic and behavioural voice therapies, either alone, or in combination with indirect therapies that may involve education and vocal hygiene [74,75]. More recently an extensive evaluation of the evidence for the efficacy of therapy for functional, organic and neurological voice disorders has shown similar findings [76]. These studies did not appear to distinguish between patients within their broadly defined functional dysphonia groups (i.e. no organic structural abnormality) and those traditionally termed 'psychogenic/conversion aphonia dysphonia' as being discussed in this paper.

Another subtype of functional communication disorders is *functional mutism*, in which the patient does not produce sound, even with a whisper, or may mouth words with accurate but inaudible articulatory movements. This is in contrast to selective mutism which reflects voluntary refusal to speak, sometimes only in specific circumstances (often in the context of anxiety). In functional mutism the inability to speak is experienced as involuntary. Selective mutism and functional mutism sometimes overlap. In some cases the history reveals a breakdown in communication with significant others, and/or there is a conflict over speaking out or expressing negative emotions. The person may ask for access to an electronic device to assist with communication, which raises interesting issues about offering aids that may serve to perpetuate the ongoing pattern of mutism. When possible, communication without aids should be encouraged.

Specific symptoms - Functional stuttering

Functional stuttering is distinguished from developmental or neurogenic stuttering by extremes of variability or consistency on sound, syllable, word or phrase repetitions, unusual patterns of rate and

pausing, increased dysfluency with more simple speech tasks, and lack of improvement with activities that usually promote fluency. Of note, functional dysfluency may be internally inconsistent but may also be unusually consistent in presentation compared to developmental stuttering, such as stuttering on every syllable or word, or on the first word of every sentence [26,45,77,78]. Helpful assessment methods and positive diagnostic features are shown in **the full version**.

Case reports suggest functional dysfluency may follow stressful life events associated with conflict and difficulties with communication of negative emotions in close relationships or with an important person; dealing with high burden of responsibility or criticism in the work place where it is difficult to speak out and defend oneself; recent accident or illness sometimes in association with mild head injury leading to transient concussion; in situations where personal injury lawsuit or workers compensation may be an issue; or in association with posttraumatic stress disorder following combat. Clinicians emphasise that close attention needs to be given to these psychosocial issues, while also recognizing that the absence of a clear psychological trigger should not discount a functional diagnosis. Functional dysfluency can co-occur with other functional neurological symptoms, and in patients with comorbid neurologic disease including stroke, epilepsy, or traumatic brain injury [49,77,79,80].

Although positive outcomes have been reported in case studies of treatment of functional stuttering in adults, it remains unclear what elements of these treatments explain their effectiveness[49,77]. Some potential approaches to symptomatic treatment are summarised in **Table 6**.

When functional dysfluency does not resolve quickly with treatment, psychological impacts can be severe. Generalised anxiety and social anxiety in anticipation of speaking activity have significant implications for self-identity, close relationships, social participation and quality of life. While diagnosis of a psychological disorder is outside the scope of practice for speech language professionals, recognition of psychosocial factors in functional stuttering (as in developmental stuttering) allows therapists to appreciate the lived experience of stuttering and to guide appropriate therapy. Alongside symptomatic treatment, the therapist might helpfully include psychological approaches targeting features of avoidance, rumination and self-doubt [81,82]. As with developmental and neurogenic presentations of stuttering, collaboration with mental health professionals may be helpful in the management of secondary anxiety disorders and psychological distress [83].

Specific symptoms – Functional articulation symptoms

Functional articulation disorders are characterised by substitutions or distortions of specific sounds, some of which may be associated with developmental errors (e.g. 'wead'/'read', 'wittle'/'little', 'thome thoap'/'some soap'). Some sounds are produced with marked variability and unusual and exaggerated tongue, lip or jaw movements. These distortions may be accompanied by other unusual prosodic features, such as inappropriate patterns of loudness, with telegraphic speech and hesitations or exaggerated facial movements. Errors may be consistent and limited to particular sound, or unusual and associated with unusual tongue posturing (e.g. speaking with consistent tongue retraction). The patient may complain of weakness while exhibiting paradoxical strained voice quality. Functional articulation symptoms sometimes develop after dental, surgical or traumatic injury to the mouth, tongue or facial structures, or in combination with other functional symptoms affecting voice or fluency [5,84,85]. Examination features are detailed in **the full version**.

In addition to the general treatment approaches outlined above, traditional treatment approaches used for developmental and neurological articulatory disorders may be effective. Some treatment strategies are suggested in **Table 5**.

Specific symptoms – Other functional communication disorder symptoms (e.g., language, prosody, and accent)

Language impairments impacting on understanding, word finding, syntax, reading, and writing may occur in functional neurological disorders, often along with other functional cognitive symptoms [86]. Diagnosis is generally made on the basis of significant internal inconsistency in performance compared to well-described lesion-based patterns of aphasia, dysgraphia and alexia. An example of such inconsistency would be disproportionate difficulty with reading during formal assessment in comparison to day-to-day reading. In some cases, however, these problems may be abnormally consistent in comparison with lesion-based aphasia, dysgraphia, etc.

Subjective word finding or memory and concentration difficulties are not uncommon in patients with FND, and often appear to reflect inefficient allocation of attentional resources. Once other speech or communication symptoms, or other functional symptoms, are effectively treated, such cognitive symptoms may resolve. If the symptoms persist, some patients may benefit from being taught simple compensatory strategies for word retrieval deficits and similar difficulties.

Foreign accent syndrome (FAS) is a disorder of speech in which listeners perceive the affected individual as speaking with a foreign or regional accent. Onset of FAS may occur in neurological disease

or damage, for example after stroke or brain injury. Recent review of cases of self-reported FAS suggest that in some cases symptoms are the result of a functional neurological disorder. Functional FAS can be identified by the presence of internally inconsistent changes in the person's articulation and prosody, alterations to vowel and consonant production, stress, rhythm and intonation [48,87–90] (**Full version**).

Similarly, while immature features (e.g., developmental articulation errors) may persist in the speech of some adults, the sudden emergence of such features, and incongruity with the person's former manner of speaking, age, level of maturity, and occupation, suggests a functional disorder [50]. Such immature speech is often characterised by a combination of prosodic, voice and articulatory alterations such as elevated pitch, exaggerated inflectional patterns, and common developmental errors (e.g. th/s, w/r); immature speech may be accompanied by infantile gestures and expressions. Functional immature speech may co-occur with functional voice disorders or stuttering and may disappear when the voice or fluency symptoms have resolved with intervention. Treatment by the speech and language professional may be directed towards modification of these obvious speech, voice and infantile pragmatic behaviours. However, in view of the possible symbolic implications of these regressive symptoms, referral for family therapy with an emphasis on close interpersonal relationships or psychodynamic psychotherapy may be necessary.

Functional FAS may resolve spontaneously or during treatment; but there is relatively little information about the best treatment approaches to use when symptoms persist. Of note, FAS may or may not impact on communicative effectiveness. Others have suggested attention to detailed phonetic analysis with traditional speech therapy while recognising co-morbid psychological factors [91], or strategies routinely used for accent reduction in non-native speakers of English [92]. In a case described by Lee et al., (2016), functional FAS resolved with speech and language therapy approaches combined with CBT. Some treatment suggestions for functional FAS and other disorders of language, prosody and accent are offered in **the full version.**

Specific symptoms – Globus pharyngeus

Globus pharyngeus is a functional disorder which presents as a recurrent, non-painful but uncomfortable sensation of a lump in the throat, in the absence of dysphagia, odynophagia, gastro-oesophageal reflux (GORD/GERD) or a histopathology-based oesophageal motility disorder. Globus commonly co-occurs with functional voice disorders.

Symptoms may be persistent or intermittent and are experienced as a sensation of a foreign body in the throat (e.g., hair, crumb); a tightening or choking feeling; a lump in the throat; or sensations of throat strain or itch. Globus is more obvious between meals and improves with eating, but there is often a sense of food and/or liquid sticking or passing with difficulty through the oesophagus. Globus is often associated with throat clearing, a sense of mucus build up or dry throat, repeated swallowing, chronic cough or hoarseness and, over time, dysphonia with pharyngolaryngeal tension [44,93].

Studies have shown links between globus and psychological stress [94,95], with many patients reporting exacerbation of their symptoms during periods of high emotional intensity. Although common, psychological and psychiatric disorders may be an outcome rather than a predisposing factor.

Globus must be distinguished from dysphagia, but while the two symptoms do not necessarily co-occur, empirical data suggests that 20% of patients with functional dysphagia experience globus sensation with swallowing [96]. Within gastroenterology, globus is defined often using the Rome IV criteria as a diagnosis of exclusion [44,46]. This is in contrast to the inclusive methods preferred here for diagnosis of functional voice and speech disorders.

There are few adequately controlled treatment trials for globus. Although spontaneous remission may occur with reduction in psychological stress, 75% are still symptomatic after 3 years. One study suggested that globus symptoms resolved after reassuring diagnostic investigation by an ENT physician [93,97,98]; others have cautioned against over investigation [93,98].

While therapeutic trials of proton-pump inhibitors are sometimes recommended in order to exclude GERD as a cause of globus, it should be noted that in a randomised controlled trial, globus resolved as frequently in patients administered esomeprazole as in those given placebo [99]. Antidepressants may be helpful, even in the absence of mood symptoms, in reducing oesophageal pain and discomfort [100]. In one small trial, the SSRI antidepressant paroxetine was found both effective and superior to low dose amitriptyline (a tricyclic antidepressant), which was superior to the proton-pump inhibitor lansoprazole in treatment of refractory globus [101].

There is good preliminary evidence for the effectiveness of speech and language therapy in treating globus [47,98,102,103]. These approaches to management are summarised in **the full version.**

Specific symptoms – Functional dysphagia

Functional Dysphagia is more often *oropharyngeal* rather than *oesophageal* since oropharyngeal musculature is under voluntary rather than autonomic control. For both types of dysphagia exclusion of disease is vital, but for oropharyngeal dysphagia identifying positive features is an important part of the diagnosis and explanation when due to a functional disorder. Positive signs include inability to swallow in the absence of drooling or excessive oral secretions, or inability to control anything in the mouth but ability to spit saliva into a cup.

Symptoms of 'globus', a feeling of it being 'hard' to swallow, pain on swallowing, choking sensations, and coughing [104] are often described by patients with functional dysphagia. Patients often adopt avoidance behaviours as an attempt to reduce the perceived risk of choking. Examples include subtly reducing food intake and textures, changing head postures, eating slowly and with raised bodily tension, and social avoidance. Fear of choking is common and functional dysphagia may ultimately lead to unintended weight loss, social withdrawal, anxiety, panic and depression [96,105,106]. The impacts on quality of life are not dissimilar to those experienced by patients suffering dysphagia in association with head and neck cancer [107,108].

Functional *oesophageal* dysphagia can be diagnosed using Rome IV criteria, which unlike other disorders in this paper, are based on exclusion of disease rather than positive clinical features of functional disorder, with diagnostic criteria requiring that the following symptoms are present for at least 3 months, with onset 6 months before diagnosis: 1) a sense of solid or liquid food sticking, lodging, or passing abnormally through the oesophagus: 2) an absence of mechanical obstruction, GERD, or oesophageal motility disorder causing these symptoms [109]. Such patients require varying levels of investigation, the details of which are outside the scope of this article.

In some cases functional dysphagia is an isolated symptom, with muscle tension or laryngeal hyper-sensitivity [110]; in other cases dysphagia may be present as one of a range of functional motor symptoms, e.g. in stroke-like presentations; or may be associated with significant phagophobia or psychiatric symptoms. Functional symptoms elsewhere in the gastrointestinal tract, such as cyclical vomiting, may impact on food intake goals.

There have been no randomised controlled trials for treatments specifically targeted at functional dysphagia as opposed to globus. Antidepressants are sometimes used on the basis of evidence of benefit in overlapping disorders causing oesophageal discomfort [100].

An overview of educational, behavioural and psychological strategies that may be used by speech and language professional in the management of functional dysphagia are summarised in **the full version.** Of note, a recent trial of Cognitive Behaviour – Enhanced Swallowing Therapy (CB-EST) in patients recovering from head and neck cancer had promising outcomes; a similar approach may be beneficial in treatment of functional dysphagia [108].

Specific symptoms – Cough and vocal cord dysfunction (laryngeal hypersensitivity syndrome)

The group suggests that conceptualising laryngeal hypersensitivity syndrome as a functional disorder is appropriate. Chronic cough and vocal cord dysfunction (also known as paradoxical vocal fold motion and inducible laryngeal obstruction) can be considered manifestations of laryngeal hypersensitivity syndrome. Symptoms can occur in the absence of a known cause or persists despite thorough medical management. Cough and vocal cord dysfunction persist as a result of reversible changes in function or aberrant involuntary learned behaviours, rather than primarily due to ongoing disease or damage, but not necessarily in the presence or as a result of significant psychological distress. Importantly, it is possible to have laryngeal hypersensitivity syndrome without meeting criteria for DSM-5 somatic symptom disorder (in which disproportionate time, energy, thoughts, anxious feelings and behaviours persist in relation to the seriousness of the symptoms), which is the way the American College of Chest Physicians have framed conditions previously described as psychogenic cough [111,112].

It seems likely that the term *psychogenic cough* has been used inappropriately for a range of types of refractory cough. Idiopathic cough [113], medically unexplained cough [10,114], chronic refractory cough [115], neurogenic cough or laryngeal/cough hypersensitivity syndrome [116], all refer to cough of unknown aetiology that persists despite medical treatment. Psychiatric co-morbidity is far from universal and often secondary rather than causal [113,117].

Referral should follow respiratory assessment by a physician, which should usually include investigations including spirometry. This group recognises two patterns of dysfunctional cough: 1) persistent habitual cough, and 2) cough which occurs intermittently in a 'hypersensitive' pattern but without objective evidence of airway hypersensitivity, in response to salient stimuli as part of a conditioned response, and with or without perceived panic or autonomic arousal. Respiratory exposure chamber testing may be indicated in some persistent cases. In most cases the diagnosis should be clearly established prior to referral for speech therapy. However, in those cases where patients may self-refer, they should be encouraged to seek formal assessment by a respiratory physician.

The assessment process can help the patient to understand the nature of their disorder, to recognise the key triggers that stimulate their urge to cough and then, how they respond behaviourally to those triggers. Strategies and behavioural guidelines for treatment, as recommended by a speech and language professionals, physiotherapists and respiratory physicians specialising in this area are summarised in **the full version.** [118–120].

Conclusion

Functional communication, swallowing, and cough symptoms are common, and may be effectively treated with a range of techniques that already form part of the considerable expertise of speech and language professionals.

It is intended that these recommendations help speech and language professionals who work in a variety of settings to feel better able to approach the assessment and treatment of functional disorders with confidence and good outcomes.

We also hope that, by fostering interest into functional disorders as a key part of the work of speech and language professionals, our recommendations might stimulate research towards developing more evidence-based treatments for these disorders.

Table 1. A model of predisposing, precipitating and perpetuating risk factors for functional communication, swallowing, and cough disorders [7,13,14,45,62]

Factors:	Biological	Psychological	Social
Predisposing vulnerabilities	▪ Genetic factors ▪ Previous functional symptoms and disorders ▪ Pre-existing medical illness, especially affecting communication, e.g. traumatic brain injury ▪ Biological vulnerabilities in nervous system, lower/upper respiratory system, head & neck	▪ Personality traits (neuroticism, low social potency, stress reactivity, emotional inhibition, low self-esteem, perfectionism) ▪ Interpersonal difficulties ▪ Suggestibility ▪ Coping styles ▪ Attachment profiles ▪ Anxiety or depressive disorders	▪ Adverse life events ▪ Stress ▪ Poor relationships ▪ Symptom modelling (e.g. of family members)
Precipitating mechanisms	▪ Physical injury; strain/pain; surgery; medical illness ▪ Habituated muscle tension patterns; dysregulated movement patterns; excessive inhibition of movement ▪ Viral infection affecting upper or lower respiratory tract ▪ Inhaled toxic substances ▪ Exposure to noxious odours ▪ Historical or recent choking incident with persisting belief something still caught in the throat ▪ Drug/medication induced side effect ▪ Severe fatigue	▪ Dilemmas with forced choices leading to negative consequences ▪ Ambivalence over expression of negative emotions, conflict over speaking out, sense of entrapment ▪ Anticipation of difficult encounter, illness, or pending surgical procedure	▪ Significant adverse life events ▪ Interpersonal stress
Perpetuating factors	▪ Hypersensitivity to subtle changes in air pressure, temperature, sensation in respiratory and vocal tract ▪ Physiological arousal ▪ Pain	▪ Fear – avoidance ▪ Tendency to 'all or nothing' or catastrophic thinking ▪ Perception that voice use or swallowing are dangerous, harmful, effortful ▪ Hypervigilance and excessive self-monitoring ▪ Belief that symptoms are due to damage or	▪ Litigation or disability compensation issues ▪ Medical uncertainty ▪ Excessive reliance on unreliable sources of information ▪ Stigma

		suspected or confirmed disease/illness; unusual illness beliefs ▪ Entrenched symptoms have become part of one's sense of self or personal identity	

Table 2. Positive clinical features of functional communication and swallowing disorders

Positive clinical signs of FND	**General examples in functional communication and swallowing disorders**
Symptoms are inconsistent with clinical examination and laboratory/imaging findings	▪ Severity of speech deficit is disproportionate to severity of injury or locus of lesion (e.g. single lacunar stroke; mild traumatic brain injury) ▪ Total or partial loss of voice despite normal structure and function of vocal folds during laryngoscopy
Symptoms are internally inconsistent	▪ Resolution or reduced severity during small talk or other spontaneous discussion, when attention is diverted, or during natural automatic functions, preverbal and/or automatic utterances, playful, emotionally expressive activities, during laryngeal manipulation (voice disorders).*[2] ▪ Suggestibility – e.g. the symptom becomes much more prominent when it is being discussed
Symptoms are associated with inefficient and non-ergonomic patterns of movement	▪ When weakness is major complaint, speech, voice, swallowing fatigues in the direction of muscle hyperfunction ▪ Struggle behaviours - over-mouthing, eye blinking, facial contortions, excessive effort in breathing, neck, shoulders, strap muscles, shifts in body posture – including during non-speech oromotor tasks.
* Note that many structural/neurological communication disorders can show symptom fluctuations. The core difference is that in structural/primarily 'organic' cases one can discern plausible predictability in how/when/where symptoms vary – e.g., in relation to fatigue, time in medication cycle, cognitive load, and language variables such as word frequency, syllable complexity, stress placement in word/sentence. These underlying regularities tend not to be present in functional communication and swallowing disorders.	

Table 3. Explaining the diagnosis

Important elements of the explanation of a functional communication, swallowing, and other upper airway-related (e.g. cough and breathing) disorder

Although we have used the term 'functional disorder' for consistency, we understand that a range of terms may be used to describe these conditions. For example, cough might be more clearly explained in terms of hypersensitivity or hyperresponsiveness. We also recommend that the explanation be tailored appropriately to the patient's level of understanding. Examples of explanatory phrases used by the authors are listed below:

Take the problem seriously

- "These symptoms are real and not 'in your head'"
- "This is a genuine problem, and I believe you"
- "I imagine this must be making things at work/home really difficult"

Name the diagnosis

- "You have a functional speech disorder affecting your articulation"
- "You have a functional stuttering problem affecting your fluency"
- "This sensation of a lump in your throat is called functional globus"
- "This is a type of functional neurological disorder"

Explain the diagnosis in terms of what it <u>is</u> rather than saying what it is <u>not</u>

- "The symptoms are caused by abnormal brain functioning rather than structural damage or disease."
- "A software problem, not a hardware problem."
- "Software not broken, but has a glitch."
- "The machinery is still present and whole, but someone switched the outlets so now when it gets plugged in, it doesn't work smoothly anymore. We need to switch the outlets back."
- "The server is busy."
- "Your muscles have the potential to work properly but the messages are having problems getting through."
- "The train is off the tracks. The train and the tracks are both working correctly but only run smoothly when properly aligned."
- "Your brain has forgotten the path to produce voice for speech; we need to find the path to the voice again and memorize that feeling."
- "For a time you couldn't use the most efficient route (The Motorway) and instead needed to use a "B road" to make the movement. Now we know the Motorway is open, which will be more efficient, we can help you to use the Motorway consistently again."
- In explaining aetiology, using the analogy "sometimes people throw their back out but don't know what happened" and explain that the body can respond to experiences that we are not acutely aware of."
- Describe other non-structural causes of physical symptoms: stomach ache before an important exam; headache from a stressful day at work; shoulder/neck/arm tension from being tense over some issue."
- Explain that throat muscles are particularly vulnerable to stress/anxiety (analogy of lump in throat when cross/upset/holding back tears) and when they get into a habit of tightening it can alter how our voice sounds, contribute to breathing difficulties and cough. They need to be shown how to relax/release.
- "You have very efficiently learned how to use your voice (clear or protect your airway) when you needed this protection. This learning was so helpful that you kept using it when it was no longer necessary. Now you no longer need this technique and may benefit from reacquainting yourself with how you previously spoke (breathed, swallowed, etc)."
- Explain conditioned learning (e.g. "Pavlov's dogs"), especially when symptoms are intermittent, paving the way to "unlearning" with treatment.
- Explain "your brain is clever, and it knows that you need to stop and look after yourself".
- Explain the diagnosis using a sketch of a straight line balanced on the tip of a triangle, and discuss the importance of a balance between capacities and demands (bringing into the explanation the Demands and Capacities Model; when demands (internal and external) exceed capacity (compromised by pain, headache, sleep deprivation, etc), the neurologic demands on the brain's finite resources are compromised.

Use the analogy of demands as noise in the brain, impacting the finite synapses we depend on for rapid transmission and storage of information (capacities).
Explain and demonstrate the rationale for the diagnosis. Explain that the presence of variability suggests that improvement should be possible with treatment. • Demonstrate and explain positive clinical features, e.g.: "When you imitated my voice in this way, I was able to hear your voice, even though momentarily. This suggests that the vocal cords are able to move normally when automatic control takes over, and tells us that we should be able to get your voice working normally again and back under your voluntary control."
Provide written information and direct to other resources (see Appendix 1) • Printed symptom information sheets • Online information such as www.neurosymptoms.org • It is good practice to write clinical letters to patients when possible, and to enable access to clinical reports when respective specialists give permission.

Table 4: Treatment of functional voice disorders

Domains of intervention	Examples of possible strategies
Education & explanatory	• A key part of treatment is clear explanation of the nature of the disorder (see **table 3** for helpful phrases) and the rationale for the diagnosis. • Review the laryngoscopy examination and/or images together with the patient. It is particularly important to explain that 'abnormal movements' and similar remarks in written reports reflect reversible habitual movements and not irreversible structural abnormality, as patients may misunderstand the implications of such phrases. • Explain that voice disorders can result from excessive muscle tension which may prevent normal speech but does not represent an irreversible or uncontrollable abnormality and that it can brought under their control.
Symptomatic	Natural, reflexive, or instinctive behaviours usually accompanied by sound: • Cough and clear the throat (allowing voice to be present if possible). • Yawn followed by a sigh (as if with genuine relief). • Whimper sounds (as if a small distressed animal such as a kitten) or invite extremely high-pitched voice. • Grunt or groan (as if in pain, shifting posture, lifting a heavy item). • Comfort moaning sounds (associated with pleasure, eating something delicious). • Gargling with a firm sound (firstly with water then simulated without water • Pretend to be snoring. • Use slow easy onset with prolonged speech sounds such as /mmyyy-mmuumm. • Phonation on inhalation while maintaining a very relaxed body. Playful pre-linguistic vocal sounds that we might enjoy with a young child: • Blow raspberries while voicing. • Phonate with a rising and falling scale blowing the lips like a horse. • Move finger rapidly in between the lips shaped for 'ooh' with a falling inflection from high to low (you are so cute). • Pat the lips with hand while phonating (gentle affectionate tone as if to infant). • Gently pat the patient's back while they sigh out 'ah' (as if with comfort). • Patient pats own chest firmly while sighing 'ah' (with a sense of comfort or relief). • Siren quietly down the scale using nasal sounds such as /m/ /n/ or /ng/. • Produce a low-pitched glottal fry at the very bottom of the vocal range. • Giggle or laugh (as if in absolute delight). • Hold a tube of paper to the lips, phonate 'ooh' and notice sensation of lips vibrating. • Sing rising and falling scale on tongue trill with firmly voiced consonant, e.g., 'drr'. Automatic phrases and utterances with minimal communicative responsibility • Respond with short "Mm mm" "Okay" "Uh huh "(as in response to question). • Count and recite days of the week, sing "Happy Birthday" or favourite song. Physical and or postural manoeuvres:

	• Reposturing/repositioning/lowering of the larynx including circumlaryngeal massage with concurrent vocalisation. It is important to clearly explain and check with the patient before touching their neck. • During these manoeuvres, patient may be asked to phonate gently on an open vowel such as /ah/, nasal sounds such as /mm/, or to glide down the scale from high to low on a /whooo/, which will often facilitate a tentative squeak, an uncertain pitch break from falsetto phonation into modal voice, or a brief sound resembling their normal voice. For some it may even prompt more irregular phonation, so the therapist needs to reassure the patient that different stages of dysphonia may be heard as it returns to its normal pitch, quality and function. • Postural manipulations such as phonating while bending over or while leaning back and looking at the ceiling. Redirection of attentional focus: • Bubble blowing into water with vocalisation. • Large body movements such as jumping, shaking out body whilst make 'shivering noises' facilitates redirection and release. • Invite patient to communicate and interact while walking along, inside or outside the clinical setting, against the noise of traffic. • Use of amplification or headphones to alter or enhance auditory feedback. Use of electroglottography (EGG) and electromyography (EMG)as forms of laryngeal biofeedback which may also serve to redirect attention.
Psychological	• Communication counselling attending to predisposing, precipitating and perpetuating issues related to onset and maintenance of voice symptoms. • Identify and gently address patterns of avoidance of speaking or excessive dependence on aids to communication. • Identify any social or other phobic anxiety – i.e. of speaking in particular situations. Support to increase exposure (and so reduce anxiety) to feared situations. In some cases collaborative work with, or onward referral to, mental health professionals for structured psychotherapy (e.g. CBT) may be helpful.

Table 5. Treatment of functional dysfluency/stuttering

Domains of intervention	Examples of possible strategies
Education & explanatory	• Reassurance regarding nature of symptoms and good prognosis for resolution. • Explanation for rationale behind diagnosis of functional stuttering. • Explanation that dysfluencies can reflect effects of excessive muscle tension which may prevent normal speech but does not represent an irreversible or uncontrollable abnormality and that it can brought under their control. • Highlight the importance of forward airflow during speech to achieve smoothness.
Symptomatic	Reduction of excessive musculoskeletal tension in both speech and non-speech muscles often associated with stuttering: • Reduce muscle tension, drawing on techniques used for functional voice disorders. • Select high frequency abnormal behaviours associated with dysfluencies. • Palpate or manipulate facial muscles or lower the larynx to reduce muscle tension. • Reduce muscular tension in head, neck, shoulders and postural alignment. Eliminate secondary or accessory movements which may involve asking them to do something **differently** or adding **a distraction** which is faded out as speech normalises • Speak while lying on their back. • Invite person to squeeze a ball while speaking. • Invite person to sort blocks into different patterns while speaking. • Suggest finger tapping thumb and finger while speaking. • Speak while listening to music through headphones. **Modification of stuttering behaviours** Once excessive tension has been reduced, and the patient can produce some sounds, words or phrases with less struggle, normal speech may return in some cases. If not, it may be appropriate to introduce techniques currently used successfully for the treatment of developmental stuttering such as: **Speech restructuring and fluency shaping techniques, e.g. the Prolonged Speech Treatment Model, the Camperdown Program for adults who stutter, or the La Trobe Smooth Speech Clinic Program.** These intensive treatment programs offered individually or in groups may include: • Slowing rate of speech. • Easy, gentle onset. • Elongating vowels and producing prolonged speech. • Linking words together with controlled phrasing. • Emphasising speech naturalness. • Determining hierarchy of speaking situations with desensitization tasks.
Psychological	• Communication counselling attending to predisposing, precipitating perpetuating issues related to onset, presentation, and maintenance of stuttering behaviours. • Address abnormal illness beliefs, excessive attention and vigilance towards bodily sensations, and the sense of loss of control over speech fluency. • Teach person to respond to moments of stuttering and feelings of loss of control in more adaptive ways, using less struggle and tension which can be beneficial, both psychologically and physically. • Refer to mental health professionals for psychotherapy; Acceptance and Commitment Therapy; or CBT for treatment of anxiety in relation to stuttering.

Table 6. Treatment of functional articulation disorders

Domains of intervention	Examples of possible strategies
Education & explanatory	• Reassurance regarding nature of symptoms and good prognosis for resolution. • General principles already discussed as for functional voice and fluency including their understanding of diagnosis, the rationale for current diagnosis. • Education about how we actually speak versus how we think we speak e.g. we do not necessarily pronounce words according to spelling.
Symptomatic	• Reduction of excessive musculoskeletal tension in speech and non-speech muscles often associated with articulation: in head, neck, shoulders, face and mouth. • Where there is functional facial weakness, spasm, or trismus, collaborative treatment with physiotherapy or occupational therapy may be helpful. • Eliminate secondary or accessory movements which may involve the patient doing something **differently,** which acts as **a distraction, later to be** faded out as speech normalises. • Focusing on normal movements and sounds, distracting from abnormal sounds etc. • Dual tasking while speaking as form of distraction. • Invite non-speech articulation such as singing. • Introduce skills in 'mindfulness' during oromotor tasks as a way of maintaining focus on easy, smooth movements where possible. • Slow speech down or elongate a sound rather than building tension around it, which can be explained as 'resetting the system'. • Use nonsense words or syllable repetitions as way to demonstrate potential for 'normal' function. • Advance communication with higher cognitive linguistic content in hierarchical fashion (similar to the strategies for functional voice and stuttering). • Redirect patient focus on speech to other topics, monitoring if speech improves and in which contexts. If functional voice or fluency problems are also present the treatment of a single communication problem may result in resolution of all communication symptoms.
Psychological	• Attention to psychosocial issues as for other symptom groups. • Address cognitive features related to locus of control, executive function, abnormal illness beliefs, hypervigilance to bodily functions, etc. • Help person gain insight into the positive changes in articulation, and how they are achieving more normal control over speech movements.

Psychological	• Counselling by the speech and language professional in relation to psychological and life stresses contributing to symptoms.
	• Education about the physiology of anxiety, the anxiety arousal curve, and the importance of avoiding avoidance.
	• Treatment of any comorbid or secondary psychiatric disorder e.g. anxiety, depression, phagophobia.
	• Cognitive Behavioural Therapy strategies may be useful. Identify and challenge:
	  o Beliefs and cognitions, e.g. 'food will stick in my throat' 'I will choke and die'.
	  o Self-reported sensations, e.g. 'My throat feels tight and narrow' 'Food is sticking there and won't move'.
	  o Maladaptive behaviours, e.g. Avoidance of solids, withdrawing from others, eating in isolation.
	• Self-directed attention, e.g. Preoccupations with throat sensations 'Chewing is hard, swallowing is difficult'.
	• Recommend positive self-statements during the swallow such as 'my throat feels easy', 'this swallow is easy'.

Medical	• Provide information and advice to reduce acid reflux. Signpost for appropriate medical management of acid reflux and/or post nasal drip if present. • SSRI antidepressants or low-dose amitriptyline may be helpful for globus.

References

1 Espay AJ, Aybek S, Carson A, *et al.* Current concepts in diagnosis and treatment of functional neurological disorders. *JAMA Neurol* 2018;**75**:1132–41. doi:10.1001/jamaneurol.2018.1264

2 Carson AJ, Ringbauer B, Stone J, *et al.* Do medically unexplained symptoms matter? A prospective cohort study of 300 new referrals to neurology outpatient clinics. *J Neurol Neurosurg Psychiatry* 2000;**68**:207–10. doi:10.1136/jnnp.68.2.207

3 Heyman I. Mind the gap: Integrating physical and mental healthcare for children with functional symptoms. Arch. Dis. Child. 2019;**104**:1127–8. doi:10.1136/archdischild-2019-317854

4 Barnett C, Mitchell C, Tyson S. The management of patients with functional stroke: speech and language therapists' views and experiences. *Disabil Rehabil* Published Online First: 2021. doi:10.1080/09638288.2020.1867910

5 Duffy JR. Functional speech disorders: clinical manifestations, diagnosis, and management. In: Hallett M, Stone J, Carson A, eds. *Functional Neurologic Disorders, Volume 139 of the Handbook of Clinical Neurology series.* 2016. 379–88. doi:10.1016/B978-0-12-801772-2.00033-3

6 Nicholson C, Edwards MJ, Carson AJ, *et al.* Occupational therapy consensus recommendations for functional neurological disorder. *J Neurol Neurosurg Psychiatry* 2020;**91**:1037–45. doi:10.1136/jnnp-2019-322281

7 Nielsen G, Stone J, Matthews A, *et al.* Physiotherapy for functional motor disorders: a consensus recommendation. *J Neurol Neurosurg Psychiatry* 2015;**86**:1113–9. doi:10.1136/JNNP-2014-309255

8 Baker J, Ben-Tovim D, Butcher A, *et al.* Development of a modified diagnostic classification system for voice disorders with inter-rater reliability study. *Logop Phoniatr Vocology* 2007;**32**:99–112. doi:10.1080/14015430701431192

9 Barnett C, Armes J, Smith C. Speech, language and swallowing impairments in functional neurological disorder: a scoping review. Int. J. Lang. Commun. Disord. 2019;**54**:309–20. doi:10.1111/1460-6984.12448

10 Short J, Harding S. A systematic exploration of the terminology used in the diagnosis and treatment of oropharyngeal dysphagia (swallowing difficulty) in the absence of a clear medical explanation. In: *RCSLT Conference*. Nottingham: 2019. doi:10.1007/s00455-018-9912-9

11 Baker J. The role of psychogenic and psychosocial factors in the development of functional voice disorders. Int. J. Speech. Lang. Pathol. 2008;**10**:210–30. doi:10.1080/17549500701879661

12 Baker J, Ben-Tovim D, Butcher A, *et al.* Psychosocial risk factors which may differentiate between women with Functional Voice Disorder, Organic Voice Disorder and a Control group. *Int J Speech Lang Pathol* 2013;**15**:547–63. doi:10.3109/17549507.2012.721397

13 Butcher P, Elias A, Cavalli L. *Understanding and treating psychogenic voice disorder: A CBT framework*. New York: : Chichester and Wiley 2007.

14 Deary V, Miller T. Reconsidering the role of psychosocial factors in functional dysphonia. Curr. Opin. Otolaryngol. Head Neck Surg. 2011;**19**:150–4. doi:10.1097/MOO.0b013e328346494d

15 O'Hara J, Miller T, Carding P, *et al.* Relationship between fatigue, perfectionism, and functional dysphonia. *Otolaryngol - Head Neck Surg* 2011;**144**:921–6. doi:10.1177/0194599811401236

16 Roy N, Bless DM. Personality traits and psychological factors in voice pathology: a foundation for future research. *J Speech, Lang Hear Res* 2000;**43**:737–48. doi:10.1044/jslhr.4303.737

17 Roy N, Bless DM. Toward a theory of the dispositional bases of functional dysphonia and vocal nodules: Exploring the role of personality and emotional adjustment. In: *The handbook of voice quality measurement*. 2000. 461–80.https://www.researchgate.net/profile/Nelson_Roy/publication/313695030_Toward_a_Theory_of_the_Dispositional_Bases_of_Functional_Dysphonia_and_Vocal_Nodules_Exploring_the_Role_of_Personality_and_Emotional_Adjustment/links/58a31cb992851cb987733ebb/Toward-a-T (accessed 19 Jan 2021).

18 Van Mersbergen M, Patrick C, Glaze L. Functional dysphonia during mental imagery: Testing the trait theory of voice disorders. *J Speech, Lang Hear Res* 2008;**51**:1405–23. doi:10.1044/1092-4388(2008/06-0216)

19 Ludwig L, Pasman JA, Nicholson T, *et al.* Stressful life events and maltreatment in conversion (functional neurological) disorder: systematic review and meta-analysis of case-control studies. *The Lancet Psychiatry* 2018;**5**:307–20. doi:10.1016/S2215-0366(18)30051-8

20 Edwards MJ. Neurobiologic theories of functional neurologic disorders. In: Hallett M, Stone J, Carson A, eds. *Functional Neurologic Disorders, Volume 139 of the Handbook of Clinical Neurology series.* 2016. 131–7. doi:10.1016/B978-0-12-801772-2.00012-6

21 Edwards MJ, Adams RA, Brown H, *et al.* A Bayesian account of 'hysteria'. *Brain* 2012;**135**:3495–512. doi:10.1093/brain/aws129

22 Pareés I, Kojovic M, Pires C, *et al.* Physical precipitating factors in functional movement disorders. *J Neurol Sci* 2014;**338**:174–7. doi:10.1016/j.jns.2013.12.046

23 Hallett M, Stone J, Carson A. *Functional Neurologic Disorders, Volume 139 of the Handbook of Clinical Neurology series.* Amsterdam: : Elsevier 2016.

24 Haggard P. Sense of agency in the human brain. *Nat Publ Gr* Published Online First: 2017. doi:10.1038/nrn.2017.14

25 Elias A, Raven R, Butcher P, *et al.* Speech therapy for psychogenic voice disorder: A survey of current practice and training. *Int J Lang Commun Disord* 1989;**24**:61–76. doi:10.3109/13682828909011946

26 Griffith MM. Identifying speech-language pathologists' current perceptions and practice patterns. 2015. https://encompass.eku.edu/etd (accessed 19 Jan 2021).

27 Keulen S, Verhoeven J, De Witte E, *et al.* Foreign accent syndrome as a psychogenic disorder: a review. *Front Hum Neurosci* 2016;**10**:168. doi:10.3389/fnhum.2016.00168

28 Baker J. *Psychosocial perspectives on the management of voice disorders*. Oxford: : Compton Publishing 2017.

29 Dilollo A, Neimeyer R. *Counseling in speech-language pathology and audiology*. San Diego: : Plural Publishing 2014. doi:10.1097/00003446-199410000-00012

30 Fourie RJ. *Therapeutic processes for communication disorders: A guide for clinicians and students*. New York: : Psychology Press 2010. doi:10.4324/9780203839706

31 Holland AL. *Counseling in Communication Disorders*. Brisbane: : Plural Publishing 2007. https://www.bookdepository.com/Counseling-Communication-Disorders-Audrey-Holland/9781597560498 (accessed 19 Jan 2021).

32 Mills M, Stoneham G. The voice book for trans and non-binary people : a practical guide to creating and sustaining authentic voice and communication. 2017;:222.https://www.amazon.co.uk/Voice-Book-Trans-Non-Binary-People/dp/1785921282 (accessed 19 Jan 2021).

33 American Speech-Language-Hearing Association. Scope of practice in speech-language pathology. 2016. https://www.asha.org/siteassets/uploadedfiles/sp2016-00343.pdf

34 Speech Pathology Australia. Scope of Practice in Speech Pathology. 2015. https://www.speechpathologyaustralia.org.au/SPAweb/About_us/SPA_Documents/spaweb/About_Us/SPA_Documents/SPA_Documents.aspx?hkey=3c5269c1-51eb-45cf-8081-ab9c0544180a#anchor_sp

35 Royal College of Speech and Language Therapists. Counselling Guidance: Responsibilities. https://www.rcslt.org/members/delivering-quality-services/counselling/counselling-guidance#section-3 (accessed 20 Jan 2021).

36 Freeburn J. Speech therapy: being understood clearly. In: LaFaver K, Maurer C, Nicholson T, *et al.*, eds. *Functional Movement Disorder: An Interdisciplinary Case-Based Approach*. 2021.

37 Talmon M. *Single-session therapy: Maximizing the effect of the first (and often only) therapeutic encounter.* Jossey-Bass 1990. https://psycnet.apa.org/record/1990-98311-000 (accessed 20 Jan 2021).

38 Lehn A, Gelauff J, Hoeritzauer I, *et al.* Functional neurological disorders: mechanisms and treatment. *J Neurol* 2016;**263**:611–20. doi:10.1007/s00415-015-7893-2

39 Stone J. Functional neurological disorders: The neurological assessment as treatment. Pract. Neurol. 2016;**16**:7–17. doi:10.1136/practneurol-2015-001241

40 Adams C, Anderson J, Madva EN, *et al.* You've made the diagnosis of functional neurological disorder: Now what? *Pract Neurol* 2018;**18**:323–30.

41 Gilmour GS, Nielsen G, Teodoro T, *et al.* Management of functional neurological disorder. *J Neurol* 2020;**267**:2164–72. doi:10.1007/s00415-020-09772-w

42 LaFaver K. Treatment of Functional Movement Disorders. Neurol. Clin. 2020;**38**:469–80. doi:10.1016/j.ncl.2020.01.011

43 Stone J, Edwards M. Trick or treat? Showing patients with functional (psychogenic) motor symptoms their physical signs. *Neurology* 2012;**79**:282–4.

44 Baumann A, Katz PO. Functional disorders of swallowing. In: *Handbook of Clinical Neurology*. 2016. 483–8. doi:10.1016/B978-0-12-801772-2.00039-4

45 Duffy J. *Motor Speech Disorders*. 4th ed. St Louis: : Elsevier 2020.

46 Galmiche J, Clouse R, Balint A, *et al.* Functional esophageal disorders. *Gastroenterology* 2006;**130**:1459–65.https://www.sciencedirect.com/science/article/pii/S0016508506005075 (accessed 19 Jan 2021).

47 Harvey PR, Theron BT, Trudgill NJ. Managing a patient with globus pharyngeus. *Frontline Gastroenterol* 2018;**9**:208–12. doi:10.1136/flgastro-2017-100844

48 McWhirter L, Miller N, Campbell C, *et al.* Understanding foreign accent syndrome. *J Neurol Neurosurg Psychiatry* 2019;**90**. doi:10.1136/jnnp-2018-319842

49 Roth CR, Cornis-Pop M, Beach WA. Examination of validity in spoken language evaluations: Adult onset stuttering following mild traumatic brain injury. NeuroRehabilitation. 2015;**36**:415–26. doi:10.3233/NRE-151230

50 Aronson A, Bless DM. *Clinical voice disorders*. 4th ed. New York: : Thieme 2009. doi:10.1016/s0214-4603(10)70007-3

51 Roy N. Assessment and treatment of musculoskeletal tension in hyperfunctional voice disorders. *Int J Speech Lang Pathol* 2008;**10**:195–209. doi:10.1080/17549500701885577

52 Roy N, Dietrich M, Blomgren M, *et al.* Exploring the neural bases of primary muscle tension dysphonia: a case study using functional magnetic resonance imaging. *J Voice* 2019;**33**:183–94. doi:10.1016/j.jvoice.2017.11.009

53 Titze IR, Verdolini Abbott K. *Vocology The Science and Practice of Voice Habilitation*. Salt Lake City: : National Center for Voice and Speech 2012.

54 Yiu EML, Verdolini K, Chow LPY. Electromyographic study of motor learning for a voice production task. *J Speech, Lang Hear Res* 2005;**48**:1254–68. doi:10.1044/1092-4388(2005/087a)

55 Squire LR. *Mechanisms of memory*. Univ. of California Press 1986. http://science.sciencemag.org/ (accessed 20 Jan 2021).

56 Boone D. *The voice and voice therapy*. New Jersey: : Prentice-Hall 1977.

57 Baker J. Psychogenic dysphonia: Peeling back the layers. *J Voice* 1998;**12**:527–35. doi:10.1016/S0892-1997(98)80061-1

58 Goldstein LH, Robinson EJ, Mellers JDC, *et al.* Cognitive behavioural therapy for adults with dissociative seizures (CODES): a pragmatic, multicentre, randomised controlled trial. *The Lancet Psychiatry* 2020;**7**:491–505. doi:10.1016/S2215-0366(20)30128-0

59 Richardson M, Isbister G, Nicholson B. A novel treatment protocol (Nocebo Hypothesis Cognitive Behavioural Therapy; NH-CBT) for functional neurological symptom disorder/conversion disorder: A retrospective consecutive case series. *Behav Cogn Psychother* 2018;**46**:497–503. doi:10.1017/S1352465817000832

60 Butcher P, Elias A. Cognitive-behavioural therapy with dysphonic patients: An exploratory investigation. *Coll Speech Ther Bull* 1983;**377**:1–3.https://scholar.google.com/scholar?hl=en&as_sdt=0%2C5&q=Butcher%2C+P.%2C+%26+Elias%2C+A.+%281983%29.+Cognitive-behavioural+therapy+with+dysphonic+patients%3A+An+exploratory+investigation.+The+College+of+Speech+Therapists+Bulletin%28377%29%2C+1-3.+&btnG= (accessed 19 Jan 2021).

61 Carding P, Deary V, Miller T. Cognitive behavioural therapy in the treatment of functional dysphonia in the United Kingdom. In: Yiu E, ed. *International Perspectives on Voice Disorders*. UK: : Multilingual Matters / Channel View Publications 2013. 133–48. doi:10.21832/9781847698742-014

62 Deary V, McColl E, Carding P, *et al.* A psychosocial intervention for the management of functional dysphonia: Complex intervention development and pilot randomised trial. *Pilot Feasibility Stud* 2018;**4**. doi:10.1186/s40814-018-0240-5

63 Miller T, Deary V, Patterson J. Improving access to psychological therapies in voice disorders: A cognitive behavioural therapy model. Curr. Opin. Otolaryngol. Head Neck Surg. 2014;**22**:201–5. doi:10.1097/MOO.0000000000000056

64 Gutkin M, McLean L, Brown R, *et al.* Systematic review of psychotherapy for adults with functional neurological disorder. J. Neurol. Neurosurg. Psychiatry. 2021;**92**:36–44. doi:10.1136/jnnp-2019-321926

65 Baker J. The therapeutic relationship once established, need never be broken. Int. J. Speech. Lang. Pathol. 2010;**12**:309–12. doi:10.3109/17549501003749842

66 Spengler FB, Becker B, Kendrick KM, *et al.* Emotional dysregulation in psychogenic voice loss. Psychother. Psychosom. 2017;**86**:121–3. doi:10.1159/000452306

67 Baker J. Functional voice disorders: clinical presentations and differential diagnosis. In: Hallett M, Stone J, Carson A, eds. *Functional Neurologic Disorders, Volume 139 of the Handbook of Clinical Neurology series.* Amsterdam: : Elsevier 2016. 389–406.

68 Verdolini K, Rosen C, Branski R. *Classification Manual for Voice Disorders-I*. New Jersey: : Laurence Erlbaum Associates 2006. doi:10.4324/9781410617293

69 Dietrich M, Verdolini Abbott K. Psychobiological stress reactivity and personality in persons with high and low stressor-induced extralaryngeal reactivity. *J Speech, Lang Hear Res* 2014;**57**:2076–89. doi:10.1044/2014_JSLHR-S-12-0386

70 Roy N, Bless DM, Heisey D. Personality and voice disorders: A multitrait-multidisorder analysis. *J Voice* 2000;**14**:521–48. doi:10.1016/S0892-1997(00)80009-0

71 Kollbrunner J, Seifert E. Encouragement to increase the use of psychosocial skills in the diagnosis and therapy of patients with functional dysphonia. J. Voice. 2017;**31**:132.e1-132.e7. doi:10.1016/j.jvoice.2015.11.021

72 Kiese-Himmel C. Klinisch-psychologische Bausteine in der Diagnostik funktioneller Dysphonien - eine Übersicht. Laryngorhinootologie. 2015;**94**:156–62. doi:10.1055/s-0034-1394454

73 Behrendt S. Die psychogene aphonie auf dem hintergrund psychotherapeutischer modelle und erfahrungen. *Spr Stimme Gehor* 2002;**26**:9–13. doi:10.1055/s-2002-23117

74 Ruotsalainen J, Sellman J, Lehto L, *et al.* Systematic review of the treatment of functional dysphonia and prevention of voice disorders. Otolaryngol. - Head Neck Surg. 2008;**138**:557–65. doi:10.1016/j.otohns.2008.01.014

75 Speyer R. Effects of voice therapy: A systematic review. J. Voice. 2008;**22**:565–80. doi:10.1016/j.jvoice.2006.10.005

76 Carding P, Bos-Clark M, Fu S, *et al.* Evaluating the efficacy of voice therapy for functional, organic and neurological voice disorders. *Clin Otolaryngol* 2017;**42**:201–17. doi:10.3109/13682829209012036

77 Baumgartner J, Duffy JR. Psychogenic stuttering in adults with and without neurologic disease. *J Med Speech Lang Pathol* 1997;**5**:75–95.https://www.researchgate.net/profile/Joseph_Duffy/publication/279897923_Psychogenic_stuttering_in_adults_with_and_without_neurologic_disease/links/565493ca08aeafc2aabbe37d.pdf (accessed 19 Jan 2021).

78 Deal JL. Sudden onset of stuttering: A case report. *J Speech Hear Disord* 1982;**47**:301–4. doi:10.1044/jshd.4703.301

79 Binder LM, Spector J, Youngjohn JR. Psychogenic stuttering and other acquired nonorganic speech and language abnormalities. *Arch Clin Neuropsychol* 2012;**27**:557–68. doi:10.1093/arclin/acs051

80 Helm-Estabrooks N, Hotz G. Sudden onset of 'stuttering' in an adult: Neurogenic or psychogenic? *Semin Speech Lang* 1998;**19**:23–9. doi:10.1055/s-2008-1064032

81 Connery A, McCurtin A, Robinson K. The lived experience of stuttering: a synthesis of qualitative studies with implications for rehabilitation. Disabil. Rehabil. 2020;**42**:2232–42. doi:10.1080/09638288.2018.1555623

82 Scheurich JA, Beidel DC, Vanryckeghem M. Exposure therapy for social anxiety disorder in people who stutter: An exploratory multiple baseline design. *J Fluency Disord* 2019;**59**:21–32. doi:10.1016/j.jfludis.2018.12.001

83 Beilby J. Psychosocial impact of living with a stuttering disorder: Knowing is not enough. *Semin Speech Lang* 2014;**35**:132–43. doi:10.1055/s-0034-1371756

84 Baizabal-Carvallo JF, Jankovic J. Speech and voice disorders in patients with psychogenic movement disorders. *J Neurol* 2015;**262**:2420–4. doi:10.1007/s00415-015-7856-7

85 Chung DS, Wettroth C, Hallett M, *et al.* Functional speech and voice disorders: case series and literature review. *Mov Disord Clin Pract* 2018;**5**:312–6. doi:10.1002/mdc3.12609

86 Jones A, Smakowski A, O'Connell N, *et al.* Functional stroke symptoms: A prospective observational case series. *J Psychosom Res* 2020;**132**. doi:10.1016/j.jpsychores.2020.109972

87 Keulen S, Verhoeven J, De Page L, *et al.* Psychogenic foreign accent syndrome: a new case. *Front Hum Neurosci* 2016;**10**:143. doi:10.3389/fnhum.2016.00143

88 Keulen S, Verhoeven J, Bastiaanse R, *et al.* Perceptual accent rating and attribution in psychogenic FAS: some further evidence challenging whitaker's operational definition. *Front Hum Neurosci* 2016;**10**:1–14. doi:10.3389/fnhum.2016.00062

89 Lee O, Ludwig L, Davenport R, *et al.* Functional foreign accent syndrome. *Pract Neurol* 2016.

90 Romö N, Miller N, Cardoso A. Segmental diagnostics of neurogenic and functional foreign accent syndrome. *J Neurolinguistics* 2021;**58**. doi:10.1016/j.jneuroling.2020.100983

91 Haley KL, Roth HL, Helm-Estabrooks N, *et al.* Foreign accent syndrome due to conversion disorder: Phonetic analyses and clinical course. *J Neurolinguistics* 2010;**23**:28–43. doi:10.1016/j.jneuroling.2009.08.001

92 Sikorski LD. Foreign accents: Suggested competencies for improving communicative pronunciation. *Semin Speech Lang* 2005;**26**:126–30. doi:10.1055/s-2005-871208

93 Karkos PD, Wilson JA. The diagnosis and management of globus pharyngeus: Our perspective from the United Kingdom. Curr. Opin. Otolaryngol. Head Neck Surg. 2008;**16**:521–4. doi:10.1097/MOO.0b013e328316933b

94 Deary IJ, Wilson JA, Kelly SW. Globus Pharyngis, Personality, and Psychological Distress in the General Population. *Psychosomatics* 1995;**36**:570–7. doi:10.1016/S0033-3182(95)71614-0

95 Harris MB, Deary IJ, Wilson JA. Life events and difficulties in relation to the onset of globus pharyngis. *J Psychosom Res* 1996;**40**:603–15. doi:10.1016/0022-3999(96)00024-4

96 Elias A. Our voice and neuro caseloads - making the links. NHS 2019.

97 Järvenpää P, Arkkila P, Aaltonen LM. Globus pharyngeus: a review of etiology, diagnostics, and treatment. Eur. Arch. Oto-Rhino-Laryngology. 2018;**275**:1945–53. doi:10.1007/s00405-018-5041-1

98 Lee BE, Kim GH. Globus pharyngeus: A review of its etiology, diagnosis and treatment. World J. Gastroenterol. 2012;**18**:2462–71. doi:10.3748/wjg.v18.i20.2462

99 Noordzij JP, Khidr A, Evans BA, *et al.* Evaluation of omeprazole in the treatment of reflux laryngitis: A prospective, placebo-controlled, randomized, double-blind study. *Laryngoscope* 2001;**111**:2147–51. doi:10.1097/00005537-200112000-00013

100 Weijenborg PW, de Schepper HS, Smout AJPM, *et al.* Effects of antidepressants in patients with functional esophageal disorders or gastroesophageal reflux disease: A systematic review. Clin. Gastroenterol. Hepatol. 2015;**13**:251-259.e1. doi:10.1016/j.cgh.2014.06.025

101 Chen D, Jia L, Gu X, *et al.* Comparison of paroxetine and amitriptyline in the treatment of refractory globus pharyngeus. *Dig Liver Dis* 2016;**48**:1012–7. doi:10.1016/j.dld.2016.05.025

102 Khalil HS, Reddy VM, Bos-Clark M, *et al.* Speech therapy in the treatment of globus pharyngeus: How we do it. Clin. Otolaryngol. 2011;**36**:388–92. doi:10.1111/j.1749-4486.2011.02326.x

103 Wareing M, Elias A, Mitchell D. Management of globus sensation by the speech therapist. *Logop Phoniatr Vocology* 1997;**22**:39–42. doi:10.3109/14015439709075313

104 Kang CH, Zhang N, Lott DG. Muscle tension dysphagia: contributing factors and treatment efficacy. *Ann Otol Rhinol Laryngol* 2020;:000348942096633. doi:10.1177/0003489420966339

105 Verdonschot RJCG, Baijens LWJ, van de Kolk I, *et al.* Affective symptoms in patients with oropharyngeal dysphagia: A systematic review. J. Psychosom. Res. 2017;**97**:102–10. doi:10.1016/j.jpsychores.2017.04.006

106 Bülow M. Psychogenic dysphagia. In: *Principles of Deglutition: A Multidisciplinary Text for Swallowing and its Disorders*. Springer New York 2013. 771–6. doi:10.1007/978-1-4614-3794-9_52

107 Patterson JM. Psychological Interventions for the Head and Neck Cancer Population Who Are Experiencing Dysphagia. *Perspect ASHA Spec Interes Groups* 2019;**4**:1049–54. doi:10.1044/2019_pers-sig13-2019-0001

108 Patterson JM, Exley C, McColl E, *et al.* Feasibility and acceptability of combining cognitive behavioural therapy techniques with swallowing therapy in head and neck cancer dysphagia. *BMC Cancer* 2018;**18**:1–11. doi:10.1186/s12885-017-3892-2

109 Aziz Q, Fass R, Gyawali CP, *et al.* Esophageal disorders. *Gastroenterology* 2016;**150**:1368–79. doi:10.1053/j.gastro.2016.02.012

110 Kang CH, Hentz JG, Lott DG. Muscle tension dysphagia: symptomology and theoretical framework. *Otolaryngol - Head Neck Surg (United States)* 2016;**155**:837–42. doi:10.1177/0194599816657013

111 Vertigan AE. Somatic cough syndrome or psychogenic cough-What is the difference? *J Thorac Dis* 2017;**9**:831–8. doi:10.21037/jtd.2017.03.119

112 Vertigan AE, Murad MH, Pringsheim T, *et al.* Somatic cough syndrome (previously referred to as psychogenic cough) and tic cough (previously referred to as habit cough) in adults and children: CHEST guideline and expert panel report. *Chest* 2015;**148**:24–31. doi:10.1378/chest.15-0423

113 McGarvey LP, Carton C, Gamble L, *et al.* Prevalence of psychomorbidity among patients with chronic cough. *Cough* 2006;**2**:1–6. doi:10.1186/1745-9974-2-4

114 Gibson P, Wang G, McGarvey L, *et al.* Treatment of unexplained chronic cough chest guideline and expert panel report. *Chest* 2016;**149**:27–44. doi:10.1378/chest.15-1496

115 Gibson PG, Vertigan AE. Management of chronic refractory cough. *BMJ* 2015;**351**. doi:10.1136/bmj.h5590

116 Song WJ, Morice AH. Cough hypersensitivity syndrome: A few more steps forward. Allergy, Asthma Immunol. Res. 2017;**9**:394–402. doi:10.4168/aair.2017.9.5.394

117 Dicpinigaitis P V., Tso R, Banauch G. Prevalence of depressive symptoms among patients with chronic cough. *Chest* 2006;**130**:1839–43. doi:10.1378/chest.130.6.1839

118 Chamberlain Mitchell SAF, Ellis J, Ludlow S, *et al.* Non-pharmacological interventions for chronic cough: The past, present and future. Pulm. Pharmacol. Ther. 2019;**56**:29–38. doi:10.1016/j.pupt.2019.02.006

119 Mathur A, Liu-Shiu-Cheong PSK, Currie GP. The management of chronic cough. QJM. 2019;**112**:651–6. doi:10.1093/qjmed/hcy259

120 Vertigan AE, Theodoros DG, Gibson PG, *et al.* Efficacy of speech pathology management for chronic cough: A randomised placebo controlled trial of treatment efficacy. *Thorax* 2006;**61**:1065–9. doi:10.1136/thx.2006.064337

SLT consensus recommendations - Appendix 1 – Helpful resources

For professionals:

- The international Functional Neurological Disorder Society streams a wide programme of webinars, with back catalogue available to members.
- 'Emotion Matters' is a resource for health and social care professionals working with adults with long term physical healthy issues, and includes the **SWIFT Check Up** – a tool to help develop a clear picture of a patient's social, occupational, and emotional background.
- Northern Speech Services dysphagia app is helpful for showing patients how swallowing works.
- USA Mental Health Resources at National Institutes of Mental Health (NIMH), National Alliance on Mental Illness (NAMI), and the American Psychological Association.
- Medline Plus on voice disorders
- The Voice Foundation
- The National Center for Voice and Speech (NCVS) (USA)
- University of Wisconsin Madison Voice and Swallowing Lecture Series

For patients:

Functional neurological disorders in general:

- Neurosymptoms - Functional neurological disorders: a patient's guide. This website is also available in German, Dutch, French, Italian, Spanish, Portuguese, Swedish, and Russian.
- FND Australia Workbook
- FND Portal blog (and the associated @fndportal twitter account)
- FND Hope International
- FND Action UK
- FND Forum
- My FND – a free app for people with FND

Foreign Accent Syndrome

- University of Texas at Dallas 'Foreign Accent Syndrome' website

Voice problems

- British Voice Association has a range of leaflets about the voice, and about looking after your voice, including ' The Effects of Stress and Emotion on the Voice'.
- Voice Doctor

Counselling and psychological therapies

- (USA only) – Psychology Today – Find a Therapist

Trauma

- USA Trauma Research Foundation

Functional Neurological Disorder and Personal Injury

Laura McWhirter

Ingrid Hoeritzauer

Alan Carson

Jon Stone*

Diagnosis; Neurological disorders; Personal injury

Introduction

The situation in which a person develops symptoms and impairments are greater than, or inconsistent with, the extent of their injuries or severity of pathophysiological identifiable disease is not unique to personal injury litigation, but commonly encountered in all fields of clinical medicine.

In Functional Neurological Disorder ("FND"), neurological symptoms occur which are involuntary and experienced as real—usually distressing and disabling—but which are not a direct result of structural damage or pathophysiological disease. Common symptoms of functional neurological disorder include paralysis (weakness) and other abnormalities of movement, sensory abnormalities, seizure-like episodes, and cognitive (memory and concentration) difficulties. Importantly, FND does not only occur as a stand-alone diagnosis, but is commonly comorbid with symptoms which do relate directly to structural damage or disease; that is, a person with symptoms due to neurological injury might *also* have functional symptoms—sometimes described as "functional overlay" (although best described as functional disorder comorbidity in our view). FND is therefore one reason why a person may develop symptoms and disability which seem excessive, or incongruent with the extent and nature of an injury sustained.

As clinicians and researchers closely involved in the treatment of patients with FND, and who also have experience of providing expert opinion in litigation regarding FND and cases where there is functional disorder comorbidity, we are familiar with the challenges which FND and allied disorders can pose to both legal and non-neuropsychiatric medical experts. In this review, we explain what functional neurological disorders are, how they overlap with other conditions, how they are diagnosed and defined, and with regard to causation what factors may predispose, precipitate and perpetuate symptoms. Finally, we will summarise current scientific understanding regarding the neurobiological mechanisms of FND.

Case A: Functional Neurological Disorder

A 56-year-old roofer falls from 10m in the course of his work. He sustains a serious fracture of the left leg which is repaired operatively with excellent objective outcome. He is predicted by the orthopaedic surgeon to be able to return to work within six months. However, he is slow and fearful of mobilising after surgery, has difficulty walking, and one year after the injury still walks cautiously, and effortfully with elbow crutches. On examination, there is intermittent "give way" weakness of both legs. Hoover's sign is positive in the left leg: he is unable to push his left leg down onto the chair, but when prompted to

* Centre for Clinical Brain Sciences, University of Edinburgh.

move his attention to the task of lifting the opposite leg, full strength returns. He receives a diagnosis of functional neurological disorder, which he appears to accept. He is angry and persistently ruminates about the effect the accident has had on his life. He goes through multidisciplinary rehabilitation but does not improve. He continues to take significant doses of opiate and sedative medications; his activities remain severely limited, and he is unable to mobilise without a wheelchair when out of his house. Covert surveillance demonstrates no discrepancy between reported and observed function. There are arguments about a pre-accident history of pain and depression for which he had treatment but didn't take time off work, and about whether the legal case is interfering with his motivation to improve.

Case B: Complex Regional Pain Syndrome ("CRPS")/Functional Neurological Disorder

A 47-year-old right-handed woman slips on ice and sustains a fracture of the left wrist. The fracture is reduced (re-aligned) and the arm treated in a cast for six weeks. After removal of the cast, she finds that it is too painful to move the arm and holds it immobile, flexed against her body and protected. The arm becomes more and more painful, but also feels "different", as if it is not really her own arm. Her hand feels weak and clumsy, and her fingers begin to curl in towards her palm. On examination, the arm is a little thinner than the other and the left hand feels cooler than the right. Any touch or attempts to move the hand and wrist are met with complaints of severe burning pain. She receives a diagnosis of Complex Regional Pain Syndrome from a Pain Medicine specialist, but a neurologist considers that elements of her condition are better explained as a functional neurological disorder. There are debates about whether she has a psychiatric or medical disorder and whether a neurologist, psychiatrist or pain medicine expert is best placed to provide a diagnosis and prognosis.

Case C: Functional cognitive disorder as part of a "post-concussion syndrome"

A 23-year-old man is struck by a falling object at work. He is "knocked out" for a few seconds and has no external injury. He feels "dazed" after he comes round, but is not confused and has clear recall of his journey in an ambulance to the hospital emergency department. He returns home the same day and spends several days off work, mostly in bed, as he feels "groggy", dizzy, and tired. When he returns to work the following week he feels "spaced out", unwell, has a headache when using the computer and has to go home. Over the following weeks and months his memory gets worse and worse. He walks into rooms and forgets what he went in for, misses appointments, forgets passwords and pin numbers, and starts to depend on lists and a calendar where he didn't need to before; his partner notices that he sometimes loses the thread of what he is saying in conversation. Crowded environments make him feel worse, and he stops going to the supermarket and the gym. He has a neuropsychological assessment which concludes that he has widespread deficits in executive function, attention and memory compatible with a traumatic brain injury. Following this he joins a head injury support group and fails to improve. Neuropsychiatric assessment finds him to be anxious and slightly depressed. There is a discrepancy between his neuropsychological test performance and his "real world" cognitive abilities. His "post-concussional" symptoms are assessed as being primarily the result of a functional disorder, including functional cognitive disorder, with onset precipitated by the mild traumatic brain injury from which most people would ordinarily recover within three months.

Case D: Post-Traumatic Stress Disorder with dissociative seizures (also called Non-Epileptic Attacks or functional seizures)

A 31-year-old women is a restrained driver in a car which rolls down an embankment following a collision. She sustains bruising but no serious injury. Over the following months she is unable to drive or travel in a car because of memories of the accident. Distressing memories of being inside the car as it rolled jump into her head without warning, together with physical symptoms of shakiness, dry mouth, and "butterflies" in the stomach. She is generally nervous and quick to startle, and sleeps poorly. One day, two months after the accident, she feels strange and then falls to the ground with eyes closed and arms and legs shaking irregularly. The episode is witnessed by her partner who reports the event lasted at least five minutes and that she was tearful but not confused afterwards. These seizures—subsequently diagnosed as dissociative or non-epileptic attacks—continue until she undergoes psychological treatment for Post-Traumatic Stress Disorder ("PTSD"), during which seizures initially become more frequent but then resolve completely.

Case E: Wilful exaggeration of symptoms of Complex Regional Pain Syndrome/Functional Neurological Disorder

A 28-year-old mechanical engineer trips over equipment at work and sustains an ankle fracture, treated with open reduction and internal fixation by the orthopaedic surgeons. After six months he is unable to return to work and reports severe ongoing pain, inability to bear weight, extreme sensitivity to touch over the foot and ankle, and his foot is held twisted inwards in an abnormal position. He walks with crutches, dragging the top of his foot behind him on the ground and says that he can never mobilise better than this. The orthopaedic surgeons cannot identify an orthopaedic cause, and he is referred to a consultant neurologist who makes a diagnosis of functional neurological disorder. However, contemporaneous surveillance footage is obtained in which the man can be seen walking normally, and apparently comfortably, without crutches, over a distance of 500m, and without any abnormal position of the foot. With this additional information, the neurologist determines that it seems more likely that the man is wilfully exaggerating his symptoms and therefore no diagnosis can be made.

Terminology and classification

Two main diagnostic classification systems are used when a precise definition is required for a neuropsychiatric disorder. The *Diagnostic and Statistical Manual of Mental Disorders* ("DSM 5") is produced by the American Psychiatric Association,[1] and the *International Classification of Diseases* ("ICD 11") by the World Health Organisation.[2] Broader discussion of the validity of the operationalised diagnoses contained in these systems lies outside the scope of this article. However, it is worth noting that functional and somatoform or "'psychosomatic"' disorders have always sat awkwardly in these classification systems, both for metaphysical reasons (are mind and body really separate?) and practical reasons (are these conditions the domain of neurologists or psychiatrists?).

The 2013 (5th) edition of DSM replaced the previous edition's "Conversion Disorder", with origins in Freud's theory of conversion of psychological distress into physical symptoms, with "Conversion Disorder (Functional Neurological Symptom Disorder)". ICD 11, released in 2018, replaced the 10th version's "Conversion Disorder" with "Dissociative Neurological Symptom Disorder": the term "dissociative" here denoting abnormal separation of neurological function from conscious awareness. These terms essentially describe the same condition. The move away from "conversion" is the result of a better understanding

[1] *Diagnostic and Statistical Manual of Mental Disorders*, 5th edn (American Psychiatric Association).
[2] *International Classification of Diseases*, 11th edn (World Health Organisation).

that functional disorders often occur in the absence of a psychological stressor, and correspondingly DSM-5 dropped the requirement for a psychological stressor in order to fulfil diagnostic criteria.

There are terms used in the past which we tend to avoid: "medically unexplained" is outdated, as with the research gains of the last 20 years we can now make a positive diagnosis of FND and explain the cause of symptoms with as much precision as we can for most other neurological disorders. The terms "psychogenic" and "psychosomatic" are often used by specialists but reflect a theoretical division between body and mind which has not been substantiated by neuroscientific research.

The term "functional disorder" is now widely understood by health professionals, and is generally acceptable to patients, who lead several support groups under the banner of FND.[3] Within neurological practice the term FND is increasingly diagnosed and treated in the same way that gastroenterologists might diagnose and treat irritable bowel syndrome.

Related and overlapping diagnoses

Patients considered to have excessive distress and disability following injury attract other relevant diagnoses. Complex Regional Pain Syndrome is a post-injury pain syndrome in which symptoms of sensory change and weakness are often present, and share the characteristic internal inconsistency of FND; many neurologists consider CRPS and FND to be overlapping conditions with shared pathophysiology, although this has been resisted by other specialities because of the stigma attached to FND diagnoses in the past.[4] "Post-concussion syndrome", particularly that which persists for months or years after the most minor of head injuries, usually presents with a variety of symptoms such as headache, fatigue, dizziness and cognitive symptoms which benefit from careful assessment but are, in broad terms, often part of a functional disorder. Somatic Symptom Disorder, in DSM-5, describes the presence of symptoms (which may be caused by recognised pathophysiological disease) associated with excessive worry and distress; this diagnosis can be criticised for being unhelpfully broad and commonly a consequence as much of a dysfunctional health care system as the patient's condition. Illness anxiety disorder (previously hypochondriasis) describes excessive worry and anxiety about health, often with a preoccupation that underlying disease is present, and with a characteristic inability to be reassured by explanation or normal investigations. Chronic pain syndromes, chronic fatigue syndrome, occurring in the absence of structural explanation as well as depressive and anxiety disorders are also common concomitants of FND.

Diagnosis

The diagnosis of a functional neurological disorder should usually be made by a neurologist, or a neuropsychiatrist with particular expertise in this area.

Historically, functional neurological disorder (then "hysteria" or "conversion disorder") was diagnosed on the basis of an absence of evidence of disease, with an assumption or the presence of a psychological stressor. The last 20 years, however, have seen a sea-change in the approach to diagnosis of FND. The requirement for a psychological stressor is gone, and diagnosis is now made on the basis of positive clinical signs (Table 1): clinical features which are only present in FND. These signs commonly involve demonstrating internal inconsistency, for example: weakness that is present during voluntary movement, but is not present during "automatic" movements (Figure 1). One strength of this approach is that the presence of one or more positive clinical signs can indicate that FND is present even in patients with

[3] J. Stone, W. Wojcik and D. Durrance, "What should we say to patients with symptoms unexplained by disease? The 'number needed to offend'" (2002) 325 B.M.J. 1449–50.

[4] S. Popkirov, I. Hoeritzauer, L. Colvin, A. J. Carson and J. Stone, "Complex regional pain syndrome and functional neurological disorders—time for reconciliation" (2019) 90 J Neurol Neurosurg Psychiatry 608–614.

structural neurological injury or neurological disease, where the FND comorbidity is sometimes called "functional overlay".

Table 1: Examples of positive signs in Functional Neurological Disorder

Functional symptom	Example of positive sign
Weakness/paralysis	Intermittent/ "give-way"/"collapsing" weakness: On examination, muscle strength varies from second to second between "collapsing" and brief moments of full strength.
	Hoover's sign: (Figure 1) Hip flexion (pushing down on the chair while seated) is weak, but returns to full strength when asked to extend opposite hip (raise opposite leg from chair).
Gait (walking) abnormality	Walking with the foot of the weak leg dragging behind.
	Gait that improves dramatically when walking backwards, or if asked to slide, as if on ice skates (in absence of better explanation).
Tremor	Variable in frequency and amplitude.
	When asked to copy a rhythm with opposite hand or foot the tremor may "entrain" (join in) or transiently cease.
Dissociative (non-epileptic) seizures	Sudden "fall down lie still with eyes closed for longer than 60 seconds"; eyes closed, hyperventilation during generalised shaking.

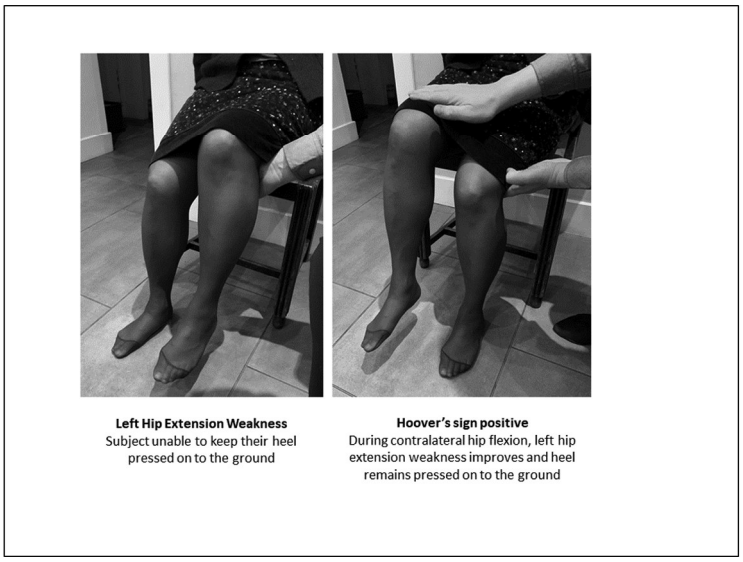


Figure 1: Hoover's sign of functional leg weakness is one of the positive signs of FND. It shows that voluntary movement is impaired but automatic movements are normal

Wilful exaggeration

Deliberate exaggeration or falsification of symptoms is generally considered more frequent in people assessed as part of personal injury litigation than in routine NHS care. Ultimately, the court must decide whether wilful exaggeration is present. However, for medical professionals working in this area, clinical

decisions involving the veracity of symptom description area are part of day-to-day practice, so providing their personal view may be a legitimate component of a report to the court.

There are no tests which can confidently identify symptoms which are intentionally produced. An additional challenge, in FND, is that internal inconsistency or symptom variability is characteristic of the condition and often a requirement for confident diagnosis. The important question, therefore, is: What is the difference between internal inconsistency in FND, and internal inconsistency due to wilful exaggeration?

The strongest evidence in support of suspected wilful exaggeration is the observation of major discrepancy between reported and observed function. For example, where a person who attends clinical assessment in a wheelchair, and reports during the assessment that they are unable to walk at all, but who is observed in other circumstances walking without difficulty; or a person who is unable to move their arm during assessment (and, importantly, who reports that the arm is weak at all times) is observed playing golf. Evidence of this level of discrepancy might also be supported by evidence of lying or unreliability in other areas of the history, such as denying employment since the injury on direct questioning, despite evidence to the contrary.

In our experience, medical experts often make errors in assessment about wilful exaggeration for one of the following reasons:

- **Observing discrepancy between reported and observed symptoms.**

  Patients with functional disorders may characteristically have difficulty reporting the severity and duration of symptoms over time. In a study of people with functional or organic tremor, wearing tremor-recording devices and keeping tremor diaries over five days, both groups, but especially those with functional tremor, recorded that their tremor was present for much more of the day than it actually was (83% v 4%)—even though they knew that the tremor was being recorded.[5] This suggests that symptom report can be inaccurate (and importantly, *involuntarily* inaccurate), especially in those with functional disorders, where is seems that the more attention is paid to the symptom the more it is present. Recent theories suggest that functional symptoms are, at one level of brain functioning, the product or consequence of abnormal attention. The same person with a functional tremor should however be able to accurately report what they can and cannot do in day to day life.

- **Noting discrepancy between reported severity of symptoms and reported function.**

  Lack of "credibility" of reported severity of symptoms is also unhelpful in assessing whether wilful exaggeration is present. People communicate about illness in different ways, and this is undoubtedly also influenced by the perceived purpose of the assessment. Patients in ordinary clinical settings, and pursuers in medicolegal cases, often omit or exaggerate information even when they are fully aware that we have been provided with their medical records. Although it may seem unlikely that a person sitting comfortably is experiencing pain of "10 out of 10" severity, this might be a communication of total distress, or a representation of the worst severity of a pain which has fluctuated over time, especially (and paradoxically) in a situation where the patient fears they may not be taken seriously.

- **Reliance on cognitive performance validity/effort tests.**

  In our experience, effort tests (also called symptom validity tests or performance validity tests) are often given undue weight in discriminating functional symptoms from wilful

[5] I. Parees, T. A. Saifee and P. Kassavetis, "Believing is perceiving: mismatch between self-report and actigraphy in psychogenic tremor" (2012) 135 *Brain* 117–123.

exaggeration. A minority of people with "medically unexplained" symptoms fail effort tests.[6] Performance in effort tests can also be confounded by pain, fatigue, and attitude toward the examination. However, it is worth noting that failure in effort tests makes other cognitive tests difficult to interpret, and very low scores—especially in tests of forced choice—can be taken in to account in an overall opinion.

In balancing evidence for and against wilful exaggeration, a presentation with a cluster of symptoms typically encountered in clinical practice might require more evidence to reach a conclusion of wilful exaggeration than an atypical presentation.

If a person is overwhelmingly assessed to be wilfully exaggerating or simulating symptoms of illness, the next question will be "Why?" Malingering describes simulation or deliberate exaggeration of illness for external (financial, material, or social) benefit and is not a medical diagnosis. In contrast, a person with factitious disorder simulates or consciously exaggerates illness for complex psychological reasons which they may or may not be aware of.

Causation

Where Functional Neurological Disorder occurs after an injury, the important question for the medical expert is: "But for the injury, what might have happened to this person?". To address this question, we must address the extent to which predisposing, precipitating and perpetuating factors contribute to the clinical presentation at the time of the medical examination (Figure 2).

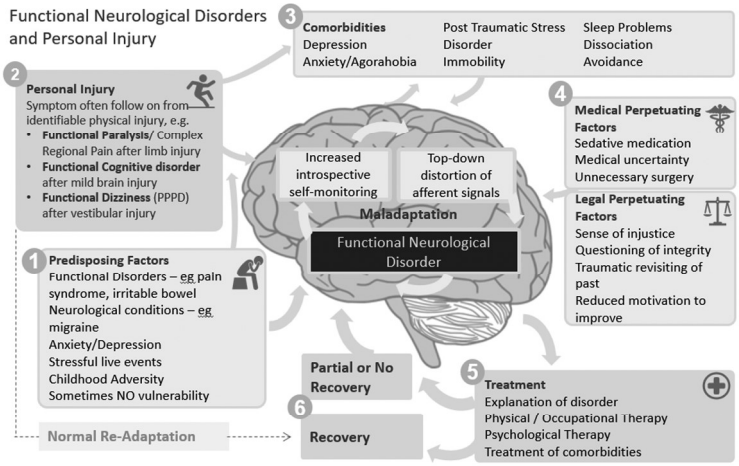


Figure 2: Functional Neurological Disorders and Personal Injury. Aetiology, Mechanism and Treatment

Predisposing factors

People who develop FND are more likely to have experienced stressful events or maltreatment during childhood or adult life than healthy controls or controls with other diseases; however, importantly, a

[6] S. Kemp, A. K. Coughlan, C. Rowbottom, K. Wilkinson, V. Teggart and G. Baker, "The base rate of effort test failure in patients with medically unexplained symptoms" (2008) 65 J Psychosom Res 319–325.

proportion of people with FND report no previous such stressors.[7] Previous functional symptoms including in other body systems (for example, irritable bowel syndrome, atypical/non-cardiac chest pain), chronic pain or health anxiety, or recurrent or persistent anxiety and depression increase probability of developing a functional disorder in the future.

An assessment of resilience in response to this and previous illness and injury is also important. Functional symptoms and anxiety and depression are common in the population. Is this a person who has retained employment and relationships despite previous setbacks? Or is this a person who has experienced catastrophic escalations in pain, fatigue, irritable bowel, mood or anxiety symptoms, with long absences from work, in response to minor injuries and illnesses? These previous responses are important considerations in establishing the extent to which the current symptoms and disability might be considered to have been caused by the injury in question.

In addition, it is important to assess the patient's general social and occupational vulnerability. Severe bullying or disciplinary proceedings at work, intolerable stress at home related to illness or impaired relationships may need to be factored in to decisions about the extent to which the individual was vulnerable to illness with either a functional or psychiatric disorder.

Precipitating factors

Functional neurological disorders can occur de novo without apparent trigger, but up to 40% of functional motor disorders are preceded by a physical injury.[8] There is not a linear relationship between injury severity and risk of FND; even seemingly insignificant physical injuries, with no permanent structural disfigurement or disability, can precipitate FND in the presence or absence of predisposing factors. This is similar to the situation with Complex Regional Pain Syndrome.

Where a minor injury precedes FND, it might be important to consider whether the injury was nevertheless out of the ordinary. This is because if, on the other hand, the injury was innocuous and might have occurred in everyday life, the vulnerability to developing FND (for whatever other reasons) must have been such that this specific injury cannot be considered the cause of the symptoms.

Although severity of injury does not predict risk, the nature and circumstances of the injury may be significant to the symptoms which develop thereafter. In our experience, although the injury may be mild, there (or, in some cases, the consequent medical assessments or interventions) may be a plausible description of why it was distressing for some reason or another: painful, threatening, associated with a "dazed" feeling, or with perceived subsequent poor medical care, injustice, humiliation, or loss of control.

Perpetuating factors

Functional neurological disorders can present acutely after injury and resolve quickly—within days or weeks—or may persist for longer or even become chronic. The predisposing factors described above also increase probability of a prolonged symptom course. In addition, we recognise a number of post-injury factors which may prevent recovery or worsen symptoms and disability in FND. Indeed, a gradually worsening presentation is common.

Strong opiate (morphine-like) medication may be given in the immediate aftermath of an injury, but continuation and escalating doses of these medications after tissue healing is not beneficial. It can lead to increased sensitivity to pain in general (opiate-induced hyperalgesia) and, in our experience, commonly, a worsening of FND.

[7] L. Ludwig, J. A. Pasman and T. Nicholson, "Stressful life events and maltreatment in conversion (functional neurological) disorder: systematic review and meta-analysis of case-control studies" (2018) 5 *The Lancet Psychiatry* 307–320.

[8] J. Stone, A. Carson and H. Aditya, "The role of physical injury in motor and sensory conversion symptoms: A systematic and narrative review" (2009) 66 J Psychosom Res 383–390.

The behavioural response to injury significantly influences recovery. Where rest and withdrawal from usual activities may be necessary in the first instance, prolonged avoidance of activities (particularly those feared to worsen symptoms) often worsens FND, causes physical deconditioning, and leads to subsequent fatigue and anxiety when normal activities are later attempted.

Psychiatric illnesses such as depression, generalised anxiety disorder or phobic anxiety disorder can worsen symptoms of FND and prevent effective engagement in treatment or return to normal activities. When significant Post-Traumatic Stress Disorder ("PTSD") develops after traumatic injury, functional symptoms seem more likely to develop and to persist. It is likely that PTSD strengthens links between psychological re-experiencing (in "flashbacks") and somatic re-experiencing (persistent bodily pain and dysfunction), in part by amplifying fear-arousal processes. In a medicolegal setting, the presence of PTSD can therefore strengthen a causal link for both the psychological *and* physical symptoms.

There is a consensus that ongoing litigation and receipt of disability benefits are also associated with symptom persistence and poorer outcomes. Even in genuine claimants the litigation process is designed in a way that is highly anti-therapeutic. Individuals in whom therapeutically one would be trying to help move on from the past or blame for an event, are constantly asked to reconsider and describe past events. The questioning of integrity, including discovery by claimants that they have undergone surveillance, is particularly problematic for individuals whose symptoms are the subject of suspicion by many doctors even in routine clinical care.

Current scientific understanding

There have been great leaps in understanding about what happens in the brain in Functional Neurological Disorder over the last 10–20 years.[9] It is no longer appropriate to call these conditions "medically unexplained". Although we have some way to go in understanding why FND develops in a particular individual at a particular time, the same can be said of many other neurological conditions, such as multiple sclerosis or Parkinson's disease, and people with FND should be treated with the same care and respect as those with other neurological conditions.

Functional MRI scans (showing areas of brain activation and connectivity in real time) in groups of people with FND compared with healthy controls have demonstrated abnormal activity in areas of the prefrontal cortex (involved with planning, behaviour and control of movements); central "limbic" areas (involved with emotion and memory); and in areas of the parietal lobe involved with self-agency (the feeling of ownership of one's own actions).[10] Laboratory studies of brain physiology (neurophysiology) in patients with FND have shown that although parts of the brain responsible for movement and sensation (primary motor and sensory cortex) are unimpaired in FND, areas responsible for modulation and planning of movements (premotor and association areas) are abnormal.[11] Additional studies have shown differences between patients with FND and those feigning similar symptoms.

Disordered attention is a key feature of FND. The importance of attention can be seen clinically, when we observe a temporary improvement in symptoms when attention is diverted to another task, or experimentally, as in the Parees study described previously, where patients with functional tremor seemed to experience the tremor as present whenever they paid attention to it.[12] A compelling and commonly accepted contemporary theory is that, at one level functional symptoms arise as a result of abnormally

[9] A. J. Espay, S. Aybek and A. Carson, "Current Concepts in Diagnosis and Treatment of Functional Neurological Disorders" (2018) JAMA Neurol at *https://www.ncbi.nlm.nih.gov/pubmed/29868890* [accessed 21 April 2020].

[10] A. Aybek and P. Vuilleumier, "Imaging studies of functional neurologic disorders" in M. Hallett, J. Stone and A. Carson (eds), *Handbook of Clinical Neurology* Vol.139, 3rd series Functional Neurologic Disorders (Amsterdam: Elsevier, 2016), 73–84.

[11] M. Hallet, "Neurophysiologic studies of funtional neurologic disorders" in M. Hallett, J. Stone and A. Carson (eds), *Handbook of Clinical Neurology* (Elsevier, 2016), 61–68.

[12] I. Parees, T. A. Saifee and P. Kassavetis, "Believing is perceiving: mismatch between self-report and actigraphy in psychogenic tremor" (2012) 135 *Brain* 117–123.

precise prior, and involuntary, expectations about movements or sensations, combined with excessive attention towards the affected body part, causing brain "processing errors" which appear in the form of symptoms like weakness, numbness and tingling, or abnormal movements.[13] If one accepts that the brain is largely a "predictive organ" that is usually correct with its guesses about movement and sensation in relation to the body and the outside world, FND is an expected consequence of that process going wrong.

Treatment

Treatment of FND begins with a clear explanation of the diagnosis by the treating neurologist or neuropsychiatrist. Demonstration and explanation of positive clinical signs is often helpful. Patients should also be offered additional printed or online information about the diagnosis; free comprehensive patient-information website about functional neurological disorders can be found at *www.neurosymptoms.org*, and similar advice for those who have sustained a mild traumatic brain injury can be found at *www.headinjurysymptoms.org*.[14] There are also several patient-led FND organisations with good information. Ideally, after this step, there is a patient who has confidence in their diagnosis, understands there is potential for reversibility and is motivated to change with the help of rehabilitation. In reality, helping some patients gain confidence in a heavily stigmatised diagnosis such as FND can be difficult, especially in personal injury situations where a patient has had a structural injury triggering the symptoms.

Medical treatment often includes optimising medications—reducing unhelpful opiates and sedative medications, and in some cases, where appropriate introducing antidepressant medication for anxiety, mood, pain or sleep issues.

For some usually with mild symptoms, explanation and advice will be enough treatment to allow a recovery. For those with more severe or persistent symptoms, additional treatments might be necessary, and Cognitive Behavioural Therapy or Physiotherapy are those with the current best evidence of effectiveness. It is crucially important, however, that these therapies are provided by therapists with experience in treating FND, as there are important differences compared with treatment for other conditions. In physiotherapy for FND, whole body exercises which prevent abnormal attentional focus and require the person to depend on "automatic" movements are employed rather than the sort of focussed strength exercises such as might be used for a musculoskeletal injury.[15] For example, in physiotherapy for FND the patient might be supported to run on a treadmill (where "automatic" movements take over from the faulty effortful movements) even if they are usually unable to walk. Early trial data are encouraging.[16] Alternatively, Cognitive Behavioural Therapy provides a framework to address unhelpful patterns in the inter-relations between thought, emotion, behaviour, and symptoms: such as avoiding activity because of anxiety and catastrophic thoughts about one's health. There is specific CBT for some types of FND such as dissociative (non-epileptic) seizures.[17] Although a range of patient and symptom factors inform clinical judgement as to the most suitable modality of treatment, ultimately, it is likely that both physiotherapy and psychotherapy (CBT) work by reducing fear and avoidance of activity.[18]

The stressful process of litigation, which requires pursuers to describe the injury, symptoms, and disability repeatedly, and perceived financial incentive to maximise symptoms and disability, can also prevent effective engagement with the goals of treatment, although—as in NHS treatment—patients with

[13] M. J. Edwards, R. A. Adams, H. Brown, I. Parees and K. J. Friston, "A Bayesian account of 'hysteria'" (2012) 153 *Brain* 3495–3512.
[14] Both free sites made by the authors of this article.
[15] G. Nielsen, J. Stone and A. Matthews, "Physiotherapy for functional motor disorders: a consensus recommendation" (2015) 86 J Neurol Neurosurg Psychiatry 1113–1119.
[16] G. Nielsen, M. Buszewicz and F. Stevenson, "Randomised feasibility study of physiotherapy for patients with functional motor symptoms" (2017) 88 J Neurol Neurosurg Psychiatry 484–490.
[17] L. H. Goldstein, T. Chalder and C. Chigwedere, "Cognitive-behavioral therapy for psychogenic nonepileptic seizures: A pilot RCT" (2010) 74 *Neurology* 1986–1994.
[18] T. Chalder, K.A. Goldsmith, P. D. White, M. Sharpe and A. R. Pickles, "Rehabilitative therapies for chronic fatigue syndrome: a secondary mediation analysis of the PACE trial" (2015) 2 *The Lancet Psychiatry* 141–152.

limited motivation to improve may still "go through the motions" of treatment. Although starting treatment prior to conclusion of litigation may seem desirable in order to help establish treatability and prognosis, our experience is that recovery is unlikely in the late stages of litigation. While we have successfully treated patients with ongoing legal claims, more often it is better to wait until conclusion of litigation in order to maximise the long-term benefits of treatment for that person, and also to ensure that post-litigation treatment is not prejudiced by failure under unfavourable circumstances during litigation. In some ways it is not surprising that some patients with these disorders, when faced with treatment of uncertain outcome, and a possibility of relapse after settlement, may prefer to wait until they have some financial security before focusing on treatment.

Outcome/prognosis

Functional neurological disorders are potentially reversible, but outcomes are highly variable. For those with symptoms severe enough to be clinically referred to a neurologist, prognosis is poor: a recent follow-up study of 107 people with functional motor disorder found 80% still symptomatic after 14 years.[19] It is not clear to what extent this cohort aligns with the population of individuals receiving a diagnosis of FND only as part of a personal injury claim.

Those with a better prognosis, in whom a more or less complete recovery might be predicted, are more likely to have had a good level of social and occupational function premorbidly, to agree with the diagnosis of FND, to demonstrate motivated engagement with treatments offered, and to have made efforts to re-engage with activities. Those with a poor prognosis may disagree with the diagnosis of FND, or be preoccupied with ideas that there is a dangerous, permanent, or undetected underlying cause of their symptoms, fail or struggle to engage with treatment, have withdrawn from activities and employment and to have become dependent on mobility aids, opiate painkillers and other sedative agents, and disability welfare benefits. Some patients with FND fail to improve despite a good understanding and motivation.

The largest longitudinal study of functional neurological disorder reported higher death rates than expected in the general population, and although the reasons for this may be complex—most deaths were due to cardiovascular, rather than neurological causes, possibly due to immobility or confounding lifestyle factors—on balance, available evidence suggests that FND is independently associated with a slight reduction in life expectancy.[20]

Need for care

The question of whether ongoing care is needed in FND often arises during the process of a legal claim. This needs to be assessed on an individual basis, and poses a dilemma, in that provision of excessive care and assistance can be an obstacle in some individuals with FND to returning to activity.[21] Ideally the goals of care should be rehabilitative, supporting the person to regain independence with a reduction in provision of care and support over time. In our experience, however, this is not often the case, but nevertheless for those with severe and disabling FND, or those who have not benefited from treatment, provision of care and disabled adaptations should be similar to those with comparable neurological conditions, with the proviso that improvement may still be possible at some stage.

For a condition with such a variable prognosis, it may be appropriate for the expert to provide the court with a range of possible outcomes and different care needs.

[19] J. M. Gelauff, A. Carson, L. Ludwig, M. A. J. Tijssen and J. Stone, "The prognosis of functional limb weakness: a 14-year case-control study" (2019) *Brain* at *https://academic.oup.com/brain/article/142/7/2137/5510175* [accessed 21 April 2020].

[20] J. M. Gelauff, A. Carson, L. Ludwig, M. A. J. Tijssen and J. Stone, "The prognosis of functional limb weakness: a 14-year case-control study" (2019) *Brain* at *https://academic.oup.com/brain/article/142/7/2137/5510175* [accessed 21 April 2020].

[21] P. Gardiner, L. MacGregor, A. Carson and J. Stone, "Occupational therapy for functional neurological disorders: a scoping review and agenda for research" (2018) 23 CNS Spectr 205–212.

Conclusion

Functional neurological disorder is common, but not always well understood or described by medical professionals, particularly in fields other than neurology and psychiatry. Functional neurological disorder challenges the assumption that brain/body and mind operate independently from each other—the concept of dualism described by Descartes. Clinical work with people with functional disorders teaches us daily that the body and brain respond to injury as a united but complex unit. When this already complex disorder becomes entangled with a legal process further complexity arises, but ultimately it is a disorder with its own set of diagnostic rules and where treatment outside the context of a personal injury claim, can provide surprisingly good outcomes.

Management of mild traumatic brain injury

Anne van Gils,[1] Jon Stone ,[2,3] Killian Welch,[2,4] Louise R Davidson,[2] Dean Kerslake,[5] Dave Caesar,[5] Laura McWhirter,[3] Alan Carson[2,3,4]

[1]University of Groningen, University Medical Center Groningen, Interdisciplinary Center Psychopathology and Emotion Regulation, Groningen, The Netherlands
[2]Department of Clinical Neurosciences, Western General Hospital, University of Edinburgh, Edinburgh, UK
[3]Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK
[4]Department of Rehabilitation Medicine, Astley Ainslie Hospital, Edinburgh, UK
[5]Department of Emergency Medicine, Royal Infirmary of Edinburgh, Edinburgh, UK

Correspondence to
Professor Alan Carson, Royal Edinburgh Hospital, Edinburgh EH10 5HF, UK;
A.Carson@ed.ac.uk

Accepted 2 January 2020

To cite: van Gils A, Stone J, Welch K, *et al. Pract Neurol* 2020;**20**:213–221.

SUMMARY

Mild traumatic brain injury (TBI) is common and associated with a range of diffuse, non-specific symptoms including headache, nausea, dizziness, fatigue, hypersomnolence, attentional difficulties, photosensitivity and phonosensitivity, irritability and depersonalisation. Although these symptoms usually resolve within 3 months, 5%–15% of patients are left with chronic symptoms. We argue that simply labelling such symptoms as 'postconcussional' is of little benefit to patients. Instead, we suggest that detailed assessment, including investigation, both of the severity of the 'mild' injury and of the individual symptom syndromes, should be used to tailor a rehabilitative approach to symptoms. To complement such an approach, we have developed a self-help website for patients with mild TBI, based on neurorehabilitative and cognitive behavioural therapy principles, offering information, tips and tools to guide recovery: www.headinjurysymptoms.org.

INTRODUCTION

…Up Jack got

And home did trot,
As fast as he could caper;
And went to bed
And plastered his head
With vinegar and brown paper

Head injury is the the most common reason for those under 65 to be admitted to the hospital. In most developed countries, the incidence of emergency department (ED) attendance is around 270–330 per 100 000 per annum.[1]

The overwhelming majority (around 93%) of brain injuries are mild.[2] According to the WHO criteria: 'Mild traumatic brain injury (TBI) is an acute brain injury resulting from mechanical energy to the head from an external force. Operational criteria for clinical identification include: (i) one or more of the following: confusion or disorientation, loss of consciousness for ≤30 min, post-traumatic amnesia (PTA) for <24 hours and/or other transient neurological abnormalities, such as focal signs, seizure and intracranial lesion not requiring surgery; AND (ii) a Glasgow Coma Scale (GCS) score of 13–15 after 30 min post head injury or later on presentation for healthcare. These manifestations of mild TBI must not be due to drugs, alcohol, medications, caused by other injuries or treatment for other injuries (eg, systemic injuries, facial injuries or intubation), caused by other problems (eg, psychological trauma, language barrier or coexisting medical conditions) or caused by penetrating craniocerebral injury'.[3]

Patients with mild TBI are usually discharged from the hospital directly or within 24 hours after a period of observation. The vast majority of delayed intracranial pathologies, such as bleeding or an expanding lesion, occur in the first 24 hours and are exceptionally rare after 21 days (<0.1%).[4] But although dangerous complications are unusual, many people who sustain a mild TBI develop non-specific symptoms, such as headache, nausea, dizziness, fatigue, hypersomnolence, attentional difficulties, photosensitivity and phonosensitivity, irritability and depersonalisation. Although often referred to as 'postconcussion syndrome', research suggests multifactorial causes and we find this label unhelpful.[3 5]

In 2004, the WHO provided an authoritative epidemiological analysis of outcome after mild TBI with a programme of systematic reviews, updated in 2014 without change to the main conclusions. Their key finding was that 'early cognitive deficits in mild TBI are largely resolved within a few months post injury, with most studies suggesting resolution within 3 months. As this evidence is based on a variety of study designs, in a number of different mild TBI populations and through comparisons with both injured

Box 1 Mayo trauma brain injury (TBI) classification system

A. Classify as moderate-severe (definite) TBI if one or more of the following criteria apply:
   1. Death due to this TBI.
   2. Loss of consciousness of ≥30 min.
   3. Post-traumatic anterograde amnesia of ≥24 hours.
   4. Worst Glasgow Coma Scale full score in first 24 hours <13 (unless invalidated upon review eg, attributable to intoxication, sedation, systematic shock).
   5. One or more of the following present:
      - Intracerebral haematoma.
      - Subdural haematoma.
      - Epidural haematoma.
      - Cerebral contusion.
      - Haemorrhagic contusion.
      - Penetrating TBI (dura penetrated).
      - Subarachnoid haemorrhage.
      - Brainstem injury.

B. If none of criteria A apply, classify as mild (probable) TBI if one or more of the following apply:
   1. Loss of consciousness momentarily to <30 min.
   2. Post-traumatic anterograde amnesia momentarily to <24 hours.
   3. Depressed, basilar or linear skull fracture (dura intact).

C. If none of the criteria A or B apply, classify as symptomatic (possible) TBI if one or more of the following symptoms are present:
   1. Blurred vision.
   2. Confusion (mental state changes).
   3. Daze.
   4. Dizziness.
   5. Focal neurological symptoms.
   6. Headache, nausea.

TBI, trauma brain injury.

Box 2 Example of an information sheet, provided after discharge from the ED with a head injury

Important things to look for after a head injury

Advice for the person taking a patient home from the emergency department

[Name] has suffered a head injury, but does not need to be admitted to a hospital ward. We have examined the patient and believe that the injury is not serious. Please watch the patient closely over the next day or so as very rarely complications may develop as a result of the injury. Overnight rouse the patient gently every couple of hours, and follow this advice:

1. Do not leave the patient alone at home.
2. Make sure that there is a nearby telephone and that the patient stays within easy reach of medical help.
3. Symptoms to look out for:
   - Is it difficult to wake the patient up?
   - Is the patient very confused?
   - Does the patient complain of a very severe headache?
   - Has the patient:
     - Vomited (been sick)?
     - Had a fit (collapsed and felt a bit out of touch afterwards)?
     - Passed out suddenly?
     - Complained of weakness or numbness in an arm or leg?
     - Complained about not seeing as well as usual?
     - Had any watery fluid coming out of their ear or nose?

If the answer to any of these questions is 'yes' or you are worried about anything else,you should telephone the emergency department on: [tel. no.]

Or if you are very worried, take the patient straight back to the emergency department.

and non-injured control groups, we consider it persuasive and consistent evidence'.[6]

We accept the WHO's findings in general but recommend a more nuanced position.

First, the WHO definition of mild TBI spans a considerable range of injury severity. The likely contribution of structural damage differs vastly between a person who bumps their head on a desk and feels dazed, and a motorcyclist in a high-speed collision who is unconscious for 25 min, GCS 13 on admission to hospital and has PTA of 23 hours. For more severe 'mild' injuries, with lesions on imaging (sometimes referred to as 'complicated mild injuries'), the Mayo criteria (box 1) provide additional clarity by incorporating imaging findings and classifies them as 'moderate severe'.[4]

Second, mild TBI does not occur randomly but pre-injury risk factors, such as alcohol misuse, predispose to both injury and poor outcome.

Third, we find it helpful to take a wider view of functioning beyond the initial injury, in terms of the International Classification of Functioning, Disability and Health Framework.[7] This framework recognises that impairment (structural damage) is only one component of disability (symptoms and consequences) and handicap/participation. We find a cognitive behavioural framework helps in understanding how expectations might drive behavioural responses to injury.

Why do we need to think about head injury information?

SIGN 110 and National Institute for Health and Care Excellence (NICE) CG176 have described well the acute assessment of head injury, and we will not reiterate it here. After acute attendance with mild TBI, the failure to provide a head injury advice sheet describing 'red flag' symptoms requiring the patient to return to hospital urgently (box 2) is considered negligent. However, this essential information can also cause

anxiety, putting the patient on high alert so that when an unpleasant but common symptom occurs the patient worries about whether it too is a 'red flag'. We think it is crucially important to supplement advice about 'red flags' with a description of common symptoms after mild TBI.

Information that helps patients to make sense of symptoms, and signposts to the correct treatment, is likely to be helpful. Early sensible information can reduce anxiety and unhelpful beliefs, prevent maladaptive responses and therefore optimise outcome.[8] Recent reviews show modest supportive evidence for early educational interventions.[9 10]

Current sources of information for patients (such as www.nhs.uk/conditions/concussion, www.healthline.com/health/concussion and www.familydoctor.org/condition/concussion) give poor treatment advice: 'Remember, it is important to take time to rest after any concussion. This allows the brain to heal', 'Only return to work, college or school when you feel you have completely recovered'. Such advice goes against the principles of rehabilitation. For severe brain injuries, there is level 1 evidence that early mobilisation and rehabilitation improve outcome.[11] Although there is no level 1 evidence after mild TBI, available evidence and clinical experience suggest a similar approach is beneficial.[12] Indeed, it would be remarkable if mild TBI required the opposite approach —rest until complete recovery—which we believe iatrogenically reinforces worries and avoidance behaviour.

Here we describe an approach to assessment and treatment after mild TBI. We have also developed a self-help website, based on cognitive behavioural therapy and rehabilitation principles: www.headinjurysymptoms.org (figure 1). The website encourages patients to play an active role in their recovery, and we hope it will be a useful supplement for neurologists.

DIAGNOSIS IN THE NEUROLOGY CLINIC: WAS IT A MILD TBI?

Reconstructing the history and getting the records

Neurologists are most likely to become involved months post-injury when a patient with ongoing symptoms is referred 'for a scan'. The starting point of the assessment is to ascertain the severity of the acute brain injury, via peri-injury markers including duration of loss of consciousness, retrograde and PTA. In our experience, referral history cannot be relied on, and the first rule is 'take no-one's word for it': get the information yourself. We have encountered patients with prolonged periods of hospitalisation after apparent severe brain injuries who turned out to have the most trivial of knocks to the head. More rarely, significant injuries are missed: in cases of polytrauma, where life-saving attention is paid to other injuries and

Figure 1 Screenshot of www.headinjurysymptoms.org

a moderate TBI passes under the radar, or on a Friday night where signs of developing coma are mistaken for drunkenness. In our experience, however, EDs almost always triage the latter injuries correctly.

Although the patient will be unable to distinguish loss of consciousness from PTA[13] (there will just be a memory gap) they will often have been told by onlookers and the ambulance record usually contains a comment. Be cautious when a very short loss of consciousness accompanies prolonged PTA, although such anomalies are possible. If the history suggests PTA of weeks but the patient was discharged from the ED, read the acute assessment yourself. It is also unusual to have had a severe injury with retrograde amnesia of <30 min.[14 15]

Drugs, in particular, opiates, can artificially prolong both coma and the apparent duration of PTA. Normal forgetting can be reported as PTA.[16] Pay attention to what the patient actually did during the supposed period of amnesia. Did they make their own way home, navigate unaided around their home town, cook, shop, work? Although someone may seem superficially normal during PTA in a structured hospital environment, being in this state is incompatible with all but the simplest of independent tasks.

In most circumstances, the mechanisms behind a significant brain injury will include a degree of diffuse axonal injury.[17 18] This insult is particularly destructive to white matter subcortical tracts. Patients usually display some impairment in language, or in higher communication, such as turn-taking or selective attention (ie, being able to follow group conversation), and at least subtle signs of disinhibition, deficits in metacognition and distractibility.-[19] If these features are absent, carefully consider whether a moderate-to-severe brain injury has taken place.

Role of clinical neuroimaging

In our experience taking time to review case records is almost always more informative than rushing to request 'a scan'. That said, there is a role for imaging in assessing mild TBI, even sometime after the event. The investigation of choice is generally an MR scan of the brain with susceptibility-weighted imaging (SWI).[20 21] There is debate as to the extent SWI shows diffuse vascular injury as opposed to diffuse axonal injury; although the two frequently coexist, they are not synonymous. Both, however, correlate with the poorer cognitive outcomes and give some indication of the extent of neuronal damage. Our practice is to consider imaging if there was PTA beyond 1 hour, a dangerous mechanism, an elderly subject, taking anticoagulant medications, unexpected cognitive or psychiatric trajectory post injury, abnormal neurological signs or uncertainty about peri-injury markers. A CT scan of the head should only be used when there is urgent concern about a late bleed or hydrocephalus and does not have a routine role in the late assessment of mild TBI.

Neurological, vestibular and psychiatric symptoms after mild TBI

The risk of head injury is not random but heavily skewed to those with health or lifestyle problems that predispose to risk-taking or falls. Although the largest group are those with substance or alcohol misuse, neurological disorders, including dementia, increase falls risk, so that mild TBI may in some cases be a secondary consequence of brain disease. Additionally, a mild TBI causing injury may have other components that seem to indicate 'brain damage' but rather arise through vestibular (eg, benign paroxysmal positional vertigo (BPPV)), psychological (eg, depersonalisation) or other neurological mechanisms (eg, post-traumatic migraine).

COMMON SYMPTOMS AFTER MILD TBI

Headache

Migraine and other headaches are commonly triggered or exacerbated by a head injury. A systematic review found chronic headache was more common in mild (75%) versus moderate or severe TBI (32%).[22] Migraine can be especially alarming to the patient who has not previously experienced it and has just had an injury. Medication overuse, neck injuries, sleep disturbance and psychological comorbidity may all contribute to headache after mild TBI. The management of headaches is along standard lines, but it is particularly important to make the diagnosis clear so reducing anxiety about the cause.

Dizziness

Dizziness after a head injury has many potential causes. The most common is BPPV related to the dislodging of debris into the posterior semicircular canal during the injury. It is easy to underestimate just how alarming is sudden rotatory vertigo from BPPV, especially to someone already in a state of arousal after an injury. Most neurologists will recognise how much harm is done when a patient with post-head injury BPPV is not given the correct diagnosis and continues to believe dizziness is evidence of brain damage.

Vestibular migraine is the second most common cause of dizziness in this population, often part of new-onset migraine or worsening of pre-existing migraine. Central vestibular disorders can occur but are more typical after moderate or severe brain injury.[23]

Persistent postural-perceptual dizziness describes a functional disorder of chronic subjective dizziness after a vestibular trigger.[24] The diagnosis depends on the presence of unsteadiness or non-spinning vertigo that is prolonged and exacerbated by upright posture, active or passive motion, without regard to direction or position and exposure to moving or complex visual patterns. Symptoms wax and wane but tend to worsen over time. Secondary anxiety and avoidance of precipitating stimuli are common, as is a rather stiff posture as a form of excessive compensation. Treatment

involves accurate diagnosis and explanation, then exposure and desensitisation in the context of either vestibular physiotherapy or cognitive behavioural therapy. SSRI and SNRI antidepressants can often help.

Dissociation is a common cause of reported dizziness in the neurology clinic, especially after the 'shock' of mild head injury, and is discussed further.

Fatigue

Fatigue is common after mild TBI. Although direct effects of trauma may play a role, particularly early after the injury, other factors become more important over time. Acute headache or nausea, head injury as a result of violence, depression and post-traumatic stress disorder (PTSD) are some reported risk factors for post injury fatigue.[25 26]

Although clinicians often advise rest after mild TBI, available evidence suggests that prolonged rest does not improve outcomes.[27–29] Physical deconditioning and social isolation resulting from prolonged withdrawal from normal activities precipitate fatigue and overwhelm on return to activities with a 'cascade' of activity avoidance and exercise intolerance.[29] Beliefs such as 'my brain is fragile' and fatigue is a 'warning sign' of damage' contribute; negative predictions about mild TBI and all-or-nothing cognitions predict persistent symptoms.[8]

We advise a timely explanation of expected symptoms and advice about the early return to activity, avoiding a 'boom or bust' pattern of activity. Clinicians should suggest a gentle progressive activity programme and adherence is usually better if patients receive specific advice:[30] prescribing a daily walk starting with a distance the patient can comfortably manage then handwritten instructions to increase it gently on a fortnightly basis is better than advice to 'do a bit more'.

Sleep disturbance

A longitudinal study showed that 65% of 346 adults who suffered from a mild TBI experienced sleep difficulties within the first 2 weeks after the injury and 41% continued to have sleep difficulties 1 year later.[31] Sleep problems a fter mild TBI can be divided into three broad categories: insomnia (difficulty initiating sleep, maintaining sleep or waking up too early), hypersomnia (excessive sleeping and sleepiness) and nightmares, which might occur in the context of PTSD.[32] Basic sleep hygiene advice is often effective.[33]

Concentration and memory problems

Cognitive symptoms usually resolve quickly after mild TBI; a minority have memory and concentration problems by 3 months.[34 35] Psychological factors, such as depression, anxiety, PTSD, and litigation, may be important where cognitive symptoms persist.[36] Memory lapses—forgetting appointment dates, groceries, or forgetting why you entered a room or where the car is parked—are common in the general population, as is difficulty retrieving overlearned information, such as PINs or passwords.[37] For a patient who believes that they have sustained brain damage, such 'normal' experiences are unusually frightening and can cause anxiety that itself diverts attention towards the threatening stimulus (in this situation, 'brain failure') and away from the task at hand.[38]

The functional cognitive disorder[39] frequently causes cognitive morbidity after trivial mild TBI and is diagnosed on the basis of positive features of internal inconsistency (see table 1 and McWhirter *et al* for detailed review).[40] Patients are typically distressed by their primarily inattentive cognitive symptoms and provide detailed descriptions of episodes of cognitive failure. Functional (dissociative) amnesias sometimes occur, either as total retrograde amnesia or retrograde amnesia with a reverse temporal gradient. Patients with the functional cognitive disorder may perform poorly in cognitive tests that require sustained attention (such as calculations), verbal fluency and information transfer from working to episodic memory (such as address recall), whereas performance

Table 1 Clinical features suggesting a functional cognitive disorder[65]

Functional	Brain injury
Cognitive disorder develops over a period of time	Cognitive disorder worse at time of injury then improves
Attends alone	Attends with someone
Patient more aware of the problem than others	Others more aware of the problem than patient
Able to detail list of drugs, previous interactions with doctors	Less able
Watches TV dramas	Stops following drama
Marked variability	Less variability
Types of memory symptoms are usually within most people's normal experience	Types of memory symptoms are often outwith normal experiences
'I used to have a brilliant memory'	Does not highlight previous 'brilliant memory'
Loss of own identity or family members	Able to communicate basic facts of own identity and who family are
Aan answer questions with multiple components	Can only manage single component questions
Answering questions with normal flow	Tend to delay before answering questions;
Frequently offer elaboration and detail	Unlikely to give spontaneous elaboration of detail
Normal, or anxious, conversational interaction	Impulsive conversational interaction with loss of normal 'turn taking'
No loss of theory of mind	Loss of theory of mind
Motor sequencing and praxis preserved	Motor sequencing and praxis impaired
Receptive and higher language unimpaired	Impairments of receptive and higher language function
Total retrograde amnesias or marked reverse temporal gradient	Retrograde amnesia follows normal pattern

on construction, motor sequencing and social cognition tasks are, in our experience, generally preserved. Performance validity (effort) tests do not seem useful in detecting functional cognitive symptoms.[40]

We encounter functional cognitive disorder that has been misdiagnosed as neuronal damage with alarming frequency. We recommend against referral for detailed psychometric testing after a very mild injury, as do national clinical guidelines (SIGN 130), finding more value in a careful assessment of the nature of the injury and symptoms, including bedside cognitive tests.[12] In our opinion, cognitive testing should be used only for assessing the extent of known damage and not for considering whether damage has actually occurred.

In those people who present with new cognitive impairment many weeks, months or years after mild TBI, we can be confident that the impairment is not due to direct effects of the injury, and so consider other causes: medical, neurological or psychiatric disorders (including functional cognitive disorder), and effects of alcohol or medications.

Irritability

Irritability is a non-specific symptom, occurring after both mild and severe brain injury, in conditions of global and local disturbance of brain function, in both mild and severe mental illness and as part of a normal response to situational stress or tiredness. Irritability after mild TBI may result from any or all of these factors, and in some cases may also represent a preinjury factor contributing to the risk of mild TBI.

Clinical assessment should aim to identify comorbid psychiatric disorders, without which the natural history is of gradual resolution. Those with troublesome persistent irritability may benefit from a trial of medication: reasonable options include propranolol, also helpful for aggression after severe brain injury,[41] or an SSRI.

Anxiety

Mild TBI can provoke or aggravate anxiety.[42] Patients often have worries about the symptoms they experience: 'Are the symptoms signs of brain damage?', 'Will I fully recover?', but some get caught up in their worries and are very difficult to reassure. They might frequently visit their doctor and look up information on their symptoms online. Health anxiety can worsen symptoms such as dizziness, headache and fatigue, and when it becomes intrusive and cannot be ameliorated with reassurance, cognitive behavioural therapy or prescription of an SSRI may be indicated.

A traumatic injury can precipitate PTSD, an anxiety disorder characterised by hyperarousal, re-experiencing of the traumatic event through nightmares, flashbacks and intrusive memories, and avoidance of reminders.[42] Treatment involves SSRI antidepressants and either trauma-focused cognitive behavioural therapy or eye movement desensitisation and reprocessing therapy.

Depression

Although depressive symptoms often predate the injury, acting as a risk factor for persistent symptoms, there can be a reattributing narrative in which patients focus on the impact of the injury on their lives with thoughts such as, 'This injury has made my life miserable'. Such thoughts can contribute to feelings of sadness, frustration, hopelessness, loneliness and avoidance behaviours.

The presence of anhedonia (absence of the ability to perceive pleasure) is key: depression is more about emptiness than being upset. It is helpful to orientate questions to activities that the patient can still participate in, such as: 'do you still feel pleased or excited if your child/grandchild comes home with some good news', 'if you are watching football and your team are playing do you still get excited and engaged with the game'. The diagnosis may be supported by symptoms like sleep disturbance (particularly early morning waking), diurnal variation in mood (worse in the morning), anergia, poor concentration, and loss of appetite and libido. Diagnosis depends on symptoms persisting over time; 2 weeks is specified in DSM 5, but we would usually look for at least a month.

When the patient has depression, it is mandatory to enquire briefly about suicidal thoughts. Some clinicians worry that this will 'put the idea into the patient's head', but depressed patients have thoughts of suicide long before any clinician mentions it, and questions such as 'does it ever get so bad that you feel you just can't go on?' are generally welcomed. Concern should grow if the patient is developing definite plans ('I have been saving up my tablets') and does not have protective factors (such as 'yes, but I would never put my family through that'). Imminent suicidal plans are a reason for emergency referral to psychiatry.

Management of depression after mild TBI follows standard approaches of advice, antidepressants and psychotherapy, where appropriate. We recommend neurologists are familiar with at least one tricyclic drug (or dual-acting drug such as duloxetine or venlafaxine) and one SSRI. Start on the lowest available dose and build to treatment dose over a few weeks, cautioning patients on likely side effects. Explain that antidepressants are not addictive but, unlike sedatives, they actively treat mood disorder as opposed to masking feelings and that it may take several weeks for therapeutic effects to take place.

Dissociation

Dissociative symptoms are greatly underestimated as a cause of dizziness in the neurology clinic. Dissociation describes many kinds of bodily and psychological symptoms related to a lack of integrity of brain functioning, but in a neurological context the most important are depersonalisation (a sense of disconnection from the body) and derealisation (a feeling of disconnection from the environment). Dissociation is a normal experience in states of shock or sleep deprivation and can

occur in migraine, epilepsy, drug use and psychiatric disorders. 'Peritraumatic dissociation' at the moment of a physical injury or traumatic event independently predicts PTSD, including in brain injury.[43] Dissociation commonly occurs with vestibular disorders, where it predicts disability.[44] It is common after mild TBI, as a result of the initial injury, a vestibular trigger such as BPPV,[45] sleep deprivation or fatigue.

Patients struggle to find the words for dissociation. Ask the patient whether their dizziness is a 'light-headedness', 'a feeling of movement' and 'a sense of disconnection/unreality'. If prompted, ask them if it feels like they are, or are not, 'floating', 'detached', 'far away' or 'in a place of their own' (derealisation) or whether they have a feeling that they feel 'zoned out', 'not quite there' or as if their legs or arms are not their own (depersonalisation).

Dissociation thrives on attention. Education helps the patient starve the symptom of attention by allowing them to recognise, name it and accept it as a normal result of post injury processes, which usually settle in time. There are now some good podcasts[46] and videos-[47] for patients to learn more about dissociation.[48] Treatment of chronic dissociation is more difficult and poorly evidenced, although there is a promise from cognitive behavioural therapy.[49]

Alcohol use

Up to half of TBI patients have a preinjury history of alcohol problems, with similar proportions intoxicated at the time of injury.[50] Up to a third have a history of illicit drug use.[51]

Everyone knows that alcohol use can lead to headaches, nausea, tiredness, poor concentration, irritability, impulsivity, anger outbursts and poor decision making. Even small amounts of alcohol can interfere with learning new information, cause poor quality sleep and interfere with sexual function. These symptoms overlap with common symptoms after mild TBI, leading to both patients and clinicians misattributing alcohol-related symptoms to the mild TBI. Hypervigilance to what may actually be largely alcohol-driven symptoms promotes anxiety, which in turn leads to drinking for perceived relaxing or soporific effects, inevitably worsening symptoms.

Clinical contacts after mild TBI offer a 'teachable moment'. If alcohol played a role in their injury, patients may be particularly receptive to information about the impact of alcohol on their health. A recent meta-analysis found that 5–10 min of feedback and advice to ED presenters intoxicated or with alcohol-related injuries resulted in a reduction significant at a population level.[52] In terms of the 'active ingredient', prompting self-recording of alcohol intake is associated with greater effect sizes,[53] and patients can be directed to resources that support this, for example, www.drinkaware.co.uk. Simply asking 'how much do you drink?' may trigger positive behaviour change.[54]

LONG-TERM OUTCOMES, CHRONIC TRAUMATIC ENCEPHALOPATHY AND DEMENTIA

There has been much media attention on long-term outcomes of concussion—particularly the possibility of increased dementia risk—but the evidence underpinning these reports is more conflicting and prone to confounding than many appreciate.[55] To date, meta-analyses examining the question have found no association.[56–58] Further, the largest report on pathology studies from population-based cohort studies found no evidence of an increased association between head trauma of any severity and Alzheimer's pathology.[59] A subsequent high-quality study of Danish health records suggested a weak association (weaker than the risk of failing to eat a Mediterranean diet) but could not fully address multiple confounders.[60] Furthermore, dementia and TBI diagnoses are not entirely reliable in routine practice, limiting the precision of 'big data' studies.[61 62] Our practice is to reassure patients that a single mild TBI does not cause future dementia.[63] Note this is a different scenario to repeated concussions and potential risk of chronic traumatic encephalopathy; we acknowledge greater uncertainty here although consider the evidence less convincing than is often appreciated. The best available evidence comes from a recent well conducted cohort study of retired scottish football players, which found mortality due to neurodegenerative disease in 1.7% among former soccer players compared to 0.5% among matched controls although after adjustment for the competing risks of death from ischemic heart disease and death from any cancer, this higher mortality was partially attenuated.[64] It should be noted that late neuropsychiatric symptoms may not be the direct result of neuronal damage [61 62 63]

CONCLUSIONS

Most people recover spontaneously within 3 months of a head injury. Although there has been much debate as to the exact nature of more persistent symptoms after mild TBI, there has been little practical advice on how to treat them. We suggest that lumping symptoms together under the 'postconcussional' banner is actively

Key points

- Mild traumatic brain injury (TBI) is common and causes a range of diffuse, non-specific symptoms.
- Although the symptoms usually resolve within 3 months, 5%–15% of patients have persistent symptoms and disability.
- The term 'mild TBI' spans a clinically significant range of severities; detailed assessment including targeted imaging can be helpful.
- A detailed assessment of individual symptom syndromes after mild TBI allows effective individualised treatment.
- The term 'postconcussional syndrome' does not help assessment and treatment.

unhelpful. Instead we recommend careful consideration of the severity of the initial injury, followed by a detailed assessment of the individual neurological and neuropsychiatric symptoms, guiding individualised treatment. This approach is, in our experience, more satisfactory for both patient and clinician.

Twitter Jon Stone @jonstoneneuro and Alan Carson @alancarson15

Acknowledgements The Emergency Medicine Department of the Royal Infirmary of Edinburgh.

Contributors AC: conceived the idea. AvG: co-ordinated the development of the website. AC, LMW, LRD, JS: contributed to website content. DC and DK: facilitated testing of website. All authors contributed to writing the manuscript.

Funding AvG was on a training fellowship funded by the University of Groningen, University Medical Center Groningen, Interdisciplinary Center Psychopathology and Emotion regulation, Groningen, the Netherlands.

Competing interests AC, JS and LMW: provided independent testimony in Court on a range of neurological and neuropsychiatric topics including mild brain injury. AC: an associate editor of *Journal of Neurology Neurosurgery and Psychiatry*.

Patient consent for publication Not required.

Provenance and peer review Commissioned. Externally peer reviewed by David Sharp, London, UK, Sallie Baxendale, London, UK, and Colette Griffin, London, UK.

ORCID iD
Jon Stone http://orcid.org/0000-0001-9829-8092

REFERENCES

1 Swann IJ, Walker A. Who cares for the patient with head injury now? *Emerg Med J* 2001;18:352–7.
2 Scottish Intercollegiate Guidelines Network. *Early management of patients with a head injury: a national clinical guideline*. Edinburgh, 2009.
3 Carroll L, Cassidy JD, Holm L, *et al*. Methodological issues and research recommendations for mild traumatic brain injury: the who collaborating centre Task force on mild traumatic brain injury. *J Rehabil Med* 2004;36:113–25.
4 Malec JF, Brown AW, Leibson CL, *et al*. The Mayo classification system for traumatic brain injury severity. *J Neurotrauma* 2007;24:1417–24.
5 Sharp DJ, Jenkins PO. Concussion is confusing us all. *Pract Neurol* 2015;15:172–86.
6 Carroll L, Cassidy JD, Peloso P, *et al*. Prognosis for mild traumatic brain injury: results of the who collaborating centre Task force on mild traumatic brain injury. *J Rehabil Med* 2004;36:84–105.
7 Anon, World Health Organization. *How to use the ICF: a practical manual for using the International classification of functioning, disability and health ICF*, 2013.
8 Hou R, Moss-Morris R, Peveler R, *et al*. When a minor head injury results in enduring symptoms: a prospective investigation of risk factors for postconcussional syndrome after mild traumatic brain injury. *J Neurol Neurosurg Psychiatry* 2012;83:217–23.
9 Borg J, Holm L, Peloso P, *et al*. Non-surgical intervention and cost for mild traumatic brain injury: results of the who collaborating centre Task force on mild traumatic brain injury. *J Rehabil Med* 2004;36:76–83.
10 Snell DL, Surgenor LJ, Hay-Smith EJC, *et al*. A systematic review of psychological treatments for mild traumatic brain injury: an update on the evidence. *J Clin Exp Neuropsychol* 2009;31:20–38.
11 Turner-Stokes L, Pick A, Nair A, *et al*. Multi-Disciplinary rehabilitation for acquired brain injury in adults of working age. *Cochrane Database Syst Rev* 2015;29.
12 Scottish Intercollegiate Guidelines Network. *Brain injury rehabilitation in adults: a national clinical guideline*. Edinburgh, 2013.
13 King NS, Crawford S, Wenden FJ, *et al*. Measurement of post-traumatic amnesia: how reliable is it? *J Neurol Neurosurg Psychiatry* 1997;62:38–42.
14 Stiell IG, Clement CM, Rowe BH, *et al*. Comparison of the Canadian CT head rule and the new Orleans criteria in patients with minor head injury. *JAMA* 2005;294:1511–8.
15 Stiell IG, Wells GA, Vandemheen K, *et al*. The Canadian CT head rule for patients with minor head injury. *The Lancet* 2001;357:1391–6.
16 Friedland D, Swash M. Post-Traumatic amnesia and confusional state: Hazards of retrospective assessment. *J Neurol Neurosurg Psychiatry* 2016;87:1068–74.
17 Povlishock JT, Katz DI. Update of neuropathology and neurological recovery after traumatic brain injury. *J Head Trauma Rehabil* 2005;20:76–94.
18 Smith DH, Meaney DF. Axonal damage in traumatic brain injury. *The Neuroscientist* 2000;6:483–95.
19 Rabinowitz AR, Levin HS. Cognitive sequelae of traumatic brain injury. *Psychiatr Clin North Am* 2014;37:1–11.
20 Haacke EM, Mittal S, Wu Z, *et al*. Susceptibility-Weighted imaging: technical aspects and clinical applications, part 1. *AJNR Am J Neuroradiol* 2009;30:19–30.
21 Huang Y-L, Kuo Y-S, Tseng Y-C, *et al*. Susceptibility-Weighted MRI in mild traumatic brain injury. *Neurology* 2015;84:580–5.
22 Nampiaparampil DE. Prevalence of chronic pain after traumatic brain injury: a systematic review. *JAMA* 2008;300:711–9.
23 Arshad Q, Roberts RE, Ahmad H, *et al*. Patients with chronic dizziness following traumatic head injury typically have multiple diagnoses involving combined peripheral and central vestibular dysfunction. *Clin Neurol Neurosurg* 2017;155:17–19.
24 Popkirov S, Staab JP, Stone J. Persistent postural-perceptual dizziness (PPPD): a common, characteristic and treatable cause of chronic dizziness. *Pract Neurol* 2018;18:5–13.
25 Stulemeijer M, van der Werf S, Bleijenberg G, *et al*. Recovery from mild traumatic brain injury: a focus on fatigue. *J Neurol* 2006;253:1041–7.
26 Hoge CW, McGurk D, Thomas JL, *et al*. Mild traumatic brain injury in U.S. soldiers returning from Iraq. *N Engl J Med* 2008;358:453–63.
27 Schneider KJ, Iverson GL, Emery CA, *et al*. The effects of rest and treatment following sport-related concussion: a systematic review of the literature. *Br J Sports Med* 2013;47:304–7.
28 Thomas DG, Apps JN, Hoffmann RG, *et al*. Benefits of strict rest after acute concussion: a randomized controlled trial. *Pediatrics* 2015;135:213–23.
29 DiFazio M, Silverberg ND, Kirkwood MW, *et al*. Prolonged activity restriction after concussion: are we worsening outcomes? *Clin Pediatr* 2016;55:443–51.
30 White PD, Goldsmith KA, Johnson AL, *et al*. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. *Lancet* 2011;377:823–36.

31 Theadom A, Cropley M, Parmar P, *et al*. Sleep difficulties one year following mild traumatic brain injury in a population-based study. *Sleep Med* 2015;16:926–32.
32 Orff HJ, Ayalon L, Drummond SPA. Traumatic brain injury and sleep disturbance: a review of current research. *J Head Trauma Rehabil* 2009;24:155–65.
33 Sullivan KA, Berndt SL, Edmed SL, *et al*. Poor sleep predicts subacute postconcussion symptoms following mild traumatic brain injury. *Appl Neuropsychol* 2016;23:426–35.
34 McCrea M, Guskiewicz KM, Marshall SW, *et al*. Acute effects and recovery time following concussion in collegiate football players. *JAMA* 2003;290:2556–63.
35 Schretlen DJ, Shapiro AM. A quantitative review of the effects of traumatic brain injury on cognitive functioning. *Int Rev Psychiatry* 2003;15:341–9.
36 Belanger HG, Curtiss G, Demery JA, *et al*. Factors Moderating neuropsychological outcomes following mild traumatic brain injury: a meta-analysis. *J Int Neuropsychol Soc* 2005;11:215–27.
37 McCaffrey RJ, Bauer L, Palav AA, *et al*. *Practitioner's guide to symptom base rates in the general population*. New York: Springer Science & Business Media, 2006.
38 Eysenck MW, Derakshan N, Santos R, *et al*. Anxiety and cognitive performance: attentional control theory. *Emotion* 2007;7:336–53.
39 Griem J, Stone J, Carson A, *et al*. Psychologic/functional forms of memory disorder. *Handb Clin Neurol* 2016;139:407–17.
40 McWhirter L, Stone J, Ritchie C, *et al*. *Functional cognitive disorders: a systematic review*. Lancet Psychiatry in press, 2019.
41 Fleminger S, Greenwood RJ, Oliver DL. Pharmacological management for agitation and aggression in people with acquired brain injury. *Cochrane Database Syst Rev* 2006:CD003299.
42 Cole WR, Bailie JM. Neurocognitive and psychiatric symptoms following mild traumatic brain injury. In: Laskowitz D, Grant G, eds. *Translational research in traumatic brain injury*. Boca Raton, FL: Taylor & Francis Group, LLC, 2016.
43 Jones C, Harvey AG, Brewin CR. Traumatic brain injury, dissociation, and posttraumatic stress disorder in road traffic accident survivors. *J Trauma Stress* 2005;18:181–91.
44 Tschan R, Wiltink J, Adler J, *et al*. Depersonalization experiences are strongly associated with dizziness and vertigo symptoms leading to increased health care consumption in the German general population. *J Nerv Ment Dis* 2013;201:629–35.
45 Sang FYP, Jáuregui-Renaud K, Green DA, *et al*. Depersonalisation/derealisation symptoms in vestibular disease. *J Neurol Neurosurg Psychiatry* 2006;77:760–6.
46 Anon. Available: https://www.youtube.com/watch?v=GWyidaGteGg
47 Anon. Available: https://soundcloud.com/bmjpodcasts/watching-the-world-through-a-clear-fog-recognising-depersonalisation-and-derealisation
48 Hunter ECM, Charlton J, David AS. Depersonalisation and derealisation: assessment and management. *BMJ* 2017;356:j745.
49 Hunter ECM, Baker D, Phillips ML, *et al*. Cognitive-behaviour therapy for depersonalisation disorder: an open study. *Behav Res Ther* 2005;43:1121–30.
50 Parry-Jones BL, Vaughan FL, Miles Cox W. Traumatic brain injury and substance misuse: a systematic review of prevalence and outcomes research (1994–2004). *Neuropsychol Rehabil* 2006;16:537–60.
51 Taylor LA, Kreutzer JS, Demm SR, *et al*. Traumatic brain injury and substance abuse: a review and analysis of the literature. *Neuropsychol Rehabil* 2003;13:165–88.
52 Schmidt CS, Schulte B, Seo H-N, *et al*. Meta-Analysis on the effectiveness of alcohol screening with brief interventions for patients in emergency care settings. *Addiction* 2016;111: 783–94.
53 Michie S, Whittington C, Hamoudi Z, *et al*. Identification of behaviour change techniques to reduce excessive alcohol consumption. *Addiction* 2012;107:1431–40.
54 O'Donnell A, Anderson P, Newbury-Birch D, *et al*. The impact of brief alcohol interventions in primary healthcare: a systematic review of reviews. *Alcohol and Alcoholism* 2014;49:66–78.
55 Carson A. Concussion, dementia and CTE: are we getting it very wrong? *J Neurol Neurosurg Psychiatry* 2017;88:462–4.
56 Xu W, Tan L, Wang HF, *et al*. Meta-Analysis of modifiable risk factors for Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 2015;86:1299–306.
57 Li Y, Li Y, Li X, *et al*. Head Injury as a Risk Factor for Dementia and Alzheimer's Disease: A Systematic Review and Meta-Analysis of 32 Observational Studies. *PLoS One* 2017;12: e0169650.
58 Cassidy JD, Carroll L, Peloso P, *et al*. Incidence, risk factors and prevention of mild traumatic brain injury: results of the who collaborating centre Task force on mild traumatic brain injury. *J Rehabil Med* 2004;36:28–60.
59 Crane PK, Gibbons LE, Dams-O'Connor K, *et al*. Association of traumatic brain injury with late-life neurodegenerative conditions and neuropathologic findings. *JAMA Neurol* 2016;73:1062–9.
60 Fann JR, Ribe AR, Pedersen HS, *et al*. Long-Term risk of dementia among people with traumatic brain injury in Denmark: a population-based observational cohort study. *Lancet Psychiatry* 2018;5:424–31.
61 Mitchell AJ, Meader N, Pentzek M. Clinical recognition of dementia and cognitive impairment in primary care: a meta-analysis of physician accuracy. *Acta Psychiatr Scand* 2011;124:165–83.
62 Corrigan JD, Selassie AW, Orman JAL. The epidemiology of traumatic brain injury. *J Head Trauma Rehabil* 2010;25:72–80.
63 Godbolt AK, Cancelliere C, Hincapié CA, *et al*. Systematic review of the risk of dementia and chronic cognitive impairment after mild traumatic brain injury: results of the International collaboration on mild traumatic brain injury prognosis. *Arch Phys Med Rehabil* 2014;95:S245–56.
64 Mackay DF, Russell ER, Stewart K, *et al*. Neurodegenerative disease mortality among former professional soccer players. *N Engl J Med* 2019;381:1801–8.
65 Al Sayegh A, Sandford D, Carson AJ. Psychological approaches to treatment of postconcussion syndrome: a systematic review. *J Neurol Neurosurg Psychiatry* 2010;81:1128–34.