Clinical presentation and neuropsychological profiles of Functional Cognitive Disorder patients with and without co-morbid depression

Title page

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Abstract

Introduction: Functional Cognitive Disorder (FCD) is poorly understood. We sought to better characterise FCD in order to inform future diagnostic criteria and evidence based treatments. Additionally, we compared FCD patients with and without co-morbid depression, including their neuropsychological profiles, to determine whether these two disorders are distinct.

Methods: 47 FCD patients (55% female, mean age: 52 years) attending a tertiary neuropsychiatric clinic over a one year period were included. We evaluated sociodemographic characteristics and clinical features including presentation, medications, the presence and nature of co-morbid psychiatric or physical illnesses, and the results of neuropsychometric testing.

Results: 23/47 (49%) patients had co-morbid depression. Six had cognitive difficulties greater than expected from their co-morbid conditions suggesting 'functional overlay'. 34 patients had formal neuropsychological testing; 12 demonstrated less than full subjective effort. 16/22 (73%) of the remaining patients had non-specific cognitive impairment in at least one domain. There were no significant differences between those with and without co-morbid depression.

Conclusions: Our study informs future diagnostic criteria. For example, they should not exclude patients with co-morbid psychiatric illness or abnormal neuropsychometric testing and clinicians should remain open to the possibility of 'functional overlay'. Furthermore, FCD and depression are distinct disorders that can exist co-morbidly.

Introduction

Functional cognitive disorder (FCD) is a poorly characterised and understood condition describing persistent and genuinely experienced subjective cognitive difficulties in the absence of underlying neurodegenerative pathology (Schmidtke, Pohlmann, & Metternich, 2008). We favour this terminology (Pennington, Newson, Hayre & Coulthard, 2015a) over the alternative, Functional Memory Disorder (FMD), as it more completely describes a wider range of cognitive difficulties such as concentration lapses, absent mindedness and reduced attention as well as memory problems (Metternich, Schmidtke, & Hull, 2009). However, the literature that focusses primarily on FMD (Griem, Stone, Carson, & Kopelman, 2016) is still relevant.

Though subjective cognitive complaints are common in healthy people (Commissaris, Ponds, & Jolles, 1998) and can represent an early, subclinical manifestation of dementia (Mitchell, Beaumont, Ferguson, Yadegarfar, & Stubbs, 2014), certain features are known to distinguish patients with FCD. These include hypervigilance towards cognitive failures, poor metacognitive ability which leads to poor self-appraisal of cognitive performance (Bharambe & Larner, 2018; Larner, 2018; Pennington, Hayre, Newson & Coulthard, 2015b), heightened anxiety in everyday situations where cognitive ability is tested (Metternich et al., 2009; Pennington, Hayre, Newson & Coulthard, 2015b), positive identification of psychosocial or emotional causative factors (Schmidtke et al., 2008; Stone et al., 2015) and a lack of reassurance despite evidence of non-concerning test results. There is also a discrepancy between self-appraisal and day-to-day functioning as well as performance on neuropsychological testing (Pennington et al., 2015a).

Patients with FCD are seen in a wide range of healthcare settings including primary care, older adult memory services geared towards diagnosing and managing dementia as well as cognitive disorder clinics and neuropsychiatric services. Indeed, the prevalence appears to be rising and this may be associated with increased public awareness about dementia (Bell, Harkness, Dickson, & Blackburn, 2015). Pennington et al. (2015b) reported that a third of all

patients under 60 attending a memory clinic in Bristol had FCD while Bharambe and Larner (2018) identified the diagnosis in more than half of all patients attending a secondary care cognitive disorders clinic. Despite this, there has been relatively little research into FCD and there is no consensus on how to best diagnose and manage this patient group. Further, uncertainty surrounding diagnosis and management leaves patients vulnerable to iatrogenic harm (Stone et al., 2015).

Two groups have attempted to formulate diagnostic criteria. Amongst Schmidtke and Metternich's (2009) criteria are identifiable causative psychological stressors, unimpaired performance on neuropsychometric testing, the absence of an organic cause and the absence of a major psychiatric illness. Delis and Wetter's (2007) diagnostic criteria for cogniform disorder, which is akin to FCD, focuses on the demonstration of inconsistencies between different aspects of neuropsychometric functioning or between reported symptoms and everyday performance. The validity of these criteria for FCD have been questioned, as they were largely derived to assist with the assessment of claimants in medicolegal settings following head injury (Stone et al., 2015). Stone et al (2015) have argued that it may be inappropriate to attempt to define diagnostic criteria for a condition that is currently so poorly characterised. Rather, they advise a more dimensional approach to the assessment of non-organic memory symptoms.

Despite its significant impact on individual well-being and healthcare utilisation, FCD remains under-researched. Better characterisation of the condition would allow more accurate diagnostic criteria to be established and tailored treatments to be developed and evaluated. Therefore, the aim of this retrospective analysis was to characterise the FCD cases seen, over the course of a year, at a tertiary neuropsychiatry referral centre in London. Another aim was to compare the characteristic presenting features and assessment of FCD patients with and without depression as there is a lack of consensus in the literature as to whether they can be independently co-morbid or, if not, to what extent one contributes to the other (Blackburn et al., 2014; Schmidtke et al., 2008; Stone et al., 2015). We hypothesised that

patients with co-morbid depression may be more impaired in terms of social functioning, for example, being unemployed, and on specific areas of neuropsychiatric testing such as executive function and memory which are known to be affected in depression (Rock, Roiser, Riedel, & Blackwell, 2014), due to the additive burden of having both disorders.

Methods

We conducted a retrospective review of clinical records of patients attending a tertiary care neuropsychiatry clinic at The National Hospital for Neurology and Neurosurgery (NHNN), University College London Hospitals NHS Foundation Trust (UCLH), over the course of a year, between 1st April 2016 and 31st March 2017. The clinical records were accessed through e-Care Logic Clinical Data Repository (CDR), an electronic patient records system used in the trust. Patients with a diagnosis of FCD were identified for evaluation.

Description of cases

Given the lack of well-established diagnostic criteria for FCD, cases of FCD were diagnosed based on there being a) no evidence of neurodegenerative disease; b) cognitive difficulties being the primary presenting complaint and c) cognitive difficulties that could not be explained in the context of a co-morbid psychiatric or physical health co-morbidities. Additional features included a discrepancy between self-appraisal of cognitive function and day to day functioning as well as performance on cognitive testing, either assessed during the initial meeting or more formally through neuropsychometric testing. Therefore, we did not categorically exclude patients with psychiatric or physical illness but considered the temporal relationship between the onset of the co-morbid illness and the cognitive symptoms, whether there was a resolution of cognitive symptoms on treating the illness and the clinician's impression to evaluate whether the illness was likely to be accountable for the cognitive symptoms. Depression was diagnosed by a clinician based on ICD-10 criteria.

Functional cognitive symptoms often arise in the context of co-morbid functional disorders (Teodoro, Edwards & Isaacs, 2018) but we classified such patients as having FCD providing that their cognitive symptoms were their primary complaint. Contrary to previous work (Schmidtke et al., 2008) we did not exclude patients on the basis of poor performance on

neuropsychometric testing as we would anticipate patients with FCD to show non-specific deficits on cognitive testing (Stone et al., 2015).

Ethical approval

Ethical approval from NHS Health Research Authority (HRA) and Health and Care Research Wales (HCRW) was received for the use of patient data in this study.

Study variables

Having identified patients with FCD, we extracted information relating to sociodemographic characteristics, referral source, presentation features, psychosocial stressors, co-morbid psychiatric or physical illnesses, prescribed psychotropic medications and the results of neuropsychometric testing and neuroimaging. In addition, the duration of follow-up and resource use in the form of clinic appointments and investigations were quantified. Finally, the treatments offered to patients were evaluated.

In terms of demographic features, we categorised patients' occupations based on a modified version of 'Social Class based on Occupation' (Centre for longitudinal study information and user support (CeLSIUS), 2013). Relationship status included 'in a relationship' for patients who were married, cohabiting or described having a partner. Patients who were retired or chose to fulfil roles as a 'househusband' or 'housewife' were not counted as being unemployed. Considering psychosocial stressors, we deemed any psychological distress arising from events within a year of symptom onset to be classed as 'acute psychological distress' to distinguish this from more chronic psychological distress. Functional pain disorder included somatic pain syndromes such as fibromyalgia while functional gastrointestinal symptoms referred predominantly to irritable bowel syndrome. Where there were missing data this was recorded as 'unknown'.

Information from neuropsychometric testing was extracted from clinical reports. Measures of IQ (verbal, performance and pre-morbid estimates) were classed as normal if in the 85-115 range. The Visual Object and Space Perception battery (VOSP) was used uniformly to

assess visuospatial perception and the assessing neuropsychologists used the 5th percentile norm as distinguishing between normal and abnormal performance. For verbal memory, visual memory, executive function, processing speed and nominal ability we deemed performance below 25th percentile norms to be in the inferior range, 25th to 75th percentile norms to be in the normal range, 75th percentile norms or above to be in the superior range. Where performance in a particular cognitive domain as well as the assessment of effort was not reported quantitatively we have used the assessors' descriptive interpretations. The neuropsychological tests used to assess each domain are shown in the supplementary material (see table S1 published as supplementary material online).

Suboptimal effort was determined by the subjective reports of the neuropsychologist performing testing. This was based on internal inconsistencies on testing such as a patient demonstrating greater recall on backward compared to forward digit span. In addition, in two cases, neuropsychologists used the Test of Memory Malingering (TOMM) where they had doubts about the patients' effort.

Analysis

We calculated descriptive statistics for the study cohort and compared patients with and without co-morbid depression using non-parametric statistical tests. Pearson's chi-squared and Mann-Whitney U tests were used to compare categorical and continuous variables respectively. IBM SPSS Version 25 was the software used for statistical analysis.

Results

Out of a total of 692 patients seen in a neuropsychiatry outpatient clinic between April 2016 and March 2017, 52 (8%) had either a current or historic diagnosis of FCD. The chief complaint of these 52 patients had been cognitive difficulties at the time of initial referral. Some patients were new (n=9) and others were follow-ups. Five (10%) of these patients were initially diagnosed with FCD but subsequently diagnosed with either a neurosurgical (frontal arteriovenous malformation, multiple chronic subdural haematomas), neurological (epilepsy), neurodegenerative (early-onset Alzheimer's disease) or systemic (Fahr's disease) condition which alternatively explained their cognitive difficulties.

Of the remaining 47 diagnosed with FCD, 23 had co-morbid depression, 11 had isolated FCD, 6 had FCD in the context of a broader functional neurological disorder and one patient had retrograde dissociative amnesia. In addition, six patients had cognitive difficulties which were far in excess of those expected from their potentially relevant predisposing conditions, namely historical mild head injury (n=2), previous alcohol dependence (n=2) and the use of potentially relevant medications (n=2).

In **Table 1** sociodemographic characteristics of patients with and without co-morbid depression are compared. Overall, slightly more than half of all patients were female (55%) although this increased to almost two-thirds in the patients with co-morbid depression (p=0.18). The mean age at presentation to the clinic was 52.43 and though the mean age was higher amongst patients with co-morbid depression, this was not statistically significant (Mann-Whitney U=334, p=0.27). There were significant ($\chi^2(3)=8.73$, p=0.03) differences between the groups in terms of level of education and of the seven patients in the cohort who had accessed university education, all had co-morbid depression. More than half of all patients were unemployed at the time of presentation, the proportion being greater amongst those who were depressed (61% vs 42%, $\chi^2(1)=1.73$, p=0.19). There were no significant differences ($\chi^2(5)=2.60$, p=0.76) in occupations between the two groups.

Clinical characteristics are presented in **Table 2**. Patients were referred to the neuropsychiatry clinic from primary care, secondary mental health services, cognitive neurology clinics or other neurological specialties and the source of referral differs ($\chi^2(3)=8.72$, p=0.03) between patients with and without co-morbid depression. Half of all patients in the latter group were referred by the GP compared to 30% of patients with depression. Conversely, patients referred by secondary mental health services and by cognitive neurologists were more likely to have co-morbid depression. 17/47 (36%) patients attended alone and this proportion was greater amongst patients without co-morbid depression (30% vs 50%, $\chi^2(1)=1.87$, p=0.17). More than half of all patients (27/47) had a documented history of some form of preceding psychological distress and the rates were similar amongst both clinically depressed and non-depressed patients. 49% of all patients had at least one co-morbid non-cognitive functional illness, with slightly higher rates amongst depressed patients (52% vs 46%, $\chi^2(1)=0.19$, p=0.66). Aside from depression and/or anxiety, only eleven patients had a history of another psychiatric illness. The use of tricyclic antidepressants (TCAs) was higher amongst non-depressed patients (39% vs 13%, $\chi^2(1)=3.70$, p=0.06). Polypharmacy of medications potentially implicated in affecting cognition was higher amongst depressed patients (44% vs 25%, $\chi^2(1)=1.79$, p= 0.18).

Resource use and management are presented in **Table 3**. The average length of follow-up was 18.55 months amongst all 47 patients, with depressed FCD patients being followed up, on average, for 2.66 months longer than FCD patients without clinical depression (Mann-Whitney U=265, p=0.82). Similarly, patients with FCD and depression had, on average, more outpatient appointments then their non-depressed counterparts (6.09 vs 4.88, Mann-Whitney U=296, p=0.67). The overall number of neuroimaging scans and neuropsychometric testing were comparable between both groups. There were no significant differences in the management strategies implemented.

We do not have access to objective outcome data. Three patients, all with additional non-cognitive functional neurological symptoms, reported improvement in cognitive symptoms after participating in a multidisciplinary treatment programme.

Neuropsychometric profiles were available for 34 patients, of whom 12 (5 with depression) were considered to demonstrate less than full subjective effort. **Table 4** evaluates the neuropsychometric profiles of the remaining 22 patients (for neuropsychometric profiles of all 34 patients see tables S2 and S3 published as supplementary material online). NART (National Adult Reading Test) scores were available for 19 patients. Only one patient scored in the inferior range while the majority (15/19) of assessed patients were in the normal range. 6/22 patients did not have any focal cognitive deficits on neuropsychometric testing (4/10 non-depressed vs 2/12 depressed). Patients with co-morbid depression were more likely to have impaired verbal memory (66% vs 30%, $\chi^2(2)=3.41$, p=0.18) and executive function (50% vs 22%, $\chi^2(1)=1.19$, p=0.55) compared to non-depressed FCD patients but there were no statistically significant differences in these domains. 10/21 patients whose processing speed was assessed were impaired with similar rates between depressed and non-depressed patients (50% vs 44%, $\chi^2(1)=0.31$, p=0.86).

Discussion

The most striking finding from our retrospective analysis is that nearly half of all patients with FCD were clinically depressed, which is in keeping with the FCD cohort previously described by Pennington and colleagues (2015b). Recently, an even higher prevalence of low mood, detected using a two question screening tool, has been reported (Elhadd, Bharambe, & Larner, 2018). This is far higher than the general population where prevalence rates are about 3% (McManus, Bebbington, Jenkins, & Brugha, 2014).

There is growing evidence that cognitive impairment may be an independent feature of depression (Rock et al., 2013) that persists despite clinical resolution of the depressive episode (Hasselbalch, Knorr, & Kessing, 2011). We would argue that this does not necessarily preclude a diagnosis of FCD in patients with current or historical depression. Indeed, all patients in our study were seen by a consultant psychiatrist, experienced in assessing patients with affective disorders, who deemed that the cognitive difficulties experienced by the FCD patients with co-morbid depression and/or anxiety were in excess or different to those that would be expected in such disorders. Some distinguishing features of FCD which are not generally seen with cognitive impairment in depression include excessive and unwarranted concern about cognitive performance (Pennington et al., 2015a), memory-related perfectionism (Schmidtke et al., 2009) and the avoidance of utilising cognition which may have become linked to the experience of failure (Stone et al., 2015). We would hypothesise that the increased propensity for negative cognitions (Beevers and Miller, 2005) and neuroticism (McWilliams, 2003) which patients with depression experience may exaggerate these features thereby exacerbating any actual cognitive impairment. This, in turn, could give rise to a reinforcing cycle of worsening cognitive and mood symptoms. Therefore, whilst depression and FCD are distinct disorders, when they co-exist, their symptoms may intensify and become more difficult to treat.

We identified six patients whose cognitive difficulties could in part be potentially explained by either historical mild head injury, previous alcohol dependence or the polypharmacy of

medications known to alter cognition. We consider that these patients potentially represent a subset of FCD patients who have 'functional overlay', which is seen commonly in other functional neurological conditions (Stone, 2009) and can be explained by the presence of actual but relatively benign cognitive deficits giving rise to excessive concern about cognitive performance and avoidance of cognition use, especially in patients with other predisposing factors.

When considering diagnostic criteria, a significant minority of patients (20/47) did not have obvious acute or chronic psychological distress. Based on this and as suggested previously (Griem et al., 2016) the presence of psychological distress should not be a prerequisite for diagnosing FCD. We noted that 60% of all patients had co-morbid non-cognitive functional neurological, rheumatological or gastroenterological illnesses which may suggest that FCD overlaps with these conditions. This occurred more frequently than has been reported previously (Bharambe and Larner, 2018) and would support previous work (Stone et al., 2015; Pennington et al., 2015a) which has suggested that FCD is best considered within the umbrella of functional neurological symptom (FNS) disorder or conversion disorder.

Interestingly, there were no significant differences in the rates of unemployment due to illness in FCD patients with and without depression. Overall, the rate was more than 50% suggesting that FCD has a significant social impact on its own accord. Future work on FCD must evaluate additional measures of social functioning.

If FCD is considered to be an FNS disorder, patients are likely to have genuine cognitive deficits on neuropsychometric testing. Accordingly, we found that only six of the 22 patients who demonstrated normal effort on cognitive testing did not have any impairment. However, the remaining patients all had deficits in at least one cognitive domain and in keeping with a recent systematic review (Teodoro et al., 2018) these deficits were not generalised. Patients with co-morbid depression showed greater impairment overall, with executive function and memory domains being worst effected as has been described previously (Rock et al., 2013). There were no particular patterns of cognitive performance which we could identify as being

indicative of FCD although the neuropsychological profiles lacked detailed assessment of attention which has recently been proposed as a cognitive domain that is affected in functional disorders (Teodoro et al., 2018).

Our findings suggest that a significant proportion of FCD patients will not have normal neuropsychometric test results and so these tests should not be used in isolation as a means of distinguishing FCD from neurodegenerative disorders. Additionally, based on our findings we would advise caution against causing iatrogenic harm by attributing a more sinister underlying pathology to objectively measured but non-specific deficits. Clearly, a sophisticated interpretation of performance on neuropsychometric testing is required, taking into account effort, anxiety during testing, premorbid ability and the patient's proficiency in the language that the tests are carried out in (Pennington et al., 2015b).

A range of treatment strategies were used in our cohort and this may reflect the lack of an evidence base or any kind of consensus on best management. Nearly half (47%) of the FCD patients we evaluated were followed up with interval assessment comprising further neuroimaging and neuropsychiatry. This strategy, while providing a safety net for clinicians and patients, may delay the diagnosis of FCD being made. There are arguments in favour of a less risk-averse approach through making an earlier diagnosis of FCD based on the presence of certain clinical features (Bharambe & Larner., 2018; Elhadd et al., 2018; Randall & Larner, 2018), accepting that in rare cases atypically presenting neurological or neurodegenerative pathologies will be missed (Stone et al., 2015).

We noted that three patients with co-morbid FNS who participated in a four week long MDT treatment programme comprising occupational therapy (OT), cognitive behavioural therapy (CBT) and physiotherapy reported some subjective improvement in their cognitive functioning but we have no means of objectively measuring this. In this programme, a psychologist appraises the cognitive lapses experienced by a patient together with them and provides cognitive restructuring around these lapses to improve self-perception of cognitive performance. They also provide psychoeducation about what constitutes 'normal' cognitive

difficulties. In parallel, the patient will work with an occupational therapist to practically overcome their avoidance of situations where they feel their cognitive abilities will be challenged. For example, they may go shopping where the patient needs to recollect what to buy and to manage their money in doing so. Such MDT approaches for treatment of FNS have been reported to lead to sustained improvements (Demartini et al., 2014).

FCD is aetiologically heterogenous and treatment often focusses on treating contributory factors such as co-morbid depression or rationalising medication lists (Stone et al., 2015). We would suggest that a unifying feature of FCD, regardless of aetiology, are deficits in metacognition (Bharambe and Larner, 2018; Larner, 2018; Pennington et al., 2015b), which is an individual's ability to appraise their own cognitive ability. Given there are now means of measuring this objectively (Fleming and Lau, 2014) and potentially improving metacognition (Carpenter et al., 2019), this should be explored further as a targeted therapeutic intervention.

Limitations

This study has some key limitations. Firstly, as a retrospective study, it is limited by the clinical information available in patients' records. We were unable to obtain information on the nature of the clinical interaction between patients and healthcare professionals which is increasingly recognised as providing crucial clues as to the likely diagnosis (Jones et al., 2016). Similarly, by retrospectively analysing neuropsychometric performance, we were unable to measure more subtle aspects of testing such as patient engagement, effort, anxiety levels and language ability.

Our retrospective analysis was based on FCD patients referred to a tertiary neuropsychiatric service. This patient group may not be representative of FCD patients being seen and managed in primary and secondary care. We can expect patients in our cohort had greater psychiatric co-morbidity and increased diagnostic uncertainty which had warranted their onward referral.

Finally, the cohort is relatively small thereby limiting the power of the analyses and this makes it difficult to draw firm inferences about sociodemographic, clinical and neuropsychometric testing differences between FCD patients with and without co-morbid depression.

Implications

This descriptive study provides further information on the characteristics of patients with FCD. Future diagnostic criteria should not exclude patients with co-morbid psychiatric illness or abnormal neuropsychometric testing and should remain open to the possibility of 'functional overlay'. Our work further highlights the difficulties and lack of consensus in managing this patient group. An MDT approach with CBT and OT may be indicated.

Conflicts of Interest

None declared.

Description of Authors' Roles

All authors made a substantial contribution to this work. RB, GP, JH and RH all contributed to the conception and design of the study. RB extracted data from anonymised clinical records. RB drafted the paper with all the authors critically reviewing it and suggesting amendments prior to submission. RB and GP had access to all the data in the study and can take responsibility for the integrity of the reported findings.

Data Sharing statement

Extra data is available by emailing the corresponding author.

References

Beevers, C. G. & Miller, I. W. (2005). Unlinking negative cognition and symptoms of depression: evidence of a specific treatment effect for cognitive therapy. *J Consult Clin Psychol, 73*, 68-77. doi: 10.1037/0022-006X.73.1.68.

Bell, S., Harkness, K., Dickson, J. M. & Blackburn, D. (2015). A diagnosis for pound55: what is the cost of government initiatives in dementia case finding. *Age Ageing,* 44, 344-510. doi: 1093/ageing/afu205.

Bharambe, V. & Larner, A. J. (2018). Functional cognitive disorders: demographic and clinical features contribute to a positive diagnosis. *Neurodegener Dis Manag,* 8, 377-383. doi: 10.2217/nmt-2018-0025.

Blackburn, D. J., Wakefield, S., Shanks, M. F., Harkness, K., Reuber, M. & Venneri, A. (2014). Memory difficulties are not always a sign of incipient dementia: a review of the possible causes of loss of memory efficiency. *Br Med Bull,* 112, 71-81. doi: 10.1093/bmb/ldu029.

Carpenter, J., Sherman, M.T., Kievit, R.A., Seth, A.K., Lau, H. & Fleming, S.M. Domain-448 general enhancements of metacognitive ability through adaptive training. *J Exp Psychol* 449 Gen, 148, 51-64.

Centre for longitudinal study information and user support (CeLSIUS). Social Class (SC). (2013). Available from: https://www.ucl.ac.uk/celsius/online-training/socio/se040100. Last accessed on 21/05/18

Commissaris, C. J., Ponds, R. W. & Jolles, J. (1998). Subjective forgetfulness in a normal Dutch population: possibilities for health education and other interventions. *Patient Educ Couns,* 34, 25-32.

Delis, D. C. & Wetter, S. R. (2007). Cogniform Disorder and Cogniform Condition: proposed diagnoses for excessive cognitive symptoms. *Arch Clin Neuropsychol, 22*, 589-604. doi: 10.1016/j.acn.2007.04.001.

Demartini, B., Batla, A., Petrochilos, P., Fisher, L., Edwards, M.J., & Joyce E.(2014). Multidisciplinary treatment for functional neurological symptoms: a prospective study. J Neurol, 261, 2370-2377. doi: 10.1007/s00415-014-7495-4

Elhadd, K., Bharambe, V. & Larner, A.J. (2018). Functional cognitive disorders: can sleep disturbance contribute to a positive diagnosis? *J. Sleep Disord. Ther,* 7, 291.

Fleming, S. M. & Lau, H. C. (2014). How to measure metacognition. *Front Hum Neurosci,* 8, 443. doi: 10.3389/fnhum.2014.00443.

Griem, J., Stone, J., Carson, A. & Kopelman, M. D. (2016). Psychologic/functional forms of memory disorder. *Handb Clin Neurol,* 139, 407-417. doi: 10.1016/B978-0-12-801772-2.00035-7.

Hasselbalch, B. J., Knorr, U. & Kessing, L. V. (2011). Cognitive impairment in the remitted state of unipolar depressive disorder: a systematic review. *J Affect Disord,* 134, 20-31. doi: 10.1016/j.jad.2010.11.011.

Jones, D., Drew, P., Elsey, C., Blackburn, D., Wakefield, S., Harkness, K. & Reuber, M. (2016). Conversational assessment in memory clinic encounters: interactional profiling for

differentiating dementia from functional memory disorders. *Aging Ment Health,* 20**,** 500-9. doi: 10.1080/13607863.2015.1021753.

Larner, A. J. (2018). Dementia screening: a different proposal. Future Neurol, 13, 177-9. doi.org/10.2217/fnl-2018-0018

McManus S, Bebbington P, Jenkins R, Brugha T. Mental health and wellbeing in England: Adult Psychiatric Morbidity Survey. (2014). Leeds: NHS Digital 2016. Available at: http://content.digital.nhs.uk/catalogue/PUB21748/apms-2014-full-rpt.pdf [Accesed 2 September 2018]

McWilliams, L. (2003). Neuroticism and depression. *Br J Psychiatry,* 182**,** 80

Metternich, B., Schmidtke, K. & Hull, M. (2009). How are memory complaints in functional memory disorder related to measures of affect, metamemory and cognition? *J Psychosom Res,* 66**,** 435-44. doi: 10.1016/j.jpsychores.2008.07.005.

Mitchell, A. J., Beaumont, H., Ferguson, D., Yadegarfar, M. & Stubbs, B. (2014). Risk of dementia and mild cognitive impairment in older people with subjective memory complaints: meta-analysis. *Acta Psychiatr Scand,* 130**,** 439-51. doi: 10.1111/acps.12336.

Pennington, C., Newson, M., Hayre, A. & Coulthard, E. (2015a). Functional cognitive disorder: what is it and what to do about it? *Pract Neurol,* 15**,** 436-44. doi: 10.1136/practneurol-2015-001127.

Pennington, C., Hayre, A., Newson, M. & Coulthard, E. (2015b). Functional Cognitive Disorder: A Common Cause of Subjective Cognitive Symptoms. *J Alzheimers Dis,* 48 Suppl 1**,** S19-24. doi: 10.3233/JAD-150182.

Randall, A., & Larner, A.J. (2018) La maladie du petit papier: a sign of functional cognitive disorder? Int J Geriatr Psychiatry, 33, 800.

Rock, P. L., Roiser, J. P., Riedel, W. J. & Blackwell, A. D. (2014). Cognitive impairment in depression: a systematic review and meta-analysis. *Psychol Med,* 44**,** 2029-40. doi: 10.1017/S0033291713002535.

Schmidtke, K. & Metternich, B. (2009). Validation of two inventories for the diagnosis and monitoring of functional memory disorder. *J Psychosom Res,* 67**,** 245-51. doi: 10.1016/j.jpsychores.2009.04.005.

Schmidtke, K., Pohlmann, S. & Metternich, B. (2008). The syndrome of functional memory disorder: definition, etiology, and natural course. *Am J Geriatr Psychiatry,* 16**,** 981-8. doi: 10.1097/JGP.0b013e318187ddf9.

Stone, J. (2009). The bare essentials: Functional symptoms in neurology. *Pract Neurol,* 9**,** 179-89. doi: 10.1136/jnnp.2009.177204.

Stone, J., Pal, S., Blackburn, D., Reuber, M., Thekkumpurath, P. & Carson, A. (2015). Functional (Psychogenic) Cognitive Disorders: A Perspective from the Neurology Clinic. *J Alzheimers Dis,* 48 Suppl 1**,** S5-S17. doi: 10.3233/JAD-150430.

Teodoro, T., Edwards, M.J. & Isaacs, J.D. (2018). A unifying theory for cognitive abnormalities in functional neurological disorders, fibromyalgia and chronic fatigue syndrome: systematic review. *J Neurol Neurosurg Psychiatry*, 89,1308-1319. doi: 10.1136/jnnp-2017-317823

World Health Organization. (1992). *International statistical classification of diseases and related health problems* (10th Revision). Retrieved from: https://icd.who.int/browse10/2016/en

Variable	Overall FCD patients (n=47)	FCD patients with co-morbid depression (n=23)	FCD patients without co-morbid depression (n=24)	P-value
Female sex, No. (%)	26 (55)	15 (65)	11 (46)	**0.18**
Mean Age	52.43 (12.85)	54.74 (13.77)	50.21 (11.76)	**0.56**
Ethnicity, No. (%)				**0.71**
White	25 (53)	13 (57)	12 (50)	
Black	4 (9)	1 (4)	3 (12)	
Asian	8 (17)	4 (17)	4 (17)	
Mixed	1 (2)	0 (0)	1 (4)	
Other	9 (19)	5 (22)	4 (17)	
Relationship status, No. (%)				**0.18**
In a relationship	27 (57)	10 (44)	17 (71)	
Single	15 (32)	9 (39)	6 (25)	
Separated	4 (9)	2(9)	2 (8)	
Unknown	1 (2)	0 (0)	1 (4)	
Level of Education, No. (%)				**0.03**
Primary	7 (15)	4 (17)	7 (21)	
Secondary	21 (45)	9 (39)	12 (50)	
University graduate	7 (15)	7 (30)	0 (0)	
Unknown	8 (17)	3 (13)	5 (21)	
Occupation (current or previous), No. (%)				**0.76**
Professional	15 (32)	7 (30)	8 (33)	
Managerial and technical	3 (6)	2 (9)	1 (4)	
Skilled	3 (6)	2 (9)	1 (4)	
Unskilled	11 (23)	6 (26)	5 (21)	
Never employed	5 (11)	1 (4)	4 (17)	
Unknown	10 (21)	5 (22)	5 (21)	
Unemployed due to illness, No. (%)	24 (51)	14 (61)	10 (42)	**0.19**

Table 1. Sociodemographic characteristics.

	Overall FCD patients (N=47)	FCD patients with current co-morbid depression (N=23)	FCD patients without current co-morbid depression (N=24)	P-value
Referral source. No. (%)				**0.03**
GP	19 (40)	7 (30)	12 (50)	
Secondary Mental Health services	7 (15)	6 (26)	1 (4)	
Cognitive Neurologist	10 (21)	8 (35)	2 (8)	
Other Neurologist	11 (23)	2 (9)	9 (38)	
Attended first appointment alone, No. (%)	17 (36)	7 (30)	12 (50)	**0.17**
Psychological distress, No. (%)				
No	20 (43)	10 (43)	10 (42)	**0.90**
Yes	27 (57)	13 (57)	14 (58)	
-Acute psychological distress	10 (21)	4 (17)	6 (25)	**0.52**
-Chronic psychological distress	17 (36)	9 (39)	8 (33)	**0.68**
Co-morbid functional illness, No. (%)				
No	24 (51)	11 (48)	13 (54)	**0.66**
Yes	23 (49)	12 (52)[†]	11 (46)[‡]	
-Functional neurological disorder	11 (23)	4 (17)	7 (29)	**0.34**
-Functional pain disorder	14 (30)	7 (30)	7 (29)	**0.92**
-Functional gastroenterological symptoms	4 (9)	2 (9)	2 (8)	**0.97**
Past or current co-morbid psychiatric illness, No. (%)				
No	20 (43)	0 (0)	20 (83)	**<0.001**
Yes	29 (62)	23 (100)[§]	6 (25)[¶]	
-Depression and/or anxiety	24 (51)	23 (100)	1 (4)	**<0.001**
-PTSD	1 (2)	0 (0)	1 (4)	**0.32**
-OCD	3 (6)	1 (4)	2 (8)	**0.58**
-Anorexia Nervosa	3 (6)	1 (4)	2 (8)	**0.58**
-Substance Misuse	3 (6)	1 (4)	2 (8)	**0.58**
-Psychotic illness	1 (2)	0 (0)	1 (4)	**0.32**
Current psychotropic medication, No. (%)				
No	8 (17)	1 (4)	7 (29)	**0.20**
Yes	39 (83)	22 (96)[††]	17 (71)[‡‡]	
-Atypical antipsychotics	0 (0)	0 (0)	0 (0)	-
-SSRI/SNRI/NaSSa	25 (53)	20 (87)	5 (21)	**<0.001**
-Tricyclic antidepressants	12 (23)	3 (13)	9 (39)	**0.04**
-Benzodiazepines	4 (9)	3 (13)	1 (4)	**0.28**
-Opioids	9 (19)	6 (26)	3 (13)	**0.24**
-Gabapentinoids	6 (13)	3 (9)	3 (13)	**0.96**

Polypharmacy of medications known to affect cognition, No. (%)	16 (34)	10 (44)	6 (25)	**0.18**

PTSD, post-traumatic stress disorder; OCD, Obsessive compulsive disorder; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-noradrenaline reuptake inhibitor; NaSSa, Noradrenergic and specific serotonergic antidepressants
†, 3 patients had multiple co-morbid functional disorders; ‡, 4 patients had multiple co-morbid functional disorders; §, 3 patients had multiple past or current co-morbid psychiatric illnesses; ¶, 3 patients had multiple past or current co-morbid psychiatric illnesses; ††, 10 patients were taking multiple psychotropic medication; ‡‡, 6 patients were taking multiple psychotropic medications.

Table 2. Clinical characteristics.

	Overall FCD patients (N=47)	FCD patients with co-morbid depression (N=23)	FCD patients without co-morbid depression (N=24)	P-value
Length of Follow up (months), mean (SD)	18.55 (19.88)	19.91 (23.62)	17.25 (16.61)	**0.82**
Number of outpatient appointments, mean (SD)	5.40 (7.05)	6.09 (7.51)	4.88 (6.60)	**0.67**
Combined number of volumetric MRIs	54	28	26	**0.57**
Combined number of Neuropsychometric assessments	49	25	24	**0.69**
Treatment offered following first assessment				
Monitor with interval assessments	22 (47)	10 (44)	12 (50)	**0.65**
Pharmacological management	9 (19)	4 (17)	5 (21)	**0.76**
Psychological intervention	8 (17)	4 (17)	4 (17)	**0.95**
Specialist MDT programme	8 (17)	4 (17)	4 (17)	**0.95**
Refer to CMHT	6 (13)	4 (17)	2 (8)	**0.35**
Other (Discharged to GP, non-engagement, lost to follow up)	8 (17)	4 (17)	4 (17)	**0.95**

Table 3. Follow-up, investigations and treatment offered.

Cognitive domain	Overall FCD patients (N=22)[†]	FCD patients with co-morbid depression (N=12)[†]	FCD patients without co-morbid depression (N=10)[†]	P-value
NART, No. (%)	**N=12**	**N=6**	**N=6**	**0.51**
Superior	3 (25)	1 (17)	2 (33)	
Normal	9 (75)	5 (83)	4 (67)	
Inferior	0 (0)	0 (0)	0 (0)	
Verbal IQ, No. (%)	**N=17**	**N= 10**	**N=7**	**0.27**
Superior	4 (24)	3 (30)	1 (14)	
Normal	11 (65)	5 (50)	6 (86)	
Inferior	2 (12)	2 (20)	0 (0)	
Non-verbal IQ, No. (%)	**N=21**	**N=12**	**N=9**	**0.94**
Superior	3 (14)	2 (17)	1 (11)	
Normal	9 (43)	5 (42)	4 (44)	
Inferior	9 (43)	5 (42)	4 (44)	
Visual Memory, No. (%)	**N=21**	**N=11**	**N=10**	**0.46**
Superior	4 (19)	3 (27)	1 (10)	
Normal	8 (38)	3 (27)	5 (50)	
Inferior	9 (43)	5 (46)	4 (40)	
Verbal Memory, No. (%)				**0.18**
Superior	4 (18)	2 (17)	2 (20)	
Normal	7 (32)	2 (17)	5 (50)	
Inferior	11 (50)	8 (67)	3 (30)	
Executive Function, No. (%)	**N=21**	**N=12**	**N=9**	**0.55**
Superior	5 (24)	2 (17)	3 (33)	
Normal	8 (38)	4 (33)	4 (44)	
Inferior	8 (38)	6 (50)	2 (22)	
Processing speed, No. (%)	**N=21**	**N=12**	**N=9**	**0.86**
Superior	3 (14)	2 (17)	1 (11)	
Normal	8 (38)	4 (33)	4 (44)	
Inferior	10 (48)	6 (50)	4 (44)	
Visuospatial, No. (%)	**N=21**	**N=12**	**N=9**	**0.16**
Normal	18 (86)	9 (75)	9 (100)	
Inferior	3 (14)	3 (25)	0 (0)	
Nominal, No. (%)	**N=20**	**N=10**	**N=10**	**0.15**
Superior	3 (15)	1 (10)	2 (20)	
Normal	11 (55)	4 (40)	7 (70)	
Inferior	2 (10)	1 (10)	1 (10)	

† unless stated (N less than overall N signifies missing data); NART, National Adult Reading Test.

Table 4. Neuropsychometric profiles.