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CYSTIC FIBROSIS-RELATED DIABETES (CFRD) AND COGNITIVE FUNCTION IN ADULTS WITH CYSTIC FIBROSIS

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Abstract

Background: Being able to function cognitively is imperative for successful achievement in school, working life, and disease self-management. Diabetes is known to cause changes in brain structure and long-term cognitive dysfunction. This work investigated cystic fibrosis-related diabetes (CFRD) as a mechanism for cognitive impairment in people with CF. It was hypothesised that cognition would be poorer in adults with CFRD than in those with CF without diabetes (CFND) or in healthy controls.

Methods: Cognitive performance was assessed using the Cambridge Neuropsychological Test Automated Battery which provides a comprehensive cognitive assessment with tests mapping onto specific brain regions. Demographic, clinical and self-reported health data were documented for all participants. CF specific clinical variables were recorded for the two CF groups.

Results: Ninety-eight people with CF (49CFRD,49CFND) and 49 healthy controls were recruited. People with CF demonstrated deficits in aspects of verbal and spatial memory, processing speed and cognitive flexibility compared with healthy controls, with all areas of the brain implicated. Those with CFRD had additional difficulties with higher-level processes known collectively as ‘executive function’, which demand greater cognitive load and recruit the prefrontal cortex. Compared with healthy controls, those with CFND and CFRD had an estimated 20% and up to 40% reduction in processing speed respectively.

Conclusion: Managing CF requires higher order executive function. Impairments may be sufficient to interfere with self-care and the ability to perform everyday tasks efficiently. At which point in the CF disease trajectory these difficulties begin, and what may attenuate them, has yet to be determined.

Keywords

Cystic fibrosis-related diabetes; cognition; cognitive tests; executive function

Introduction

Cystic fibrosis-related diabetes (CFRD) is an important and well-established complication of cystic fibrosis (CF), affecting up to 50% of patients by the third decade of life (1). This unique form of diabetes occurs most commonly in those with severe CF mutations, increases with age, and results from anatomical and functional pancreatic abnormalities as well as defective CFTR function within the pancreatic β cells (2–4). CFRD is neither Type 1 (T1DM) nor Type 2 diabetes mellitus (T2DM), but shares clinical characteristics of both (4). Diabetes has been shown to cause changes in brain metabolism, structure and function (5–7) and previous studies have shown that people with impaired glucose regulation, including those with T1DM and T2DM exhibit long term cognitive dysfunction (8–13).

A small number of studies have suggested that cognition may also be impaired in children and adults with CF (14–24) with end-stage/severe lung disease, hypoxaemia/hypoxia, sleep disturbances and pulmonary exacerbations suggested as facilitating factors for cognitive deficits. The majority of early research was published using children with CF as control or comparison groups, comparing their performance to people with other diseases, which allowed the effects of chronic illness and early hospitalisations to be controlled for (20–22). The first known studies to investigate cognitive function as the primary outcome in adults with CF were conducted by Maddrey and colleagues in 1997 (23), with impairments observed for domains of attention (23%), memory (32%), and executive function (the ability to organise and retrieve information; 61%) compared to (age, gender and education appropriate) normative data (24). Pulmonary exacerbations are likely to have a negative effect on accuracy and processing speed due to symptomology (e.g. sleep disruption; 14). People with CF who have severe disease (ppFEV1 <40%) experience increased daytime sleepiness and have been found to perform at a level 60% of the healthy controls (16). Patients with end-stage disease have been found to show the greatest impairments in verbal memory and executive function as a result of progressive decline in lung function (15). More recent research has postulated that regular physical

activity may have a positive effect on cognitive function in people with CF due to its effect on the peripheral nervous system (25), which is defective in CF due to CFTR expression (26, 27). Whilst most previous studies have found impairments in people with CF, the results are inconsistent, and this may be due to underpowered studies, lack of control groups, different aspects of cognition investigated, or different cognitive tests being used across studies.

To date, there is no published work which examines the effect of CFRD on cognitive function. The aim of this study was to investigate a range of cognitive functions in CF using valid, reliable and standardised measures to evaluate aspects of memory, the accuracy and speed of processing information and higher order executive functions (e.g. being cognitively flexible and able to switch easily between tasks). Employing the Cambridge Neuropsychological Test Automated Battery (CANTAB®) allows mapping cognitive tasks to specific brain regions. This test battery has previously been used in diabetic populations (28). This is the first case-controlled study to investigate CFRD as a mechanism for cognitive impairment in people with CF. It was hypothesised that cognition would be poorer in patients with CFRD than in people with CF without diabetes (CFND) or in healthy controls.

Methods

Design

A between subjects design was used incorporating three groups: older teenagers and adults with CFRD, older teenagers and adults with CF without diabetes (CFND) and older teenagers and adult healthy controls. Patients were recruited so that groups were similar in terms of gender, age, and education level (highest qualification) and CF groups were similar in terms of the number of heterozygous F508del patients. The study was approved by Leeds West Research Ethics Committee (13/YH/0219; 20/08/2013).

Recruitment and Participants

Participants with CF

Eligible patients with CF were identified using the Leeds Adult CF Unit electronic patient register, EMIS (29). Inclusion criteria included age 16 years or over, no history of previous solid organ transplantation, pancreatic insufficiency, able to provide informed consent and adequate comprehension of written and spoken English. Patients were excluded if they were pregnant or had been pregnant within the past six months, or if they were receiving continuous or overnight oxygen therapy. Patients with CFRD were insulin-treated and had a confirmed CFRD diagnosis which was made following routine annual oral glucose tolerance test (OGTT) screening and confirmatory blood glucose profiling. Patients with CFND had received a normal OGTT result within the past 12 months and had no prior diagnosis of CFRD. Patients were recruited when clinically stable, on a consecutive basis, either from outpatient clinics or as an inpatient towards the end of their treatment and assessed in their preferred location.

Healthy controls

A community sample of healthy controls was recruited from the general population via public advertisement (leaflets, posters, email distribution lists). Exclusion criteria consisted of self-reported pregnancy, smoking, diabetes, impaired glucose tolerance, neurological disorder, cardiovascular disease, or current use of any medication (excluding oral contraceptives). Healthy controls were recruited to age-match the patient groups, therefore, by default their inclusion criteria for age was the same as the patient groups. Healthy controls were recruited and tested toward the end of patient testing. Participants contacted the chief investigator (by email, telephone) to express interest in the study. They were required to confirm they met the inclusion/exclusion criteria, and to provide details of their age, gender and highest education qualification to ensure the group was

similar on these characteristics to the two CF groups. Assessments took place in the Human Appetite Research Unit, School of Psychology, University of Leeds.

Demographic and Clinical Measures

For all participants, demographic data were collected: age, gender, education level, and occupation. Clinical data, obtained for all participants, consisted of BMI, blood carbon monoxide concentration (Bedfont® Micro+ Smokerlyzer gold standard monitor) and capillary blood glucose (GlucoMen®). Healthy controls and people with CF were required to have a glucose reading of 4-8mmol/L and 4-12mmol/L respectively immediately prior to cognitive testing. For patients with CF, additional clinical characteristics were extracted from their electronic patient records: ppFEV1, FVC predicted, HbA1c, age at CF diagnosis, CFRD duration, C-reactive protein (CRP), oxygen saturation, pseudomonas aeruginosa status, and whether they were receiving intravenous antibiotics at the time of participation.

Subjective Health, Sleepiness, Anxiety and Depression

Participants were asked to rate their health 'today' in terms of how well they felt on a scale of 1 = 'not very healthy' to 10 = 'extremely healthy', adapted from the EQ-5D (30). Sleep was measured using a visual analogue scale ('not at all sleepy' = 0 to 'very sleepy' = 100) adapted from the validated Leeds Sleep Evaluation Questionnaire (LSEQ; 31) with a lower score indicating better sleep quality. The LSEQ assesses changes in sleep and next morning behaviour, and demonstrates both sensitivity and reliability, and it has high construct validity with objective sleep indices (31) and face validity (32). As it is brief and simple to complete, it reduces participant burden, and has been used in studies with people with CF (ClinicalTrials.gov Identifier: NCT0212980, 33). Anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS) (34). The scale has been shown to be reliable, valid and have good sensitivity and specificity (35,36).

Cognitive Performance

Cognitive performance was assessed using a 45-minute battery comprising seven tests from the Cambridge Neuropsychological Test Automated Battery. CANTAB® is used worldwide (37) and provides a comprehensive cognitive assessment which has been shown to be sensitive to normal cognitive ageing (28,38) and neurodegenerative changes in brain function (39). Construct validity has been obtained from studies of patients with long-term health conditions (including diabetes) and healthy, normal functioning adult populations (40,41). The tests are able to map onto specific brain regions, and have good test-retest reliability (39,42), proven brain-behaviour reliability (43) and activate brain regions which may be affected by changes in the Central Nervous System (CNS) and immune functioning (37,44). The tests assess a range of cognitive functions and are described in order in Table 1, together with the brain area/s involved and why these tasks are important in everyday life. The CANTAB battery was administered using a touch screen tablet (Tablet Kiosk i400series; with some tests requiring the use of a two-button response box, Cambridge Cognition 2-button press pad V2.0).

Procedure

All participants were tested after a two hour fast. They completed the consent form, questionnaires (demographic information, health rating, sleepiness and HADS) and blood carbon monoxide concentration and capillary blood glucose were measured. Participants undertook the cognitive tests in the following order: Motor Screening Test (MOT), Paired Associates Learning (PAL), Verbal Recognition Memory (VRM), Pattern Recognition Memory (PRM), Rapid Visual Processing (RVP), Spatial Span Processing (SSP) and Attention Switching Task (AST). They received a £10 Love2Shop Voucher as an honorarium upon completion.

Statistical analysis

The sample size was based on an *a priori* power calculation for the Least Significant Difference test with $\alpha = 0.05$ for each comparison and did not include a multiple comparison adjustment. The calculation indicated that 42 participants would be required in each group, based on a two-sided test, to detect a difference of 5% on the number of correctly identified patterns at immediate recall on the Pattern Recognition Memory (PRM) test (CANTAB®).

Two separate between groups comparisons were made for participant characteristics and for the cognitive tests. These were (i) between healthy controls and CF without diabetes (CFND) and (ii) CF without diabetes (CFND) and CF with diabetes (CFRD). Therefore, the two comparisons of primary interest were healthy controls versus CFND and CFND versus CFRD. These are independent comparisons and are presented as unadjusted contrasts. For proportions a Fisher's exact test was used and for measures a Mann-Whitney U test was used. The roles of demographic, clinical and self-reported measures as potential confounders were explored by correlating these measures with cognitive function outcomes using Kendall's tau coefficient of correlation. If a measure differed between the three groups, then that measure might be a confounder which could partly explain any difference in a cognitive function outcome between the groups. In this case a within group correlation between the measure and the outcome would be observed and observed particularly in the healthy control group. $P < 0.05$ was used as a guide to significance and all computations used IBM SPSS v25.0 and higher versions.

Results

Participant characteristics

Eighty-six patients met the CFRD inclusion criteria and 269 met the CFND inclusion criteria. Recruitment and testing started with six patients with CFRD and subsequently commenced for those with CFND so that groups could be matched on characteristics. Healthy controls were recruited and tested towards the end of patient testing. Two hundred and fourteen individuals expressed initial interest in the study, with nine not meeting the inclusion/exclusion criteria and 29 were refused as they did not match on age. In total, 98 patients with CF (49 insulin treated CFRD, 49 CFND) and 49 healthy controls were recruited and completed the study. An extra seven participants were recruited in each group to account for potential dropouts. This resulted in over 50% of the eligible CFRD population being tested.

As expected, people with CFND had a lower mean blood glucose level compared to people with CFRD, and a higher mean blood glucose level compared to controls (Table 2). People with CFRD had higher HbA1c levels than those with CFND. Of those with CF, 47 patients with CFRD and 45 patients with CFND were heterozygous F508del, and 35 people with CFRD and 31 people with CFND were colonised with *Pseudomonas aeruginosa*.

The three groups were similar in terms of gender, highest level of education, BMI, and levels of anxiety (Table 2). People with CFND were younger than people with CFRD and the healthy controls. More of the healthy controls were in full time work, had a lower COppm, depression level, sleepiness rating, and higher subjective health rating compared to people with CFND. Mean scores for depression were in the normal range for each of the three groups. However, in terms of

'caseness', 2 healthy controls, 10 people with CFND and 9 people with CFRD had depressive symptomatology.

Cognitive Function

Memory

Table 3 shows the scores for each memory test. There were no differences between the three groups in ability to accurately and quickly recognise ten patterns (Pattern Recognition Memory). No differences emerged between the two CF groups in being able to (a) recall and recognise a list of 18 words immediately and after a 20-minute delay (Verbal Recognition Memory), (b) locate patterns (Paired Associates Learning Test) and (c) recall the length of a colour changing box sequence (Spatial Span). However, compared to patients with CFND, healthy controls were able to (a) correctly recall more words immediately after seeing a list of 18 words and after a 20-minute delay (Verbal Recognition Memory), (b) locate patterns more easily (Paired Associates Learning Test), and (c) recall a longer sequence of boxes which changed colour (Spatial Span).

Attention, processing speed and motor speed

There were no differences between the three groups in the accuracy of touching an X (Motor Speed) but the CF groups were slower. Although those with CF performed with similar speed when finding sequences of digits (Rapid Visual Processing) their accuracy was poorer than healthy controls (Table 4).

Cognitive flexibility

People with CFND, compared to healthy controls, were less accurate in switching attention and slower to do so (Attention Switching Task; Table 4). Between the two CF groups, those with diabetes

were slower in attention switching for both levels of task complexity (congruent and incongruent matching). Compared with healthy controls, those with CFND and CFRD had an estimated 20% and up to 40% reduction in processing speed respectively (Table 4).

To check if these results were due to confounding, age, blood glucose level, HbA1c, sleepiness rating, and level of depression were correlated with the attention switching reaction times (Table 5). Only one correlation out of 85 was significant at the 5% level and this could have occurred due to multiple testing. Hence, it was unlikely that these variables confounded the results. However, HADS depression score and subjective health rating both showed correlations of about 0.2 in the healthy controls and both variables differ between groups with the CF groups having greater depression and poorer health rating than the healthy controls. Hence depression and health are not confounders but may be part of the causal pathway between CFND/CFRD and cognitive flexibility.

Discussion

This study demonstrates that people with CF have aspects of cognitive dysfunction compared with healthy controls. Aspects of verbal and spatial memory, processing speed and cognitive flexibility are impacted, with all areas of the brain implicated. More strikingly, those with CFRD have additional difficulties with higher-level processes known collectively as 'executive function': multitasking/cognitive flexibility, organising and planning activities, sequencing, concentrating and problem solving. These activities demand greater cognitive load and primarily engage the prefrontal cortex. Additionally, the executive function processing speeds demonstrated a stepping-down effect: those with CFRD were slower to respond than those with CFND, who in turn, were slower than healthy controls. Compared with healthy controls, those with CFND and CFRD had an estimated 20% and up to 40% reduction in processing speed respectively.

There are three major hypothesised mechanisms for poorer cognition in CF and CFRD: (a) the regulation of glucose and insulin (b) cystic fibrosis transmembrane conductance regulator (CFTR) and (c) chronic inflammation. It would be naïve to assume that these mechanisms are independent from each other, but for brevity each will be addressed in turn. There is some evidence that hyperglycaemia is linked to alterations in brain structure and cognitive impairment (5–13) and so it is not surprising that people with CFRD demonstrate similar cognitive deficits. People with T2DM and CFND exhibit deficits in memory and learning, and a slowing in processing speed. Additionally, T1DM, like CFRD is characterised by reduced executive functioning/cognitive flexibility (44-46). More complex tasks involve increased cognitive load which increases glucose metabolism within the brain (47). The CANTAB Attention Switching task (cognitive flexibility/multitasking) is associated with high-level cortical functioning involving the frontal and parietal regions of the brain (48,49). Age of onset of CFRD is insidious (50) and therefore it is possible that some patients might have been experiencing the negative effects of diabetes prior to the date of their confirmed diagnosis. Duration of diabetes or age of CFRD diagnosis could have contributed to the degree of cognitive dysfunction, as seen in the diabetes mellitus literature (13, 51). In our sample, diabetes duration ranged from 0.5 to 26 years, with a median of 9 years (IQR 0-22.5), and the age of diagnosis ranged from 1 to 39.5 years, with a median of 21 years (IQR 9.2-30.2). It is noteworthy that the CF cohort were routinely screened with annual oral glucose tolerance testing, resulting in early diagnosis of CFRD, prompt treatment before clinical deterioration, and significant improvement in health. It could be argued that a diabetes comparison group, in addition to a healthy control group, would have been informative. However, the characteristics of CFRD do not map onto either T1DM or T2DM and meaningful comparisons may have required two diabetes groups, producing an overcomplicated study design. Additionally, the literature on cognition and diabetes is consistent and robust enabling meaningful comparison with data derived from people with CF.

CFRD as a mechanism for cognitive impairment

It is possible that the observed changes in cognitive function in CF reflect multi-organ disease and the sequelae of CFTR dysfunction. CFTR is extensively expressed in the neurons of the brain and this creates the potential for alterations in the CNS and cognitive performance, although the influence of CFTR on cognition has yet to be determined. Additionally, there is some evidence that CFTR plays a direct role in insulin secretion (52). Increased insulin secretion and, in some cases, a reversal of CFRD, may have important implications for the maintenance of cognitive function in people with CF, both with and without CFRD. Investigations of the effects of modulators on CFRD, inflammation and cognition are awaited.

People with CF have chronic systemic inflammation, and this may impact brain structure and cognition. The increasing levels of pro-inflammatory factors in the blood affect the inflammatory state of the CNS through direct and indirect pathways (53). Indeed, studies have demonstrated that markers of inflammation, notably, increased Interleukin-6 (IL-6) and CRP modulate central inflammatory processes that affect cognitive function (54,55). Receptors for IL-6 are concentrated in the hippocampus and prefrontal cortex (56,57) with smaller hippocampal and prefrontal grey matter volume associated with poorer memory and executive functions in healthy adults (58,59). Inflammatory markers have consistently been associated with poor cognitive performance in both cross-sectional and longitudinal studies in 'healthy' adults aged over 30 years (54,55,60,61). People with COPD have also shown significant cognitive impairment, together with increased inflammatory markers, especially in advanced disease or pulmonary exacerbation (62). It is noteworthy that in this study there was a higher range of CRP levels in people with CFRD. Persistent inflammation leads to permanent structural damage of the CF airways and impaired lung function with several defective inflammatory responses being linked to CFTR deficiency (63,64,65,66). The relationship between CF/CFRD, inflammatory markers/CFTR and cognition has yet to be investigated and remains an interesting area of future study.

Managing CF, a complex, multi-treatment disease requires higher order executive function (67,68). The cognitive impairments may be sufficient to interfere with self-care, disease management and the ability to perform everyday tasks efficiently (11,69,70). People with CF are required to (a) self-motivate and initiate treatments, (b) organise, plan and time-manage treatments, and (c) flexibly shift between treatments (71,72,73,74). Those with CFRD have the additional burden of making clinical judgments about the required insulin dose (75). Psychological difficulties in people with CF are prevalent (76) and depression is associated with poorer survival (77) and quality of life (78,79). For those with CFRD the treatment burden is increased with greater decrements across patient-reported HRQoL domains; most notably, social and emotional functioning, body image, respiratory symptoms and treatment issues (80). Such factors may indirectly impact cognitive function by contributing to chronic inflammation (81). Achieving everyday goals (e.g. completing tasks at work etc.) may require more effort in those with CF compared to healthy peers (82) and cognitive performance is likely to be worsened during pulmonary exacerbations (14). This resonates with patient-reported indicators of a pulmonary exacerbation and indicators of improvement, which highlighted the importance of concentration and fatigue (83,84). Patients with severe CF disease (mean ppFEV₁ 28%) showed both sleep disturbances and poorer cognitive performance compared with controls (16). Similarly, in this study, people with moderate CF disease also reported worse sleep quality than controls. However, sleep quality did not explain the impairment in cognitive flexibility seen in people with CF and may not directly affect cognitive function.

The analyses presented here were not sophisticated but do demonstrate well the relationship between CFRD and cognitive function. More complex regression type analyses with adjustments for potential confounders were tried also and gave conclusions comparable to those presented here. The comparisons of primary interest were healthy controls versus CFND and CFND versus CFRD.

These were unadjusted comparisons with a significant level set at 0.05 a priori. Post hoc adjustment to 0.025 for two multiple comparisons did not impact the conclusions. It may be argued that the results of the current study are compromised given that some participants were receiving intravenous antibiotics. Indeed, 44 people with CF (20 CFRD, 24 CFND) were on treatment at the time of testing. However, of these, 32 were elective and prescribed as 'maintenance antibiotics' rather than treatment for a pulmonary exacerbation. Previous work has demonstrated that cognitive performance is poorer at the beginning of a pulmonary exacerbation than towards the end (14). Therefore, for those with a pulmonary exacerbation as the indication, ten patients were tested at either mid (2 CFND, 2 CFRD) or end (3 CFND, 3 CFRD) of their IVs to minimise the negative effect on cognition.

At which point in the CF disease trajectory alterations in brain structure and cognition begin is unknown. This is a novel and emerging area of research. Recently, in a small sample of 19 children with CF, no overall executive function impairment was found, although some children did exhibit executive function difficulties. Executive functions were associated with increasing age, poorer family functioning/communication, higher treatment burden, poorer lung function and adherence (17). However, executive functions were determined by parent report and there is evidence that patient/parent-reported and tested executive function impairments are not comparable (85).

Being able to function cognitively is imperative for successful achievement in school and working life. The impact of CF and its treatments on cognition is an aspect of quality of life that has largely gone unnoticed. The indication that ivacaftor therapy may improve cognitive ability is remarkable and provides a rationale for considering cognition as an additional outcome measure for future clinical trials of CFTR modulators.

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Declaration of Competing Interest

The authors declare no conflict of interests.

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Table 1. CANTAB® tests and examples of how these translate to everyday tasks

Test (Version; Duration in minutes)	Cognitive domain	Brain area (lobe)	What the test measures	Examples of relevance in everyday tasks	Test Description
Motor Screening Test (MOT) (Clinical; 2)	Motor speed (motor skill; accuracy and speed)	Frontal	Measures accuracy and speed of touching the centre of a 'X'	Everyday tasks that require hand-eye coordination such as putting the key in the door, being able to catch something, picking up or holding small items such as medication tablets.	Ten crosses appear in different locations on the screen one at a time. The participant must touch the centre of each cross as quickly as possible with their dominant hand whilst it is alternatively flashing pink and green. If it is touched properly, the cross disappears, and a sound is played. If the cross is not touched properly, it will stay on the screen and no sound will be played.
Paired Associates Learning (PAL) (Clinical; 5)	Memory (visuo- spatial)	Temporal	Measures accuracy in the ability to locate patterns behind boxes	Being able to remember the location of items e.g. remembering where you left your keys, medication.	White boxes, with a pattern contained behind some of them, are displayed on the screen for 3200ms, and open in a randomised order. Once all boxes have been opened, the patterns which were displayed appear in the middle of the screen. The participant must touch the box where the patterns were located. If an error is made, the patterns are re-presented in their original location for 2200ms. The test involves two trials of locating 1,2,3 patterns respectively, and one trial locating 6 and 8 patterns, respectively. The participant must correctly locate all the original pattern locations in a trial within 10 attempts otherwise the test is terminated.
Verbal Recognition Memory (VRM) (Clinical- immediate 18 words; 7) (Clinical- delayed 18 words; 5)	Memory (verbal; immediate and delayed free recall, and immediate and delayed recognition)	Temporal	Measures accuracy of recalling and recognising of a list of 18 words	Being able to remember, and recognise, words from memory e.g. a shopping list, people's names, remember and differentiate between (similar) drug names.	A list of 18 words is shown in the centre of the screen, one at a time for 3 seconds, with a 2 second delay in between. Participants must read each word aloud once and remember as many words as possible. The screen is then turned away and the participant must freely recall as many of the words as possible in one minute, whilst the researcher records the words on the screen. The screen is then turned back to face the participant and they are instructed to identify, from a list of 36 words (18 target and 18 distractor), which words were presented in the presentation phase. After a 30-minute delay, the participant is asked to verbally and freely recall as many of the list of 18 words they can remember in a minute, without seeing the words again. They are then required to recognise which words were shown in the presentation phase from another list of 36 words (18 target and 18 distractor).
Pattern Recognition Memory (PRM) (Immediate; 4) (Delayed; 2)	Memory (visual; immediate and delayed)	Temporal	Measures accuracy and reaction time in recognising patterns	Recognise the difference between similar images or pictures e.g. similar looking tablets or drug names, similar facially looking individuals.	Twelve patterns are presented in the centre of the screen one at a time, at a pace of every 3 seconds. The participant is subsequently asked to recognise the stimuli when presented with distractors in a two- choice forced task, with no time limit to respond. A second (different) set of 12 patterns are then shown and told to

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					remember them. After a 30-minute delay, the participant must recognise the patterns from the second set, with additional distractor, with no time limit to respond. The distractors are different to those presented in the first task.
Rapid Visual Processing (RVP) <i>(Clinical; 7)</i>	Attention and processing speed (vigilance)	Frontal, parietal and occipital	Measures accuracy and reaction time in finding sequences of digits presented one at a time in a pseudo-random order	Everyday tasks which require sustained concentration and focus for a particular period of time such as driving, preparation of medication of different quantities for administration	Single digits, ranging from 2-9, are presented inside a white box in a pseudo-random order at a rate of 100 digits per minute. The task of the participant is to detect target sequences of 3 digits and press the right button on the response box when they have seen the last number of the sequence. There is a practise phase lasting 2 minutes, and an assessed phase lasting 4 minutes. In the practise phase, participants must find the target sequence '3-5-7', initially with the help of cues, and then advancing to the cues disappearing and the test resembling the assessed phase. In the assessed phase, numbers are only presented in white (there are no cues) and participants must detect three pre-set target sequences: 2-4-6, 3-5-7, and 4-6-8. There are a total of 36 target sequences in the assessed phase (9 target sequences per minute).
Spatial Span (SSP) <i>(Clinical; 6)</i>	Memory (spatial/executive function)	Frontal	Measures accuracy in recalling a sequence of boxes changing colour	How much information you can remember ('hold') and process in one go e.g. recalling a phone number after initially hearing it, verbal instructions which require remembering procedure or timings of medication.	A pattern of white boxes is displayed on the screen with a number of boxes (ranging from 2 to 9) turning a different colour one at a time. Within a span length, each box changes colour for 3000ms. When instructed by a tone, the participant must click on the boxes in the order that they changed colour as quickly as possible. The test starts at span length 2 (two box sequence to recall). The subject has three attempts at each level. If the sequence is correctly recalled on the first attempt, the participant advances to the subsequent span length (number box sequence). If after three attempts the participant has not successfully recalled the sequence at a particular span length, the test is terminated
Attention Switching Task (AST) <i>(Version 5.0.0 Press pad; 7)</i>	Cognitive flexibility/Multitasking/Executive functions (organising and planning activities, sequencing, concentrating and problem solving)	Frontal and parietal	Measures accuracy and reaction time in switching attention between responding to the direction of an arrow and which side of the screen the arrow appears. Congruent trials (the direction of the arrow is the same as the side of the screen in which the arrow appears) are easier than incongruent (direction of the arrow is different to the side of the screen in which the arrow appears)	The ability to return to a task after being interrupted or performing tasks simultaneously, e.g. taking the correct dose of multiple medications if distracted or after a memory lapse, keeping a track of finances (e.g. paying bills), holding a conversation whilst performing another task.	An arrow, pointing either left or right, appears on either the left- or right-hand side of the screen, on each trial. The participant is directed by a rule as to what they should attend and respond to; either the direction of the arrow, or the side of the screen where the arrow is displayed. There are 4 practise stages and one assessed stage. These range from the participant being instructed to respond to the direction of the arrow when it is placed in the centre of the screen (stage 1), then to the direction of the arrow when it is placed either side of the screen (stage 2), then to which side the arrow is on (regardless of the direction of the arrow; stage 3), then to respond to either the side the arrow is displayed or the direction as cued (stage 4). The assessed stage (stage 5) follows the same procedure as stage 4. There are 160 assessed trials.

Table 2. Participant characteristics for people with CFRD, CFND and healthy controls, median and IQR unless otherwise stated.

	Healthy controls Median (IQR)	Controls and CFND (p-value)	CFND Median (IQR)	CFND and CFRD (p-value)	CFRD Median (IQR)
Gender (n)	24	.999	23	.224	30
Age (years)	31.0 (23.5 – 36.0)	.034	25.5 (21 – 32.0)	.002	32.0 (27.5 – 37.5)
Education (n = degree qualification or higher)	15	.493	11	.366	16
Occupation (n = employed full time)	31	.001	14	.819	12
Heterozygous F508del (n)			45	.678	47
Pseudomonas aeruginosa (n)			31	.519	35
BMI (kg/m ²)	23.2 (22.1 – 26.4)	.056	22.4 (19.7 – 25.6)	.634	23.0 (20.8 – 24.9)
Blood glucose (mmol/L)	5.5 (5.2 – 6.2)	.048	5.8 (5.2 – 7.0)	<.001	7.6 (6.3 – 9.5)
COppm	3.0 (2.0 – 4.0)	.043	3.0 (3.0 - 4.3)	.895	4.0 (2.5 – 4.0)
Anxiety Score (HADS)	5.0 (3.0 - 8.0)	.283	6.0 (3.0 – 8.3)	.965	5.0 (3.0 - 9.5)
Depression Score (HADS)	1.0 (0.0 – 4.0)	.003	3.0 (1.0 – 7.0)	.713	4.0 (1.0 – 6.5)
Health Rating (1-10; higher is better)	8.0 (7.0 – 9.0)	.006	7.0 (5.0 – 8.0)	.591	7.0 (5.5 – 8.0)
Sleepiness rating (0-100; higher is sleepier)	13.0 (5.0 – 31.0)	.009	34.0 (11.5 – 58.0)	.994	32.0 (16.0 – 56.5)
ppFEV ₁			58.5 (38.8 – 78.8)	.165	48.0 (33.5 – 68.0)
FVC% predicted			78.0 (62 – 95.3)	.175	71.0 (53.5 – 87.5)
Oxygen saturation (%)			97.0 (95.0 – 98.0)	.303	97.0 (94.5 – 98.0)
HbA1c (mmol/mol; IFCC)			39.0 (36.0 – 42.0)	<.001	57.0 (46.5 – 71.5)
Age at CF Diagnosis (yrs)			0.4 (0.1 – 1.8)	.696	0.5 (0.1 – 2.2)
CRP (mg/L)			5.0 (5.0 – 12.5)	.453	5.0 (5.0 – 19.7)

Table 3. Scores (Median and IQR) for tests assessing memory ability (Pattern Recognition, Verbal Recognition, Paired Associates Learning, Spatial Span)

	Healthy Controls Median (IQR)	Controls and CFRD (p-value)	CFND Median (IQR)	CFND and CFRD (p-value)	CFRD Median (IQR)
Pattern Recognition Memory (PRM): Accuracy and reaction time in recognising patterns immediately and after a 20-minute delay					
Immediate (# correct)	12.0 (11.5 – 12.0)	.194	12.0 (11.0 – 12.0)	.712	12.0 (11.0-12.0)
Immediate (RT)	1708.0 (1385.7 – 1988.5)	.073	1845.8 (1516.9 – 2292.8)	.602	1902.4 (1562.0 – 2364.9)
Delayed (# correct)	11.0 (9.0 – 12.0)	.111	10.0 (8.0 – 11.5)	.425	10.0 (8.0 – 10.50)
Delayed (RT)	1811.6 (1583.4 – 2108.1)	.192	1986.3 (1537.7 – 2359.8)	.178	2102.8 (1839.7 – 2540.4)
Verbal Recognition Memory (VRM): Accuracy of recalling and recognising a list of 18 words immediately and after a 20-minute delay					
Immediate memory (# correct words, max 18)	10.0 (9.0 – 12.5)	.004	9.0 (8.0-11.0)	.485	9.0 (7.0 – 11.0)
Immediate memory (# incorrect novel words ¹)	0.0 (0.0 – 0.0)	.003	0.0 (0.0 – 0.0)	.719	0.0 (0.0 – 0.0)
Immediate memory (# excess repetitions ¹)	0.0 (0.0 - 0.0)	.013	0.0 (0.0 – 0.5)	.475	0.0 (0.0 – 1.0)
Immediate recognition (# correct words; max 18)	18.0 (17.0 – 18.0)	.802	18.0 (17.0 – 18.0)	.667	18.0 (17.0 – 18.0)
Immediate recognition (# false positives ¹)	0.0 (0.0 -1.0)	.396	0.0 (0.0 – 1.0)	.638	0.0 (0.0 – 1.0)
Delayed memory (# correct words, max 18)	10.0 (8.0 -13.0)	<.001	9.0 (6.0 – 10.0)	.524	9.0 (6.0 – 11.0)
Delayed memory (# incorrect novel words ¹)	0.0 (0.0 – 0.0)	.002	0.0 (0.0 – 1.0)	.530	0.0 (0.0 – 1.0)
Delayed memory (# excess repetitions ¹)	0.0 (0.0 – 0.0)	.001	0.0 (0.0 – 0.0)	.664	0.0 (0.0 – 0.5)
Delayed recognition (# correct, max 18)	18.0 (17.0 -18.0)	.063	17.0 (16.0 – 18.0)	.597	17.0 (16.0 – 18.0)
Delayed recognition (# false positives ¹)	0.0 (0.0 – 0.5)	.617	0.0 (0.0 – 1.0)	.812	0.0 (0.0 – 1.0)
Paired Associates Learning Test: Accuracy in recalling the location of patterns which are hidden behind boxes					
Stages completed (max 8)	8.0 (8.0 – 8.0)	.568	8.0 (8.0 – 8.0)	.552	8.0 (8.0 – 8.0)
Stages completed on first trial	7.0 (6.0 – 7.0)	.002	6.0 (5.5 – 7.0)	.455	6.0 (6.0 – 7.0)
Total number of trials (min 8)	9.0 (9.0 – 10.0)	<.001	10.0 (10.0 – 13.0)	.547	10.0 (9.0 – 12.0)
Total number of errors	2.0 (1.0 – 5.5)	.001	6.0 (3.0 – 12.5)	.664	6.0 (3.0 – 9.5)
Spatial Span: Accuracy in recalling a sequence of boxes changing colour					
Span length (2-9; higher is better)	8.0 (6.5 – 9.0)	.022	7.0 (6.0 – 8.0)	.324	6.0 (5.0 – 8.0)
Total errors	12.0 (7.0 – 16.5)	.543	13.0 (9.5 – 17.0)	.859	12.0 (8.0 – 18.5)
Usage errors	1.0 (0.0 – 2.0)	.002	2.0 (1.0 – 3.0)	.351	2.0 (1.0-3.0)

¹For all groups, median and IQR were 0.0 (0.0 – 0.0) or 0.0 (0.0 – 1.0). The differences between groups, where present, were detected in the upper quartiles of the group values.

Table 4. Scores (Median and IQR) for tests assessing attention, processing speed and motor speed (Rapid Visual Processing, and Motor Speed) and cognitive flexibility (Attention Switching Task)

	Healthy controls Median (IQR)	Controls and CFND (p-value)	CFND Median (IQR)	CFND and CFRD (p-value)	CFRD Median (IQR)
Motor Speed: Accuracy and speed of touching the centre of a 'X'					
Accuracy ¹	7.2 (5.3 – 8.6)	.180	7.3 (6.1 – 9.4)	.445	7.1 (5.7 – 8.6)
Accuracy and speed	840.0 (752.4 – 1027.4)	.050	975.8 (814.9 – 1076.2)	.840	936.6 (803.6 – 1080.8)
Rapid Visual Processing: Accuracy and reaction time in finding sequences of digits (max 36) presented one at a time					
# Correct detections	32.0 (25.5 – 34.0)	<.001	22.0 (17.5 – 25.5)	.921	23.0 (17.0 – 27.0)
# False positives	1.0 (0.5 – 3.0)	.633	1.0 (0.0 – 3.0)	.101	2.0 (1.0 – 3.0)
RT for correct detections	345.9 (324.8 – 403.1)	.285	369.9 (335.9 – 398.4)	.912	365.2 (337.1– 412.2)
Attention Switching Task: Accuracy and reaction time (RT) in switching attention between responding to the direction an arrow and which side of the screen the arrow appears					
# Correct trials (n=160)	155.0 (150.5 – 157.5)	.007	151.0 (144.5 – 156.0)	.161	152.0 (150.0 – 157.0)
# correct direction trials (n=80)	77.0 (75.0 – 79.0)	.092	76.0 (73.0 – 78.0)	.112	76.0 (74.5 – 79.0)
# of correct side trials (n=80)	78.0 (76.0 – 79.0)	<.001	77.0 (72.0 – 78.0)	.310	76.0 (74.5 – 78.5)
# correct congruent trials ² (n=80)	80.0 (79.0 – 80.0)	.016	79.0 (78.0 – 80.0)	.497	80.0 (78.0- 80.0)
# correct incongruent ² trials (n=80)	76.0 (71.0 – 77.5)	.019	72.0 (67.0 – 76.5)	.142	74.0 (70.5 – 77.0)
RT for correct trials	566.7 (466.4 – 726.4)	.022	683.8 (542.4 – 824.8)	.030	767.6 (633.9 – 896.8)
RT for correct direction trials	609.6 (492.6 – 747.1)	.097	673.9 (567.0 – 829.8)	.008	774.4 (660.3 – 923.4)
RT for correct side trials	506.8 (446.1 – 672.7)	.003	682.3 (516.5 – 811.9)	.072	727.4 (607.7 – 908.8)
RT for correct congruent ² trials	530.8 (415.7 – 689.8)	.022	630.2 (514.2 – 785.5)	.025	719.9 (583.2 – 846.5)
RT for correct incongruent ² trials	612.5 (514.2 – 757.1)	.018	720.5 (588.9 – 873.7)	.035	798.5 (695.6 – 947.2)

¹Mean distance off target when touching the centre of the cross

²Congruent means the direction of the arrow is the same as the side of the screen in which the arrow appears. Incongruent means the direction of the arrow is different to the side of the screen in which the arrow appears.

Table 5. Within group Kendall's correlation coefficient performed on Attention Switching Task reaction time outcome measures and potential confounders (age, blood glucose level, HbA1c, depression level, and subjective sleepiness and health rating).

	Healthy controls correlation	p-value	CFRD correlation	p-value	CFRD correlation	p-value
Age						
RT for correct trials	0.07	0.51	0.05	0.61	0.03	0.75
RT for correct direction trials	0.07	0.47	0.07	0.50	0.03	0.76
RT for correct side trials	0.05	0.63	0.04	0.69	0.05	0.75
RT for correct congruent trials	0.06	0.55	0.04	0.67	0.01	0.92
RT for correct incongruent trials	0.06	0.52	0.05	0.65	0.07	0.47
Blood glucose						
RT for correct trials	-0.02	0.86	-0.13	0.19	0.12	0.23
RT for correct direction trials	-0.05	0.65	-0.12	0.22	0.06	0.56
RT for correct side trials	0.03	0.76	-0.14	0.17	0.18	0.07
RT for correct congruent trials	-0.02	0.86	-0.11	0.25	0.11	0.27
RT for correct incongruent trials	-0.01	0.90	-0.14	0.18	0.13	0.19
Subjective sleepiness rating						
RT for correct trials	0.02	0.81	0.002	0.99	-0.07	0.51
RT for correct direction trials	-0.01	0.91	-0.01	0.92	-0.07	0.51
RT for correct side trials	0.04	0.72	0.02	0.84	-0.08	0.42
RT for correct congruent trials	0.03	0.73	-0.005	0.96	-0.05	0.60
RT for correct incongruent trials	-0.01	0.92	0.02	0.82	-0.09	0.36
HADS Depression Score						
RT for correct trials	0.20	0.06	0.17	0.11	0.03	0.74
RT for correct direction trials	0.19	0.08	0.18	0.08	0.04	0.72
RT for correct side trials	0.18	0.09	0.14	0.19	0.01	0.95
RT for correct congruent trials	0.22	0.04	0.18	0.09	0.01	0.90
RT for correct incongruent trials	0.16	0.14	0.17	0.11	0.03	0.77
Subjective health rating						
RT for correct trials	-0.21	0.06	-0.16	0.13	0.05	0.62
RT for correct direction trials	-0.20	0.07	-0.19	0.07	0.05	0.66
RT for correct side trials	-0.19	0.09	-0.12	0.26	0.05	0.66
RT for correct congruent trials	-0.20	0.06	-0.16	0.13	0.04	0.68
RT for correct incongruent trials	-0.18	0.10	-0.17	0.11	0.05	0.67
HbA1c						
RT for correct trials			0.14	0.17	0.03	0.74
RT for correct direction trials			0.14	0.18	-0.03	0.76
RT for correct side trials			0.12	0.23	0.10	0.32
RT for correct congruent trials			0.15	0.13	0.04	0.69
RT for correct incongruent trials			0.12	0.24	0.01	0.90

Highlights

- This is the first study to investigate CFRD and as a mechanism for cognitive function impairment
- Adults with CF show deficits in cognitive function compared with healthy controls
- Adults with CFRD experience additional difficulties with 'executive function'
- Adults with CF without CFRD had an estimated 20% reduction in processing speed
- Adults with CF with CFRD had an estimated up to 40% reduction in processing speed

