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Title:

Functional Cognitive Disorder affects reaction time, subjective mental effort and global metacognition

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Abstract

We previously hypothesised that Functional Cognitive Disorder is characterised by heightened subjective mental effort, exhausted attentional reserve and metacognitive failure.

To test this hypothesis, we administered a colour-word Stroop task in which attentional demand was varied by task difficulty (congruent versus incongruent cues) and the presence of a secondary auditory stimulus (passive or active listening to an oddball-type paradigm). We measured subjective mental effort, objective performance (reaction times and accuracy), metacognition and EEG-based biomarkers of mental workload.

We tested 19 Functional Cognitive Disorder patients and 23 healthy controls. Patients reported higher levels of depression, anxiety, fatigue, pain, sleep disruption, dissociation and obsessiveness. They rated their memory as significantly poorer than healthy controls; however, accuracy did not differ between groups in any condition. In contrast to healthy controls, patients rated their performance as poorer on the congruent Stroop task with background noise compared to silent conditions. Functional Cognitive Disorder was consistently associated with slower reaction times but this was not exacerbated by increased attentional demand. Patients

but not healthy controls reported greater mental workload in noisy conditions but EEG biomarkers were similar between groups, regardless of task difficulty.

Functional Cognitive Disorder has significant syndromic overlap with mood disorders and chronic fatigue and pain. It is associated with global metacognitive failure whereas local (task-specific) metacognition is only selectively impaired. Patients were slower than healthy controls, which might contribute to the "brain fog" reported in this condition. Although subjective mental effort was increased in noisy conditions, we found no evidence of attentional exhaustion in Functional Cognitive Disorder. Our results suggest that Functional Cognitive Disorder is a multisystem condition affecting reaction time, subjective mental effort and global metacognition.

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Abbreviations: FCD = Functional Cognitive Disorder; FND = Functional Neurological Disorder; GAD-7 = Generalised Anxiety Disorder-7 scale; HC = healthy controls; NASA-TLX = NASA Task Load Index; SCWT = modified Stroop colour-word task; PD-Q = painDETECT questionnaire; PHQ-9 = Patient Health Questionnaire - 9; SDQ-20 = Somatoform Dissociation Questionnaire; SMC = Subjective Memory Complaints;

Introduction

Functional cognitive disorder (FCD) is the experience of persistent, problematic cognitive symptoms that are not explained by central nervous system pathology.

FCD appears to be an increasing problem, with around a quarter of patients attending memory clinics being diagnosed with a functional cognitive disorder or given a label likely in many cases to represent FCD e.g. subjective cognitive impairment or "pseudodementia".[1]

Functional cognitive symptoms are proposed to present heterogeneously; as an 'isolated' disorder, alongside other functional neurological symptoms (such as functional non-epileptic seizures) or as part of another disorder characterised by persistent physical symptoms (such as fibromyalgia, chronic fatigue syndrome or some forms of long Covid-19), in the context of anxiety or depression[2,3] or health anxiety about dementia.[4]

As in other functional neurological disorders (FNDs), FCD should be diagnosed on the basis of positive features rather than by exclusion of organic disease. In particular, "internal inconsistency" is a feature common to FNDs, demonstrable through a mismatch between subjective experience and objective assessment or variability in symptom presence or severity.[5] However, although there has been recent progress on the clinical definition of FCD[1,5–7], very little is known about its underlying mechanisms.

We utilised the extensive literature on cognitive symptoms in other FNDs and somatoform disorders to generate mechanistic hypotheses about FCD. In a systematic review of neuropsychological findings in patients with fibromyalgia, chronic fatigue syndrome and non-cognitive FNDs, we found a discrepancy between subjective cognitive symptoms, including forgetfulness and distractibility, and objective performance on neuropsychometric assessment[8].

Patients with these conditions do not show impaired performance in domains affected by canonical dementia syndromes, such as memory, language or visuospatial function. We found some evidence of objective deficits in impaired selective and divided attention, slow information processing and vulnerability to distraction.[8] These cognitive profiles are similar to those proposed to be typical of FCD, suggesting common mechanistic underpinnings.

People with FCD often report routine cognitive processes as being unduly effortful and fatiguing; an experience often described as "brain fog". We hypothesised that this could reflect a switch from an automatic to a less efficient "controlled" or explicit cognitive mode, a mechanism that has also been proposed for impaired motor control in functional movement disorders.[9] This might result in attentional "exhaustion" during periods of sustained or divided attention, thereby explaining the findings of our review. We further hypothesised that metacognitive failures (impaired self-awareness of one's own cognitive abilities) might generate symptoms through incorrect prior assumptions about cognitive performance mechanisms (sometimes manifesting as "memory perfectionism").[8]

We performed an exploratory experimental study to test these hypotheses. Alongside baseline characteristics including self-rated memory, we probed attention, susceptibility to distraction, metacognition, self-reported effort, and EEG-based objective measures of mental workload in people with FCD and healthy controls (HC) on a modified Stroop colour-word task (SCWT). Attentional demand was varied by task difficulty (congruent versus incongruent) and the presence of active or passive listening to an auditory stimulus (oddball-type task). We hypothesised that people with FCD would show greater susceptibility to distraction as attentional demand increased, leading to poorer performance, and that this would be accompanied by heightened self-reported effort, a corresponding increment in EEG-based measures of mental workload and overly pessimistic self-assessment of performance.

Methods

We recruited patients aged between 18 and 70 with a diagnosis of FCD and HC.Exclusion criteria were a known diagnosis of dementia or mild cognitive impairment, epilepsy, a history of severe head injury, ischaemic stroke or any other form of significant structural brain damage, a severe psychiatric disorder or moderate to severe depression defined by a PHQ-9[10] score >= 15 on the day of the experiment.

Participants were asked to rate their memory on a five-point SMC Likert scale[11] and on 'short' and 'long' versions of functional memory disorder inventories[12], and also filled in the following questionnaires: Chalder Fatigue Scale[13]; Generalised Anxiety Disorder (GAD)-7 scale[14], Jenkins Sleep Scale[15], Obsessive-Compulsive Inventory[16], painDETECT questionnaire (PD-Q)[17], Patient Health Questionnaire (PHQ-9)[10], Somatoform Dissociation Questionnaire (SDQ-20)[18].

We developed an experimental paradigm consisting of a modified SCWT in which attentional demand was varied by (i) task difficulty (congruent versus incongruent); (ii) the presence or absence of an auditory stimulus (oddball-type task); (iii) active or passive listening to the auditory stimulus(Supplementary Figure 1).

The experiment started with an Oddball-type task, consisting of passive listening to sequences of common (500 Hz) and rare ('Odd') sounds (2000 Hz). This task consisted of 20 sequences of sounds, each with 10 sounds, including 9 common and 1 rare sounds (total 20 rare and 180 common).

After "*Condition 0 - Oddball*", four conditions were presented in a pseudorandomised order, counterbalanced at group level. "*Condition 1 - SCWT congruent silent*" consisted of a SCWT

with congruent ink colour and word, performed in a silent environment. "*Condition 2 - SCWT congruent noisy*" consisted of a SCWT with congruent ink colour and words, performed in a noisy environment; we played the sounds of an Oddball task (similar to condition 1) in the background while subjects performed the SCWT (passive listening). "*Condition 3 - SCWT incongruent silent*" corresponded to SCWT with incongruent ink colour and words, performed in a silent environment. "*Condition 4 - SCWT incongruent noisy*" consisted of SCWT with incongruent ink colour and words, this time performed in a 'noisy' (Oddball-type) environment.

The last condition was always "*Condition 5 - SCWT incongruent count"*, which was a "SCWT incongruent noisy" similar to condition 4, but participants were instructed to silently count and memorise the number of Oddball sounds while performing the SCWT task (active listening).

After each of conditions 1-5, participants were requested to self-rate the workload involved in using the NASA Task Load Index (NASA-TLX)[19].

We assessed subjective effort and objective performance on the SCWT (reaction time and accuracy), and EEG-based biomarkers of mental workload, primarily P300 suppression but also mid-frontal theta enhancement, posterior (parietal) alpha suppression and their ratio.

The primary measure of subjective effort was a composite score ("mental effort") corresponding to the sum of 'Mental Demand' and 'Effort' subscores of NASA-TLX[19]. The primary measure of objective performance was response time in the modified SCWT. The primary measure of local (task-specific) metacognition was the score on the item 'Performance' (Perfect 0 – Failure 100) on NASA-TLX, self-rated after each condition. The primary biomarker of mental workload was suppression of P300 in the midline. P300 is a positive potential elicited in an odd-ball paradigm, and peaking at 250-300 ms or more after

the onset of a rare stimulus.[20] In subjects performing a primary task of variable difficulty, the P300 elicited by background tones is reported to decrease in amplitude and increase in latency as the difficulty of the primary task increases, thus providing an objective measure of mental workload.[21–23]

A description of secondary outcome measures, methods for recording event-related potentials and oscillatory activity, pre-processing EEG data and statistical analysis is provided in the supplementary materials.

Ethics

The study was approved by NRES Committee South West – Central Bristol (16/SW/0333/AM01). Participants provided written informed consent to take part in the study.

Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Results

5 prospective subjects with FCD were excluded due to high PHQ-9 scores and 2 due to resolution of cognitive symptoms; 4 prospective HC were excluded due to the presence of cognitive symptoms, and 2 due to high PHQ-9 scores.

After screening, we recruited 19 patients with FCD and 23 HC.

Co-existing neurological and psychiatric diagnoses and psychotropic medication were more frequent in subjects with functional cognitive disorders (Table I, Supplementary tables I and II).

As expected, patients with FCD reported greater subjective memory difficulties on screening questionnaires (Table II). In addition, subjects with FCD scored higher on screening instruments for depression, anxiety, fatigue, pain, sleep problems, dissociative symptoms and obsessiveness.

Subjective effort

We compared participants' subjective effort while performing congruent and incongruent SCWT, in silent and noisy conditions (Figure 1, Table III, Supplementary table III). In the unadjusted analysis of 'mental effort', the impact of 'background noise' on perceived 'mental effort' differed between groups (p 0.019 for the interaction 'group' x 'background noise'). Further analysis revealed that subjects with FCD (but not HC) reported greater subjective effort when performing the Stroop task in the presence of background noise, as compared to silence. Indeed, the estimated difference between mean 'mental effort' in noisy and silence backgrounds was 14 (95% CI 3 24) among FCD patients (p 0.014) and 1 [95% CI -9 to 11] among HC (p 0.888) (Supplementary table III). The adjusted analysis including covariates for all co-morbidities and education gave similar results, as did crude and adjusted analysis of our secondary outcome of subjective effort (total score of NASA-TLX).

Objective performance

In the unadjusted analysis, response times were slower in 'incongruent' colour-word conditions ($p < 0.001$ for the effect of 'cue congruence'), confirming that our experiment elicited a Stroop effect. The estimated difference between mean 'response times' (milliseconds) in incongruent and congruent conditions was 67 (95% CI 54 81) ($p < 0.001$). Overall, subjects with FCD performed slower than HC. The estimated difference between mean response times in FCD

and HC groups was 63 (95% CI 1.4 124) (p 0.045)((Figure 2, Table III, Supplementary table IV). However, the effects of 'background noise', and interactions 'group' x 'cue congruence' and 'group' x 'background noise' were not significant. In the adjusted analysis including all pre-defined co-morbidities and education, the difference in response times between groups lost significance (p 0.268), while participants in both groups continued to perform slower in 'incongruent' colour-word conditions. Both groups performed with high accuracy {proportion of correct answers [mean (standard deviation)] - HC: 0.96 (0.03); FCD: 0.93 (0.1)}, and there were no significant differences between groups or conditions (Table III).

Metacognition

Both unadjusted and adjusted analyses of the metacognition sub-score (*'how successful were you in accomplishing what you were asked to do?'*) showed that the impact of background noise in metacognition was different between groups (unadjusted p 0.025 for interaction 'group' x 'background noise') and that this effect was further modulated by 'cue congruence' (unadjusted p 0.007 for 'group' x 'background noise' x 'cue congruence')(Figure 3, Table III, Supplementary table V). To test our predetermined hypothesis of greater self-reported difficulties in the presence of background noise, we compared metacognition sub-scores in the presence and absence of background noise, for each 'cue congruence' and 'group'. In the congruent conditions, patients with FCD reported *worse* performance in the presence of background noise, with anestimated difference in metacognition sub-scores between noisy and silent backgrounds of 9 (95% CI 2 17) (p 0.016). However, in the incongruent conditions, patients with FCD reported *better* performance in the presence of background noise. This corresponded to an estimated difference of -8 (95% CI -15 0) (p 0.046) between noisy and silent backgrounds . In contrast, HC reported similar quality of performance in all conditions.

Indeed, for HC, the estimated difference between noisy and silent backgrounds was -2 (95% CI -9 4) in congruent conditions (p 0.492) and 0 (95% CI -6 7) in incongruent conditions (p 0.901).

Biomarkers of mental workload

Both crude and adjusted analyses of the amplitude of P300 ('positive area' between 300 and 600 ms) did not reveal significant effects for 'group', 'cue congruence' or the interaction 'group' x 'cue congruence' (p-values 0.797, 0.680 and 0.860, respectively - crude analysis) (Figure 4, Table III and Supplementary Figure 2).

Likewise, both crude and adjusted analyses of the power of midfrontal theta, parietal alpha and ration theta / alpha did not reveal any significant effects of 'group', 'cue congruence', 'background noise' or their respective interactions.

Fifth condition – 'multi-tasking'

We compared performance in the Stroop colour-word condition consisting of incongruent cues and passive listening to background noise with the fifth condition where participants were asked to silently count and memorise the number of 'rare' sounds played in the background (active listening/multi-tasking) (Supplementary Tables VI and VII). Active listening was associated with an increase in subjective 'mental effort', slower reaction times (but similar accuracy) and lower self-reporting of performance, in both unadjusted and adjusted analysis ($p < 0.001$ for the effect of 'active listening' on 'mental effort', p 0.023 on reaction times, p 0.353 on accuracy and p 0.052 on metacognition, in unadjusted analysis). However, the impact of active listening on these outcomes was similar in subjects with FCD and HC (non-significant

interaction ‘group’ x ‘counting oddball sounds’ for all outcome measures). Notably, subjects with FCD did not perform slower than HC (p 0.276 for ‘group’, unadjusted). Our analysis of the biomarkers of mental workload (P300, midfrontal theta, posterior alpha and ratio theta / alpha) also did not reveal significant differences between group or condition.

Finally, the proportion of participants who correctly remembered the number of ‘rare’ sounds that were played(20) was similar in both groups (13/23 HC and 12/19 patients with FCD, p 0.509).

Discussion

Despite increasing recognition of FCD, relatively little primary research has been performed to investigate its neuropsychological basis. Here we report several novel findings.

People with FCD have higher levels of depression, anxiety, fatigue, pain, sleep disruption, dissociation and obsessiveness than HC. This suggests that FCD occurs predominantly in people who are experiencing a range of other somatoform symptoms, alongside subsyndromal levels of mood disturbance and who are predisposed to FCD by obsessiveness and a tendency to dissociation. This supports our contention that the experience and aetiology of cognitive symptoms in chronic fatigue syndrome and fibromyalgia are likely to be similar, perhaps identical, to what in the memory clinic is labelled as FCD. We conjecture that amongst patients with cognitive symptoms in the context of mild traumatic brain injury, whiplash and long-COVID-19, a subset will have similar characteristics to our cohort. In other words, FCD is one facet of a broader somatoform syndrome in which pain, fatigue and mood changes are also prominent features, and which can occur in response to range of physiological and psychological triggers.

People with FCD consistently displayed slower reaction times than HC although this was not exacerbated by increasing task difficulty. Indeed, the magnitude of the Stroop effect was similar in patients with FCD and HC. Reaction times in the hardest (5th) condition, in which attention was divided between visual and auditory tasks, were not significantly different between people with FCD and HC, although the trend for slower reaction times in FCD was maintained. This suggests that slow reaction times in FCD are a trait and not a function of task difficulty.

Notably the difference in reaction times between people with FCD and HC lost significance after adjusting for confounders, suggesting that the slowness could be related to comorbidities such as mood disturbance, fatigue or pain.

Our observation of cognitive slowness in people with FCD is consistent with prior findings in depression, CFS and fibromyalgia, further supporting the syndromic and pathophysiological overlap between these conditions. In depression, clinically evident motor slowing is one of the diagnostic criteria endorsed by DSM-5.[24] Patients with depression have been reported to respond slower than HC in reaction-time tasks and (less consistently) to display greater interference in SCWT (indexing poor selective attention).[25,26] Although we excluded people with current depression or a PHQ-9 => 15, our FCD group scored a median of 10 (IQR 6-13). In people experiencing depressed mood and/or anhedonia, scores within this range are thought to correspond to mild to moderate depression. Therefore, mild to moderate depressive illness could have contributed to the global slowness.

We did not find a significant difference between FCD and HC in response accuracy on both the SCWT task and a combined oddball counting task. This negates our hypothesis that FCD is a state of attentional exhaustion, in which a ramping up of attentional demand leads to impaired performance.

Patients with FCD were more likely than HC to report applying greater effort when performing the congruent and incongruent SCWT in noisy conditions. However, our EEG-based biomarkers of mental workload were similar in patients with FCD and HC in both silent and noisy conditions. Therefore, for the same objective level of mental workload, patients with FCD reported greater mental effort. This suggests that what patients subjectively describe as "mental effort" does not always correlate with measurable mental work.

FCD patients rated their overall memory more poorly than HC despite being as accurate on all the tasks. This suggests that a deficit in "global" metacognition is a key driver of the inconsistency between subjective and objective experience in FCD.

In contrast, there were only small differences between FCD and HC on self-rated task performance. On the congruent SCWT, FCD patients were more likely than controls to perceive a decline in performance in the presence of noise. This was associated with an increase in mental effort. In contrast on the incongruent SCWT, FCD patients experienced a subjective improvement in performance in the presence of noise, without a corresponding decrease in subjective mental effort. This suggests a non-linear relationship between task complexity and subjective achievement in FCD. A possible explanation for this is that the more attentionally demanding incongruent task does not afford sufficient bandwidth for negative automatic thoughts when the environment is made more distracting by the addition of noise. However, these findings warrant replication in larger samples.

In summary, "local" or task-specific metacognition is less impaired than global metacognition in FCD. Poor metacognition has been proposed to be a key feature of functional cognitive disorder.[5,27–29] However, empirical evidence to support this assumption is relatively scarce. Self-reporting poor memory in combination with a Mini-Addenbrooke's Cognitive Examination > 25 is reported to have high sensitivity and specificity for the diagnosis of

FCD.[30,31] 'Memory self-efficacy scores' (based on Metamemory in Adulthood Questionnaire)] were also reported to predict a diagnosis of FCD.[32] Bhome et al.[27] hypothesised that people with poor metacognition experience greater concern about objectively normal cognitive performance and poorer monitoring and increased salience of attentional lapses, leading to a vicious, reinforcing cycle that would drive illness experience, while people with normal metacognition are relatively unaffected by episodic, trivial day to day cognitive lapses. However, while their subsequent experimental work confirmed a difference in global metacognition, they were not able to demonstrate impaired local metacognition[33] Further, a recent study by Pennington et al.[34] also failed to find differences in metacognitive efficacy between FCD, neurodegenerative mild cognitive impairment and HC, in either memory or perceptual tasks. This discrepancy between global and local metacognition found by us and others is tantalising because it suggests that people with FCD are aware that they perform accurately "in the moment" but aren't able to adjust global assumptions about their cognition on the basis of day-to-day experience.

We did not find evidence of systematic underperformance, and all EEG-based biomarkers of mental workload were similar in patients with FCD and HC. These findings support the observation that only a minority of patients with FCD fail on performance validity testing.[8,35]

We hypothesise that the sensation of 'brain fog' reported by people across all functional cognitive disorders could result from subjectively increased mental effort in distracting environments combined with mild psychomotor slowing. For people with high expectations of their cognitive function, this experience might be uncomfortable, producing a feeling that the brain is 'foggy' and that they are working harder than normal to think clearly, although not necessarily misjudging their task-specific performance.

Do our findings have implications for therapy? We hypothesise that advising people with FCD to restrict themselves to straightforward tasks in which distractions are not present is not likely to reduce their symptoms. Likewise, behavioural strategies that are commonly suggested for people with dementia and structural brain injury such as breaking down tasks into multiple components ("chunking") and writing checklists which need to be followed strictly might directly worsen symptoms in those with FCD. This emphasises the need for care in diagnosis, in particular in patients where there might be uncertainty or both functional and organic factors present, such as those with mild traumatic brain injury. In fact, tasks with greater complexity, and which are therefore more immersive are no more (and might be less) likely to be experienced as unduly effortful or frustrating. Our findings also support the reassurance given to patients with FCD that although they experience genuine cognitive symptoms, these are not underpinned by damage to or dysfunction of core cognitive faculties, even if they are marginally slower than completely healthy people. Finally, the high prevalence of co-morbidities such as pain, depression, anxiety, fatigue and sleep disturbances highlight the need to screen patients with FCD for those problems, and to treat them accordingly.

Long-COVID-19 is an growing public health problem corresponding to symptom persistence following an acute COVID-19 infection.[36] Its symptoms can be wide-ranging, fluctuating in intensity, might change over time, and do not appear to correlate with the severity of the acute infection[36]. Notably, cognitive problems are among the most frequent symptoms reported by *non-hospitalised* patients developing long-COVID-19, alongside fatigue, headaches, sleep disorders and respiratory symptoms.[37] Patients experience mental fog, memory lapses, poor concentration and word-finding difficulties.[38] There is ongoing discussion about the possible overlap between long-COVID-19 and both chronic fatigue syndrome and fibromyalgia.[39,40] The pathophysiology of long-COVID-19 remains uncertain and might be multifactorial. It is possible that for many people with long-COVID-19, cognitive difficulties are best understood

as a form of FCD. Further research is needed to investigate the relevance of our findings to the understanding of the pathogenesis and management of cognitive symptoms in long-COVID-19.

Limitations of our work include the moderate sample size and the fact that our task did not exhaust attentional reserve in either healthy people or those with FCD. In the most demanding task, we might have been underpowered to detect slowing of reaction times or inaccuracy among participants with FCD. Our study had an exploratory character, and our findings should seek replication in other, larger samples.

We excluded patients who had a known diagnosis of MCI. Consequently, our findings might not be generalisable to patients with FCD who underperform on neuropsychological testing to the extent that they meet MCI criteria.[41]

In summary, we have shown that FCD is not an isolated disorder, but significantly co-morbid with mood and somatoform symptoms. This suggests that Stone's' classification of FCDs into separate "isolated", "mood-related" and "somatoform-associated" categories might be unnecessary, as most patients will display all of these traits to some extent.[7] Finally, we show that FCD is associated with cognitive slowing, retained attentional capacity, heightened effort perception during distraction and consistent global but inconsistent local metacognitive failure, reflecting a failure of "bottom up" sensory feedback to alter "top down" prior assumptions (Figure 5). These findings should inform the design of rehabilitative strategies for FCD.

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Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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Figure legends

Figure 1 – Subjective mental effort (composite score corresponding to the sum of 'Mental Demand' and 'Effort' subscores of NASA-TLX; box-and-whisker plots showing median, interquartile interval, minimum, maximum and outliers)

Figure 2 – Objective performance – reaction time (milliseconds; box-and-whisker plots showing median, interquartile interval, minimum, maximum and outliers)

Figure 3 – Metacognition (self-rated performance; box-and-whisker plots showing median, interquartile interval, minimum, maximum and outliers)

Figure 4 – P300 (Difference wave 'Odd sounds' – 'Common sounds'; amplitude μV; time milliseconds)

Figure 5 - Proposed mechanism for FCD: Cognitive symptoms are produced by the combination of and interaction between abnormal global metacognition (priors), pain, fatigue, mood and other mental changes, and psychomotor slowing. Benign cognitive experiences are over-interpreted, generate a heightened subjective sense of mental effort and lead to an inefficient cognitive mode, all of which reinforce symptoms in a feedback loop. Objectively normal performance is accompanied by preserved local (task-specific) metacognition, but this is unable to reset abnormal priors, perhaps due to the overwhelming drive from somatoform and mood changes and ongoing over-interpretation of "normal" cognitive lapses.

Title:

Functional Cognitive Disorder affects reaction time, subjective mental effort and global metacognition

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Abstract

We previously hypothesised that Functional Cognitive Disorder is characterised by heightened subjective mental effort, exhausted attentional reserve and metacognitive failure.

To test this hypothesis, we administered a colour-word Stroop task in which attentional demand was varied by task difficulty (congruent versus incongruent cues) and the presence of a secondary auditory stimulus (passive or active listening to an oddball-type paradigm). We measured subjective mental effort, objective performance (reaction times and accuracy), metacognition and EEG-based biomarkers of mental workload.

We tested 19 Functional Cognitive Disorder patients and 23 healthy controls. Patients reported higher levels of depression, anxiety, fatigue, pain, sleep disruption, dissociation and obsessiveness. They rated their memory as significantly poorer than healthy controls; however, accuracy did not differ between groups in any condition. In contrast to healthy controls, patients rated their performance as poorer on the congruent Stroop task with background noise compared to silent conditions. Functional Cognitive Disorder was consistently associated with slower reaction times but this was not exacerbated by increased attentional demand. Patients

but not healthy controls reported greater mental workload in noisy conditions but EEG biomarkers were similar between groups, regardless of task difficulty.

Functional Cognitive Disorder has significant syndromic overlap with mood disorders and chronic fatigue and pain. It is associated with global metacognitive failure whereas local (task-specific) metacognition is only selectively impaired. Patients were slower than healthy controls, which might contribute to the "brain fog" reported in this condition. Although subjective mental effort was increased in noisy conditions, we found no evidence of attentional exhaustion in Functional Cognitive Disorder. Our results suggest that Functional Cognitive Disorder is a multisystem condition affecting reaction time, subjective mental effort and global metacognition.

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Abbreviations: FCD = Functional Cognitive Disorder; FND = Functional Neurological Disorder; GAD-7 = Generalised Anxiety Disorder-7 scale; HC = healthy controls; NASA-TLX = NASA Task Load Index; SCWT = modified Stroop colour-word task; PD-Q = painDETECT questionnaire; PHQ-9 = Patient Health Questionnaire - 9; SDQ-20 = Somatoform Dissociation Questionnaire; SMC = Subjective Memory Complaints;

Introduction

Functional cognitive disorder (FCD) is the experience of persistent, problematic cognitive symptoms that are not explained by central nervous system pathology.

FCD appears to be an increasing problem, with around a quarter of patients attending memory clinics being diagnosed with a functional cognitive disorder or given a label likely in many cases to represent FCD e.g. subjective cognitive impairment or "pseudodementia".[1]

Functional cognitive symptoms are proposed to present heterogeneously; as an 'isolated' disorder, alongside other functional neurological symptoms (such as functional non-epileptic seizures) or as part of another disorder characterised by persistent physical symptoms (such as fibromyalgia, chronic fatigue syndrome or some forms of long Covid-19), in the context of anxiety or depression[2,3] or health anxiety about dementia.[4]

As in other functional neurological disorders (FNDs), FCD should be diagnosed on the basis of positive features rather than by exclusion of organic disease. In particular, "internal inconsistency" is a feature common to FNDs, demonstrable through a mismatch between subjective experience and objective assessment or variability in symptom presence or severity.[5] However, although there has been recent progress on the clinical definition of FCD[1,5–7], very little is known about its underlying mechanisms.

We utilised the extensive literature on cognitive symptoms in other FNDs and somatoform disorders to generate mechanistic hypotheses about FCD. In a systematic review of neuropsychological findings in patients with fibromyalgia, chronic fatigue syndrome and non-cognitive FNDs, we found a discrepancy between subjective cognitive symptoms, including forgetfulness and distractibility, and objective performance on neuropsychometric assessment[8].

Patients with these conditions do not show impaired performance in domains affected by canonical dementia syndromes, such as memory, language or visuospatial function. We found some evidence of objective deficits in impaired selective and divided attention, slow information processing and vulnerability to distraction.[8] These cognitive profiles are similar to those proposed to be typical of FCD, suggesting common mechanistic underpinnings.

People with FCD often report routine cognitive processes as being unduly effortful and fatiguing; an experience often described as "brain fog". We hypothesised that this could reflect a switch from an automatic to a less efficient "controlled" or explicit cognitive mode, a mechanism that has also been proposed for impaired motor control in functional movement disorders.[9] This might result in attentional "exhaustion" during periods of sustained or divided attention, thereby explaining the findings of our review. We further hypothesised that metacognitive failures (impaired self-awareness of one's own cognitive abilities) might generate symptoms through incorrect prior assumptions about cognitive performance mechanisms (sometimes manifesting as "memory perfectionism").[8]

We performed an exploratory experimental study to test these hypotheses. Alongside baseline characteristics including self-rated memory, we probed attention, susceptibility to distraction, metacognition, self-reported effort, and EEG-based objective measures of mental workload in people with FCD and healthy controls (HC) on a modified Stroop colour-word task (SCWT). Attentional demand was varied by task difficulty (congruent versus incongruent) and the presence of active or passive listening to an auditory stimulus (oddball-type task). We hypothesised that people with FCD would show greater susceptibility to distraction as attentional demand increased, leading to poorer performance, and that this would be accompanied by heightened self-reported effort, a corresponding increment in EEG-based measures of mental workload and overly pessimistic self-assessment of performance.

Methods

We recruited patients aged between 18 and 70 with a diagnosis of FCD and HC.Exclusion criteria were a known diagnosis of dementia or mild cognitive impairment, epilepsy, a history of severe head injury, ischaemic stroke or any other form of significant structural brain damage, a severe psychiatric disorder or moderate to severe depression defined by a PHQ-9[10] score >= 15 on the day of the experiment.

Participants were asked to rate their memory on a five-point SMC Likert scale[11] and on 'short' and 'long' versions of functional memory disorder inventories[12], and also filled in the following questionnaires: Chalder Fatigue Scale[13]; Generalised Anxiety Disorder (GAD)-7 scale[14], Jenkins Sleep Scale[15], Obsessive-Compulsive Inventory[16], painDETECT questionnaire (PD-Q)[17], Patient Health Questionnaire (PHQ-9)[10], Somatoform Dissociation Questionnaire (SDQ-20)[18].

We developed an experimental paradigm consisting of a modified SCWT in which attentional demand was varied by (i) task difficulty (congruent versus incongruent); (ii) the presence or absence of an auditory stimulus (oddball-type task); (iii) active or passive listening to the auditory stimulus(Supplementary Figure 1).

The experiment started with an Oddball-type task, consisting of passive listening to sequences of common (500 Hz) and rare ('Odd') sounds (2000 Hz). This task consisted of 20 sequences of sounds, each with 10 sounds, including 9 common and 1 rare sounds (total 20 rare and 180 common).

After "*Condition 0 - Oddball*", four conditions were presented in a pseudorandomised order, counterbalanced at group level. "*Condition 1 - SCWT congruent silent*" consisted of a SCWT

with congruent ink colour and word, performed in a silent environment. "*Condition 2 - SCWT congruent noisy*" consisted of a SCWT with congruent ink colour and words, performed in a noisy environment; we played the sounds of an Oddball task (similar to condition 1) in the background while subjects performed the SCWT (passive listening). "*Condition 3 - SCWT incongruent silent*" corresponded to SCWT with incongruent ink colour and words, performed in a silent environment. "*Condition 4 - SCWT incongruent noisy*" consisted of SCWT with incongruent ink colour and words, this time performed in a 'noisy' (Oddball-type) environment.

The last condition was always "*Condition 5 - SCWT incongruent count"*, which was a "SCWT incongruent noisy" similar to condition 4, but participants were instructed to silently count and memorise the number of Oddball sounds while performing the SCWT task (active listening).

After each of conditions 1-5, participants were requested to self-rate the workload involved in using the NASA Task Load Index (NASA-TLX)[19].

We assessed subjective effort and objective performance on the SCWT (reaction time and accuracy), and EEG-based biomarkers of mental workload, primarily P300 suppression but also mid-frontal theta enhancement, posterior (parietal) alpha suppression and their ratio.

The primary measure of subjective effort was a composite score ("mental effort") corresponding to the sum of 'Mental Demand' and 'Effort' subscores of NASA-TLX[19]. The primary measure of objective performance was response time in the modified SCWT. The primary measure of local (task-specific) metacognition was the score on the item 'Performance' (Perfect 0 – Failure 100) on NASA-TLX, self-rated after each condition. The primary biomarker of mental workload was suppression of P300 in the midline. P300 is a positive potential elicited in an odd-ball paradigm, and peaking at 250-300 ms or more after

the onset of a rare stimulus.[20] In subjects performing a primary task of variable difficulty, the P300 elicited by background tones is reported to decrease in amplitude and increase in latency as the difficulty of the primary task increases, thus providing an objective measure of mental workload.[21–23]

A description of secondary outcome measures, methods for recording event-related potentials and oscillatory activity, pre-processing EEG data and statistical analysis is provided in the supplementary materials.

Ethics

The study was approved by NRES Committee South West – Central Bristol (16/SW/0333/AM01). Participants provided written informed consent to take part in the study.

Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

Results

5 prospective subjects with FCD were excluded due to high PHQ-9 scores and 2 due to resolution of cognitive symptoms; 4 prospective HC were excluded due to the presence of cognitive symptoms, and 2 due to high PHQ-9 scores.

After screening, we recruited 19 patients with FCD and 23 HC.

Co-existing neurological and psychiatric diagnoses and psychotropic medication were more frequent in subjects with functional cognitive disorders (Table I, Supplementary tables I and II).

As expected, patients with FCD reported greater subjective memory difficulties on screening questionnaires (Table II). In addition, subjects with FCD scored higher on screening instruments for depression, anxiety, fatigue, pain, sleep problems, dissociative symptoms and obsessiveness.

Subjective effort

We compared participants' subjective effort while performing congruent and incongruent SCWT, in silent and noisy conditions (Figure 1, Table III, Supplementary table III). In the unadjusted analysis of 'mental effort', the impact of 'background noise' on perceived 'mental effort' differed between groups (p 0.019 for the interaction 'group' x 'background noise'). Further analysis revealed that subjects with FCD (but not HC) reported greater subjective effort when performing the Stroop task in the presence of background noise, as compared to silence. Indeed, the estimated difference between mean 'mental effort' in noisy and silence backgrounds was 14 (95% CI 3 24) among FCD patients (p 0.014) and 1 [95% CI -9 to 11] among HC (p 0.888) (Supplementary table III). The adjusted analysis including covariates for all co-morbidities and education gave similar results, as did crude and adjusted analysis of our secondary outcome of subjective effort (total score of NASA-TLX).

Objective performance

In the unadjusted analysis, response times were slower in 'incongruent' colour-word conditions ($p < 0.001$ for the effect of 'cue congruence'), confirming that our experiment elicited a Stroop effect. The estimated difference between mean 'response times' (milliseconds) in incongruent and congruent conditions was 67 (95% CI 54 81) ($p < 0.001$). Overall, subjects with FCD performed slower than HC. The estimated difference between mean response times in FCD

and HC groups was 63 (95% CI 1.4 124) (p 0.045)((Figure 2, Table III, Supplementary table IV). However, the effects of 'background noise', and interactions 'group' x 'cue congruence' and 'group' x 'background noise' were not significant. In the adjusted analysis including all pre-defined co-morbidities and education, the difference in response times between groups lost significance (p 0.268), while participants in both groups continued to perform slower in 'incongruent' colour-word conditions. Both groups performed with high accuracy {proportion of correct answers [mean (standard deviation)] - HC: 0.96 (0.03); FCD: 0.93 (0.1)}, and there were no significant differences between groups or conditions (Table III).

Metacognition

Both unadjusted and adjusted analyses of the metacognition sub-score (*'how successful were you in accomplishing what you were asked to do?'*) showed that the impact of background noise in metacognition was different between groups (unadjusted p 0.025 for interaction 'group' x 'background noise') and that this effect was further modulated by 'cue congruence' (unadjusted p 0.007 for 'group' x 'background noise' x 'cue congruence')(Figure 3, Table III, Supplementary table V). To test our predetermined hypothesis of greater self-reported difficulties in the presence of background noise, we compared metacognition sub-scores in the presence and absence of background noise, for each 'cue congruence' and 'group'. In the congruent conditions, patients with FCD reported *worse* performance in the presence of background noise, with anestimated difference in metacognition sub-scores between noisy and silent backgrounds of 9 (95% CI 2 17) (p 0.016). However, in the incongruent conditions, patients with FCD reported *better* performance in the presence of background noise. This corresponded to an estimated difference of -8 (95% CI -15 0) (p 0.046) between noisy and silent backgrounds . In contrast, HC reported similar quality of performance in all conditions.

Indeed, for HC, the estimated difference between noisy and silent backgrounds was -2 (95% CI -9 4) in congruent conditions (p 0.492) and 0 (95% CI -6 7) in incongruent conditions (p 0.901).

Biomarkers of mental workload

Both crude and adjusted analyses of the amplitude of P300 ('positive area' between 300 and 600 ms) did not reveal significant effects for 'group', 'cue congruence' or the interaction 'group' x 'cue congruence' (p-values 0.797, 0.680 and 0.860, respectively - crude analysis) (Figure 4, Table III and Supplementary Figure 2).

Likewise, both crude and adjusted analyses of the power of midfrontal theta, parietal alpha and ration theta / alpha did not reveal any significant effects of 'group', 'cue congruence', 'background noise' or their respective interactions.

Fifth condition – 'multi-tasking'

We compared performance in the Stroop colour-word condition consisting of incongruent cues and passive listening to background noise with the fifth condition where participants were asked to silently count and memorise the number of 'rare' sounds played in the background (active listening/multi-tasking) (Supplementary Tables VI and VII). Active listening was associated with an increase in subjective 'mental effort', slower reaction times (but similar accuracy) and lower self-reporting of performance, in both unadjusted and adjusted analysis ($p < 0.001$ for the effect of 'active listening' on 'mental effort', p 0.023 on reaction times, p 0.353 on accuracy and p 0.052 on metacognition, in unadjusted analysis). However, the impact of active listening on these outcomes was similar in subjects with FCD and HC (non-significant

interaction ‘group’ x ‘counting oddball sounds’ for all outcome measures). Notably, subjects with FCD did not perform slower than HC (p 0.276 for ‘group’, unadjusted). Our analysis of the biomarkers of mental workload (P300, midfrontal theta, posterior alpha and ratio theta / alpha) also did not reveal significant differences between group or condition.

Finally, the proportion of participants who correctly remembered the number of ‘rare’ sounds that were played(20) was similar in both groups (13/23 HC and 12/19 patients with FCD, p 0.509).

Discussion

Despite increasing recognition of FCD, relatively little primary research has been performed to investigate its neuropsychological basis. Here we report several novel findings.

People with FCD have higher levels of depression, anxiety, fatigue, pain, sleep disruption, dissociation and obsessiveness than HC. This suggests that FCD occurs predominantly in people who are experiencing a range of other somatoform symptoms, alongside subsyndromal levels of mood disturbance and who are predisposed to FCD by obsessiveness and a tendency to dissociation. This supports our contention that the experience and aetiology of cognitive symptoms in chronic fatigue syndrome and fibromyalgia are likely to be similar, perhaps identical, to what in the memory clinic is labelled as FCD. We conjecture that amongst patients with cognitive symptoms in the context of mild traumatic brain injury, whiplash and long-COVID-19, a subset will have similar characteristics to our cohort. In other words, FCD is one facet of a broader somatoform syndrome in which pain, fatigue and mood changes are also prominent features, and which can occur in response to range of physiological and psychological triggers.

People with FCD consistently displayed slower reaction times than HC although this was not exacerbated by increasing task difficulty. Indeed, the magnitude of the Stroop effect was similar in patients with FCD and HC. Reaction times in the hardest (5th) condition, in which attention was divided between visual and auditory tasks, were not significantly different between people with FCD and HC, although the trend for slower reaction times in FCD was maintained. This suggests that slow reaction times in FCD are a trait and not a function of task difficulty.

Notably the difference in reaction times between people with FCD and HC lost significance after adjusting for confounders, suggesting that the slowness could be related to comorbidities such as mood disturbance, fatigue or pain.

Our observation of cognitive slowness in people with FCD is consistent with prior findings in depression, CFS and fibromyalgia, further supporting the syndromic and pathophysiological overlap between these conditions. In depression, clinically evident motor slowing is one of the diagnostic criteria endorsed by DSM-5.[24] Patients with depression have been reported to respond slower than HC in reaction-time tasks and (less consistently) to display greater interference in SCWT (indexing poor selective attention).[25,26] Although we excluded people with current depression or a PHQ-9 => 15, our FCD group scored a median of 10 (IQR 6-13). In people experiencing depressed mood and/or anhedonia, scores within this range are thought to correspond to mild to moderate depression. Therefore, mild to moderate depressive illness could have contributed to the global slowness.

We did not find a significant difference between FCD and HC in response accuracy on both the SCWT task and a combined oddball counting task. This negates our hypothesis that FCD is a state of attentional exhaustion, in which a ramping up of attentional demand leads to impaired performance.

Patients with FCD were more likely than HC to report applying greater effort when performing the congruent and incongruent SCWT in noisy conditions. However, our EEG-based biomarkers of mental workload were similar in patients with FCD and HC in both silent and noisy conditions. Therefore, for the same objective level of mental workload, patients with FCD reported greater mental effort. This suggests that what patients subjectively describe as "mental effort" does not always correlate with measurable mental work.

FCD patients rated their overall memory more poorly than HC despite being as accurate on all the tasks. This suggests that a deficit in "global" metacognition is a key driver of the inconsistency between subjective and objective experience in FCD.

In contrast, there were only small differences between FCD and HC on self-rated task performance. On the congruent SCWT, FCD patients were more likely than controls to perceive a decline in performance in the presence of noise. This was associated with an increase in mental effort. In contrast on the incongruent SCWT, FCD patients experienced a subjective improvement in performance in the presence of noise, without a corresponding decrease in subjective mental effort. This suggests a non-linear relationship between task complexity and subjective achievement in FCD. A possible explanation for this is that the more attentionally demanding incongruent task does not afford sufficient bandwidth for negative automatic thoughts when the environment is made more distracting by the addition of noise. However, these findings warrant replication in larger samples.

In summary, "local" or task-specific metacognition is less impaired than global metacognition in FCD. Poor metacognition has been proposed to be a key feature of functional cognitive disorder.[5,27–29] However, empirical evidence to support this assumption is relatively scarce. Self-reporting poor memory in combination with a Mini-Addenbrooke's Cognitive Examination > 25 is reported to have high sensitivity and specificity for the diagnosis of

FCD.[30,31] 'Memory self-efficacy scores' (based on Metamemory in Adulthood Questionnaire)] were also reported to predict a diagnosis of FCD.[32] Bhome et al.[27] hypothesised that people with poor metacognition experience greater concern about objectively normal cognitive performance and poorer monitoring and increased salience of attentional lapses, leading to a vicious, reinforcing cycle that would drive illness experience, while people with normal metacognition are relatively unaffected by episodic, trivial day to day cognitive lapses. However, while their subsequent experimental work confirmed a difference in global metacognition, they were not able to demonstrate impaired local metacognition[33] Further, a recent study by Pennington et al.[34] also failed to find differences in metacognitive efficacy between FCD, neurodegenerative mild cognitive impairment and HC, in either memory or perceptual tasks. This discrepancy between global and local metacognition found by us and others is tantalising because it suggests that people with FCD are aware that they perform accurately "in the moment" but aren't able to adjust global assumptions about their cognition on the basis of day-to-day experience.

We did not find evidence of systematic underperformance, and all EEG-based biomarkers of mental workload were similar in patients with FCD and HC. These findings support the observation that only a minority of patients with FCD fail on performance validity testing.[8,35]

We hypothesise that the sensation of 'brain fog' reported by people across all functional cognitive disorders could result from subjectively increased mental effort in distracting environments combined with mild psychomotor slowing. For people with high expectations of their cognitive function, this experience might be uncomfortable, producing a feeling that the brain is 'foggy' and that they are working harder than normal to think clearly, although not necessarily misjudging their task-specific performance.

Do our findings have implications for therapy? We hypothesise that advising people with FCD to restrict themselves to straightforward tasks in which distractions are not present is not likely to reduce their symptoms. Likewise, behavioural strategies that are commonly suggested for people with dementia and structural brain injury such as breaking down tasks into multiple components ("chunking") and writing checklists which need to be followed strictly might directly worsen symptoms in those with FCD. This emphasises the need for care in diagnosis, in particular in patients where there might be uncertainty or both functional and organic factors present, such as those with mild traumatic brain injury. In fact, tasks with greater complexity, and which are therefore more immersive are no more (and might be less) likely to be experienced as unduly effortful or frustrating. Our findings also support the reassurance given to patients with FCD that although they experience genuine cognitive symptoms, these are not underpinned by damage to or dysfunction of core cognitive faculties, even if they are marginally slower than completely healthy people. Finally, the high prevalence of co-morbidities such as pain, depression, anxiety, fatigue and sleep disturbances highlight the need to screen patients with FCD for those problems, and to treat them accordingly.

Long-COVID-19 is an growing public health problem corresponding to symptom persistence following an acute COVID-19 infection.[36] Its symptoms can be wide-ranging, fluctuating in intensity, might change over time, and do not appear to correlate with the severity of the acute infection[36]. Notably, cognitive problems are among the most frequent symptoms reported by *non-hospitalised* patients developing long-COVID-19, alongside fatigue, headaches, sleep disorders and respiratory symptoms.[37] Patients experience mental fog, memory lapses, poor concentration and word-finding difficulties.[38] There is ongoing discussion about the possible overlap between long-COVID-19 and both chronic fatigue syndrome and fibromyalgia.[39,40] The pathophysiology of long-COVID-19 remains uncertain and might be multifactorial. It is possible that for many people with long-COVID-19, cognitive difficulties are best understood

as a form of FCD. Further research is needed to investigate the relevance of our findings to the understanding of the pathogenesis and management of cognitive symptoms in long-COVID-19.

Limitations of our work include the moderate sample size and the fact that our task did not exhaust attentional reserve in either healthy people or those with FCD. In the most demanding task, we might have been underpowered to detect slowing of reaction times or inaccuracy among participants with FCD. Our study had an exploratory character, and our findings should seek replication in other, larger samples.

We excluded patients who had a known diagnosis of MCI. Consequently, our findings might not be generalisable to patients with FCD who underperform on neuropsychological testing to the extent that they meet MCI criteria.[41]

In summary, we have shown that FCD is not an isolated disorder, but significantly co-morbid with mood and somatoform symptoms. This suggests that Stone's' classification of FCDs into separate "isolated", "mood-related" and "somatoform-associated" categories might be unnecessary, as most patients will display all of these traits to some extent.[7] Finally, we show that FCD is associated with cognitive slowing, retained attentional capacity, heightened effort perception during distraction and consistent global but inconsistent local metacognitive failure, reflecting a failure of "bottom up" sensory feedback to alter "top down" prior assumptions (Figure 5). These findings should inform the design of rehabilitative strategies for FCD.

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Competing interests

The authors report no competing interests.

Supplementary material

Supplementary material is available at *Brain* online.

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Figure legends

Figure 1 – Subjective mental effort (composite score corresponding to the sum of 'Mental Demand' and 'Effort' subscores of NASA-TLX; box-and-whisker plots showing median, interquartile interval, minimum, maximum and outliers

Figure 2 – Objective performance – reaction time (milliseconds; box-and-whisker plots showing median, interquartile interval, minimum, maximum and outliers)

Figure 3 – Metacognition (self-rated performance; box-and-whisker plots showing median, interquartile interval, minimum, maximum and outliers)

Figure 4 – P300 (Difference wave 'Odd sounds' – 'Common sounds'; amplitude μV; time milliseconds)

Figure 5 - Proposed mechanism for FCD: Cognitive symptoms are produced by the combination of and interaction between abnormal global metacognition (priors), pain, fatigue, mood and other mental changes, and psychomotor slowing. Benign cognitive experiences are over-interpreted, generate a heightened subjective sense of mental effort and lead to an inefficient cognitive mode, all of which reinforce symptoms in a feedback loop. Objectively normal performance is accompanied by preserved local (task-specific) metacognition, but this is unable to reset abnormal priors, perhaps due to the overwhelming drive from somatoform and mood changes and ongoing over-interpretation of "normal" cognitive lapses.

Table I – Demographics

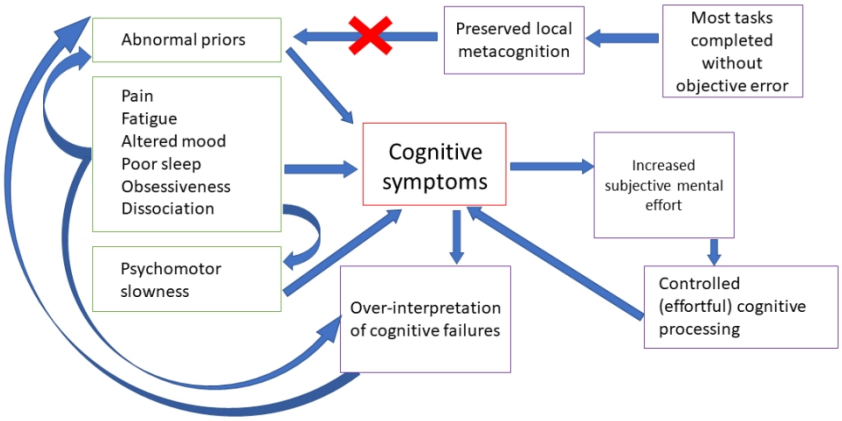
	HC	FCD	p-value
Total N	23	19	
Mean Age (years) (SD)	51 (9)	49 (10)	0.507
Sex (females)	17	12	0.453
Mean Years in Education (SD)	18 (4)	15 (5)	0.063
Employed	19	14	0.769
Support from social services	0	2	0.111
Any neurological or psychiatric condition	3	10	0.006
Any psychotropic medication	2	6	0.060
Right-handed	22	18	0.361

Table Ⅱ – Subjective cognitive symptoms and comorbidities

	HC	FCD	p-value
Total N	23	19	
Screening questionnaires for subjective cognitive symptoms			
SMC Likert *(In general, how would you rate your memory?) (Mean)*	3 [3-4]	2 [1-2]	<0.001
1: Poor	0	8	
2: Fair	0	10	
3: Good	12	1	
4: Very Good	9	0	
5: Excellent	2	0	
Functional Memory Disorder inventory (short version) *(0-10)*	1 [0-2]	7 [6-9]	<0.001
Functional Memory Disorder inventory (long version) *(22-88)*	39 [35-43]	62 [56-76]	<0.001
Comorbidities			
Depression *(PHQ-9) (0-27)*	1 [0-4]	10 [6-13]	<0.001
Anxiety *(GAD-7) (0-21)*	1 [0-4]	8 [3-11]	<0.001
Fatigue *(Chalder Fatigue Scale) (0-33)*	11 [11-12]	19 [12-23]	<0.001
Pain *(PainDETECT-Q) (0-38)*	1 [0-5]	6 [2-11]	0.02
Sleep *(Jenkins Sleep Scale) (0-20)*	4 [3-7]	9 [5-15]	0.015
Dissociation *(SDQ-20) (20-100)*	20 [20-21]	23 [21-29]	0.004
Obsessiveness *(OCI scale) (0-168)*	4 [0-11]	18 [5-24]	0.013

Table Ⅲ – Self-rated and behavioural outcomes

Group	Congruence	Background	Mental effort	NASA-TLX	Reaction time (ms)	Accuracy	Metacognition
HC	Congruent	Silent	99 (54)	239 (117)	653 (93)	0.96 (0.01)	27 (22)
		Noisy	91 (57)	223 (130)	636 (89)	0.97 (0.02)	25 (21)
	Incongruent	Silent	100 (49)	247 (118)	724 (119)	0.95 (0.04)	28 (21)
		Noisy	110 (46)	267 (113)	708 (102)	0.95 (0.03)	29 (20)
FCD	Congruent	Silent	94 (53)	252 (126)	727 (107)	0.95 (0.04)	30 (19)
		Noisy	110 (54)	292 (131)	695 (113)	0.95 (0.03)	39 (20)
	Incongruent	Silent	113 (53)	304 (126)	803 (144)	0.91 (0.11)	39 (22)
		Noisy	123 (53)	319 (144)	747 (116)	0.92 (0.15)	31 (18)



Proposed mechanism for FCD: Cognitive symptoms are produced by the combination of and interaction between abnormal global metacognition (priors), pain, fatigue, mood and other mental changes, and psychomotor slowing. Benign cognitive experiences are over-interpreted, generate a heightened subjective sense of mental effort and lead to an inefficient cognitive mode, all of which reinforce symptoms in a feedback loop. Objectively normal performance is accompanied by preserved local (task-specific) metacognition, but this is unable to reset abnormal priors, perhaps due to the overwhelming drive from somatoform and mood changes and ongoing over-interpretation of "normal" cognitive lapses.

162x91mm (200 x 200 DPI)

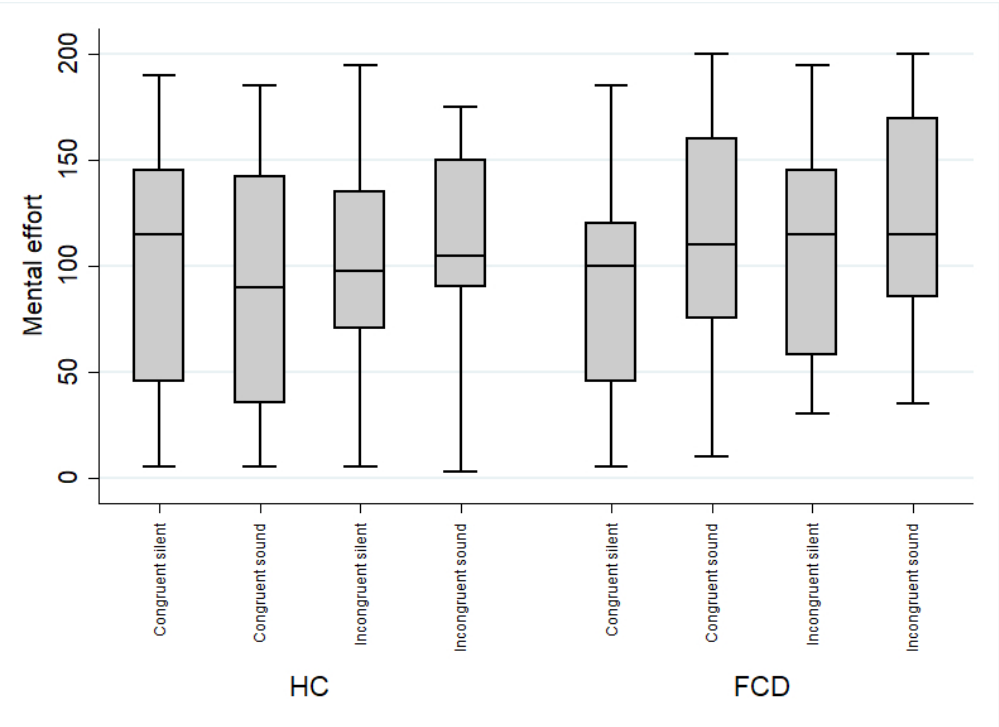


Figure 1 – Subjective mental effort (composite score corresponding to the sum of 'Mental Demand' and 'Effort' subscores of NASA-TLX; box-and-whisker plots showing median, interquartile interval, minimum, maximum and outliers)

279x203mm (72 x 72 DPI)

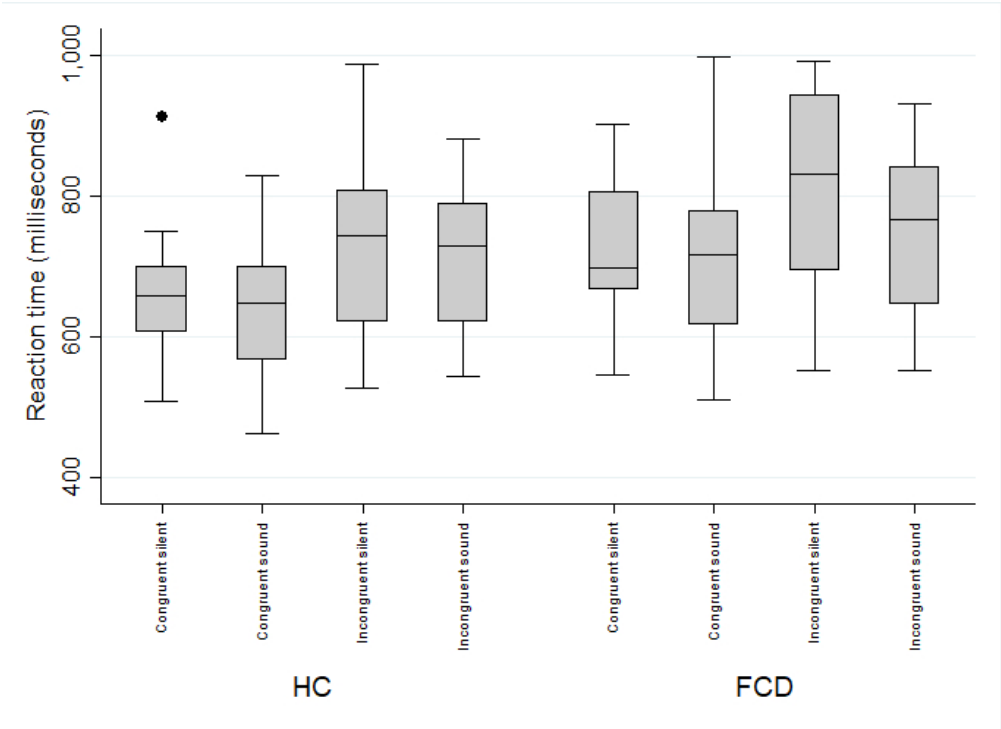


Figure 2 – Objective performance – reaction time (milliseconds; box-and-whisker plots showing median, interquartile interval, minimum, maximum and outliers)

240x174mm (72 x 72 DPI)

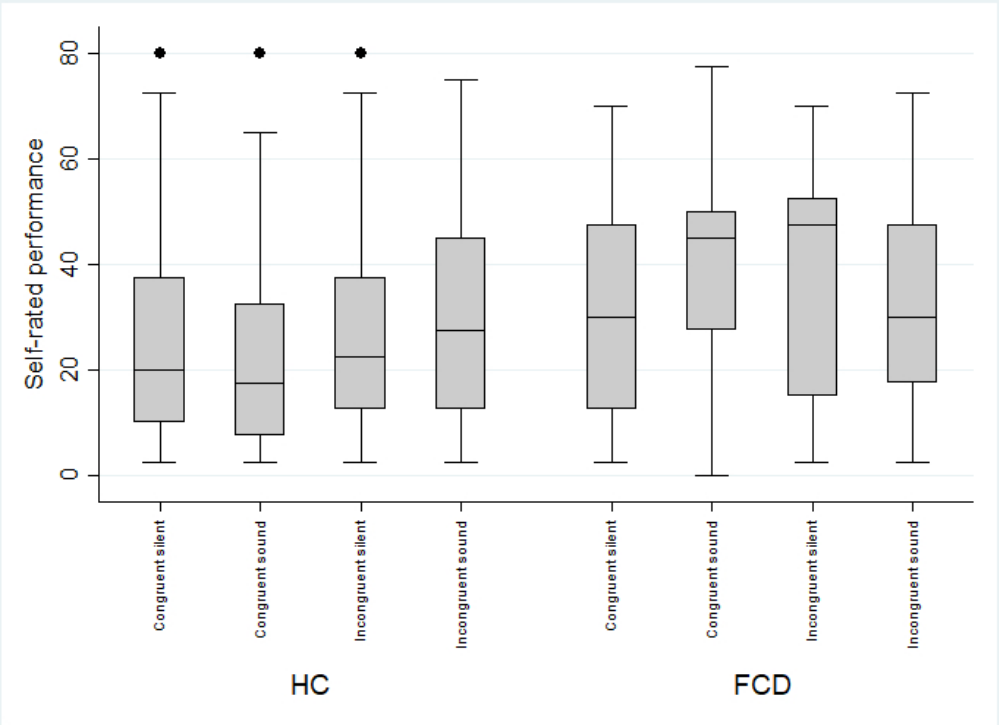


Figure 3 – Metacognition (self-rated performance; box-and-whisker plots showing median, interquartile interval, minimum, maximum and outliers)

240x174mm (72 x 72 DPI)

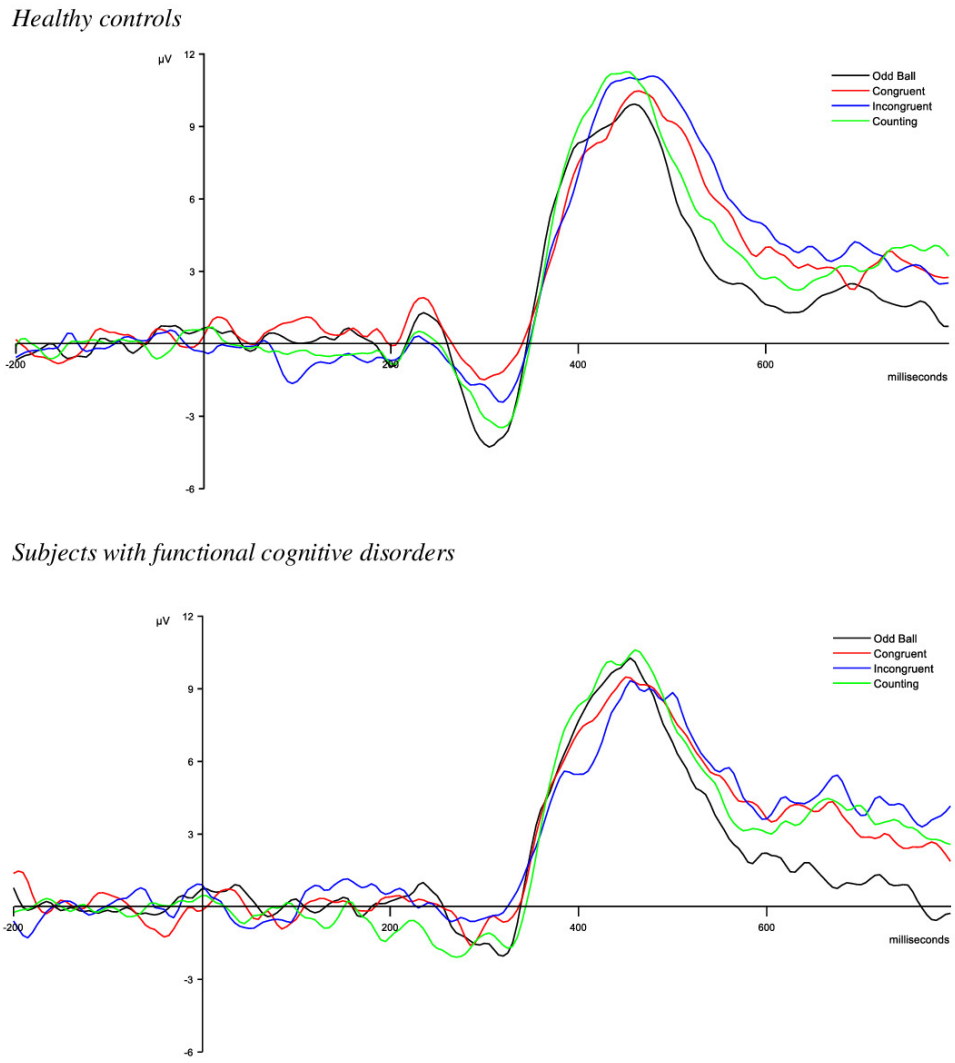


Figure 4 – P300 (Difference wave 'Odd sounds' – 'Common sounds'; amplitude μV; time milliseconds)

358x387mm (78 x 78 DPI)

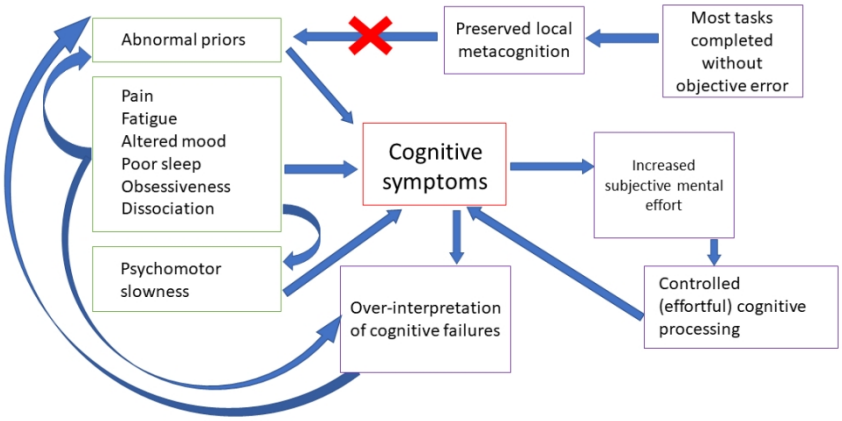


Figure 5 - Proposed mechanism for FCD: Cognitive symptoms are produced by the combination of and interaction between abnormal global metacognition (priors), pain, fatigue, mood and other mental changes, and psychomotor slowing. Benign cognitive experiences are over-interpreted, generate a heightened subjective sense of mental effort and lead to an inefficient cognitive mode, all of which reinforce symptoms in a feedback loop. Objectively normal performance is accompanied by preserved local (task-specific) metacognition, but this is unable to reset abnormal priors, perhaps due to the overwhelming drive from somatoform and mood changes and ongoing over-interpretation of "normal" cognitive lapses.

338x190mm (96 x 96 DPI)

Methods (detailed)

Participants

Patients aged between 18 and 70 years with a diagnosis of FCD were recruited from Neurology and Neuropsychiatry Clinics at St George's University Hospitals NHS Foundation Trust, South West London & St George's Mental Health Trust and Ashford and St Peter's Hospitals NHS Foundation Trust. All patients were diagnosed by clinicians with a special interest in Cognitive Disorders and/or Functional Neurological Disorder. Control participants were healthy subjects recruited through 'Join Dementia Research'.

We excluded subjects with diagnoses of dementia, mild cognitive impairment, epilepsy or a history of severe head injury, ischaemic stroke or any other form of significant structural brain damage, a severe psychiatric disorder or moderate to severe depression defined by a PHQ-9 (1) score >= 15 on the day of the experiment. Healthy controls were matched for age.

All participants were tested in a single study visit. We collected demographic and medical history. Participants completed the following questionnaires: Chalder Fatigue Scale(2); Generalised Anxiety Disorder (GAD)-7 scale(3), Jenkins Sleep Scale (4), Obsessive-Compulsive Inventory(5), painDETECT questionnaire (PD-Q)(6), Patient Health Questionnaire (PHQ-9)(1), Somatoform Dissociation Questionnaire (SDQ-20)(7).

In addition, all participants also rated their memory on a five-point SMC Likert scale *('In general, how would you rate your memory?': 1 = poor, 2 = fair, 3 = good, 4 = very good, 5 = excellent*)(8) as well as a functional memory disorder inventories 'short' and 'long' versions(9).

Modified Stroop colour-word task

We developed an experimental paradigm consisting of a modified Stroop colour-word task (SCWT) in which attentional demand was varied by task difficulty (congruent versus incongruent) and the presence of active or passive listening to an auditory stimulus (oddball-type task) (Figure 1). The experiment was programmed on PsychoPy v1.90.1 (10).

Prior to starting the formal paradigm, all subjects completed a training block for the colour-word Stroop task, to ensure adequate understanding of the task before proceeding to the main task. The ARROW keys of a QWERTY keyboard of a laptop were coloured as follows: 'UP' – Blue, 'DOWN' – Yellow, 'LEFT' – Red, 'RIGHT' – Green. Participants were instructed to select the key according with the colour of the ink of the word displayed in the screen of the laptop, while ignoring what was written. For training purposes, we only included congruent colour-word combinations (i.e. word naming corresponding ink colour). The training session consisted of two rounds of 20 colour-words.

Subsequently, each participant performed six experimental tasks.

The experiment always started with an Oddball-type task **(condition 0- Odd Ball)**. It consisted in the passive listening to sequences of common (500 Hz) and rare ('Odd') sounds (2000 Hz). Each sound had a duration of 150 ms, 5 ms rise/fall and an approximate intensity of 70 dB.

The Oddball task consisted of 20 sequences of sounds, each with 10 sounds, including 9 standard and 1 oddball sound (hence 20 oddball sounds and 180 standard sounds). On a sequence of sounds, a sound was played every 2 seconds, and there was a pause of 5.85 seconds after the last sound (sequence duration was 24 seconds).

In a 10-sound sequence, an oddball sound was played in the 7^{th}, 8^{th}, 9^{th} or 10^{th} position. We included five similar 10-sound sequences for each of the 4 possible 'positions' of an oddball sound (hence a total of 20 sequences per 'Oddball' condition 0 / subject). The order of sequences was randomised in each experiment (Table I).

Table I – Sound sequence ('Odd' – Odd sound; 'C' - Common sound)

Sequence	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th
1	C	C	C	C	C	C	Odd	C	C	C
2	C	C	C	C	C	C	C	Odd	C	C
3	C	C	C	C	C	C	C	C	Odd	C
4	C	C	C	C	C	C	C	C	C	Odd
5	C	C	C	C	C	C	Odd	C	C	C
6	C	C	C	C	C	C	C	Odd	C	C
7	C	C	C	C	C	C	C	C	Odd	C
'S'	C	C	C	C	C	C	…	…	…	…

After **condition 0 'Oddball'**, four conditions were presented in a pseudorandomised order (counterbalanced at a FCD / HC group level). Participants were simply informed that they might hear background sounds in some of the conditions, but were not give any further instructions (i.e. **passive listening**). The conditions were as follows:- Stroop colour-word task (SCWT) with congruent ink colour and word, performed in a silent environment **(condition 1 - SCWT congruent silent)** - e.g. word RED coloured with red ink – participants were required to press the red key;

- SCWT with congruent ink colour and words, performed in a noisy environment; we played the sounds of an Oddball task (similar to condition 1) in the background while subjects performed the SCWT **(condition 2 - SCWT congruent noisy)**; There was a 1-second-long interval between colour-word display in the screen and playing Oddball sound.

- SCWT with incongruent ink colour and words, performed in a silent environment **(condition 3 - SCWT incongruent silent)** - e.g. word RED coloured with blue ink – participants were required to press the blue key;

- SCWT with incongruent ink colour and words, performed in a 'noisy' (Oddball-type) environment **(condition 4 - SCWT incongruent noisy)**;

The last condition was always:

- A **SCWT incongruent noisy** similar to condition 4, but this time participants were instructed to silently count the number of oddball sounds while performing the SCWT task. At the end of the task participants were asked about the total number of oddball sounds that were played **(condition 5 - SCWT incongruent *count*)**.

The order of conditions 1-4 was counterbalanced between subjects, and each subject was randomly allocated with a unique order among the 24 possible combinations (pseudo randomisation) (Table II). Pragmatically, and based on this design, we aimed at recruiting 24 subjects per group in this pilot experimental study.

Table II – Sequence of experimental conditions per participant (our paradigm included a total of 6 conditions, labelled 0 to 5)

Participant	1st condition	2nd condition	3rd condition	4th condition	5th condition	6th condition
1	Oddball (0)	Congruent Silent (1)	Incongruent Sound (4)	Congruent Sound (2)	Incongruent Silent (3)	Incongruent Count (5)
2	Oddball (0)	Incongruent Sound (4)	Congruent Silent (1)	Congruent Sound (2)	Incongruent Silent (3)	Incongruent Count (5)
3	Oddball (0)	Congruent Sound (2)	Incongruent Silent (3)	Incongruent Sound (4)	Congruent Silent (1)	Incongruent Count (5)
'p'	Oddball (0)	…	…	…	…	Incongruent Count (5)

Participants were requested to self-rate the workload involved in performing conditions 1-5 using the NASA Task Load Index (NASA-TLX)(11). NASA-TLX assesses the workload by asking the subjects to rate their 'Mental Demand', 'Physical Demand', 'Temporal Demand', 'Effort' and 'Frustration' (Very Low – Very High) and also 'Performance' (Perfect – Failure), by using Likert-type scales (with 21 gradations, each of the six sub scores rated 0-100 – total sum 600).

Outcomes

We measured subjective effort and objective performance on the modified SCWT (speed and accuracy), and EEG-based biomarkers of mental workload, primarily P300 suppression but also mid-frontal theta enhancement, posterior (parietal) alpha suppression and their ratio.

The primary measure of **subjective effort** was a composite score corresponding to the sum of 'Mental Demand' and 'Effort' subscores of NASA-TLX(11), corresponding to a total score between 0 and 200. The secondary measure was the total score NASA Task Load Index (0-600).

The primary measure of **objective performance** was response time in the modified SCWT. Response time in milliseconds (time from presentation of the word to key press) was averaged across trials with a correct response (key press) for each condition 1-5 and participant. The secondary measures were response accuracy in the SCWT (proportion of correct key presses per condition) and ability to remember the correct number of sounds (twenty) were played on condition 5. The primary measure of **metacognition** was the sub score on the item 'Performance' (Perfect 0 – Failure 100) on NASA-TLX.

The primary biomarker of **mental workload** involved in the modified SCWT was suppression of P300 in the midline. The secondary biomarkers were midfrontal theta enhancement and posterior (parietal) alpha suppression and ratio midfrontal theta – parietal alpha powers.

P300 is a positive, broad event-related potential that typically peaks at 250-300 ms or more after the onset of a rare stimulus, and is elicited in an odd-ball paradigm.(12) In this type of paradigm, rare stimulus can elicit P300 regardless of whether participants are attending (active listening) and not attending (passive listening) to the rare stimulus.(13,14) In subjects performing a primary task of variable difficulty, the P300 elicited by background tones (passive listening) is reported to decrease in amplitude and increase in latency as the difficulty of the

primary task increases, thus providing an objective measure of mental workload.(14–16)

Spectral power in the theta (4-7 Hz) and alpha (8-12 Hz) power bands are also proposed to be sensitive to workload manipulations. Midfrontal theta power was reported to be directly related to task difficulty and memory load, while posterior (parietal) alpha power is proposed to be inversely related to the amount of attentional resources allocated to a task.(17,18) Conversely, the ratio of midfrontal theta power – parietal alpha power is thought to increase with increments in mental workload.(19) Much of the evidence on alpha and theta power as measures of mental workload results from experiments in aircraft pilots, air traffic controllers and car drivers.(18,20–22)

Recording event-related potentials and oscillatory activity

Continuous EEG was recorded from Ag/AgCl surface electrodes, using a Biosemi® 64+2 channels conforming to the 10/20 electrode layout. Electrode impedances were <5 kOhm. The sampling rate was 2048 Hz. Our reference was an average of the mastoid electrodes. For horizontal electrooculography (EOG) we added an electrode between the lateral canthi of each eye and the corresponding hairline. For vertical EOG we added an electrode above the right eyebrow and another on the right cheek, equidistant from the right pupil. For ECG recording we added one electrode to the distal fifth of the posterior surface of each forearm.

Pre-processing

For data processing we used EEGLAB v2019.1(23), ERPLAB v8.01(24) and MATLAB®. First, we downsampled the data from 2048 to 200 Hz. We then defined ‘events’ corresponding to the onset of sounds (common and rare) and cues (congruent and incongruent colour-word

pairs) on each of the six conditions. These events were marked on the continuous EEG data, which was then epoched to frames from -200 to 800 ms relative to each event. The epochs were baseline-corrected relative to the interval -200 to 0.

Epochs were visually inspected for artifacts. Trials with very prominent artifacts were discarded. Channels with prominent prolonged artifacts were also identified and removed, based on visual inspection and analysis of channel spectra and scalp maps.

We decomposed the resulting data by Independent Component Analysis using EEGLAB(23). We then visually inspected ICA components and also ran ICLabel on EEGLAB to identify, mark and remove artefactual ICA components (e.g. line noise, eye movements, muscle contraction, heart-related). TT performed this step blinded for the labelling of the epochs (condition). Finally, we interpolated the channels removed in a previous step.

Pre-processing resulted in baseline corrected power as a function of time (-200 800) for the following conditions / events: **Condition 0 Oddball** (standard and oddball sounds); **Condition 1 - SCWT congruent silent** (congruent cues); **Condition 2 – SCWT congruent sound** (congruent cues, standard and oddball sounds); **Condition 3 – SCWT incongruent silent** (incongruent cues); **Condition 4 – SCWT incongruent sound** (incongruent cues, standard and oddball sounds); **Condition 5 – SCWT incongruent count** (incongruent cues, standard and oddball sounds).

For subsequent analysis of P300, we used ERPLAB to average trials according with events / conditions and low-pass filtered (30 Hz) the resulting ERPs. We included all trials regardless of response correctness (i.e. key press selecting the correct ink colour).

Again, for analysis of P300, we generated ‘difference waves’ subtracting standard sound ERPs from oddball sound ERPs for each of the four conditions with sounds (0, 2, 4, 5). We transferred the resulting EEG data from midline channels (Fz, FCz, Cz, CPz, Pz) for each of those

conditions in each participant, for further analysis on STATA®.

For analysis of alpha and theta power, we used the 'Spectopo' function of MATLAB® to extract the power of alpha band (8-12 Hz) on Pz and the power of theta band (4-7 Hz) on Fz, for each of the 'cue'-type events on each of the conditions 1-5, and then also averaged data over trials without excluding those with incorrect responses. This data on the amplitude of alpha band on Pz and theta band on Fz, as well as their respective ratio (mid-frontal theta / posterior alpha) for each cue on conditions 1-5 for each participant was then also exported to STATA® for further analysis.

Statistical analysis

Statistical analysis was performed using Stata® (version 13.1). As described above, our outcome measures were:

1) For **subjective effort**, we analysed 'Mental effort' (a sum of 'Mental Demand' and 'Effort' subscores of NASA-TLX(11)) and total score of NASA-TLX;
2) For **objective performance**, we analysed response times and accuracy on modified SCWT and the ability to remember correct number of oddball sounds played on the sixth condition (20);
3) For **metacognition**, we analysed the sub score on item 'Performance' of NASA-TLX;
4) For **biomarkers of mental workload**, we analysed the amplitude of P300 in the midline, as well as the amplitudes of frontal theta (channel Fz) and parietal alpha (channel Pz) and their respective ratio (frontal theta / parietal alpha). The amplitude of P300 is known to be larger in the midline electrodes(12) and therefore we selected five midline channels (Fz, FCz, Cz, CPz, Pz) for further analysis. P300 was defined as the 'positive' area between 300 and 600 ms relative to sound onset(25). 'Positive area' was defined as the area under the curve of the 'region(s)' with values above baseline (>0).

In order to select which channel would be used for the final analysis of P300, we performed a grand average of all 'difference waves' in all participants, and compared the size of P300 between channels. The amplitude of P300 was largest on Cz, although the difference was only significant in comparison with Pz (p 0.025). This result was consistent with previous knowledge about P300(12), and therefore we performed all further analysis with data from channel Cz.

Mixed effects multilevel linear modelling allowed us to take into account the dependency in data caused by repeated measurements within-subjects. For our main analysis we included conditions 1-4, and fitted the following models:

1) For **measures of subjective effort, objective performance on SCWT and metacognition**: including the effects of 'group' (subjects with FCD or healthy controls, 'cue congruence' on SCWT (congruent or incongruent colour-word cues) and 'background noise' (presence or absence of Oddball-type noises in the background), their interactions and an individual level random effects factor.

   We predicted that incongruent cues and background noise would increase the levels of subjective effort among subjects with FCD. We expected to observe a greater slowing of response times when responding to incongruent colour-word cues among subjects with FCD. Finally, we also expected to find worse metacognition in subjects with FCD as a group – i.e. a more inaccurate self-assessment of their own performance.

2) For **P300**: including the effects of 'group', 'cue congruence', their interactions and individual level random effects factors for intercept and slope.

3) For **alpha- and theta-band powers and ratio midfrontal theta / posterior (parietal) alpha**: including the effects of 'group', 'cue congruence' and 'background noise', their interactions and an individual level random effects factor.

As mentioned above, **Condition 5 (SCWT incongruent count)** was similar to Condition 4 (SCWT incongruent noisy), but involved silently counting the number of oddball sounds and reporting the total number at the end of the experiment. Our aim was to simulate a situation of multi-tasking, which are often described as particularly challenging by patients with FCD. Our main hypothesis related to this additional analysis was that subjects with FCD would report a greater increase subjective effort in the condition with multitasking (condition 5), but with a preserved ability to remember the total number of oddball sounds that were played (20). Again, we fitted a mixed effects linear model including the effects of 'group', 'counting' sounds, their interaction and an individual level random effects factor for each of the relevant outcome measures.

For each of the aforementioned models was ran a 'crude' unadjusted analysis and whenever relevant also as an 'adjusted' analysis including the covariates chronic fatigue (Chalder Fatigue Scale's score(2)), anxiety (GAD-7's score(3)), sleep-related problems (Jenkins Sleep Scale's score (4)), obsessive-compulsive symptoms (Obsessive-Compulsive Inventory's score(5)), chronic pain (PD-Q's score(6)), depression (PHQ-9's score)(1) and somatoform/dissociative symptoms (SDQ-20's score(7)). Statistical significance was predefined as p-value (p) < 0.05.

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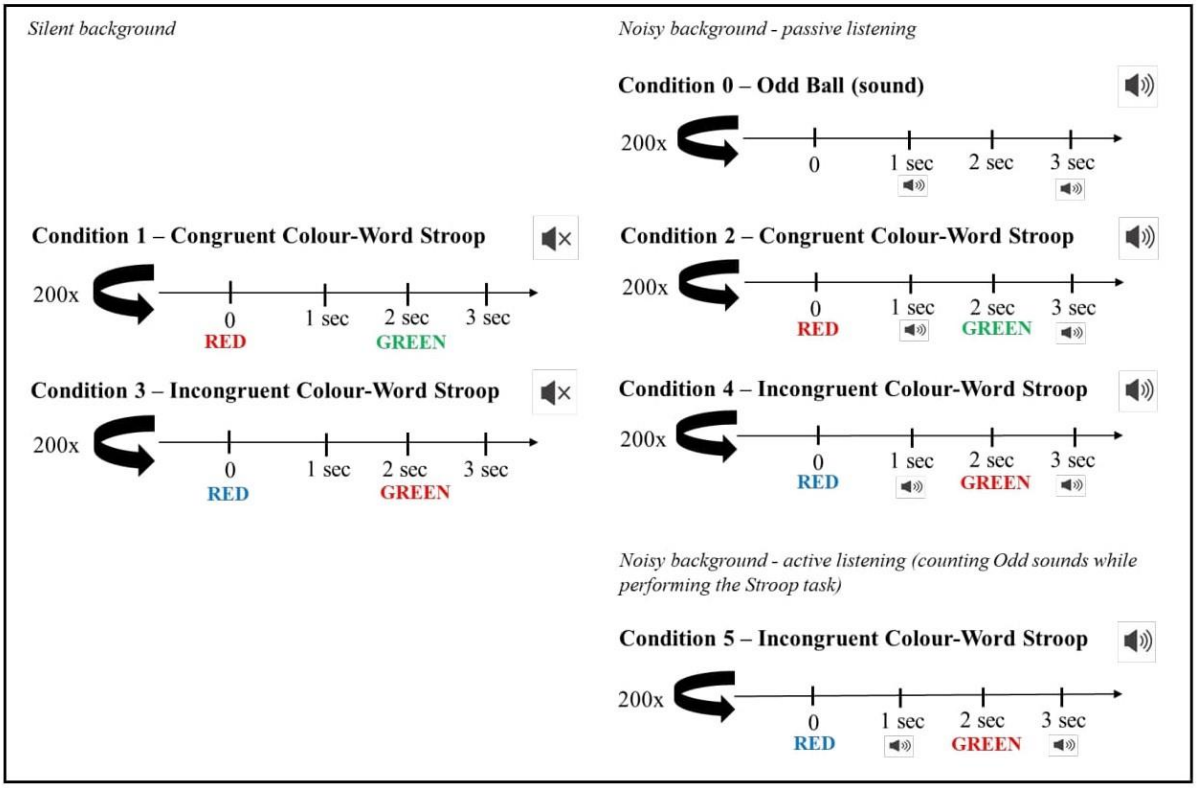
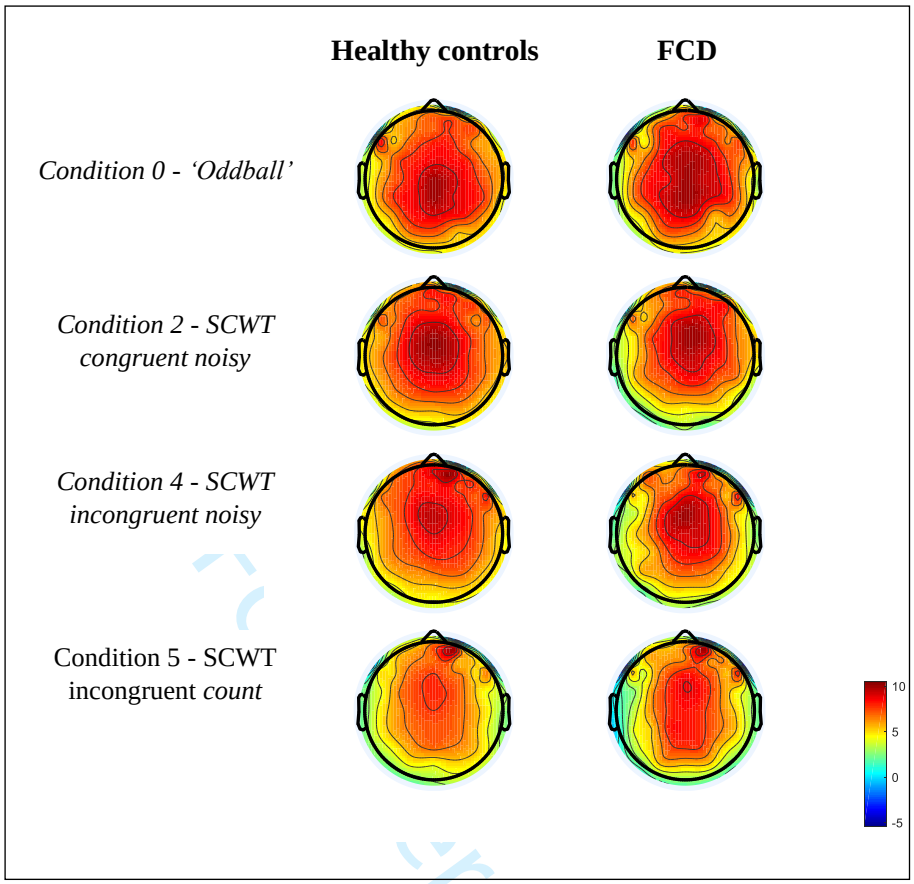
Supplementary Figures



Supplementary Figure 1 – Outline of the experimental paradigm



Supplementary Figure 2 – Scalp maps P300 (difference Odd sound – rare sounds of instantaneous amplitudes at t=459 ms; t= 459 ms was the mean peak latency between 300 and 600 ms in an analysis combining all study participants).

Supplementary Tables

Supplementary Table I - neurological and psychiatric comorbidities

	HC	FCD
Total N	23	19
N subjects with history of at least one neurological or psychiatric condition	3	10
	Migraine (2) Depression (controlled / resolved) (1) Anxiety disorder (controlled / resolved) (1)	Migraine (3) Depression (controlled / resolved) (3) Anxiety disorder (controlled / resolved) (2) Fibromyalgia or chronic generalised pain (2) ADHD (1) Essential tremor (1) Functional neurological disorder (functional dystonia) (1)

Supplementary Table II - psychotropic medication

	HC	FCD
Total N	23	19
N subjects using at least one psychotropic medication	2	6
	Amitriptyline (1) Mirtazapine (1)	Pregabalin (2) Paroxetine (1) Sertraline (1) Citalopram (1) Methylphenidate (1)

Supplementary Table III - Mental effort (composite score based on NASA-TLX; unadjusted analysis)

Group	Background	Estimated Mean (95% CI)	Difference means (95% CI)	p-value
HC	Silent	100 (80 119)	1 (-9 11)	0.888
	Noisy	100 (80 120)		
FCD	Silent	103 (81 125)	14 (3 24)	0.014
	Noisy	117 (95 138)		

Supplementary Table IV – Reaction time (milliseconds; unadjusted analysis)

		Estimated Mean (95% CI)	Difference means (95% CI)	p-value
Stroop	Congruent	675 (643 706)	67 (54 81)	<0.001
	Incongruent	743 (711 774)		
Group	HC	680 (639 722)	63 (1 124)	0.045
	FCD	743 (698 789)		

Supplementary Table V – Metacognition (Self-rated performance item from NASA-TLX scale; unadjusted analysis)

Group	Congruence	Background	Estimated Mean (95% CI)	Difference means (95% CI)	p-value
HC	Congruent	Silent	27 (19 35)	-2 (-9 4)	0.492
		Noisy	25 (16 33)		
	Incongruent	Silent	28 (20 37)	0 (-6 7)	0.901
		Noisy	29 (21 37)		
FCD	Congruent	Silent	30 (21 39)	9 (2 17)	0.016
		Noisy	39 (30 48)		
	Incongruent	Silent	39 (30 48)	-8 (-15 0)	0.046
		Noisy	31 (22 40)		

Supplementary Table VI – Outcome measures for 'passive listening' versus 'active listening' conditions

Group	Incongruent	Mental effort	NASA-TLX	Reaction time (ms)	Accuracy	Metacognition	P300	Midfrontal theta	Parietal alpha
HC	Passive listening	110 (46)	267 (113)	708 (102)	0.95 (0.03)	29 (20)	2.1 (1.6)	6.3 (3.4)	2.9 (1.7)
	Active listening	128 (48)	309 (131)	732 (122)	0.94 (0.03)	38 (20)	1.9 (1.1)	6.3 (4.2)	3.2 (1.3)
FCD	Passive listening	123 (53)	319 (144)	747 (116)	0.92 (0.15)	31 (18)	1.9 (1.9)	5.2 (2.4)	2.4 (1.0)
	Active listening	142 (53)	366 (139)	774 (133)	0.88 (0.20)	46 (23)	1.8 (0.9)	4.6 (2.3)	3.3 (3.1)

Supplementary Table VII – performance recalling number of "rare" sounds on fifth condition

Group	Proportion of subjects answering correctly ("20 Odd sounds")	Median answer (IQR 25-75)
HC	13/23	20 (19-20)
FCD	12/18	20 (20-20)