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Cognitive dysfunction in chronic fatigue syndrome: a review of recent evidence

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ABSTRACT

Cognitive difficulties represent a common and debilitating feature of the enigmatic chronic fatigue syndrome (CFS). These difficulties manifest as self-reported problems with attention, memory, and concentration, and present objectively as slowed information processing speed particularly on complex tasks requiring sustained attention. The mechanisms underlying cognitive dysfunction remain to be established; however alterations in autonomic nervous system activity and cerebral blood flow have been proposed as possibilities. Heterogeneity in the experience of cognitive impairment, as well as differences in the methods utilised to quantify dysfunction, may contribute to the difficulties in establishing plausible biological underpinnings. The development of a brief neurocognitive battery specifically tailored to CFS and adoption by the international research community would be beneficial in establishing a profile of cognitive dysfunction. This could also provide better insights into the underlying biological mechanisms of cognitive dysfunction in CFS, and enhance the development of targeted treatments.

Introduction

Chronic fatigue syndrome (CFS) is a complex condition characterised by six or more consecutive months of medically-unexplainable fatigue which causes functional impairment. This debilitating fatigue is accompanied by a range of constitutional and neuropsychiatric symptoms, including neurocognitive difficulties, irritable and depressed mood, muscle and joint pain, headaches, poor sleep quality, and post-exertional malaise [1]. In the absence of curative treatments, best-practice interventions combining cognitive-behavioural therapy (CBT) with graded exercise therapy (GET) offer moderately effective symptom management with documented improvements in functional capacity [2-5]. The underlying aetiology and pathophysiology of this enigmatic condition remain unclear, despite concentrated research efforts internationally [6].

Heterogeneity in the manifestation of symptoms is commonly observed in studies of CFS [7-11]; yet self-reported cognitive dysfunction in the form of impaired attention, difficulties concentrating, and poor memory, are almost universally endorsed by patients [12-14]. Due to the strong link with occupational and social impairment, cognitive dysfunction represents one of the more disabling symptoms for individuals with CFS [15-17]. As such, an understanding of the nature of cognitive dysfunction in CFS, as well the biological underpinnings remain critical to guiding future research and the development of effective targeted treatments. The purpose of this narrative review is to provide an update on the most recent studies appearing in the literature over the last four years that examine aspects of cognitive dysfunction in individuals with CFS.

Search Strategy

MEDLINE, EMBASE, Web of Science, and PsychInfo databases were searched for articles published or available in press between January 2012 and January 2016 that contained the term ‘chronic fatigue syndrome’ and included at least one of the following terms: cognition, cognitive, neuropsychological tests, neurocognitive, or neuropsychology. A title-abstract review was conducted by the first author (EC) and cross-referenced by the second author (RCB) to identify reports of original research, published in English, which focused on aspects of cognitive dysfunction in adults with CFS diagnosed according to recognised criteria. Relevant studies that involved individuals with a comorbid diagnosis of fibromyalgia (CFS/FM) [18], myalgic encephalomyelitis (CFS/ME) [19], or postural orthostatic tachycardia syndrome (CFS/POTS) were also included. For coverage of papers published

prior to the period included in this review, the reader is referred to the following reviews [20-24].

In the specified period, and after the removal of review, hypotheses, protocol, and opinion articles, a total of 26 manuscripts that met the inclusionary criteria were identified (Table 1). The majority of studies used the 1994 Centers for Disease Control and Prevention (CDC) criteria for CFS [1]. After accounting for the repeated use of study cohorts across publications, the average sample size for cross-sectional studies was 76 (mean age = 44 ± 12 years), whereas case-control studies averaged 23 participants with CFS (mean age = 37 ± 11 years). A wide range of subjective and objective measures were used to quantify cognitive dysfunction, with minimal overlap across research groups, as shown in Table 1.

[Insert Table 1 about here]

Subjective cognitive difficulties reported by patients with CFS

Given their role in the diagnosis of CFS and high frequency of reporting in clinical practice [1, 25], it is not surprising that self-reported cognitive difficulties in CFS have been consistently described in recent studies (albeit using different measures, see Table 1). In one cohort of participants with CFS, difficulties concentrating were endorsed by 82%, and memory problems by 62% of patients, in contrast to no endorsement of such symptoms by healthy individuals matched for age, sex, education, and estimated premorbid intelligence [26, 27]. This was consistent with findings from separate cohorts of individuals with CFS and CFS/FM who described more memory problems, poorer attention, and greater information processing difficulties compared to both healthy controls [27-31] and individuals with multiple sclerosis [31]. Subjectively reported difficulties in more specific cognitive domains, such as visuo-perceptual ability, verbal and visuospatial memory, and language have also been reported by individuals with CFS and CFS/FM [29-31]. Furthermore, in the absence of any form of intervention, the severity of these self-reported impairments appeared to remain stable over an 18-month period [29].

Correlates of subjective cognitive complaints

Negative emotional symptoms are commonly endorsed by individuals with CFS, and are frequently associated with self-reported cognitive difficulties. Symptoms of depression have been found to be related to subjective complaints of memory and attention problems [27], and along with increased anxiety and female sex, can predict self-reported cognitive failures (i.e.,

common everyday mistakes, like forgetting appointments or not listening when being spoken to) [32]. Similarly, cognitive failures and retrospective (but not prospective) memory have been associated with ratings of fatigue, depression, and self-efficacy in individuals with CFS [33]. Self-reported physical symptoms, such as the experience of pain, have been positively associated with visuo-perceptual difficulties (e.g., difficulties gauging distances or following visual diagrams) in participants with CFS, and with verbal memory both in participants with CFS and CFS/FM [29]. Better physical functioning in participants with CFS was associated with less visuo-perceptual difficulty, whereas fewer language processing complaints were associated with better physical functioning in participants with CFS/FM [29]. Collectively these findings suggest that subjective perceptions of cognitive difficulties in CFS are influenced by a number of factors related to physical and mental health, with poorer health status being associated with greater subjective cognitive complaints.

There is also evidence to suggest that cognitive complaints are associated with inflammatory processes in brain regions critical to the regulation of cognitive and emotional processes. A positive relationship between self-reported cognitive difficulties and neuroinflammation (inferred from the density of a translocator protein expressed by activated microglia and astrocytes) of brain regions associated with arousal, awareness states, and attention modulation has been documented in a small preliminary study utilising positron emission tomography (PET) in participants with CFS/ME [28]. Neuroinflammation of the left thalamic intralaminar nucleus, amygdala, and midbrain were found to positively correlate with a subjective cognitive impairment score in participants with CFS/ME. Although no objective measure of cognitive performance was employed, the tentative findings of this study highlight the possibility of uncovering a biological mechanism underpinning the cognitive difficulties frequently experienced by individuals with CFS, which would have important implications for the development of targeted treatments.

Objective cognitive dysfunction in patients with CFS

It has been well established that individuals with CFS demonstrate some degree of cognitive dysfunction as assessed by objective task performance. The outcome of a recent meta-analysis identified that cognitive disturbances in CFS manifest as slowed response speeds relative to matched healthy individuals on simple and complex information processing tasks, and on tasks requiring sustained attention, whereas global functioning, reasoning, language, and fine motor speed appear unimpaired [20]. The body of work covered in this review have largely reported comparable findings across studies which are consistent with this outcome.

On tasks requiring speeded button-press responses to the presentation of simple visual stimuli appearing at variable intervals, participants with CFS tended to take longer to respond than healthy individuals [26, 30, 31, 34-36]. However, one study found this only to be the case for participants with CFS that also fulfilled diagnostic criteria for depression [37]. A greater number of lapses in attention (i.e., missing the presentation of a target resulting in no response being made) were also reported in some studies [30, 31, 34]. Importantly, the outcome from assessment of fine motor functioning via finger tapping tasks revealed no difference between participants with CFS and healthy individuals [26, 38], suggesting that delayed response speed is not simply due to slowing of motor function.

When the cognitive load associated with such time-critical tasks is increased by introducing choice responses [26], or requiring more complex information processing in the form of digit-symbol substitutions [38, 39] or cancellation of specific targets within item arrays [38], the response speed of participants with CFS was again slowed compared to healthy individuals. Similarly, the assessment of executive functioning using variants of the Stroop task (traditionally a colour and word naming task requiring inhibition of pre-potent reading responses [40]) has consistently identified slowed response speeds in participants with CFS [30, 31, 34, 39] and those with CFS and comorbid FM [35, 36] relative to healthy controls. One study reported that the magnitude of the Stroop interference effect did not differ amongst individuals with or without CFS [26], indicating a consistent slowing of response speed across task conditions. Slowed response times during executive functioning have also been demonstrated using other tasks (i.e., Attention Network Test [41]) requiring complex information processing and inhibition [37, 42].

Despite responses slowing, comparable performance accuracy on tasks requiring information processing has consistently been found between participants with CFS and healthy individuals [26, 30, 31, 34-39, 42]. Evidence from imaging studies suggests that greater neural engagement of sub-cortical and cortical areas during cognitive task completion is required in CFS to maintain performance accuracy [43, 44]. Differential patterns of neural activation with increased task demands [45], and altered functional connectivity between brain regions involved in cognitive functioning [46], have also been documented in patients with CFS, which may lead to less efficient cognitive processes compared to healthy individuals [47]. This reduced neural efficiency has been proposed as a plausible biological mechanism underlying the documented post-exertional exacerbation of fatigue experienced by patients with CFS after engaging in cognitively demanding laboratory-based [48] and simulated real-world (i.e., driving) tasks [49].

The assessment of more specific cognitive domains, including working memory [26, 30, 34-36, 39, 50], verbal ability [26, 51], and logical thinking [26, 50, 51] has yielded similar levels of performance for both healthy individuals and participants with CFS.

Correlates of objective cognitive performance

Investigations into the correlates of objectively assessed cognitive performance in participants with CFS have generated inconsistent findings. Fatigue was not found to be linked to cognitive performance (i.e., response speed or accuracy) in a number of studies [26, 39, 42]; yet was associated with an increased number of attentional lapses when using a state-based (but not a trait-based) questionnaire in one study [30], and emerged as a significant predictor of executive functioning impairment in another sample of female participants with CFS [52]. Similarly, depression and anxiety were not significantly correlated with information processing speed or accuracy in several studies [26, 39, 42]. However, anxiety and depression predicted verbal memory dysfunction in a sample of female participants with CFS [52], and depression (along with napping, particularly in the afternoon) predicted task-switching performance in a relatively large sample of participants with CFS [32]. Mixed findings regarding an association of cognitive performance with pain have also been documented. In one cohort of female participants with CFS, Ickmans and colleagues [30] found no correlation between self-rated pain severity and cognitive performance; yet in a subsequent study, significant associations between pain and psychomotor response speed were uncovered in a predominantly female sample of participants with CFS [36]. Working memory capacity could also be predicted from conditioned pain modulation for participants with CFS/FM [36].

The potential role of autonomic nervous system (ANS) functioning in CFS symptomatology is receiving increased attention [53, 54], and has been linked to cognitive performance outcomes. Heart rate variability (HRV; the small variations in beat-to-beat intervals of the heart) was linked in one study with spatial working memory and information processing speed [39]. Higher HRV during rest, reflecting a more flexible autonomic system that is better able to adapt and respond to stressors, was found to be predictive of better cognitive performance.

Orthostatic intolerance (characterised by tachycardia, dizziness, and visual disturbances when in an upright position) frequently accompanies CFS in the form of POTS [13]. Individuals with CFS/POTS perform poorer on a working memory task during orthostatic challenge than healthy individuals [55-57]. The potential role for alterations in

cerebral blood flow (CBF) underlying this dysfunction have been explored generating mixed findings. Using transcranial Doppler sonography, no difference in CBF velocity (CBFv) was observed between participants with CFS/POTS and healthy individuals [56], nor was CBFv activation (typically linked closely to cognitive neuronal activity) related to objective cognitive performance in CFS/POTS [55]. However, a more recent study observed a greater reduction of CBFv in CFS/POTS than healthy individuals during orthostatic challenge; an effect mitigated by the administration of phenylephrine (resulting in increased blood pressure) which subsequently benefited working memory performance [57]. Although interesting, the role of CBF alterations in objective cognitive performance in CFS remains unclear.

The possible link between cardiovascular and muscular deconditioning and cognitive dysfunction in CFS has also been examined. In a cohort of females with CFS, lower peak heart rate and peak oxygen uptake (as assessed during a cycle ergometer exercise task) were associated with slowed psychomotor response speeds [34]. This finding, along with the observed positive associations between maximal handgrip strength and working memory [34], and the correlation between upper limb muscle function recovery after a fatiguing physical task with information processing speed and sustained attention [35], suggest that better physical health may lead to improved cognitive outcomes in CFS. Indeed, the notion that improved physical fitness can have positive effects on cognitive functioning is consistent with the documented efficacy of exercise-based therapies, such as GET, for improving the daily functioning of individuals suffering from CFS [58].

Relationship between subjective complaints and objective performance

The body of literature indicates that subjective perceptions and objective indices of cognitive performance do not always correspond well both in healthy and patient populations, including individuals with CFS [59-61]. For example, individuals may report experiencing memory problems, however show no objective dysfunction when performing laboratory-based memory tasks. Two recent studies examining the relationship between subjective complaints and objective performance generated mixed results. In a female-only cohort, Ickmans and colleagues [30] observed positive correlations between self-reported concentration difficulties, and information processing speed and number of lapses in sustained attention for participants in CFS, but not healthy participants. In contrast, Cockshell and Mathias [27] found no significant association between subjective reports of impaired

memory, attention, and concentration, with any objective cognitive performance measure in both healthy individuals and participants with CFS.

Discrepancy in reported outcomes may stem from differences in the measures used to index subjective complaints and cognitive performance. Additionally, other more general reasons for such divergence require consideration. Some tasks that are utilised may be better suited for detecting more pronounced cognitive deficits (such as those associated with traumatic brain injury or dementia) rather than the subtle dysfunction associated with CFS [25]. Alternatively, traditional laboratory-based cognitive tasks may poorly reflect real-world cognitive processes that individuals with CFS experience difficulties with on a day-to-day basis. The use of tasks more sensitive to subtle cognitive difficulties, and that better simulate real-world situations relevant to individuals with CFS (e.g., driving [49]), should be further explored. Beyond methodological concerns, the mismatch between perceived problems and objective cognitive performance may also arise due to other factors known to influence the appraisal of one's own cognitive ability, such as personality, cognitive style, general physical and mental health, and premorbid cognitive capacity.

The role of underperformance in CFS

The notion that cognitive dysfunction observed in some participants with CFS may be due to suboptimal effort has recently been explored in two studies. Using a test that identifies patterns of suboptimal effort and distinguishes intentional and unintentional poor performance on problem solving and verbal ability tasks (which are not typically impaired in CFS), participants with CFS achieved comparable scores to matched healthy individuals on verbal and nonverbal task elements [51]. Furthermore, no participant performed in a manner consistent with an intention to perform poorly [51]. In contrast, when a memory-based test of underperformance was utilised, 16% of participants with CFS achieved scores determined to be indicative of suboptimal effort [62]. Individuals labelled as underperformers also demonstrated poorer performance on simple and choice response speed and complex information processing. However, this study has been criticised for a possible confounding of applied effort by actual ability to perform the working memory task [63]. Regardless, it seems unlikely that poor effort can adequately account for impaired cognitive test performance in this patient group.

Heterogeneity in the manifestation of cognitive symptoms in CFS

Many of the disparate findings across studies of cognitive dysfunction in CFS could be driven by heterogeneity in the manifestation of objective impairments. A recent preliminary study compared the cognitive performance of a cohort of female participants with CFS on a comprehensive neurocognitive battery with normative data to quantify the proportion of participants demonstrating impairment (indicated by performance at more than one standard deviation below the normative mean) [52]. Even when using this fairly conservative threshold for impairment, only 50% of the cohort showed impaired attention and motor functioning, and almost 40% had impaired executive functioning and information processing speed. Visual memory impairments were uncovered in 30% of participants, with around 15% showing impairments on verbal memory and problem solving tasks [52]. Although tentative, these findings suggest that there may be subgroups of individuals with CFS who experience similar patterns of cognitive dysfunction. Furthermore, some individuals may not appear cognitively impaired when compared to normative data; yet report experiencing difficulties relative to their own premorbid cognitive capacity. The very well established heterogeneity in symptom manifestation and severity [7-10] clearly highlights the need for a more individualised approach to CFS; in research by utilising appropriately matched control participants, and in clinical practice by way of tailoring treatments that target specific symptoms and impairments experienced by patients.

Improving the neurocognitive performance of individuals with CFS

Despite the common report of cognitive difficulties and established impairments in information processing speed and attention, very few studies to date have examined whether it is possible to improve the cognitive functioning of participants with CFS. A small-scale double-blinded randomised control trial has demonstrated greater improvements in self-reported executive function (in addition to reduced pain and fatigue) of individuals with CFS after six weeks of using lisdexamfetamine dimesylate, a long-acting amphetamine-based psychostimulant medication, compared to placebo [64]. The author posits that the observed improvement may be due to the stimulant properties of the drug centrally modulating dopaminergic and noradrenergic systems in the pre-frontal cortex; however, the exact mechanism of action, including whether this improvement translates to improved objective performance, remains to be established. Improvements in working memory consequent to a behavioural intervention have also been observed in a small non-randomised trial [65]. Individuals with CFS or ME that showed signs of working memory impairment completed an

intensive computerised cognitive training program over a five week period, which resulted in improved working memory and general attention back to average normative levels. This raises the possibility that cognitive remediation may induce neuroplastic changes; however this also awaits investigation in appropriately randomised and controlled studies.

Future research directions

The efficacy of interventions for CFS is almost exclusively determined from self-reported improvements in functional capacity by way of increased physical function and reduced levels of fatigue [5, 66]. However, few studies explore improvements in cognitive functioning, despite high levels of patient endorsement of cognitive difficulties. It is also becoming increasingly evident that at least a subgroup of individuals with CFS experience objective cognitive dysfunction. Yet, beyond indicating the experience of memory, attention, or "thinking" difficulties, a definitive profile of what constitutes "cognitive dysfunction" remains to be established.

Several reasons can be proposed as to why this might be the case. Existing comprehensive neurocognitive test batteries that utilise normative data are time consuming to administer and come at a high financial cost. As such, various tasks (see Table 1) and modified versions have been employed (often in differing combinations) by research groups around the world, making it difficult to compare the resulting cognitive profiles across studies, as well as reliably identify correlates of performance. Additionally, despite efforts to gauge premorbid intelligence (e.g., using standardised vocabulary measures, or years of formal education as a proxy), the cognitive capability of an individual prior to the onset of CFS are unlikely to be accurately estimated, further contributing to the difficulty in defining the magnitude of dysfunction. The development and adoption of a brief repeatable neurocognitive battery specifically targeting key cognitive domains of interest for individuals with CFS, which can be standardised and made freely accessible, would indeed be a beneficial focus for future research. Similar proposals have previously been made [25, 67], but are yet to be embraced by the broader CFS research community. Such a battery could be employed as part of routine clinical practice to provide a sensitive and valid measure of cognitive dysfunction, as well as assist in evaluating the efficacy of new treatments as they become available.

Conclusion

In line with the outcome of previous reviews and meta-analyses, a review of the most recent evidence indicates that individuals with CFS experience impairments in cognitive functioning, as measured by both subjective complaints, and objective impairment on laboratory-based tasks. Difficulties with memory, attention and concentration, in addition to problems in higher-order cognitive domains such as verbal and visuospatial memory and language processing are often self-reported by individuals with CFS; however, objective task performance indicates a more global, non-specific deficit, with impairments consistent with generalised slowing of response speed on tasks requiring simple and complex information processing and sustained attention. Performance on logical thinking, spatial working memory, and verbal and non-verbal reasoning tasks appears to be comparable to that of healthy individuals. However, the mechanisms underlying both subjective and objective cognitive dysfunction in CFS have yet to be established. Further studies are required to elucidate plausible biological underpinnings of cognitive dysfunction in CFS.

Inconsistencies between subjectively reported and objectively observed cognitive dysfunction, and more general disparate findings across studies, may reflect heterogeneity in the experience of cognitive dysfunction among individuals with CFS, as well as individual differences in symptom severity and comorbidities. However, they may also come about due to methodological inconsistencies, the utilisation of cognitive tasks that are not sensitive enough to detect the subtle difficulties experienced by individuals with CFS, or from relying on laboratory-based tasks that poorly reflect real-wold cognitive processes. The development of a brief and repeatable neurocognitive battery specifically tailored and standardised for individuals with CFS is recommended, which can be employed both in routine clinical practice and as a research and evaluation tool. Widespread adoption of such a battery by the broader CFS research community would lead to an improved understanding of the nature of cognitive dysfunction in CFS, and guide future research exploring the development and efficacy of targeted treatments aimed at ameliorating disability associated with this enigmatic condition.

Compliance with Ethics Guidelines

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Conflict of Interest

All authors declare no conflict of interest.

Human and Animal Rights and Informed Consent

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References

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

[1] Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A, et al. The Chronic Fatigue Syndrome: A Comprehensive Approach to Its Definition and Study. Ann Intern Med. 1994;121:953-9.

[2] White PD, Chalder T, Sharpe M. The planning, implementation and publication of a complex intervention trial for chronic fatigue syndrome: the PACE trial. BJPsych Bulletin. 2015;39(1):24-7. doi:10.1192/pb.bp.113.045005.

[3] White PD, Goldsmith K, Johnson AL, Chalder T, Sharpe M, PACE Trial Management Group. Recovery from chronic fatigue syndrome after treatments given in the PACE trial. Psychol Med. 2013;43(10):2227-35. doi:10.1017/S0033291713000020.

[4] White PD, Goldsmith KA, Johnson AL, Potts L, Walwyn R, DeCesare JC, et al. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. Lancet. 2011;377(9768):823-36. doi:10.1016/S0140-6736(11)60096-2.

[5] Castell BD, Kazantzis N, Moss-Morris RE. Cognitive Behavioral Therapy and Graded Exercise for Chronic Fatigue Syndrome: A Meta-Analysis. Clin Psych: Sci Practice. 2011;18(4):311-24. doi:10.1111/j.1468-2850.2011.01262.x.

[6] Lloyd AR, van der Meer JWM. The long wait for a breakthrough in chronic fatigue syndrome. BMJ. 2015;350. doi:10.1136/bmj.h2087.

[7] Aslakson E, Vollmer-Conna U, Reeves WC, White PD. Replication of an empirical approach to delineate the heterogeneity of chronic unexplained fatigue. Popul Health Met. 2009;7(17):1-10. doi:10.1186/1478-7954-7-17.

[8] Aslakson E, Vollmer-Conna U, White PD. The validity of an empirical delineation of heterogeneity in chronic unexplained fatigue. Pharmacogenomics. 2006;7(3):365-73. doi:10.2217/14622416.7.3.365.

[9] Cella M, Chalder T, White PD. Does the Heterogeneity of Chronic Fatigue Syndrome Moderate the Response to Cognitive Behaviour Therapy? An Exploratory Study. Psychother Psychosom. 2011;80(6):353-8.

[10] Vollmer-Conna U, Aslakson E, White PD. An empirical delineation of the heterogeneity of chronic unexplained fatigue in women. Pharmacogenomics. 2006;7(3):355-64. doi:10.2217/14622416.7.3.355.

[11] Wilson A, Hickie I, Hadzi-Pavlovic D, Wakefield D, Parker G, Straus SE, et al. What is chronic fatigue syndrome? Heterogeneity within an international multicentre study. Aust N Z J Psychiatry. 2001;35(4):520-7. doi:10.1046/j.1440-1614.2001.00888.x.

[12] Komaroff A. *Clinical presentation of chronic fatigue syndrome*, in G.W.J. Bock (ed), *Chronic Fatigue Syndrome*. 1993, Ciba Foundation Symposium: Hoboken, New Jersey. p. 43–61.

[13] Ocon AJ. Caught in the thickness of brain fog: exploring the cognitive symptoms of Chronic Fatigue Syndrome. Frontiers in Physiology. 2013;4. doi:10.3389/fphys.2013.00063.
[14] Holgate ST, Komaroff AL, Mangan D, Wessely S. Chronic fatigue syndrome: understanding a complex illness. Nat Rev Neurosci. 2011;12(9):539-44.
[15] Christodoulou C, DeLuca J, Lange G, Johnson SK, Sisto SA, Korn L, et al. Relation between neuropsychological impairment and functional disability in patients with chronic fatigue syndrome. J Neurol Neurosurg Psychiatry. 1998;64(4):431-4. doi:10.1136/jnnp.64.4.431.
[16] Jason LA, Richman JA, Rademaker AW, Jordan KM, Plioplys AV, Taylor RR, et al. A community-based study of chronic fatigue syndrome. Arch Intern Med. 1999;159(18):2129-37. doi:10.1001/archinte.159.18.2129.
[17] Jason LA, Shanks LL, Evans M, Brown A. Cognitive Impairments Associated with CFS and POTS. Frontiers in Physiology. 2013;4. doi:10.3389/fphys.2013.00113.
[18] Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The american college of rheumatology 1990 criteria for the classification of fibromyalgia. Arthritis Rheum. 1990;33(2):160-72. doi:10.1002/art.1780330203.
[19] Carruthers BM, van de Sande MI, De Meirleir KL, Klimas NG, Broderick G, Mitchell T, et al. Myalgic encephalomyelitis: International Consensus Criteria. J Intern Med. 2011;270(4):327-38. doi:10.1111/j.1365-2796.2011.02428.x.
[20] Cockshell SJ, Mathias JL. Cognitive functioning in chronic fatigue syndrome: A meta-analysis. Psychol Med. 2010;40:1253-67. doi:10.1017/S0033291709992054.
[21] Michiels V, Clydts R. Neuropsychological functioning in chronic fatigue syndrome: A review. Acta Psychiatr Scand. 2001;103(2):84-93. doi:10.1034/j.1600-0447.2001.00017.x.
[22] Christley Y, Duffy T, Everall I, Martin C. The Neuropsychiatric and Neuropsychological Features of Chronic Fatigue Syndrome: Revisiting the Enigma. Curr Psychiatry Rep. 2013;15(4):1-9. doi:10.1007/s11920-013-0353-8.
[23] Glass JM. Cognitive dysfunction in fibromyalgia and chronic fatigue syndrome: New trends and future directions. Current Rheumatology Reports. 2006;8(6):425-9. doi:10.1007/s11926-006-0036-0.
[24] Moss-Morris R, Petrie KJ, Large RG, Kydd RR. Neuropsychological deficits in chronic fatigue syndrome: artifact or reality? Journal of Neurology, Neurosurgery, and Psychiatry. 1996;60(5):474-7.
[25] Reeves WC, Lloyd A, Vernon SD, Klimas N, Jason LA, Bleijenberg G, et al. Identification of ambiguities in the 1994 chronic fatigue syndrome research case definition and recommendations for resolution. BMC Health Services Research. 2003;3(1):1-9. doi:10.1186/1472-6963-3-25.
[26] Cockshell SJ, Mathias JL. Cognitive deficits in Chronic Fatigue Syndrome and their relationship to psychological status, symptomatology, and everyday functioning. Neuropsychology. 2013;27(2):230-42. doi:10.1037/a0032084.
[27●] Cockshell SJ, Mathias JL. Cognitive functioning in people with chronic fatigue syndrome: A comparison between subjective and objective measures. Neuropsychology. 2014;28(3):394-405. doi:10.1037/neu0000025. *This study provides convincing evidence of a disconnect between subjective perceptions and objective cognitive performance, that is not specific to individuals with chronic fatigue syndrome.*
[28●●] Nakatomi Y, Mizuno K, Ishii A, Wada Y, Tanaka M, Tazawa S, et al. Neuroinflammation in Patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: An ^{11}C-(*R*)-PK11195 PET Study. J Nucl Med. 2014;55(6):945-50. doi:10.2967/jnumed.113.131045. *Provide preliminary evidence of an association between positron emission tomography-derived neuroinflammation and self-reported cognitive difficulties in chronic fatigue syndrome.*

[29] Schmaling K, Betterton K. Neurocognitive complaints and functional status among patients with chronic fatigue syndrome and fibromyalgia. Qual Life Res. 2015:1-7. doi:10.1007/s11136-015-1160-y.
[30] Ickmans K, Meeus M, Kos D, Clarys P, Meersdom G, Lambrecht L, et al. Cognitive performance is of clinical importance, but is unrelated to pain severity in women with chronic fatigue syndrome. Clin Rheumatol. 2013;32(10):1475-85. doi:10.1007/s10067-013-2308-1.
[31] Meeus M, Ickmans K, Struyf F, Kos D, Lambrecht L, Willekens B, et al. What is in a name? Comparing diagnostic criteria for chronic fatigue syndrome with or without fibromyalgia. Clin Rheumatol. 2014:1-13. doi:10.1007/s10067-014-2793-x.
[32] Gotts ZM, Ellis JG, Deary V, Barclay N, Newton JL. The Association between Daytime Napping and Cognitive Functioning in Chronic Fatigue Syndrome. PLoS One. 2015;10(1):e0117136. doi:10.1371/journal.pone.0117136.
[33] Attree EA, Arroll MA, Dancey CP, Griffith C, Bansal AS. Psychosocial factors involved in memory and cognitive failures in people with myalgic encephalomyelitis/chronic fatigue syndrome. Psychology Research and Behavior Management. 2014;7:67-76. doi:10.2147/prbm.s50645.
[34] Ickmans K, Clarys P, Nijs J, Meeus M, Aerenhouts D, Zinzen E, et al. Association between cognitive performance, physical fitness, and physical activity level in women with chronic fatigue syndrome. J Rehabil Res Dev. 2013;50(6):795-810. doi:10.1682/JRRD.2012.08.0156.
[35] Ickmans K, Meeus M, De Kooning M, Lambrecht L, Pattyn N, Nijs J. Can Recovery of Peripheral Muscle Function Predict Cognitive Task Performance in Chronic Fatigue Syndrome With and Without Fibromyalgia? Phys Ther. 2014;94(4):511-22. doi:10.2522/ptj.20130367.
[36] Ickmans K, Meeus M, De Kooning M, Lambrecht LJ, Pattyn N, Nijs J. Associations Between Cognitive Performance and Pain in Chronic Fatigue Syndrome: Comorbidity with Fibromyalgia Does Matter. Pain Physician. 2015;18(5):E841-E52.
[37] Togo F, Lange G, Natelson BH, Quigley KS. Attention network test: Assessment of cognitive function in chronic fatigue syndrome. Journal of Neuropsychology. 2015;9(1):1-9. doi:10.1111/jnp.12030.
[38] Neu D, Mairesse O, Montana X, Gilson M, Corazza F, Lefevre N, et al. Dimensions of pure chronic fatigue: psychophysical, cognitive and biological correlates in the chronic fatigue syndrome. European Journal of Applied Physiology. 2014;114(9):1841-51. doi:10.1007/s00421-014-2910-1.
[39●] Beaumont A, Burton AR, Lemon J, Bennett BK, Lloyd A, Vollmer-Conna U. Reduced cardiac vagal modulation impacts on cognitive performance in chronic fatigue syndrome. PLoS One. 2012;7(11):e49518. doi:10.1371/journal.pone.0049518. *First study to demonstrate an association between resting heart variabiltiy and objective measures of cognitive performance in participants with chronic fatigue syndrome.*
[40] Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol. 1935;18:643-62.
[41] Fan J, McCandliss BD, Sommer T, Raz A, Posner MI. Testing the Efficiency and Independence of Attentional Networks. J Cogn Neurosci. 2002;14(3):340-7. doi:10.1162/089892902317361886.
[42] Hou R, Moss-Morris R, Risdale A, Lynch J, Jeevaratnam P, Bradley BP, et al. Attention processes in chronic fatigue syndrome: Attentional bias for health-related threat and the role of attentional control. Behav Res Ther. 2014;52:9-16. doi:10.1016/j.brat.2013.10.005.
[43] Cook DB, O'Connor PJ, Lange G, Steffener J. Functional neuroimaging correlates of mental fatigue induced by cognition among chronic fatigue syndrome patients and controls. Neuroimage. 2007;36(1):108-22. doi:10.1016/j.neuroimage.2007.02.033.

[44] Lange G, Steffener J, Cook DB, Bly BM, Christodoulou C, Liu WC, et al. Objective evidence of cognitive complaints in Chronic Fatigue Syndrome: A BOLD fMRI study of verbal working memory. Neuroimage. 2005;26(2):513-24. doi:10.1016/j.neuroimage.2005.02.011.

[45] Caseras X, Mataix-Cols D, Giampietro V, Rimes KA, Brammer M, Zelaya F, et al. Probing the Working Memory System in Chronic Fatigue Syndrome: A Functional Magnetic Resonance Imaging Study Using the n-Back Task. Psychosom Med. 2006;68(6):947-55. doi:10.1097/01.psy.0000242770.50979.5f.

[46●] Boissoneault J, Letzen J, Lai S, O'Shea A, Craggs J, Robinson M, et al. Abnormal resting state functional connectivity in patients with chronic fatigue syndrome: An arterial spin-labeling fMRI study. Magn Reson Imaging. in press. doi:10.1016/j.mri.2015.12.008.*Utilise novel neuroimaging techniques to explore abnormalities in resting state functional connectivity in chronic fatigue syndrome.*

[47] Mizuno K, Tanaka M, Tanabe HC, Joudoi T, Kawatani J, Shigihara Y, et al. Less efficient and costly processes of frontal cortex in childhood chronic fatigue syndrome. NeuroImage: Clinical. 2015;9:355-68. doi:10.1016/j.nicl.2015.09.001.

[48] Arroll MA, Attree EA, O'Leary JM, Dancey CP. The delayed fatigue effect in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Fatigue: Biomedicine, Health & Behavior. 2014;2(2):57-63. doi:10.1080/21641846.2014.892755.

[49] Keech A, Sandler CX, Vollmer-Conna U, Cvejic E, Lloyd AR, Barry BK. Capturing the post-exertional exacerbation of fatigue following physical and cognitive challenge in patients with chronic fatigue syndrome. J Psychosom Res. 2015;79(6):537-49. doi:10.1016/j.jpsychores.2015.08.008.

[50] Yamamoto S, Ouchi Y, Nakatsuka D, Tahara T, Mizuno K, Tajima S, et al. Reduction of [^{11}C](+)3-MPB Binding in Brain of Chronic Fatigue Syndrome with Serum Autoantibody against Muscarinic Cholinergic Receptor. PLoS One. 2012;7(12):e51515. doi:10.1371/journal.pone.0051515.

[51●] Cockshell SJ, Mathias JL. Test effort in persons with Chronic Fatigue Syndrome when assessed using the Validity Indicator Profile. J Clin Exp Neuropsychol. 2012;34(7):679-87. doi:10.1080/13803395.2012.668176. *Provide good evidence that poor test effort unlikely accounts for the neurocognitive dysfunction in chronic fatigue syndrome.*

[52] Santamarina-Perez P, Eiroa-Orosa FJ, Rodriguez-Urrutia A, Qureshi A, Alegre J. Neuropsychological Impairment in Female Patients with Chronic Fatigue Syndrome: A Preliminary Study. Applied Neuropsychology: Adult. 2013:1-8. doi:10.1080/09084282.2013.771264.

[53] Van Cauwenbergh D, Nijs J, Kos D, Van Weijnen L, Struyf F, Meeus M. Malfunctioning of the autonomic nervous system in patients with chronic fatigue syndrome: a systematic literature review. Eur J Clin Invest. 2014;44(5):516-26. doi:10.1111/eci.12256.

[54] Meeus M, Goubert D, De Backer F, Struyf F, Hermans L, Coppieters I, et al. Heart rate variability in patients with fibromyalgia and patients with chronic fatigue syndrome: A systematic review. Semin Arthritis Rheum. 2013;43(2):279-87. doi:10.1016/j.semarthrit.2013.03.004.

[55] Stewart JM, Medow MS, Messer ZR, Baugham IL, Terilli C, Ocon AJ. Postural neurocognitive and neuronal activated cerebral blood flow deficits in young chronic fatigue syndrome patients with postural tachycardia syndrome. American Journal of Physiology - Heart and Circulatory Physiology. 2012;302(5):H1185-H94. doi:10.1152/ajpheart.00994.2011.

[56] Ocon AJ, Messer ZR, Medow MS, Stewart JM. Increasing orthostatic stress impairs neurocognitive functioning in chronic fatigue syndrome with postural tachycardia syndrome. Clin Sci. 2012;122(5):227-38. doi:10.1042/cs20110241.
[57] Medow MS, Sood S, Messer Z, Dzogbeta S, Terilli C, Stewart JM. Phenylephrine alteration of cerebral blood flow during orthostasis: effect on n-back performance in chronic fatigue syndrome. J Appl Physiol. 2014;117(10):1157-64. doi:10.1152/japplphysiol.00527.2014.
[58] Larun L, Brurbeg KG, Odgaard-Jensen J, Price JR. Exercise therapy for chronic fatigue syndrome. Cochrane Database of Systematic Reviews. 2015;Issue 2:Art. No.:CD003200. doi:10.1002/14651858.CD003200.pub3.
[59] Wearden A, Appleby L. Cognitive performance and complaints of cognitive impairment in chronic fatigue syndrome (CFS). Psychol Med. 1997;27(1):81-90. doi:10.1017/S0033291796004035.
[60] Vollmer-Conna U, Wakefield D, Lloyd A, Hickie I, Lemon J, Bird KD, et al. Cognitive deficits in patients suffering from chronic fatigue syndrome, acute infective illness or depression. Br J Psychiatry. 1997;171:377-81. doi:10.1192/bjp.171.4.377.
[61] Ray C, Phillips L, Weir WRC. Quality of attention in chronic fatigue syndrome: Subjective reports of everyday attention and cognitive difficulty, and performance on tasks of focused attention. Br J Clin Psychol. 1993;32(3):357-64. doi:10.1111/j.2044-8260.1993.tb01068.x.
[62] Goedendorp MM, van der Werf SP, Bleijenberg G, Tummers M, Knoop H. Does neuropsychological test performance predict outcome of cognitive behavior therapy for Chronic Fatigue Syndrome and what is the role of underperformance? J Psychosom Res. 2013;75(3):242-8. doi:10.1016/j.jpsychores.2013.07.011.
[63] Twisk FNM. Underperformance of myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS) patients at neurocognitive tests should be assessed objectively without an a priori judgment about the etiology. J Psychosom Res. 2014;76(4):339. doi:10.1016/j.jpsychores.2013.10.016.
[64] Young JL. Use of lisdexamfetamine dimesylate in treatment of executive functioning deficits and chronic fatigue syndrome: A double blind, placebo-controlled study. Psychiatry Res. 2013;207(1–2):127-33. doi:10.1016/j.psychres.2012.09.007.
[65] Maroti D, Westerberg AF, Saury J-M, Bileviciute-Ljungar I. Computerized training improves verbal working memory in patients with myalgic encephalomyelitis/chronic fatigue syndrome: A pilot study. Journal of Rehabilitation Medicine. 2015;47(7):665-8. doi:10.2340/16501977-1976.
[66] Adamowicz J, Caikauskaite I, Friedberg F. Defining recovery in chronic fatigue syndrome: a critical review. Qual Life Res. 2014;23(9):2407-16. doi:10.1007/s11136-014-0705-9.
[67] DiPino RK, Kane RL. Neurocognitive functioning in chronic fatigue syndrome. Neuropsychol Rev. 1996;6(1):47-60. doi:10.1007/bf01875419.

Table 1. Summary of original research articles included in this review, highlighting the relevant measures used to assess cognitive dysfunction. Participant characteristics (sex and mean age) have been provided. Individuals with CFS were diagnosed according to CDC criteria, unless otherwise specified.

Author / Year	Design	Participant characteristics	Relevant cognitive measures
Arroll 2014 [48]	Cross-sectional	32 CFS/ME[a] (23♀; 44±11 years)	Cambridge Neuropsychological Test Automated Battery, Multidimensional Fatigue Inventory
Attree 2014 [33]	Cross-sectional	87 CFS/ME[a] (85♀; 55±10 years)	Prospective and retrospective memory questionnaire, CFQ
Beaumont 2012 [39]	Case-control	30 CFS (20♀; 36±12 years) 40 HC (24♀; 35±12 years)	SDMT, SWM, Stroop
Cockshell 2012 [51]	Case-control	54 CFS (42♀; 43±12 years) 54 HC (42♀; 43±12 years)	Validity Indicator Profile
Cockshell 2013 [26]	Case-control	50 CFS (39♀; 42±12 years) 50 HC (40♀; 42±12 years)	Simple RT, Choice RT, Stroop, PASAT, CVLT-II, ROCFT, FTT, verbal fluency, CFS Symptom Inventory, CIS
Cockshell 2014 [27]	Case-control	50 CFS (39♀; 42±12 years) 50 HC (40♀; 42±12 years)	Stroop, PASAT, CVLT-II, ROCFT, Memory and attention symptom severity, CFQ, EAQ
Goedendorp 2013 [62]	Cross-sectional	169 CFS (135♀; 37±10 years)	Simple RT, Choice RT, SDMT, ASTM
Gotts 2015 [32]	Cross-sectional	101 CFS (82♀; 42±13 years)	TMT, CFQ
Hou 2014 [42]	Case-control	27 CFS (18♀; 41±13 years) 35 HC (20♀; 36±15 years)	Visual probe task, Attention Network Test
Ickmans 2013a [34]	Case-control	31 CFS (31♀; 36±8 years) 13 HC (13♀; 29±12 years)	Stroop, PVT, OSPAN
Ickmans 2013b [30]	Case-control	29 CFS (29♀; 35±8 years) 17 HC (17♀; 36±9 years)	Stroop, PVT, OSPAN, CIS
Ickmans 2014 [35]	Case-control	18 CFS (17♀; 41±13 years) 30 CFS/FM (29♀; 40±11 years) 30 HC (25♀; 37±15 years)	Stroop, PVT, OSPAN
Ickmans 2015 [36]	Case-control	18 CFS (17♀; 41±13 years) 30 CFS/FM (29♀; 40±11 years) 30 HC (25♀; 37±15 years)	Stroop, PVT, OSPAN
Keech 2015 [49]	Case-control	11 CFS (4♀; 37±9 years) 11 HC (4♀; 35±13 years)	Simulated driving
Maroti 2015 [65]	Non-RCT	9 CFS or ME (5♀; 39±9 years)	Digit Span

		12 CFS or ME Controls (10♀; 42±12 years)	
Medow 2014 [57]	Case-control experimental	15 CFS/POTS (7♀; 24±1 years) 11 HC (14♀; 22±1 years)	*n*-back task during upright tilt test
Meeus 2014 [31]	Case-control	48 CFS (46♀; 38±12 years) 19 MS (13♀; 38±15 years) 39 HC (24♀; 42±11 years)	Stroop, PVT, OSPAN, CIS, CFS Symptom Inventory
Nakatomi 2014 [28]	Case-control	9 CFS/ME (6♀; 38±5 years) 10 HC (7♀; 39±6 years)	Cognitive impairment score
Neu 2014 [38]	Case-control	16 CFS (13♀; 35±5 years) 14 HC (10♀; 32±8 years)	Zazzo-Cancellation Task, SDMT, PVT, FTT
Ocon 2012 [56]	Case-control experimental	16 CFS/POTS (21±1 years) 20 HC (23±1 years)	*n*-back task during upright tilt test, WAIS-III, WMS-III
Santamarina-Perez 2013 [52]	Cross-sectional	68 CFS (68♀; 47±8 years)	Mental Control, PASAT, Digit Span, SDMT, TMT, Controlled Oral Word Association Test, Tower of London, Rey Auditory Verbal Learning Test, ROCFT, RT, Grooved Pegboard, WAIS-III
Schmaling 2015 [29]	Cross-sectional longitudinal	50 CFS (37♀; 44±9 years) 43 CFS/FM (41♀; 44±11 years)	Multiple Ability Self-Report Questionnaire
Stewart 2012 [55]	Case-control	25 CFS/POTS (22±1 years) 20 HC (23±1 years)	*n*-back task during upright tilt test
Togo 2015 [37]	Case-control	22 CFS (43±10 years) 19 CFS+MDD (47±8 years) 29 HC (44±8 years)	Simple RT, ANT
Yamamoto 2012 [50]	Case-control	11 CFS (6♀; 35±6 years) 11 HC (5♀; 33±7 years)	Wechsler Card Sorting, TMT, ROCFT, Japanese WMS-R.
Young 2013 [64]	RCT	26 CFS (25♀; 45 years, range: 21-59)	Behavioral Rating Inventory of Executive Function-Adult

[a] CFS/ME diagnosis made by a qualified medical practitioner without specification of the diagnostic criteria; RCT = randomised control trial; CFS = chronic fatigue syndrome; ME = myalgic encephalomyelitis; FM = fibromyalgia; POTS = postural orthostatic tachycardia syndrome; HC = healthy control; MDD = major depressive disorder; ♀ = female; CFQ = Cognitive Failures Questionnaire; SDMT = Symbol Digit Modalities Test; SWM = Spatial Working Memory task; RT = response task; PASAT = Paced Auditory Serial Addition Test; CVLT-II = California Verbal Learning Test; ROCFT = Rey-Osterreith Complex Figure Test; FTT = finger tapping test; CIS = Checklist of Individual Strengths; EAQ = Everyday Attention Questionnaire; ASTM: Amsterdam Short-Term Memory Test; TMT = Trail-Making Test; PVT = Psychomotor Vigilance Test; OSPAN = Operation Span; ZCT = Zazzo-Cancellation Task; WAIS-III = Wechsler Adult Intelligence Scale; WMS = Wechsler Memory Scale.