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REVIEW ARTICLE

Cognitive functioning in chronic fatigue syndrome: a meta-analysis

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Background. Cognitive problems are commonly reported in persons with chronic fatigue syndrome (CFS) and are one of the most disabling symptoms of this condition. A number of cognitive deficits have been identified, although the findings are inconsistent and hindered by methodological differences. The current study therefore conducted a meta-analysis of research examining cognitive functioning in persons with CFS in order to identify the pattern and magnitude of any deficits that are associated with this condition.

Method. A comprehensive search of the PubMed and PsycINFO databases for studies that examined cognitive functioning in CFS between 1988 and 2008 identified 50 eligible studies. Weighted Cohen's *d* effect sizes, 95% confidence intervals and fail-safe *N*s were calculated for each cognitive score.

Results. Evidence of cognitive deficits in persons with CFS was found primarily in the domains of attention, memory and reaction time. Deficits were not apparent on tests of fine motor speed, vocabulary, reasoning and global functioning.

Conclusions. Persons with CFS demonstrate moderate to large impairments in simple and complex information processing speed and in tasks requiring working memory over a sustained period of time.

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Key words: Chronic fatigue syndrome, cognitive, meta-analysis, review.

Introduction

Chronic fatigue syndrome (CFS) is defined by a severe and unexplained fatigue of at least 6 months duration, resulting in a substantial reduction in occupational or leisure activities (Fukuda *et al*. 1994; US Centre for Disease Control). Secondary symptoms include self-reported memory and concentration problems, tender lymph nodes, muscle pain, multi-joint pain, sore throat, headaches, unrefreshing sleep and post-exertional malaise; four or more of which must be present for a diagnosis of CFS. Interestingly, cognitive problems are one of the most frequent and disabling symptoms associated with this disorder (Abbey & Garfinkel, 1991), with 89% of people with CFS reportedly experiencing memory and concentration problems (Jason *et al*. 1999). This raises the question of whether these problems translate to measurable deficits on objective cognitive tests.

Research conducted over the past 20 years has provided some evidence of cognitive deficits in people with CFS (e.g. Grafman *et al*. 1993; Smith *et al*. 1996; DeLuca *et al*. 2004*a*), although the results are inconsistent (e.g. Krupp *et al*. 1994; Short *et al*. 2002). For example, while some studies have reported deficits in complex information-processing speed (e.g. DeLuca *et al*. 1995; Johnson *et al*. 1997; Marshall *et al*. 1997), other studies have not (e.g. Kane *et al*. 1997; Short *et al*. 2002). Contradictory findings have also been noted for tests of verbal memory, with some (e.g. Michiels *et al*. 1998; Tiersky *et al*. 1998; Vercoulen *et al*. 1998), but not all (e.g. Fiedler *et al*. 1996; Lawrie *et al*. 2000) studies finding that CFS is associated with poorer performance. Similar inconsistencies are apparent for other cognitive domains.

Methodological limitations are likely to contribute to some of the variation in findings, along with the suggestion that any deficits are likely to be relatively subtle (Moss-Morris *et al*. 1996; Tiersky *et al*. 1997). One limitation of some early studies is that they failed to use control groups (e.g. Altay *et al*. 1990; McDonald *et al*. 1993; Schmaling *et al*. 1994) and, instead, used normative data that were not well-matched for age, education or IQ (see Tiersky *et al*. 1997). Other studies did not use published CFS criteria, which may impact on sample selection (e.g. Prasher *et al*. 1990; Smith *et al*. 1993; Krupp *et al*. 1994), or used small samples ($n<15$,

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e.g. Scheffers *et al*. 1992; Sargent *et al*. 1997). None of this research reported effect sizes to assess the magnitude of group differences independently of sample size and statistical significance, making it difficult to determine whether non-significant findings were due to poor statistical power. In addition, a wide variety of tests have been used to measure cognitive performance, which, in the absence of effect sizes to standardize test scores, cannot be directly compared. The present study therefore undertook a meta-analysis of research examining the cognitive performance of people with CFS, when compared with healthy controls, in order to determine whether CFS is associated with measurable deficits in cognitive functioning and the nature and magnitude of these deficits.

Method

Identification of studies

The PubMed and PsycINFO databases were searched for 'chronic fatigue syndrome' and alternate terms (chronic fatigue and immune dysfunction syndrome, chronic fatigue disorder, chronic fatigue-fibromyalgia syndrome, chronic infectious mononucleosis-like syndrome, myalgic encephalomyelitis, post viral fatigue syndrome and royal free disease) from January 1988 (when the first operational definition of CFS was published; Holmes *et al*. 1988) to November 2008.

All studies had to meet the following inclusion criteria: (*a*) CFS was diagnosed using Center for Disease Control (CDC) criteria (Fukuda *et al*. 1994) or earlier variants (Holmes *et al*. 1988; Sharpe *et al*. 1991; Schluederberg *et al*. 1992); (*b*) a healthy control group was assessed; (*c*) participants were adults (>16); (*d*) objective cognitive tests were administered (self-report measures were excluded); (*e*) if treatment was provided, cognition must have been assessed prior to treatment; (*f*) the provision of statistics that could be converted into a Cohen's *d* effect size (means and standard deviations; univariate *F* scores; *t* scores); (*g*) the study had been published in a journal; (*h*) it was written in English.

This search identified 4086 articles. The titles and abstracts of these articles were examined against the inclusion criteria. Full-text versions of 158 articles were obtained to establish study eligibility, with the reference lists of these papers yielding a further six articles. Of the 164 full-text articles, 27 were literature reviews or editorials and 137 were research studies; 56 of which met all of the inclusion criteria. Of the 81 research studies that were excluded, the primary reasons for this were that three did not assess a CFS group, 11 did not use the specified diagnostic criteria for CFS, 31 did not include a healthy control group, 22 did not administer cognitive tests, three only evaluated cognitive functioning after treatment, four used the cognitive test as an independent rather than dependent variable and seven did not provide statistics that would enable the calculation of effect sizes. The latter seven studies reported both significant and non-significant findings (three significant, two non-significant and two both significant and non-significant results), reducing the likelihood of any systematic bias resulting from the exclusion of studies with non-significant findings.

Data from different studies must be independent to ensure that any given sample of participants is not over-represented in the calculation of an effect size (Matt & Cook, 1994). Seven studies with the same or overlapping participants were identified (and confirmed by the authors: Johnson *et al*. 1996, 1997, 1998; DeLuca *et al*. 1997*a*, *b*; and DeLuca *et al*. 2004*a*, *b*). These seven studies were therefore treated as three separate studies, reducing to 52 the number of independent studies that were eligible for analysis.

Data preparation

Each test was categorized into one of eight cognitive domains, based on information provided in test compendiums (Lezak *et al*. 2004; Strauss *et al*. 2006) and descriptions provided by the test developer and/or the study authors. The cognitive domains were attention (working memory, attention span), memory, reaction time (RT), motor functioning, visuospatial ability, verbal abilities and language, cognitive reasoning and flexibility and global functioning.

Some of the 52 eligible studies did not report the data necessary to calculate effect sizes for *all* of the tests that they administered ($N_{\text{studies}}=19$). For example, 13 studies did not provide standard deviations or exact *p* values for some of the tests, five did not provide data for non-significant findings and one failed to provide data for a single test. All authors were contacted in order to request the missing data, with only four authors providing the necessary data (Smith *et al*. 1996; Claypoole *et al*. 2001; Moss-Morris & Petrie, 2003; Schmaling *et al*. 2003).

Composite test scores were sometimes calculated to provide comparable scores across studies (e.g. total score for the Paced Auditory Serial Addition Test). A small number of studies provided data for specific CFS subgroups: with and without coexisting psychiatric disorders (DeLuca *et al*. 1997*a*, 2004*a*, *b*; Tiersky *et al*. 2003); pre-morbid and no pre-morbid psychiatric history (Gaudino *et al*. 1997; Tiersky *et al*. 2003); depressed and non-depressed (Wearden & Appleby, 1997); gradual *versus* sudden onset of CFS (DeLuca *et al*. 1997*b*); medicated *versus* medication free (Sargent

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et al. 1997; Michiels *et al*. 1998) and morning *versus* afternoon test administration (Lawrie *et al*. 2000). Unfortunately, there were too few studies to examine the data for these subgroups. The means for these subgroups were therefore averaged (weighting by sample size) and the standard deviations combined (Higgins & Deeks, 2008) to provide a single score for the CFS group.

Effect size calculations and analyses

Cohen's d effect sizes were used in this study to determine whether persons with CFS demonstrated cognitive deficits relative to their healthy peers. This statistic measures the difference between the mean scores of two groups, divided by a pooled standard deviation (Cohen, 1988). If means and standard deviations were not available, standard errors were converted into standard deviations and t values and one-way F statistics were converted to d using the formulas provided by Zakzanis (2001). Effect sizes were calculated in several stages. First, effect sizes were calculated for each test score that was used by an individual study. Next, if a study had more than one score for a test variable (e.g. per minute scores for a RT task), the effect sizes for these scores were averaged so that the study contributed only one effect size for each test variable. Effect sizes were then combined across studies. As small samples are associated with greater variability, which affects the reliability of the effect size (Lipsey & Wilson, 2001), it is recommended that an effect size be weighted by the inverse of its variance (i.e. the inverse of the squared standard error; Hedges, 1982). Thus, a mean weighted effect size d_w was calculated for each test variable by summing the effect size for each study (weighted by its inverse variance) and dividing by the sum of the weights (Lipsey & Wilson, 2001). Additionally, effect sizes were calculated for each cognitive domain (i.e. attention, memory) by averaging the weighted effect sizes (weighted by sample size) of each study for that domain. If a single study provided multiple measures for a domain, a mean weighted effect size for that study was calculated before combining it with the effect sizes from other studies. According to Cohen (1988), a small effect is defined as $d=0.2$, a moderate effect as $d=0.5$ and a large effect as $d=0.8$. A medium effect size of 0.5 indicates that the mean test performance of the two groups differs by half a standard deviation. All effect sizes were calculated in such a way that a positive effect size represented poorer performance by CFS participants.

For the weighted effect sizes 95% confidence intervals (Cls) were additionally calculated (Lipsey & Wilson, 2001), which if they do not span zero indicates a significant difference between the performance of the CFS and healthy control groups. As there is a tendency for journals to publish studies with significant findings (Easterbrook *et al*. 1991), fail-safe N (N_{fs}) statistics were also calculated (Cooper, 1979). This statistic provides a measure of the number of unpublished studies with small effects ($d=0.2$) that would need to be in existence in order to reduce the mean weighted effect size d_w to a small effect (Wolf, 1986). The larger the N_{fs}, the more confidence can be placed in that finding.

Only those effect sizes for tests that were used by two or more studies are reported here because effect sizes that are based on a single study do not provide a reliable measure of group differences (Rosenthal, 1995). This removed the findings of two studies, resulting in a total of 50 studies that underwent analysis.

Data interpretation

Researchers and clinicians would be more confident that CFS has impacted on cognitive functioning if there were moderate to large group differences in the performance of people with CFS compared with healthy controls ($d_w \geqslant 0.5$), the performance of the two groups differed significantly (i.e. 95% CIs do not span zero) and that it was unlikely that unpublished findings would draw the current findings into question (i.e. the number of unpublished studies with non-significant findings is greater than the number of studies already published: $N_{fs} > N_{studies}$). For the purposes of the current meta-analysis, an effect size had to meet all three criteria in order to conclude that cognitive performance is compromised by CFS.

Results

Study and participant characteristics

The 50 studies included in the meta-analysis provided data for 1544 CFS participants and 1487 healthy controls (see Table 1). The majority of participants were female and approaching middle age, with participants ranging from 17 to 79 years of age. There were small and non-significant differences between the CFS and control groups in terms of their age [$t(93)=-0.70$, $p=0.49$; $d=-0.17$] and educational level [$t(64)=1.72$, $p=0.09$; $d=0.42$].

The average duration of CFS was almost 6 years; however, participants in some studies had experienced CFS for up to 48 years. People with CFS experienced significantly greater levels of depression than healthy controls on the Beck Depression Inventory (BDI) [$t(20)=-9.95$, $p<0.01$, $d=4.32$] and the depression subscale of the Hospital Anxiety and Depression Scale (HADS) [$t(14)=-9.83$, $p<0.01$, $d=6.05$]. While the average BDI scores indicate clinical

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Table 1. *Descriptive statistics for the study participants*

	CFS				Healthy controls			
	$N_{studies}$	$N_{participants}$	Mean	S.D.	$N_{studies}$	$N_{participants}$	Mean	S.D.
Sample size	50	1544	30.9	24.0	50	1487	29.7	26.2
Gender								
Female (%)	44	1090	76.7	12.7	41	989	75.9	13.8
Male (%)	44	454	23.3	12.7	41	498	24.1	13.8
Age (years)	48	1509	39.7	5.2	47	1431	38.9	4.8
Education (years)	33	997	14.7	1.0	33	806	15.1	1.0
CFS duration (years)	22	687	5.7	2.2				
Beck Depression Inventory	13	334	13.8	2.1	9	285	3.5	2.7
HADS								
Depression	8	172	7.1	1.3	8	144	2.1	0.7
Anxiety	8	172	7.8	2.5	8	144	5.5	1.0

CFS, Chronic fatigue syndrome; HADS, Hospital Anxiety and Depression Scale.

levels of depression, the use of this measure with CFS patients has been questioned (Farmer *et al*. 1996). In contrast, the mean HADS depression score, which has been validated for use with CFS patients (Morriss & Wearden, 1998; Henderson & Tannock, 2005), was within the normal to borderline range. For the eight studies that reported HADS anxiety scores, the average for the CFS group was also in the normal to borderline range, with moderate and significant differences to that of the healthy controls [$t(14) = -2.43$, $p = 0.03$, $d = 0.51$]. Psychiatric examinations were only undertaken by half of the studies ($N_{studies} = 29$), with 10 studies using them to exclude participants with a co-existing psychiatric disorder. Of the remaining studies that reported their results ($N_{studies} = 10$), approximately one third of their CFS sample had a co-existing psychiatric condition (35%, range 16–50%), which was primarily major depressive disorder or dysthymia (80%) and, to a lesser extent, panic disorder (18%), phobias (14%), anxiety (12%), post-traumatic stress disorder (1%) and obsessive compulsive disorder (1%).

The current CDC diagnostic criteria (Fukuda *et al*. 1994) was most frequently used to diagnose CFS ($N_{studies} = 27$), followed by the first published criteria (Holmes *et al*. 1988, $N_{studies} = 15$) and its various revisions (Sharpe *et al*. 1991, $N_{studies} = 13$; Schluederberg *et al*. 1992, $N_{studies} = 8$). A total of 11 studies used more than one set of diagnostic criteria. Of those studies that reported the methods used to diagnose CFS ($N_{studies} = 33$), only five used the comprehensive approach that is advocated by the CDC, which requires a full patient history, physical examination, laboratory tests to exclude other conditions and a psychiatric examination. Other methods of diagnosis included self-ratings and diagnosis by the participant's doctor.

Medication usage was not commonly reported ($N_{studies} = 14$) and, while CFS participants were not on any medication in six studies, the other eight studies reported that between 10% and 71% of the CFS participants were on some form of medication. Low doses of antidepressants were the most commonly used medication, followed by benzodiazepines, endocrine replacements, hypnotics/anxiolytics, anti-inflammatories and gamma-globulin for the immune system.

Cognitive domains

When effect sizes were calculated for each of the eight cognitive domains (see Fig. 1), it was found that RT and attention were the only two domains to show moderate and significant group differences ($d \geqslant 0.5$, 95% CI $\neq 0$). However, the effect sizes contributing to these, and two other domains, were not homogeneous; hence, these scores should be interpreted with caution: RT [$Q(20) = 58.86$, $p < 0.05$], attention [$Q(44) = 84.15$, $p < 0.05$], motor functioning [$Q(12) = 29.50$, $p < 0.05$] and visuospatial ability [$Q(11) = 26.53$, $p < 0.05$]. For the visuospatial domain, the removal of one outlier created a homogeneous grouping [$Q(10) = 7.71$, $p = 0.66$]. This was not the case for the other three domains. Moreover, an examination of some of the variables that may have influenced these scores found that there were no significant correlations between age and RT ($r = 0.12$, $n = 19$, $p = 0.63$), attention ($r = 0.10$, $n = 45$, $p = 0.52$) or motor functioning ($r = -0.43$, $n = 12$, $p = 0.17$), or between education and RT ($r = 0.15$, $n = 11$, $p = 0.65$), attention ($r = -0.13$, $n = 32$, $p = 0.49$) or motor functioning ($r = -0.27$, $n = 7$, $p = 0.56$). There were insufficient data to examine any other relationships.

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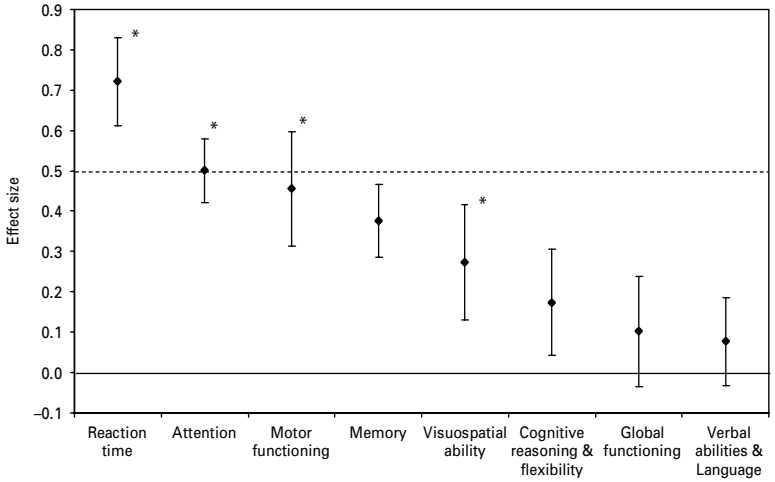


Fig. 1. Cognitive domains: weighted Cohen's *d* effect sizes with 95% confidence intervals, in descending order from left to right. * Significant test of heterogeneity (*Q* statistic), $p < 0.05$.

Cognitive tests

The 50 studies examined here used a total of 80 cognitive tests, which yielded 79 different scores.

Attention, which encompasses attention span and working memory, was one of the most commonly assessed cognitive domains ($N_{studies} = 45$, $N_{tests} = 19$). There were positive mean effect sizes for all tests, indicating that the CFS group showed deficits to varying degrees in this cognitive domain (see Table 2). Moderate to large and significant effect sizes with acceptable N_{fs} were evident for eight tests: the N-Back Memory Task, Stroop Colour Word Task, Paced Auditory Serial Addition Test (plus visual and threshold versions), Short Term Memory Scanning Task, Wechsler Adult Intelligence Scale – Revised (WAIS-R) Digit Symbol subtest and Spatial Working Memory test. Although very commonly used ($N_{studies} = 9$–13), the Trail Making Test and WAIS – Revised (WAIS-R) Digit Span only showed small, albeit significant, deficits.

Memory was assessed by the majority of studies ($N_{studies} = 32$) using a large number of verbal and visual memory tests ($N_{tests} = 29$, see Table 3), the majority of which assessed memory for word lists ($N_{tests} = 20$). While the effect sizes for most tests of word list learning and recall were statistically significant, only seven were moderate to large in size, suggesting that some tests are more sensitive to memory deficits in CFS than others. The tests that met the study criteria were single presentation word list learning tasks (immediate recall, delayed recognition), the Auditory Verbal Learning Test (immediate recall, distraction list recall, delayed recall, recognition) and the Selective Reminding Test (number of trials). Whereas one of the least commonly used tests of memory for figures [Wechsler Memory Scale Revised (WMS-R) Visual Reproduction – immediate recall, $N_{studies} = 2$] had a significant medium effect size with acceptable N_{fs}, a more commonly used test of memory for figures was only associated with small but significant group differences (Rey–Osterreith Complex Figure – immediate recall, $N_{studies} = 5$).

RT was significantly impaired for responses to both simple and complex (choice) stimuli in people with CFS, with all five tests showing medium to large and significant group differences and large N_{fs} (see Table 4). The visual domain was assessed more frequently than the auditory domain.

Motor functioning in CFS was assessed using three tests of manual dexterity (Finger Tapping Test, Grooved Pegboard, Hand–Eye Coordination Test) and the movement time of simple and complex RT tasks (see Table 4). Only the movement times revealed significant moderate group differences with good N_{fs} statistics, with the CFS group taking longer to perform the motor component of RT tasks.

Three tests of *visuospatial ability* were used to assess figure copying, pattern matching and block construction ($N_{studies} = 12$). However, these tests only revealed small effects (see Table 4), indicating minimal impairment in this domain.

Of the tests assessing *verbal abilities and language*, only the Category Fluency Test revealed moderate and significant group differences and good N_{fs} (refer to Table 4). The most frequently used test was the Controlled Oral Word Association Test, which only showed small but significant group differences.

There was little overlap in the tests used to assess *cognitive reasoning and flexibility*, with most tests only evaluated by two studies (see Table 4). None of the results for these tests met the study criteria, yielding

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Table 2. *Attention: weighted Cohen's* d *effect sizes for each test, in descending order*

Test name	$N_{studies}$	N_{CFS}	Mean d_w	S.D.	95% CI	N_{fs}	Study references
N-Back Memory Task	2	37	**0.82**	1.04	0.30 to 1.33	6	Caseras *et al*. 2006; Dobbs *et al*. 2001
Stroop Colour Word Task	12	334	**0.73**	0.39	0.58 to 0.89	32	Claypoole *et al*. 2007; Creswell & Chalder, 2002; DiClementi *et al*. 2001; Fiedler *et al*. 1996; Fuentes *et al*. 2001; Mahurin *et al*. 2004; Marcel *et al*. 1996; Marshall *et al*. 1997; Metzger & Denney, 2002; Moss-Morris & Petrie, 2003; Short *et al*. 2002; Smith *et al*. 1996
Paced Visual Serial Addition Test	2	52	**0.70**	1.17	0.20 to 1.20	5	Johnson *et al*. 1996; Michiels *et al*. 1999
Short Term Memory Scanning	5	186	**0.63**	0.60	0.39 to 0.86	11	Chiaravalloti *et al*. 2003; DeLuca *et al*. 2004*a*; Mahurin *et al*. 2004; McCue *et al*. 2002; Michiels *et al*. 1999
Visual Threshold Serial Addition Test	2	96	**0.58**	0.01	0.25 to 0.92	4	Chiaravalloti *et al*. 2003; DeLuca *et al*. 2004*a*
WAIS-R Digit Symbol	9	228	**0.58**	0.16	0.39 to 0.77	17	Blackwood *et al*. 1998; Claypoole *et al*. 2007; Fiedler *et al*. 1996; Gaudino *et al*. 1997; Kane *et al*. 1997; Krupp *et al*. 1994; Lawrie *et al*. 2000; Michiels *et al*. 1996; Vercoulen *et al*. 1998
Paced Auditory Serial Addition Test	15	486	**0.52**	0.27	0.37 to 0.67	24	Chiaravalloti *et al*. 2003; Claypoole *et al*. 2007; DeLuca *et al*. 1993, 1995, 1997*a*, *b*, 2004*b*; Johnson *et al*. 1996; Kane *et al*. 1997; Lawrie *et al*. 2000; Marshall *et al*. 1997; Michiels *et al*. 1999; Schmaling *et al*. 2003; Short *et al*. 2002; Tiersky *et al*. 1998, 2003
Spatial Working Memory – strategy	3	121	**0.50**	0.15	0.27 to 0.74	5	Capuron *et al*. 2006; Joyce *et al*. 1996; Majer *et al*. 2008
Auditory Threshold Serial Addition Test	2	96	0.41	0.02	0.08 to 0.74	2	Chiaravalloti *et al*. 2003; DeLuca *et al*. 2004*a*
Stroop Colour Word Task – interference	3	84	0.39	0.03	0.08 to 0.69	3	Metzger & Denney, 2002; Michiels *et al*. 1998; Ray *et al*. 1993
Trail Making Test Part A	11	375	0.37	0.41	0.21 to 0.53	9	Claypoole *et al*. 2007; DeLuca *et al*. 1995; Dobbs *et al*. 2001; Krupp *et al*. 1994; Lawrie *et al*. 2000; Michiels *et al*. 1996, 1998; Starr *et al*. 2000; Tiersky *et al*. 1998, 2003; Vercoulen *et al*. 1998
Trail Making Test Part B	12	400	0.36	0.32	0.21 to 0.52	10	Claypoole *et al*. 2007; DeLuca *et al*. 1995; Dobbs *et al*. 2001; Gaudino *et al*. 1997; Krupp *et al*. 1994; Lawrie *et al*. 2000; Michiels *et al*. 1996, 1998; Starr *et al*. 2000; Tiersky *et al*. 1998, 2003; Vercoulen *et al*. 1998
WAIS-R Digit Span Backward	12	401	0.31	0.52	0.16 to 0.47	7	Blackwood *et al*. 1998; Claypoole *et al*. 2001; DeLuca *et al*. 1997*a*, *b*; Dobbs *et al*. 2001; Fiedler *et al*. 1996; Johnson *et al*. 1996; Lawrie *et al*. 2000; Michiels *et al*. 1996, 1998; Tiersky *et al*. 1998, 2003; Vercoulen *et al*. 1998
WMS-R Mental Control	3	100	0.28	0.16	−0.03 to 0.59	1	DeLuca *et al*. 2004*b*; Grafman *et al*. 1993; Marcel *et al*. 1996
Short Term Memory Scanning – visuospatial	5	217	0.27	0.09	0.08 to 0.46	2	Capuron *et al*. 2006; Chiaravalloti *et al*. 2003; DeLuca *et al*. 2004*a*; Joyce *et al*. 1996; Majer *et al*. 2008
Continuous Performance Task	7	274	0.26	0.28	0.10 to 0.42	2	Capuron *et al*. 2006; Kane *et al*. 1997; Mahurin *et al*. 2004; Marcel *et al*. 1996; Marshall *et al*. 1997; Smith *et al*. 1996, 1999
Continuous Performance Task – reaction time	5	206	0.25	0.29	0.08 to 0.43	1	Capuron *et al*. 2006; Fiedler *et al*. 1996; Majer *et al*. 2008; Michiels *et al*. 1998; Smith *et al*. 1999
WAIS-R Digit Span Forward	13	430	0.25	0.31	0.10 to 0.40	3	Blackwood *et al*. 1998; Claypoole *et al*. 2001; DeLuca *et al*. 1997*a*, *b*; Dobbs *et al*. 2001; Fiedler *et al*. 1996; Johnson *et al*. 1996; Lawrie *et al*. 2000; Marcel *et al*. 1996; Michiels *et al*. 1996, 1998; Tiersky *et al*. 1998, 2003; Vercoulen *et al*. 1998
WAIS-R Digit Span Total	9	220	0.25	0.19	0.06 to 0.43	2	Claypoole *et al*. 2007; DeLuca *et al*. 1993, 1995; Fiedler *et al*. 1996; Gaudino *et al*. 1997; Johnson *et al*. 1997, 1998; Krupp *et al*. 1994; Short *et al*. 2002; Vercoulen *et al*. 1998

CI, Confidence interval; WAIS-R, Weschsler Adult Intelligence Scale – Revised.
Tests with bold effect sizes met the study criteria.

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Table 3. *Memory: weighted Cohen's* d *effect sizes for each test, in descending order*

Test name	$N_{studies}$	N_{CFS}	Mean d_w	S.D.	95% CI	N_{fs}	Study references
Word List Learning – verbal delayed recognition	2	44	**0.84**	0.43	0.40 to 1.27	6	Fuentes *et al*. 2001; McCue *et al*. 2002
Auditory Verbal Learning Test – delayed recognition	2	52	**0.67**	0.06	0.23 to 1.11	5	Claypoole *et al*. 2007; Lawrie *et al*. 2000
Selective Reminding Test – number of trials	3	125	**0.62**	0.03	0.33 to 0.90	6	Chiaravalloti *et al*. 2003; DeLuca *et al*. 2004*b*; Michiels *et al*. 1999
Auditory Verbal Learning Test – delayed recall	2	52	**0.61**	0.27	0.18 to 1.05	4	Claypoole *et al*. 2007; Lawrie *et al*. 2000
WMS-R Visual Reproduction – immediate recall	2	38	**0.57**	0.33	0.10 to 1.04	4	Fiedler *et al*. 1996; Grafman *et al*. 1993
Auditory Verbal Learning Test – immediate recall	2	52	**0.55**	0.01	0.12 to 0.99	4	Claypoole *et al*. 2007; Lawrie *et al*. 2000
Word List Learning – verbal immediate recall	2	96	**0.53**	0.62	0.26 to 0.79	3	Marcel *et al*. 1996; Smith *et al*. 1996
Auditory Verbal Learning Test – distraction	2	52	**0.51**	0.48	0.07 to 0.94	3	Claypoole *et al*. 2007; Lawrie *et al*. 2000
Selective Reminding Test – long-term retrieval	5	121	0.49	0.39	0.23 to 0.76	7	Kane *et al*. 1997; Krupp *et al*. 1994; Marshall *et al*. 1997; Michiels *et al*. 1996, 1999
Selective Reminding Test – sum recall all trials	3	89	0.49	0.25	0.20 to 0.78	4	Gaudino *et al*. 1997; Michiels *et al*. 1996, 1999
WMS-R Visual Reproduction – delayed recall	2	38	0.47	0.39	0.00 to 0.93	3	Fiedler *et al*. 1996; Grafman *et al*. 1993
Selective Reminding Test – delayed recall	6	172	0.45	0.35	0.22 to 0.68	8	DeLuca *et al*. 2004*b*; Kane *et al*. 1997; Krupp *et al*. 1994; Marshall *et al*. 1997; Michiels *et al*. 1996, 1999
Selective Reminding Test – long-term storage	4	101	0.44	0.35	0.16 to 0.73	5	Kane *et al*. 1997; Marshall *et al*. 1997; Michiels *et al*. 1996, 1999
California Verbal Learning Test – list A trials 1–5	8	310	0.44	0.46	0.26 to 0.62	10	DeLuca *et al*. 1995, 1997*a*, *b*; Fiedler *et al*. 1996; Johnson *et al*. 1994; Michiels *et al*. 1998; Tiersky *et al*. 1998, 2003; Vercoulen *et al*. 1998
California Verbal Learning Test – long delay cued recall	2	77	0.44	0.20	0.11 to 0.76	2	DeLuca *et al*. 1995; Vercoulen *et al*. 1998
WMS-R Logical Memory – delayed recall	4	98	0.43	0.19	0.13 to 0.73	5	Claypoole *et al*. 2007; DeLuca *et al*. 1995; Grafman *et al*. 1993; Tiersky *et al*. 1998
WMS-R Logical Memory – immediate recall	8	187	0.42	0.28	0.21 to 0.62	9	Claypoole *et al*. 2007; DeLuca *et al*. 1995; DiClementi *et al*. 2001; Gaudino *et al*. 1997; Grafman *et al*. 1993; Krupp *et al*. 1994; Short *et al*. 2002; Tiersky *et al*. 1998
California Verbal Learning Test – short delay cued recall	2	77	0.39	0.29	0.07 to 0.72	2	DeLuca *et al*. 1995; Vercoulen *et al*. 1998
California Verbal Learning Test – long delay free recall	7	292	0.39	0.32	0.21 to 0.57	7	DeLuca *et al*. 1995, 1997*a*, *b*; Johnson *et al*. 1994; Michiels *et al*. 1998; Tiersky *et al*. 1998, 2003; Vercoulen *et al*. 1998
Rey Osterreith Complex Figure – immediate recall	5	165	0.35	0.42	0.13 to 0.58	4	Claypoole *et al*. 2007; DeLuca *et al*. 1995, 1997*a*, *b*; Tiersky *et al*. 1998; Vercoulen *et al*. 1998
California Verbal Learning Test – short delay free recall	7	292	0.33	0.30	0.15 to 0.52	5	DeLuca *et al*. 1995, 1997*a*, *b*; Johnson *et al*. 1994; Michiels *et al*. 1998; Tiersky *et al*. 1998, 2003; Vercoulen *et al*. 1998
California Verbal Learning Test – recognition	5	149	0.31	0.16	0.07 to 0.55	3	DeLuca *et al*. 1995; Johnson *et al*. 1994; Lawrie *et al*. 2000; Michiels *et al*. 1998; Vercoulen *et al*. 1998
Rey Osterreith Complex Figure – delayed recall	4	107	0.30	0.37	0.03 to 0.58	2	Claypoole *et al*. 2007; DeLuca *et al*. 1995, 1997*a*, *b*; Short *et al*. 2002
Paired Associate Learning – verbal delayed recall	2	42	0.30	0.41	−0.15 to 0.74	1	Claypoole *et al*. 2007; Grafman *et al*. 1993
Paired Associate Learning – visual	3	88	0.24	0.28	−0.11 to 0.58	1	Grafman *et al*. 1993; Joyce *et al*. 1996; Wearden & Appleby, 1997
Selective Reminding Test – delayed recognition	2	64	0.23	0.07	−0.13 to 0.59	0	Michiels *et al*. 1996, 1999
Paired Associate Learning – verbal	5	115	0.21	0.42	−0.07 to 0.49	0	Claypoole *et al*. 2007; Grafman *et al*. 1993; Joyce *et al*. 1996; Lawrie *et al*. 2000; Short *et al*. 2002
7/24 Test	2	96	0.16	0.04	−0.16 to 0.49	0	Chiaravalloti *et al*. 2003; DeLuca *et al*. 2004*b*
Pattern Recognition Test	5	181	0.04	0.24	−0.16 to 0.24	0	Capuron *et al*. 2006; Joyce *et al*. 1996; Mahurin *et al*. 2004; Majer *et al*. 2008; Marcel *et al*. 1996

CI, Confidence interval; WAIS-R, Weschsler Adult Intelligence Scale – Revised; WMS-R, Weschsler Memory Scale – Revised.
Tests with bold effect sizes met the study criteria.

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Table 4. *Weighted Cohen's* d *effect sizes in descending order for reaction time tasks, tests of motor functioning, visuospatial ability, verbal abilities and language, cognitive reasoning and flexibility, and global functioning*

Cognitive domain/Test name	$N_{studies}$	N_{CFS}	Mean d_w	S.D.	95% CI	N_{fs}	Study references
Reaction time							
Simple Visual Reaction Time – variable fore-period	9	303	**0.84**	0.49	0.67 to 1.00	29	DeLuca *et al*. 2004*a*; Fuentes *et al*. 2001; Mahurin *et al*. 2004; McCue *et al*. 2002; Michiels *et al*. 1998, 1999; Sargent *et al*. 1997; Smith *et al*. 1999; Vercoulen *et al*. 1998
Choice Visual Reaction Time	14	480	**0.77**	0.43	0.64 to 0.90	40	Capuron *et al*. 2006; Chiaravalloti *et al*. 2003; DeLuca *et al*. 2004*a*; Fuentes *et al*. 2001; Hou *et al*. 2008; Mahurin *et al*. 2004; Majer *et al*. 2008; Marshall *et al*. 1997; McCue *et al*. 2002; Michiels *et al*. 1998; Sargent *et al*. 1997; Scheffers *et al*. 1992; Smith *et al*. 1996, 1999
Simple Auditory Reaction Time – variable fore-period	3	94	**0.61**	0.31	0.29 to 0.93	6	Davey *et al*. 2001; DeLuca *et al*. 2004*a*; McCue *et al*. 2002
Simple Visual Reaction Time	10	361	**0.58**	0.47	0.43 to 0.73	19	Capuron *et al*. 2006; Chiaravalloti *et al*. 2003; Claypoole *et al*. 2007; Fiedler *et al*. 1996; Lawrie *et al*. 2000; Majer *et al*. 2008; Marcel *et al*. 1996; Marshall *et al*. 1997; Michiels *et al*. 1999; Smith *et al*. 1999
Choice Auditory Reaction Time	4	139	**0.57**	0.17	0.30 to 0.83	7	Chiaravalloti *et al*. 2003; Davey *et al*. 2001; DeLuca *et al*. 2004*a*; McCue *et al*. 2002
Motor functioning							
Motor Complex Reaction Time	5	185	**0.58**	0.40	0.38 to 0.78	9	Capuron *et al*. 2006; Davey *et al*. 2001; Majer *et al*. 2008; Marshall *et al*. 1997; Vercoulen *et al*. 1998
Motor Reaction Time	6	174	**0.53**	0.56	0.32 to 0.74	10	Capuron *et al*. 2006; Davey *et al*. 2001; Lawrie *et al*. 2000; Majer *et al*. 2008; Marshall *et al*. 1997; Sargent *et al*. 1997
Finger Tapping Test	4	113	0.31	0.63	0.05 to 0.58	2	Claypoole *et al*. 2007; Gaudino *et al*. 1997; Mahurin *et al*. 2004; Michiels *et al*. 1996
Hand–eye Coordination Test	2	47	0.24	0.07	−0.17 to 0.66	0	Fiedler *et al*. 1996; Marcel *et al*. 1996
Grooved Pegboard	2	40	0.15	0.10	−0.29 to 0.59	0	Claypoole *et al*. 2007; Fiedler *et al*. 1996
Visuospatial ability							
Rey Osterreith Complex Figure – copy	6	188	0.30	0.31	0.09 to 0.51	3	Claypoole *et al*. 2007; DeLuca *et al*. 1995, 1997*a*, *b*; Short *et al*. 2002; Tiersky *et al*. 1998; Vercoulen *et al*. 1998
Pattern Matching	2	49	0.28	0.08	−0.13 to 0.68	1	Joyce *et al*. 1996; Marcel *et al*. 1996
WAIS Block Design	5	243	0.16	1.03	−0.05 to 0.36	0	Busichio *et al*. 2004; Claypoole *et al*. 2007; DeLuca *et al*. 1997*a*, *b*; Fuentes *et al*. 2001; Lawrie *et al*. 2000

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Verbal abilities and language							
Category Fluency	3	70	0.58	0.01	0.23 to 0.92	6	Claypoole *et al*. 2001; Joyce *et al*. 1996; Marcel *et al*. 1996
Controlled Oral Word Association Test	9	194	0.35	0.38	0.14 to 0.55	7	Blackwood *et al*. 1998; Claypoole *et al*. 2001, 2007; Gaudino *et al*. 1997; Joyce *et al*. 1996; Kane *et al*. 1997; Krupp *et al*. 1994; Lawrie *et al*. 2000; Marcel *et al*. 1996
WAIS Vocabulary	8	432	0.00	0.20	−0.15 to 0.15	0	Busichio *et al*. 2004; DeLuca *et al*. 1997*a*, *b*, 2004*b*; Fuentes *et al*. 2001; Gaudino *et al*. 1997; Michiels *et al*. 1996; Short *et al*. 2002; Tiersky *et al*. 2003
Wide Range Achievement Test – Reading	2	76	−0.02	0.34	−0.31 to 0.27	0	Fiedler *et al*. 1996; Majer *et al*. 2008
National Adult Reading Test	2	73	−0.04	0.19	−0.43 to 0.35	0	Moss-Morris & Petrie, 2003; Wearden & Appleby, 1997
Boston Naming Test	2	59	−0.18	0.06	−0.59 to 0.23	0	Lawrie *et al*. 2000; Marcel *et al*. 1996
Cognitive reasoning and flexibility							
Tower of London	2	40	0.27	0.54	−0.18 to 0.73	1	Grafman *et al*. 1993; Joyce *et al*. 1996
Logical Reasoning	2	98	0.27	0.18	0.01 to 0.53	1	Mahurin *et al*. 2004; Smith *et al*. 1999
WAIS Arithmetic	2	58	0.19	0.18	−0.18 to 0.57	0	Claypoole *et al*. 2007; DeLuca *et al*. 1997*a*, *b*
Tower of London – perfect solutions	3	121	0.17	0.22	−0.06 to 0.40	0	Capuron *et al*. 2006; Joyce *et al*. 1996; Majer *et al*. 2008
Category Test	5	173	0.08	0.32	−0.13 to 0.28	0	Capuron *et al*. 2006; Claypoole *et al*. 2007; Krupp *et al*. 1994; Majer *et al*. 2008; Tiersky *et al*. 1998
WAIS Picture Completion	2	45	0.02	0.30	−0.39 to 0.43	0	Claypoole *et al*. 2007; Short *et al*. 2002
WAIS Similarities	2	34	−0.04	0.09	−0.52 to 0.44	0	Claypoole *et al*. 2007; DeLuca *et al*. 1993
Global functioning							
Shipley Institute of Living Scale	2	34	0.25	0.22	−0.22 to 0.72	0	Kane *et al*. 1997; Ross *et al*. 2001
WAIS Information	3	70	0.12	0.12	−0.19 to 0.43	0	Claypoole *et al*. 2007; Gaudino *et al*. 1997; Short *et al*. 2002
North American Adult Reading Test – IQ estimate	4	77	0.07	0.56	−0.26 to 0.39	0	DiClementi *et al*. 2001; Fuentes *et al*. 2001; Johnson *et al*. 1998; LaManca *et al*. 1998
WAIS Vocabulary – verbal IQ	3	57	0.06	0.07	−0.33 to 0.46	0	Claypoole *et al*. 2007; DeLuca *et al*. 1993; Johnson *et al*. 1997
National Adult Reading Test – IQ estimate	4	127	0.03	0.30	−0.21 to 0.27	0	Blackwood *et al*. 1998; Joyce *et al*. 1996; Lawrie *et al*. 2000; Smith *et al*. 1999
Raven's Progressive Matrices	3	84	−0.03	0.25	−0.34 to 0.28	0	Michiels *et al*. 1996, 1998, 1999

CI, Confidence interval; IQ, intelligence quotient; WAIS, Weschsler Adult Intelligence Scale (all editions).
Tests with bold effect sizes met the study criteria.

only small effect sizes. Additionally, all but one of the confidence intervals spanned zero, further indicating that this domain is not impaired in people with CFS.

Finally, measures of *global functioning* were used by 17 studies, with all tests producing small and non-significant effect sizes (see Table 4), indicating that people with CFS performed comparably with healthy controls on these measures.

Discussion

Overall, the data from 52 studies ($N_{CFS}=1595$; $N_{controls}=1533$) were analysed in order to determine whether CFS is associated with deficits in cognitive functioning. The groups appeared well matched for gender, age and education, making it unlikely that differences in these variables were contributing to the findings. Persons with CFS were significantly more depressed than the controls, but it was not possible to directly analyse the contribution of depression to cognitive functioning because very few studies provided the necessary data. However, the majority of studies that examined the impact of self-reported depression in CFS on cognitive functioning failed to find a relationship (e.g. DeLuca *et al*. 1995; Johnson *et al*. 1997; Vercoulen *et al*. 1998; Short *et al*. 2002; Busichio *et al*. 2004), although some studies did find an association (e.g. Krupp *et al*. 1994; Marshall *et al*. 1997). Additionally, using clinical interviews, those studies that categorized CFS participants on the basis of psychiatric diagnosis (most commonly major depressive disorder or dysthymia) found that cognitive impairment was greater for people *without* a co-existing psychiatric disorder than for those with a co-morbid diagnosis (e.g. DeLuca *et al*. 1997*a*; Tiersky *et al*. 2003). Hence, while the increased levels of depression in people with CFS may explain some of the cognitive problems found in this study, the results from a number of studies suggest that it is unlikely to account for all of the observed problems.

A large number of tests have been used to assess cognitive functioning in CFS and there is considerable variability in the extent to which performance on these measures is affected by this condition. This is likely to have hindered the integration of research findings to date. A total of 24 of the 80 test scores met the study criteria for impairment ($d \geqslant 0.5$, 95% CI $\neq 0$, $N_{fs} > N_{studies}$), including tests of attention, memory, RT, motor functioning and verbal abilities. In contrast, none of the tests of visuospatial ability, cognitive reasoning and flexibility and global functioning met the study criteria.

Measures of both simple (RT tasks) and complex (Paced Auditory Serial Addition Test) information-processing speed showed moderate to large and significant impairments in persons with CFS, confirming the findings of two previous literature reviews (Tiersky *et al*. 1997; Michiels & Cluydts, 2001). It is also likely that information-processing deficits contributed to the deficits noted in the movement time of RT tasks, which are reportedly not pure measures of motor speed (Smith & Carew, 1987; Vercoulen *et al*. 1998). Moreover, fine motor speed was not impaired in persons with CFS, making it unlikely that motor functioning is predominately responsible for slower RTs.

In addition to deficits in information-processing speed, persons with CFS were impaired on tests that assess working memory over a sustained period of time (i.e. N-Back Memory Task, Short Term Memory Scanning Task, Spatial Working Memory). Moderate and significant impairments were also found for the WAIS-R Digit Symbol Test and the Stroop Task, which showed only minimal impairment when the speed of reading patches and words was taken into account. Michiels & Cluydts (2001) have suggested that this pattern of performance on the Stroop Task may be due to an 'overall slowness' in persons with CFS. While this is consistent with the delays in simple information processing, it is not clear why other simple tests of attention were not also impaired (e.g. Trail Making Test, WMS-R Mental Control).

Previous reviews of the literature have not been able to resolve the conflicting findings regarding verbal and non-verbal memory deficits in persons with CFS (Tiersky *et al*. 1997; Michiels & Cluydts, 2001). With regard to verbal memory, moderate to large and significant deficits were found on several tests of word list learning (e.g. Auditory Verbal Learning Test and other word list learning tasks). Immediate recall was impaired, as was delayed recall and recognition. DeLuca *et al*. (2004*b*) suggest that these memory problems may be due to poor initial learning. The deficits in information-processing speed and working memory identified by this study may contribute to these problems with initial learning. In support of this, persons with CFS took more trials to learn on a task that controlled for initial learning (Selective Reminding Test) but had only minimally impaired immediate and delayed recall.

Non-verbal memory for complex figures and spatial location were not impaired, with only one test of memory for figures showing moderate and significant deficits (WMS-R Visual Reproduction – immediate recall). Thus, memory deficits associated with CFS may be predominately verbal, despite the absence of modality-specific impairments in RT and attention.

Verbal abilities and language were also largely preserved, except for category fluency, which may be reliant on working memory for successful completion

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(Lezak *et al*. 2004). Finally, higher order cognitive functions appear to be intact, consistent with the findings of previous reviews (Tiersky *et al*. 1997; Michiels & Cluydts, 2001).

The magnitude of the deficits in persons with CFS is rarely reported. This study found that there were deficits of 0.5–1.0 S.D. below that of their healthy peers. The practical impact this has on people with CFS appears to have only been explored by one study, which found that people with a greater number of deficits reported more days of inactivity (Christodoulou *et al*. 1998).

Overall, the impairments identified by objective cognitive tests are congruent with the memory and concentration problems reported by persons with CFS. While most studies have not found a relationship between self-reported cognitive problems in persons with CFS and their test performance (e.g. Wearden & Appleby, 1997; Vercoulen *et al*. 1998), their self-rating of performance on specific tests is reliable (Wearden & Appleby, 1997).

The cause of these cognitive deficits is uncertain. Depression may be a contributing factor but, as previously discussed, greater deficits have been found in people with CFS *without* co-morbid depression. Other research has investigated the role of a sudden *versus* gradual onset of the condition, with those who report a sudden onset being more impaired, possibly representing a subgroup with a viral cause for their condition (e.g. DeLuca *et al*. 1997*b*; Claypoole *et al*. 2007). Other factors that may contribute to the cognitive deficits, while not a cause, are the fluctuations that occur in CFS symptoms (Fuentes *et al*. 2001), such as fatigue, which may result in inconsistent levels of effort being applied during cognitive testing. Although the cause of cognitive deficits in CFS is still not known, treatments with cognitive behaviour therapy and graded exercise have resulted in some improvements (e.g. Thomas *et al*. 2006; de Lange *et al*. 2008).

Limitations

There are several limitations that may have influenced the study findings. First, a large number of effect sizes were calculated due to the large number of tests that were used by researchers, which may result in some effect sizes being significant by chance alone (i.e. type 1 error). The requirement for an effect size of interest to meet multiple criteria ($d \geqslant 0.5$, 95% CIs $\neq 0$, $N_{fs} > N_{studies}$) should improve the robustness of our findings; however, we cannot exclude the possibility that type 1 errors have occurred.

Second, while publication bias may have influenced the findings of this study, we attempted to evaluate the potential robustness of our findings by calculating an N_{fs} statistic and ensuring that the number of studies contributing to a finding exceeded this value. Furthermore, nearly half of the studies reported small effect sizes for most tests, indicating that non-significant results are being reported in the literature, thereby reducing the likelihood of publication bias.

Third, many studies did not report data on variables that may have influenced cognitive functioning, such as psychiatric status, depression and the nature of the onset of the condition (sudden *versus* gradual), thereby precluding an analysis of their impact on cognition. There was also considerable variability in the methods used to diagnosis CFS. Hence, there may be important differences between the CFS participants that may have contributed to the findings. Reeves *et al*. (2003) have provided guidelines to resolve some of the ambiguities in the CDC CFS criteria (Fukuda *et al*. 1994), which may help to standardize the procedures used in future research. However, the cognitive tests that they proposed may need to be reconsidered based on the findings of this meta-analysis.

Finally, the impact of medication usage on cognitive functioning could not be explored in this study. However, individual studies suggest that its impact may be minimal, with one study finding no difference between the performance of medicated and unmedicated persons with CFS (Michiels *et al*. 1998) and another finding significant performance decrements in unmedicated (but not medicated) CFS participants compared with controls (Sargent *et al*. 1997).

Conclusions

In conclusion, this study provides objective evidence of cognitive deficits in persons with CFS, primarily in the domains of attention, memory and RT. In general, these deficits are consistent with those that are reported by patients. Both simple and complex information processing speed are impaired, along with working memory. The data also suggest that memory deficits may be due to the poor initial acquisition of information but more studies are needed to investigate this. The deficits in performance are around 0.5–1.0 S.D. below that of their healthy peers, which is likely to have an impact on day-to-day activities. In contrast, CFS does not appear to have an impact on perceptual abilities or fine motor speed; nor does it appear to affect higher order cognitive abilities, such as language, reasoning or intelligence.

Declaration of Interest

None.

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* Indicates studies that were included in the meta-analysis

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