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Neurocognitive improvements after best-practice intervention for chronic fatigue syndrome: Preliminary evidence of divergence between objective indices and subjective perceptions

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Abstract

Background: Neurocognitive difficulties are commonly reported by patients suffering from chronic fatigue syndrome (CFS). Moderate improvements from 'best practice' therapy are promising, but to date reported efficacy is based entirely on subjective measures. This is problematic, given the well-documented divergence between subjective perceptions and actual neurocognitive performance, including in this patient group.

Material and Methods: Subjective and objective measures of neurocognitive performance were obtained from 25 patients with well-characterized CFS before and after the completion of a 12-week graded-activity program incorporating a cognitive training component. Additionally, self-reported symptoms, cardiac autonomic activity (a relevant biomarker of stress responsivity), and their relation to neurocognitive improvements were examined.

Results: Substantive post-intervention improvements in subjective ($p = 0.006$) and objective (including faster responses speeds and greater accuracy, p's < 0.001) neurocognitive performance were documented. Participants also demonstrated reduced autonomic reactivity to the cognitive challenge at follow-up (p's ≤ 0.01). These improvements were accompanied by improvements in symptom ratings (p's ≤ 0.01). However, subjective ratings of neurocognitive difficulties, and CFS-related symptoms were not linked to objective performance improvements.

Conclusions: These initial data provide the first evidence of objective neurocognitive performance improvements accompanied by a significant reduction in responsiveness in stress-related neural pathways consequent to cognitive-behavioral/graded exercise therapy programs. These findings provide support for the effectiveness of such programs in remediating clinical status. These promising findings warrant further investigation, including replication in a larger sample utilizing more controlled study designs.

1. Introduction

Chronic fatigue syndrome (CFS) is a complex and debilitating disorder characterized by six or more consecutive months of medically-unexplained fatigue and multiple constitutional and neuropsychiatric symptoms [1]. No curative treatments exist and, despite intense research efforts, the etiology and pathophysiology of CFS remain unclear. Significant heterogeneity in specific symptom manifestations and severity has been documented in patient samples fulfilling diagnostic criteria for CFS [2], yet neurocognitive difficulties including impairments in concentration and memory are almost universal complaints, and are strongly linked to occupational and social impairment [3–5].

Objective impairments across a number of cognitive domains have been observed in individuals with CFS relative to healthy controls, most consistently manifesting as slowed response speeds on complex executive tasks and decreased working memory capacity [5–9]. These difficulties in neurocognitive performance in CFS are not attributable to subjective fatigue, mood disturbance, or a lack of applied effort [10–13]. Moreover, performance accuracy is usually maintained in patients with CFS, but this often comes at the cost of response speed [5]. Evidence from imaging studies

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suggests that cognitive performance in CFS is associated with increased neural engagement in sub-cortical and cortical areas [14–16]; and this has been proposed as a possible mechanism underlying the subjective sensation of fatigue reported by patients with CFS after engaging in cognitively demanding activities [14,16]. Additionally, several studies have reported increased sensitivity to stressors and challenges reflected in greater reactivity in stress-responsive networks, including the autonomic nervous system (ANS) [5,17]. In particular, chronic sympathetic hyper-arousal and reduced parasympathetic activity (indexed by increased heart rate [HR], increased time to HR recovery post-challenge, and reduced HR variability [HRV]) have been documented in CFS and linked to key symptoms, including objective cognitive performance [5,17–21]. The perturbations in autonomic signaling characteristic of CFS reflect an energy-costly state of physiological hyper-vigilance and stress reactivity (i.e., a system under stress) [22].

In the absence of curative treatments for CFS, therapeutic interventions focusing on functional improvements have been widely adopted by clinicians. In particular, cognitive-behavioral therapy (CBT) and graded exercise therapy (GET) have consistently produced moderate improvements in levels of reported fatigue as well as cognitive and social functioning in controlled trials. Consequently, CBT/GET programs have been promoted as 'best practice' in the management of CFS [23–26], yet the level of efficacy varies across studies [24,27–30]. Although promising, these improvements are based exclusively on self-report measures [31,32]. When cognitive performance is assessed this is potentially problematic, as it is widely acknowledged that subjective perceptions and objective performance indices do not correlate well [33–35], which has also been consistently observed in patients with CFS [9,36–39]. In both healthy and patient populations, subjective evaluation of cognitive difficulties typically relates better to personality and psychological factors (e.g., mood), than to objective measures [36,40]. Thus, subjective improvements in neurocognitive functioning alone may not provide a reliable reflection of therapeutic efficacy.

In the current study, subjective perceptions and objective measures of neurocognitive performance were examined in patients with well-characterized CFS before and after the completion of a 12-week CBT/GET intervention program (incorporating a graded cognitive activity component). As the factors contributing to objective neurocognitive performance remain unknown, improvements in additional CFS-related symptoms and general functioning were also explored. Additionally, the possibility that cardiac autonomic activity contributes to objective neurocognitive performance outcomes was examined. It was hypothesized that this best-practice intervention would impact on both subjective ratings and objective measures of neurocognitive performance; but that actual improvements would not be clearly linked with subjectively perceived improvements, as these measures likely reflect different constructs.

2. Materials and methods

2.1. Participants

Twenty-eight patients fulfilling international diagnostic criteria for CFS [1] were recruited from a tertiary referral clinic associated with the University of New South Wales (UNSW) in Sydney, Australia, which provides a 12-week outpatient graded-activity oriented CBT program for CFS. Medications known to affect autonomic functioning (including beta-blockers, corticosteroids, and benzodiazepine) and comorbid neurological conditions (e.g., recent head injury, epilepsy) were exclusionary. The use of antidepressant medication was documented. The UNSW Human Research Ethics Committee approved this research (Approval #HC12091). All participants gave informed written consent prior to taking part, and were treated in accordance with the principles expressed in the Declaration of Helsinki.

2.2. Study design

A within-subject, repeated-measures design was employed for this study. Such a design, in which each participant acts as their own control, is particularly beneficial where heterogeneous symptom profiles and individual differences in treatment responsiveness are likely to reduce statistical power in between-group comparisons [41]. Participants were initially assessed within two weeks of commencing the intervention (intake), and again within two weeks of completion (average time between assessments = 11 ± 1.96 weeks).

2.3. Intervention

The multi-disciplinary outpatient treatment program for CFS [42] has been established within a clinical academic framework combining interventions tailored to individual patients by providing CBT along with physical remediation and cognitive retraining. The program is delivered by one of two clinical psychologists and one of two exercise physiologists across six to eight individual one-hour sessions. These sessions incorporate an integrated modular treatment approach that has educational components, addressing difficulties with physical activity and exercise regulation (using a GET approach), sleep–wake cycle, neurocognitive functioning, and mood. Importantly, analogous to GET, patients are asked to pace and then gradually escalate their cognitive tasks (e.g. reading, responding to emails) by completing one or more timed sessions of such structured mental activity every day. When a tolerated routine was in place, the time spent on each activity and the level of intensity was progressively increased. The aim of this program is to assist patients with re-conditioning, both physically and cognitively, toward normal everyday functioning.

2.4. Procedure

Prior to visiting the lab, participants were asked to abstain from caffeine for four hours, and alcohol and vigorous physical activity for 12 hours. All assessments were carried

out under controlled laboratory conditions. After providing informed consent, participants completed several questionnaires to ascertain demographic, lifestyle, and symptom information. Participants were then connected to physiological sensors and seated in a comfortable chair in a semi-reclined position. A ten minute resting baseline was recorded, during which participants listened to a nature soundscape over headphones at a comfortable volume with their eyes closed. At the conclusion of baseline recording, and after each neurocognitive task, participants rated their current sensation of "physical" and "mental" fatigue on a 10-point Likert scale (where a rating of "1" indicated no fatigue, and "10" reflected extreme fatigue). Participants then completed a computerized battery of four neurocognitive tasks, presented in counter-balanced order (to control for possible order or carry-over effects on performance, including learning and fatigue). However the Stroop task was always performed last, as our previous studies [5] indicate that this task generally elicits the greatest autonomic reactivity compared to other tasks. The fixed task duration of five minutes also makes it the most suitable for HRV assessment [43], and to assess the timing of return-to-resting HR.

2.5. Questionnaires

Physical and psychological symptoms were assessed with the 34-item Somatic and Psychological Health Report (SPHERE) and its empirically-derived and validated SOMA subscale which reflects key clinical features of prolonged fatigue states [44]. A cognitive difficulties subscale derived from SPHERE items (including "poor concentration", "poor memory", and "feeling lost for the word") was used to assess subjective cognitive functioning [45]. Psychological distress was gauged with the Kessler 10 [K10; 46]. The Pittsburgh Sleep Quality Index [PSQI; 47] assessed sleep quality. The Perceived Stress Questionnaire [PSQ; 48] elucidated current levels of everyday stress. Impairments in everyday functioning were assessed using the empirically derived and validated physical and mental composite scores of the Medical Outcomes Study 36-Item Short-Form Health Survey [SF-36; 49].

2.6. Objective neurocognitive assessment

A computerized battery of four neurocognitive tasks was utilized (graphically represented in Fig. 1), which is described in detail elsewhere [5,50,51]. To minimize potential practice effects, parallel versions of each task were used across assessments. The Digit Symbol Coding (DSC) task required rapid matching-to-sample judgements of symbols to corresponding numerical digits for a period of two minutes. Accuracy (as percent correct) and response times (RTs) for correct responses provided an indication of information processing ability and speed, respectively. Short term memory was gauged with a symmetry identification (SYM) task, requiring participants to retain portions of a string of characters in memory, and compare these with the remaining parts to determine whether the entire string was palindromic. Only two characters of the string were visible at once in a movable viewing rectangle. The task increased the total string length with correct responses, with performance reflected by the average length of correctly identified symmetrical strings, and number of forward moves and reversals per character in the string.

A visuospatial memory task assessed spatial working memory (SWM). Participants were required to memorize and reproduce a sequence of individually illuminating squares on a 3-by-3 grid, which continued to grow in length until an error was made. The average path length achieved across six trials was recorded. Finally, a modified Stroop task [52] was used to measure inhibition of pre-potent responses and executive functioning over a five-minute period. Two words were simultaneously on a black background. The lower word was either "RED", "BLUE", "GREEN", or "XXXX", presented on screen in either red, blue, green, or gray font. The upper word was either "NAME" or "COLOR", reflecting which aspect of the lower word to respond to. "NAME" trials required responses based on the semantic meaning of the word, whereas "COLOR" trials required a response based on the color of the font presented on-screen (regardless of the presented word). Overall performance accuracy was determined, and average RT calculated for correct responses.

2.7. Cardiac autonomic measures and data preparation

Physiological measurements were acquired using a PowerLab 16SP sampled at 1 kHz and recorded in LabChart 7 (ADInstruments, Bella Vista, Australia). Standard Ag/AgCl chest electrodes with a three-lead electrocardiogram (ECG) were used to record HR. Respiration was monitored via a strain gauge transducer. Raw ECG and respiratory data were used to calculate mean HR (beats/min) and breathing rate (breaths/min). Time-domain measures of HRV, specifically the standard deviation of beat-to-beat intervals (SDNN) and the root mean square of successive differences of beat-to-beat intervals (RMSSD) obtained during resting baseline were determined from artifact-free ECG traces using the HRV module of LabChart 7. These HRV measures provide a reliable index of vagal/respiratory sinus arrhythmia modulation of HR [43]. Following a stressor, the vagus nerve plays a major role in restoring HR to baseline values [53]. HR recovery was defined as the point at which instantaneous HR had returned to baseline for at least five seconds after completing the Stroop task.

2.8. Statistical analyses

Analyses were performed in SPSS version 22 (IBM, Chicago, IL, USA). Normality assumptions for all variables were satisfactorily met. Two-tailed significance was set at $p < 0.05$. Within-subjects, repeated measures analysis of variance was used to assess changes in self-reported symptoms, objective cognitive performance, and autonomic

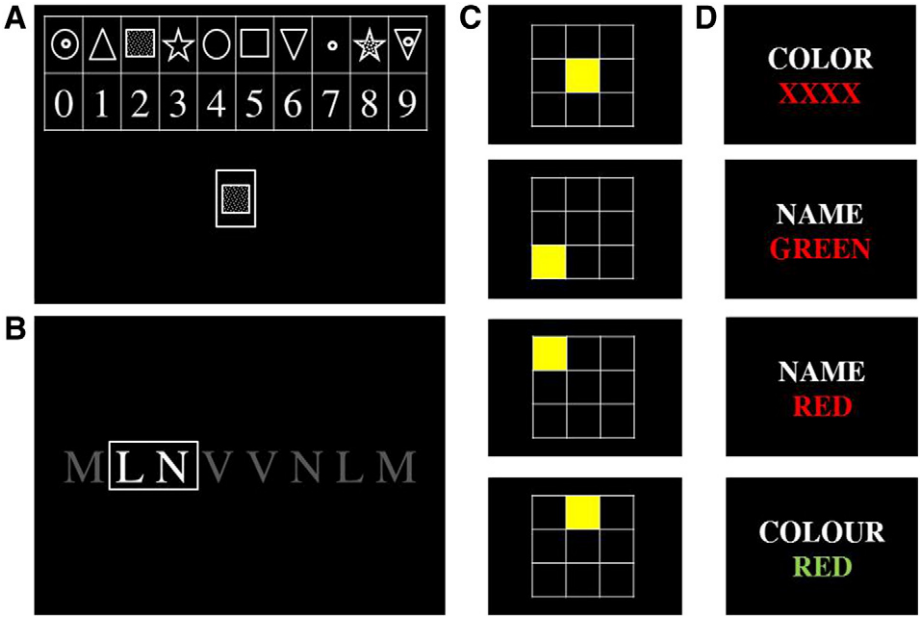

Fig. 1. Graphical representation of the neurocognitive test battery. The DSC task (A) required rapid matching-to-sample judgements. The SYM task (B) required the identification of palindromic letter, number, and symbol strings from restricted displays, and adapted in length based on the participant's performance. The SWM task (C) required the reproduction of a visually presented sequence of illuminating squares. The Stroop task (D) required responding to either the semantic meaning of a printed word, or the color that the word was presented in.

reactivity between intake and follow-up assessments. Partial eta square (η_p^2) provided a measure of effect size. Paired samples *t*-tests (with Cohen's *d* reflecting effect size) were used to examine changes in ratings of physical and mental fatigue across assessments. The association between subjectively rated symptoms, objective performance measures and autonomic parameters was examined with Pearson bivariate correlations (interpreted with a Bonferroni-adjusted *p*-value of 0.025 for multiple comparisons). Kaplan–Meier survival analysis was used to assess differences in time-to-recovery to resting HR after the Stroop task. Based on preliminary data, an estimated sample size of 30 was deemed appropriate to obtain correlation coefficients of approximately 0.5, and effect sizes in the vicinity of 0.55, with greater than 80% power and two-tailed significance of 0.05.

3. Results

3.1. Participant characteristics

Three of the 28 participants enrolled in the study were lost-to-follow up; one withdrew from the intervention, one completed a protracted version of the intervention, and one declined to return. These participants did not differ from those that completed the intervention in any demographic, self-reported symptom, or neurocognitive performance measure at intake, and were excluded from subsequent analysis. Demographics of the 25 participants who completed the study are shown in Table 1. Nine participants were stably medicated with antidepressants for at least three months prior to, and throughout the entire duration of, the intervention. Four participants were taking selective serotonin reuptake inhibitors (SSRIs), three were taking serotonin–norepinephrine reuptake inhibitors (SSNRIs), and two were taking tricyclic antidepressants (TCAs). No participant commenced or ceased antidepressant medication use during the intervention.

3.2. Self-reported clinical symptoms

Following the intervention, participants showed improvements in a number of CFS-associated symptoms (Table 2; note that a small amount of data was non-systematically missing due to responses for two questionnaires being collected directly by the clinical service providing the intervention). Participants reported significantly fewer illness symptoms (SPHERE), including lower scores on

Table 1
Demographics at intake of participants that completed the 12-week intervention program (n = 25).

Demographic	Mean (SE)	Range
Age (years)	41.36 (3.16)	18–68 years
Sex (M/F)	8/17 (68% female)	
Current episode duration (weeks)	279.12 (43.14)	24–520 weeks
Formal education (>12 years)	96%	
Body mass index (BMI)	24.61 (0.72)	19.60–31.16
Daily caffeine intake (cups per day)	1.92 (0.38)	0–7 cups/day
Weekly alcohol (units per week)	1.20 (0.35)	0–6 units/week
Moderate intensity exercise (hours per week)	3.81 (0.85)	0–15 h/week
Antidepressant medication use (n)	9 (36%)	

Current episode duration is capped at 520 weeks.

the SOMA subscale which reflects key clinical features of prolonged fatigue states, and fewer neurocognitive difficulties (e.g., problems concentrating). Psychological symptoms were also significantly reduced reflected by improvements in K10 and SF-36 (mental composite) scores. Participants reported significantly better sleep quality (PSQI), and lower levels of perceived stress (PSQ) post-intervention. Functional improvements were also apparent, with improvements in the physical composite score of the SF-36. The magnitude of improvement on self-reported clinical symptoms did not differ between participants as a function of antidepressant medication use.

3.3. Neurocognitive performance

Improvements in neurocognitive performance were evident across some tasks following the intervention. Performance levels and statistics are presented in Table 3. At intake, performance was comparable to that of cases (and lower than that of controls) in a previously reported CFS case–control study of neurocognitive performance by our group [5], indicating objective impairment. There were small, but statistically significant post-intervention improvements in task accuracy on both the DSC (~2%) and Stroop (~3%) tasks. There was a trend toward improved performance in working memory (~1 additional position in SWM); however this failed to reach statistical significance. Performance was maintained on the SYM task, with participants achieving near-ceiling levels of performance across both assessments. Substantial improvements were observed in RTs on both the Stroop (~400 ms faster) and DSC tasks (~115 ms faster).

Performance measures across tasks were highly inter-correlated at both intake and follow-up assessments. To minimize the number of comparisons in subsequent analyses, an "accuracy" and "response speed" composite were created by averaging the accuracy and RTs across the Stroop and DSC tasks, respectively. Both the accuracy [$r = 0.54$, $p = 0.006$] and response speed [$r = 0.88$, $p < 0.001$] composite measures obtained at intake and follow-up were strongly correlated. Improvements in response speed and accuracy across sessions were also strongly associated [$r = 0.68$, $p < 0.001$], suggesting that improvements were not the consequence of a speed/accuracy trade-off. As with self-reported clinical symptoms, the magnitude of improvement did not differ between participants as a function of antidepressant medication use.

3.4. Ratings of fatigue before and after task completion

Fig. 2 displays the progression of self-reported physical and mental fatigue after task completion at each assessment. No differences in physical or mental fatigue at baseline were found between assessments. Assessment-induced exacerbation of both physical fatigue [$t(24) = 3.06$, $p = 0.005$, $d = 0.64$] and mental fatigue [$t(24) = 2.50$, $p = 0.020$, $d = 0.42$] was significantly lower at follow-up compared to intake.

3.5. Association between indices of neurocognitive difficulties and subjective states

At intake, self-reported cognitive difficulties were strongly associated with greater fatigue symptoms ($r = 0.64$, $p = 0.001$), greater physical symptom severity ($r = 0.66$, $p < 0.001$), and poorer sleep ($r = 0.61$, $p = 0.001$). Psychological distress at intake was not associated with self-reported cognitive difficulties, but was correlated with greater fatigue ($r = 0.41$, $p = 0.044$), increased physical symptom severity ($r = 0.65$, $p < 0.001$), and poorer sleep ($r = 0.50$, $p = 0.011$). Objective

Table 2
Self-reported clinical symptoms at intake and follow-up assessments.

Measure (maximum score)	Intake, *M* (SE)	Follow-up, *M* (SE)	Test statistics			
			F-value	*p*	η_p^2	95% C.I.
SPHERE[a]						
Somatic symptoms (/12)	7.8 (0.6)	4.1 (0.7)**	22.38	<0.001	0.50	2.1–5.3
Cognitive difficulties (/6)	2.9 (0.4)	1.6 (0.4)**	9.17	0.006	0.30	0.4–2.1
Total symptoms (/68)	24.1 (2.1)	13.5 (2.4)**	22.18	<0.001	0.51	6.0–15.4
K10						
Psychological distress (/50)	22.8 (1.1)	19.5 (1.0)**	14.33	0.001	0.37	1.6–5.3
PSQI						
Sleep quality (/21)	7.9 (0.7)	6.1 (0.6)**	13.47	0.001	0.39	0.8–2.7
PSQ						
Perceived stress (/120)	72.4 (2.5)	65.0 (2.6)*	7.87	0.010	0.25	2.0–12.9
SF36[a]						
Physical composite score (/100[b])	41.5 (2.8)	53.4 (3.0)**	19.50	<0.001	0.51	6.2–17.4
Mental composite score (/100[b])	43.8 (2.4)	57.5 (2.6)**	14.45	0.001	0.43	6.1–20.9

[a] These data were collected directly through the clinical service providing the intervention, and as such, a small amount of data is missing.
[b] A higher value reflects better functioning.
* Mean differences significant at $p < 0.05$ level.
** Mean differences significant at $p < 0.01$ level.

Table 3
Neurocognitive performance at intake and follow-up assessments.

Measure	Intake, *M* (SE)	Follow-up, *M* (SE)	Test statistics			
			F-value	*p*	η_p^2	95% C.I.
Digit Symbol Coding						
Accuracy (%)	96.9 (0.8)	98.9 (0.4)*	5.10	0.033	0.17	0.2–3.7
RT (ms)	2124.4 (81.9)	2007.0 (96.3)**	9.80	0.005	0.29	40.0–194.8
Symmetry Identification						
Average string length	11.9 (0.3)	11.9 (0.2)	0.06	0.81	0.00	−0.4–0.5
Moves per character	1.8 (0.1)	1.6 (0.1)	2.44	0.13	0.09	−0.1–0.4
Reversals per character	1.7 (0.4)	1.3 (0.3)	2.76	0.11	0.10	−0.1–0.9
Spatial Working Memory						
Path length	5.6 (0.3)	6.2 (0.5)	4.18	0.052	0.15	0.0–1.3
Stroop						
Accuracy (%)	91.3 (1.4)	94.6 (1.2)*	7.22	0.013	0.23	0.8–5.9
Average RT (ms)	2433.0 (184.3)	2034.3 (130.8)**	18.10	<0.001	0.43	205.3–592.3
Composite Measures						
Accuracy (%)	94.1 (0.8)	96.7 (0.7)**	12.84	<0.001	0.35	1.1–4.2
Response Speed (*ms*)	2355.9 (148.9)	2027.5 (114.0)**	19.79	<0.001	0.45	176.1–480.8

* Mean differences are significant at $p < 0.05$ level.
** Mean differences are significant at $p < 0.01$ level.

indices of neurocognitive performance at intake showed no association with subjective cognitive complaints (all *p*'s > 0.45). However, objective performance accuracy was significantly related to greater HRV at rest (SDNN: $r = 0.56$, $p = 0.003$; RMSSD: $r = 0.46$, $p = 0.020$).

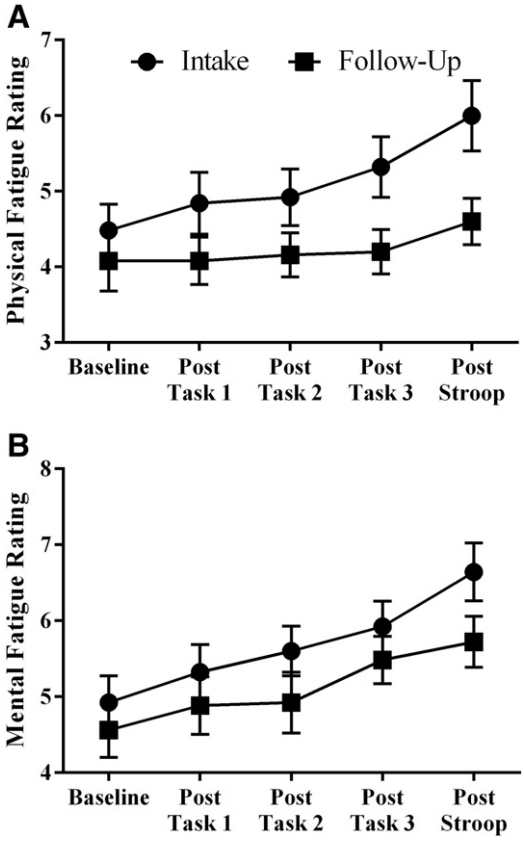

Fig. 2. Ratings of perceived physical (A) and mental (B) fatigue in response to task completion at intake and follow-up assessments. Error bars indicate the standard error of the mean.

Improvements in self-reported cognitive ability between intake and follow-up were positively associated with improvements in self-rated fatigue symptoms ($r = 0.69$, $p < 0.001$) and greater reductions in physical health symptoms ($r = 0.63$, $p = 0.002$). Similarly, greater improvements in psychological health were associated with greater improvements in fatigue ($r = 0.63$, $p = 0.001$), greater reductions in physical symptoms ($r = 0.62$, $p = 0.002$) and greater functional improvements in the mental ($r = 0.57$, $p = 0.009$) and physical ($r = 0.61$, $p = 0.004$) composite scores of the SF-36. Consistent with the observations at intake, and as hypothesized, the magnitude of objective cognitive performance improvement was not associated with the degree of improvement on any subjective measure of cognitive difficulties, or physical or psychological health variables.

3.6. Cardiac autonomic reactivity

Autonomic reactivity was explored by examining changes in HR and HRV from baseline, and time to return to resting HR after completing the Stroop task, across assessments. At follow-up, the Stroop task induced less autonomic reactivity, as reflected by a significantly smaller increase in HR [$F(1,24) = 13.36$, $p = 0.001$, $\eta_p^2 = 0.36$] and a smaller decrease in HRV from baseline indexed by RMSSD [$F(1,24) = 7.75$, $p = 0.01$, $\eta_p^2 = 0.24$]. Time-to-event analysis (Kaplan–Meier, depicted in Fig. 3) identified a faster recovery of resting HR after completing the Stroop task post-intervention [$M = 30.60 \pm 2.52$ s] compared to intake [$M = 49.40 \pm 6.03$ s; $\chi^2(1) = 9.17$, $p = 0.0025$; hazard ratio = 2.91, 95% CI: 1.46–5.79]. However, differences in the speed of recovery to resting HR were not associated with improvements in objective measures of cognitive performance.

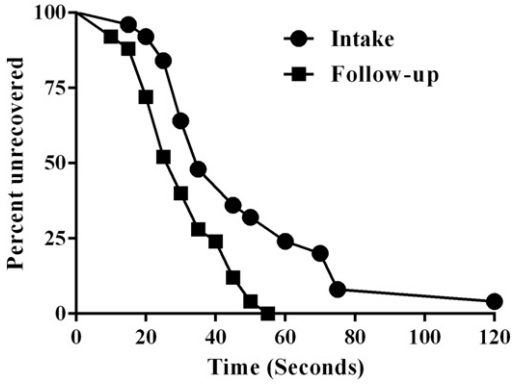

Fig. 3. Percent of participants who had not returned to baseline HR values during the two minute recovery period after completing the Stroop task. HR = heart rate.

4. Discussion

The current study provided the first assessment of improvements in objective neurocognitive performance in patients with CFS subsequent to engaging in a best-practice CBT/GET intervention, and explored the relationships between objective cognitive performance, subjective cognitive complaints and concomitant symptoms, as well as autonomic parameters. Extending previous reports of subjective cognitive improvements [31], we found that patients with CFS additionally showed increased accuracy on some tasks and faster response speeds, accompanied by fewer physical and psychological symptoms, as well as improvements in everyday functioning after completing the intervention. While completion of computer-based neurocognitive tasks after the intervention was experienced as less fatiguing and was accompanied by a significant reduction in autonomic reactivity to the challenge, clinical symptom reports, including fatigue, were not correlated with performance improvements.

Considering that impaired neurocognition in CFS generally manifests independent of mood disturbances [9,13] or functional status [10], the lack of an association between improvements in concomitant symptoms and objective neurocognitive performance is not altogether unexpected. Symptom heterogeneity in patients with CFS [2,54] clearly highlights the need for individualized treatment approaches such as the one employed here, in which symptoms causing the greatest impairment for the individual (e.g., mood, disturbed sleep, physical or cognitive fatigue) are given greater therapeutic attention. The magnitude of improvement in each of these domains therefore differs both within- and between-individuals, making it unlikely to find reliable inter-correlations with improvements in symptoms (particularly with a relatively small sample).

Poor correspondence between an individual's self-rated cognitive ability and objective performance indices is also common [9,36–39]. This discrepancy may result in part from the difficulty to accurately judge one's cognitive abilities, which may be linked to personality, cognitive style, and pre-morbid capacity. For example, individuals with an anxious or neurotic predisposition may be more critical in their self-appraisal of cognitive performance and ability than others [55]. This suggests that self-assessment of cognitive ability, or improvements thereof, can only provide a poor reflection of actual ability to perform neurocognitive tasks. As such, objective assessment of performance should be included routinely in the evaluation of treatment efficacy. Given previous findings in the literature [5,7–10] as well as the observations here, the use of executive functioning tasks that require speeded choice responses that can be implemented in parallel forms, such as digit symbol substitution and Stroop tasks, is recommended. Furthermore, the development of a standardized cognitive test battery would be highly advantageous for evaluating treatment efficacy, but requires more systematic exploration to determine the most relevant tasks for inclusion.

In view of the evidence supporting a state of sympathetic hyperactivity and loss of vagal modulation in CFS [5,17–19], the potential contribution of cardiac autonomic activity to neurocognitive performance outcomes was also explored here. Consistent with previous reports [5,56], higher HRV at rest was associated with more accurate neurocognitive performance. Reliable differences were also observed in autonomic reactivity to the Stroop task across assessments, with significantly less sympathetic activation to the cognitive challenge at follow-up. During rest and recuperation, the prefrontal cortex is known to exert important inhibitory control over limbic and physiological stress response systems [56–59]. Loss of this inhibitory control over stress-related neural networks has been shown to result in a perturbation of autonomic outflow characterized by heightened stress reactivity and reduced vagal tone (indexed as low HRV and prolonged return to resting HR after stress exposure). Behaviorally, such a state interferes with optimal self-regulation by a shift toward inflexible, pre-potent response patterns to environmental challenges [56,58,59]. The observed reduction in stress reactivity and faster return-to-resting HR may be interpreted as a trajectory toward improved vagal functioning as a consequence of the CBT/GET intervention, and are suggestive of pathophysiological mechanisms underlying the disorder.

The combined outcome of improved neurocognitive performance, reduced autonomic reactivity, increased functional capacity, and a reduction of CFS-associated symptoms supports the putative efficacy of CBT/GET-based interventions for CFS. However, the mechanisms underlying performance improvements remain to be established. It may be argued that the observed performance improvements may simply be due to the use of a repeated measures design, with previous exposure, familiarity, and reduced anxiety to neurocognitive tasks eliciting quicker responses during follow-up assessment. However, given that the average period between assessments was 11 weeks, combined with the use of parallel forms of computerized tasks, this is unlikely. Moreover, a previous study utilizing a test–retest paradigm

over two weeks with a comparable version of the Stroop task in healthy volunteers [60] showed an average RT improvement of only 35 ms. In comparison, a substantially greater improvement in RT (~400 ms) without loss of accuracy was observed here post-intervention, indicating that something more than a repetition effect likely underlies performance improvements.

A novel feature of the intervention employed here was the patients' engagement in daily structured mental activity, the intensity and duration of which was gradually increased at an individually-tolerated pace. Analogous to graded exercise [26], cognitive activity was progressively increased allowing the threshold at which tasks can be performed without experiencing fatigue to be increased. Thus, neurocognitive tasks requiring sustained attention and speeded responses may be better tolerated after increasing the individual's threshold over the 12-week intervention. Indeed, this appears to be the case here, as patients with CFS performed tasks quicker without loss of accuracy and with less stress reactivity, and experienced less fatigue after task completion at follow-up. It is possible, as a consequence of such cognitive training, that less neural work is required for task completion, accompanied by a reduction in the engagement of stress-responsive systems. Together, this may allow attention to be sustained for longer periods while inducing less fatigue [5,14].

4.1. Limitations

The use of a within-subject design without an appropriate comparison group limits the findings of this study. The diagnosis of CFS for all patients was confirmed by clinical staff during the delivery of the first week of the treatment program, which precluded the option of waitlist control comparisons. Similarly, with CBT/GET considered best-practice for CFS, withholding treatment without a suitable alternative in a randomized control design would violate the principles of clinical equipoise. With the marked heterogeneity in patients with CFS, within-subject comparisons provide a more meaningful evaluation of treatment efficacy. Notably, the current sample was representative of those attending tertiary referral clinics, and was closely comparable to samples previously obtained from the same clinic [5,19]. However, this patient cohort tends to fall toward the lower end of the severity spectrum, and may be substantively different from those too impaired to attend such an intervention (i.e., patients with CFS that are bedridden). Thus, the efficacy of CBT/GET interventions in improving neurocognitive performance, and the relationship between objective performance and concomitant symptom improvements remain to be examined for those individuals with more severe functional impairment.

5. Conclusion

Patients with CFS demonstrated objective improvements in some neurocognitive performance tasks after completing an individually tailored CBT/GET program incorporating a cognitive training component. These improvements were accompanied by reduced autonomic reactivity to a cognitive challenge as well as reductions in clinical symptoms and improved everyday functioning. These findings provide the first objective evidence of neurocognitive improvements subsequent to a best-practice intervention for CFS, and suggest that a reduction in reactivity in stress-responsive neural networks may contribute to such functional improvements. The poor correspondence between subjective complaints and actual task performance highlights the need to include objective measures of performance when evaluating the efficacy of behavioral interventions for CFS.

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