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Cognitive remediation training improves performance in patients with chronic fatigue syndrome

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ABSTRACT

Neurocognitive disturbance with subjectively-impaired concentration and memory is a common, disabling symptom reported by patients with chronic fatigue syndrome (CFS). We recently reported preliminary evidence for benefits of cognitive remediation as part of an integrated cognitive-behavioral therapy (CBT)/ graded exercise therapy (GET) program. Here, we describe a contemporaneous, case-control trial evaluating the effectiveness of an online cognitive remediation training program (cognitive exercise therapy; CET) in addition to CBT/GET (n = 36), compared to CBT/GET alone (n = 36). The study was conducted in an academic, tertiary referral outpatient setting over 12 weeks (11 visits) with structured, home-based activities between visits. Participants self-reported standardized measures of symptom severity and functional status before and after the intervention. Those in the CET arm also completed standardized neurocognitive assessment before, and following, treatment. The addition of formal CET led to significantly greater improvements in self-reported neurocognitive symptoms compared to CBT/GET alone. Subjective improvement was predicted by CET group and lower baseline mood disturbance. In the CET group, significant improvements in objectively-measured executive function, processing speed, and working memory were observed. These subjective and objective performance improvements suggest that a computerized, home-based cognitive training program may be an effective intervention for patients with CFS, warranting randomized controlled trials.

1. Introduction

Chronic fatigue syndrome (CFS) is a complex disorder characterized by persistent fatigue and reduced capacity to sustain effortful physical and mental activity (Fukuda et al., 1994; Wilson et al., 2001). The pathophysiological mechanisms underlying these signature features of CFS are not well understood (Afari and Buchwald, 2003), although it is likely that the primary site of disturbance is in the brain (Lloyd and Meer, 2015; Prins et al., 2006). Many patients report that neurocognitive difficulties are equally, if not more, debilitating than the physical manifestations of fatigue (Cockshell and Mathias, 2010; Cvejic et al., 2016a; Nijhof et al., 2012) impacting significantly on everyday functioning (including occupational and social functioning). In terms of neurocognitive disturbance, patients with CFS complain of unexplained reduction in the capacity to sustain mental activity requiring executive functioning, as well as mental clouding, and difficulties with short-term recall. In comparison to the prominent subjective complaints, formal neurocognitive performance testing has revealed only relatively subtle decrements in attention, processing speed, and working memory (Cockshell and Mathias, 2010; Cvejic et al., 2016a; Majer et al., 2008; Michiels and Cluydts, 2001; Michiels et al., 1998). Despite a consensus that neurocognitive disturbance is a cardinal symptom of CFS, there are no controlled studies examining cognitive interventions targeting this symptom domain.

The only therapeutic interventions with consistent evidence for overall symptom reduction and improvement in functional status in patients with CFS are cognitive-behavioral therapy (CBT; Sharpe et al., 1996) and graded exercise therapy (GET; Larun et al., 2015; Smith et al., 2015). We have previously reported the positive outcomes of an integrated CBT and GET intervention (Sandler et al., 2016). In addition, we recently reported beneficial effects of a pilot cognitive intervention, which we have termed cognitive exercise therapy (CET), in which

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patients in the CBT / GET program were also encouraged to gradually increase cognitive tasks such as reading, by completing one or more timed sessions of such structured mental activity every day, analogous to GET (Cvejic et al., 2016b).

Computerized cognitive remediation has been demonstrated to be effective in reducing cognitive dysfunction in other clinical populations, including cancer survivors with ongoing cognitive impairment (Kesler et al., 2013; Spencer, 2006), schizophrenia (Wykes et al., 2007), attention deficit hyperactivity disorder (Stevenson et al., 2002), and ageing-associated mild cognitive impairment (Finn and McDonald, 2011). The rationale for cognitive remediation in these various conditions may primarily be rehabilitative (Fleeman et al., 2015), although there is growing evidence for functional reorganisation within the brain, especially in prefrontal, occipital and anterior cingulate regions after repeated performance of working memory and executive tasks (Isaac and Januel, 2016; Porter et al., 2013; Thorsen et al., 2014). The efficacy of such interventions have typically been measured both via self-report and also formal neurocognitive performance assessments. Currently, there are no guidelines regarding the number of sessions, or duration, of such cognitive training programs (Kesler et al., 2013). However, positive findings have been reported from programs ranging from 4 to 12 weeks or more, characterized by training that was spread across sessions accumulating to at least several hours in total (Finn and McDonald, 2011).

In the literature relating to cognitive remediation training, two potential limitations are: durability of improvement (long term benefit); and generalization of cognitive improvements to everyday functioning (Green and Bavelier, 2008). The first limitation relates to the manner in which task difficulty is progressed, the motivational state of the learner, and the type of feedback the training provides, which are all key variables to ensuring a sustained improvement rather than a transient adaptation. Pertinent to the second limitation is that training paradigms which successfully demonstrate learning that generalizes to real-life experiences need to be complex; train at the correct level to allow both mastery and challenge; require appropriate participant motivation and arousal; and provide feedback (Ahissar and Hochstein, 2000, 2004; Sireteanu and Rettenbach, 2000).

The current study considered these issues in the design of a formal computerized cognitive training program to implement in patients with CFS, who are heterogeneous in terms of cognitive ability, level of functioning, and motivation. The program included repetitive practice to foster implicit learning (Fisher et al., 2009), as well as hierarchical and adaptive difficulty levels. An internet-based program was selected that determined the participant's ability on each task and then provided training at that level with reflexive adjustment in task difficulty following success or failure on task items (i.e., inter-task adaptation). Additionally, there was significant variability across tasks in terms of duration, modality, appearance and cognitive domain being assessed. Finally, the platform selected provided regular feedback and flexibility in terms of implementing breaks between tasks. These determinants meant that the likelihood of both 'near' transfer of learning – i.e., closely related contexts and performances (Perkins and Salomon, 1992) and 'far' transfer of learning – i.e., different contexts and performances (Perkins and Salomon, 1992) were likely to be optimized. By training on cognitive tasks requiring executive functioning including working memory the likelihood of generalization to real-life tasks was enhanced (Klingberg, 2010). It is generally accepted that executive functioning is integral to adaptive responses to the changing demands of the environment (Hanna-Pladdy, 2007).

The aim of this study was to evaluate the benefits of the addition of an internet-based cognitive remediation program to CBT / GET for patients with CFS.

2. Methods

2.1. Participants

Two groups of 36 patients with CFS were recruited from an academic, tertiary referral clinic specializing in management of chronic fatigue states in Sydney, Australia. This clinic provides an integrated CBT and GET program for patients with CFS delivered in 11 sessions over 12 weeks (Sandler et al., 2016). All patients had been diagnosed according to the international diagnostic criteria for CFS with exclusion of alternative medical or psychiatric explanations for the fatigue state (Fukuda et al., 1994). Individuals with only minimal complaint of neurocognitive disturbance, or with limited self-reported computer literacy, were excluded. Allocation occurred in consecutive time windows over a two year period; approximately consecutive patients (as excluded patients were not offered enrolment) were recruited and initially offered standard CBT and GET, followed by approximately consecutive patients who were offered enrolment into the CET group. As such, the allocation of patients was not concealed from the recruiting researcher. Informed written consent was obtained from each patient for this research evaluation. The study was approved by the University of NSW Human Research Ethics Committee (HREC No. 12212).

2.2. Procedures

2.2.1. Standard CBT and GET protocol

The standard CBT and GET protocol was developed within a clinical academic framework, and provides integrated multi-disciplinary treatment with a clinical psychologist and an exercise physiologist (Sandler et al., 2016). The protocol includes four core modules: psycho-education, activity pacing and graded exercise therapy, interventions for the sleep-wake cycle, and an intervention for neurocognitive disturbance. This standard neurocognitive intervention involved advice on graded training in everyday mental tasks (such as reading, or working on the computer) that were identified by the patient as cognitively effortful (Cvejic et al., 2016b). In addition, three optional modules of problem-focused CBT for management of depression, anxiety, and coping were included, as appropriate, by the clinicians to form an individually-tailored treatment approach based on assessment of these co-morbid problems. The two clinicians maintained regular communication to ensure coordinated administration of CBT and GET elements.

2.2.2. Cognitive remediation training program

The CET intervention consisted of an online, computerized training program completed at home by participants on their personal computer. The program included 24 different game-based tasks designed to improve attention, working memory, processing speed, and executive functioning. This program was selected by a neuropsychologist (R.M.) using existing cognitive exercises created by Lumos Labs Inc. (San Francisco, CA; http://www.lumosity.com/). The tasks were chosen based on the cognitive domains being affected in CFS (Cockshell and Mathias, 2010; Cvejic et al., 2016a), with a preponderance of tasks focussed on executive functioning, complex attention, and processing speed. Additionally, tasks with combined visual and verbal stimuli were favoured. The tasks were intended to train working memory, cognitive flexibility, and complex attention. Task difficulty was reflective of intra- and inter-task performance, and was determined by programmed algorithms. Participants were required to login to an individual online account, and complete sessions of 3–5 exercises up to a total of 40 sessions. Each time the participant logged in, the program automatically delivered the exercises assigned for that session. Each task contained written and animated instructions. The program provided immediate visual and auditory feedback, and reinforcement regarding performance. Guidelines regarding the recommended frequency of sessions and breaks within the session were tailored by the clinical psychologist on the basis of the participant's baseline level of cognitive