Chapter

Hypothalamic-Pituitary-Adrenal (HPA) Axis and Chronic Fatigue Syndrome in Older Adults: The Rehabilitation Perspectives

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Abstract

Chronic fatigue syndrome (CFS) is a long-term and debilitating condition that regards as a neurological disease. Its symptoms include profound physical and mental fatigue (characteristically made worse by exertion), muscle and joint pain, disturbed sleep, and both concentration and memory problems. CFS is a kind of human stress-related disorders that are characterized by alterations in hypothalamic-pituitary-adrenal (HPA) axis activity. Investigation of abnormal activity of the HPA axis in various neurological and neuropsychiatric disorders can date back at least 60 years, and its relation to CFS had been reported in the early 1990s. This chapter further disseminated updated evidence for disruption of HPA function in CFS, with the explanation on the relationship between cytokines and HPA activities. Moreover, very limited literature had addressed the importance of rehabilitation to them . This chapter addresses this gap by sharing a pilot rehabilitation outcome on a single-blinded randomized control trial with a parallel group experimental design in the application of activity scheduling (AS) program of occupational therapy for a group of community-dwelling older adults with CFS. The primary objective is to study the outcome of physical functioning of individual participants. The second objective is to study the outcome of AS on impact of caring role through assessing individual caregivers' perceived burden in care. The third objective is to study the time that needed in taking care; individuals' perception of enjoyment and achievement in their participated activities will be evaluated. There was a significant effect of AS on the physical functioning of participants as measured by Functional Independence Measure (FIM), as the primary outcome measure, in experimental group, with Wilk's $\lambda = 0.72$, $F\ (2,57) = 18.75$, $p < 0.001$. Moreover, in secondary outcome measures, there is a significant decrease in the impact of caring role as reflected by their perceived burden as measured by the Chinese Zarit Burden Interview (CZBI) in caring for experimental group, with Wilk's $\lambda = 0.72$, $F\ (2,97) = 18.75$, $p < 0.001$. Another study set out to examine the effect of time on caring activities for those recruited couples in AS group. There was significant effect of AS on caring activities with Wilk's $\lambda = 0.71$, $F\ (2,97) = 12.47$, $p < 0.001$. With proper coaching and regular facilitation regarding AS, activity participation in older adults with CFS can be greatly enhanced. Behavioral intervention, such as AS, can supplement therapeutic treatment or may lead to decline in CFS symptoms.

Keywords: chronic fatigue syndrome (CFS), hypothalamic-pituitary-adrenal (HPA) axis, activity scheduling (AS)

1. Introduction

There are two perspectives in developing this chapter [1–3]. The first perspective is to provide an up-to-date and intensive literature search in analyzing the physiological, neurological, and molecular factors that lead to chronic fatigue syndrome (CFS). This part will provide the reader with background information on the importance of neuroimaging, clinical relationship between CFS and hypothalamic-pituitary-adrenal (HPA) axis, and its physiological causes with different cytokines. The second perspective addresses the impact of CFS to individuals' life role through the behavioral intervention by activity scheduling (AS). Its effectiveness was examined by a single-blinded randomized control trial with a parallel group experimental design.

CFS is a complex illness characterized by a broad range of physiological, cognitive, neurological, and emotional symptoms [4]. The signs and symptoms of CFS include fatigue, loss of concentration, unexplained muscle or joint pain, headache, unrefreshing sleep, and extreme exhaustion [5]. It continues to evolve as a disabling phenomenon characterized by debilitating fatigue and consequential components that limit the functional ability of persons afflicted with the disease [6]. One important theory in the cause of CFS is the deficits in the central nervous system and HPA in short [4, 7, 8].

1.1 Biomedical marker: neuroimaging

The proper diagnosis of CFS should come with specific biomedical markers, such as neuroimaging, in order to confirm with the subjective information, signs, and symptoms provided by the patient in order to make the proper clinical diagnosis with strong clinical definition of this syndrome [9]. Reported cognitive difficulties and complaints of headache can be scientifically reviewed by brain imaging [10]. Three neuroimaging approaches have been commonly used clinically. The first of these is the functional magnetic resonance imaging (fMRI), which allows researchers to look at where in the brain activation is associated with a task or an experience [11, 12]. The diffusion tensor imaging (DTI) enables researchers to look at the health of the brain's white matter [13], and *voxel-based morphometry* (VBM) allows researchers to investigate structural changes in the brain [14, 15]. These three approaches were used to scientifically examine by imaging on how likely it was for the reported fatigue from patients. Moreover, a number of well-cited correlational studies between neuroimaging and clinical measurements showed the strong evidence in applying neuroimaging [16] and particularly for CFS [17]. There was a significant negative correlation between micro-structural integration, such as radial kurtosis, reflecting biological microenvironment imaging metric in the hypothalamus [17, 18] and fatigue-related scale in traumatic patients [19].

1.2 Relationship between CFS and HPA

Symptoms of CFS include persistent fatigue, difficulty with memory and concentration, a disturbed sleep pattern, and severe musculoskeletal pain [20]. The symptoms displayed vary from individuals; some may need to remain bed rest for long periods of time [8], while others are able to manage their fatigue by maintaining their own activities of daily living [3]. CFS presents with symptoms

and abnormalities of HPA [21]. The HPA axis dysregulation may have a causal role in CFS [1, 19, 22]. Diagnosis is difficult because there is no diagnostic marker for the disease and no standard test; rather, a diagnosis is based on the description and duration of symptoms [2], degree of impairment [7], and clinical findings that rule out other diseases [23]. The effect on lifestyle and self-image are considerable because of significant changes in participation in activities, identity, and occupational issues [24].

Dysregulation of the biological systems which mediate the response to stress potentially has an important role in the etiopathogenesis of CFS [25, 26]. The neurobiological stress system comprises a range of networks that form intricate pathways; an important part of this is the HPA axis [27, 28] which is a self-regulated feedback system which contributes to the maintenance of homeostasis and which is impacted by multiple factors such as time of day and physical and psychological stressors [20]. CFS is a debilitating illness which was classified as a neurological disease [29]. Experimentally induced, or pathological, hypocortisolemia (as in Addison's disease) is associated with symptoms typical of CFS, including fatigue, weakness, and abdominal pain, but it is also associated with a range of other features which are not typical of CFS [30]. Inactivity, sleep disturbance, psychiatric comorbidity, medication, and ongoing stress experienced by people with CFS will affect HPA axis function [1, 28, 31, 32], and the findings that HPA axis dysregulation is more prominent in patients with a longer duration of illness suggest that the endocrine changes may be secondary [33, 34]. Researchers further supported that the individual variation in HPA axis regulation in patients with CFS argues for a heterogeneous and multifactorial bidirectional relationship between the endocrine disturbance and the disorder [35].

1.3 Physiological causes of CFS

Feelings of fatigue are common symptoms associated with infectious diseases and many other physical [36] and mental pathologic conditions [37]. Since the early 1990s, there has been a systematic study on changes in CFS that occur with infection or following microbial product-induced cytokine production in relation to CFS [38–40]. Moreover, research has shown a strong interaction between the HPA axis and the immune system [41, 42]. Some cytokines have stimulating effect on the HPA axis, whereas cortisol, the end product of the HPA axis, suppresses secretion. Elevated tumor necrosis factor α (TNFα), interleukin-2 (IL-2), and/or interleukin-6 (IL-6) levels may be the mediators of fatigue associated with primary or secondary adrenal insufficiency.

1.4 Tumor necrosis factor α

TNFα is an inflammatory cytokine that is predominantly produced by activated macrophages. In addition, TNFα is also expressed by other immune cells (lymphoid cells, mast cells, fibroblasts) as well as endothelial cells and nerve cells. TNFα is a key signaling molecule for cell death process (by activation of NF-κB and JNK-MAPK pathways). Therefore, TNFα may indicate pathological mechanisms of numerous diseases, including neural degeneration common to neurocognitive disorders. Indeed, TNFα has been associated with Alzheimer's disease and mild cognitive impairments. Increased levels of TNFα have been found in serum and CSF [43], as well as postmortem brain tissues [44] of Alzheimer's disease patients compared with control subjects. Moreover, the elevation in TNF was apparent before the emergence of overt cognitive deficits [44]. Its potential as an early marker therefore certainly warrants investigation, especially from a longitudinal perspective. TNFα secretion

in young adults showed a statistically significant circadian rhythm with a peak close to the offset of sleep [45]; such a rhythm was not present in older adults [46].

1.5 Interleukin-6

IL-6 is a pleiotropic cytokine released by a host of immune cells (T cells and monocytes) [47], and it plays a critical role in the regulation of the inflammatory responses in the host immune defense. Specifically, IL-6 stimulates B-cell differentiation and antibody production. Higher levels of IL-6 are associated with various autoimmune and inflammatory diseases. The risk of a decline in Mini-Mental State Examination (MMSE) over a 10-year period is higher among people with higher IL-6 levels (odds ratio = 1.81, $CI_{95\%}$, 1.20, 2.71) [48]. The same study also showed that IL-6 levels predicted the magnitude of 10-year decline in reasoning (high IL-6, 20.35; $CI_{95\%}$, 20.37, 20.33 vs. low IL-6, 20.29; $CI_{95\%}$, 20.31, 20.27). Through synergistic interaction with other cytokines, IL-6 also regulates platelet production by bone marrow cells (via synergy with IL-3-regulated megakaryocyte development), secretion of acute-phase proteins by liver cells (via synergy with IL-1), and bone homeostasis (e.g., via RANKL-mediated mechanism) [48].

IL-6 in humans caused profound somnolence and fatigue [49]. Literature reviewed the decrease in overall secretion of IL-6 is associated with a good sleep that is associated with decreased exposure of tissues to the proinflammatory [50] and potentially detrimental actions of IL-6 on the cardiovascular system, insulin sensitivity, and bones [51–53].

1.6 Adrenal insufficiency

Adrenal insufficiency is associated also with chronic fatigue [4, 54]. Previous studies indicated that untreated patients with adrenal insufficiency demonstrated increased sleep fragmentation [55, 56], findings that may explain the patients' fatigue. These sleep abnormalities were reversed following treatment with a replacement dose of hydrocortisone. These results suggest that cortisol secretion may be needed to facilitate both initiation and maintenance of REM sleep. It should be noted that in normal individuals, exogenous glucocorticoids have been found to reduce REM sleep [57]. Behaviorally, excessive daytime sleepiness is prominent in patients with secondary adrenal insufficiency [58].

1.7 Impact of CFS to individuals' life roles

Fatigue, a poorly defined phenomenon and subjective in nature, was described by CFS sufferers as continuous, resulting in diminished engagement in activities [59]. It was found that most individuals with CFS actually underreported their disabilities [6]. Moreover, functional limitations consequently affect the successful completion of tasks and roles [3]. The loss or diminishment of these roles as providers, family members, and peers affects not only functional relationships but also the quality of life of their partners, family members, and significant others [60, 61].

1.8 Intervention

Because the etiology of CFS is unidentified, the relief of symptoms is the primary goal when treating this population. Previously, the effectiveness of many of the treatments was unproven (Berne, 2002). Nowadays, apart from pharmacological interventions [62, 63], some directions were shown to be effective,

like nutrition [64] and use of exercise [65–68] and cognitive behavioral therapy [69, 70]. The general consensus was that graded exercise therapy (GET), cognitive behavioral therapy (CBT), and "pacing" (energy conservation) showed the most positive results.

1.9 Consideration of rehabilitation for CFS

Literature has shown behavioral intervention can supplement therapeutic treatment [71] or may lead to decline in CFS symptoms [72, 73]. Occupational therapy addresses problems for those individuals at risk or already experiencing problems in performing activities that affect functional independence, health, and wellbeing due to accident, illness, or delays [3]. As a holistic practice, occupational therapy addresses individuals' physical, social, and psychological areas of life. Much has been contributed by occupational therapists to populations with chronic disease and populations with fatigue, loss of concentration, unexplained musculoskeletal pain, and amotivational symptoms that are similar to CFS [6]. The focus of occupational therapy is placed on individuals' meaningful participation of activities [74]. This may act as structuring the engagement in activities of older adults need to do (self-care), enjoy doing (leisure), and do for progress (productivity) and help them to develop a sense of self-worth and wellbeing [75–78].

Activity scheduling is a tailor-made personalized activity that can be used as a media for behavioral activation [79, 80]. AS is the technique that compromise the advantages of GET, CBT, and energy conservation techniques. It has been established as a core component of evidence-based treatment for depression with equivalent outcomes to cognitive behavioral therapy [81], through introducing small and easily achievable changes, gradually building up levels of activity toward individualized short-term to long-term goals [80]. In their meta-analysis on randomized effect studies of AS, 16 studies with 780 subjects were included. The pooled effect size indicating the difference between AS intervention and control conditions yield a large effect size of 0.87 (95% CI, 0.60–1.15). Moreover, there was a robust association between AS during treatment and self-reported activity engagement as well as clinically significant improvements in depression [82, 83]. AS is an effective behavioral intervention that can address social isolation in older adults [83, 84]. Older adults can experience higher degrees of engagement in social activities, more chances to experience positive emotions [83], and a sense of not being negatively affected or neglected in their limited interactions with their environments [85]. Moreover, AS has been shown to be effective in enhancing individuals' quality of life through increasing their active participation in activities [80, 82].

This study is a pioneer attempt to examine if AS would show its effectiveness in the management of older adults whom suffered from CFS. The primary objective is to study the outcome of physical functioning of individual participants. The second objective is to study the outcome on impact of caring role through assessing individual caregivers' perceived burden in care. The third objective is to study the time that needed in taking care and individuals' perception of enjoyment and achievement in their participated activities.

2. Methods

This 10-week longitudinal study was a single-blinded randomized control trial with a parallel group experimental design.

2.1 Participants

Older adults with CFS and their spouse caregivers would be recruited. Both of them should be age-ranged from 65 to 70 years. Participants with CFS should have a diagnosis in their medical history under the ICD-10 criteria which was diagnosed by a physician. Individuals' cognitive function would be screened by the Montreal Cognitive Assessment Hong Kong Version (MoCA-HK) [86]. To ensure participants having intact cognitive function, both participants with CFS and their spouse caregivers would be screened with MoCA-HK and should have a score >26. After provision of clear verbal and written explanation on the purpose of this study, they will provide their consent with the presence of their social workers. Approval was given by the local research ethics committee, and the study was conducted according to the Declaration of Helsinki.

2.2 Interventions

Participants with CFS and their spouse caregivers in both groups received a health education program with weekly themed topics, such as the importance of exercise and healthy eating, sleep management, counseling, acceptance therapy, and commitment therapy in the first and second weeks. For the following 8 weeks, they would be randomized and received one of the two interventions. Healthcare Education group, as control group, would receive eight weekly education sessions on health and physical care education offered by lecturers of occupational therapy from a local university. In experimental arm, Healthcare Education-Activity Scheduling (Healthcare ED-AS group) would receive the same health and physical care education program and AS training, focusing on pleasant activities and improving communication.

After receiving three-session training from two occupational therapists, AS became a caregiver-delivered intervention, and it involves five steps: (1) baseline assessment, (2) discussion, (3) homework, (4) enhancing motivation and encouragement, and (5) reassessment. Moreover, those two occupational therapists who conducted the training would provide weekly telephone follow-up for caregivers as the strategy in encouraging individuals' completion of program.

In the baseline assessment, researcher interviewed each couple in their own home. The occupational therapist would document the activities pattern of older adults over the course of a week. For each activity, participants should rate their own sense of enjoyment (E) and achievement (A) between 0 and 10 ("0" = no sense of enjoyment or achievement and "10" = you enjoyed the activity very much or felt a strong sense of achievement). Participants would mark this immediately after completing the activity or at the end of the day. Moreover, measures on the amount of time in taking care and individuals' perception of enjoyment and achievement in their participated activities would serve as the baseline reading of their current activity levels. In discussion, activities chosen in AS had to be related on what the participants had been avoiding and help them to act in accordance with their valued directions. Spouse caregivers were asked to monitor the mood when they participated in their scheduled activities. They would be evaluated whether or not what they did was in keeping with their goals and valued directions. They were encouraged to make notes, and the occupational therapist would provide regular support in regard to assessing areas that were still avoided and activities that are overused. In homework, spouse caregivers could use the activity achievement worksheet to indicate how they spent their time, as well as how the activities affected their mood. In enhancing motivation and encouragement, individuals' adherence and compliance to AS would be documented through this homework in reflecting their level of participation. Strategies on regular telephone follow-ups would be used to enhance

individuals' motivation to complete the 8-week intervention. Depending on the couple's progress, changing or adding activities might be appropriate. In reassessment, the set of measurements as in the baseline measures would be reassessed.

2.3 Outcomes/instrument

The primary objective is to study the outcome of physical functioning of individual participants. The second objective is to study the outcome of AS on impact of caring role through assessing individual caregivers' perceived burden in care. The third objective is to study the time that needed in taking care; individuals' perception of enjoyment and achievement in their participated activities will be evaluated.

The primary outcome on impact of physical functioning is measured by the Functional Independence Measure (FIM). It is an 18-item measurement tool that explores an individual's physical, psychological, and social function [87]. The tool is used to assess a patient's level of disability as well as change in patient status in response to rehabilitation [88, 89] or medical intervention [90]. FIM is comprised of 18 items, grouped into 2 subscales—motor and cognition. The motor subscale includes eating, grooming, bathing, dressing upper body; dressing lower body, toileting, bladder management, and bowel management; transfers, bed/ chair/ wheelchair; transfers, toilet; transfers, bath/shower; walk/wheelchair; and stairs. The cognition subscale includes comprehension, expression, social interaction, problem-solving, and memory. Each item is scored on a 7-point ordinal scale, ranging from a score of 1 to a score of 7. Score 1 is total assistance with helper, 2 is maximal assistance with helper, 3 is moderate assistance with helper, 4 is minimal assistance with helper, 5 is supervision or setup with helper, 6 is modified independence with no helper, and 7 is complete independence with no helper. The higher the score, the more independent the patient is in performing the task associated with that item. The total score for the FIM motor subscale (the sum of the individual motor subscale items) will be a value between 13 and 91. The total score for the FIM cognition subscale (the sum of the individual cognition subscale items) will be a value between 5 and 35. The total score for the FIM instrument (the sum of the motor and cognition subscale scores) will be a value between 18 and 126.

The secondary outcome is to study the caregiving burden. The 22-item Chinese Zarit Burden Interview (CZBI) [91, 92] would be used to measure individuals' care burden. Scores range from 0 to 88 and higher scores indicate higher levels of burden.

The third outcome will be individuals' record of time, and activities; their perception of enjoyment and achievement will be recorded in the activity achievement worksheet (**Figure 1**) by the family caregivers. The activity achievement worksheet helps caregivers to plan activities for the week ahead that give opportunities for

Record of Activities	Sunday			Monday			Tuesday			Wednesday			Thursday			Friday			Saturday		
	Activity	E	A	Activity	E	A	Activity	E	A	Activity	E	A	Activity	E	A	Activity	E	A	Activity	E	A
0600-0800																					
0800-1000																					
1000-1200																					
1200-1400																					
1400-1600																					
1600-1800																					
1800-2000																					
2000-2200																					
2200-2400																					

Sense of enjoyment (E) and achievement (A) between 0 and 10 ('0' = no sense of enjoyment or achievement and '10' = you enjoyed the activity very much or felt a strong sense of achievement).

Figure 1.
Activity achievement worksheet.

social interaction, enjoyment, and social interaction with others. To ensure the measure of fidelity of the AS program, both experimental and control group will log their activities. With the presence of blinded assessor, these outcome measures would be administrated in baseline and after the 8-week program.

3. Results

From August 2014 to August 2018, a total of 64 community-dwelling couples, composed of older adults with CFS and their spouse caregivers, were recruited from two local day activity centers for older adults. Four participants failed to complete the consent due to language barrier. Of these couples, 30 were randomly assigned to control group and 30 were randomly allocated to experimental AS group. Two pairs of couples in control group defaulted their follow-up after the first week program. In the experimental group, one pair of couples defaulted follow-up and another one family caregiver passed away within the first two sessions of the study. Therefore, 56 pairs of couples were resulted as shown in **Figure 2**.

3.1 Baseline data

The 28 pairs of couples in the Healthcare Education group comprised 14 males and 14 females with ages ranging from 66 to 82 years (mean age = 69.25, SD = 16.32) and educational levels from 3 to 13 years (mean = 7.82, SD = 4.29). Moreover, the 28

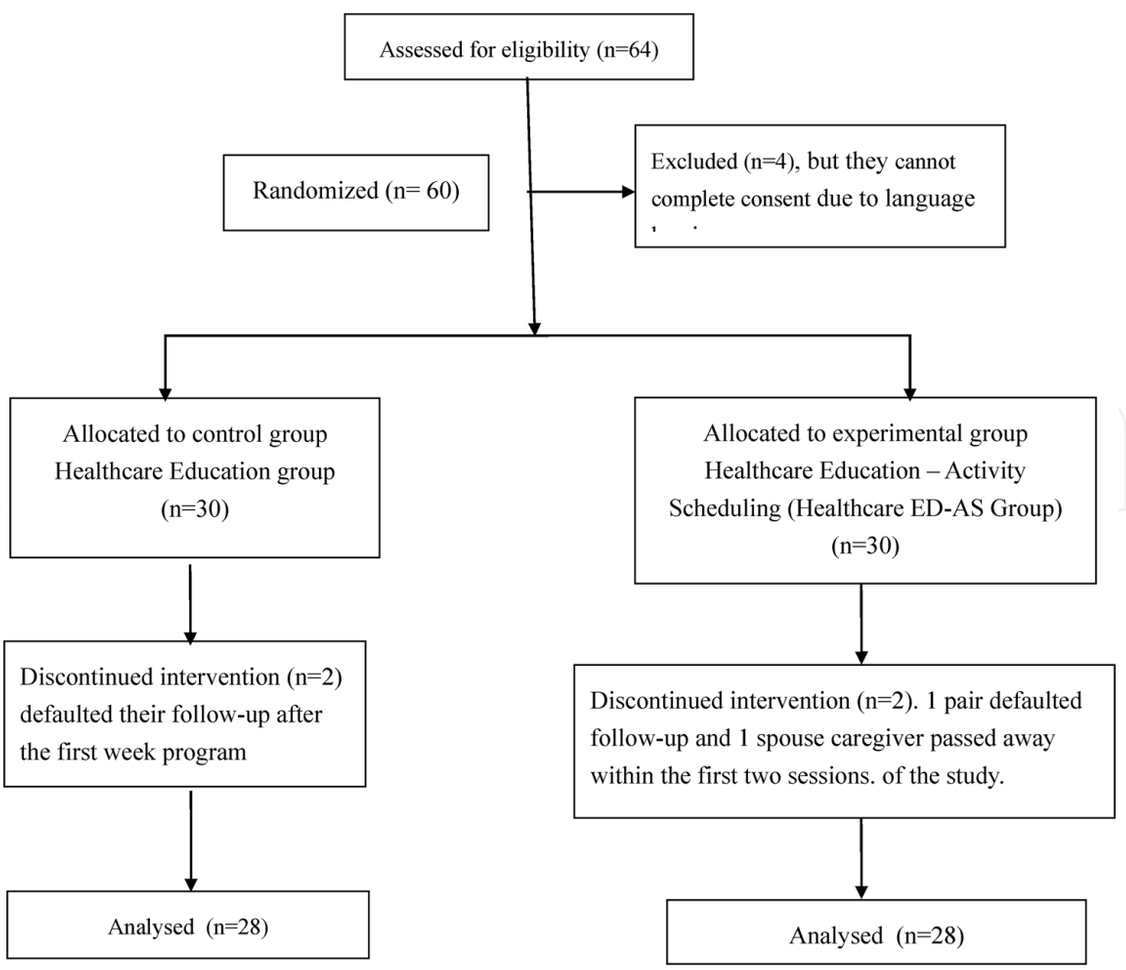

Figure 2.
Participant flow in CONSORT diagram.

participants in the Healthcare Education-Activity Scheduling (Healthcare ED-AS group) were composed of 17 males and 11 females, with ages ranging from 67 to 84 years (mean age = 70.23, SD = 12.34) and educational levels from 3.5 to 13.2 years (mean = 7.52, SD = 5.23). All recruited participants were home living. There were no significant differences between the two groups regarding age, years of education, or cognitive ability at baseline, as determined by the MoCA score (as shown in **Table 1**), and outcome measures among these groups are depicted in **Table 2**.

There were no significant differences in the baseline measurements taken for primary outcome measure on individuals' physical functioning as measured by FIM (with Cohen's d ranged from 0.02 to 0.08, $p > 0.05$). Moreover, there were no significant differences in individuals' impact of caring role (with Cohen's d ranged from 0.02 to 0.08, $p > 0.05$) and no significant difference in the amount of time spent taking care of relatives with CFS (with Cohen's d ranged from 0.03 to 0.06, $p > 0.05$).

After 8-week intervention, there were some changes in different outcome measures. For the primary outcome measure on individuals' physical functioning, paired t-test revealed a significant improvement in motor-FIM score in experimental group (with t (59) = −0.38, $p < 0.05$, with Cohen's d ranging from 0.30 to 0.44, 95% CI, 0.25 to 0.78), but not in control groups ($p > 05$).

In secondary outcome measure on the impact of caring role that was assessed using the CZBI, paired t-test revealed a significant improvement in uncertainty, subjective feeling, negative emotion, dependency, feelings of inadequacy, and total burden of care in experimental group (with t (59) = −0.38, $p < 0.05$, with Cohen's d ranging from 0.30 to 0.44, 95% CI, 0.25 to 0.78), but not in control groups ($p > 0.05$).

In the third outcome measure on caring activities, there was a significant decrease in reported caring activities on communication, use of transport, dressing, eating, and looking for appearance with Cohen's d ranging from 0.23 to 0.53.

	Healthcare Education group (n = 28)	**Healthcare Education-Activity Scheduling (Healthcare ED-AS group) (n = 28)**
Gender		
Older adult with CFS	Male: 14 Female: 14	Male: 17 Female: 11
Spouse caregivers	Male: 14 Female: 14	Male: 11 Female: 17
Age		
Older adult with CFS	69.25 ± 5.32	70.23 ± 5.32
Spouse caregivers	71.23 ± 4.68	71.49 ± 3.73
Education level of caregivers	From 3 to 13 years (mean = 7.82 ± 2.18)	From 3.5 to 11 years (mean = 7.79 ± 2.06)
Cognitive function (Montreal Cognitive Assessment-HK version)		
Older adults with CFS	18.16 ± 0.64	18.06 ± 0.52
Spouse caregivers	27.16 ± 0.58	28.06 ± 0.39

Table 1.
Baseline demographics and clinical characteristics for each group.

	Healthcare Education group (n = 28)	Healthcare Education-Activity Scheduling (Healthcare ED-AS group) (n = 28)	Healthcare Education group (n = 28)	Healthcare Education-Activity Scheduling (Healthcare ED-AS group) (n = 28)
	Before intervention		**After 8-week intervention**	
Primary outcome measure				
Functional Independence Measure				
Motor-FIM	48.07 ± 1.35	48.23 ± 1.37	51.97 ± 1.57	77.47 ± 1.71
Cognitive-FIM	18.07 ± 1.36	18.19± 1.31	21.87 ± 1.82	26.53 ± 1.68
Total-FIM	66.13 ± 4.56	67.25 ± 4.35	83.96 ± 2.82	102.63 ± 1.71
Secondary outcome measure				
Caregiver burden				
Uncertainty	8.07 ± 1.36	8.13 ± 1.31	7.97 ± 1.47	7.47 ± 1.71
Subjective feeling	22.80 ± 1.86	22.73 ± 1.74	22.70 ± 2.51	23.66 ± 2.45
Negative emotion	11.87 ± 2.22	11.70 ± 2.13	11.72 ± 3.70	10.37 ± 2.11
Dependency	9.47 ± 1.31	9.33 ± 1.30	9.48 ± 1.22	9.10 ± 1.30
Feeling of inadequacy	5.37 ± 1.40	5.40 ± 1.40	5.23 ± 1.34	4.70 ± 1.34
Total	57.56 ± 4.25	57.43 ± 4.05	57.21 ± 3.76	54.70 ± 4.46
Secondary outcome measure				
Activity achievement worksheet				
Number of activities	11.23 ± 2.61	11.26 ± 2.32	10.84 ± 2.87	12.24 ± 1.32
Enjoyment	4.65 ± 1.79	4.71 ± 1.89	4.67 ± 1.81	6.22 ± 2.19
Achievement	4.32 ± 1.79	4.45 ± 1.85	4.26 ± 1.97	5.32 ± 1.87

Table 2.
Outcome measures for each group.

Moreover, there is a significant decrease in reported caring hour from 6.98 to 5.98 hours (with t (59) = −0.89, p < 0.05, Cohen's d = 0.53 with 95% CI, 0.51 to 0.68) in the experimental AS group and no significant difference in caring hours in control group from 7.02 to 7.42 hours.

In the measurement of spouse caregivers' subjective perception of enjoyment and achievement in activities they were instructed to complete an achievement worksheet. After 8-week intervention, the experimental group outperformed the control group in their number of activity participation (Cohen's d = 0.90 with 95% CI = 0.68–0.95), level of enjoyment (Cohen's d = 0.74 with 95% CI = 0.65–0.82), and sense of achievement (Cohen's d = 0.55 with 95% CI = 0.49–0.71). Moreover, in experimental group, participants reported with more physical exercise (ranging

from physical exercise to more leisurely exercise, such as walking, gardening, yoga, or hiking) in their later reported figures from week 5 onward than less active physical activities (including shopping, baking, attending community events, arts and crafts, singing, and tea or lunch with friends or family) as in their earlier reported activities. Moreover, gradually increasing levels of social interaction with others were noted in experimental group than in control group. On the contrary, control group showed some more passive activities (such as reading a newspaper, watching TV, listening to the radio, looking at photo albums, and writing in a journal) throughout the period of 8-week intervention.

3.2 Within-group difference

After 8-week intervention, there were significant differences in some measures within experimental group but not in control group. For the primary outcome measure on individuals' physical functioning, paired t-test revealed a significant improvement in motor-FIM and total-FIM (with t (27) = 11.45, $p < 0.05$, with Cohen's d ranging from 0.68 to 1.64, 95% CI, 0.38 to 1.78), but not in control groups ($p > 0.05$). The secondary outcome measures on the impact of caring role. Paired t-test revealed a significant improvement in uncertainty, subjective feeling, negative emotion, feelings of inadequacy, and total burden of care in experimental group (with t (27) = −0.45, $p < 0.05$, with Cohen's d ranging from 0.43 to 0.64, 95% CI, 0.38 to 0.78), but not in control groups ($p > 0.05$).

There was significant difference in spouse caregivers' own subjective perception of enjoyment and achievement in activities within experimental group but not in control group. Following 8-week intervention, within the experimental group yielded the following results: the number of activity participation (Cohen's d = 0.52 with 95% CI = 0.48–0.65), level of enjoyment (Cohen's d = 0.74, 95% CI = 0.65–0.81), and sense of achievement (Cohen's d = 0.46 with 95% CI = 0.43–0.62).

3.3 Examine the improvement over time in intervention group

A two-group pretest-posttest ANOVA with repeated measures was conducted to compare the effect of time before and after the 8-week intervention. There was a significant effect of AS on the physical functioning of participants with CFS in experimental group, with Wilk's $\lambda = 0.72$, F (2,57) = 18.75, $p < 0.001$. Moreover, there was a significant decrease in the impact of caring role as reflected by the perceived burden of caring in the experimental group, with Wilk's $\lambda = 0.72$, F (2,97) = 18.75, $p < 0.001$. Furthermore, a study of the effect of time on caring activities for those recruited couples in AS group revealed a significant effect of AS on caring activities with Wilk's $\lambda = 0.71$, F (2,97) = 12.47, $p < 0.001$.

4. Discussion

The present study revealed that there was a positive effect of AS on improvements in activity participation in older adults with CFS. This finding echoes previous work on AS in regard to depression in older adults [82, 83]. Through this study, it became obvious that there were more activities that older adults with CFS and their spouse caregivers would like to and could participate than we expected. AS showed its advantages with the GET, CBT, and energy conservation techniques. This is very important topic as non-pharmacological interventions are needed for this hard to treat population. With the application of AS in experimental group, there was more significant improvement regarding individuals'

physical functioning, as our primary outcome measure, in the experimental group. Moreover, there will be lighter perceived impact of caring role and significant reductions in uncertainty, dependency, and the feeling that caregivers were providing inadequate care. These positive changes can be partially explained by having proper channel in having more regular feedback and sharing on their caring with occupational therapists in the AS program. This channel had shown to be a strong form of support to caregivers in regard to caregiving [83, 93].

Moreover, in experimental group, AS training offered by occupational therapists focused on pleasant event scheduling and improving individuals' communication. Results indicated individuals' feelings of uncertainty and inadequacy can be greatly alleviated if they participate in activities together with the people for whom they care. The present findings echoed the effectiveness of this type of activity participation, and support had been well documented that can lower the impact of caring role in their daily lives [84, 94]. It is very important to note that not only CFS but also depression would affect people differently when it comes to their daily activities [95, 96]. It had been found that fatigue and depression had mutual interactions [97] and there can be some overlap between the two [98]. AS training showed its effectiveness in behavioral intervention for CFS. The application of AS and findings of this study can be applied to other common neuropsychological metrics such as in depression and for others with mild cognitive impairment. There were some studies that had documented its effectiveness in depression [80].

One of the most attractive assets of AS was its relatively straightforward and personalized metric in nature. With not much preparation and resources needed, it makes easy for different healthcare providers to adopt this approach in motivating our patients and their caregivers to have more activity participation. This easy-operation intervention can bring benefits to various sociodemographic levels of our society.

This study provided insights on the importance of biopsychosocial approach in the evaluation and management for CFS. Moreover, in rehabilitation, it is fundamentally important to let the participants choose activities by themselves, in order to enhance their levels of participation in the activities [99]. There were gradually increases of enjoyment and achievement and levels of social interaction noted in their reported activity achievement worksheet. It is reasonable to believe that with proper coaching and regular facilitation regarding AS by occupational therapists, activity participation in older adults with CFS can be greatly enhanced, just as it can be for other older adult populations [82, 100, 101]. This study further echoed previous well-cited studies in indicating behavioral intervention can supplement therapeutic treatment or may lead to decline in CFS symptoms [71–73, 102].

The present study relied on self-report and completion of daily activity logs in reflecting individuals' activity participation. This will limit the power of this study as social desirability bias and forgotten to complete the report would jeopardize the outcome of AS. A more standardized environment would much enhance the efficiency in building events for AS. Also, a well-cited experimental research in using neuroimaging to probe mechanisms of behavior change is needed [103]. Further resources should be solicited in making a correlation analyses with neuroimaging on justifying the effectiveness of this behavioral intervention.

Up till present, there was limited literature in showing the effectiveness of rehabilitation service for older adults with CFS. The effectiveness of AS can be further justified by conducting a study with larger group of participants and with longer-term follow-up. Regular telephone follow-ups had shown to be an effective method to maintain satisfactory compliance and adherence of caregivers; therefore, more resources should be prepared to work up closer on compliance and adherence of individuals' participation in activity and their scheduling.

Conflict of interest

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

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