

Research Paper

Effect of Online Compassion-focused Therapy on the Symptoms severity, Post-traumatic Growth, Quality of Life, and Hippocampal and Amygdala Volume in Patients recovered from COVID-19



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ABSTRACT

Background: Acute epidemics and physical risks have serious psychological consequences for post-COVID-19 patients. COVID-19 survivors who are afraid of dying are susceptible to post-traumatic stress symptoms.

Objective: This study determines the efficacy of online compassion-focused therapy (CFT) in reducing the severity of post-traumatic stress disorder (PTSD) symptoms, increasing post-traumatic growth (PTG), improving quality of life (QoL), and studying changes in hippocampus and amygdala volume in recovered COVID-19 patients in Shiraz City, Iran. It was completed in 2022. Acute epidemics and physical risks have negative psychological effects on post-COVID-19 patients.

Methods: Patients with the delta version of COVID-19 were studied in Shiraz City, Iran, from May 2021 to July 2022. The study included 40 patients with the delta variation (COVID-19) who had been diagnosed with PTSD. Individuals were selected to form the control (n=20) and experimental (n=20) groups. They answered the World Health Organization (WHO) short form QoL questionnaire, the PTSD checklist for the diagnostic and statistical manual of mental disorders, the fifth edition questionnaire, and the Tedeschi and Calhoun PTG and development questionnaire. The hippocampal and corpus amygdaloideum (amygdaloid body) volumes were assessed. A segment with a thickness of 3 mm was used to capture an oblique coronal plane 1.5 T magnetic resonance imaging without any gaps. We also investigated volume differences between the right and the left hippocampus and corpus amygdaloideum. For data analysis, multivariate and univariate analyses of covariance, Mean±SD were used.

Findings: Self-compassion psychotherapy significantly improved the QoL (P<0.001, F=30.675), PTG (P<0.001, F=62.548), and reduced post-traumatic stress (P<0.001, F=103.335). In addition, the volume of the hippocampus and amygdala in the compassionate therapy group increased in the post-test phase (P<0.001, F=21.995).

Conclusion: Self-compassion therapy can have positive effects on post-traumatic patients and lead to PTG. As these psychological treatments do not involve physical risks, special emphasis can be placed on the use of this treatment in clinics.

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Introduction

Post-traumatic stress disorder (PTSD) is defined as a psychological reaction to a distressing incident [1]. PTSD symptoms can be classified into four groups as follows [1]: 1) Reliving trauma, marked by nightmares or flashbacks; 2) Avoiding particular situations, that is avoiding people or situations that remind the person of the unpleasant experience; 3) Negative alterations in feelings and beliefs, a shift in how a person perceives themselves, coworkers, relatives, and friends, thus, they may be unable to communicate with others and express their affection; and 4) Hyper-arousal, this is characterized by trouble sleeping, concentrating, or being easily startled. PTSD is more prevalent among veterans who serve on the front line [2].

Hands-on nurses, and front-line caregivers for COVID-19 patients are more likely to develop PTSD. Several studies of combat veterans who served in Southeast Asia during the Vietnam War support the identification of chronic PTSD symptoms [2]. Concerns about physical health have been raised. Pain connected with physical disability is addressed prescriptively and through self-prescribed remedies. These events contribute to the maintenance of the pain-medication cycle, which is a habitual situation. Furthermore, PTSD may erode happiness, as indicated by increased issues with marriage, parenthood, and a healthy sex life. According to the [American Psychiatric Association \(APA\)](#), emotional avoidance is a key diagnostic criterion of PTSD [3].

Evidence suggests that individuals with high levels of trait anxiety may be more susceptible to developing PTSD [4]; however, symptomatology did not correlate with the singularity or length of the traumatic experience, and in this case, COVID-19. Instead, the researchers concluded that either could be involved in the development or aggravation of PTSD. They concluded concepts of personal trauma are flexible and context-dependent [4]. This demonstrates how distinctive individuals are. Impulsivity or a predisposition toward rapid and unplanned responses to internal or external stimuli regarding negative consequences [5] could explain the previously mentioned and unpredictable behaviors that nurse leaders face in their organizations. The most sensible workers may become irritated due to PTSD brought on by COVID-19. Leaders' mental health problems are connected to the stress of making decisions. Nurse leaders had to carefully assess their moral and ethical principles before making several COVID-19-related decisions [6]. PTSD-causing events include COVID-19 as a potential trigger.

COVID-19, which is caused by SARS-CoV-2, was first diagnosed in December 2019 in Wuhan, China. On January 30, 2020, the secretary-general of the [World Health Organization \(WHO\)](#) announced that this pandemic was an international health emergency. This global pandemic has had and will continue to have a significant impact on people's quality of life (QoL) and mental health for a long time [7]. The human COVID-19 is one of numerous viral species thought to have neurotrophic potential. Studies have shown that when the SARS pandemic leads to PTSD, the symptoms of which are closely similar to the PTSD of patients who face severe stressful situations, such as an earthquake. In certain cases, experiencing a traumatic event can lead to positive changes in people's lives [8].

Magnetic resonance imaging (MRI) is an important research tool where the brains of neuropsychiatric patients can be investigated in vivo. The Hippocampus is a popular structure for MRI morphometry. This virus is similar to acute respiratory syndrome, but it is not the same [8].

By the end of April 2021, the COVID-19 outbreak had spread worldwide, with over 150 million cases confirmed and 2.3 million deaths in over 200 nations [9]. Most patients with COVID-19 have recovered. The return of respiratory symptoms serves as the primary indicator of recovery; however, it is questionable whether these patients are over an increasing number of studies suggests that coronaviruses can move to non-respiratory tissues, particularly the central nervous system [10, 11]. Previous outbreaks have shown that respiratory coronaviruses can enter the central nervous system, the brain, and cerebrospinal fluid in less than a week before becoming apparent in the cerebrospinal fluid [11].

There is evidence that cognitive deficits happen independently of psychiatric issues and are related to the severity of the infection, despite that anxiety, depression, and post-traumatic stress syndrome are also frequent in patients with acute respiratory distress syndrome and may worsen cognitive function [12]. It is questionable which group is more vulnerable to mental issues, including extreme anxiety, mental stress, and thinking disorders [13]. Following earlier outbreaks of human coronaviruses, high rates of psychiatric symptoms, particularly anxiety, depression, suicidal behavior, and PTSD have been documented in the general population, regardless of infection status [14, 15]. Most importantly, COVID-19 survivors who have experienced fear for survival are vulnerable to post-traumatic stress symptoms [16]. In particular, survivors of COVID-19 who were afraid for their lives are susceptible to PTSD. People's mental distress is exacerbated by constant, often contradic-

tory news published by the government or health authorities along with fake news on websites and television programs. In addition, the quarantine and its measures implemented by governments to reduce the risk of disease exacerbate psychological distress and lead to fear, panic, mistrust, and aggression [17]. The COVID-19 pandemic has had a wide-spread global impact and has caused deaths, social restrictions, and psychological distress [18].

In certain cases, experiencing a traumatic event can lead to positive changes in life. This concept is known as post-traumatic growth (PTG). PTG is the experience of positive personal changes caused by facing a crisis or traumatic event, which may not neutralize the experience of psychological trauma; however, despite the heartbreaking experiences, many people find new meaning and purpose in life. This encourages them to make positive personal changes. This positive growth can be seen in various fields, including improving interpersonal relationships, increasing feelings of personal power, and being grateful for life [19].

As the outbreak of this pandemic has significantly disrupted the provision of mental health care (such as reduced or unavailable in-person referrals for psychiatric outpatient treatment or psychotherapy), community members may face even greater barriers to providing care from professionals compared to the era before the pandemic [20]. Quarantine reduces the availability of timely psychological intervention, and regular psychological counseling is unfeasible at the peak of the COVID-19 pandemic [21]. The path toward the gradual acceptance of information and communication technology in the field of psychology started before the COVID-19 pandemic, in different degrees in different countries, and it is currently available in some countries. On the other hand, it is still rare in some countries because of legislation or norms, which have implications for the availability of psychological services [22]. Today, new methods have been used in the field of cognitive psychology to reduce the severity of stress symptoms after an accident, improve QoL, and increase growth after an injury. Among them, cognitive therapy is based on the compassionate mind [23].

According to the above findings, it seems that the rehabilitation of patients suffering from mental disorders is important after being affected by the COVID-19 virus. Therefore, considering the emergence of this type of viral infection, its physical and psychological effects on patients and even their survivors, and its presence is the cause of the spread of the COVID-19 virus. The investigation of various biological and social treatments, such as psychological online and offline treatments has been conducted.

In addition to the destructive mental and cognitive effects of COVID-19, the rapid spread and death rate of this virus are two of its most obvious features. A large number of countries worldwide, especially developed countries face numerous problems. However, mental health is faced with great challenges. How long this crisis will continue worldwide, despite vaccination, remains an unanswered question. Therefore, in the current high-risk situation, it is necessary to examine the health status the mental health of people in society, which is somehow exposed to danger, and to identify the best treatment method to maintain the mental health of people in society.

The results of this research, regardless of how to perform psychotherapy correctly and remotely using up-to-date facilities, such as video conferencing, online programs, the use of related applications, and the telephone, can lead to the reduction of psychological problems and also provide treatment in the conditions of a similar and possible epidemic in the future, a clear perspective, and a good theoretical and practical basis for counselors and psychotherapists.

Since this disease has a significant impact on different levels of human life, including physical, mental, and subsistence, and despite the treatment, the fear of catching new species is still in the human being, research on the identification of people susceptible to mental diseases and retrofitting them with related psychotherapies is at its beginning, and more effort and investigation is required. So far, significant clinical studies have not been conducted on patients recovering from COVID-19 with PTSD, and treatment focused on compassion, evaluation of recovery, and PTG, along with the volume of the hippocampus and amygdala in these patients using brain imaging.

Materials and Methods

From May 2021 to July 2022, individuals with the delta variant of COVID-19 were treated at the COVID-19 hospitals in Shiraz City, Fars Province, Iran. The inclusion criteria were the absence of particular mental illnesses, the ability to read and write, and the presence of COVID-19. Meanwhile, the exclusion criteria included incomplete participation in psychotherapy lessons and having a mental illness. A total of 40 recovered post-COVID-19 patients were enrolled through the purposive sampling method. The total number of patients was divided into the experimental group (compassion therapy; n=20) and the control group (n=20). The selected individuals were matched based on their education level,

age, marital status, and disease duration using a stratified sampling method. Accordingly, the percentages and proportions of education, age, marriage, and the duration of the disease in the two groups were almost equal. The sample size was determined as the minimum sample size based on an experimental plan [24]. A total of 100 individuals were selected using the list of patients who visited the coronary hospitals in Shiraz City, Iran. After conducting a clinical interview, 40 were selected as the sample size using the Morgan table.

These two groups were compared in terms of age, education, marital status, and duration of the disease. The participants (both the experimental and control groups) first completed the research questionnaires as a pre-test. Then, the experimental groups participated in therapy sessions. The first experimental group underwent compassion-focused therapy (CFT) online (depending on the conditions and tools available to the patient) over eight sessions. The control group received the standard treatment during this period. After completing the treatment sessions, all subjects completed the questionnaires again as a post-test and were evaluated in the follow-up phase about three months later. Finally, the scoring of questionnaires and statistical analysis were done using the relevant software. The tools used for data collection in this study were the PTG questionnaire, the post-traumatic stress disorder (PTSD) checklist for the diagnostic and statistical manual of mental disorders, the fifth edition (DSM-5) questionnaire (PCL-5), and the short form of the WHO QoL questionnaire. Data collection was performed through social media platforms (WhatsApp and Telegram). Brain imaging was performed using a standard 1.5 T1 18-channel MRI scanner. The hippocampus and corpus amygdaloideum volume bodies were measured. Right-left volume differences in the hippocampus and corpus amygdaloideum were also investigated. The patients were asked to stay awake, maintain their heads still, and keep their eyes open during the scan (Figure 1).

PTG and development questionnaire

This questionnaire was developed by Tedeschi and Calhoun in 1996 aiming to measure personal achievements after a traumatic event. This questionnaire has 21 questions and 5 subscales, including subjects related to others (7 items), new opportunities (5 items), personal power (4 items), understanding the value of life (3 items), and changes in the philosophy of life (2 items). Tedeschi and Calhoun [19] found the Cronbach α coefficient for the entire PTG and development questionnaire at 0.90, for the subscales of communication with others at 0.85, new opportunities at 0.84, personal strength at 0.72, spiritual

change at 0.85, and understanding the value of life at 0.67. Meanwhile, retest reliability coefficients (2 months apart) for the whole questionnaire was 0.71, for the three subscales of communication with others, new opportunities and spiritual change reported from 0.65 to 0.71, personal power 0.37, and understanding the value of life 0.47 [20].

PTSD questionnaire

PCL-5 is a 20-item self-report instrument that is fully compatible with the PTSD diagnostic criteria based on the DSM-5. This tool is scored based on a 5-point Likert scale (0 to 4), with scores ranging from 0 to 80. This questionnaire consists of the following four scales: Annoyance (criterion B), avoidance (criterion C), negative mood changes (criterion D), and overexcitement (criterion E), which are placed on the clusters of PTSD symptoms in the DSM-5. The Cronbach α of the English version of this tool was obtained at 0.95, while for the French version, it was 0.94. The convergent validity of the English version of this scale is reported at 0.89. In the present study, the Cronbach α coefficient for the whole scale is 0.92. For the factors of disturbances B, avoidance C, negative changes in cognition and mood D, arousal and restlessness E, and emotional numbness F, the rates were 0.90, 0.67, 0.74, 0.70, and 0.85, respectively.

WHO QoL questionnaire-short form (2000)

The short-form scale of the QoL of the WHO has 26 questions and measures 4 dimensions of physical, mental, social, and physical health. It is used as a comprehensive scale and includes overall QoL and general health levels. In the quality-of-life scale of the WHO, which was conducted in 15 international centers of this organization, the Cronbach α coefficient was reported from 0.73 to 0.89 for the four subscales and the whole scale, and in Iran. For the reliability of the scale, Nasiri (2008) used the retest method with a three-week interval, split, and the Cronbach α were 0.84, 0.67, and 0.87, respectively. Also, the reliability of the quality-of-life scale was measured by Rahimi (2008), and the Cronbach α coefficient for the whole scale was 0.77, including 0.88 for physical health, 0.70 for mental health, 0.77 for social relations, and 0.65 for the quality of the living environment.

Brain imaging to measure the hippocampus and amygdala

Survivors of COVID-19 (patients whose clinical diagnosis and testing were positive for delta strain and were discharged from Shiraz hospitals at the time of testing) and

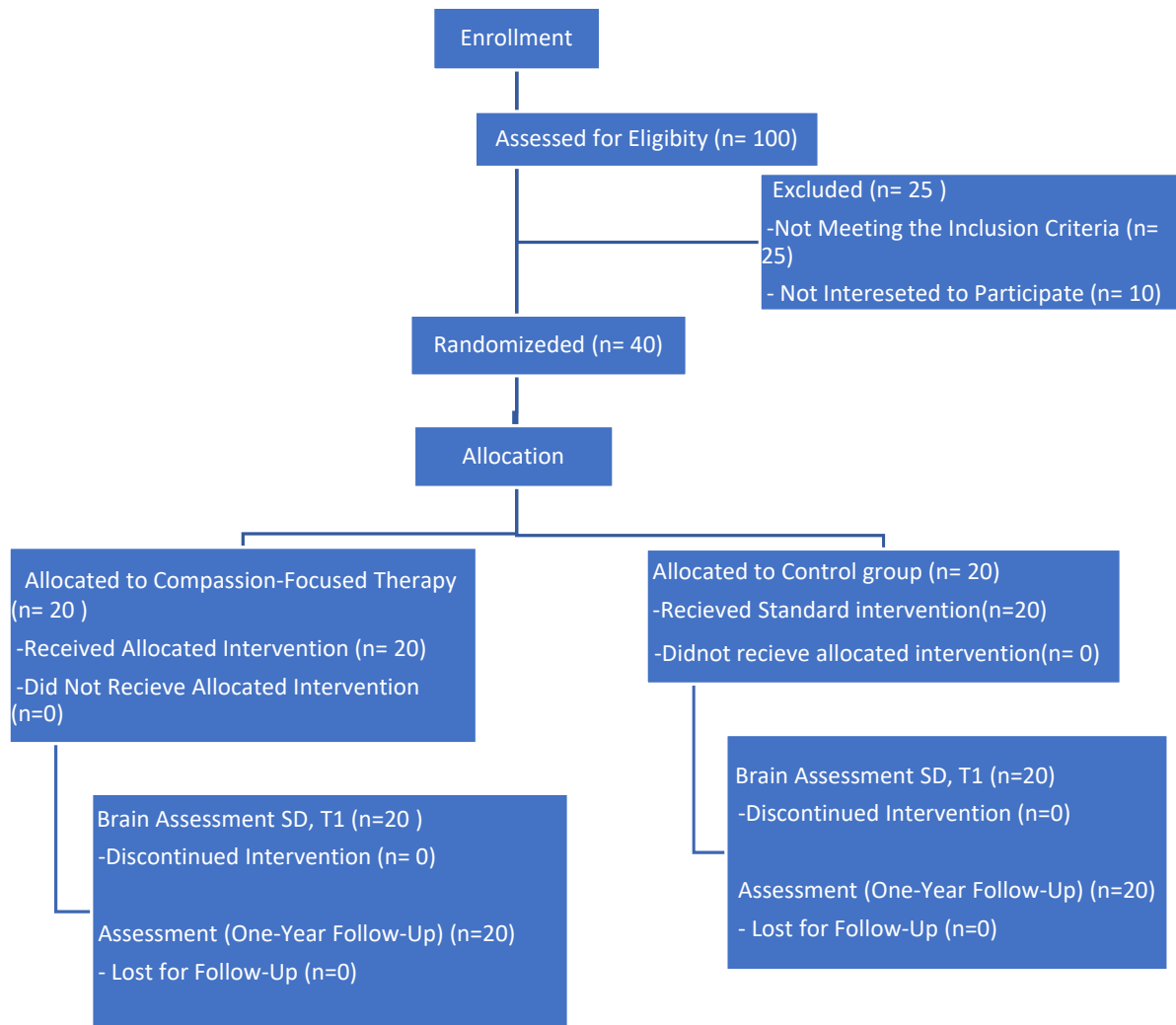


Figure 1. Consort diagram of sample selection

control groups of COVID-19, under home care, matched with age and gender from the community, were chosen. The first brain imaging sessions were performed on two consecutive days. The evaluation set of scales included PCL-5 and a statistical manual of mental disorders. The second session of brain imaging was done one year after stopping and completing online psychotherapy, returning to normal life, and receiving two doses of the vaccine on July 25 and 26, 2022. The brain imaging data of all participants were collected from the radiology department of a private imaging center in Shiraz City, Iran. The brain imaging data were acquired using a standard 1.5 T1 18-channel MRI scanner. The subjects were asked to stay awake, maintain their heads still, and keep their eyes open during the scan. Brain structural images (hippocampus and amygdaloid body) were obtained in an oblique coronal plane using a thickness of 3 mm without any slits and using a high-resolution T1 inversion recovery sequence.

Statistical analysis

The data was entered into the SPSS software, version 26 (SPSS Inc., Chicago, IL, USA). The normality of the data was checked using kurtosis and skewness. Considering the normality, the independent t-test and one-way repeated-measures analysis of variance were used to compare the changes in the mean of three variables' scores between the study groups at different time points. The significance level for all tests was $P < 0.05$.

Results

The balanced distribution of demographic characteristics in the comparison-focused therapy (intervention) and control groups is provided in Table 1. In the post-test phase, the results showed a significant difference between post-traumatic stress symptoms, increased

Table 1. Demographic information of participants in the comparison-focused therapy and control groups (n=20 per group)

Variables	Groups	No. (%)	
		CFT	Control
Gender	Female	11(55)	8(40)
	Male	9(45)	12(60)
Age (y)	20-30	6(30)	5(25)
	30-40	6(30)	8(40)
	>40	8(40)	7(35)
Marital status	Single	6(30)	8(40)
	Married	14(70)	12(60)

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PTG, and the QoL in the groups. There was a significant difference between the psychotherapy and control groups in the post-test phase ($P<0.001$). The scores of the online therapy in terms of QoL ($P<0.001$, $F=27.42$) and PTG ($P<0.001$, $F=104.46$) increased in the post-test phase, while the post-traumatic stress scores decreased ($P<0.001$, $F=178.4$) (Table 2).

In the follow-up stage, there was a significant difference between the psychotherapy and control groups ($P<0.001$) (Table 2). The scores for online therapy in terms of QoL ($P<0.001$, $F=6.612$) along with PTG ($P<0.001$, $F=17.3$) increased, while the post-traumatic stress scores ($P<0.001$, $F=32.04$) decreased.

The hippocampal and amygdala volume in participants were measured using brain and neuroimaging in two stages before treatment and after treatment due to its high cost, in the two groups of compassion treatment and control presented in mm (Tables 2 and 3). To verify the volume of the hippocampus and amygdala, brain structural images (hippocampus and amygdaloid body) were acquired in the oblique coronal plane using a section thickness of 3 mm without any gap and using a high-resolution T1 inversion recovery sequence. The results showed that online therapy had a significant effect on the size of the amygdala and hippocampus ($P<0.001$) (Table 2). To check which of the dimensions of the hippocampus and amygdala were affected by online therapy, a univariate covariance test was performed. Accordingly, there was a significant difference between the volume of the right hippocampus ($P<0.001$), left hippocampus ($P<0.001$), right amygdala ($P<0.001$), and left amygdala ($P<0.001$) in the two groups in the post-test stage. The

volume of the hippocampus and amygdala of the online therapy group increased in the post-test phase.

Discussion

This result is consistent with evidence from previous research [23-27]. Based on the theory of CFT, threat, drive, and satisfaction systems are rooted in the evolutionary history of humans in the direction of survival. Early humans tended to avoid or overcome threats, seek food sources or intimacy, and enjoy being a part of a social community. The proponents of CFT believe that these systems are still active and influence the beliefs, activities, and emotions of humans today. For example, if a person is exposed to a threatening stimulus, they may experience different emotions (fear, anxiety, and anger), perform different behaviors (submission or fight-and-flight response), and have specific cognitive biases (judgment, stereotyped thinking, or the belief that it is better to be safe than sorry) [28]. In explaining this result, the goal of CFT is to help people improve emotionally and psychologically by encouraging them to be compassionate toward themselves and others. Its purpose is to create motivation, sympathy, sensitivity, and distress tolerance compassionately through the use of specific exercises. These exercises help people develop a non-judgmental and non-blaming perspective [28].

The autonomic nervous system and the hypothalamic-pituitary-adrenal axis control the stress response. This axis is significant in stress neurobiology and plays a role in social isolation. In response to stress, the hypothalamus and brainstem are the most significant parts of the brain. The Corticotropin-releasing factor is produced in

Table 2. Statistical analysis of RM-Anova of the effective variables among the intervention and control groups

Variables		Groups		Effects	F	P	Partial η^2
		Intervention	Control				
QoL	Pre-test	56.85±11.07	55.3±8.75	Factor	27.42	0.001*	0.33
	Post-test	68.05±8.6	54.55±7.9	Group	7.35	0.001*	0.21
	Follow-up	66.85±8.45	56.85±6.12	Factor, group	6.61	0.002*	0.19
PTG	Pre-test	52±6.34	51.5±6.02	Factor	104.46	0.001*	0.65
	Post-test	64.05±4.64	52.5±6.1	Group	12.6	0.001*	0.31
	Follow-up	63.05±4.96	59.95±5.96	Factor, group	17.3	0.001*	0.38
PTSD	Pre-test	66.45±7.64	66±6.3	Factor	178.4	0.001*	0.76
	Post-test	52.25±5.6	65.05±5.7	Group	12.51	0.001*	0.31
	Follow-up	53±6.15	63.6±5.4	Factor, group	32.04	0.001*	0.53
Right hippocampus	Pre-test	3242.05±121.35	3289.45±126.62	Factor	142.85	0.001*	0.79
	Post-test	3764.35±128.04	3289.45±126.62	Group	41.45	0.001*	0.52
	Follow-up	3764.35±128.04	3289.45±126.62	Factor, group	142.85	0.001*	0.79
Left hippocampus	Pre-test	3233.15±100.31	3281.1±115.68	Factor	135.92		0.78
	Post-test	3760.9±108.63	3304.25±142.45	Group	50.3	0.001*	0.57
	Follow-up	3760.9±108.63	3304.25±142.45	Factor, group	114.03		0.75
Right amygdala	Pre-test	1729.8±74.8	1690±69	Factor	76		0.67
	Post-test	2004.65±106.6	1703±79.3	Group	67.9	0.001*	0.64
	Follow-up	2004.65±106.6	1703±79.3	Factor, group	63.27		0.62
Left amygdala	Pre-test	1673.05±70.51	1651.45±76.77	Factor	90.7		0.71
	Post-test	1955±97.22	1641.65±84.8	Group	58	0.001*	0.6
	Follow-up	1955±97.22	1641.65±84.8	Factor, group	104.24		0.73

*Significant relationship.

greater quantities. Stress can cause changes in the neuro-anatomy and nerves of the glands, which might damage the immune system. TNF- α , IL-1b, IL-6, and interferon will all be elevated. This raises the likelihood of autoimmune and inflammatory illnesses. During times of stress, noradrenaline levels rise. This increases the amygdala's sensitivity. [29].

Also, the results of the tests showed a significant difference between the volume of the hippocampus and the right and left amygdala of the treatment group focused on online compassion and the control group in the post-test phase. According to the averages observed in the descriptive section, it was found that the hippocampus and amygdala volumes of the online compassion-focused treatment group increased in the post-test phase. The

amygdala becomes sensitive due to acute stress, and the specificity of the amygdala will decrease. Therefore, it becomes more difficult to distinguish between stimuli. In adverse circumstances, it may be beneficial to acknowledge any potential hazards.

Stress and emotional impacts on memory consolidation are mediated by the basolateral complex, which comprises the insula, anterior cingulate cortex, prefrontal cortex, and amygdala. During the COVID-19 pandemic, memory consolidation can result in frightening memory loss. Long-term anxiety problems can be caused by fear. Ultimately, the amygdala's spine count rises to produce more synapses. Conversely, lowering stress alters the amygdala's anatomical structure. Gray matter is also decreased by reducing stress. When faced with fear, the left amygdala was shown

Table 3. Hippocampal volume in patients before and after intervention

Variables	Groups	Mean± SD
Right hippocampus	Pre-exam	3763.63±370.76
	Control	3809.43±413.98
	Post-test	3326.88±355.77
	Control	3600.43±390.97
Left hippocampus	Pre-exam	3709.55±378.67
	Control	3654.66±342.77
	Post-test	3308.44±354.77
	Control	3509.66±332.55

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to be more active. This indicates that in the case of a stressor, the amygdala is experiencing adverse effects. In traumatic situations like PTSD, the left amygdala is more often stimulated than the right [29].

COVID-19 causes neuropsychiatric symptoms that indicate brain involvement. SARS-CoV-2 may enter the brain by damaging the olfactory mucosa and through other possible ways, such as damage to the blood-brain barrier. Neurogenic disorders in adults are associated with many psychiatric disorders, including depression, bipolar disorder, schizophrenia, and PTSD. Noradrenaline increases during periods of stress and makes the amygdala more sensitive. The amygdala mediates stress and emotional effects on memory consolidation, and memory consolidation during the COVID-19 pandemic can lead to fearful memories. When we are afraid, the left amygdala becomes more active. However, lowering stress will alter the amygdala's anatomical structure. The results of this study confirmed the effectiveness of CFT in post-coronavirus patients [29].

Conclusion

Online CFT can reduce PTSD severity and improve post-traumatic growth and quality of life of patients with PTSD. It can also increase the hippocampus and amygdala volumes. Since this method do not involve physical risks for patients, it is recommended to be used in clinics.

Ethical Considerations

Compliance with ethical guidelines

In this study, people entered the study knowingly and with personal consent, and to respect the rights of the

participants, their information was included in the analysis anonymously. This study has been registered in [Iran's Clinical Trial Registration Center \(IRCT\)](#) (Code: IRCT20230408057849N1).

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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