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An open trial of biofeedback for long COVID

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ABSTRACT

Objective: Biofeedback is a therapeutic treatment model that teaches self-regulation of autonomic functions to alleviate stress-related symptoms. "Long COVID" refers to chronic physical and cognitive sequelae post-SARS-CoV-2 infection. This study examined the efficacy of a six-week intervention, consisting of weekly one-hour sessions combining heart rate variability and temperature biofeedback, for alleviating mood symptoms, somatic symptoms and sleep disturbance of patients diagnosed with long COVID.

Methods: Data were collected from 20 adult participants aged 22–63 (M_{age} = 44.1, SD_{age} = 12.2) with varying long COVID symptoms. Within this single arm design, 16 of the 20 participants completed all six sessions of biofeedback; 14 completed an assessment at the three-month post-treatment time point.

Results: Participants self-reported significant improvements in somatic, anxiety, and depressive symptoms, sleep quality, quality of life, and number of "bad days" immediately after the intervention and three months later (Cohen's d effect size (ES) = 1.09–0.46). Reduced number of medical doctor visits (ES = 0.85) and prescription drug use over the last month (odds ratio = 0.33), as well as improved emotional wellbeing (ES = 0.97) were observed at the three-month time point only.

Conclusion: Results suggest that this short, readily scalable intervention can be potentially efficacious in alleviating symptoms of long COVID. Despite notable improvements, the major limitation of this study is its lack of control group. While a randomized trial merits study, biofeedback appears to be a brief, effective, non-invasive, and low-cost treatment option for patients with chronic somatic symptoms secondary to SARS-CoV-2 infection. *Clinicaltrials.gov ID*: NCT05120648

Long COVID (also referred to as 'post-acute sequelae of COVID-19' or PASC) is a multisystemic condition comprising of continuous and developing symptoms that persist at least three months after SARS-CoV-2 infection [1]. Long COVID symptoms are diverse and manifest across ten organ systems [2,3]. Of the 200 symptoms associated with the syndrome [1], the most common are dyspnea, palpitations, dizziness, pain, brain fog, and neuropsychiatric symptoms (depression, anxiety and posttraumatic stress) [3]. Current estimates indicate that 6% of patients infected by SARS-CoV-2 will develop long COVID [4]. The long-term recovery rates remain low (85% of patients reporting persistent symptoms one year later [5]; 90% reporting persistent symptoms two years later [6]).

Understanding and treating long COVID has profound clinical and economic implications. Recent estimates of medical costs associated with long COVID range from $43 to $172 billion annually [7] with similar magnitudes for indirect costs of unemployment and disability [7,8]. Upwards of one in three patients diagnosed with long COVID do not return to employment [9]. Loss of baseline functioning is also associated with the development of secondary anxiety and depression in the context of newfound disability [10].

At least 65 million individuals have been estimated to suffer from long COVID globally [11]. While long COVID can occur after both mild and severe infections, the incidence is higher in patients who required hospitalization [12] and lower in those who are vaccinated [13]. Several subtypes of long COVID have been identified: myalgic encephalomyelitis or chronic fatigue syndrome (ME/CFS) and postural orthostatic tachycardia syndrome (POTS) syndromes being particularly common [14,15].

The mechanism and risk factors for long COVID have eluded clinicians and researchers alike [11,12]. Several epidemiological

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mechanisms have been posited including chronic viral infection, inflammatory and autoimmune changes, and stress-responses in the central nervous system [11,12]. Other researchers have struggled to demonstrate direct links to pathophysiological processes, as evidenced by chronic symptoms persisting despite unremarkable medical findings. For instance, some patients with complaints of orthostatic intolerance show normal results on tests [16] and patients complaining of neurocognitive effects appear to perform within normal limits despite feeling as though they exert more effort [17].

Autonomic nervous system (ANS) dysfunction, also known as dysautonomia, has been associated with the development and maintenance of chronic somatic symptoms [18]. Biofeedback is a therapeutic treatment model that teaches self-regulation of symptoms linked to sympathetic over activity. In biofeedback, providers teach patients physiological self-regulation via behavioral coaching with visual feedback of ANS functioning (respiration, heart rate, temperature, muscle tension, etc.).

Heart rate variability (HRV) is one established measure of ANS functionality. Higher HRV is associated with good adaptability to and recovery from environmental stressors [19]; lower HRV has been observed in chronic functional symptoms such as fatigue [20] and pain [21]. The variability of the heart rate reflects the nervous system's overall ability to control heart rate in times of stress [22]. HRV has been identified as a key signal for understanding the status of the ANS since the parasympathetic nervous system (PNS) and sympathetic nervous system (SNS) work jointly to balance the human heart rate. In fact, changes to either branch of the nervous system have profound impact on the cardiovascular system [22]. Correlation between HRV and cardiological issues are well established [23].

Heart-rate variability (HRV) biofeedback works to increase the variation in time between consecutive heartbeats to trigger parasympathetic (i.e., calming) nervous system responses, thereby rebalancing the nervous system to minimize over activity in the sympathetic or 'fight or flight' nervous system [21]. In practice, HRV biofeedback patients practice paced diaphragmatic breathing with real time feedback of their breathing and heart rate, allowing them to regulate their heart rhythm through respiration [19]. HRV biofeedback has demonstrated utility in improving symptoms across a variety of conditions [20,21,24–30]. Another biofeedback technique, which teaches patients to raise their peripheral body temperature, has been shown to help alleviate migraines [31] essential hypertension [32] and Raynaud's disease [33]. This modality is also intrinsically tied to cardiovascular health given that the human body's vascular reactivity index, which measures the time it takes temperature to rebound after stress, has also been identified as a measure of sympathetic activity, with quicker returns to baseline temperatures being associated with healthier endothelial functioning and better cardiovascular health [34].

Many symptoms of long COVID overlap with dysautonomia, suggesting that ANS impairment may be central to long COVID pathophysiology [3,35]. COVID 19 has also been linked to a multitude of cardiovascular complications including heart failure, venous thromboembolism, and cerebrovascular events [36]. Recent studies have further extended that long-COVID 19 symptoms may be related to persistent cardiovascular dysfunction via persistent effects on endothelial functioning [36]. While HRV biofeedback has not been studied in long COVID, reductions in HRV have been linked to increases in C-reactive proteins, which are an established inflammatory marker of disease severity during SARS-CoV-2 infection [37]. SARS-CoV-2 infection has also been reliably linked to abnormalities on autonomic testing [38]. Despite these links, few non-pharmacological treatments have been proposed to reduce symptoms. Those that have (e.g. structured pacing protocols for fatigue) have focused on symptom palliation rather than on curative treatments that aim for a return to baseline functioning [3].

Taking into consideration the effects of SARS-CoV-2 on long-term cardiovascular dysfunction and reduced vascular reactivity, this study examined the efficacy of a six-session intervention that combined HRV and temperature biofeedback in alleviating chronic somatic symptoms of patients diagnosed with long COVID. We hypothesized that the intervention would lead to reductions in self-reported depression, generalized anxiety, health anxiety, and somatic symptoms; as well as improvements in self-reported self-efficacy, and sleep. The secondary aim of this pilot study was to determine whether the intervention was associated with reduced healthcare utilization as measured by fewer medical visits, ER visits, hospitalizations, and use of prescription medications, by self-report.

1. Methods

1.1. Participants

The sample consisted of 20 participants who reported chronic somatic complaints after contracting SARS-CoV-2 infection. Data were collected between December 2021 and March 2023. Prior SARS-CoV-2 infection was verified with prior positive PCR testing for all but two participants who were infected prior to universal testing availability. For these two participants, their symptom presentation was consistent with SARS-CoV-2 infection and had been retrospectively inferred by their primary physician. While some participants described persistent COVID symptoms that originated from their infection (e.g., shortness of breath, fatigue), others experienced new symptoms that emerged after recovering from the acute infectious period. Consistent with participants in other long COVID studies, chronic somatic symptom severity and duration were not directly related to the severity of the initial infection. Likewise, the sample consisted of participants who had been infected at varying times during the pandemic. Some but not all had been vaccinated at the time of infection. (See Table 1).

1.2. Inclusion and exclusion criteria

The study was approved by the University of California, Los Angeles (UCLA) Institutional Review Board. Participants were referred to the study from the UCLA Long COVID Program by their physician. The study was also posted on clinicaltrials.gov. Prospective participants called the principal investigator and were screened by phone for eligibility. Inclusion criteria included: (1) age $\geq$ 18 years; (2) English proficiency; (3) reporting a qualifying somatic complaint (e.g., tachycardia, pain,

Table 1
Demographic variables.

Variables	N = 20
Sex (%)	
Female	65%
Male	35%
Age (years; mean ± SD)	44.1 ± 12.2
Education (years; mean ± SD)	13.6 ± 1.0
Number of Lifetime Traumatic Experiences	4.5 ± 3.2
Race/Ethnicity (%)	
Asian	5%
Hispanic	5%
White Non-Hispanic	90%
Time since COVID infection at Time 1 (months; mean ± SD)	16.8 ± 8.8
Time since COVID infection at Time 3 (months; mean ± SD)	19.4 ± 8.9
Severity of Initial COVID Infection	
Mild	65%
Moderate (ER visit / antibiotics or steroid treatment)	25%
Severe (Hospitalized)	10%
Primary Symptom (%)	
Chronic pain (e.g. migraines)	20%
Gastrointestinal symptoms (e.g. IBS)	5%
Anxiety symptoms (e.g. panic attacks)	10%
Neurocognitive symptoms (e.g. brain fog)	15%
Cardiac symptoms (e.g. tachycardia, POTS)	10%
Nausea	5%
Fatigue	10%
Respiratory symptoms (e.g. SOB)	25%

nausea); and (4) having psychosocial distress related to this symptom (anxiety, depressed mood, reduced quality of life). Exclusion criteria included severe psychopathology (e.g., psychosis, dementia, active suicidality, and moderate to severe intellectual impairment). Prior to starting the six-session biofeedback treatment, participants self-reported current symptoms and recent healthcare utilization via a RedCap survey (Time 1). Participants completed the surveys again immediately after completing the six-week protocol (Time 2), and again at three months-post treatment (Time 3).

1.3. Intervention

Participants completed six sessions of biofeedback training, lasting approximately one hour each over the course of six weeks. The biofeedback protocol was informed by similar short-term heart-rate variability training extensively researched by Lehrer and colleagues for a variety of somatic mind-body conditions [39]. We added temperature biofeedback training given that some participants struggle to learn HRV biofeedback and may need another self-regulation skill. Since HRV decreases with age, it was posited that HRV biofeedback may be harder to learn for older adults with long COVID [40]. Reduction in peripheral temperature have also been proposed as central to chronic dysautonomia and preliminary research suggests that it may be helpful for fatigue, a common symptom of long COVID [41]. *Session 1* focused on collecting the participant's history regarding long COVID symptoms, providing psychoeducation on the rationale and evidence for the treatment, teaching participants diaphragmatic breathing technique with an extended exhale, and having participants practice different breathing rates using the *Biotrace* + biofeedback software and the NeXus-10 MKII hardware [42]. Longer exhalation to inhalation ratios have been shown to promote higher HRV [43]. After *Session 1*, participants were asked to practice breathing at a rate of six breaths per minutes two times a day for 10 minutes each, guided by a free, non-proprietary phone application with an individualized breathing pacer.

In *Session 2*, participants learned to practice different diaphragmatic breathing rhythms including even breathing, box breathing, and extended exhale breathing. This practice allows for continued practice of diaphragmatic breathing techniques towards better physiological control of breathing muscles. Following this practice, participants completed a *Resonance Frequency Assessment*, an evaluation that identifies the optimal breathing rate for optimizing HRV. The theory behind HRV biofeedback proposes that the human cardiorespiratory system has a fixed *resonance frequency* at which the heart produces the greatest heart rate oscillations by stimulating the *baroreflex*, which is the homeostatic system that regulates blood pressure using *baroreceptors* [44]. This resonance frequency in humans ranges from 4.5 to 6.5 breaths per minute [45]. With repeated practice of slowed diaphragmatic breathing at the individualized preferred rate (identified here in *Biotrace*+ during Session 2), the participants can practice maximizing their HRV by breathing at their resonant frequency. This protocol was originated by Lehrer and colleagues [45]. HRV is measured using time domain via a Blood Volume Pulse (BVP) Finger Sensor.

In *Session 3*, participants received continued education and practiced HRV training through video games in a biofeedback software named *Alive* [46]. *Session 4* repeated session 3 but with more challenging practice of HRV video games. In *Session 5*, participants continued HRV practice through practice in *Alive* and/or *Biotrace*+. HRV practice in *Biotrace* + is considered more challenging as participants cannot rely on a breath pacer. *Session 5* also included an introduction to temperature biofeedback in which participants were coached to use imagery and guided visualization to raise their peripheral body temperature, also using the *Biotrace*+ software and the NeXus-10 MKII hardware [42]. The final session, *Session 6*, continued the practice of peripheral temperature control and HRV practice with added games and relaxation exercises. In between sessions, participants were instructed to practice their *Resonance Frequency* breathing rate two times a day for 10 minutes each, guided by a free, non-proprietary phone application with an individualized breathing pacer.

1.4. Measures

All participants completed a demographic survey completed prior to treatment. This survey asked standard demographic questions as well as information about long COVID symptomatology. Given the established overlap between past traumatic experiences and somatic symptoms, participants also completed the *Life Events Checklist for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (LEC-5), a 17-item, self-report measure designed to screen for potentially traumatic events in a respondent's lifetime [47]. Demographic and trauma history questions were not repeated post-intervention or at three-month post-treatment follow up. Given the aim of the study was to determine whether participants felt better after the intervention rather than whether their HRV increased, we relied on self-report measures. Improvements in physical symptoms, depressive symptoms, anxiety symptoms, self-efficacy, health anxiety, and sleep were primary outcomes of the study and measured via the following self-report questionnaires. We also explored changes in quality of life via self-report questionnaires.

Somatic, anxiety, and depressive symptoms. To assess for frequency and severity of chronic somatic symptoms, participants completed *the Patient Health Questionnaire - 15* (PHQ-15) [48], a 15-item, self-administered questionnaire that assesses for somatization and somatic symptom severity. The PHQ-15 has been useful for predicting a variety of functional outcomes such as sick days and healthcare use. To assess for comorbid depressive symptoms, participants completed *Patient Health Questionnaire - 9* (PHQ-9), a nine-item self-report tool for depression that has demonstrated satisfactory sensitivity, specificity, diagnostic agreement, and overall diagnostic accuracy compared to clinical interviews of depression [49]. To assess for comorbid anxiety symptoms, participants completed *the Generalized Anxiety Disorder - 7* (GAD-7), a seven-item, self-report anxiety questionnaire that has demonstrated satisfactory sensitivity, specificity, diagnostic agreement, and associations with functional impairment [50].

Self-efficacy. *The Self-Efficacy for Managing Chronic Disease 6-item Scale* is a six-item self-report questionnaire designed to assess a person's perceived ability to manage their illness and to thrive despite symptoms, complications, and management issues [51]. It covers several domains common to many chronic diseases, including symptom control, role function, emotional functioning and communicating with physicians.

Health anxiety. Participants completed *the Health Anxiety Inventory* (HAI-18): a measure of health anxiety and hypochondriasis found to reliably distinguish people who are excessively concerned about their health from those with anxiety disorders and from those with established medical conditions [52].

Sleep. Sleep quality was measured using *The Pittsburgh Sleep Quality Index* (PSQI), a 19-item self-rated questionnaire that has demonstrated validity and reliability for assessing global sleep quality [53].

Health quality & utilization. Reduction in health utilization was a secondary outcome of this study. This was assessed via a self-report measure created for this study that asked participants abut their health utilization and perceived health burden over the last month. This included number of hospital admissions, medical visits, ER visits, missed days of work, and medication and substance use over the last month. Participants were also asked to estimate the number of "bad days" in terms of subjective long COVID symptomatology they had in the last thirty days.

Quality of life. *The SF-36 Health Survey* is a 36-item self-report health survey that measures general self-perceived health status. It is well-validated across many illness populations [54].

1.5. Statistical analyses

Data were entered at the time of collection and analyzed after completion of the trial. All data were inspected for outliers, homogeneity of variance and other assumptions to ensure their appropriateness for parametric statistical tests. Continuous outcomes (PHQ-15, PHQ-9, GAD-7, PSQI, Self-efficacy, HAI-18, SF-36, number of medical visits to doctors, missed workdays, number of "bad days") were analyzed using a mixed effects general linear model, as implemented in SAS PROC MIXED, with time as the within-subject factor. We present test scores and statistics as well as effect sizes (Cohen's d) for within-group changes. We also analyzed the change in the number of participants on disability, on prescription and over-the-counter drugs from baseline to post-intervention and then at the 3-month follow-up, using generalized linear mixed models (SAS PROC GLIMMIX). Given the novel and preliminary nature of the study, we present results of analyses conducted on a range of outcome measures and set the level of significance at the alpha level of $p \leq .05$, two-tailed, without accounting for multiple comparisons, thus increasing the possibility of a Type 1 error. As such, results should be interpreted with caution.

2. Results

Data were collected from 20 adult participants aged 22–63 (M_{age} = 44.1, SD_{age} = 12.2). Participants had established diagnoses of long COVID and were referred by a long-COVID specialist practicing through the UCLA Health System. Referring provider specialty included internal medicine, extensivist medicine, pulmonology, cardiology, neurology, and psychitatry. Expressions of long COVID varied greatly, as did severity of initial SARS-CoV-2 infection (see Table 1). Of the 20, 16 completed all six sessions of biofeedback, and 14 of the 16 completed the assessments at the three-month post-treatment time point (see Fig. 1).

Outcome measures at baseline, post-intervention, and three months post-treatment, as well as estimated effect sizes (Cohen's *ds*) are presented in Table 2. Participants reported significant improvements in self-reported somatic, anxiety, and depressive symptoms, and global sleep quality immediately after the six sessions, with improvements sustained three-months later. In terms of health quality, patients reported fewer "bad days" both at post-intervention and at the longer follow-up, compared to baseline. Significant improvements were also found in QOL subdomains of the SF-36, namely improved energy, physical functioning, social functioning, and general health, both immediately after treatment and three months later. Some outcome variables showed significant improvement at the longer follow-up but did not reach

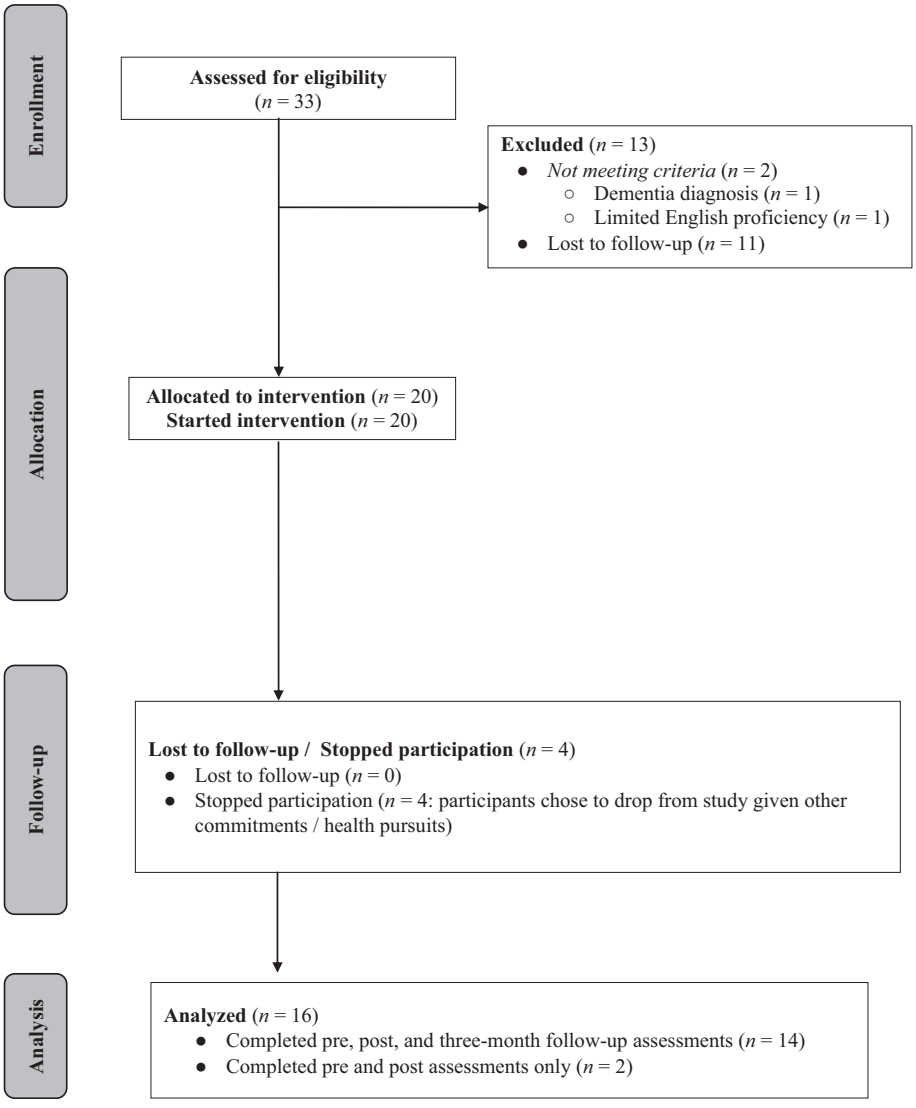

Fig. 1. PRISMA flowchart.

Table 2
Main effects and effect sizes at baseline, post-intervention, and three months post-treatment, as well as estimated effect sizes.

Measure	Baseline*	Post Intervention*	3 Months Post-Treatment*	Time Main Effect^	Baseline-Post Intervention#		Baseline-Post 3 Months#	
	$N = 20$	$N = 16$	$N = 14$	Statistics	Statistics	Effect size$	Statistics	Effect size$
Primary Outcomes:								
PHQ-15 (Somatic Symptoms)	14.7 (3.9)	11.6 (5.2)	10.1 (4.0)	**$F(2,19) = 5.6$, $p = .01$**	**$t(19) = 2.12$, $p = .05$**	−0.46	**$t(19) = 3.30$, $p = .004$**	−1.04
Self-Efficacy	5.0 (2.5)	6.6 (1.8)	6.4 (1.7)	*$F(2,19) = 2.71$, $p = .09$*	**$t(19) = -2.20$, $p = .04$**	0.35	**$t(19) = -2.25$, $p = .04$**	0.48
Health Anxiety	25.4 (6.3)	22.9 (6.7)	23.6 (5.1)	$F(2,19) = 0.69$, $p = .51$	$t(19) = 1.07$, $p = .30$	−0.14	$t(19) = 0.96$, $p = .35$	0.03
GAD-7 (Anxiety)	9.0 (5.6)	5.3 (4.1)	4.1 (4.7)	**$F(2,19) = 14.95$, $p = .0001$**	**$t(19) = 3.18$, $p = .005$**	−0.73	**$t(19) = 5.42$, $p < .0001$**	−1.42
PHQ-9 (Depression)	10.5 (5.6)	7.5 (4.9)	6.5 (5.2)	**$F(2,19) = 4.73$, $p = .02$**	**$t(19) = 2.99$, $p = .008$**	−0.68	**$t(19) = 2.97$, $p = .008$**	−0.99
PSQI (Sleep)	10.6 (3.0)	8.3 (4.2)	8.9 (3.1)	**$F(2,19) = 6.69$, $p = .01$**	**$t(19) = 3.17$, $p = .005$**	−0.81	**$t(19) = 3.16$, $p = .005$**	−0.72
Secondary Outcomes: Health Quality and Utilization (Last Month)								
Number of Bad Days	19.7 (9.0)	11.4 (8.2)	7.8 (4.3)	**$F(2,19) = 11.65$, $p = .001$**	**$t(19) = 3.41$, $p = .003$**	−0.83	**$t(19) = 4.82$, $p = .0001$**	−1.90
Number of Visits to Medical Doctors	4.3 (3.6)	3.1 (3.1)	1.6 (1.3)	**$F(2,19) = 6.10$, $p = .01$**	$t(19) = 1.14$, $p = .27$	−0.21	**$t(19) = 3.43$, $p = .003$**	−0.85
Number of Missed Work Days	12.5 (13.5)	9.8 (14)	10.1 (13.4)	*$F(2,19) = 2.92$, $p = .08$*	$t(19) = 2.03$, $p = .06$	−0.52	$t(19) = 2.31$, $p = .03$	−0.73
On Disability (Yes/No)	8 (40.0%)	7 (43.8%)	6 (42.9%)	$F(2,28) = 0.95$, $p = .40$	$t(28) = -0.06$, $p = .95$	1.17	$t(28) = 1.19$, $p = .25$	1.13
On Rx Drugs (Yes/No)	15 (75.0%)	11 (68.8%)	7 (50.0%)	**$F(2,28) = 4.12$, $p = .03$**	$t(28) = 0.66$, $p = .51$	0.73	**$t(28) = 2.79$, $p = .01$**	0.33
On OTC Drugs (Yes/No)	12 (60.0%)	6 (37.5%)	5 (35.7%)	$F(2,28) = 1.35$, $p = .28$	$t(28) = 1.38$, $p = .18$	0.40	$t(28) = 1.41$, $p = .17$	0.37
Exploratory Outcomes: SF-36 (Quality of Life)								
Physical Functioning	44.8 (25.1)	58.0 (23.3)	63.6 (28.7)	**$F(2,19) = 5.08$, $p = .02$**	**$t(19) = -2.66$, $p = .02$**	0.58	**$t(19) = -3.11$, $p 0.02$**	0.90
Emotional Wellbeing	54.6 (20.9)	62.3 (16.9)	70.3 (15.3)	**$F(2,19) = 5.92$, $p = .01$**	$t(19) = -1.88$, $p = .08$	0.39	**$t(19) = -3.44$, $p = .003$**	0.97
Energy	21.3 (17.2)	38.4 (22.9)	37.5 (23.0)	**$F(2,19) = 7.12$, $p = .005$**	**$t(19) = -3.75$, $p = .001$**	0.93	**$t(19) = -2.39$, $p = .03$**	0.71
Social Functioning	23.1 (22.7)	42.2 (31.3)	47.3 (33.3)	**$F(2,19) = 6.10$, $p = .01$**	**$t(19) = -3.30$, $p = .004$**	0.83	**$t(19) = 3.05$, $p = .01$**	1.13
Pain	52.1 (21.2)	56.4 (28.1)	49.3 (29.0)	$F(2,19) = 0.21$, $p = .81$	$t(19) = -0.58$, $p = .57$	0.13	$t(19) = 0.16$, $p = .87$	−0.12
General Health	35.8 (20.1)	48.1 (19.7)	44.6 (14.5)	**$F(2,19) = 10.41$, $p = .001$**	**$t(19) = -4.37$, $p = .0003$**	1.09	**$t(19) = -2.95$, $p = .008$**	0.83

^Time main effect statistics are from mixed models; significant findings are bolded and those approaching significance are italicized.
* Mean (SD) for continuous and N (%) for categorical measures.
# Baseline-Post Intervention and Baseline-Post 3 Months are follow-up tests on the primary mixed model estimations.
$ Effect size estimates are Cohen's d for continuous and odds ratios for categorical measures. For those measures (PHQ-15, Health anxiety, GAD-7, PHQ-9, PSQI), where a higher score represents worse symptoms, a negative value of Cohen's d indicates improvement; for those measures (Self Efficacy, SF-36), where a higher score represents better symptoms, a positive value of Cohen's d indicates improvement. Odds ratios (OR) are calculated with respect to baseline: hence an OR of <1 represents improvement from baseline to post-intervention/3 Months.

significance immediately post-intervention. These included decreased number of medical doctor visits and prescription drug use over the last month, and improved emotional wellbeing on the SF-36. Changes to self-efficacy, health anxiety, pain, work absenteeism, and self-reported use of OTC drugs were not significant. A few health utilization variables (number of hospital admissions and ER visits) were not endorsed enough in our sample to analyze statistically. Effect sizes for significant changes ranged from 1.09 to 0.58 for the acute period (from baseline to post-intervention) and from 1.90 to 0.71 for the sustained effect (from baseline to 3-month follow-up).

3. Discussion

This study had two objectives. The first was to evaluate whether biofeedback, an established mind-body therapeutic practice, could improve self-reported depression, anxiety, and somatic symptoms, self-efficacy, and sleep developed as a result of prior SARS-CoV-2 infection. The second goal was to determine whether participants reported a reduced need for healthcare utilization after program completion. Using prospective data from pre-, post-, and 3-month post-treatment, we found that patients with various long COVID complaints had significant improvements in somatic symptoms, anxiety, and depressive symptoms, as well as several domains of health-related quality of life, and global sleep quality. They also reported fewer "bad days" both after the six sessions and three months later. Healthcare utilization, as measured by visits to medical doctors and prescription drug use in the last month, were not immediately reduced after the six sessions but did show significant reductions three months later. The same pattern was found for the emotional wellbeing subscale of the SF-36.

The aforementioned findings suggest that a short course of HRV and temperature biofeedback could be a promising treatment option for patients with long COVID. This raises the question as to whether long COVID is a *psychosomatic* syndrome. We refute the use of this term as it encourages an erroneous and archaic dichotomy of mind and body. This term is generally poorly understood by the medical community and has long contributed to patients being dismissed by traditional biomedical systems that relegate untreatable physical symptoms as psychiatric. It may be more accurate to consider long COVID as a syndrome of

dysautonomia; patients are experiencing genuine physiological symptoms in the absence of pathophysiology. While this may lead to negative biomedical workups and suboptimal response to biomedical interventions, the symptoms are real and cannot be dismissed as health anxiety. Moreover, as in dysautonomia, providers should be mindful that patients do not have conscious control over their symptoms. The links between SARS-CoV-2 and its immediate and longitudinal impact on cardiovascular functioning merit continued exploration.

Setting etiology and mechanisms aside, symptoms of dysautonomia secondary to acute stress (e.g. SARS-CoV-2 infection) may exacerbate the effects of chronic stress responding from significant allostatic load. In fact, known chronic stressors such as economic vulnerability and income insufficiency have been shown to be risk factors for the development of long COVID [55]. In cases of largely unremarkable medical tests, ANS dysfunction may be responsible for the development and maintenance of chronic somatic symptoms. Dysautonomic symptoms can be seen as a danger signal gone awry, the ANS may remain in an activated state, issuing acute stress signals (pain, panic symptoms, fatigue, etc.) despite the absence of immediate danger [56]. In long COVID, symptoms may be sustained by aberrations in the respiratory and cardiovascular systems [37]. Hyperventilation or over breathing, common in stress responses, may trigger sympathetic responding by the body, leading to a deprivation in the oxygen needed to return to homeostasis after stress [57]. By normalizing these breathing patterns and restoring the synchrony between respiration and heart rate, HRV biofeedback may reduce peripheral signals of *fight or flight* and correct the underlying pathophysiology that sustains long COVID [20,42].

We note that, while mood symptoms did improve significantly, HRV biofeedback is not currently indicated as a primary treatment for depression or anxiety disorders despite some preliminary evidence that it may be efficacious [58]. Many patients with long COVID develop secondary anxiety and depressive symptoms related to the increased stress of dealing with reduced functioning and worsened quality of life. While these may improve adjunctively to somatic symptom improvement, clinically significant depressive and anxiety symptom may need further treatment via psychotherapy or psychotropics.

Some but not all participants in the study were co-enrolled in psychotherapy and other treatment modalities such as acupuncture, which may have contributed to self-reported improvements. One participant with remaining health anxiety after the six sessions was referred to cognitive behavioral therapy and outpatient psychiatry. Furthermore, participants in this study were generally encouraged to return to meaningful activities as they made progress. The re-instilling of confidence to pursue activities that improve quality of life may have significantly contributed to self-reported improvements, especially given that most participants had reduced their occupational and social engagement in hopes of mitigating long COVID symptoms.

History of trauma may be another important factor. Participants in this study endorsed a mean of 4.5 ($SD = 3.2$) traumatic experiences in their lifetime (e.g., natural disaster, car accident, assault, etc.), which is significantly higher than norms of control groups ($M = 2.28$, $SD = 1.92$) [59]. While the development of somatic symptoms has historically been tied to chronic [60] rather than to acute stress, individuals who report exposure to trauma are nearly three times more likely to develop a functional somatic syndrome than those without [61]. While we cannot infer causality, it is possible that the considerable amount of lifetime trauma in the current sample may have predisposed physiological stress responses that were ripe for chronicity and ignited by the stress of a subsequent COVID infection.

Although this study has shown promising results, there are several limitations that must be acknowledged. First, this pilot study featured a small sample size and a within-subject design that did not include a comparison or control group, thus limiting the generalizability of the findings. As such, we cannot conclude that the benefits found in this study are replicable and due to biofeedback alone. It is possible that a placebo effect, the improved social connection created with the provider as well as the empowerment that comes with learning and mastering a tool of self-regulation, may have contributed to the observed outcomes. Given our lack of control group, it is also possible that improvements were an effect of time and natural remission rates. However, mean enrollment date of our participants was 16.8 months after initial infection, corroborating existing literature, which suggests that most symptoms persist without treatment (See Table 1) [4,5]. Nevertheless, it is also possible that there may be non-specific benefits of being in the protocol unrelated to biofeedback itself, such as emotional support from the provider, placebo effects related to perceived growths in self-efficacy, and the like.

Second, our sample was made up of patients with varying original infection severity, numerous long COVID symptoms, and who were infected at various stages of the pandemic (pre-vaccine, post-vaccine, and post-booster vaccines). They were also free to engage in other healthcare pursuits and many were co-enrolled in psychotherapy, acupuncture, and other mind-body approaches. Since our results were not adjusted for these treatment modalities, we cannot rule out the possibility that some of these treatments contributed to overall patient rehabilitation.

Additionally, patient questionnaires are susceptible to recall bias which could overstate the effectiveness of the intervention. Including estimates of HRV scores (e.g., SDNN) and temperature pre- and post-intervention may bolster results of future studies. See Pham et al. (2021) for a review of HRV measurement options [62]. Finally, the effect of the intervention was assessed using several outcomes, without correction for multiple comparisons, thus increasing the possibility of a Type 1 error; as such all findings should be interpreted with caution.

Future researchers may choose to focus on specific long COVID subtypes (e.g. chronic fatigue syndrome versus POTS) to determine whether HRV biofeedback is differentially beneficial for patients with different presentations [14]. Comparison of our six-session protocol to other treatment options for long COVID (e.g., pulmonary rehabilitation) as well as to sham treatment options described by Lehrer and colleagues [25] may also be useful. The addition of biomarkers may present an additional opportunity to quantify improvement objectively especially given recently established cytokine profiles in long COVID [63].

Despite these limitations, the results of this study suggest that biofeedback may be a promising treatment for patients with long COVID who have not responded well to standard biomedical approaches. Biofeedback is a non-invasive, relatively low cost, and scalable treatment option that could provide long-term relief and rehabilitation to patients. Helping patients regain a sense of autonomy over their chronic symptoms may facilitate a return to baseline functioning. This is particularly important for minimizing the direct and indirect costs of long COVID on healthcare spending and occupational disengagement.

Credit authorship contribution statement

Natacha D. Emerson: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Helen Lavretsky:** Writing – review & editing, Writing – original draft. **William Q. Pittman:** Writing – review & editing, Writing – original draft. **Nisha Viswanathan:** Writing – review & editing, Writing – original draft. **Prabha Siddarth:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis.

Declaration of competing interest

None.

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