Neuroplasticity Intervention, Amygdala and Insula Retraining (AIR), Significantly Improves Overall Health and Functioning Across Various Chronic Conditions

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Abstract

Chronic conditions, sometimes referred to as functional somatic disorders, such as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), fibromyalgia (FM), and more recently, long COVID (LC), affect millions of people worldwide. Yet, after decades of research and testing, the etiology and treatment for many of these diseases is still unclear. Recently, a consortium of clinicians and researchers have proposed that while many different chronic conditions exist, the root cause of each may be a similar brain-body connection, as the brain responds to perceived biological threats and transmits danger signals to the body that manifest as somatic symptoms. This hypothesis suggests that treating chronic conditions requires an approach that addresses the neural networks involved. One such method, known as Amygdala and Insula Retraining (AIR), otherwise known as The Gupta Program, has shown promise in recent years for treating such conditions, including ME/CFS, FM, and LC. The present study aimed to demonstrate that AIR could be an effective approach for numerous other chronic illnesses (e.g., Lyme disease, mold illness, mast cell activation syndrome [MCAS]) and others. This novel and exploratory research examined self-reported health and functioning levels before and after using AIR. A series of paired-sample *t* tests with Bonferroni correction demonstrated that after 3+ months of using AIR (the minimum recommended time for the intervention), participants experienced a significant increase in overall health and functioning for 14 of 16 conditions tested ($P < .001$ for all but one, which was $P = .001$) and approached significance for the remaining two conditions ($P = .039$ and $P = .005$). Of the 14 signficant findings, 11 had a large effect size and three had a medium effect size. Naturally, this study has limitations. It was a cross-sectional design with a small convenience sample and self-reported data. Future research with larger samples and randomized controlled trials is needed to provide further evidence of AIR's effectiveness. Nonetheless, these preliminary findings suggest that AIR is a viable method for improving the health of people suffering from chronic conditions, and clinicians and researchers might consider incorporating AIR into their protocols for these patients.

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INTRODUCTION

Chronic conditions, sometimes referred to as functional somatic disorders,[1] are complex diseases often with unknown etiology. There are numerous such conditions, though myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), fibromyalgia (FM), pain syndromes, and more recently, long COVID (LC) are arguably the most commonly recognized. While each condition has its own set of wide-ranging symptoms, these chronic diseases are often characterized by similar symptoms, such as extreme fatigue, myalgia, sleep problems, digestive issues, and cognitive impairment.[2-4] Therefore, chronic conditions are debilitating and negatively impact millions of people worldwide,[2,5,6] costing the global economy trillions of dollars.[7]

Consequently, effective treatment is necessary. Yet it remains elusive for these conditions. Decades of research exploring numerous causes and remedies have yet to identify a "gold standard" method of treatment.[8,9] Additionally, clinicians and researchers have only recently concluded that the root cause of these various conditions might be found in neural networks, implying that while numerous different chronic conditions exist, treatment for them could largely be the same.[10] This suggestion does not mean the bodily symptoms experienced by patients are not real or "all in their head" as some providers often suggest. Rather, these clinicians and researchers propose that when a threat to well-being is perceived, it triggers alarm systems in our neural networks that manifest as bodily symptoms, such as fatigue or pain. The symptoms act as warning signals that we are not safe and that the body must adapt to

the perceived danger. While such a brain-body response may be evolutionarily helpful in the moment, in some cases, it can persist because the neural networks interpret the bodily symptoms as another threat, thus reactivating the neural networks and sending more danger signals back to the body. Consequently, the brain and body get locked in a never-ending loop of misinterpreted signals that ultimately develop into chronic illness.[10]

Currently, few treatments are available for chronic conditions that are grounded in the idea that many of these illnesses are caused by misdirected or misfiring neural networks. Still, one such approach has shown promise in recent years. A neuroplasticity program, known as the Amygdala and Insula Retraining (AIR) or The Gupta Program, is a method that allows patients to self-manage their symptoms via a low-cost and easily accessible online intervention. Neuroplasticity refers to the brain's ability to "re-wire" its neural connections. Thus, AIR is effectively a brain-retraining program whereby individuals learn how to disrupt adverse neural pathways and create new, positive connections that lead to better overall health and functioning.

AIR has demonstrated effectiveness in treating symptoms of ME/CFS, FM, and LC in pilot randomized controlled trials. In one study, AIR significantly improved energy and reduced pain and fatigue in patients with ME/CFS.[11] Additionally, AIR, in combination with treatment-as-usual, has effectively reduced pain, fatigue, anxiety, and depressive symptoms among people with FM.[11,12] In a more recent investigation, AIR significantly reduced fatigue and increased energy among people suffering from LC.[13] Therefore, the evidence suggests AIR has the potential to address various chronic conditions, though to date, it has only been tested for ME/CFS, FM, and LC. Accordingly, the purpose of the present study was to evaluate the effectiveness of AIR in addressing the overall health and functioning of people across various chronic conditions beyond just ME/CFS, FM, and LC.

AIR is based on the hypothesis that the root cause of numerous chronic conditions may be a disorder in the brain (specifically in the amygdala and insula) that continually triggers the immune and nervous systems unnecessarily, causing various bodily symptoms.[14,15]

More specifically, the AIR hypothesis proposes the following sequence of events that triggers and perpetuates a vicious chronic illness cycle, as proposed by Ashok Gupta,[14,15] the founder of the AIR intervention.

(1) Factors such as genetic predisposition (i.e., an individual's genetic makeup), lifestyle (e.g., smoking, alcohol, lack of sleep and exercise, etc.), environmental (e.g., exposure to toxins, chemicals, and pollution, etc.), and psychosocial (e.g., loneliness, stress, trauma, etc.) inputs can increase inflammation in the body and adversely impact immune responses,[16-24] making it vulnerable to acute traumatic assaults, such as infection, virus, or even a damaging psychological event.

(2) Gupta proposes that any combination of these factors can lead to maladaptive responses by the immune and nervous systems via the amygdala and insula.[14,15] The amygdala is part of the limbic system and its primary role is detecting threats and activating responses to them.[25-27] The insula or insular cortex (IC) is located between the temporal lobe and inferor parietal cortex, and is important in regulating the nervous and immune systems.[28-29] Prior research suggests that the amygdala and insula are implicated in nervous and immune responses to signals coming from the viscera.[30-31] The insula is involved in acquiring and evoking conditioned immune responses, while the amygdala appears to mediate the visceral inputs that are needed at acquisition.[31-32] Further, the signature of a previous immune response can be re-triggered in the insula. Indeed, the IC has recently been shown to store and receive immune responses, indicating that internal and external stressors can cause IC neurons to misfire, which initiates an inappropriate immune response from the stored memory.[33] These inaccurate signals are sent to the immune and nervous systems, which manifest as functional somatic symptoms. In turn, these symptoms are interpreted as danger signals that reactivate the inappropriate immunological response, thereby creating a self-perpetuating cycle that keeps the brain and body in a hyper-vigilant state (i.e., on high alert, constantly scanning for threats) with chronically over-triggered immune and nervous systems.[14-15]

(3) Gupta also theorizes that there are a range of primary and secondary symptoms that can occur and feed into the cycle.[14,15] Primary symptoms include but are not limited to pain, fatigue, cognitive dysfunction, muscle atrophy, and post-exertional malaise, etc. Secondary symptoms might include exhaustion of the adrenal glands and compromised mitochondrial function, as well as allergies and sensitivies to food and chemicals, etc. Both sets of symptoms contribute to the signals sent back to the brain, where the amygdala and insula interpret them as threats and respond accordingly. Thus, the amygdala and insula are effectively creating the symptoms they are trying to mitigate in the self-perpetuating loop.

Thus, per the hypothesis outlined above, if the brain and body are constantly in a hyper-vigilant and overactive state, it is reasonable to propose that one possible method of addressing the condition is to calm the nervous and immune systems, and re-wire the signals that are being sent between the brain and body. The AIR intervention was developed from this logic.

AIR is hypothesized to strengthen neurological inhibitory mechanisms in areas of the prefrontal cortex, insula, and anterior and posterior cingulate. This bolstering helps reduce the magnification of incoming somatic signals and down-regulate the hyper-stimulation of the autonomic nervous system and aspects of the immune system by the amygdala and the insula so that the immune system and the autonomic nervous system can return to normal function, and the body can achieve homeostasis.[14-15]

The AIR intervention includes specialized neuroplasticity techniques, supported by secondary techniques such as breathing, meditation, and other lifestyle therapies. A key component of AIR is consistent repetition of neuroplasticity techniques to enable the development of new neural pathways that signal safety to the brain and body. Indeed, prior research indicates that users of AIR experience greater benefits after they have been actively engaged with the program for at least 3 months.[13] Therefore, as the present study aimed to determine the effect of AIR across numerous conditions, the hypothesis was that self-reported health and functioning among chronic condition patients would significantly improve after using AIR for 3+ months. This investigation was important because of the practical implications. Namely, that numerous chronic conditions negatively impact millions of people who often suffer from them for years without effective therapy or treatment,[8-9] and it is possible that AIR could be a helpful approach for reducing or eliminating their symptoms.

Methods

Research design and participants

The current research was an international cross-sectional study. Participants were recruited from The Gupta Program database of people who had purchased the intervention. Emails were sent to the database, inviting respondents to participate in an online survey. This recruitment process may have resulted in self-selection bias, which limits the generalizability of findings. However, it was the only feasible method available given time and budget constraints.

Two screening criteria determined eligibility. First, participants had signed up for The Gupta Program at least one month before taking the survey. Second, they had been actively using The Gupta Program for at least one month. Before completing the survey, participants were informed that the purpose of it was to gather feedback on The Gupta Program and its effectiveness in addressing various chronic conditions. They were also reassured that their responses would be kept strictly confidential. Participation in the study was voluntary, and respondents could choose to disengage at any point during the survey.

A total of N = 315 participants completed the survey, among which n = 222 reported actively using the program for 3 months or more. As noted above, 3+ months of actively using AIR is optimal for noticeable improvement. Therefore, for the purpose of this study, only participants who self-reported using the program for 3+ months were considered. Table 1 displays the demographic information for this sample. Importantly, the use of self-report data for length of time participants engaged in the program and the measured outcome variables introduced the possibility of risk of response bias (i.e., that respondents do not provide accurate answers), which may have impacted the data collected and subsequent analyses.

Table 1. Demographic Information for Study Participants

	Used AIR 3+ Months (n = 222)	
	Count	**Percentage**
Gender		
Male	25	11%
Female	196	88%
Another Identity	1	0%
Mean Age (*SD*)	51.1 (*12.30*)	NA
Country		
United States	75	34%
United Kingdom	49	22%
Rest of Europe	71	32%
Other Countries	27	12%
Length of time using AIR		
3-5 months	69	31%
6-11 months	67	30%
12 months or more	86	39%

Note*:* AIR, Amygdala and Insula Retraining (also known as The Gupta Program). Other countries included Australia, Canada, Columbia, India, New Zealand, and South Africa.

The AIR Intervention

The AIR intervention is comprised of specialized neuroplasticity techniques and breathing, meditation, and other lifestyle therapies. The foundational hypothesis of the intervention is that numerous chronic conditions are caused and perpetuated by brain signals that continually and needlessly activate the immune and nervous systems. This non-stop triggering of the immune and nervous systems manifests as a range of symptoms experienced in the body, including but not limited to pain, fatigue, insomnia, cognitive issues, and distress. Therefore, the primary neuroplasticity technique of AIR is intended to disrupt these brain signals that lead to adverse somatic symptoms and replace them with new, positive neural connections that signal safety to the brain and reduce hyperactivity in the immune and nervous systems. Creating these new neural pathways requires repetition. Consequently, individuals are encouraged to practice the primary neuroplasticity technique daily over a period of at least 3 months, and ideally for 6 months.

The AIR program also recommends that participants engage in some secondary supporting techniques. These include mindfulness-based meditation, where participants listen to soothing guided meditations that help them focus on the present; specific breathing techniques, including alternate nostril breathing; and other lifestyle modifications, such as eating anti-inflammatory foods, getting enough sleep, and developing a calming morning routine to ease into the day.

Participants are advised to spend approximately 30-60 minutes daily practicing the various AIR components, preferably in the morning. The division of time is typically

2-5 minutes of alternate nostril breathing, 20 minutes in meditation, and 15-30 minutes engaging in the main neuroplasticity process. Additionally, short versions (i.e., 30-60 seconds) of the neuroplasticity techniques are recommended at various points during the day to interrupt any in-the-moment somatic signals and provide further repetition in training the new neural pathways.

The intervention is provided digitally via a website member area and consists of a video course with audio exercises and meditations. There are 15 modules that teach and demonstrate meditation, breathing techniques, the primary neuroplasticity techniques and abbreviated versions of them, attitudes for success, how to pace oneself, and reintegrate back into daily life once symptoms have diminished. A printed manual of the whole program is also mailed to participants. Additionally, weekly live and recorded webinars are led by Ashok Gupta. Optional one-on-one and group coaching is also available upon demand with AIR-trained coaches. Since this study was conducted, the program is now also delivered via a mobile app, and offers live daily experiential sessions led by an AIR-trained coach providing a supportive community environment, which may make the program easier to use for patients.

Measures

Health and Functioning. Overall health and functioning were measured using a variation of the EQ-5D Visual Analogue Scale.[34] The EQ-5D Visual Analogue Scale asks respondents to rate their present health state from 0 (*worst*) to 100 (*best*). The modified version used in this study asked participants to rate their overall health and functioning before and after using The Gupta Program: *How would you rate your overall health and functioning (before starting/at present, after using) The Gupta Program? Please rate this using a scale of 0 to 100, where 100 represents full health and functioning. For example, 10 would be poor health and low functioning, and 80-90 would be great health and high functioning.* The length of time noted between the two measures was dependent on how long participants self-reported using The Gupta Program. For example, if a respondent reported using the program for 4 months, the time between the before and after measures was allocated as such.

Analyses

A series of paired-sample *t* tests along with effect sizes were used to analyze the data in IBM SPSS v26.0. The data were normal, with skewness and kurtosis scores within the ±2 acceptable range. Additionally, no outliers were detected. Five respondents did not answer the measures and were removed from the dataset to allow for an accurate and complete investigation of the remaining n = 217 respondents. While removing cases from a dataset can sometimes impact findings, that was not expected with so few removed in this instance (i.e., 2.25% of cases). Therefore, the final analyses were performed for n = 217, with an initial alpha level set at .05 for significance. However, conducting multiple tests across the same dataset can increase the chance of a Type I error (i.e., a false positive). Therefore, the Bonferroni correction was applied for the 16 tests, reducing the required alpha level for significance from .05 to .003.

Results

Paired-sample *t* tests demonstrated that at the Bonferroni-adjusted significance level of .003, AIR participants experienced a significant increase in overall health and functioning across 14 of the 16 different chronic conditions. Two conditions approached significance. These were chronic inflammatory response syndrome (CIRS; $P = .039$) and small intestinal bacterial overgrowth (SIBO; $P = .005$). The remaining 14 conditions were significant at $P < .001$ for all but electromagnetic hypersensitivity (EHS; $P = .001$), and each with a medium or large Cohen's *d* effect size (Cohen's *d* small effect size is 0.2; medium effect size is 0.5; large effect size is 0.8). Among the 14 conditions that yielded significant findings, the increase in mean scores from before to after using AIR ranged from 15.64 points for mast cell activation syndrome (MCAS), a 52% improvement rate, to 28.26 points for Lyme disease, a 116% improvement rate. Specifically, among those suffering from ME/CFS and FM, post-AIR health mean scores were 70% and 62% higher, respectively, than before-AIR mean scores. Among those with LC, the health mean score was 84% higher after using AIR. Table 2 displays the mean scores for each condition before and after using AIR for 3+ months, the change in those scores, and the results from the *t* tests. Still, it is worth noting the small sample sizes for each condition and the variability in the data, with standard deviation scores ranging from 17.88 (Panic pre-AIR) to 29.22 (EHS post-AIR), suggesting that larger sample sizes are needed to provide more robust analysis. Indeed, conditions with higher *p* values had some of the smallest sample sizes, which could have impacted statistical power.

Subgroup analysis within the various conditions was not possible due to the small sample sizes for each of them. However, the full sample was examined at a subgroup level to highlight additional findings. The Bonferroni-adjusted alpha level for these tests was .004 taking into account the 12 subgroups analyzed. As displayed in Table 3, regardless of gender, age group, country of residence, or length of time using the AIR intervention, paired sample *t* test results were significant; $P < .001$ for all subgroups except men, which showed $P = .001$. Additionally, the Cohen's *d* effect sizes were all medium or large and the percentage change improvement from pre- to post-AIR was 50% or higher. Notably, participants who reported using AIR for 12 months or more experienced an improvement of 102%, as compared to 50% and 52% for those using it for 3-5 months or 6-11 months, respectively. This finding suggests that prolonged consistency with the AIR intervention can yield enhanced health and functioning outcomes.

Table 2. Health and Functioning Before and After 3+ Months of Using AIR by Condition

Condition (sample size)	Pre-AIR *M*(*SD*)	Post-AIR *M*(*SD*)	Diff.	Percent Change	*df*	*t*	Sig. (2-tailed)	Cohen's d
ME/CFS (n = 139)	28.20 (20.24)	47.80 (27.49)	19.60	**70%**	138	9.49	<.001	0.81
Fibromyalgia (n = 52)	27.04 (20.21)	43.79 (25.69)	16.75	**62%**	51	5.64	<.001	0.78
Long COVID (n = 30)	24.57 (21.03)	45.30 (25.65)	20.73	**84%**	29	4.05	<.001	0.74
MCAS (n = 56)	30.36 (20.56)	46.00 (24.31)	15.64	**52%**	55	4.93	<.001	0.66
MCS (n = 53)	29.62 (22.43)	54.89 (27.62)	25.27	**85%**	52	6.02	<.001	0.83
Mold (n = 40)	30.78 (21.06)	51.45 (27.06)	20.67	**67%**	39	4.42	<001	0.70
CIRS (n = 19)	24.58 (23.19)	39.37 (25.72)	14.79	**60%**	18	2.22	.039	0.51
EHS (n = 18)	27.50 (23.67)	50.11 (29.22)	22.61	**82%**	17	3.94	.001	0.93
Anxiety (n = 121)	29.21 (21.12)	49.17 (26.59)	19.96	**68%**	120	8.65	<.001	0.79
Panic (n = 34)	24.47 (17.88)	48.94 (25.50)	24.47	**100%**	33	6.12	<.001	1.05
Burnout (n = 33)	28.00 (19.53)	49.30 (25.73)	21.30	**76%**	32	4.55	<.001	0.79
IBS (n = 66)	28.44 (21.45)	46.74 (27.37)	18.30	**64%**	65	6.78	<.001	0.83
Food sensitivities (n = 97)	32.08 (21.70)	50.08 (24.65)	18.00	**56%**	96	7.71	<.001	0.78
SIBO (n = 30)	25.17 (19.33)	36.83 (23.75)	11.66	**46%**	29	3.07	.005	0.56
Pain (n = 26)	29.23 (19.44)	45.50 (25.88)	16.27	**56%**	25	3.87	<.001	0.76
Lyme (n = 27)	24.37 (20.03)	52.63 (27.27)	28.26	**116%**	26	5.30	<.001	1.02

Abbreviations: AIR, Amygdala and Insula Retraining; Diff, difference in mean scores from pre-AIR to post-AIR; Percent Change, the percentage change in mean score from pre-AIR to post-AIR; MCS, Multiple Chemical Sensitivities; CIRS, Chronic Inflammatory Response Syndrome; EHS, Electromagnetic Hypersensitivity; IBS, Irritable Bowel Syndrome; SIBO, Small Intestinal Bacterial Overgrowth; MCAS, Mast Cell Activation Syndrome.

Table 3. Health and Functioning Before and After 3+ Months of Using AIR by Subgroup

Condition (sample size)	Pre-AIR *M*(*SD*)	Post-AIR M(SD)	Diff.	Percent Change	*df*	*t*	Sig.(2-tailed)	Cohen's *d*
Overall (N = 217)	29.52 (20.83)	49.71 (27.16)	20.19	**68%**	216	12.12	<.001	0.82
Gender								
Male (n = 25)	34.40 (23.99)	57.44 (22.20)	23.04	**67%**	24	3.60	.001	0.72
Female (n = 191)	28.69 (20.24)	48.72 (27.70)	20.03	**70%**	190	11.85	<.001	0.86
Age								
18-44 (n = 67)	29.76 (20.93)	47.45 (26.79)	17.69	**59%**	66	6.18	<.001	0.76
45-54 (n = 62)	31.55 (21.82)	52.11 (26.28)	20.57	**65%**	61	6.52	<.001	0.83
55+ (n = 88)	27.91 (20.14)	49.75 (28.19)	21.84	**78%**	87	8.11	<.001	0.86
Country								
United States (n = 75)	31.11 (23.19)	49.08 (28.63)	17.97	**58%**	74	5.91	<.001	0.68
United Kingdom (n = 48)	31.85 (19.54)	49.38 (26.17)	17.52	**55%**	47	5.96	<.001	0.86
Rest of Europe (n = 69)	26.61 (19.39)	49.04 (26.70)	22.43	**84%**	68	7.21	<.001	0.87
Other Countries (n = 25)	28.32 (19.74)	54.12 (26.98)	25.80	**91%**	24	5.77	<.001	1.15
Length of time using AIR								
3-5 months (n = 68)	30.34 (19.43)	45.49 (24.92)	15.15	**50%**	67	7.60	<.001	0.92
6-11 months (n = 66)	33.27 (23.86)	50.73 (27.16)	17.46	**52%**	65	5.45	<.001	0.67
12+ months (n = 83)	25.87 (18.92)	52.73 (28.78)	26.50	**102%**	82	8.75	<.001	0.96

Abbreviations: AIR, Amygdala and Insula Retraining; Diff, difference in mean scores from pre-AIR to post-AIR; Percent Change, the percentage change in mean score from pre-AIR to post-AIR.

Though these findings are derived from cross-sectional data, they are relevant for clinical application. Considered in aggregate, the results indicated that the AIR intervention can yield statistically significant improvements in health and functioning across numerous conditions and regardless of subgroup. Of the 14 conditions that demonstrated significant results, the percentage improvement in self-reported health and functioning ranged from 52% to 116%. Similarly, across subgroups, the percentage improvement ranged from 50% to 102%. Of course, there was no control group in this study. However, other research has suggested that standard improvement rates for placebo intervention groups are 20% or less,[35] which is substantially lower than the rates observed in the present study.

Discussion

This novel and exploratory study aimed to evaluate the impact of AIR across a range of different chronic conditions. Results from a series of paired-sample *t* tests supported the hypothesis that self-reported overall health and functioning would improve after using AIR for 3+ months. Indeed, the increase in participants' wellness scores was significant for 14 of the 16 chronic conditions

tested and approached significance for two of the 16 conditions after participants actively engaged with the AIR intervention for at least 3 months.

Of course, no control group was used in this study. However, standard improvement rates among placebo intervention groups have been observed at 20% or less[35] and generally show small effect sizes,[36-38] both of which are notably less than the 52% to 116% improvement rate and medium to large effect sizes detected in this cross-sectional study.

Moreover, the study findings are consistent with randomized controlled studies. In research conducted among patients with FM and/or ME/CFS, statistically significant improvements in physical health, energy, pain, symptom distress, motivation, activity, and fatigue were observed among those who received the AIR intervention in combination with standard care compared to a control group who received only standard care.[11] Another study among FM patients also demonstrated AIR's effectiveness. Compared to an active control group who engaged in a relaxation therapy program structurally equivalent to AIR, patients who received the AIR intervention posted significantly lower scores in functional impairment, anxiety, pain catastrophizing, psychological inflexibility, clinical severity, depression, and brain-derived neurotrophic factor (BDNF). Additionally, they showed significantly higher scores in mindfulness, self-compassion, and health-related quality of life.[12] Moreover, a study conducted among people suffering from LC tested the impact of AIR compared to a structurally equivalent health and wellness intervention. Results showed that the AIR intervention was four times more effective at reducing fatigue and twice as effective at increasing levels of energy compared to a structurally equivalent wellness program. Furthermore, the AIR group approached the US adult's normal level of fatigue after 3 months.[13] Consequently, there is growing evidence that AIR is an effective method for addressing various symptoms across different chronic conditions.

AIR also seems to be a more valuable approach than other similar non-pharmacological interventions. Several therapies encompassing psychological, biofeedback, mindfulness, movement, and relaxation have shown promise in alleviating symptoms associated with specific chronic conditions, including ME/CFS and FM. However, the evidence supporting these interventions is characterized as low quality with inconsistent results.[39-40] Additionally, the lack of standardization in interventions and outcome measures further complicates the interpretation of findings.[39] Robust evidence is conspicuously absent regarding non-pharmacological treatments for the management of other chronic conditions, including LC and various post-viral fatigue syndromes.[41-42]

By contrast, AIR as a standardized intervention, has consistently demonstrated efficacy across several conditions and outcomes when tested in high-quality randomized controlled trials, with studies reporting medium to large effect sizes.[11-13] Moreover, in some of these studies, AIR demonstrated significantly better results than structurally-equivalent non-pharmacological interventions provided to the control groups.[12-13] A possible reason for AIR's superior performance could be that it is strategically designed to target the root cause of chronic conditions (discussed in further detail below), rather than just symptom management as is often the primary objective of other non-pharmacological interventions.[42]

The cross-condition and comparative effectiveness of AIR may be explained by its underlying hypothesis and the mechanisms by which neurobiological research suggests the amygdala and insula are involved in the chronic illness cycle. The AIR hypothesis proposes that the root cause of several chronic conditions is found in the brain,[10,14-15] specifically the amygdala and insula. For example, LeDoux's theory[43] implies that adverse environmental events can trigger the amygdala, which is the primary defense mechanism in the brain. Additionally, other research has suggested that the brain's defensive responses are controlled by a higher-order cortical network that involves the amygdala, insula, interior cingulate, medial prefrontal cortex, and other areas. When this higher-order cortical network does not appropriately control defensive responses, it may contribute to disorders such as posttraumatic stress disorder.[44]

As applied to chronic conditions, the foundational hypothesis of AIR is that dysregulated amygdala and insula responses lead to a continual over-triggering of defense responses that results in a vicious cycle of persistent illness. The mechanism for this cycle is activated when certain precipitating factors or threats are present (e.g., physical illness or an acute traumatic event) that spur the nervous and immune systems into action. In normal circumstances, this is an adaptive response and once the threat is mitigated, the body returns to homeostasis. However, the defense response can dysfunction when threats are re-experienced and/or previously neutral stimuli become conditioned stimuli that trigger a defense reaction.[14-15,45]

The amygdala is widely considered to play a primary role in detecting threats and activating defensive responses, as well as assigning meaning to various neutral stimuli.[30] Thus, even when a stimulus is benign, the amygdala can perceive it as a threat and trigger an unnecessary defense response.[46-49] Indeed, much research points to the amygdala's role in classical fear conditioning whereby a previously neutral stimulus becomes associated with a threat stimulus to the point where just the presence of the neutral stimulus triggers the defense response.[26,43,49-50] Studies have demonstrated that such fear conditioning is mainly controlled by the amygdala along with other areas of the brain, including the insula, anterior cingulate, and medial prefrontal cortex.[43,50-51] Consequently, the AIR hypothesis posits that the amygdala can assign threat status to a previously neutral stimulus and that information is

stored in the insula. Thus, maladaptive conditioning and defense responses can be triggered when the amygdala and insula erroneously assume that bodily symptoms are threats.[14-15] Recent neurobiological animal research has supported this theory.

In one study, the brain processes of underlying conditioned immune responses in rats were examined, revealing that the amygdala mediates the visceral input required for the acquisition of an immune response while the insular cortex plays a central role in acquisition and induction of the response.[32] In another study, the neural activity of mice was recorded while two gastrointestinal inflammatory conditions were stimulated. After removing the inflammatory stimuli and complete recovery in the mice, reactivation of the same neural activity in the insular cortex triggered the inflammatory condition. Additionally, inflammation diminished when activation in the insular cortex was inhibited.[33] Considered together, these studies suggest that the amygdala and insular cortex are crucial components in immunological conditioning.

Therefore, even absent a real threat, the amygdala and insula can trigger danger signals to the immune and nervous systems. These danger signals are experienced as bodily symptoms which, in turn, are misinterpreted as threats. In essence, the amygdala and insula seem to get trapped in a continuous cycle of receiving and sending adverse signals to the body, as they try to fight off the very symptoms they are creating. This cycle keeps the immune and nervous systems in a constant state of flux and perpetuating the symptoms of various chronic diseases.[14-15]

Given the underlying hypothesis and mechanisms, it follows that the AIR intervention would be effective in alleviating the various symptoms of chronic illness. As noted above, the intervention is designed to interrupt the danger signals going back-and-forth between the brain and body, and create new, neural pathways that signal safety. Such brain-retraining helps the amygdala and insula to reduce the hyper-vigilant activity and return the body to homeostasis.

Strengths and Limitations

This study's primary strength is its novelty in analyzing the impact of AIR across multiple chronic conditions. While other studies have used more rigorous research methods in evaluating the effectiveness of AIR, they have focused on only a few conditions (i.e., ME/CFS, FM, and LC). By contrast, the sample used in this study included people suffering from a range of chronic illnesses. Thus, the effectiveness of AIR was assessed across 16 different conditions, providing more evidence and insight into the potential reach and influence of the intervention. Additionally, these findings support the recently proposed theory that different chronic conditions can potentially be treated using an in-common neuroplasticity method.[10]

Still, the present investigation has obvious limitations. First, this study was cross-sectional and not experimental, which prohibits the ability to draw any causal inferences from the results. Second, the research design used a convenience sample that elevated the possibility of self-selection and risk of response biases that might impact the reliability and generalizability of findings. Still, it is worth noting the consistently significant findings across gender, age, country, and chronic conditions, suggesting that AIR may be helpful for various populations. Third, the sample size for several conditions and subgroups was small, which may have reduced statistical power. Fourth, the study used self-reported measures, and participants' memory of their baseline health status before using AIR could be inaccurate when recalling it 3+ months later. Finally, conducting multiple tests on the same data increases the chance of Type I error (i.e., a false positive). However, this issue was mitigated by applying the Bonferroni correction and adjusting the alpha level accordingly.

Limitations notwithstanding, the findings from this study are intriguing and promising. Together with various randomized-controlled trial outcomes, these results provide further evidence that AIR could be a viable and accessible treatment for multiple chronic illnesses. Future research should engage in more rigorous testing of AIR. This could include randomized controlled trials for various chronic illnesses, including but not limited to the 16 conditions explored in this study. It would also be helpful to conduct Phase II and Phase III clinical trials for conditions that have already demonstrated AIR's effectiveness in pilot studies for ME/CFS, FM, and LC. Moreover, evidence of AIR's cross-condition effectiveness could be expanded by conducting initial clinical trials for emerging conditions, such as Lyme disease, mold illness, mast cell activation syndrome (MCAS), and many others. Study robustness could also be bolstered by incorporating objective biomarkers and health professionals' observations in addition to self-reported measures. Finally, in addition to exploring the effectiveness of AIR in improving patient health and functioning, other studies could examine the impact of AIR on quality of life, economic productivity, and social functioning.

Practical Implications

Despite its various limitations, this novel study has numerous practical implications. From a clinical and patient-centered care perspective, AIR is a promising approach for addressing numerous conditions that are often difficult to treat. The intervention is readily accessible via a member website and app, and provides patients with a comprehensive selection of care options, including 15 video and audio modules, weekly live and recorded webinars, live daily group coaching, and customized one-on-one coaching. Anecdotal reports indicate that clinicians have been integrating AIR at various stages of the patient journey. Some patients respond well to engaging with AIR before other treatment if they are sensitive to medications and supplements; others are able to successfully incorporate

AIR alongside other treatments; and some might need other urgent primary care before working with AIR.

From a societal and health care systems perspective, AIR is also a promising avenue for addressing chronic conditions, many of which are incapacitating and adversely affect millions of people worldwide,[2,5,6] costing the global economy trillions of dollars.[7] In the United States alone, the cost of ME/CFS is estimated at $17 to $24 billion,[52] the minimum cost of FM is estimated at $7 billion,[53-54] and LC is pegged at at least $140 billion.[55] Most of these costs are due to reduced quality of life and earnings for patients, and increased medical spending because current treatments have such varied success in alleviating symptoms.[8-9] Of course, AIR is still a relatively new approach and more research is needed to bolster the evidence of its effectiveness. Nonetheless, as a low-cost and widely-available intervention it holds great potential for reducing societal and public health care costs.

Conclusion

This novel, exploratory, cross-sectional study is the first to demonstrate the effectiveness of a neuroplasticity brain-retraining program (AIR) in improving health and functioning for several chronic conditions and across various subgroups. After 3+ months of using AIR, participants' self-reported well-being for 14 different conditions significantly increased and approached significance for two other conditions, all with medium to large effect sizes. These findings are timely and important, suggesting AIR can be a valuable resource for patients, clinicians, and policymakers in managing chronic illnesses. Millions of patients worldwide suffer from these often debilitating diseases that are challenging to treat. The global economic cost is trillions of dollars due to reduced productivity and increased healthcare spending. Accordingly, innovative, low-cost, and widely-accessible treatments, such as AIR, that aim to treat the root cause of these illnesses are urgently needed. Still, more research is required. Large, randomized controlled trials testing AIR for numerous conditions can bolster the evidence of causality, further investigate the mechanisms underlying AIR and its foundational hypothesis, and demonstrate the effectiveness of AIR in improving the physical psychological, and social aspects of chronic illness across diverse populations. This study provides a springboard for further investigation and offers initial evidence that AIR could be a potentially ground-breaking approach for improving the lives of millions of chronic conditions patients around the world.

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Author Contributions

Conceptualization, methodology, data collection, data analysis, and report writing by Alexandra J. Bratty.

Informed Consent Statement

Explicit informed consent was not obtained from subjects involved in the study. However, participants were informed about the purpose of the study before participating, and the study design was a self-report survey in which respondents could voluntarily participate or drop out at any time.

Data Availability Statement

The data are not publicly available because the sample consists of vulnerable adults with chronic medical conditions. Individuals were reassured that their data would be kept strictly confidential.

Conflicts of Interest

Alexandra J. Bratty is the CEO of AB Research Consulting, which provides consulting services to The Gupta Program, the commercial version of the Amygdala and Insula Retraining (AIR) intervention. Her company was compensated for this work by independent donors.

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