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Aim and Scope

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The Effects of the PowerMens Methodology on the Measurement and Training of Attention in Young Footballers: A Pilot Study

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Abstract

In sport psychology, the use of biofeedback (BFB) is increasingly frequent, a noninvasive experimental procedure that allows the person to regulate their psychobiological functions and helps to become aware of internal processes that are not consciously controlled. Based on this, a new method was devised, PowerMens, which for the first time investigates these concepts integrated with specific training on visual attention.

The subjects were 20 professional youth football players, divided into experimental and control groups. The research was conducted in pretest, training, and posttest, where the pre- and posttest consisted of a stress attention task. The experimental group conducted the BFB PowerMens training which integrates the BFB with Mental Games software promoting the control of the arousal level and the restoration of homeostasis.

The aim of this research was to examine the psychophysiological reaction to the visual attention tasks that cause attentional and cognitive stress, predicting greater self-regulation and restoration of body homeostasis in the experimental group.

The results are auspicious because they showed a better capacity for cognitive and emotional self-regulation, a restoration of homeostasis, and also an improvement in posttest time.

Keywords: sport psychology; sport performance; biofeedback; football; PowerMens

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Introduction

In the world of sport, both professional and competitive, athletes who aspire to success must learn to face competitions with a psychological framework that allows them to excel despite environmental or mental variables.

In recent years, the scientific literature relating to sport psychology is bringing out a dimension, the mental one, as an essential component for achieving high-level performance (Bompa, 1999; Cox, 2002; Issurin, 2007). Today it is essential for athletes who aspire to have an excellent performance to learn to face performances and competitions with a psychological framework that allows them to be successful in a performance context with environmental (external) or psychological (internal) aversive variables (Blumenstein et al., 2007; Dahl, 2013). The sport involves fine motor skills, in which

the psychological aspect plays a key role in sporting performance during a competition (Rogulj et al., 2006).
Soccer is an unpredictable, acyclical team sport involving combined movements of the upper and lower limbs, which often must be performed at or near maximum speed, a frequent number of times during the entire duration of a match. These are complex movements of different types, often unpredictable and sudden and with mainly short recovery times. Cognitive involvement is therefore constant, and integrated coordination with a technical gesture is essential, especially in motion. The individual performance of each player coordinates with that of his teammates and opponents and actively contributes to any collective action. Subjective performance is, therefore, an essential part of a complex system that involves actions and reactions of the players of both teams and requires constant training as the information to be selected and processed is many, at any age (Chmura et al., 2017; Stølen et al., 2005).

The literature in sport psychology highlights how the attention processes in complex and sport-specific decision-making tasks are relevant for performance purposes; in fact, training in this regard can involve a faster evaluation of stimuli (Hack et al., 2009) and an improvement in one's own mental strength and hardness (Jones, 2002). In football, however, there are not many studies that specifically investigate attention; some highlight how cognitive skills related to attention play a fundamental role in the efficient execution of specific tasks (Memmert et al., 2020; Shimi et al., 2021; Verburgh et al., 2014). High-level footballers can perform the steps relevant to the information processing task (such as visual information processing, stimulus evaluation, and motor response output) in a shorter time than lower-level footballers. By studying and analyzing their event-related potentials (ERPs), the P100 and P300 latencies of the high-performance group were significantly shorter than those of the low-performance group (Matsutake et al., 2018). This would be very complex if the brain did not have cortical plasticity (Kandel, 1999).

Attention training, however, may not be sufficient to maintain performance consistency because the sporting context is characterized by the presence of elements, stress factors, which can affect performance (Brandão et al., 2021; Michailidis, 2014; Nippert & Smith, 2008; Santos et. al., 2014). Stress factors are stimuli of different nature that lead the organism and the psyche to experience stress and can be physical, environmental, cultural, metabolic, psychological, affective, or alimentary (Bhargava & Trivedi, 2018; Yaribeygi et al., 2017). The repercussions that stress factors can have are related to attentional bias (i.e., a reduction in attention and concentration during the performance). This results in a change in the direction in which a person focuses their attention in response to a stimulus associated with their illness or in response to a stimulus perceived as threatening (Keogh et al., 2001; O'Toole, 2014). Other studies show that there is a clear correlation between attentional bias and mental states, such as with anxiety (Bar-Haim et al., 2005; Tirinnanzi, 2007) and with depression (Harvey et al., 2004). Anxiety and depression, associated with insomnia, are the symptoms that most aggravate highly stressful and traumatic situations. The recent pandemic due to COVID-19 has shown how these symptoms have drastically increased in the collective population (Casagrande et al., 2020; Huang & Zhao, 2020; Tirinnanzi & Bianchi, 2020; Tirinnanzi & Bianchi, 2021) and in football players (Cavarretta et al., 2021; Rampinini et al., 2021).

Therefore, stressors can bring the stress level beyond a subjective threshold and can affect physiological activation, which affects the activity level of certain bodily functions such as changes in heart rate (HR), respiratory rate (bpm), skin conductance (GSR), sweating, and body temperature. These functions are controlled by the autonomic nervous system (ANS) and often escape the conscious control of the person, but there are techniques, such as biofeedback (BFB), which allow you to voluntarily manage some of these functions (Biagioli, 2013). The BFB is a noninvasive experimental procedure that can be used by a person to regulate their psychobiological functions and helps to become aware of internal processes that are not typically controlled at the level of consciousness (Zaichkowsky & Fuchs, 1988).

Today the BFB, thanks to modern technology, allows us to become aware of the effectiveness of the techniques we are implementing, allowing us to progressively adapt our behavior in real time through objective and measurable feedback, generally presented to the athlete on a PC screen. In this way the athlete, on the basis of the information or feedback received from the body, learns to control self-regulation, to consciously change their behavior in order to improve their health and performance while increasing awareness and physiological activity of one's organism. This process leads to the development of mental skills, such as attention and concentration, and facilitates the achievement of better sports performance (Blumenstein et al., 1997;

Blumenstein & Orbach, 2014; Galmonte et al., 2011).

In football, therefore, the BFB, combined with relaxation and/or activation techniques, can be used successfully in order to obtain systematic learning of the psycho-regulation process, allowing the player to subjectively define and actively face situations (Rijken et al., 2016). Based on the findings of the BFB equipment and the subjective needs of the players, various objectives can be outlined that optimize performance, such as activation control, attention and concentration management, reduction of performance anxiety, pain and fatigue management, increase in muscular effort, and restoration of homeostasis (Biagioli, 2013; Saha et al., 2013). A study by Wilson et al. (2006) highlighted how the use of the BFB may have positively supported the Italian national team during the World Cup won by the same national team in Germany.

Today, technology-based interventions include biofeedback, neurofeedback, virtual reality (VR), augmented psychology, and video game devices (Pallavicini et al., 2009; Russoniello et al., 2009; Tarrant et al., 2018; Thompson & Thompson 2007). The latter, video games, seem ideal for training on stress exposure, for learning stress management in the presence of stressors and for maintaining this ability. Furthermore, they are correlated with attention; that is, people with video game experience, unlike nonexpert people, are more superior in the domains of visual attention (Schubert et al., 2015). The attentional component is also very present in young people; for example, children are better performing than adults in directing attention to irrelevant stimuli (Plebanek & Sloutsky, 2017) and this opens up important reflections, especially on the youth sectors. Video games are designed to increase arousal (Reinecke, 2009), so a stress management software or program built into a video game can help combat and manage stress while performing an arousal activity. BFB video games can, therefore, be an effective technique for teaching relaxation skills (Bouchard et al., 2012).

For footballers, a probable advantage in integrating specific attention work with BFB could be being able to manage and control stress factors, without allowing the subjective threshold that affects physiological activation and affects performance to be exceeded. In this way, the internal resources, instead of being invested in restoring body homeostasis, will probably be greater for the purpose of sports performance.

The BFB uses instruments equipped with sensors and transducers (converters) that provide information on the status of biological functions that are usually not subject to voluntary control. In this research, skin conductance (GSR) and heart rate (HR) were detected.

EDA – Electrodermal Activity

The galvanic skin response (GSR) is a physiological response of electrodermal activity (EDA) and is a measured manifestation (Boucsein, 2012) of the activation of the ANS, in particular of the sympathetic partition (Fontanella et al., 2012). GSR is one of the most used methods in psychophysiology and is considered the golden standard (Fontanella et al., 2012). External emotional stimuli (sudden noise, sigh, phrase or word pronounced by someone) or internal (imagine erotic, fearful, or otherwise emotional scenes) cause a drop in the RS (skin resistance), due to the psycho-galvanic reflex. GSR is affected by sweat gland activity and skin responses on the palmar surface of the hand. The sweat glands are activated only by sympathetic activity. If the sympathetic branch of the ANS is very excited, the activity of the sweat glands increases and, consequently, the variations in the values of GSR.

Electrodermal activity (EDA) is linked to autonomic emotional and cognitive processing and is used as a sensitive index of emotional processing and sympathetic activity. This coupling between cognitive states, arousal, emotion, and attention allows EDA to be used as an objective index of emotional states and can also be used to examine implicit emotional responses that may occur without conscious awareness or are beyond cognitive intent. Furthermore, electrodermal activity is also a useful indicator of attention processing per se, in which salient stimuli and resource-demanding tasks evoke an increase in EDA responses (Boucsein, 2012).

EDA reflects changes in conductance at the skin surface on behalf of sweat gland activation and consists of two components: a highly subject-dependent tonic skin conductance level (SCL) and phasic response from a series of transient peaks known as skin conductance responses (SCR) found in reaction to surprise events, cognitive activity, emotional arousal, and even spontaneously (Boucsein, 2012).

Individuals and experimental situations vary greatly; there are in the literature very general estimates of "typical" force values. In terms of phasic SCRs, amplitudes can typically vary around 0.10–0.60 microsiemens (μS) on average when scores are normalized and average between 2 and 16 μS for SCL (Venables & Christie, 1980).

HRV – Heart Rate Variability

Heart rate variability (HRV) BFB is also an approach to help athletes with regular stress, and it can help the athlete cope with the stress of competition and improve neuromuscular function (Lagos et al., 2008).

The heart is innervated by both the parasympathetic and sympathetic systems. These act in an antagonistic way to normalize the time interval between consecutive heartbeats; that is, greater sympathetic activity leads to an increase in heart rate, while the addition of parasympathetic activity slows down the frequency itself.

Therefore, HRV can be used as a measure of stress and can be viewed as a phenomenon under partial voluntary control. This statement is due to the fact that fluctuations in the beat-to-beat period are driven by the respiratory cycle, as the heart rate increases during inspiration and decreases during exhalation. A study by Vaschillo et al. (2006) found that these fluctuations reach a maximum in respiratory rate of about 6 breaths per minute. Thus, considering that respiration can affect HRV, this is considered to be a phenomenon under partial voluntary control.

The hope of this research lies in finding a tangible and objective result of the effectiveness of the BFB PowerMens method in psychological work with footballers, in being able to highlight how psychophysiological and mental variables, so far very abstract in the football scene, can be observed and studied in a concrete and objective way.

Furthermore, consequently, the professional Sports Psychologist within professional clubs could have crucial importance not only in the management of the psychological and mental area but also in the maintenance and increase of the economic value of the players, the heritage of sports clubs.

Methods

Participants

Twenty (n = 20) male footballers from the professional youth sector of SS Arezzo srl, during the Italian U18 Primavera 3 football championship, were randomly selected and divided into an experimental and control group, each made up of 10 units. The two groups did not show a significant difference between them, $t(18) = 1.17$ and $p = 0.13$. The mean age of the group was 17.5 years (SD = 0.85), and the mean age of the control group was 17 years (SD = 1.05).

Before the experiment, the players provided their informed consent. To participate in the study, they had to be over the age of 16, have experience in national categories for at least one year, and be uninjured.

Compliance with Ethical Guidelines

All ethical principles have been considered in this article. Participants were briefed on the purpose of the research, confidentiality of their information was assured, and they were informed that, if desired, the results of the research would be available to them.

Materials

In this study, MindPlace ThoughtStream technology (MindPlace, Eastsound, WA), Firstbeat heart rate monitors (Firstbeat Technologies Oy, Jyväskylä, Finland), Microgate Witty SEM (Microgate, Mahopac, NY), and a Toshiba A40 laptop were used to collect data on skin conductance (GSR) and heart rate (HR).

MindPlace ThoughtStream technology is a modern GSR BFB system for the measurement and feedback of the electrical resistance of the skin. ThoughtStream interface software, or the corresponding graphical analysis software, is a program that allows more accurate real-time recordings of GSR data and is particularly suitable for evaluating them. The Mental Games multimedia software analyzes the tiny changes in your skin resistance values (GSR) sent by the ThoughtStream biofeedback system to the personal computer. The training modules of the Mental Games "feel" based on the variation of the activity of the sweat glands, the responses of the skin on the palmar surface of the nondominant hand, and how concentrated and relaxed a person is and then will change its response according to mental state.

Firstbeat heart rate monitors assess your heart rate using a strap positioned around the chest, a standard heart rate monitor belt that is comfortable and with excellent elastic properties.

Microgate Witty SEM is a technology composed of “intelligent traffic lights” composed of a matrix of multicolored 7x5 LEDs capable of managing

different symbols and colors. Thanks to the proximity sensor it contains, Witty SEM is the ideal solution for planning and managing specific tasks on reactivity, agility, and attentional and cognitive-motor skills in the best possible way.

Procedure

The experimental design in this study consists of a pretest and posttest, within which the experimental group was trained with the BFB PowerMens method, while the control group was trained with the mental preparation techniques related to sport. Both groups received the necessary information about the task and were informed about the intent of the research.

The hypothesis of this pilot research is to find in the experimental group a better restoration of homeostasis in the organism and a lower activation during a task that causes attentional stress; this would lead to an improvement in internal self-regulation and also to an improvement in attention if the results of the posttest were better than the pretest.

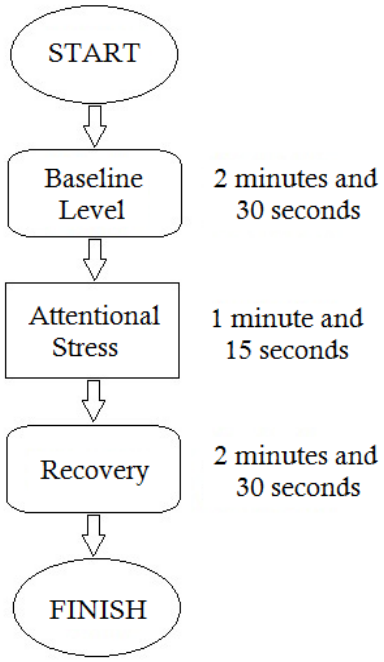
The pretest and the posttest were performed in the same way, and both were characterized by a succession of well-coded procedures that gave a psychophysiological profile of the player: (1) baseline level, (2) attentional stress, and (3) recovery. Total duration, 6 min and 15 s (Figure 1).

For an even more accurate investigation, the attentional stress phase was divided into two parts, Onset of Stress and End of Stress, in which the data were acquired.

Once seated, the football player had the experimenter place electrodes on the fingers of the nondominant hand, then relaxed for 2 min and 30 s. Baseline condition was observed and recorded via the BFB parameters discussed above, such as GSR and HR. Once the 2.5 min of relaxation were over, the athlete experienced a load of attention stress for 1 min and 15 s, where he performed the task presented by the four Witty SEMs with the dominant hand; that is, to move the hand in front of the photocell in which the target stimulus appears while in the other three traffic lights. There are other random stimuli that act as distractors; if the athlete places his hand in front of the wrong photocell, the traffic lights do not change sequence, but time goes by. The attentional stress load ends after 60 sequences are carried out correctly, or without fails after 1 min and 15 s.

After the load, the athlete had 2 min and 30 s available for the recovery phase, characterized by relaxation in place, similar to phase 1.

Figure 1. *Pre- and Posttest Protocol. Baseline Level, Attentional Stress Task, Recovery.*



Intervention with the BFB PowerMens Method – Experimental Group. The experimental group of 10 athletes each performed a path of 12 sessions of BFB PowerMens, consisting of 15 min each session, twice a week. The instrumentation used was the MindPlace ThoughtStream technology and the associated Mental Games software. During the 12 individual sessions, the athletes were instructed on the BFB; they learned how to manage their breathing and how to consciously control their psychophysiological responses. Breathing was trained by decreasing respiratory cycles per minute (bpm) in a range between 5 and 7 (Jerath et al., 2006; Song & Lehrer, 2003; Zaccaro et al., 2018).

In these sessions, techniques such as relaxation, focusing, and breathing associated with Mental Games were introduced. Mental Games are similar to classic personal computer games; however, they run through Mental Games multimedia software which analyzes small changes in skin resistance values (GSR) sent by the MindPlace ThoughtStream biofeedback system to the notebook or PC. The psychophysiological and sensorimotor levels were used in the study. The psychophysiological trains

the athlete to move specific objects, in this case a hot air balloon, on the screen as he learns to become relaxed and focused. The players in this way find out about managing their internal state in order to land the hot air balloon on a certain platform. If the psychophysiological parameters are "active," the hot air balloon will not descend and will remain suspended or swing upwards. It is important for the athlete to focus not only on relaxation and respiratory regulation but also on being present, here and now, leaving thoughts and images outside the present moment of exercise.

The sensorimotor level involves another game and the use of the mouse to perform a screen capture task. The athlete must click on each of the 10 ants that move randomly on the screen. If the psychophysiological parameters are active, the ants will move quickly, if the athlete learns to manage his inner state according to the previous psychophysiological level, then during the task the ants will move more slowly and it will be easier to catch them. The task is repeated twice, as once you have captured all the ants they will become ladybugs, and in turn, by clicking on each of them they will fly away. The goal of this game is to make all the ladybugs fly away.

Step 2 of this interface has the opposite effect; that is, the calmer and more relaxed the athlete is, the faster the ants will move. If the athlete learns to become active with his own internal physiology, the ants will move more slowly such that it will be easier to catch them to make them become ladybugs and then make them fly away.

At the completion of each session of the Mental Games, the players had to wait for the result relating to the detected skin conductance shown by the software. That way they could see their personal progress session after session.

This structured work allows the athlete to increase self-management and control in the face of stressful stimuli always present during sports, effectively coordinating the cognitive processes involved such as perception, attention, learning, thinking, and decision-making.

Intervention with the Mental Coaching Method – Control Group. The control group of 10 athletes followed a parallel path to the experimental group, with 12 sessions each, twice a week and for a duration of 15 min, in which each athlete followed a plan relating to the development of concentration and motivation through the use of specific mental coaching techniques, such as visualization, inner dialogue, definition and planning of goals, watching motivational videos, improving the ability to concentrate, creating beliefs, and winning mental habits.

Statistical Analysis

Microsoft Excel 2007 (Microsoft Inc., Redmond, WA) software (Verma, 2019) analyzed the data to decide means and standard deviations (*SD*). A paired sample *t*-test was applied to examine the differences in each group before and after treatment. In addition, an independent samples *t*-test was applied in order to examine the differences between the two groups before and after treatment. Descriptive data are expressed as mean ± standard deviation (*SD*), and all statistical tests were performed at a significance level $p < .05$.

Results

The mean (in microsiemens μS) Baseline Level (pre and post) skin conductance responses (SCR) scores of the experimental group participants were 0.201 (*SD* = 0.076) and 0.219 (*SD* = 0.071), respectively, and the mean SCR scores (pre and post) of the participants in the control group were 0.196 (*SD* = 0.082) and 0.222 (*SD* = 0.046), respectively. The mean Onset of Stress scores (pre and post) of the participants in the experimental group were 0.324 (*SD* = 0.085) and 0.253 (*SD* = 0.073), respectively, and the mean (pre and post) scores of the participants in the control group were 0.309 (*SD* = 0.081) and 0.296 (*SD* = 0.077), respectively. The mean End of Stress scores (pre and post) of the experimental group were 0.375 (*SD* = 0.083) and 0.285 (*SD* = 0.074), respectively, and the mean scores (pre and post) of the control group were 0.336 (*SD* = 0.039) and 0.347 (*SD* = 0.030), respectively. Finally, the mean recovery phase scores (pre and post) of the experimental group were 0.340 (*SD* = 0.045) and 0.221 (*SD* = 0.06), respectively, and the mean (pre and post) scores of the control group were 0.319 (*SD* = 0.054) and 0.287 (*SD* = 0.055), respectively (Table 1).

An independent sample *t*-test was applied to examine differences in pre- and posttest scores between the two groups. The *t*-test results showed that the mean of both pretest and posttest Baseline Level and Onset of Stress scores did not differ between the two groups (Table 1). Furthermore, the mean End of Stress and Recovery scores in the pretest did not differ well between the two groups, while the mean End of Stress and Recovery scores in the posttest differed well between the two groups.

The Recovery phase in the experimental group showed the best results suggesting that the PowerMens sessions were more effective than the control group training (Table 1).

Table 1

The Phases of the Pretest and Posttest of the Experimental Group and Control Group (N = 20)

SCR Variables		Experimental Group (*n* = 10)		Control Group (*n* = 10)		*t*	*p*-value
(in microsiemens µS)		*M*	*SD*	*M*	*SD*		
Baseline Level							
	Pretest	0.201	0.076	0.196	0.082	0.14	.446
	Posttest	0.219	0.071	0.222	0.046	−0.09	.462
Onset of Stress							
	Pretest	0.324	0.085	0.309	0.081	0.40	.345
	Posttest	0.253	0.073	0.296	0.077	−1.28	.107
End of Stress							
	Pretest	0.375	0.083	0.336	0.039	1.35	.097
	Posttest	0.285	0.074	0.347	0.030	−2.47**	.012
Recovery							
	Pretest	0.340	0.045	0.319	0.054	0.95	.178
	Posttest	0.221	0.060	0.287	0.055	−2.57*	.010

Note. In the posttest, the phases of End of Stress and Recovery related to the responses of skin conductance (SCR) differ statistically in the scores (** $p < .05$; * $p < .1$).

The Baseline Level (pre and post) mean heart rate variability (HRV) scores (in bpm) of the experimental group participants were 77.0 (*SD* = 7.19) and 75.4 (*SD* = 9.82), respectively, and the mean HRV scores (pre and post) of the participants in the control group were 78.1 (*SD* = 8.27) and 75.1 (*SD* = 12.68), respectively. The mean Onset of Stress scores (pre and post) of the participants in the experimental group were 88.1 (*SD* = 10.42) and 80.6 (*SD* = 9.52), respectively, and the mean (pre and post) scores of the participants in the control group were 83.1 = 4.68) and 80.5 (*SD* = 2.27), respectively. The mean End of Stress scores (pre and post) of the experimental group were 93.1 (*SD* = 7.17) and 85.0 (SD = 8.71), respectively, and the mean scores (pre and post) of the control group were 91.5 (*SD* = 5.19) and 88.5 (*SD* = 7.01), respectively. Finally, the mean Recovery phase scores (pre and post) of the experimental group were 84.4 (*SD* = 14.26) and 72.0 (*SD* = 11.43), respectively, and the mean (pre and post) scores of the control group were 82.3 (*SD* = 7.13) and 80.3 (*SD* = 4.35), respectively (Table 2).

An independent sample *t*-test was applied to examine the differences in pre- and posttest scores between the two groups. The results showed that the mean of both pretest and posttest Baseline Level, Onset of Stress, and End of Stress scores did not differ between the two groups (Table 2). Furthermore, the mean Recovery scores in the pretest did not differ between the two groups, while the mean Recovery scores in the posttest differed between the two groups (Table 2).

In addition, the paired sample *t*-test was used to understand the differences between pretest and posttest indices of Baseline Level, Onset of Stress, End of Stress, and Recovery within the same group of players. The average SCR scores of the players of the experimental group in the Baseline Level and Onset of Stress phase did not differ significantly, while the pretest and posttest of End of Stress and Recovery showed a marked statistical difference, noting that the sessions of the PowerMens method provided athletes with better and more effective management of subjective resources to cope with a task of high attentional stress (Table 3).

The control group in the SCR detections showed some visible improvements in the mean values in the Recovery phase, suggesting that the mental training pursued may have made a contribution, but these data did not emerge as statistically significant (Table 3).

Table 2
Pretest and Posttest Phases of the Experimental Group and Control Group (N = 20)

HRV Variables (in bpm)		Experimental Group (*n* = 10) *M*	*SD*	Control Group (*n* = 10) *M*	*SD*	*t*	*p*-value
Baseline Level							
	Pretest	77.0	7.19	78.1	8.27	−0.31	0.377
	Posttest	75.4	9.82	75.1	12.68	0.05	0.477
Onset of Stress							
	Pretest	88.1	10.42	83.1	4.68	1.38	0.09
	Posttest	80.6	9.52	80.5	2.27	0.03	0.487
End of Stress							
	Pretest	93.1	7.17	91.5	5.19	0.57	0.287
	Posttest	85.0	8.71	88.5	7.01	−0.99	0.168
Recovery							
	Pretest	84.4	14.26	82.3	7.13	0.42	0.341
	Posttest	72.0	11.43	80.3	4.35	−2.15	0.046

Note. In the posttest, the Recovery phase relating to heart rate variability (HRV) differs statistically in the scores detected.

Table 3
Mean and Standard Deviation (SD) of the Skin Conductance Responses (SCR) of Each Group in the Pretest and Posttest

SCR Variables (in microsiemens µS)	Experimental Group (*n* = 10) *M*	*SD*	*t*	*p*-value	Control Group (*n* = 10) *M*	*SD*	*t*	*p*-value
Baseline Level								
Pretest	0.201	0.076	−0.49	.314	0.196	0.082	−0.81	.220
Posttest	0.219	0.071			0.222	0.046		
Onset of Stress								
Pretest	0.324	0.085	1.80	.052	0.309	0.081	0.39	.353
Posttest	0.253	0.073			0.296	0.077		
End of Stress								
Pretest	0.375	0.083	2.25**	.025	0.336	0.039	−0.77	.231
Posttest	0.285	0.074			0.347	0.030		
Recovery								
Pretest	0.340	0.045	4.54*	.001	0.319	0.054	1.42	.095
Posttest	0.221	0.060			0.287	0.055		

Note. As shown in the table, there is a statistically significant difference between the participants' mean scores before and after the test in the experimental group in terms of the variation in SCR in the End of Stress and Recovery phases (** $p < .05$; * $p < .1$), but no difference was observed in the control group.

The paired sample *t*-test was also used for the analysis of HRV values in order to understand the differences between the four indices detected in the pretest and posttest.

In the control group, there were no significant differences, as well as in the experimental group the mean total scores in the Baseline Level and Onset of Stress phase did not differ significantly, while the pretest and posttest of End of Stress and Recovery showed a marked difference (Table 4).

Table 4

Mean and Standard Deviation (SD) of the Heart Rate Variability (HRV) of Each Group in the Pretest and Posttest

HRV Variables	Experimental Group (*n* = 10)				Control Group (*n* = 10)			
(in bpm)	*M*	*SD*	*t*	*p*-value	*M*	*SD*	*t*	*p*-value
Baseline Level								
Pretest	77.0	7.19	1.14	0.142	78.1	8.27	0.88	0.199
Posttest	75.4	9.82			75.1	12.68		
Onset of Stress								
Pretest	88.1	10.42	1.63	0.068	83.1	4.68	1.68	0.063
Posttest	80.6	9.52			80.5	2.27		
End of Stress								
Pretest	93.1	7.17	2.73	0.023	91.5	5.19	1.38	0.099
Posttest	85.0	8.71			88.5	7.01		
Recovery								
Pretest	84.4	14.26	2.92	0.017	82.3	7.13	0.64	0.266
Posttest	72.0	11.43			80.3	4.35		

Note. As shown in the table, there is a statistically significant difference between the participants' mean scores before and after the test in the experimental group in terms of HRV variation in the End of Stress and Recovery phase, but no difference was observed in the control group.

In addition to this, the paired sample *t*-test was also used to examine the average scores of the times used by the players in performing the high attention stress task with Microgate Witty SEM traffic lights. The analysis shows how the experimental group decreased the execution times to perform the task and that this difference is statistically significant, while, despite the difference also obtained from the control group, this did not emerge significant in the statistical analysis (Table 5).

Table 5

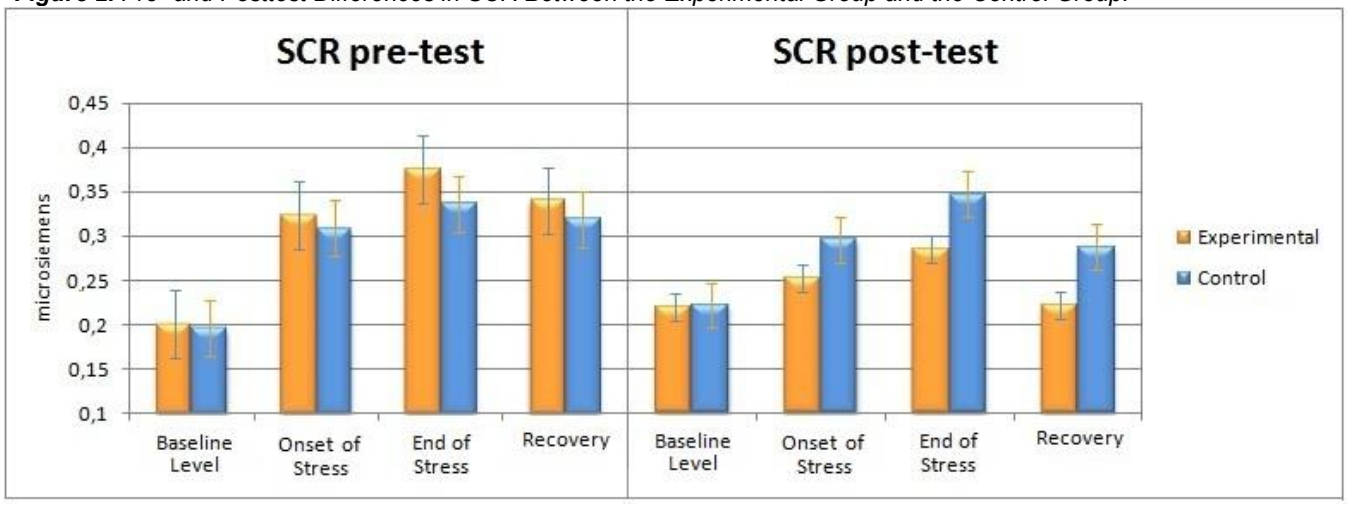
Mean and Standard Deviation (SD) of the Time Taken (in Minutes, Seconds, and Hundredths) in Carrying out the High Attention Stress Task of Each Group in the Pretest and Posttest

Attentional Stress Task Time	Experimental Group (*n* = 10)				Control Group (*n* = 10)			
	M	*SD*	*t*	*p*-value	*M*	*SD*	*t*	*p*-value
Pretest	01.05.45	00.10.37	1.94	0.042	01.05.57	00.03.27	1.31	0.111
Posttest	01.01.35	00.05.18			01.03.39	00.02.22		

Note. There is a statistically significant difference between the average scores of the participants before and after the test in the experimental group in terms of less time performed, while in the control group, although an improvement in the average time was found, no statistical difference was found significant.

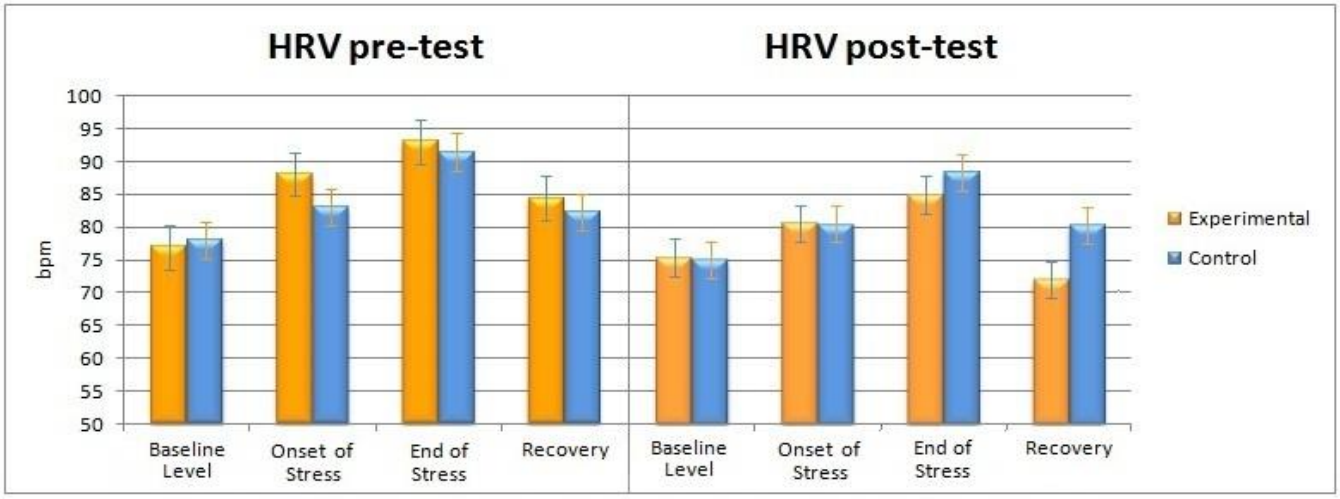
An independent sample *t*-test was then applied to examine the differences between the two groups in the pretest and posttest in the SCRs. The scores in the pretest did not differ statistically, indicating that the two groups were similar before taking the training path. In the posttest; however, the scores differed statistically (Figure 2).

Figure 2. *Pre- and Posttest Differences in SCR Between the Experimental Group and the Control Group.*



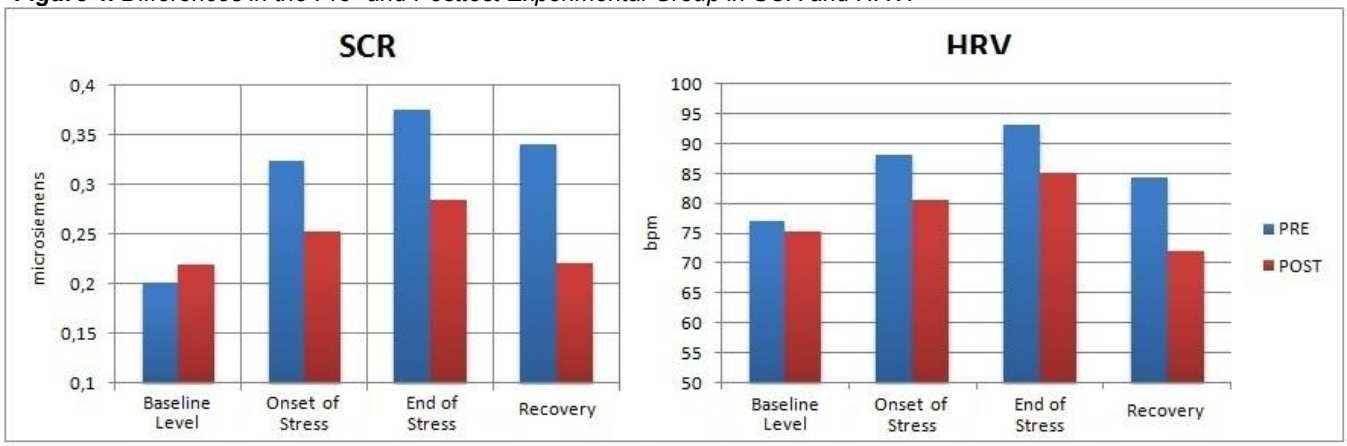
Similarly, the *t* independent sample *t*-test was applied to examine the differences between the two groups in the pretest and posttest in HRV. As in the SCRs the scores in the pretest did not differ statistically, while in the post-test the scores differed statistically (Figure 3).

Figure 3. *Pre- and Posttest Differences in HRV Between the Experimental Group and the Control Group*



Finally, the paired sample *t*-test within the same group of players was applied in the pretest and posttest, both in the SCR and in the HRV. In both psychophysiological parameters, a statistical difference was found in the level of Fine Stress and Recovery, to highlight how the BFB PowerMens method has provided the players with an added value in internal self-regulation (Figure 4).

Figure 4. *Differences in the Pre- and Posttest Experimental Group in SCR and HRV.*



Discussion

The purpose of this research was to study and investigate, in footballers, the measurement of attention and its related training, focusing on the effect of BFB PowerMens training sessions on cognitive and emotional self-regulation in the players of the experimental group, in particular in the ability and efficiency in regulating the response to attentional stress and improving performance in selective visual attention exercises.

The focus of BFB intervention was to present physiological information in a way that not only improves the players' awareness of visceral states, such as high arousal during the high attention stress task but also guides them towards the desired state such as low arousal or relaxation.

The BFB PowerMens training in footballers acted both at the baseline level where physiological information was presented directly to the athlete via the notebook, and via Mental Games where physiological information is incorporated into the game and the game itself adapts to the physiology of the player. In this way, the athlete can directly experience a way to lower the arousal or to raise it in a conscious way.
The results were promising; in fact, they indicate that the BFB PowerMens training sessions significantly reduced stress levels, especially activation or arousal during a task that causes attentional stress, and made the Recovery phase more effective, essential to restore homeostasis in the organism and favor the interaction between the central nervous system and the vegetative system. Not only that, but the significant difference in the shorter time taken in the posttest attentional stress task suggests that the players increased attention during the task itself, maintaining a more regular autonomous state organically during the task itself, indicating a greater psychophysiological balance of athletes during the stressful task.

Despite these auspicious results, a limit for this study may be the limited number of participants: it would be interesting to extend this research to a larger sample. Furthermore, even the number of training sessions, 12, if they were higher and continuous, for example evaluated from the beginning to the end of the sports season, could potentially affirm these results more markedly. Another limit relates to an unassessed psychophysiological parameter, the respiratory rate (RR), for instrumental reasons relating to the equipment. It could be interesting in the future to increase this research also with this parameter.

In general, based on the encouraging results, it seems that the BFB PowerMens method allowed the players of the experimental group to increase a better inner regulation than the control group.

Conclusions

The better performance of the experimental group compared to the control group seems to show the impact that the PowerMens sessions had in dealing with, managing, and overcoming the attention stress situations that the footballers were experiencing at the time of the assignment. The possibility of working in an integrated way with the psychophysiological and sensorimotor level and breath management seems to have provided the players with the necessary resources to face the breakdown of internal homeostasis due to a stressful event such as the pretest and posttest causes attentional stress and favoring the interconnection

between the central and autonomic nervous systems.

The average SCR and HRV scores in the Fine Stress and Recovery phase of the experimental group differ statistically, and these results could provide an important reference for the field of applied Sport Psychology and could open interesting insights also in the clinical setting on the mental health prevention of people as a response to stress.

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Conflict of Interest. The author declares no conflicts of interest.

Author's Contribution. Paolo Tirinnanzi participated in designing the study, the literature review, the acquisition and evaluation, performing the sessions, interpreting and analyzing the data, and writing the manuscript. The author contributed to and has approved the final manuscript.

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Event-related Theta and Gamma Oscillations in Cue-Reactivity Test in Individuals with Opiate Use Disorder in Buprenorphine-Maintenance Program

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Abstract

Opioid use disorder (OUD) is a major public health problem. Maintenance treatment with medication for OUD (MOUD), such as buprenorphine, has been associated with reductions in physical symptoms of withdrawal, but attentional bias towards drug cues may contribute to the high rates of noncompliance and relapse. The cue-reactivity test can be used to investigate specifics of EEG responses to drug cues. This study was aimed at comparison of EEG oscillations during exposure to drug-related and neutral images in MOUD and control participants for investigation of attention biases persistent in MOUD. We recruited 13 MOUD outpatients and 13 age-matched controls. The cue-reactivity test used emotionally neutral and drug-related images. The study used blocked design (16 images/block, 3 s/image). Time-frequency analysis of EEG from four frontal sites was performed to assess evoked, induced, and late oscillations, and theta-gamma phase-amplitude coupling during neutral and drug blocks. Exposure to drug cues in the MOUD group resulted in increased gamma and decreased theta oscillations with higher theta-gamma coupling effect. These cue-reactivity indices reflect heightened attentional bias to drug items and vulnerability to relapse in patients on MOUD and may serve as objective treatment outcomes complementing craving reports and clinical evaluations.

Keywords: EEG theta and gamma oscillations; phase-amplitude coupling; opioid use disorder; drug cue reactivity; craving; attentional bias

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Introduction

Opioid use disorder (OUD) is a neurobehavioral disorder characterized by repeated compulsive seeking and use of opioids that causes significant distress or impairment. OUD is accompanied by well-described physical dependence with a withdrawal syndrome and tolerance. Opioid addiction includes not only abuse of illicit heroin and other opium derivates but also misuse and abuse of prescription medications, such as hydrocodone, oxycodone, codeine, etc. OUD is now a major health problem, with initiation of prescription opioid abuse exceeding cocaine abuse in young people (SAMHSA, 2019). OUD represents a severe public health problem because of severe morbidity and high mortality. Medications for opioid use disorder (MOUD), including buprenorphine and methadone, represent evidence-based interventions for treating OUD (Blanco & Volkow, 2019). Although maintenance treatment with buprenorphine has been associated with reductions in heroin and other opiate use, concerns for intravenous misuse and other diversions exist (Simojoki et al., 2008). However, despite low physical symptoms of withdrawal, MOUD patients still demonstrate

vulnerability to relapse (MacLean et al., 2018). Craving and physiological arousal in response to drug cues may contribute to the high rates of noncompliance and relapse among opioid-dependent individuals in buprenorphine maintenance treatment.

Cue reactivity refers to a phenomenon in which individuals with a substance use disorder exhibit excessive cognitive, physiological, and behavioral responses to cues linked with their preferred substance of abuse (Carter & Tiffany, 1999; Drummond, 2001; Lubman et al., 2000). Cue-reactivity research studies typically include individuals with a substance use disorder who are exposed to a wide range of drug-specific cues (e.g., the sight of drugs, drug-use situations, etc.), and cue presentation modes such as photo images, words, imagery-based, or in virtual reality presentations (Carter & Tiffany, 1999). Cue reactivity is measured across several domains of functioning, and several measures are collected, including subjective self-reports (i.e., craving) and a wide range of physiological responses. There is a strong rationale for using the cue-reactivity test and monitoring attentional bias in individuals on MOUD. MacLean et al. (2018) found that participants with OUD exhibit a robust attentional bias and reactivity to drug-related cues even if they are engaged in MOUD, including methadone and buprenorphine. In clinical care of patients with OUD, methadone or buprenorphine dose is titrated to minimize craving, withdrawal symptoms, and use of nonprescribed opioids (Ayanga et al., 2016; Dematteis et al., 2017). Nevertheless, it is very likely that, even on MOUD, individuals with OUD continue to be reactive and sensitive to stimuli associated with opioid use. For example, some researchers have suggested that MOUD does not reduce cue-induced craving (Fatseas et al., 2011; Hyman et al., 2007). While MOUD may reduce tonic craving, acute craving associated with situational or environmental cues can persist. The impact of MOUD on attentional bias for opioids remains to be determined in future studies and warrants further investigations.

Preoccupation with drug and drug-related items is a typical characteristic of people living with a substance use disorder. Several research studies have provided support for the hypothesis that the process of alteration of attention—an attentional bias for reward stimuli—takes place in those with substance use disorder (Franken et al., 1999; Robinson & Berridge, 2008; Zijlstra, et al., 2009), and drug-related cues attain a greater salience and motivational significance (Robbins & Ehrman, 2004). One of the cognitive components of cue reactivity in substance users is the preferential allocation of attentional resources to drug-related items (Lubman et al., 2000). Patients on MOUD may show less attentional bias towards drug-related stimuli than active drug users, but they still show excessive psychophysiological responses during exposure to drug cues.

Craving, a process in which a stimulus is recurrently associated with feelings of pleasure, such as those elicited by drugs, is a key factor that motivates compulsive substance use (Drummond, 2001; Rosenberg, 2009). Through this stimulus-response learning process, drug-related stimuli attain a strong incentive-motivational value and elicit expectations of drug consumption and the feelings of pleasure associated with such consumption (Wilson et al., 2004). These drug-associated stimuli can elicit both subjective reports of craving and heightened activation as reflected by evoked EEG responses. The cue-reactivity paradigm is a widely used method for investigating drug craving. If MOUD treatment does influence reactivity to drug cues, such effects would be observed in physiological responses that reflect brain regions that mediate integration of motivational or affective responses. Surprisingly, few studies have investigated the association between attentional biases to drug-related information, cue reactivity, the level of craving, and their EEG manifestations during craving elicited in drug cue-reactivity tests in laboratory conditions. Assessing the level of craving as a measure of the subjective and affective experience of wanting opiates with concurrent psychophysiological measures provides a critical opportunity to investigate such an association. As attentional bias to drug cues may be predictive of poorer recovery outcomes, it is important to identify such underlying affective and neurophysiological processes (Frankland et al., 2016). It is possible that individuals on MOUD may exhibit diminished subjective and physiological cravings for opioids, suggesting an important MOUD may diminish the attention bias for drug-related stimuli. Therefore, it is important to investigate whether individuals on MOUD still exhibit attentional biases and excessive reactivity to drug-related cues.

The present study examined whether the opioid-related attentional bias operates in early pre-attentive sensory processes, such as initial orienting, in sustained attention and emotional responses, as reflected by time-frequency measures of EEG oscillations during exposure to drug-related pictorial stimuli. Of particular interest in this regard are theta (4–8 Hz) and 40 Hz-centered gamma oscillations.

Previous research suggests that theta oscillations are indicative of neural processes involved in the integration of perceptual stimuli and subsequent sequential ordering of that information, which are reflected in gamma synchronization processes (Köster et al., 2019; Lisman & Jensen, 2013). Gamma frequencies are closely associated with sensory processing, working memory, attention, and long-term memory (Lisman & Jensen, 2013).

Event-related oscillations are divided into "evoked" and "induced" components in terms of the relationship of the oscillations to the event or stimulus; these different components reflect different neural processes (Başar, 2013; Bertrand & Tallon-Baudry, 2000; Herrmann & Demiralp, 2005; Herrmann & Mecklinger, 2000; Herrmann et al., 2014). With regard to gamma oscillatory activity, there is an early, evoked gamma response that is phase-locked to stimulus onset and occurs within 150 ms of stimulus onset. This response seems to reflect matching of bottom-up signals with memory content at a perceptual processing level. There is also induced gamma activity that is not phase-locked to stimulus onset and occurs later with a variable onset, although it has been reported to start at around 250 ms (Herrmann et al., 2014; Tallon-Baudry & Bertrand, 1999). This response might be a signature of utilization processes such as response selection or context updating (Herrmann et al., 2014; Tallon-Baudry & Bertrand, 1999). Evoked gamma-band activity is indicative of early sensory processing and the integration of perceptual information within the same cortical region. In contrast, induced gamma-band activity reflects the integration of feed-forward and feedback processing in a broad network of cortical brain regions (Herrmann & Mecklinger, 2000).

EEG oscillations exhibit phase–phase coupling in certain physiological states or during performance of specific tasks, such as processing of new memories, spatial navigation, and memory retrieval. The prefrontal cortex has also been reported to engender interactions between neural oscillations, such as coupling of theta and gamma oscillations waves, in individuals with substance use disorders (Zhu et al., 2019). Research on neural oscillations suggests that the interaction between the brain regions is processed by a cross-frequency coupling between low-frequency band phase and high-frequency band amplitude. In particular, the cross-frequency coupling between the theta (4–8 Hz) phase and the gamma (predominantly in 40 Hz centered range, e.g., 35–45 Hz) amplitude may play an important functional role in emotion-related cognitive activities, as well as learning and memory (Canolty et al., 2006; Canolty & Knight, 2010). Based on the important function of coupling between theta and gamma in a large number of affective and cognitive processes, in this study we chose the wavelet-based EEG analysis of theta and gamma as the target frequency bands (Wang, 2021). Specifically, EEG responses to visual stimuli are known to be marked by readily observed changes in theta and gamma oscillations. Cross-frequency coupling measures the association between the theta oscillation phase and the gamma power. Higher-magnitude theta–gamma coupling values translate into greater gamma amplitude during the theta phase (Lisman & Jensen, 2013). Theta–gamma coupling has been shown to be a functionally important functional role for processes related to long-term memory and affective responses. Previous research suggests that phase-amplitude coupling between the prefrontal theta phase and posterior gamma amplitudes represents signaling between prefrontal cognitive control mechanisms and processing of ordered, sequential information during memory encoding or the reactivation of ordered, sequential information during memory retrieval in posterior cortical regions (Köster et al., 2014).

Many studies have analyzed EEG parameters by computing average values across only evoked and induced phases of gamma activity (Herrmann & Demiralp, 2005; Herrmann et al., 2014; Tallon-Baudry, 2003; Tallon-Baudry & Bertrand, 1999). However, besides responses within the first 500 ms window (e.g., N100, P200, N200, P300, N400), the late positive potential (LPP), also provides a valuable event-related potential (ERP) measure sensitive to affective responses (Hajcak et al., 2010). The LPP is a positive-going waveform that begins approximately 300 to 2000 ms after the onset of a stimulus that can persist for several seconds (Hajcak et al., 2011). The LPP signals processing of attention toward highly salient, motivating positive or negative affective stimuli (Castro et al., 2019; Hajcak et al., 2010; Schupp et al., 2000; Schupp et al., 2004). Because the LPP reflects the processing of motivationally salient affective stimuli, it may play an important role in the affective processing alterations observed among individuals with substance use disorders. In particular, the LPP may indicate excessive reactivity to emotionally negative stimuli. Theta and gamma oscillations within 600–800 ms occur within the window typical for the maximum of LPP and should be assumed to be reflecting similar motivational and affective processes.

This study aimed to explore the mechanism of processing drug-related cues in people with OUD receiving MOUD using frontal EEG responses elicited during exposure to neutral and drug-related pictorial stimuli. Our hypothesis was that participants with OUD on MOUD as compared to age-matched participants without OUD will show excessive reactivity to drug-related cues manifested in event-related theta and gamma EEG oscillations and their phase-amplitude coupling.

Methods

Participants

All participants in the MOUD group were recruited from the local office-based addiction recovery program and their diagnosis and eligibility were confirmed by clinical evaluations and drug tests. Participants in the control group were recruited from the community with advertisements posted using various media. Eligibility criteria for control group participants included being at least 18 years old, having no substance use disorders, and having no history of psychiatric conditions. Eligibility was confirmed through prescreening surveys.

Each participant signed informed consent approved by the local Institutional Review Board (IRB). The mean age of participants in the MOUD group (N = 13) was 36.77 ± 6.86 years, while in the control group (CNT, N = 13), the mean age was 33.38 ± 10.81 years. Age difference between group was not statistically significant, $t(12) = 1.69$, $p = .114$). Patients in the MOUD group were already enrolled in buprenorphine maintenance treatment for 10.2 ± 10.9 months. Gender was not matched between groups, as there were seven males in the MOUD group and one male in the CNT group.

Cue Reactivity Testing

Cue reactivity to salient drug or alcohol cues provides a means to examine neurophysiological activity indices of craving among individuals with substance use disorders (Back et al., 2014; MacLean et al., 2018; Zijlstra et al., 2009). The study used the pictorial drug- and affective cue reactivity test procedure to measure subjective drug craving and neurophysiological responses. Images for this procedure have been obtained from a standardized database (International Affective Picture System [IAPS]; Lang et al., 2001). Blocks of emotionally positive, negative, neutral, and drug-related pictures were presented using a blocked design, and participants provided a subjective rating of drug craving after each block. Each block of pictures consisted of 16 images that were each presented for 3 s. Order of the blocks was counterbalanced, but block of neutral cues was always preceding the drug cues block. The current study focused only on analysis of the EEG responses to neutral and drug-stimuli blocks.

Data Acquisition and Signal Processing

Physiological activity during cue reactivity test was recorded with Nexus-10 psychophysiological monitor with BioTrace+ software (Mind Media, BV, Herten, The Netherlands) with custom-made protocol. EEG activity was acquired at 256-Hz sampling rate (bandpass filter, 1–45 Hz, Notch filter at 60 Hz). Electroencephalogram (EEG) was recorded from four frontal sites (Fp1, Fp2, F3, and F4) prepared using NuPrep with Bluetrode Ag/AgCl electrodes with Ten20 gel referenced to linked earlobes with ground electrode placed at the nasion. Analysis of EEG responses was initially conducted to assess absolute amplitude and absolute power, as well as relative amplitude and relative power of delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz) and gamma (35–45 Hz) bands during resting conditions and event-related EEG responses to emotionally neutral and drug-related stimuli. Our pilot study (Ortiz et al., 2021) showed most prominent group differences in relative amplitude and relative power of theta and gamma responses in neural and drug cue conditions and our wavelet-based analysis in this study was focused only on theta (4–8 Hz) and gamma (35–45 Hz) oscillatory responses.

Method of Wavelet Analysis and Phase-Amplitude Coupling Evaluation

1. EEG segments of 256 time-samples corresponding to each of the 16 stimuli at each EEG channel is filtered in the frequency domain into theta (θ, 4–8 Hz), and gamma (γ, 35–45 Hz) using a sequence of Continuous Wavelet Transform (CWT) and a frequency-localized inverse CWT operations (Torrence & Compo, 1998). The CWT of the EEG segment *x(t)* (i.e., $X(\tau, s)$) is calculated as follows:

$$X(\tau, s) = \frac{1}{\sqrt{s}} \int_0^{\infty} x(t)\, \psi\left(\frac{t-\tau}{s}\right) dt$$

where ψ is the Morlet analysis wavelet, τ is the time shift of the wavelet, and s is the scale of the wavelet. The scale s is inversely proportional to the Fourier frequency (Torrence & Compo, 1998).

2. To extract the frequency components of the EEG signal within the theta and gamma frequency bands, a frequency-localized inverse CWT is used where the coefficients $X(\tau, s)$ corresponding to the respective frequency range are extracted and an inverse CWT is applied to the extracted coefficients $X(\tau, s)$ as follows:

$$y(t) = \frac{1}{C}\int_{s_2}^{s_1}\int_{0}^{\infty}\left(\frac{1}{s}\right)^{\frac{5}{2}} X(\tau, s)\,\varphi\left(\frac{t-\tau}{s}\right) d\tau ds$$

where *y(t)* is the theta or gamma component of the EEG signal, φ is the dual function of ψ such that both functions are orthonormal, and *C* is a constant. Also, s_1 and s_2 correspond to the lowest and highest frequencies respectively in the frequency bands of the theta or gamma waves.

3. Artifacts or anomalies within the theta and gamma time-series are discarded such that:

$$\mu_{y(t)} - 2\sigma_{y(t)} \le y(t) \le \mu_{y(t)} + 2\sigma_{y(t)}$$

where $\mu_{y(t)}$ and $\sigma_{y(t)}$ are the mean and standard deviation of *y(t)*.

4. The peak amplitude and latency for the evoked, induced and late waves are determined from the theta and gamma time-series as follows:

$$A_p = \max_t y(t) \qquad t_0 \le t \le t_f$$
$$\mathrm{y}\left(T_p\right) = \max_t y(t) \qquad t_0 \le t \le t_f$$

where A_p and T_p are the amplitude and latency of the peak. Also, t_0 and t_f represent the start and the end of the time-interval within which the evoked, induced or late waves are existent.

5. Phase amplitude coupling (*PAC*) is also calculated as follows (Tort et al., 2010):

a. A Hilbert transform is applied on *y(t)* for the evoked, induced, and late theta and gamma waves to generate a complex signal *h(t)* whose phase h_{ph} *(t)* is calculated for the theta wave and amplitude h_{amp} *(t)* is calculated for the gamma wave. The Hilbert transform can be represented as a linear convolution of *y(t)* with the Hilbert operator function ($1/\pi t$) as follows:

$$h(t) = y(t) * \left(\frac{1}{\pi t}\right)$$

b. A linear phase interval *P* is defined from -π to π and split into a number of bins (N_b).

c. The bin indices (i_b) of the phase values in *P* at which each value in h_{ph} *(t)* approximately matches are estimated. Further, the means of h_{amp} *(t)* values (i.e., μ_{Gm}) for each distinct value of i_b are calculated. μ_{Gm} is further normalized where

$$\hat{\mu}_{Gm} = \frac{\mu_{Gm}}{\sum_{n=1}^{N_b}\mu_{Gm}}$$

d. The Kullback-Leibler Distance (d_{KL}) which represents the divergence of the amplitude distribution of $\hat{\mu}_{Gm}$ from a uniform distribution (u_{Gm}) is derived as follows:

$$d_{KL} = \sum_{n=1}^{N_b} \hat{\mu}_{Gm} .* \log\left(\hat{\mu}_{Gm} ./ u_{Gm}\right)$$

where the product and division operations are executed in an elementwise fashion. Further, u_{Gm} is represented as follows:

$$u_{Gm} = \frac{1}{N_b}$$

e. The *PAC* is then derived from the d_{KL} as follows:

$$PAC = {}^{d_{KL}}/_{\log(N_b)}$$

Statistical Data Analysis

The data for all dependent variables was analyzed using repeated-measures ANOVA with factors (all within-participants) such as *Condition* (Neutral vs. Drug) and *Hemisphere* (Left vs. Right) for four EEG sites (Fp1, Fp2, F3, and F4), and only the *Condition* factor for their combinations (prefrontal, Fp1-Fp2, frontal F3-F4). The between subject factor in this cue-reactivity task was *Group* (MOUD vs. Controls). Single trial EEG theta and gamma oscillations were analyzed for above four anterior frontal EEG sites and time window (40–180 ms [evoked], 240–500 ms [induced], and late [600–800 ms] post-stimulus). All datasets were evaluated for normality and confidence intervals were defined for each set. Amplitude, latency, and PAC coupling coefficients were calculated for evoked, induced, and late theta and gamma oscillations at all four EEG sites and averaged during neutral and drug blocks (16 pictures per block) in MOUD and CNT groups. Each measure was analyzed for individual EEG sites (e.g.,

Fp1, Fp2, F3, F4) and for their combinations (Fp1-Fp2, F3-F4). Post-hoc analysis was conducted using the Tukey test for groups with equal sample size. Some group differences were tested with two-tailed Student's *t*-tests and/or one-way ANOVA. In all repeated measures ANOVAs, Greenhouse-Geisser (GG)-corrected *p*-values were employed where appropriate. Effect size was estimated using partial eta squared (η^2) and observed power measures. IBM SPSS software (v.27) was used for statistical analysis.

Results

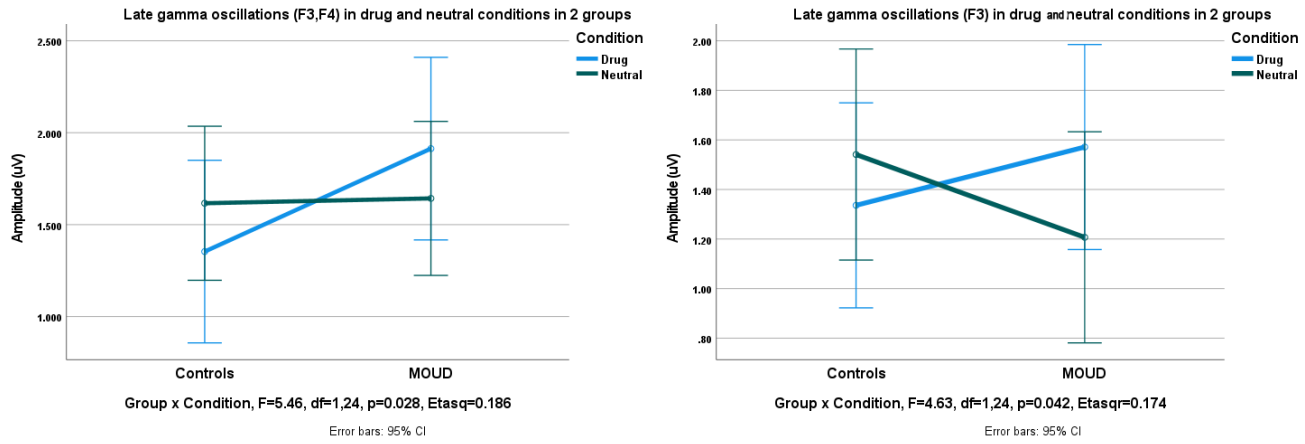
Evoked, Induced, and Late Theta and Gamma Amplitude and Latency

Gamma Oscillations. ANOVA results showed a main effect of *Condition* (Drug vs. Neutral) on evoked, induced, and late gamma oscillations only in the MOUD group (all *p*s < .01). Prefrontal sites Fp1 and Fp2 had higher amplitude of evoked gamma in MOUD as compared to control group in the drug stimuli condition, 1.42 ± 2.46 μV in MOUD vs. 0.98 ± 1.60 μV in controls, $F(1, 24) = 5.57$, $p = .028$. In the neutral condition at Fp1-Fp2 sites, the amplitude of gamma in the MOUD group was lower than in the neutral condition as compared to the control group, 1.19 ± 0.52 μV in MOUD vs. 1.74 ± 0.72 μV in the control group, $F(1, 24) = 4.58$, $p = .043$. In the MOUD group, induced gamma amplitude at Fp1-Fp2 was also higher than in the control group, $F(1, 24) = 6.06$, $p = .022$. More significant group differences were found for the late gamma at F3 and F4 sites.

In particular, for these frontal sites *Condition* (Drug vs. Neutral) x *Group* (MOUD vs. Control) interaction was statistically significant for late gamma oscillation, $F(1, 24) = 5.46$, $p = .028$, $\eta^2 = .186$, observed power = 0.613. Significant group differences were found for the late gamma at the F3 site. For this frontal site *Condition* (Drug vs. Neutral) x *Group* (MOUD vs. Control) interaction was statistically significant for late gamma oscillation, $F(1, 24) = 4.63$, $p = .042$, $\eta^2 = 0.174$, observed power = 0.570. This effect for combined F3-F4 and F3 late gamma oscillations is illustrated in Figures 1 and 2.

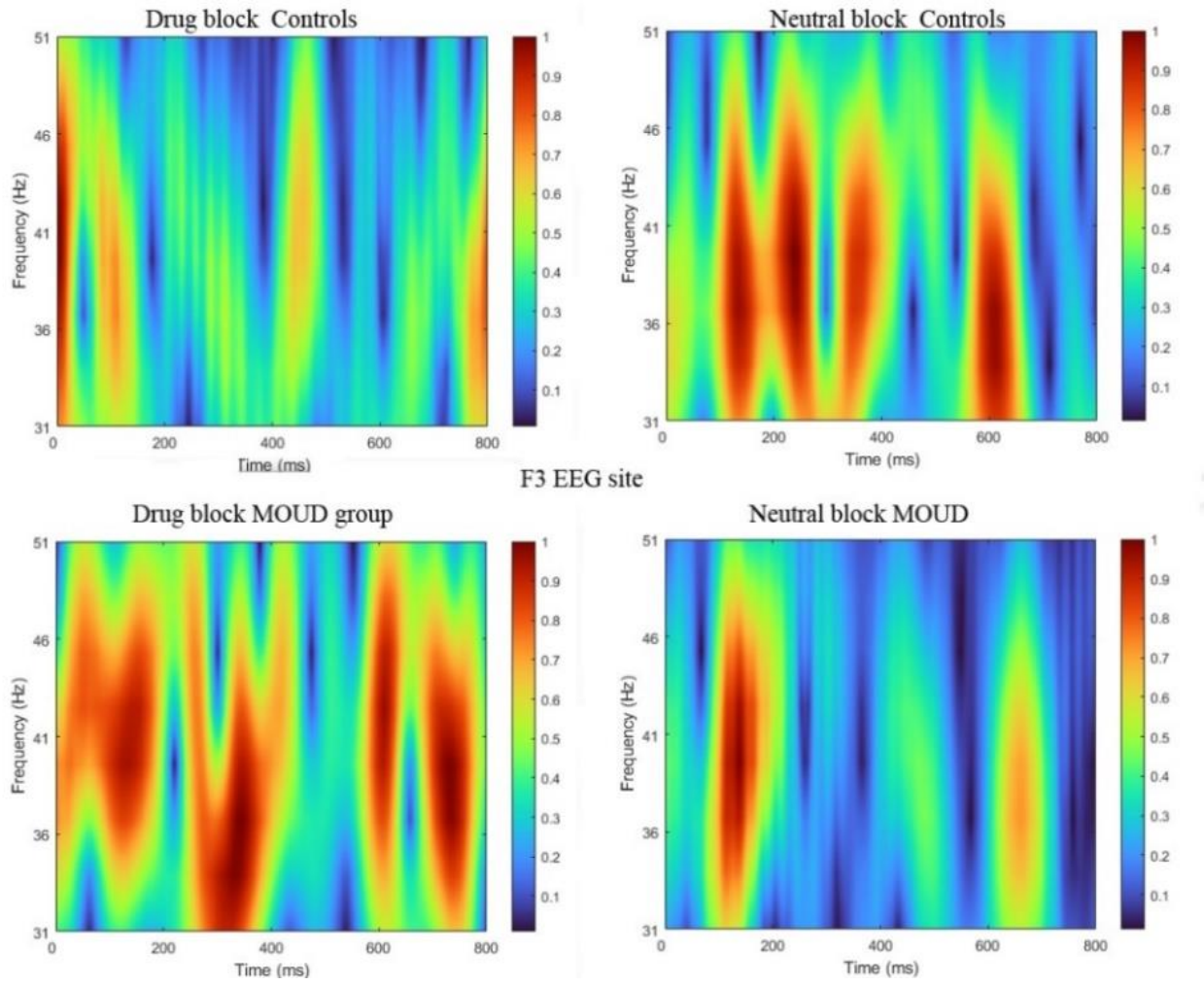
Latency of induced gamma oscillations at F3-F4 sites in drug conditions was shorter in the MOUD group, 412 ±70 ms in controls vs. 351± 62 ms in MOUD, $F(1, 24) = 5.07$, $p = .035$.

Figure 1. *Late Gamma Oscillations in Drug and Neutral Conditions in Two Groups.*



Note. Late gamma oscillations at the frontal sites (F3, F5) shows *Group* x *Condition* interaction with lower gamma oscillations amplitude in neutral condition (left). Similar interaction is presented for the left frontal site (F3) showing in addition higher late gamma amplitude in the drug condition (right).

Figure 2. *Normalized Images of Time-Frequency Power of Gamma Oscillations at the Left Frontal Site (F3) Illustrate Group Differences in Neutral and Drug Conditions.*



Note. MOUD group has higher power of induced and late gamma oscillations in the drug condition.

Theta Oscillations. Most notable group differences and interactions were found for induced theta oscillations at the frontal sites (F3, F4). *Condition (*Drug vs. Neutral*)* x *Hemisphere (*F3, F4*)* x *Group (*MOUD vs. Control*)* effect was statistically significant and expressed in a lower theta amplitude in the MOUD and was especially well pronounced at the right hemisphere (F4). This interaction is illustrated in Figure 3. The effect expressed in higher theta in the control group as compared to the MOUD group in neutral and drug conditions is depicted at Figure 4.

Latencies of the late theta oscillations at the prefrontal sites (Fp1, Fp2) showed *Condition x Group* interaction (F = 7.24, p = .014) with shorter latencies in the neutral cues condition in the CNT group (703 ± 49 ms) as compared to the MOUD group (720 ± 54 ms). Latency of induced frontal (F3, F4) oscillations in the drug cue condition was shorter in the MOUD group as compared to controls (351 ± 64 ms vs. 412 ± 71 ms).

Figure 3. *Condition* x *Hemisphere x Group Interaction of Induced Theta Oscillations Was Statistically Significant with Lower Power of Theta at the Right Hemisphere (F4, on the Left) in the MOUD Group in Drug Condition.*

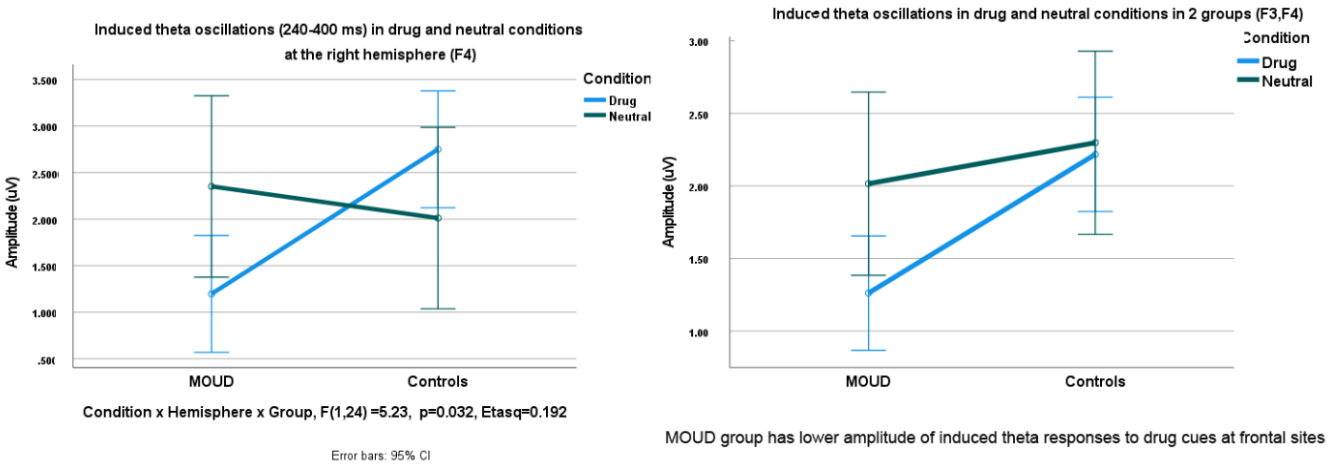
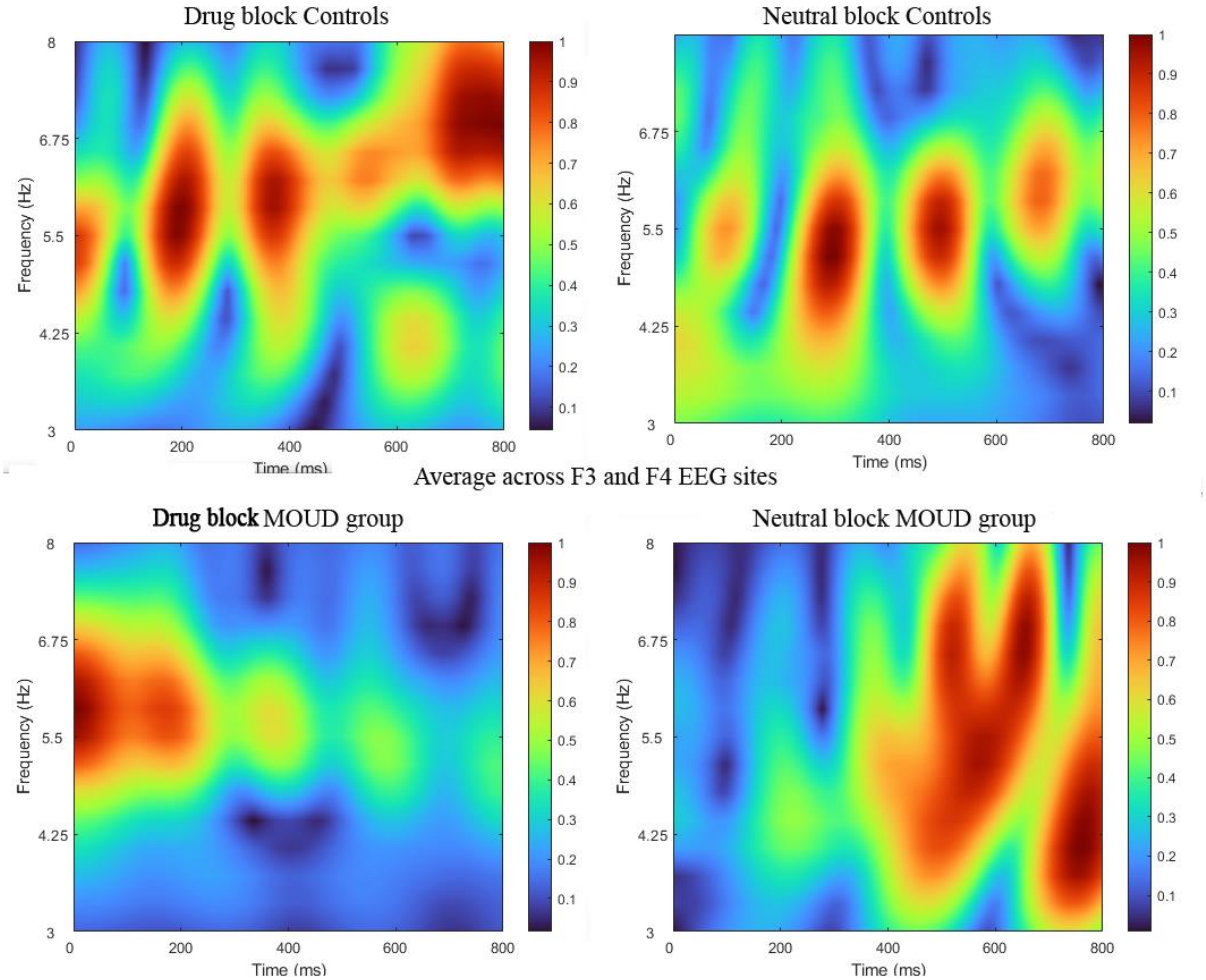


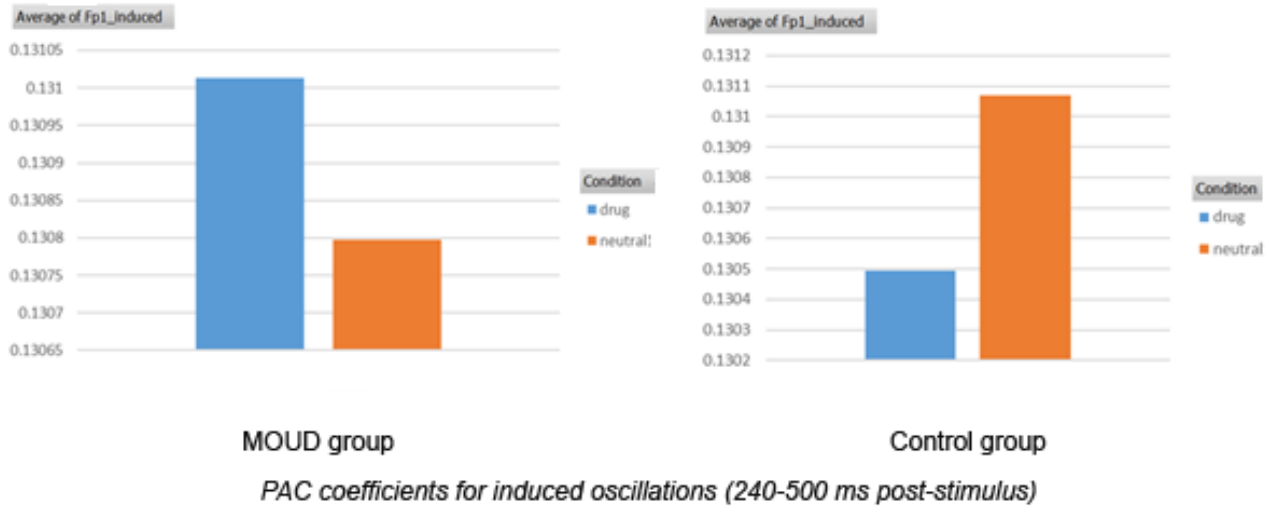
Figure 4. *Normalized Time-Frequency Power of Theta Images at the Frontal Sites (F3-F4) Illustrate Group Differences in Neutral and Drug Conditions.*



Note. MOUD group has lower power of induced and late theta oscillations in the drug condition. Control group has comparable theta oscillations in both conditions.

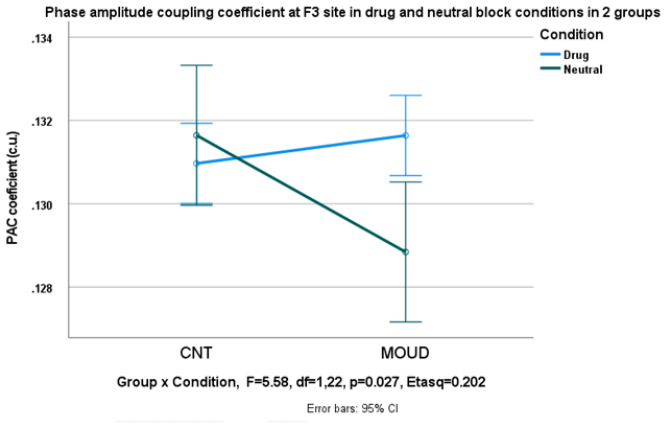
Most of the statistically significant interactions of theta–gamma phase–amplitude coupling was found during induced theta and gamma oscillations (240–500 ms range). At the left prefrontal site (Fp1) *Condition* x *Group* interaction of induced theta–gamma PAC was significant, $F(1, 24) = 5.19$, $p = .033$, $\eta^2 = 0.191$, observed power = 0.586); while at the frontal F3 site this interaction had even higher-powered effect, $F(1, 22) = 5.58$, $p = .027$, $\eta^2 = 0.202$, observed power = 0.618. These interactions are presented in Figures 5 and 6.

Figure 5. *Theta–Gamma Phase-Amplitude Coupling Coefficients in Drug and Neutral Blocks in MOUD and Control Groups (Fp1).*



Note. Induced theta–gamma phase–amplitude coupling coefficients in drug and neutral conditions at the left prefrontal site (Fp1) in both groups. PAC coefficients were higher in drug condition and lower in the neutral one in the MOUD group, whereas controls showed an opposite effect.

Figure 6. *Induced Gamma and Theta Oscillations PAC in MOUD and Control Groups.*



Note. Condition x Group interaction of induced theta and gamma oscillations' PAC at the left frontal site (F3) with lower theta–gamma coupling in the MOUD group during neutral condition. Post-hoc *t*-test yielded group difference of the induced theta–gamma PAC coefficients at Fp1 and F3 between neutral and drug conditions; Fp1, $t(24) = 22.56$, $p < .001$; F3, $t(22) = 2.54$, $p = .032$.

Discussion

Low frequency (4–8 Hz) and high frequency EEG gamma activity within the 35–45 Hz range were examined using time-frequency analysis during exposure to emotionally neutral and drug-related picture in participants with OUD enrolled in buprenorphine-based maintenance treatment (i.e., MOUD participants) and healthy controls. The MOUD participants differed significantly from control group subjects, exhibiting both decreased theta oscillations and increased 40 Hz-centered EEG oscillations with higher phase-amplitude coupling during block with the drug cues. The participants on MOUD, but not control subjects, showed significant increases in activation in the form of several bursts of high frequency oscillations in response to drug-related stimuli. Participants in the control group, but not MOUD subjects, showed significant increases in activation of low frequency theta oscillations in frontal areas while viewing emotionally neutral images with a significant group x stimulus type interaction effect at both prefrontal and frontal EEG sites.

Systemic modulation of the power of gamma oscillations over the course of the theta cycle suggests that there is a relationship between theta–gamma coupling such that attentional and emotional processes are activated during exposure to drug-related cues in individuals in MOUD. Cross-frequency interaction between theta and gamma oscillations during various forms of working memory operations is a well-known phenomenon reflecting memory processes; in the cue reactivity task, this cross-frequency interaction showed enhancement in those on MOUD. Osipova et al. (2006) found that increased frontal theta power coincided with enhanced gamma power in more posterior cortical areas for stimuli that were either remembered later or forgotten. The authors suggested that frontal theta oscillations might reflect top-down processes that modulate gamma band activity related to representations in posterior regions. Our study was limited to the frontal theta and gamma analyses, but it also showed enhancement of theta–gamma coupling during processing salient drug-related stimuli in individuals with OUD on MOUD. Our result may reflect the processes of frontal interregional gamma-theta bands phase synchronization increase during attention orienting within a distributed network of cortical regions activated during attention captured by motivationally relevant stimuli.

Unlike earlier and mid-latency ERP components, such as N100 and N200 and evoked EEG oscillations which are highly sensitive to the perceptual properties of stimuli, or late cognitive potentials like P300, the magnitude of the late theta and gamma oscillations and their phase-amplitude coupling seems to be unaffected by the properties more typical for evoked and induced oscillations. Thus, late theta–gamma oscillation coupling should be considered to reflect stimulus content rather than perceptual features, such as stimulus complexity or size (Wiens et al., 2011). The event-related theta and gamma oscillations response in our study were focused on the time window in which the LPP, which is sensitive to the motivational and salience of a stimulus, is apparent in ERP. It is plausible to suggest that theta and gamma oscillations have similar emotional and motivational relevance as the LPP. The sustained LPP, which in our study was expressed in gamma and theta neural oscillations, is proposed to be larger following both positive and negative affective stimuli compared to neutral stimuli and appears to be generated by an extensive cortical-subcortical network involved in emotional processing and visual attention (Cuthbert et al., 2000; Hajcak & Olvet, 2008; Hajcak et al., 2009; Hajcak et al., 2010). It is plausible to propose that the emotion-elicited late theta and gamma oscillations and their coupling measures might serve as an index of sustained and flexible attentional engagement towards motivationally salient visual stimuli (Hajcak et al., 2009). Consequently, in our study higher amplitude and coupling of theta and gamma EEG oscillations in the MOUD group in response to drug cues might reflect persistence of motivational salience of drug-related cue for individuals with OUD, even when they are being treated with MOUD.

Although the cue-induced opioid craving changes during neutral and drug blocks were comparable in absolute measures of self-reports, the change in craving showed a tendency to increase along with the activation of the attentional and emotional processes among the patients on MOUD. These findings suggest that, even when receiving MOUD treatment, individuals with OUD exhibit greater cue-induced craving. Such craving may reflect greater frontal activation in EEG indices that might be related to reward wanting, craving, and memory retrieval. Proposed assessment technique may provide further understanding of craving and motivation to seek drugs in opiate dependency during MOUD treatment by adding objective physiological measures to subjective reports. Furthermore, it will make possible continuous monitoring of cortical activity during the treatment course. Although individuals in maintenance treatment may classify the drug-related stimuli similar to controls and can rate their current craving scores, they may show a trend to either over or understate actual craving level. These distortions in characterizing one's own affective state are not uncommon among those with substance use disorder due to the pervasiveness of emotional numbing, anhedonia, and other affective deficits in this population (McKernan et al., 2015; Torrado et al., 2015). However, drug cue-evoked EEG oscillations and autonomic responses are capable of revealing objective levels of emotional reactivity by using techniques similar to ones used in polygraphs (i.e., "lie detectors"). Thus, indices of psychophysiological reactivity to drugs may represent a sensitive objective indicator of emotional states and relapse vulnerability supplementing subjective reports.

There are several limitations of our pilot study that should be noted. Only a limited number of EEG leads was used, and EEG was recorded only from prefrontal and frontal sites. Correlation analyses between subjective craving rating scores and individual indices of EEG oscillations (e.g., theta and

gamma amplitude and latency of evoked, induced, and late oscillations, theta-gamma PAC coefficients, etc.) were not conducted in neutral and drug block conditions. Moreover, there were more female participants in the control group, and thus gender-related factors may affect the results. Other potential moderating factors that may affect outcomes might be related to the length of stay in MOUD treatment, length of opioid use history, severity of OUD and other demographic and clinical characteristics of participants in the MOUD group.

The results of the proposed study may have important clinical implications. Most importantly, they are expected to indicate that patients with OUD on MOUD, even after prolonged periods in opiate substitute pharmacotherapy, may present a higher subjective and physiological response to motivationally salient drug-related stimuli and lower psychophysiological reactivity to emotionally neutral cues as compared to control participants. Although drug-cue EEG response is influenced by multiple other variables (such as motivation, craving, classical conditioning, and substance availability), it is possible that MOUD might contribute to a decrease in the attentional bias towards drug cues, which seems to play a critical role in achieving positive outcomes. Objective EEG-based indices of attentional bias and drug cue reactivity might serve as useful outcomes of progress in buprenorphine-maintained individuals with OUD, and potentially for other complementary interventions, such as cognitive-behavioral therapy or neurofeedback training.

Conclusion

Application of advanced assessment of the effects of exposure to drug cues using pictorial stimuli with concurrent recording of evoked, induced, and late EEG oscillations is an innovative approach to more comprehensive functional clinical evaluations. The results of this pilot study add to a body of evidence indicating that coupling between low- and high-frequency EEG oscillations is an important feature of neural networks that mediate cognitive and affective processes among individuals with substance use disorder. People with OUD on MOUD may still experience vulnerability to drug-cue-induced craving. The study findings indicate persistence of attentional bias to drug cues in individuals with OUD, even when they are in maintenance treatment. Further research should examine whether modification of this bias by cognitive behavioral treatment or neurotherapy may reduce risk of relapse. Quantitative EEG measures used in our study may serve as useful objective indices reflecting both physiological, behavioral, clinical, and subjective outcomes of interventions in individuals enrolled in MOUD treatment.

Author Disclosure

Authors have no financial interests or conflicts to disclose.

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Neurofeedback Training and Cognitive Behavior Therapy for Treatment of Generalized Anxiety Disorder in Children and Adolescents: A Comparative Study

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Abstract

Introduction. The present study aimed to evaluate the effectiveness of neurofeedback (NF) and cognitive-behavioral therapy (CBT) on the reduction of anxiety symptoms in children and adolescents with generalized anxiety disorder. **Methods**. The current pseudo-experimental study with a pre–posttest design was conducted on a population of patients with a generalized anxiety disorder (GAD) referring to the child psychiatry clinic in Alexandria's University Hospital, Egypt. The sample size comprised of 30 children and adolescents selected by random sampling method and assigned to groups of NF and CBT. Data elicited from the State-Trait Anxiety Inventory (STAI), which is a self-report scale for measuring two distinct anxiety concepts. Data were analyzed with SPSS. Student *t*-test was performed on CBT and NF groups. **Results**. The current study showed that both CBT and NF are effective in reducing the level of anxiety in the study subjects with no significant differences between the two groups. The obtained results also showed that NF therapy is an effective method with more improvement on state anxiety score, while CBT showed more improvement in trait anxiety score. **Conclusion**. Both treatments were significantly effective, and therefore neurofeedback training can be effectively used as a treatment approach for children and adolescents with GAD.

Keywords: generalized anxiety disorder; cognitive behavioral therapy; neurofeedback; State-Trait Anxiety Inventory; children and adolescents

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Introduction

Anxiety represents the most common category of psychiatric disorders in children and adolescents, constituting the main reason children and their families seek specialty mental health services. The majority of children experience stress periodically within their lifespan. This stress is related to family and academic demands, combined with changing developmental and social pressures, which makes the environment in which effective functioning may be difficult.

Epidemiological studies estimate the prevalence of anxiety disorders in youth to be between 2.2% and 9.5%, with generalized anxiety disorder (GAD) and separation anxiety disorder (SAD) being the most common (Merikangas, 2009).

Generalized anxiety disorder is one of the commonly diagnosed types of anxiety disorders, characterized by chronic worrying that can occur every day and for extended periods, affecting approximately one in eight children over a lifetime. Children with GAD express worry about daily performance, and the focus of the worry may shift from topic to topic. The

anxiety affects their ability to complete tasks or enjoy activities and may be accompanied by difficulties falling or staying asleep, fatigue, trouble with concentration, muscle tension, or irritability (American Psychiatric Association, 2013).

Childhood anxiety disorders have been found to associate with several adolescent mental health issues. In one prospective study, children who suffer from GAD are at risk to develop conduct disorder during adolescence. Also, childhood-onset anxiety disorders have been found to have a role in psychopathology of personality disorders in young adulthood, along with significantly increased suicidal behaviors. Furthermore, young adults with a history of childhood anxiety have increased rates of drug abuse, suicide attempts, utilization of health services, and employment issues compared to controls (Rudd, 2004; Weissman, 1999).

The literature review supported the application of cognitive-behavioral therapy (CBT) in children and adolescents with anxiety disorders and found that this treatment can reduce anxiety in such patients. Therefore, the current study results were consistent with such findings (Higa-McMillan et al., 2016; James et al., 2013; Reynolds, et al., 2012).

Kendall (1994) investigated the efficacy of CBT for 47 children (9–13 years) with generalized anxiety and separation anxiety disorders. The cognitive-behavioral therapy was compared with a wait-list condition. Posttreatment result was evaluated using child self-report, parent report, and behavioral observations. Also, the maintenance of gains at 1-year follow-up was examined. Results revealed that 64% of those treated no longer met diagnostic criteria. Of the subjects in the wait-list condition, only one did not qualify for an anxiety disorder diagnosis after the waiting period (Kendall, 1994).

The studies by Fisak et al. and Mychailyszyn et al. showed that programs based on CBT are among the most effective current approaches for the prevention of anxiety in children and adolescents (Fisak et al., 2011; Mychailyszyn et al., 2012).

The American Academy of Child and Adolescent Psychiatry has risen to this challenge by developing and disseminating evidence-based treatment guidelines for childhood anxiety. These practice parameters acknowledge CBT as the most studied and empirically supported type of psychotherapy for anxious youth. Furthermore, these guidelines recommend CBT as a first-line treatment for children and adolescents with mild to moderate anxiety (Connolly et al., 2007).

Drawing from a cognitive framework, the CBT model posits that thoughts affect beliefs, which affect corresponding emotions and behaviors. Therefore, CBT aims to correct distorted beliefs and learning patterns that develop emotional and behavioral disturbances (Seligman et al., 2011).

In general, CBT calls for a structured therapeutic approach, with didactic sessions, brief windows of intervention, and homework assignments. The core components of CBT programs are cognitive restructuring; skills-building that can include mindfulness, social skills, assertiveness, problem-solving techniques, self-reinforcement and reward; and exposure training. The strategy of exposure typically involves a child's real or imagined confrontation gradually with anxiety-producing stimuli and then working with the child to combat the anxiety with a variety of coping skills (Lyneham, 2005).

In the late 1960s, research established that it was possible to recondition and retrain brainwave patterns. This brainwave training is called EEG biofeedback or neurofeedback (NF; Hammond, 2011; Kamiya, 2011; Sterman et al., 2010).

There are two learning paradigms involved in neurofeedback, these are operant and classical conditioning. Operant conditioning occurs when the child is rewarded for finding a targeted brainwave state with a visual or auditory reward. It is worth noting that the brain is inherently motivated to seek pleasure and although initial attempts at finding the desired brainwave state may be awkward and sometimes frustrating, with the continued effort the brain will succeed, and the new brainwave response will be strengthened until it becomes automatic. While classical conditioning in neurofeedback occurs when the desired brainwave state is paired with another behavior, such as calm focus during an athletic performance or cognitive activation during an academic task. By pairing the desired brainwave response with a specific behavior, the child is better able to optimize his or her performance (Skinner, 2021; Turner, 2016).

Neurofeedback as a clinical approach to the resolution of psychological and behavioral problems has it is origin in the study of the brain's electrical activity and behavioral psychology. The development of the human electroencephalogram (EEG) combined with the application of principles of

learning, knowledge of the brain's neuroplasticity, and principles of biofeedback and self-regulation have made it possible to detect, monitor, and change the brain's electrical activity related to many emotional and physiological disorders. More recent advances in electronic technology have allowed these research discoveries to be readily applied to the clinical setting (Turner, 2016).

The successful use of neurofeedback training has been established with numerous adults (Dadashi et al., 2015; Hardt et al., 1978; Plotkin et al., 1981) and small groups of children with anxiety disorders. Therefore, more studies are still needed to evaluate its effectiveness. In this study, we examine the effectiveness of neurofeedback training in the treatment of anxiety disorders in children and adolescents by comparing it with cognitive behavior therapy.

Material and Methods

Participants

The present study was conducted on children and adolescents who met the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; DSM-5; APA, 2013) criteria of GAD and were attending child psychiatry clinics at El Hadara Alexandria University Hospital, Egypt.

All children and adolescents suffering from GAD attending the selected clinic who met inclusion criteria (Table 1) were invited to participate. After obtaining ethical clearance from the Ethical Committee faculty of medicine, Alexandria University, then obtained informed written consent from participants and their caregivers. First, they were informed that the study was about GAD and its treatment. Then, they were informed about the aims of the study and their right to refuse giving information as well as their right not to participate or end their participation in any stage of the treatment process.

The sample comprised of 30 participants in the age range of 7–17 years, who were selected by random sampling method and assigned to group A for neurofeedback training and group B for cognitive behavior therapy (CBT), such that each group was comprised of 15 participants. The mean age of the NF group was 12.13 ± 2.69 years (12 male and 3 females) while the mean age of the CBT group was 10.80 ± 1.52 years (7 males and 8 females).

Table 1
A Summary of the Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Both genders • Age 7–17 years old • Average or above age-related reading ability • DSM-5 diagnostic criteria of generalized anxiety disorder (GAD) • Intact sensory system • Informed written consent from the caregiver and assent from the child	• Previous head injury, or neurological disorders and treatment with medications known to influence EEG, such as tranquilizers • Intellectual disability • Substance abuse • Psychiatric disorders other than anxiety disorders • Absence of more than two sessions in the treatment process

Procedure

All studied sample was subjected to structured interviews using a predesigned questionnaire to collect the following data: sociodemographic details; developmental, education, social, past psychiatric and medical history; drug history, in addition to family psychiatric and medical history; and finally mental status examination.

Baseline assessments were conducted using the State-Trait Anxiety Inventory for Children (STAI-C) while adolescents ≥ 12 years old received State-Trait Anxiety Inventory (adult form; STAI). To examine the posttraining effect, the same baseline assessments were readministered immediately after the completion of the therapy sessions for both groups.

The State-Trait Anxiety Inventory for Children (STAI-C). It consists of separate, self-report questionnaires for assessing two distinct anxiety concepts: state anxiety and trait anxiety. The STAIC State-Anxiety scale consists of 20 statements that ask children how they feel at a specified moment in time. The STAIC Trait-Anxiety scale also consists of 20 item statements that measure relatively stable individual differences in anxiety proneness; that is, differences between children in the tendency to experience anxiety states. Individual STAI-C items are similar in content to those included in the STAI, but the format for responding to the STAI-C has been simplified to facilitate its use with young children. Also, the adult form is a 4-point scale while the child version is a 3-point scale (Spielberger et al., 1973; Spielberger et al., 1983).

Neurofeedback Training Group (A). All participants in this group were subjected to a quantitative electroencephalogram (qEEG) study. The EEG was conducted in a dimly lit, sound-attenuated room while the patient was seated comfortably. The total recording time was 40 minutes, then the raw EEG was reviewed to be sure of the absence of any abnormal or epileptogenic discharges then through NeuroGuide software (Applied Neuroscience, Inc., St. Petersburg, FL) that analyze the data quantitively then compare it with a normative database through which could be detected the electric frequency interval with an abnormal amplitude that needs to be trained depend on the absolute power, relative power, and *Z* score power ratio (Collura et al., 2016).

According to qEEG studies for the participants, the target frequency bands for training were reduced high beta in six candidates, enhanced alpha in four, enhanced sensorimotor rhythm in two, enhanced both alpha and sensorimotor rhythm in two, while only one candidate combined enhanced alpha and reduced high beta (Table 2, Figure 1, Figure 2).

Table 2
A Summary of the Target Frequency Bands According to qEEG Studies for the Participants

Target Frequency Band	Number of Candidates
Reduced high beta	6
Enhanced alpha	4
Enhanced sensorimotor rhythm (SMR)	2
Enhanced alpha and sensorimotor rhythm (SMR)	2
Enhanced alpha and reduced high beta	1

Figure 1. *qEEG Brain Mapping Shows a Decrease in Both 11–12 Hz (High Alpha) and 13–15 Hz Activity (Sensorimotor Rhythm) at Cz (Blue-colored Areas).*

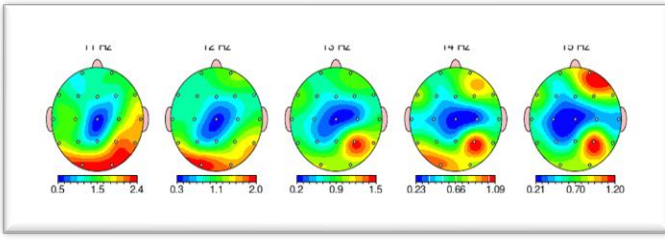
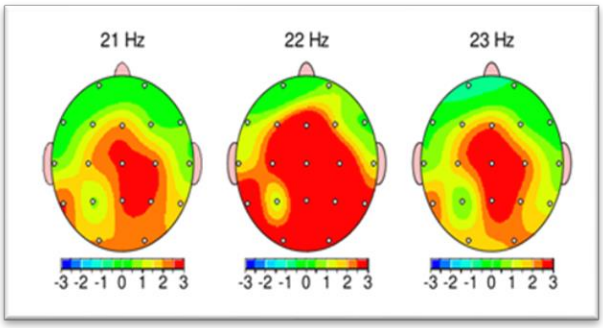


Figure 2. *qEEG Brain Mapping Shows an Increase in 21–23 Hz Activity (High Beta) at Cz (Red-colored Areas).*



***Neurofeedback Training Sessions*.** According to the international 10/20 system, to record the activity of electrical waves, the active electrode located at the selected area and two electrodes of reference and ground were placed on the left and right mastoid process, while the patient is sitting in a comfortable chair with eyes open in front of the screen. Each patient attended 20 neurofeedback sessions for training the selected brain waves amplitude twice weekly (Demos, 2005).

All of the neurofeedback sessions were arranged to follow 5 min devoted to the attainment of preparatory relaxation, 2 min devoted to recording EEG baseline data, then 30 min devoted to the training process.

The NeXus-10 MKII device with BioTrace+ software (Mind Media, Netherlands) was used. NeXus-10 and BioTrace+ are highly customizable platforms with a wide range of powerful tools for physiological research and signal processing.

Cognitive Behavior Therapy Group (B). The cognitive-behavioral therapy was applied in the current study according to the Cognitive-Behavioral Therapy for Childhood Anxiety Disorders that was designed by Bruce F. Chorpita.

Each candidate in this group was subjected to 8–12 individual sessions, with each session 50–90 minutes on a weekly basis. Parents are involved in the child-focused (individual treatment) program and meet in sessions 1, 4, and 8, as well as in other sessions as needed for the exposure tasks (Chorpita, 2007).

***Cognitive Behavior Therapy Sessions*.** The CBT protocol is presented in Table 3.

Table 3
Description of Cognitive-Behavioral Therapy Sessions

Session	Goals
1	Building rapport, treatment orientation, and the first parent meeting
2	Learning to relax by teaching relaxation exercises
3	Identifying anxious feelings, self-talk, and learning to challenge thoughts
4	Introducing problem-solving, self-evaluation, and self-reward
5	Reviewing skills already learned, practicing in low anxiety-provoking situations, and the second parent meeting
6–7	Practicing with increasingly anxiety-provoking situations
8	Practicing in high-anxiety situations, the third parent meeting, and celebrating success

***Data Analysis*.** Data were entered and checked using IBM SPSS software package version 20.0.

Qualitative data were presented using absolute and relative frequency. Quantitative data were tested for normality using the Shapiro Wilk test (Shapiro & Wilk, 1965). Data were normally distributed so presented as a range, mean and standard deviation.

Comparison between the two intervention groups was done using the Student *t*-test for quantitative variables and the chi-square test for the qualitative variable. Paired comparison within each intervention group (before and after comparison) regarding quantitative variables was conducted using paired *t*-test.

Percent of improvement regarding anxiety scores after intervention was calculated as follows: Percent improvement = {(pretreatment score − posttreatment score) / pretreatment score} * 100

Analysis was carried out at a 5% level of significance.

Results

The Effect of Neurofeedback Training on Trait-Anxiety Score and State-Anxiety Score

Table 4 illustrates there was a significant difference in Trait-Anxiety scores and State-Anxiety scores before and after neurofeedback training.

Regarding the percentage of improvement, NF training showed a 21.5% improvement in Trait-Anxiety score while 25.6% for State-Anxiety score. Thus, the obtained results showed that NF therapy caused the reduction of anxiety symptoms in children and adolescents with GAD with more improvement on the State- than Trait-Anxiety score.

Table 4
Results of t-Test for Neurofeedback Treatment

	Pretest	Posttest	Percentage of Improvement %	Paired Comparison
Trait-Anxiety Score				
Min-Max	29–62	21–49	0–36.84	$t = 6.955$ $p < .001$*
Mean ± *SD*	47.40 ± 8.36	37.26 ± 8.21	21.45 ± 10.99	
Median (IQR)	47 (44–52)	39 (32–43)	20.97 (15.21–29.79)	
State-Anxiety Score				
Min-Max	24–59	20–46	3.45–51.02	$t = 5.981$ $p < .001$*
Mean ± *SD*	41.20 ± 10.58	30.06 ± 8.26	25.63 ± 14.42	
Median (IQR)	41 (33–49)	30 (23–35)	23.73 (16.36–33.33)	

The Effect of Cognitive Behavior Therapy on Trait-Anxiety Score and State-Anxiety Score

Table 5 illustrates there was a significant difference in Trait-Anxiety scores and State-Anxiety scores before and after cognitive behavior therapy.

The mean difference between pretest–posttest of State-Anxiety score in CBT group was 39.04, while for Trait-Anxiety score was 13.4, and based on these results the difference was significant ($p < .05$), which confirms that cognitive behavior therapy had a significant impact on generalized anxiety symptoms reduction in children and adolescents.

Regarding the percentage of improvement, CBT showed 28.9% improvement in Trait-Anxiety score while 21% for State-Anxiety score, with more improvement in Trait-Anxiety than in State-Anxiety scores.

Table 5

Results of t-Test for Cognitive Behavior Treatment

	Pretest	Posttest	Percentage of Improvement %	Paired Comparison
Trait-Anxiety Score				
Min-Max	39–62	25–51	12.20–48.98	$t = 8.942$ $p < .001$*
Mean ± *SD*	46.6 ± 6.66	33.20 ± 8.31	28.99 ± 12.47	
Median (IQR)	46 (41–49)	31 (26–37)	35.00 (15.90–35.00)	
State-Anxiety Score				
Min-Max	26–50	20–44	5.88–47.50	$t = 5.223$ $p < .001$*
Mean ± *SD*	67.24 ± 7.34	28.20 ± 7.09	21.07 ± 7.14	
Median (IQR)	34 (31–40)	37 (32–49.75)	22.00 (7.14–29.41)	

Comparison Between the Two Intervention Groups Regarding Trait-Anxiety Scores, State-Anxiety Scores, and Percentage of Improvement

Table 6 illustrates that comparing CBT and NF therapy groups, revealed no significant differences in reducing anxiety symptoms as regard trait anxiety score and state anxiety score between the two studied groups, which mean that NF therapy is as effective as CBT in reducing anxiety symptoms.

Table 6

Results of Compare CBT and Neurofeedback Treatment

	Type of Intervention			
	NFB ($n = 15$) Mean ± *SD*	CBT ($n = 15$) Mean ± *SD*	Test of Significance	*p* Value
Trait-Anxiety Score				
Pre-test	47.40 ± 8.36	46.60 ± 6.66	$t = 0.290$	0.774
Post-test	37.26 ± 8.21	33.20 ± 8.31	$t = 1.349$	0.188
% Improvement	21.45 ± 10.99	28.99 ± 12.47	$t = -1.757$	0.090
State-Anxiety Score				
Pre-test	41.20 ± 10.58	36.00 ± 7.52	$t = 1.552$	0.132
Post-test	30.06 ± 8.26	28.20 ± 7.09	$t = 0.664$	0.512
% Improvement	25.63 ± 14.42	21.07 ± 7.14	$t = 0.881$	0.386

Figure 3 shows the mean Trait-Anxiety score with error bars representing 95% CI among the two intervention groups. The 95% confidence interval (CI) of the mean shows no statistically significant difference between both studied groups regarding the pretest as well as the posttest a trait anxiety score.

Figure 3. *Mean of Trait-Anxiety Score Among the Two Studied Groups Before and After the Therapy.*

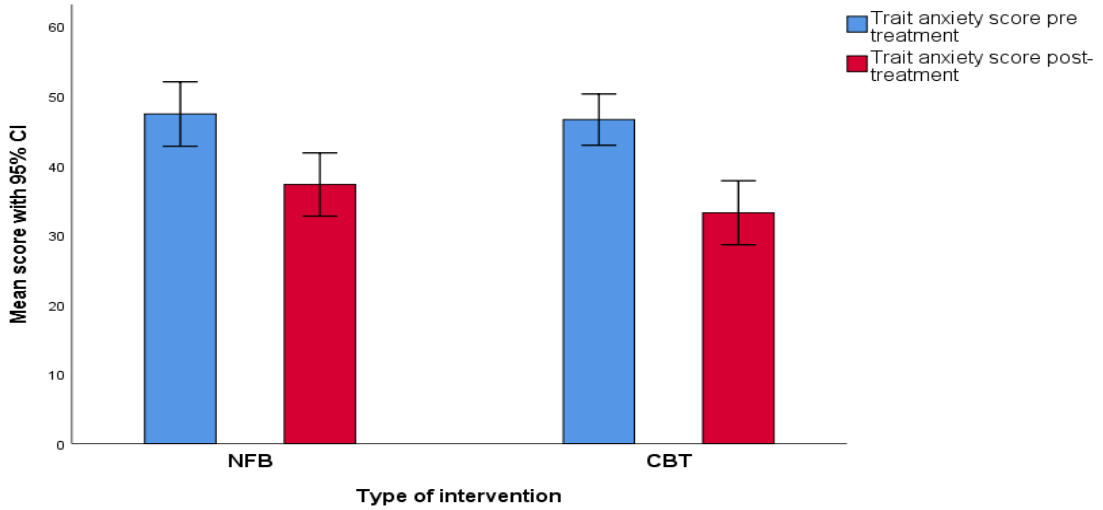
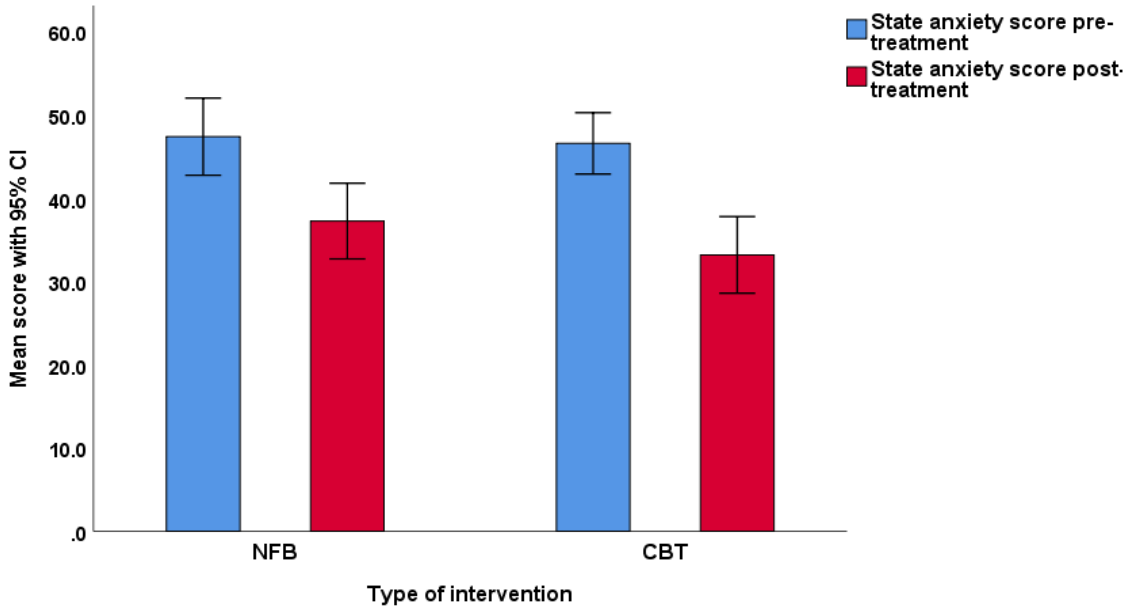


Figure 4 shows the mean State-Anxiety score with error bars representing 95% CI among the two intervention groups. The 95% CI of the mean shows no statistically significant difference between both studied groups regarding the pretest as well as the posttest State-Anxiety score.

Figure 4. *Mean of State-Anxiety Score Among the Two Studied Groups Before and After the Therapy.*



Discussion

Anxiety can affect one's everyday life and may contribute to psychological and physical well-being. The present study examined the effectiveness of neurofeedback training on reducing anxiety symptoms among children and adolescents with GAD. The result showed both CBT and NF were effective methods for reducing anxiety symptoms, but the application of neurofeedback training compared with cognitive behavior therapy did not show significant differences to reduce anxiety. This result showed that neurofeedback training may be a promising treatment for anxiety-related disorders.

Various biofeedback modalities have been implemented by clinicians before neurofeedback emerged in the treatment of anxiety such as electromyography (EMG), peripheral temperature, and electrodermal response (EDR; Price & Budzynski, 2009). NF, an EEG biofeedback, is a method of self-regulation that depends on a brain–computer interface to promote neural plasticity, by providing feedback to an individual about their brain's electrical activity at a certain location in a specified frequency band (Cannon, 2015). NF therapy makes the human brain learn to relax.

NF has been used to lower anxiety symptoms in a variety of populations. However, according to the available information, practitioners are focusing on using NF with the adult population, with few studies on children with anxiety disorders. Regarding neurofeedback therapy in adults with GAD, the studies showed positive effects on the reduction of anxiety symptoms which were consistent with those of the current study. Below are some examples.

Dadashi et al. (2015) conducted a study on 28 adult patients with ages between 18–50 divided into two groups; 14 subjects were assigned to the neurofeedback treatment group and 14 subjects in the waiting list group. The results showed that enhancement of alpha and theta brain waves amplitude in people with GAD in the occipital area can reduce symptoms of GAD and increase the global functioning level in a treatment group, but no such change was observed in the wait-list group (Dadashi et al, 2015).

The study by Hardt and Kamiya showed alpha-enhancement reduced both state and trait anxiety in high trait-anxiety subjects, suggesting it would benefit anxious patients (Hardt & Kamiya, 1978). Rice et al. (1993) suggested EMG and EEG alpha-increased feedback showed the positive effects on reduction of generalized anxiety symptoms, the improvements in anxiety were maintained 6 weeks after treatment, and the only alpha increase resulted in reductions of heart rate reactivity to stress (Rice, Blanchard, & Purcell, 1993).

Although neurofeedback studies of children and adolescents with anxiety disorders are limited, the available studies suggest that neurofeedback training is an effective method in reducing anxiety symptoms in this age group which is consistent with those of the current study. Below are some examples.

Sadjadi and Hashemian conducted a study to find out the effect of neurofeedback therapy in children with a separation anxiety disorder. The study population was school-age children from 7 to 12 years old with separation anxiety disorder, and they were assigned randomly into two groups. One group received neurofeedback therapy and the other group received sham neurofeedback therapy. Each group included 12 participants. Each child had 20 sessions, and each session was about 30 minutes in duration. The children are trained to enhance the ratio of alpha/theta in F3 throughout the 20 sessions. Results showed that neurofeedback was effective in reducing separation anxiety and the efficacy of treatment was great compared with the placebo group (Sadjadi, & Hashemian, 2014).

Éismont, Lutsyuk, and Pavlenko (2011) implemented a study to estimate the efficacy of using neurofeedback training for reducing increased anxiety levels in healthy 10- to 14-year-old children. Thirty-minute-long NF sessions were performed twice per week. The results showed significant enhancement in the ratios of the amplitudes of alpha and theta rhythms, sensorimotor and theta rhythms in tested persons of the experimental group which associated with the anxiety level decreased appreciably; in addition, the indices "feeling of inferiority" and "frustration" decreased significantly, while in the control group, changes in these values did not reach the significance level (Éismontet al., 2011).

All previously mentioned studies illustrate how NF can be a viable tool in lowering anxiety symptoms. They each have their strengths and limitations. A substantial limitation is either using the same protocol for each patient or using a protocol based on symptoms alone. Protocols based on symptoms alone or using the same protocol for each patient bypasses the time, cost, and training of running a qEEG (Thompson & Thompson, 2003). In our study,

the training protocol is not the same for all participants in the neurofeedback group. It is unreasonable to expect a one-size-fits-all approach in neurofeedback training as the brain is complex and different for everyone, so we depend on the more accurate method which is quantitative encephalogram (qEEG) to determine the target frequency band which was agreed with Hammond (Hammond, 2011) who expresses the importance of using a qEEG to identify heterogeneity in brain wave patterns, finding comorbidities, and looking for effects from medication.

Interestingly, the protocols selected in our study, based on individualized qEEG include enhanced alpha, enhanced SMR, reduced high beta, or combined between them, reflected markers already found to be associated with anxiety symptoms in literature (Hammond, 2005; Wiedemann et al., 1999)

Krigbaum and Wigton proposed the importance of qEEG guided neurofeedback as it allows the clinician to develop a more individualized treatment plan which depends on a qEEG baseline, and clinical status of the client (Wigton & Krigbaum, 2015). A study by Dreis et al. assessed 14 clients for anxiety spectrum disorders with age ranges from 11–61 years old, nine male and five female. Thirty-minute-long qEEG-guided NF treatment sessions were performed twice per week. Results showed enhancement in clients' well-being as evidenced by statistically significant improvement in symptom measures scores (Dreis et al., 2015).

In the last decade, despite an increase in the number of publications regarding neurofeedback for anxiety disorders, little attention has been paid to compare its effectiveness with established treatment methods such as CBT which consider the main behavior approach to anxiety disorders. The current study considers a step to cover this point especially in the children and adolescent population.

Limitations and Future Perspectives

There were some limitations to the current study including the small sample size. The small sample size may affect the statistical power to distinguish the efficacy of neurofeedback training. Thus, a larger sample size with an appropriate effect size is warranted. Another limitation of the present study was the problem of the absence of a placebo treatment group (placebo) such as a wait-list, which means that we cannot be sure that the improvement in anxiety symptoms was any greater than without intervention at all. This problem is due to the limitations of the sample and ethical concerns.

To conclude, the findings suggested that neurofeedback training can be effectively used as a part of a multimodal treatment approach of generalized anxiety disorders in children and adolescents. The present study also holds an implication for using different qEEG-based protocols to reduce anxiety symptoms such as alpha enhancement, sensorimotor enhancement, reduced high beta, or combined between them. Finally, further studies are now needed to pinpoint the longevity of neurofeedback training gains on anxiety symptoms across time and to understand the interindividual differences in the improvement of symptoms, self-regulation, and learning process.

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Relationship Between Caudal and Rostral Auditory Efferent Pathways: A Preliminary Investigation

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Abstract

Perception of sounds involves excitatory as well as inhibitory activities. Inhibition occurs throughout the auditory system, from the auditory cortex to the cochlea, and is predominantly mediated by the auditory efferent system. In the present study, we assessed the interactions between two measures of inhibition in neurotypical adults—contralateral inhibition of otoacoustic emissions, which is a subcortical measure, and sensory gating, a cortical measure. We found an inverse relationship between these two functions. The possible reasons for this are discussed with an implication to the auditory efferent system.

Keywords: auditory efferent system; auditory sensory gating; contralateral inhibition of otoacoustic emissions; inhibition

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Introduction

Speech perception often occurs in dynamic and complex acoustic environment. Accurate perception in complex acoustic environment entails the auditory system to extract important cues while ignoring the irrelevant ones. This necessitates an interplay of both afferent and efferent auditory systems. While the afferent auditory system processes and conducts sound from cochlea to cortex, it is proposed that the efferent auditory system modulates the bottom-up afferent processing (Hackney, 1987; Suga et al., 2000). Though the human auditory system has a rich and elaborate descending neural network, the interplay amongst these pathways and its contribution to hearing remains unclear.

Neuroanatomical evidence demonstrates the presence of four main types of descending auditory networks—the corticocortical, corticothalamic, corticocollicular, and the olivocochlear modulations (Delano & Elgoyhen, 2016; Suga, 2020). The cortico-cortical network connects the auditory cortex with other areas of the cerebral cortex, including the prefrontal cortex (Suga, 2020). The corticothalamic network extends from the auditory cortical structures to the medial geniculate body (Tang et al., 2012). The corticocollicular descending auditory pathway extend from the layer V of the auditory cortex to the neurons of inferior colliculus (Ma & Suga, 2001; Yan & Ehret, 2002). The olivocochlear bundle originates from the superior olivary complex and projects towards the cochlea. This descending fiber tract comprises of two subsystems—medial and lateral olivocochlear bundle (Guinan, 2006). The olivocochlear bundle forms the final common pathway from the central nervous system to the cochlear receptor organs (Terreros & Delano, 2015).

Maruthy et al. (2017) divided the auditory efferent systems into caudal and rostral efferent system. The efferents from subcortical level to the lower structures is termed as the caudal efferents, whereas those originating from the cortical level is referred to as the rostral efferents. Both caudal and rostral efferent systems have been investigated for their role in speech in noise perception, auditory

plasticity, and attention (Briggs & Usrey, 2008; Campbell, Nielsen, LaBrec, et al., 2020; de Boer & Thornton, 2007; Garrido et al., 2009; Kumar et al., 2010; Kumar & Vanaja, 2004).

The medial olivocochlear bundle is the extensively studied efferent pathway. This is because functioning of this pathway can be easily studied using quick and noninvasive procedures such as contralateral inhibition of otoacoustic emissions (OAEs; Collet et al., 1990). OAEs are by-products of electromotility of the outer hair cells in the cochlea. OAEs can be recorded by placing a sensitive microphone in the ear canal. The stimulation of the contralateral ear reduces the amplitude of the OAEs, which is thought to be a result of the inhibitory effects of medial olivocochlear efferent system. Several studies have shown that the magnitude of contralateral inhibition of OAE correlates with speech perception in noise, indicating an antimasking role of the olivocochlear bundle (Abdala et al., 2014; Giraud et al., 1997; Kumar & Vanaja, 2004).

The rostral efferent system, on the other hand, is sparsely studied due to its complex nature, multiple connections, and the lack of any standardized procedures. Some indirect measures that have been used to study the rostral efferent system are assessment of (a) context-dependent encoding of speech (Maruthy et al., 2012) and (b) stimulus-specific adaptation (Anderson et al., 2009; Malmierca et al., 2015; Takaura & Fujii, 2016). In context-dependent encoding, the auditory stimuli are presented in two paradigms—a repetitive paradigm and a contextual paradigm. In the repetitive paradigm, the test stimulus is presented multiple times and the auditory cortical response is recorded. On the other hand, the contextual paradigm involves presentation of the target stimulus in context of other stimuli while recording the cortical response. The amplitude of the cortical evoked response is higher in the contextual paradigm when compared to the repetitive paradigm. In stimulus-specific adaptation, the standard and deviant stimuli (termed based on probability of occurrence) are presented in an oddball paradigm. An adaptation (weakening) of evoked response is observed for the high probability stimuli, when compared to the stimuli occurring less frequently (the deviant stimuli). This waning of response (in repetitive paradigm in context-dependent encoding of speech and standard stimulus in stimulus specific adaptation) is thought to reflect the inhibition caused due to redundancy of information and is majorly mediated by the rostral efferent system. However, the use of these techniques is limited as the magnitude of inhibition (caused by the redundant stimuli) are small and highly variable.

Sensory gating refers to the phenomenon in which cortical neural responses to repetitive stimuli are reduced compared to a novel stimulus. The auditory sensory gating is commonly assessed in a conditioning-testing paradigm which involves presenting two identical stimuli in succession. Here, the amplitude of auditory evoked potential to the second stimuli (S2) is reduced compared to that of the first (S1). This is thought to be due to the detection of redundancy of information in the S1 and S2 and the activation of a gating-out process (Boutros & Belger, 1999; Freedman et al., 1987). This phenomenon reflects top-down modulation of sensory stimuli. The sensory gating effect is robust, consistent and has been investigated in a variety of population (Adler et al., 1982; Arciniegas et al., 2000; Campbell et al., 2018; Campbell, Nielsen, Bean, et al., 2020; Lijffijt et al., 2009). We presume that this inhibitory action is likely mediated by the rostral efferent system, particularly, the corticocortical and corticothalamic pathways. In a recent study, Campbell, Nielsen, LaBrec, et al. (2020) reported an association between speech perception in noise and auditory sensory gating in normal hearing individuals with and without speech in noise deficits.

The contralateral inhibition of OAE and sensory gating are functionally similar, facilitating response inhibition in the auditory system to improve the overall efficiency of sensory processing. Therefore, it would be interesting to assess the relationship between the two mechanisms—sensory gating and contralateral inhibition of OAEs. It seems likely that the two mechanisms interact with each other to achieve common goals. Given this background, we performed the current study with the aim of understanding the interplay between the two inhibitory mechanisms in the auditory system in clinically normal hearing adults. The objectives of the study were to assess and correlate the two measures of auditory inhibition: inhibition of transient evoked OAEs (TEOAEs) amplitude brought by contralateral acoustic stimulation and the amplitude ratio between auditory cortical responses to two stimuli presented in a conditioning-testing paradigm.

Materials and Methods

Participants

We recruited 15 young normal hearing volunteers (3 males and 12 females) with a mean age of 24.47 ± 2.9 years. The participants had no known speech, language, or cognitive deficits. This was ascertained by carrying out an informal interview prior to the study. Smokers and individuals with tinnitus were excluded from the study as these factors are known to interfere with the test findings (Campbell et al., 2018; Harkrider & Hedrick, 2005). Individuals with hypertension and diabetes were also excluded from the study. All participants had air-conduction hearing sensitivity within 15 dB HL at octave frequencies between 250–8000 Hz, normal middle ear functioning, and click evoked OAE present with a minimum amplitude of 6 dB SPL. A signed informed consent was obtained from all the participants prior to the study. The study adhered to the biobehavioral ethical guidelines of the All India Institute of Speech and Hearing, Mysore (Venkatesan & Basavaraj, 2009).

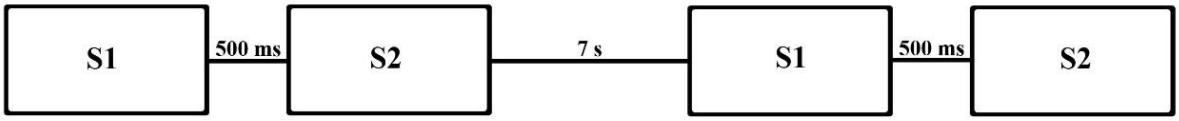
Contralateral Inhibition of TEOAE

We seated the participants comfortably and provided them with a reading material (to ensure passive attention condition) while the test was being carried out. The TEOAE probe was placed in the right ear of the participants, and an insert receiver was placed in the left ear. Following this, we presented 260 pairs of linear clicks at 70 dB peSPL using an Otodynamics ILO-V6 OAE equipment (Otodynamics Ltd., London, UK) and measured the TEOAEs. TEOAEs were recorded again in the presence of a 60 dB SPL of white noise presented to contralateral ear. The noise was delivered via an ER 3A insert receiver connected to a calibrated GSI Audiostar Pro 2-channel clinical audiometer (Grason-Stadler Inc., Eden Prairie, MN). The probe position was unaltered between the two recordings. The amplitudes obtained in these two conditions were then subtracted to obtain the magnitude of inhibition.

Sensory Gating

Stimuli. The sensory gating ability of the participants was measured in a conditioning-testing paradigm. The stimuli consisted of a pair of identical 250 Hz tone bursts with 50 ms plateau and 10 ms rise–fall times (generated in Adobe Audition, version 3.0) with a gap of 500 ms between them. The first stimulus of the pair was designated as S1 and the second stimulus was designated as S2. An interval of 7s was maintained between two consecutive pairs. Figure 1 shows the graphical representation of the stimuli.

Figure 1. *Representation of the Stimulus Paradigm Used in the Sensory Gating Experiment.*



Note. *Two pairs of identical stimuli separated with an inter stimulus interval of 500 ms and an inter-pair interval of 7s.*

Recording of Auditory Evoked Potentials. The calibrated stimuli were presented using the Continuous Acquisition Module of SmartEP equipment (Intelligent Hearing System Corp., Miami, FL). We placed the noninverting electrode at Cz, inverting electrode on the test ear mastoid, and the ground electrode on the nontest ear mastoid. A second ocular channel was used to eliminate the ocular artifacts. The gain was set to 50000 μV. All the electrode impedances were kept below 5 kΩ. Stimuli were presented to the right ear of the participants at 70 dB nHL through electrically shielded ER-3A insert earphones. Participants were sitting comfortably in a reclining chair during the recording. The participants were instructed to stay as still as possible, and to reduce their eye movements during the recording. The raw EEG was recorded with a bandpass filter of 1–100 Hz and converted into a digital signal at a sampling frequency of 1000 Hz. Artifact-free responses were recorded for a total of 150 stimulus pairs. Throughout the recording, we played a close-captioned movie of participants choice to maintain passive attention.

The continuous raw EEG of every participant was subjected to offline analyses using EEGLAB (version 14.1.2; Delorme & Makeig, 2004) implemented in MATLAB (The Mathworks Inc., Natick, MA). The continuous EEG was filtered (to 1–30Hz) and epoched for 570ms. The average event-related potentials for both S1 and S2 were extracted separately. The cortical evoked response peaks P1, N1, and P2 were identified for both S1 and S2, and the amplitudes of the peaks were noted. This was then divided (S2/S1) and multiplied by 100 to obtain the sensory gating ratio. The lower the sensory gating ratio (more difference between the amplitudes of S1 and S2 responses), the better the gating mechanism.

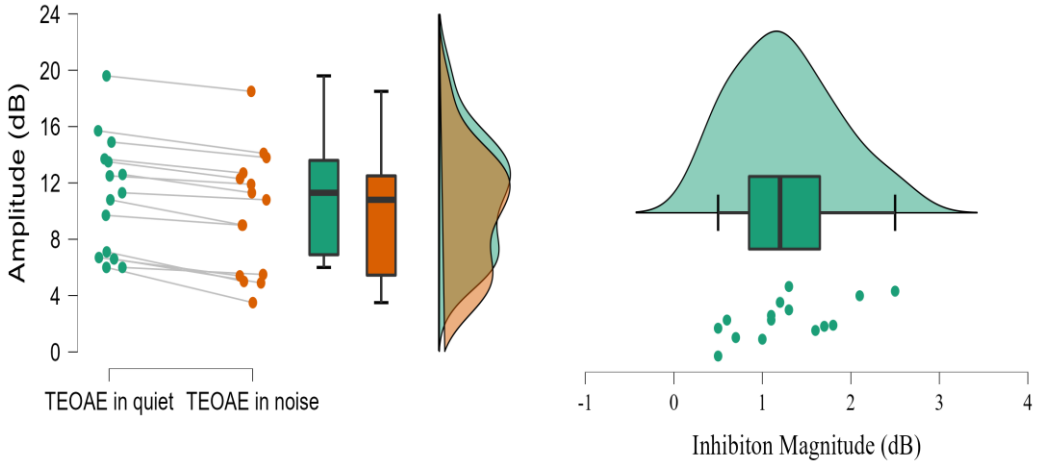
Results

All the statistical analyses were carried out using the JASP (JASP team, 2021, version 0.15.0.0) statistical software.

Contralateral Inhibition of TEOAE

A Wilcoxin Signed Rank test was run on the TEOAE amplitudes with and without contralateral stimulus (see Figure 2a, for individual and group data).

Figure 2. *(a) TEOAE Amplitudes in Quiet (Green) and with Contralateral White Noise (Orange) – Individual Data Points, Box Plots and Data Distribution; (b) The Difference Plot Depicting the Magnitude of Inhibition Brought About by the Contralateral Stimulation.*



(a) (b)

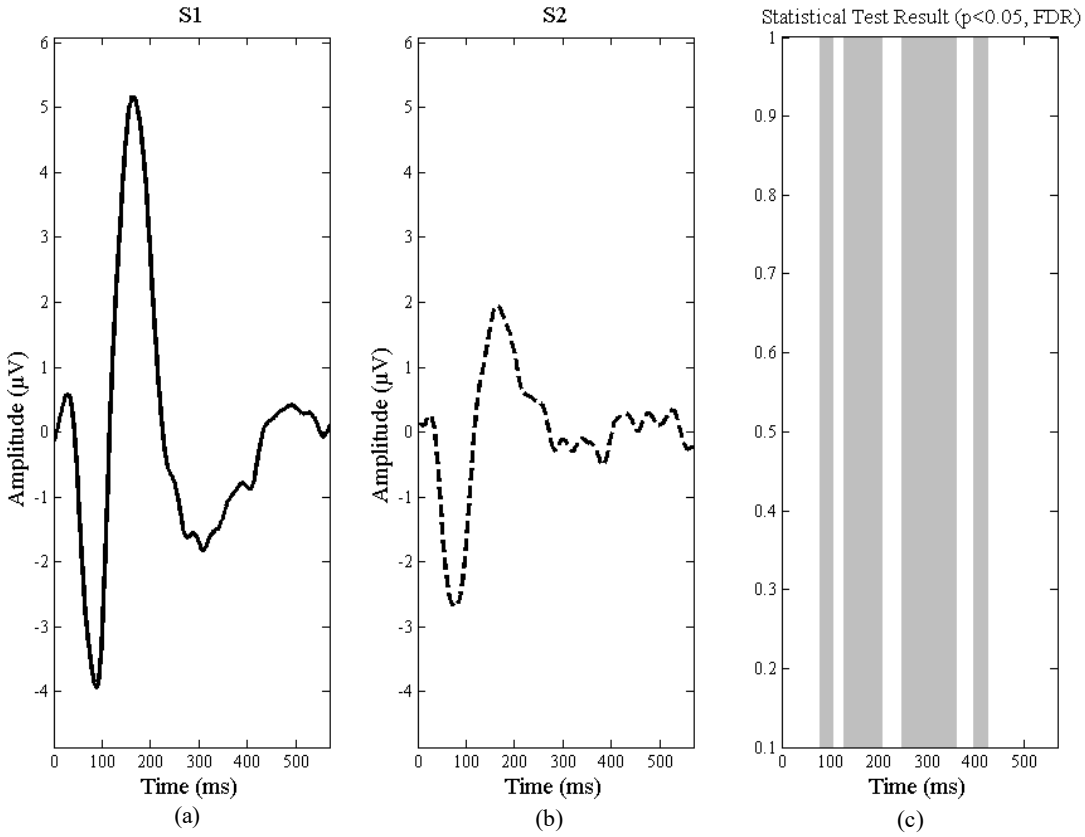
We found a significant reduction of TEOAE amplitudes in the presence of contralateral noise (Z = 3.41, p < .01). A rank-biserial correlation was performed to assess the effect size and an r value of 1 (maximum effect) was obtained (Kerby, 2014). Figure 2b depicts the inhibition magnitude (TEOAE amplitude without noise − TEOAE amplitude with noise) obtained in our study.

Sensory Gating

Figure 3a and 3b depict the grand average waveform obtained for the S1 (solid line) and S2 (dashed line) for our participants. Waveforms of S1 and S2 were analyzed using permutation-based statistics to obtain statistical significances (depicted in Figure 3c). False discovery rate (FDR) corrections were incorporated to account for multiple comparisons.

From Figure 3c it can be seen that the waveforms of S1 and S2 differed from each other between 80–110 ms (which corresponds to the N1 region), 130–210 ms (which corresponds to the P2 region), 250–360 ms, and 400–430 ms. Furthermore, peak amplitudes of P1, N1, and P2 were identified and marked.

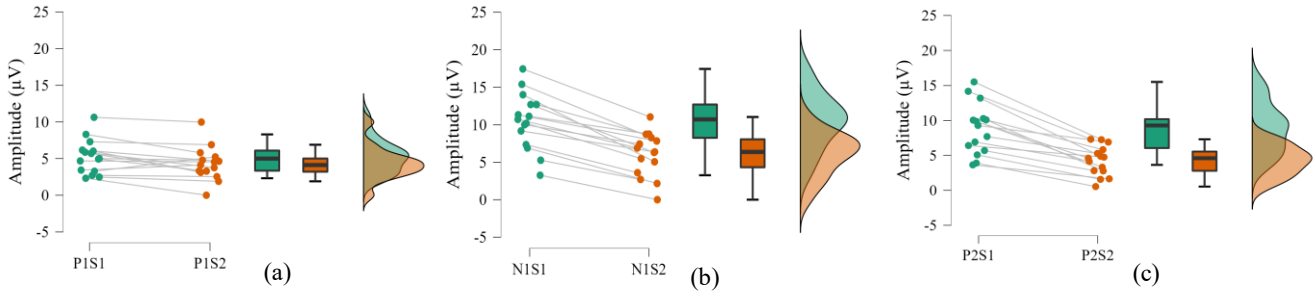
Figure 3. *Comparison of the Grand Averaged Waveform of Response Obtained in a Conditioning-testing Paradigm.*



Note. *(a) S1 – solid line. (b) S2 – dashed line. The panel (c) depicts the statistical test findings of the multiple comparisons with FDR corrections. The shaded regions indicate significant differences at 0.05 level of significance.*

Figure 4 shows the peak amplitudes (in terms of individual data points, box plots, and distribution of the data) of P1, N1, and P2 respectively for both S1 and S2 stimuli. Wilcoxon Signed Rank test showed that the amplitude of S1 was significantly higher than that of S2 for all the three peaks; P1 (Z = 2.442, p = .012, r = 0.7), N1 (Z = 3.408, p < .001, r = 1), and P2 (Z = 3.408, p < .001, r = 1).

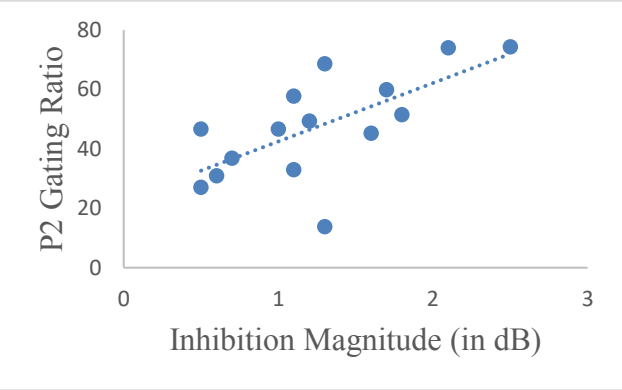
Figure 4. *The Amplitudes of the Auditory Cortical Evoked Potential in a Sensory Gating Paradigm across (a) P1, (b) N1, and (c) P2 for S1 and S2.*



Relationship Between Contralateral Inhibition of TEOAE and Sensory Gating Indices

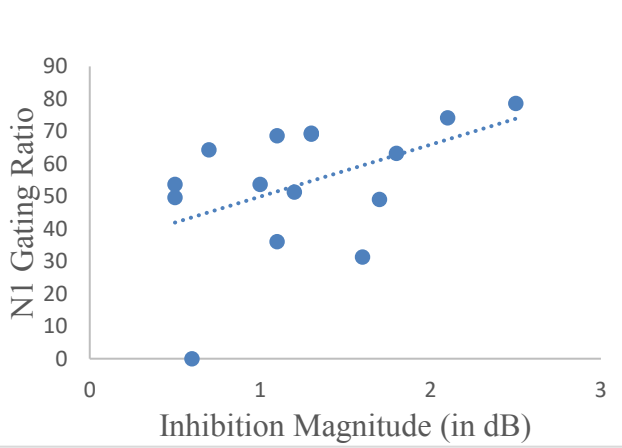
We performed the Spearman's correlation to assess the relationship between contralateral inhibition of TEOAE and sensory gating indices. The Spearman's correlation revealed a significant positive correlation between the inhibition magnitude and P2 sensory gating ratio (r = 0.666, p = .007). This indicates that individuals with higher magnitude of TEOAE inhibition showed lower sensory gating capacities. Figure 5 shows the scatter plot between TEOAE inhibition magnitude and P2 sensory gating ratio.

Figure 5. *Scatter plot depicting the relationship between magnitude of contralateral inhibition of TEOAE and P2 sensory gating ratio.*



Further, we noticed that the relationship between the inhibition magnitude and N1 gating ratio was nearing significance (r = 0.444, p =.09). Figure 6 depicts this relationship in a scatter plot.

Figure 6. *Scatter plot depicting the trend between magnitude of contralateral inhibition of TEOAE and N1 sensory gating ratio.*



Discussion

In the present study, we investigated the relationship between sensory-gating indices and magnitude of contralateral inhibition of OAEs. The results revealed a significant positive correlation between P2 sensory gating ratio and contralateral inhibition of OAEs. The contralateral inhibition of OAEs is a proven method to assess the functioning of medial olivocochlear bundle in humans (Collet et al., 1990; Guinan, 2006). The magnitude of contralateral inhibition observed in this study are comparable to those reported in literature (Maruthy et al., 2017; Stuart & Kerls, 2018). In the sensory gating experiment, we observed that amplitudes of auditory P1, N1, and P2 were significantly smaller for the second stimuli of the pair compared to the first (Figures 3, 4). The magnitude of sensory gating—as indicated by the ratios between the amplitudes of auditory evoked potential for S2 and S1—observed in the current study are also comparable to those in previous studies (Fuerst et al., 2007; Patterson et al., 2008; Rentzsch, Gomez-Carrillo de Castro, et al., 2008).

Sensory gating involves detection of redundancy of information in ongoing streams (S1 and S2) and the subsequent activation of a gating-out process (Boutros & Belger, 1999; Freedman et al., 1987). Previous studies have shown that gating response is primarily mediated by the auditory and the prefrontal cortex, with contributions from thalamic network. It is proposed that auditory cortices process the basic stimulus related information, whereas, the prefrontal cortex along with the thalamic connections inhibits further flow of sensory information in the cortex (Mayer et al., 2009). These networks are also implicated in the corticocortical and the corticothalamic auditory descending pathway (Antunes & Malmierca, 2021; Delano & Elgoyhen, 2016; Suga, 2020). Therefore, the gating response observed for auditory evoked potential may reflect the strength of the rostral efferent system. This is also in par with the predictive coding model put forth by Friston (2005). According to Friston, the cortical structures continuously monitor the incoming stimuli and generate predictions about the next stimuli. These predictions, when met, lead to an inhibition of responses following the redundant information. However, a deviation in the stimuli causes a "prediction error" and brings about facilitatory responses. The presence of such predictive mechanisms in the auditory system are supported by other studies as well (O'Reilly, 2021; Todorovic & de Lange, 2012). We propose that the presentation of S1 (in a conditioning-testing paradigm) leads to the prediction of S2, thereby causing response

inhibition. Though the sensory gating has previously been extensively evaluated in individuals with schizophrenia (Adler et al., 1985; Hirano et al., 2010), it may additionally prove to be a measure of the rostral efferents. Previous studies confirm that sensory gating can be reliably measured in healthy participants as well as in individuals with various disorders (Campbell et al., 2018; Fuerst et al., 2007; Rentzsch, Jockers-Scherübl, et al., 2008).

There is some evidence to suggest that both the rostral and caudal efferent systems aid in speech perception in noise. Campbell, Nielsen, LaBrec, et al. (2020) reported that individuals with better sensory gating abilities performed better in tasks involving perception of speech in adverse listening situations. Similarly, several studies have shown that individuals with higher magnitude of contralateral inhibition of OAEs had better speech perception in noise scores (Kumar & Vanaja, 2004; Mertes et al., 2019). These studies in combination suggest that the two subsystems of efferent auditory pathway (rostral and caudal) may function together to achieve this goal. However, as we did not assess the speech perception in noise abilities of our participants, the contribution of the descending pathways to such functions cannot be commented on.

Disruptions of these inhibitory mechanisms (both caudal and rostral) have been associated with tinnitus and schizophrenia (Adler et al., 1985; Campbell et al., 2018; Riga et al., 2007; Wahab et al., 2016). In tinnitus, the magnitude of inhibition measured using contralateral suppression of OAEs and sensory gating are reduced (Campbell et al., 2018; Riga et al., 2007). Additionally, Campbell et al. (2018) directly associated the severity of tinnitus with reduced rostral efferent activity. In schizophrenia, Wahab et al. (2016) reported increased inhibition of OAEs and Adler et al. (1985) showed reduced sensory gating. The reduced sensory gating in schizophrenia has been linked positively to increased auditory hallucinations (Smith et al., 2013).

In the present study, we observed a significant positive correlation between P2 sensory gating ratio—presumed to reflect the strength of rostral efferent system—and the magnitude of contralateral inhibition of OAEs—presumed to reflect the strength of caudal (olivocochlear) efferent system. Positive correlation indicates that individuals with higher magnitude of OAE inhibition showed lower sensory gating capacities, and vice versa. We think that the reduced activity at one level in the efferent auditory system is compensated at the other level. The precise nature and consequences of this reciprocal relationship is unclear at present. To the best of our knowledge, this is the first study to investigate the relationship between the two inhibitory effects in the auditory system—one central and other peripheral. It is possible that these two mechanisms work in tandem to balance the overall inhibitory effect on the stimuli. This reciprocal relationship between the two subsystems of the efferent system might aid in adequate inhibition of the undesired stimuli, while facilitating the processing of the desired target. The balanced/differential inhibition mediated by the auditory efferent system may play a crucial role in many auditory processes such as auditory attention, listening in the presence of competing signals, binaural hearing, and auditory plasticity. Therefore, investigating the interactions within the auditory inhibitory networks is crucial in understanding the normal auditory perception and pathophysiology of various auditory related disorders. However, the results of the present study should be generalized with caution and requires further augmentation.

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COVID-19 and the Brain: Infection Mechanisms, Electroencephalographic Findings and Clinical Implications

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Abstract

The term *long-COVID* refers to a wide array of psychological impacts arising from infection with the Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2). The virus has been reported to attack the nervous system directly, with nondirect impacts to organs and systems, such as elevated inflammation, blood pressure, and immune responses also damaging the brain. The electroencephalogram (EEG) has been used to image these insults and provides a valuable tool to guide understanding of infection mechanisms and, consequentially, therapeutic intervention. Due to the high likelihood of neurological complications, neurofeedback and other forms of neuromodulation may be particularly well suited to help long-COVID patients recover. However, clinicians providing neuromodulation interventions should be aware of, and take adequate steps to minimize, risks to themselves and others in providing face-to-face services. This review seeks to provide mental health professionals with an overview of the impacts of COVID-19 upon the nervous system, details current EEG findings, and outlines possibly relevant neurofeedback and neuromodulation interventions.

Keywords: COVID-19; long-COVID; electroencephalogram; neurofeedback; neuromodulation

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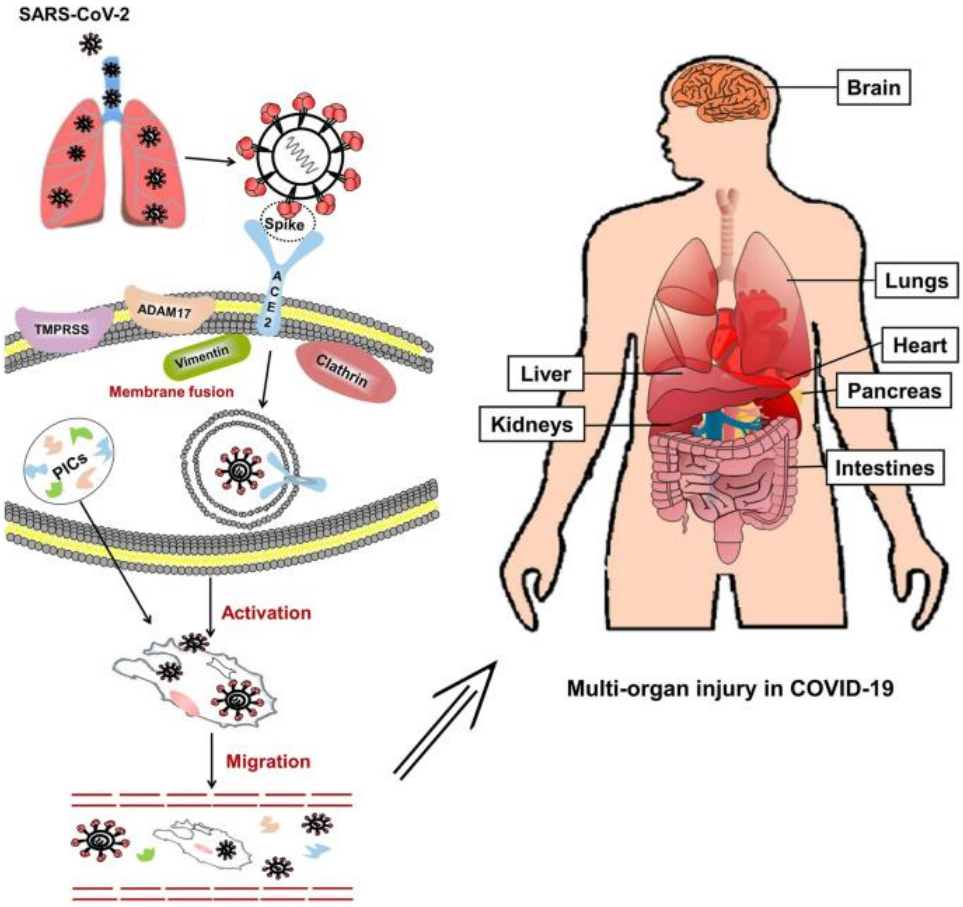
Although COVID-19 was first described as a disease-causing respiratory illness affecting the lungs, veins, and arteries, it is now recognized to have a far wider reach in the human body (Ni et al., 2020). As indicated in Figure 1, the virus can infect and damage multiple organs including the heart, kidneys, liver, intestines, muscles, and skin (Ni et al., 2020). It has also been implicated in disorders of both the brain (Bodro et al., 2021; Satarker & Nampoothiri, 2020) and the mind (Hampshire et al., 2021; Marshall, 2020).

Severe Acute Respiratory Coronavirus 2 (SARS-CoV-2), the virus that causes the Coronavirus disease of 2019 (COVID-19), is increasingly associated with neurological and psychological impacts. Many people affected have reported the loss of smell, headaches, dizziness, anxiety, movement difficulties, inattention, and cognitive difficulties (Hampshire et al., 2021). In a minority of cases, disorientation, confusion (Bodro et al., 2021; Satarker & Nampoothiri, 2020), and psychosis can occur (Marshall, 2020). However, regardless of the severity of psychological symptoms, pathological processes can occur in the brain as a result of COVID-19 infection. The virus can invade the nervous system directly, damaging brain cells (encephalopathy, encephalitis, endotheliitis, and myelitis) and can be implicated in conditions such as epilepsy, stroke, and brain hemorrhage (Bodro et al., 2021). The virus also can cause psychological symptoms by nondirect mechanisms including

Figure 1. *COVID-19 Can Infect Multiple Organs in the Body.*



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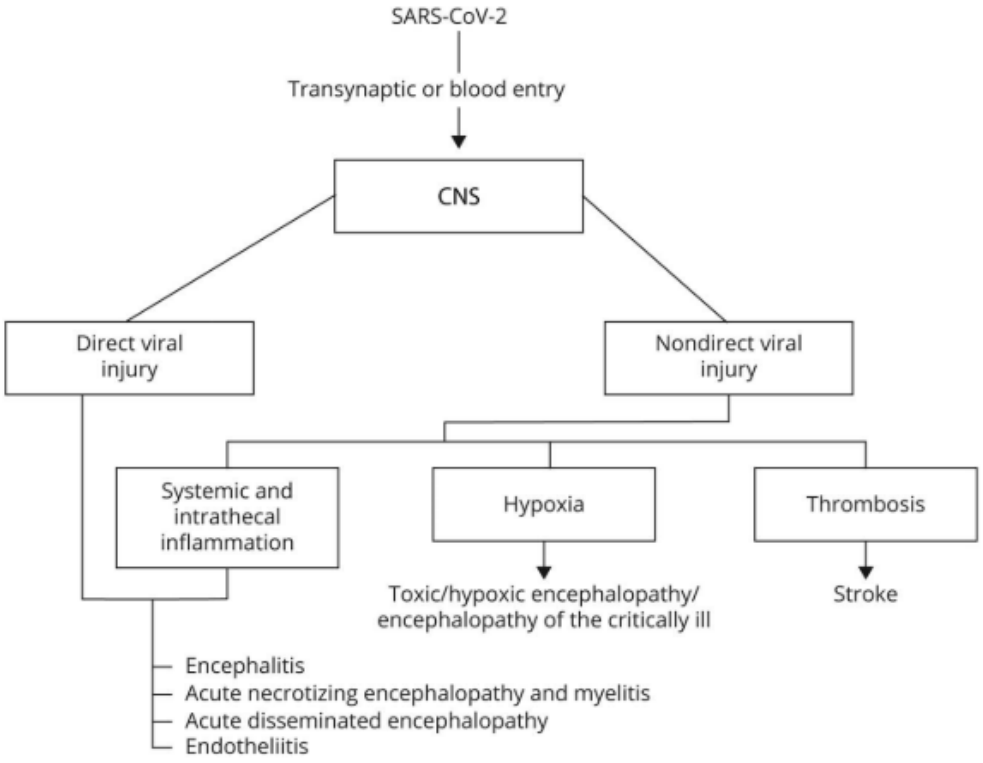
excessive inflammation, insufficient oxygen levels, organ failures, toxicity, and blood clotting produced by the virus (Panariello et al., 2020; Satarker & Nampoothiri, 2020). In part, these neurological impacts contribute to the virus being so deadly, especially the stronger and more infectious Delta variant (Davis et al., 2021; Farinholt et al., 2021; Roy et al., 2021). COVID-19 can infect anyone, but as the pandemic goes on it is becoming increasingly clear there are certain groups more at risk of serious outcomes from contracting it. From the outset, older individuals and those with preexisting health conditions were considered the most vulnerable (Australian Department of Health, 2021). Now it is becoming clear that individuals with preexisting mental health conditions are more likely to be hospitalized or die as a result of being infected by COVID-19 (Ceban et al., 2021). However, for those lucky enough to survive, the legacy of infection can leave lasting physical and mental challenges.

These longstanding mental health challenges are being referred to as “long-COVID,” which has been described as brain fog, memory issues, perceptual fuzziness, fatigue, a lack of clarity, and confusion (Hampshire et al., 2021). Long-COVID has been reported in 84.1% of individuals who were ventilated, 12.2% of those hospitalized, 9.2% of those requiring assistance at home, 5.8% requiring no assistance, and 3.8% without respiratory symptoms (Hampshire et al., 2021). This is approximately 24.4% of individuals who return positive biological test results for COVID-19 (Hampshire et al., 2021). While these figures are from one study, it is reasonable to assume a substantial number of individuals may present with long-COVID given the World Health Organization figures indicate there are 194,080,019 confirmed cases globally as of late July 2021 (World Health Organization, 2021). In previous coronavirus outbreaks, neurological symptoms were seen in 0.04% of those infected with Severe Acute Respiratory Syndrome 1, and 0.2% of those infected

with Middle East Respiratory Syndrome (Marshall, 2020). Using these figures as an estimate and current WHO case estimates, approximately 7,763,200 to 38,816,003 people may have impacts on their nervous systems as a result of COVID-19. If we assume 24.4% of the 194,080,019 global COVID-19 cases will have long-COVID symptoms, this is approximately 46,579,204 individuals. These numbers suggest there will be a substantive mental health burden from the pandemic that mental health professionals will need to understand and find ways of addressing to help impacted individuals.

The question of how COVID-19 impacts the brain and mind is still being investigated, but several possible mechanisms have emerged (Ni et al., 2020; Satarker & Nampoothiri, 2020). As shown in Figure 2, these mechanisms can be broadly classified into two main groupings; direct viral damage, where the virus impacts brain cells itself, and nondirect damage, due to the virus causing blood clots, inflammation, and toxins, and starving the brain of oxygen and nutrients (Bodro et al., 2021). For direct viral damage, how the virus gains entry into the nervous system is related to the locations and types of impairments caused (Satarker & Nampoothiri, 2020). Direct infection of the nervous system can occur through the sensory nerves in the nose responsible for our sense of smell, nerves in the eyes responsible for vision, and other nerves of the face, mouth, and throat that mediate taste and muscle movement (Satarker & Nampoothiri, 2020). Additionally, nerves in the body responsible for controlling the lungs and other organs, notably those of the digestive system can also act as pathways for a viral attack on the brain (Satarker & Nampoothiri, 2020). Via each of these access points, the virus is then able to travel to specific locations in the spine and brain and cause direct impacts at those locations (Satarker & Nampoothiri, 2020). Direct infection of the nervous system can also be a result of infection of the blood. Blood carries the virus to the blood-brain barrier, a protective lining around the brain that usually controls what can enter the brain (Marcus et al., 2003; Whitley, 1990), which can become vulnerable to COVID-19 due to inflammation and infection of cells within this barrier that allow the virus to directly attack the brain (Satarker & Nampoothiri, 2020; Wang et al., 2021).

Figure 2. *Direct and Nondirect Mechanisms of COVID-19's Nervous System Impacts.*



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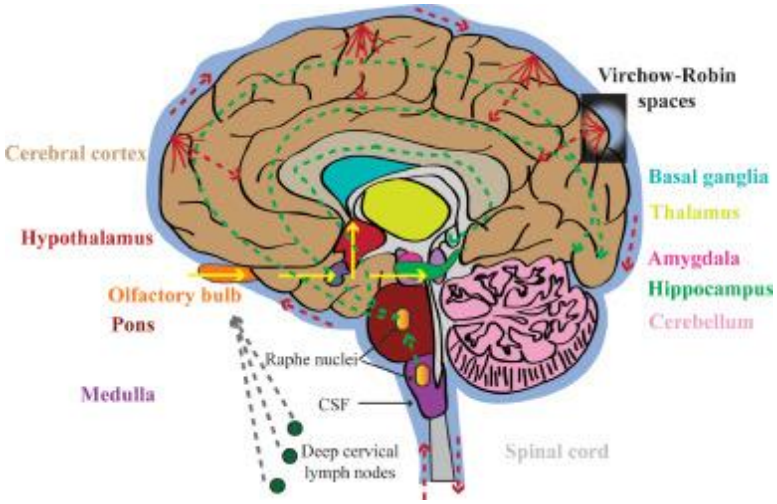
In contrast, nervous system damage via nondirect mechanisms does not involve the virus infecting the nervous system, but rather infecting and damaging organs such as the heart, lungs, and blood vessels (veins and arteries) that support the functioning of the brain, or as a consequence of overactive immune system responses (Bodro et al., 2021). These direct and nondirect mechanisms can occur independently or together which increases the diversity of symptoms between individuals (Bodro et al., 2021; Hampshire et al., 2021; Marshall, 2020; Satarker & Nampoothiri, 2020). With such a wide range of possible mechanisms and impacts of the virus, it is worth understanding the trick COVID-19 uses to enter the body in the first place.

COVID-19 is a trickster; it enters cells in the human body a bit like a thief picking a lock to open a door. In this analogy, the lock-picking tool used by the virus is called a “spike protein” and it can open the cellular lock because it mimics the shape of the real key, a protein produced by the body called Angiotensin-II (Ni et al., 2020). Angiotensin-II is a part of a complex system that regulates blood pressure and immune responses, the Renin-Angiotensin-aldosterone System (RAAS). The role of Angiotensin-II in the RAAS is to increase blood pressure and promote inflammation (Ni et al., 2020). Normally, it would bind to the cellular lock used by COVID-19, an ACE-II (Angiotensin Converting Enzyme 2) receptor, and would be converted into Angiotensin-I, which has the opposite effect, lowering blood pressure and reducing inflammation (Ni et al., 2020). However, when this lock has already been picked by COVID-19, Angiotensin-II isn’t able to use it and remains in circulation in the blood, increasing blood pressure and inflammation (Ni et al., 2020). Also, because Angiotensin-II is not converted into Angiotensin-I there is less of this protein to counterbalance the effects of Angiotensin-II. The consequence is very high blood pressure and inflammation that does damage to the linings of blood vessels, lungs, and tissue damage to organs (Ni et al., 2020). Critically, these ACE-II locks that COVID-19 uses to enter human cells are widely distributed in the body, with high concentrations in the lungs, heart, vasculature, liver, gastrointestinal tract, and kidneys (Ni et al., 2020). These receptors are also found in cells in the blood-brain barrier (Wang et al., 2021), sensory nerves of the nose and eyes, and in certain brain areas, such as the brainstem and hippocampus (Panariello et al., 2020; Zubair et al., 2020), that are respectively responsible for the control of breathing (Nattie & Li, 2012; Porges, 1995) and memory formation (DuBrow & Davachi, 2016; Fanselow & Dong, 2010). Because of the wide distribution of ACE-II receptors and the number of different organs they are associated with, the mechanisms by which COVID-19 impacts the nervous system (described in the paragraph before), are fundamentally important in identifying the causes of long-COVID and providing the appropriate interventions to help repair the associated damage.

The direct transmission of COVID-19 to the brain occurs through nerves connected to the eyes, nose, mouth, throat, and lungs (Cheng et al., 2020; Panariello et al., 2020); see Figure 3.

Figure 3. *Brain Regions Commonly Impacted by COVID-19.*



Note. Image reproduced from Cheng et al. (2020, CC BY-NC-ND 4.0).

Direct transmission results in the virus gaining access to brainstem centers associated with the control of breathing, heart rate, and areas involved in sensory perception and movement (Cheng et al., 2020; Panariello et al., 2020). Impacts to these regions may be associated with classic COVID-19 symptoms such as dry cough, difficulties breathing, and more neurological symptoms such as the loss of taste, smell, and vision issues (Cheng et al., 2020; Panariello et al., 2020). However, some long-COVID symptoms may also be linked to direct viral infection mechanisms due to COVID-19's impacts upon neurotransmitters, which are molecules used by the brain to send signals between cells. Infection of nerves responsible for the sense of smell allows the virus to travel to the hypothalamus (Nampoothiri et al., 2020), a region responsible for coordinating many bodily functions such as regulating body temperature (Dampney, 2016; Lechan & Toni, 2016). Another brain region that can be impacted by direct transmission of COVID-19 is called the striatum (Cheng et al., 2020; Panariello et al., 2020), a structure that is involved in learning and movement (Nicola, 2007; Peters et al., 2016). In both the hippocampus and striatum, the presence of Angiotensin-I increases the concentration of dopamine and GABA, while decreasing norepinephrine concentrations (Panariello et al., 2020). These neurotransmitters are critical in a range of psychological processes. Dopamine is critical for learning and movement, with insufficient levels associated with attention deficit disorder (Arns et al., 2013; Arns et al., 2014) and Parkinson's disease (Benz et al., 2014; Przedborski, 2017). GABA is the main inhibitory or "OFF" signal in the brain and low levels are associated with anxiety disorders (Agorastos et al., 2015; Wilhelm et al., 2017) and epilepsy (Taubøll et al., 2015). Norepinephrine is a stimulating neurotransmitter, with low levels associated with depression (Chrousos, 2009) and alterations in consciousness (Berridge et al., 2012). There are also ACE-II receptors in the substantia nigra (Satarker & Nampoothiri, 2020), another structure closely associated with dopamine-related functions (Schultz, 2000). As described before, by COVID-19 binding to the ACE-II receptor, there is less Angiotensin-I produced, which in the brain may be linked to lower levels of dopamine, GABA and increased norepinephrine levels (Panariello et al., 2020). These neurotransmitter changes may relate to some of the psychological changes associated with long COVID (Bodro et al., 2021; Hampshire et al., 2021; Marshall, 2020; Satarker & Nampoothiri, 2020). Consequentially, the presence of neurological symptoms, such as loss of smell or difficulties breathing may suggest COVID-19 infection of the nervous system via a direct mechanism, which may be associated with changes to neurotransmitter levels. This information could help mental health clinicians guide their therapeutic interventions.

The other direct mechanism allowing COVID-19 to access the brain is through transmission in the blood to the blood-brain barrier (Satarker & Nampoothiri, 2020). While the blood-brain barrier usually protects the brain from infection and toxins, in the case of COVID-19, the presence of ACE-II receptors in special cells called pericytes within this barrier means it becomes susceptible to infection by the virus (Wang et al., 2021). Infection of pericytes acts as a stepping-stone for COVID-19 to infect brain cells connected to pericytes such as astrocytes and neurons (Wang et al., 2021). Additionally, pericyte infection makes the blood-brain barrier leaky, with microbleeds allowing COVID-19 to slip through gaps in the barrier into the brain directly (Wang et al., 2021). Structures like the ventricles and temporal lobes are particularly affected by these microbleeds (Bodro et al., 2021). Subsequent transmission through the ventricles allows COVID-19 to reach the frontal lobes and posterior cingulate cortex (Panariello et al., 2020), which are core brain structures involved in executive and introspective processes and are implicated in most psychological disturbances (Menon, 2011). In addition, COVID-19 can damage temporal lobe structures such as the hippocampus (Bodro et al., 2021), which is generally linked to depression, memory issues, and cognitive decline (Panariello et al., 2020). The combined damage to the blood-brain barrier, frontal and temporal lobes leads to changes in the ability of brain signals to be sent around the brain, which could be associated with disorientation, confusion (Bodro et al., 2021; Satarker & Nampoothiri, 2020), and psychosis (Marshall, 2020) seen in COVID-19 patients. Making matters worse, COVID-19 causes microbleeds in the temporal lobes, which are associated with epilepsy (Bodro et al., 2021), headaches (Charles & Baca, 2013), and anger symptoms (Sugahara, 2004). The takeaway is when individuals experience symptoms like headache, confusion, and psychosis it may suggest direct impacts to the nervous system as a result of damage to the blood-brain barrier. Moreover, these symptoms are cause for great concern as they are thought to be associated with more severe neurological presentations, such as encephalopathy, encephalitis, endotheliitis, myelitis, and cerebrovascular disease (Bodro et al., 2021; Satarker & Nampoothiri, 2020). However, symptoms such as headache, confusion, and psychosis and

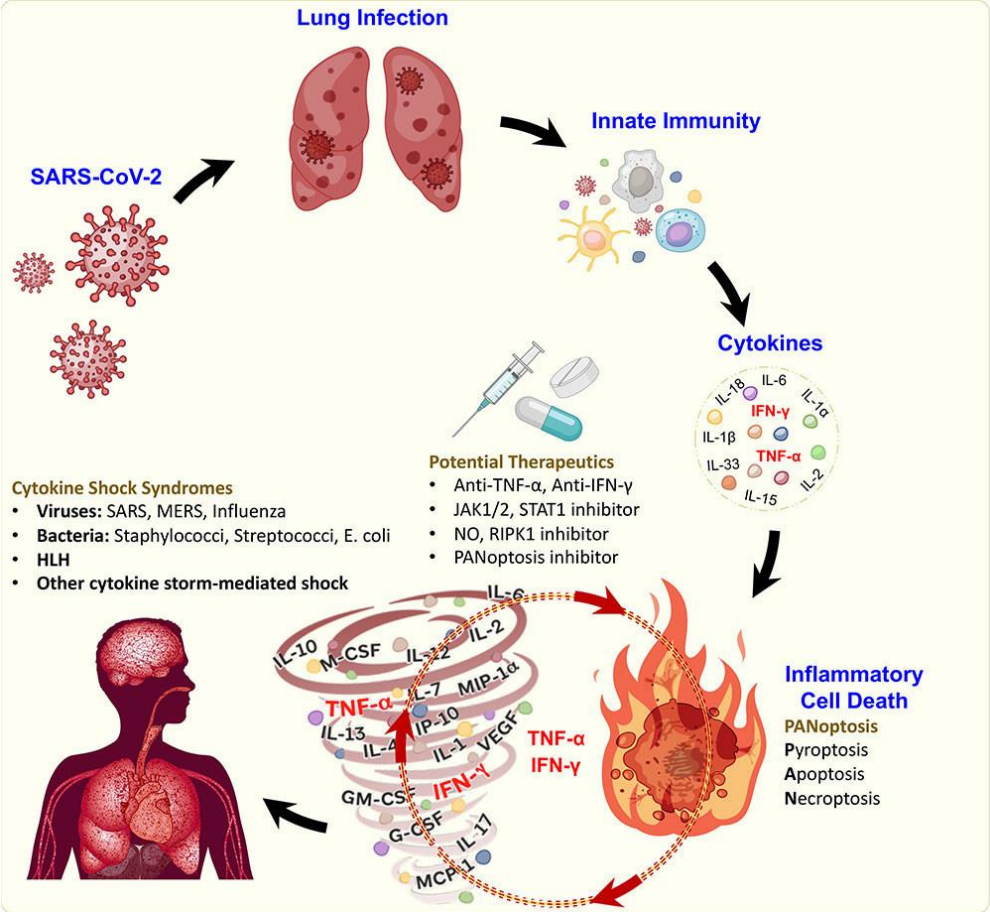
damage to the blood-brain barrier may be a result of nondirect mechanisms, including increased inflammation (Wang et al., 2021) and increased Angiotensin-II concentrations (Ni et al., 2020). This points to the importance of considering the functioning of the whole body when addressing mental health issues, which may require psychological interventions for long-COVID to be combined with health interventions to heal nondirect mechanisms impacting the nervous system. The main nondirect mechanisms through which COVID-19 impacts the nervous system are 1) by creating blood clots, which cause strokes, 2) impairing breathing, heart rate, and oxygen supply to the brain, and 3) causing organ failure, which leads to imbalances in essential systems such as those that regulate fluid, salt levels, and clear toxins (Satarker & Nampoothiri, 2020). Each of these areas should be understood in principle and deserve individual attention to understand their effects upon the brain.

In the body, COVID-19 damages blood vessels and organs, with the additional insult of increased Angiotensin-II levels promoting the formation of clots (Ni et al., 2020). Studies have estimated blood clots occur in 8% to 15% of individuals hospitalized due to COVID-19, which causes stroke in approximately 2.5% of these individuals (Bodro et al., 2021). Disturbingly, stroke is thought to be more frequent in COVID-19 patients under 50 years of age and is associated with a high probability of severe cognitive impairment or death (Bodro et al., 2021). Approximately 30–70% of intensive care patients develop blood clots in the veins and lungs, with one in four developing a clot in the heart that can cause a heart attack (Klok et al., 2020; Llitjos et al., 2020). COVID-19 can also infect heart cells directly, which may increase heart rates or cause heart failure (Ni et al., 2020). Elevated heart rates impair the supply of blood to the brain and are closely linked to reports of dizziness, while heart failure is associated with coma and death (Abdo et al., 2021; Klok et al., 2020). In combination with the damage to the heart and complications caused by blood clots, the linings of the lungs are also significantly damaged by the virus, which impairs their ability to function (Ni et al., 2020). The combined effects of all of these impacts can starve the brain of oxygen (Bodro et al., 2021). Low brain oxygen levels have been associated with symptoms of delirium, confusion, and psychosis, and have a high association with death in the acute illness and long-term cognitive dysfunction following the acute stage (Bodro et al., 2021). This may suggest breathing exercises and interventions to improve oxygen levels could be important in addressing long-COVID.

Organ failure is another nondirect mechanism by which COVID-19 can impact the brain (Satarker & Nampoothiri, 2020). Beyond the heart, lungs, veins, and arteries, COVID-19 can infect the digestive system, attacking organs such as the kidneys, pancreas, and small and large intestines (Ni et al., 2020). Approximately 6.7% of COVID-19 patients experience kidney damage (Ni et al., 2020) that impairs their ability to regulate salt and fluid levels and might be linked to some impairments of the nervous system (Cassia et al., 2021). In the pancreas, the virus can promote the development of insulin-dependent acute diabetes (Ni et al., 2020) and in some rare cases has been linked to widespread sensory neuropathy, where numbness to temperature, pain, vibration, and hot and cold is developed (Odriozola et al., 2020). Infection of the intestines (Ni et al., 2020) and gut microflora can also impair the absorption of molecules required to produce serotonin (Panariello et al., 2020). Consequentially, lower serotonin levels may reduce the ability of brain structures like the frontal lobes and hippocampus to function, which may be relevant for long-COVID symptoms (Panariello et al., 2020). This may suggest repairing gut health and gut microflora may be relevant in addressing long-COVID symptoms.

Through direct and nondirect mechanisms, COVID-19 promotes excessive immune activity, the so-called “cytokine storm,” illustrated in Figure 4, which has been implicated in both acute and long-COVID symptoms (Bodro et al., 2021; Karki et al., 2020). This “storm” damages cells in the brain and organs (Bodro et al., 2021; Karki et al., 2020). During acute infection, cytokine storms have been implicated in brain cell disorders such as encephalitis, encephalopathy, endotheliitis, and myelitis (Bodro et al., 2021; Karki et al., 2020), and damage to the blood-brain barrier and organs (Ni et al., 2020). When the onset of psychological symptoms is delayed from the immediate period of infection, these symptoms are usually attributed to auto-immune related processes driven by cytokine storms (Satarker & Nampoothiri, 2020). This is the case for the development of Guillain-Barré (Zubair et al., 2020) and Miller-Fisher syndrome (Panariello et al., 2020), which involve COVID-19 induced auto-immune damage to nerves that control movement producing paralysis symptoms like multiple sclerosis. Due to the damage to the brain, nerves, and organs, these cytokine storms are a critical factor in the generation of many of the psychological symptoms associated with acute infection and long-COVID, and interventions to reduce inflammation should be considered.

Figure 4. *Cytokine Storm and Inflammatory Cell Death.*



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Depending on specific individual vulnerabilities and direct and nondirect mechanisms of COVID-19 disease progression, a myriad of nervous system impacts and psychological symptoms can emerge. In the brain, these impacts on the nervous system and the associated psychological symptoms correspond to changes in “brain waves” or the patterns of electrical communication used by the brain that can be measured through recording an electroencephalogram (EEG). A review of EEG changes observed in COVID-19 patients estimated that abnormal background activity was present in 96.1% of patients, and generalized slowing was present in 92.3% of cases (Kubota et al., 2021). Epileptiform discharges that were not diagnostic of epilepsy were seen in 22.4% of individuals with no history of epilepsy or seizures, and in 59.5% of individuals with these conditions before they contracted COVID-19 (Kubota et al., 2021). Clinically relevant seizures, epileptic events that involve alterations in consciousness and uncontrollable movements, were seen in 2.05% of patients, while status epilepticus, a state where individuals are unresponsive due to epileptic activity, was seen in 0.80% of patients (Kubota et al., 2021). Other common EEG findings included changes in frontal lobe activity and irregular patterns of focal slowing found on both sides, and one side of the brain (Kopańska et al., 2021). The speed and shape of these patterns and their locations in the brain are likely to relate to the mechanisms by which COVID-19 has impacted the nervous system, which could hold clues to treating long-COVID symptoms.

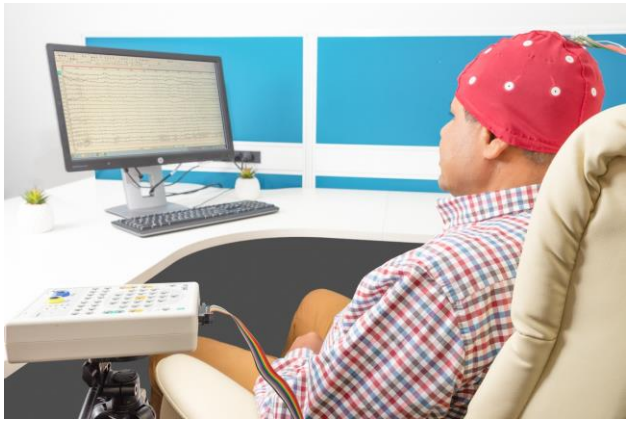
EEG patterns observed in the frontal lobes of COVID-19 patients included continuous and intermittent slow waves, which are thought to be related to insufficient oxygen; persistent theta activity, which is thought to relate to numerous microhemorrhage-related (blood-brain barrier damage) insults to brain cells that connect the frontal lobes (Kopańska et al., 2021); and frontal

sharp waves and sporadic epileptiform discharges that are associated with direct infection of the frontal lobes (via the sensory nerves for smell) and possibly also are involved with diminished organ functioning (Galanopoulou et al., 2020). Frontal patterns were also observed that developed a widespread sharp down-up-down pattern, suggesting organ failure related toxicity (Flamand et al., 2020). An irregular, unprecedented slow pattern, with a slight dominance to the right side of the brain, was also described in very severe COVID-19 patients with multiple organ failure, low brain oxygen levels, and possibly direct viral infection of the brain (Vellieux et al., 2020). Other patterns, commonly associated with encephalopathies, such as diffuse slowing and generalized or focal rhythmic slow content and epileptic activity were observed frequently (Kopańska et al., 2021; Kubota et al., 2021). In critical cases, when individuals were unresponsive or comatose, the EEG could have large bursts of activity followed by long periods of little activity at all (burst-suppression), or persistent epileptic activity (status epilepticus), or discontinuous suppression patterns (Kubota et al., 2021).

With the myriad of possible mechanisms by which COVID-19 can impact the nervous system, it is still too early to draw definitive associations between reported cases, EEG patterns, and causal mechanisms. Speculatively, there may be some association between frontal lobe EEG findings and direct viral infection mechanisms, most likely through nerves mediating smell and vision, in addition to the damage to the blood-brain barrier and low brain-oxygen levels. The presence of focal slowing or epileptiform activity to the sides of the head also suggests direct infection via the nerves mediating smell that eventually reach the temporal lobes close to the hippocampus, which is particularly prone to epilepsy due to synchronous firing properties of dendritically dense hippocampal pyramidal cell networks (Isokawa-Akesson et al., 1989; Nakahara et al., 2018), excessive neuroplasticity (Bartsch & Wulff, 2015), and the effects of stress (Dunkley et al., 2014; Gunn & Baram, 2017). The slow content in the temporal lobes may also be related to impairments in blood supply, such as blood clots, which may be more likely to show up in these locations. Slowing of the background activity and diffuse slowing suggests viral transmission to the brainstem, with changes in neurotransmitter levels possibly implicated. Although, brain cells that use these neurotransmitters, also target the frontal lobes, and may also be involved in the EEG patterns observed there. When accessing an individual experiencing acute or long-COVID symptoms it is necessary to consider their specific symptoms to understand possible mechanisms by which the nervous system has been impacted and to connect the resulting EEG patterns and psychological difficulties. Once these considerations have been made, the question of how to assist these individuals recover then arises. During acute and critical stages of the disease medical care, with antivirals such as Remdesivir or steroids such as Dexamethasone, supply of oxygen and use of anticonvulsants might be indicated depending on the individual (Zubair et al., 2020). However, addressing the psychological impairments of long-COVID often falls to psychologists and other health professionals outside emergency settings. The question then is “Are psychologists and other health services ready and able to provide these services in the middle of a pandemic?”

The emergence of new SARS-CoV-2 variants, such as the highly infectious Delta variant (Nunes-Vaz & Macintyre, 2021), poses existential questions about the future of face-to-face mental health service provision (Balcombe & De Leo, 2020). For many clinicians, services, and government agencies the immediate response involved a shift to greater use of telehealth services. At the peak of Australia’s first wave in April 2020, about 50% of mental health Medicare Benefits Schedule (MBS) subsidized were provided remotely, which gradually declined with COVID-19 case numbers to 20% of services being provided remotely in the equivalent period in 2021 (Australian Institute of Health and Welfare, 2021). Similar patterns were also observed for online mental health platforms (Australian Institute of Health and Welfare, 2021). While remote services can maintain support and assist many individuals with mental health difficulties, such as individuals that have been traumatized by the stress associated with the disease (Rajkumar, 2020) or the stress of self-isolation (Xia & Li, 2018), they are unlikely to be able to address the neurologically-based psychological impacts of COVID-19, including long-COVID. One potential intervention that may be able to address some of these issues is called neurofeedback. Neurofeedback, as shown in Figure 5, involves presenting a person’s EEG brain waves back to them in real time, allowing them to learn how to change these patterns. For neurofeedback to be effective, usually two face-to-face sessions a week are required. Given the higher levels of contact with clients associated and technology used in neurofeedback poses a greater infection risk (Hagedorn, 2014) it is critical to understand these risks and the behaviors required to reduce such risks.

Figure 5. *Image of Neurofeedback.*



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In enclosed spaces, normal to loud speech results in thousands of airborne fluid droplets per second, which remain airborne for 8 to 14 minutes depending upon their size, acting as a transmission mechanism for COVID-19 (Stadnytskyi et al., 2020). The wearing of a face mask prevents the majority of these airborne particles from entering the upper airways and lungs reducing airborne transmission risk (Xi et al., 2020). However, the mask itself, particularly at any folds, show increased concentrations of airborne material, which poses a possible transmission risk if hands are contaminated by touching the mask (Xi et al., 2020). In turn, this risk and the general risk of viral contamination from touching surfaces on which the virus is present can be minimized by hand washing and sterilization with 70–90% ethanol or 2-propanol (Noorimotlagh et al., 2021). Similarly, cleaning surfaces and equipment with sterilizing or disinfecting agents is also effective in reducing transmission risk (Noorimotlagh et al., 2021). Arguably, the most important behavior to reduce risk is being vaccinated against the virus. This is due to the reduced risk of infection or serious illness or death to yourself and the reduced risk of transmission to other individuals that vaccination against COVID-19 provides (Henry et al., 2021; Olliaro et al., 2021). Vaccination is still strongly recommended despite indications of reduced vaccine effectiveness against the Delta variant (Davis et al., 2021) and rare instances of infection despite vaccination (Farinholt et al., 2021). With the likely emergence of new variants in the future, booster vaccines are likely to be required (Rubin, 2021). Consideration of these risks and the implementation of risk minimization behaviors are required for a safe return to face-to-face service provision.

Neurofeedback and other forms of neuromodulation have been used to address many neurological and psychological issues that have similar origins, physiology, and patterns of brain activity to those occurring as a result of COVID-19. For instance, the origin of epilepsy is often linked to the activity of Angiotensin-II (Krasniqi & Daci, 2019), with the development of epileptic-like activity is thought to be one of the early EEG markers of COVID-19's impacts upon the nervous system (Bodro et al., 2021). A paper by Sterman and Friar in 1972 titled "Suppression of seizures in an epileptic following sensorimotor EEG feedback training" was the first account of neurofeedback being used clinically (Egner & Sterman, 2006; Sterman, 2010; Sterman & Egner, 2006). The "sensorimotor EEG feedback training" used by Sterman and Friar involved rewarding brain waves that occurred between 12 and 15 times per second near the crown of the head, with the reward being prevented whenever slower brain waves occurring between 4 to 8 times per second became too large (Egner & Sterman, 2006; Sterman, 2010; Sterman & Egner, 2006). This training was repeated two times a week over 2 years and resulted in the complete absence of seizures and greatly improved well-being (Egner & Sterman, 2006; Sterman, 2010; Sterman & Egner, 2006). Importantly, this account of seizure suppression worked when numerous medications had failed to achieve this outcome over 7 years before commencing neurofeedback (Yucha & Montgomery, 2008). In the subsequent 49 years since Sterman and Friar's pioneering work, numerous well-controlled research studies have replicated and supported this finding, with approximately 82% of individuals reporting seizure reductions greater than 50% (Sterman, 2010). Another review indicated 79% of individuals treated with neurofeedback had significant reductions in seizure size for a wide variety of epilepsy diagnoses, with these effects largely occurring in individuals that had not responded to antiepileptic medications (Tan et al., 2009). These improvements were seen from interventions as short as 3 weeks (Tan et al., 2009) and have also been documented in children and adolescents (Morales-Quezada et al., 2019) and the elderly (Reichert et al., 2016). Neurofeedback's ability to reduce epilepsy is one of the most well supported, understood, and efficacious applications of neurofeedback (Yucha & Montgomery, 2008). Importantly, the ability of neurofeedback to reduce epilepsy has been associated with increased GABA activity in the striatum and thalamus (Egner &

Sterman, 2006). As COVID-19, though its impact on Angiotensin-II levels, is thought to decrease GABA activity in these locations (Panariello et al., 2020), it is plausible that sensorimotor neurofeedback at central regions may address direct mechanisms by which COVID-19 impacts the nervous system. However, this is yet to be researched and no definitive recommendation can be made yet.

Another neurofeedback pioneer, Margaret Ayers, worked with stroke and closed head injury clients; her approach involved training one side of the head and then the other, focusing on the temporal lobes and locations towards the front and crown of the head.[1] Depending on the injury location, she rewarded brain rhythms between 12 and 15, or 15 and 18 times a second and prevented rewards for brain rhythms between 4 and 7 cycles per second (Evans, 2007; Hammond, 2005), which when reduced are associated with improved blood supply and stroke recovery (Ros et al., 2014). In a separate study, Ayres helped 250 individuals with closed head injuries to return to their preinjury levels of functioning by rewarding alpha activity (8–12 cycles per second). These stroke survivors also reported reductions in mood swings, anger outbursts, anxiety attacks, headaches, vertigo, light and sound sensitivity, as well as increased energy levels, concentration, memory, and cognitive performance as a result of the neurofeedback (Budzynski et al., 2009; Duff, 2016; Evans, 2007). Subsequent research has supported the premise of training both sides of the brain in stroke rehabilitation as it is thought compensatory processes in the opposite brain hemisphere lead to damaging overexcitation, which can be reduced with neurofeedback (Sitaram et al., 2017). These changes to the opposite side of the brain from the injury are associated with changes in functional connectivity and the synchrony of brain waves (Thatcher et al., 2020). In a series of case studies, training these connectivity patterns to resemble patterns observed in a group of healthy individuals led to clinical improvements (Koberda, 2015; Koberda & Stodolska-Koberda, 2014; Thatcher et al., 2020). Similarly, the reward of synchronous brain activity around 8 to 12 repetitions per second (alpha), between central brain regions involved in motor functions and the rest of the brain, has been linked to improved recovery and performance following stroke (Mottaz et al., 2015). This effect might be enhanced by coupling the audiovisual neurofeedback reward with simultaneous stimulation (Small et al., 2013), muscle biofeedback (Yucha & Montgomery, 2008), or simply imagining movement (Pichiorri et al., 2015) of the body areas with impaired movement. Importantly, rewarding either alpha activity or faster frequencies in stroke survivors is associated with improvements in verbal short- and long-term working memory; with alpha training specifically improving working memory, and training faster activity specifically improving short-term visual and spatial working memory (Kober et al., 2015), and visual acuity (Cho et al., 2015). These improvements were seen despite a wide variety of brain regions being impacted (Kober et al., 2015). Given the substantial overlap in brain regions impacted by COVID-19 related stroke (Bodro et al., 2021) and these studies, the improvements in cognitive performance are promising for long-COVID rehabilitation. However, it is unclear if improved mobility seen in the studies pairing neurofeedback and movement (Mottaz et al., 2015; Pichiorri et al., 2015; Small et al., 2013) occurred independently of the physiotherapy that was also provided (Sitaram et al., 2017). This uncertainty suggests a similar integrated rehabilitation program may be required for COVID-19 stroke survivors to regain function. Indeed, other forms of neuromodulation such as invasive stimulation (Elbaum & Benson, 2007; Moore et al., 2014) and noninvasive brain stimulation with electromagnets (Beck et al., 2017) or low-intensity lasers (Hamblin, 2016; Naeser et al., 2010) has improved motor control and cognitive functioning in stroke survivors and may be applicable in COVID-19 stroke rehabilitation. Although, at this point, no research has been undertaken to gauge the validity of these interventions in COVID-19 patients.

In the most severe COVID-19 cases, diffuse slowing and impairments in consciousness or coma may be seen (Abdo et al., 2021). While disorders of consciousness are not common presentations for neurofeedback, there are several case studies of note. Ayers, using similar methodologies as her work with stroke survivors, used neurofeedback to bring two individuals out of a level 2 coma (Ayers, 1995). Another study used neurofeedback to bring a five-year-old out of a chemotherapy-induced coma, with associated damage due to low oxygen levels in the brain (Fink et al., 2012). In two patients with unresponsive wakefulness, daily neurofeedback rewarding the ratio of fast to slow content over 3 weeks saw two of these patients increase the portion of fast brain activity and regain responsiveness and some functionality; there was no change in the third patient (Keller & Garbacenkaite, 2015). Several other case studies involving brain damage to deep and cortical

[1]Ayer's placement sites included T3-C3 & T4-C4, or C1-C5, or F8/T4.

structures that produced focal or diffuse slowing, which was associated with disorders of consciousness, have been remediated quite successfully with neurofeedback (Bearden et al., 2003; Hammond, 2011). Typically, these studies involve intensive interventions and it has been shown that the initial load of symptoms is correlated with the number of sessions required and the derived functional improvements (Bounias et al., 2002). The general prognostic recommendation for neurofeedback with diffuse slow patterns is to suppress slower activity, particularly at frontal locations, and to reward faster activity for increased effects (Johnstone et al., 2005). However, when a combination of slow and fast activity is present, it is likely the faster activity is compensatory and rewarding faster activity may paradoxically worsen symptoms (Ayers et al., 2000). In these instances, the best approach is to focus on the reduction of slow content with neurofeedback (Ayers et al., 2000). It is unknown if this heuristic and style of neurofeedback will remain true in COVID-19 rehabilitation and further evidence will be required.

In less severe COVID-19 cases there may still be an increase of slower brain waves in the frontal lobes (Bodro et al., 2021; Kubota et al., 2021). This may be a result of direct viral transmission to the frontal lobe along nerve fibers conducting the sensation of smell (Bodro et al., 2021; Hammond, 2007), or may be linked to low oxygen levels (Keller & Garbacenkaite, 2015) due to COVID-19's nondirect impacts upon the nervous system (Bodro et al., 2021; Ni et al., 2020). In COVID-19 patients who have lost their sense of smell, the frontal slowing pattern may be of particular relevance as similar patterns have been observed in individuals who have injured their olfactory nerves (Hammond, 2007). In two individuals with this presentation, neurofeedback to increase faster activity in the frontal lobes led to a reduction of slow content and the partial return of the sense of smell within 15 sessions and its full return in 22 sessions (Hammond, 2007). Beyond repairing damage to the sense of smell, frontal slowing may also be of relevance to the cognitive issues experienced by individuals with long-COVID (Hampshire et al., 2021). Frontal slow content is typically associated with cognitive difficulties at the beginning and later stages of life and is linked to the diagnoses of attention-deficit/hyperactivity disorder (Arns et al., 2013, 2014) and various forms of cognitive decline and dementia (Koberda, 2014; Saltmarche et al., 2017). In both instances, the type of neurofeedback used shares the common goal of reducing slow brain waves and increasing faster brain activity (Trammell et al., 2017; Wang & Hsieh, 2013), so-called "brain brightening" (Budzynski et al., 2009). Several forms of neurofeedback have been used for "brain brightening," including training the synchronicity of brain waves (Koberda, 2014; Simkin et al., 2014), rewarding particular frequency bands, typically faster brain waves (Arns et al., 2013, 2014; Wang & Hsieh, 2013), or the background rhythmicity of the brain (Arns et al., 2011; Sherlin et al., 2010) and adjusting the underlying base rhythmicity of the brain (Gevensleben et al., 2014; Kotchoubey et al., 2001; Strehl et al., 2017). In the context of COVID-19, its impacts upon dopamine levels in the brainstem (Schultz, 2000) and striatum (Panariello et al., 2020), areas that influence frontal lobe activity, may be linked to the cognitive issues experienced by individuals with long-COVID cognitive symptoms (Hampshire et al., 2021; Marshall, 2020) as these regions and neurotransmitters are also abnormal in attention-deficit/hyperactivity disorder (Arns et al., 2013, 2014) and cognitive decline (Koch et al., 2020; De Marco & Venneri, 2018). Indeed, it has been argued that damage to key brain regions such as the thalamus and striatum are the common origin for cognitive impairments in attention deficit disorders, traumatic brain injury, Down syndrome, autism, and stroke (Simkin et al., 2014). Consequentially, many of the neurofeedback protocols used in attention-deficit/hyperactivity disorder (Arns et al., 2013, 2014) can be applied in cases where the underlying processes are thought to be the same (Simkin et al., 2014). As these areas are impacted by COVID-19 (Bodro et al., 2021; Zubair et al., 2020), it is plausible, but not yet tested, that neurofeedback may also improve cognitive function in individuals experiencing long-COVID.

Beyond neurofeedback, a range of other neuromodulation interventions may be of relevance in addressing the neurological impacts of COVID-19. These include heart rate variability biofeedback, low-level laser therapy, audiovisual entrainment, and forms of relaxation interventions.

The impacts to veins and arteries caused by COVID-19 share some similarities to coronary artery disease. Heart rate variability biofeedback is a similar practice to neurofeedback, which focuses on the heart instead of the brain (Lehrer & Gevirtz, 2014; Shaffer et al., 2014) and may help address heart-brain physiology and associated pathologies such as hypertension, heart attack, and vascular issues caused by COVID-19. In outpatients who had been hospitalized due to an irregular heartbeat (ventricular fibrillation), this intervention lowered the risk of subsequent heart disorders and death by

86% (Yucha & Montgomery, 2008). Additionally, heart rate variability biofeedback has been shown to lower blood pressure and hypertension (Gilbert, 2003; Schroeder et al., 2003). These findings suggest heart rate variability biofeedback could be used to help offset COVID-19-related increases in blood pressure and heart rate (Ni et al., 2020). This is important for the nervous system functioning as one of the main impacts of high blood pressure, and heart rate is the reduced supply of blood and oxygen to the temporal lobes (Inui et al., 2001; Motomura et al., 2003). As mentioned before, this is associated with headaches and irritability (Bolay & Moskowitz, 2005; Charles & Baca, 2013; Drenckhahn et al., 2012; Sugahara, 2004). Prior research indicates biofeedback is efficacious and superior to many medications in reducing hypertension and headaches (Yucha & Montgomery, 2008), having been supported by the American Academy of Neurology for over 20 years to address these issues (Silberstein, 2000). By improving blood and oxygen supply to the brain, heart rate variability biofeedback can also improve connectivity patterns in the brain (Chang et al., 2013; Kumral et al., 2019), emotion regulation (Mather & Thayer, 2018), cognitive functioning (Chang et al., 2019; Liang et al., 2013) and overall mental health and resilience (Perna et al., 2019). Heart rate variability biofeedback has also been used successfully with a range of psychological disorders such as depression, anxiety, posttraumatic stress disorder, and substance use disorder (Moss & Shaffer, 2017). The mechanism underlying this wide range of applications and high effectiveness stems from the association between the control of breathing and the regulation of numerous other processes within the body (Cutsforth-Gregory & Benarroch, 2017; Shaffer & Venner, 2013; Smith et al., 2017; Thayer & Lane, 2000). In the context of COVID-19, this is highly relevant, as many of the brainstem regions damaged by the virus (Zubair et al., 2020) are activated by heart rate variability biofeedback and associated breathing practices (Jürgens, 2002; Kromenacker et al., 2018; Larsen et al., 2010; Vaschillo et al., 2002; Zelano et al., 2016), which may suggest this intervention could also help reduce the excitability of nerves targeting organs in the body (Stute et al., 2021), regulate body temperature (González-Alonso, 2012; Ramirez et al., 2019; Simon, 1974; Thayer et al., 1997), fluid and salt levels (Frank & Landgraf, 2008; Gilbert, 2003; Ranpuria et al., 2008) and angiotensin levels (Ardell, 2001; Persson & Kirchheim, 1991; Schroeder et al., 2003), which are disrupted by the virus. Moreover, it has been shown to limit inflammation (Huston & Tracey, 2015; Tracey, 2002) and improve organ functioning (Park & Thayer, 2014; Smith et al., 2017; Thayer et al., 2010). In particular, this may be of relevance to gastrointestinal symptoms caused by COVID-19 as bidirectional connections between the brain, heart, and intestines are thought to exist (Singh et al., 2014; Sundman et al., 2017), with gut microflora playing an important role in their functioning (Kazemian et al., 2020; Mayer et al., 2016; Petra et al., 2015; Tang et al., 2017). Together these findings may suggest heart rate variability biofeedback is particularly well suited to limiting direct and nondirect mechanisms by which COVID-19 attacks the nervous system and may offer a potential remedial intervention. Unfortunately, there seems to have been no research into the use of this promising intervention with COVID-19 related impacts on the body and mind.

A substantial body of research indicates that low-level laser therapy (also known as cold laser therapy or photobiomodulation), which typically uses near-infrared light frequencies to stimulate the brain (De La Torre, 2017) could help reduce inflammation, promote the repair of brain cells, and increase blood flow in the brain (Hamblin, 2016, 2019; Naeser et al., 2018). This intervention has been used to heal brain tissues damaged by low oxygen levels (Gonzalez-Lima et al., 2014; Moreira et al., 2011), traumatic brain injury (Naeser et al., 2014, 2016, 2018), Alzheimer's disease (Hamblin, 2019; Purushothuman et al., 2014), depression (Cassano et al., 2016), posttraumatic stress disorder (Naeser et al., 2014) and has been used for cognitive enhancement (De La Torre, 2017; Gonzalez-Lima & Barrett, 2014; Gonzalez-Lima et al., 2014). As many of the reported effects of this intervention target processes that are impacted by COVID-19, such as inflammation and blood flow (Ni et al., 2020; Panariello et al., 2020; Satarker & Nampoothiri, 2020), the wide range of disorders low-level-light therapy has been used for, and the reported cognitive enhancements associated with its use suggest it may be a valuable tool to address acute and long COVID. It is also worthwhile noting research involving audiovisual entrainment, where lights and sounds are used to stimulate the brain at particular frequencies, has been used to awaken comatose individuals and address a range of cognitive and psychological disorders (Budzynski et al., 2009; Evans, 2007). These interventions may be a useful inclusion amongst heart rate variability, neurofeedback, and other integrative health therapies to address long-COVID symptoms, but remain experimental interventions in the context of COVID-19 rehabilitation.

Conclusion

COVID-19 can cause significant damage to the nervous system through direct and nondirect mechanisms (Bodro et al., 2021; Panariello et al., 2020), which can cause devastating acute (Abdo et al., 2021; Liotta et al., 2020; Llitjos et al., 2020) and long-lasting (Australian Institute of Health and Welfare, 2021; Hampshire et al., 2021; Rajkumar, 2020) psychological impacts. Current estimates suggest between 7,763,200 and 38,816,003 people worldwide may have cognitive difficulties and impacts to their nervous systems as a result of COVID-19. These impacts upon the nervous system can be detected with the EEG (Flamand et al., 2020; Kopańska et al., 2021; Vellieux et al., 2020). By comparing individual symptoms and EEG patterns it may be possible to determine the mechanisms by which the virus has impacted the nervous system and consequentially guide therapeutic intervention. Due to its ability to train the nervous system directly (Hammond, 2011; Sitaram et al., 2017) and target many structures impacted by COVID-19 (Zubair et al., 2020), neurofeedback may offer important therapeutic opportunities to address the psychological impacts of the virus. Given the wide range of psychological disorders neurofeedback can address (Niv, 2013; Omejc et al., 2019; Ros et al., 2014; Yucha & Montgomery, 2008) and the shared mechanisms underpinning many symptoms (Simkin et al., 2014) common to psychological disorders and COVID-19, there are strong grounds to include neurofeedback alongside other interventions to address the psychological impacts of the disease. An integrative approach to addressing psychological impacts of the COVID-19 should also consider heart rate variability biofeedback (Lehrer et al., 2014; Shaffer et al., 2014), low-level-light therapy (Hamblin, 2016, 2019; Naeser et al., 2018) and audiovisual entrainment (Budzynski et al., 2009; Evans, 2007), which also address many underlying processes, such as inflammation, associated with Long-COVID (Bodro et al., 2021). However, despite the support for the use of neurofeedback, heart rate variability biofeedback, photobiomodulation and other forms of neuromodulation in conditions similar to those seen with COVID-19 related presentations, and anecdotal clinical reports of their usefulness in addressing Long-COVID symptoms, there is yet to be research published on the use of these interventions with this client population. Clinicians and researchers should be cautious using the suggested forms of neuromodulation for COVID-19 rehabilitation, which should be considered experimental until further research supports their efficacy. In providing face-to-face services, clinicians should be aware of the risks and take appropriate preventative steps to reduce the risk of harm to themselves and their clients.

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