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Aim and Scope

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Habit Formation and Automaticity: Psychoneurobiological Correlates of Gamma Activity

Caroline M. Leaf[1], Charles S. Wasserman[2], Alexandria M. G. Leaf[1], Nicholas Kopooshian[3], Robert P. Turner[4, 5], and René M. Paulson[6]*

[1]Switch on Your Brain, LLC, Southlake, Texas, USA
[2]University of Connecticut, Storrs, Connecticut, USA
[3]Drexel University College of Medicine, Philadelphia, Pennsylvania, USA
[4]Network Neurology Health LLC, Charleston, South Carolina, USA
[5]University of South Carolina School of Medicine, Columbia, South Carolina, USA
[6]Elite Research, LLC, Irving, Texas, USA

Abstract

Within current mental healthcare practices, a reliable mechanism is needed for transitioning therapeutic interventions into long-term habit formation. While a sizeable body of literature on habit formation and automaticity looking at simple behaviors such as overall activity level and diet exists, few studies have investigated the complex behavior formation needed to instill new beneficial mental health habits. Additionally, limited research has looked at the neurophysiological or biological correlates of these mental processes and changes. Madhavan et al. (2015) proposed that, during active learning or recall, individuals exert more cognitive energy compared to information maintenance, resulting in heightened gamma activity. This new data demonstrates that gamma increases as learning is taking place then decreases once the behavior is learned (habituated), providing evidence of habit formation and automaticity and its nonlinear nature. The current pilot study seeks to contribute to the field's developing knowledge of habit formation and automaticity as something that can be deliberately and mindfully learned, through a planned and guided approach over a specified time frame, to empower individuals to achieve lasting improvements in mental health challenges. Our research contributes practical strategies to improve interventions and achieve sustainable outcomes for the public health emergency in mental health.

Keywords: automaticity; habits; mindfulness; complex behavior; gamma; telomeres; prolactin.

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***Address correspondence to**: Charles S. Wasserman, M.S., 2140 E. Southlake Blvd., Suite L #809, Southlake, TX 76092, USA. Email: Charles.Wasserman@uconn.edu

Edited by:
Rex L. Cannon, PhD, Currents, Knoxville, Tennessee, USA

Reviewed by:
Rex L. Cannon, PhD, Currents, Knoxville, Tennessee, USA
Randall Lyle, PhD, Mount Mercy University, Cedar Rapids, Iowa, USA

Introduction

Mental health management is an emerging public health crisis (Kohn et al., 2004; Singh et al. 2022), and mental health services are insufficient (Patel et al., 2009), necessitating new effective, affordable, and accessible interventions that lead to sustainable change. To further research interventions to address this crisis, the current work examines the science of habit formation and automaticity as a possible way to create sustainable change and the improvement of mental health by building in practices leading to the discontinuation of detrimental behavior and the growth of practices that improve mental health. The present study used a unique psychoneurobiological approach, specifically looking at how habits and automaticity form using a whole person context in the hopes of contributing to how habit formation can be used in mental health interventions.

Interrelation Between Habit Formation, Automaticity, and Mental Health Intervention

The science of habit formation has been extensively researched across disciplines and has multiple definitions, mostly on a stimulus-response-reward continuum (Gardner et al., 2012; Trafimow, 2018;

Verplanken & Orbell, 2003; Wood, 2017; Wood & Neal, 2007; Wood & Rünger, 2016), but is largely defined as "mindless" learned cue-behavior of automated repeated sequences of lower-level actions requiring minimal cognitive effort and resistance to change (Harvey et al., 2022; Langer, 1989; Wood & Neal, 2009). Maddux (1997), on examining the definitions of habit formation and how theories of habit formation use habits, identified a logic error in that the "consensus definition of habit defines habit as a kind of behavior (automatic, unconscious) but our theories employ habit as a cause of behavior" (p.335). This is tautological reasoning, implying that a habit is both a "behavior and the cause of a behavior;" in essence, "a habit is caused by a habit" (Maddux, 1997, p. 335). Additionally, Maddux proposes that it would be more meaningful to look for the cause of a habit intentionally and deliberately in the context of an individual's life experiences (Maddux & DuCharme, 1997). Furthermore, Gardner's (2014) extensive review of 136 empirical studies and eight literature reviews of habit formation underscores the need for a more coherent definition of habit formation to make it more useful for the research and treatment of complex mental health and health behaviors. As most research on habit formation has been conducted using very simple behaviors, Gardener suggested an alternative way of seeing habits is as a "cognitive-motivational process, conceptually distinct from behavior" (Gardner, 2014, p. 289).

A further, important aspect of habit formation intervention involves the concept of automaticity, which is the "active ingredient" or "essence" (Gardner, 2012, p. 33) of a habit that transforms the pure meaningless repetition of a habit into a meaningful, mindful, and useful response that will override a trigger at any point in the future. It has, at its core, the characteristics of increasing self-regulation and therefore self-management and engagement (Gardner, 2012; Lally et al., 2010; Neal & Wood, 2009; Stone et al., 2023).

For habit formation and automaticity to happen, the process involves a pairing of sequential behavior with context in a repeated way to reinforce it, which motivates and strengthens the repetition in a cyclic way until stabilization occurs (Gardner & Lally, 2018). The repetition is growth-oriented in the sense that each "repetition" brings more insight into the reason they are forming a new habit. Therefore, the habit can be seen as the end product of the mindful process of automaticity (Maddux, 1997). Wood and Neal (2007) emphasized that habit formation involves controlled and deliberate higher-order cognitive capabilities. Automaticity is therefore the active process that strengthens the habit to the point where it is initiated and applied efficiently with less conscious control (Aarts & Dijksterhuis, 2000; Carden & Wood, 2018; Lally et al., 2010; Orbell & Verplanken, 2010). This suggests it takes more than just an intention to form a habit, but also deliberate effort, as intentions do not always translate into consistent action (Sheeran, 2001).

Furthermore, mindfulness and habit formation are often seen as opposites, with a habit defined as mindless behavior (Langer, 1989) and mindfulness as "paying attention in a particular way: on purpose, in the present moment, and nonjudgmentally" (Kabat-Zinn, 1994, p. 4). It is proposed in the literature that habit formation needs an expanded view that requires the mindfulness aspect in order to be better applied to the treatment of complex issues (Gardner, 2012; Harvey et al., 2022; Lally et al., 2011; Lally & Gardener, 2013; Robinson et al., 2022; Rothman et al., 2009). A comprehensive review of this literature across different disciplines shows that mindfulness involves deliberate and intentional focused reflection (Casey et al., 2022; Liu et al., 2021; Mitchell et al., 2021; Wong et al., 2022), which are elements that need to be incorporated into intervention that has the effective use of habit formation and automaticity (Ariyasinghe & Arachchige, 2020; Lewis et al., 2021). To establish habit formation and automaticity, it therefore requires mindful self-regulation and action planning, not just a mindless repetitive action (Fleig et al., 2013; Sniehotta, 2009; Sniehotta & Presseau, 2012). Mindful self-regulation thus becomes an elucidative requirement in forming new habits and their automatization, to change behavior leading to improved mental health outcomes (Frazier et al., 2021).

There is a consensus in the literature that including the science of habit formation and automaticity in the design and delivery of evidence-based therapies (EBT) for mental health challenges would appear to enhance their effectiveness (Fiorella, 2020; Harvey et al., 2022; Kazdin, 2018; Lally et al., 2011; Lally & Gardener, 2013; Robinson et al., 2022; Rothman et al., 2009). In patient care settings, the potential benefits of automating complex healthy habits are often overlooked due to the immediate effects of brief advice. Traditional methods of behavioral change tend to prioritize easily induced maintenance mechanisms rather than gradual habit stabilization (Gardner et al., 2012). While establishing long-term complex habits can be time-consuming and challenging, the effective development of

automaticity in habit formation has demonstrated numerous advantages. These include an increased sense of autonomy (Gardner et al., 2012) and the ability of habits to act as a form of self-control and facilitate desired long-term behaviors, especially during periods of short-term motivational lapses (Gardner & Lally, 2018).

Habit formation and automaticity appear to involve phases: a conscious and deliberate process of formation of a habit, followed by the stabilization of the newly formed habit through learning in order to increase its strength (Gardner et al., 2012). The habit's strength is based on the intensity of these two stages and will determine how effectively an individual has a "ready response when distraction, time pressure, lowered willpower, and stress reduce the capacity to deliberate about action and tailor responses to current environments" (Wood & Rünger, 2016, p.307; Stojanovic et al., 2022; van der Weiden, 2020).

In understanding the process of habit formation and automaticity, it is also necessary to understand the timing of habit formation and automaticity in order for it to guide intervention that leads to sustainable change in mental health treatment. Despite the much-quoted myth that it takes 21 days to form a habit, which is based on anecdotal evidence from a plastic surgeon's recovering patients (Lally et al., 2010; Maltz, 1960), research on the timing of habit formation is still in its infancy, and it is known that habits do not form overnight and even over a few weeks. Most of the limited literature in this specific area of timing of habit formation and automaticity suggest it takes around 18–254 days, with peak automaticity plateauing around 59–66 days after the first daily implementation (Armitage, 2005; Gardner et al., 2012; Greeson et al., 2018; Keller et al., 2021; Lally et al., 2010; Raja-Khan et al., 2017; van der Weiden, 2020). The range of 66–254 days would appear to depend on the complexity and interrelated complicated networks of habits that may represent one or more issues being worked on (Carden & Wood, 2018; Gardner et al, 2012; Harvey et al., 2020; Hussam et al., 2017; Judah et al., 2013; Lally, et al., 2010).

Van der Weiden et al. (2020) demonstrated that a large increase in habit strength with complex behaviors such as improved relationships and health can occur over a period of 3 months (van der Weiden, 2020). Lewis et al. (2021) found a significant overall change in simple habit automaticity in the first 21 days, with it taking about 3 weeks to transform the mindfulness behavior of breathing into a habit (Lewis et al., 2021). Furthermore, consistency over that time period is important in habit formation and automaticity (Gardner & Lally, 2018; Lally et al., 2010).

Forming a habit involves learning because learning is "the process by which a relatively stable modification in stimulus–response relations is developed as a consequence of functional environmental interaction via the senses" (Lachman, 1997, p.477). An effective habit could then be defined as one that is learned successfully, or automatized, and will be accessible even without use for a period of time; thus, habits do not have to be enacted frequently to be useful (Gardner, 2012; Leaf et al., 1997). When a person is triggered, it will still lead to the automatized mentally healthy behavior being activated so that the person does not revert to the previous behavior. Essentially, habit formation and automaticity require an active learning phase (Leaf et al., 1977) to attain sustainable habits that improve mental health.

Gamma as a Delicate Balance Linked to Habit Formation, Automaticity, and Mental Health

Neuroscientific research has consistently demonstrated the involvement of gamma activity in cognitive functions such as learning, memory, and executive functioning (Barry et al., 2010; Jensen et al., 2007; Roh et al., 2016). Specifically, a correlation has been established between an increase in gamma activity and improved learning, memory formation, and recall (Jensen et al., 2007; Madhavan et al., 2015). A study by Madhavan and colleagues (2015) demonstrated that gamma increases in the temporal lobes during learning, and then decreases once the behavior is learned. They proposed that during active learning or recall, individuals exert more cognitive energy, resulting in heightened gamma activity, and then lessens after learning has taken place when the information is being maintained (Madhavan et al., 2015).

Similarly, greater cognitive resources are needed during the initial phases of habit formation (Lally et al., 2011); therefore, gamma activity should be higher. As the habit becomes more automatic, maintenance demands decrease (Gardner & Lally, 2018; Wood & Neal, 2007), which could potentially result in a corresponding decrease in gamma activity. According to Smith and Graybiel (2022), habitual behavior is a complex process and can be characterized by multiple neuronal changes across the same or different brain regions. These changes may be representative of gamma activity as well, since gamma is considered to be responsible for

higher levels of cognition and awareness (Hima et al., 2020). While these concepts need to be explored further, this research sheds important insight into neurophysiological mechanisms that play a role in learning and habit formation.

Furthermore, in a recent review article exploring gamma activity (30–100 Hz) and memory, numerous studies revealed that increased gamma band synchronization was positively correlated with short-term and working memory maintenance (Howard et al., 2003; Jenson et al., 2007; Jokisch & Jensen, 2007; Mainy et al., 2007; Tallon-Baudry et al., 1998). The same review also found that both gamma activity and synchrony were implicated in long-term memory, which they explained to be due to increased gamma-modulated synaptic plasticity (Jensen et al., 2007; Wespatat et al., 2004). These findings demonstrate the potential of using gamma band activity as a marker for neurological and psychiatric disorders that affect memory and memory formation, which could be related to habit formation and automaticity.

Gamma activity has also been shown to be involved in healthy executive functioning (Barry et al., 2010; Lawson, 2013; Roh et al., 2016), which is important for higher level cognitive abilities including problem-solving, self-regulation, planning, and self-control (Diamond, 2013; Dovis et al., 2015; Henry & Bettenay, 2010). Barry et al. (2010) studied resting-state EEGs in 40 children with attention-deficit/hyperactivity disorder (ADHD) and 40 age-matched controls and found that children with ADHD had reduced relative and absolute global gamma (30–80 Hz) activity compared to controls. Additionally, they discovered a negative correlation between the inattention scores of the children with ADHD and gamma, demonstrating that decreased gamma activity could be linked to impaired executive functioning and increased inattention, which may be related to conditions like ADHD (Barry et al., 2010). Similarly, a study investigating the relationship between qEEG bands and inattention in major depressive disorder (MDD) also found that inattention scores and low gamma (30–50 Hz) activity in the frontal-central regions were negatively correlated (Roh et al., 2016), while another suggested that gamma band synchrony is decreased in people diagnosed with autism spectrum condition (ASC; Lawson, 2013). These findings further emphasize the involvement of gamma waves in healthy executive functioning paradigms. This idea could be related to an individual's sense of autonomy, self-control (Diamond, 2013), and ability to effectively stop unhealthy habits, given that executive functioning is implicated in the cessation of habits like those found in individuals with obesity (Allom et al., 2018).

Studies have also shown an association between gamma band activity (30–80 Hz) and anxiety and depression (Li et al., 2016; Noda et al., 2017; Oathes et al., 2008), both of which can be a result of an unhealthy habit related to having negative thoughts about one's self-image (Verplanken, 2006). In Noda et al. (2017), 31 patients diagnosed with MDD and a HAM-D score of greater than 10 were studied to evaluate the effects of repetitive transcranial magnetic stimulation (rTMS) on qEEG band patterns demonstrating a significant correlation between increased gamma activity at the F3 electrode and improved Hamilton Depression Rating Scale (HAM-D) scores. This has supported the conclusion that gamma power could be used as a biomarker for potential therapies for MDD, as gamma was shown to be connected to mood disorders (Noda et al., 2017). These findings are further supported by Hima et al. (2020), who proposed that an increase of gamma (40–100 Hz) is associated with states of happiness and compassion and Oathes et al. (2008) who found that there was a higher level of gamma activity in posterior electrode sites in patients with generalized anxiety disorder (GAD) during worry induction. Differences between these results could be related to the timing of when gamma activity is measured, under what conditions, and the brain region of the measurement.

The literature emphasizes the delicate balance required for gamma activity, as it represents a "goldilocks" frequency that is achieved through the excitation and inhibition of different neuronal circuits (Fitzgerald & Watson, 2018). It can be too low or too high, revealing the work of change, and its interpretation is based on the location of its source (Fitzgerald & Watson, 2018). Additionally, gamma can be seen as a representative of neighborhood communication between higher-level cortical sites (Hima et al., 2020; Jensen et al., 2007). Therefore, depending on which cortical areas you are talking about, the increase or decrease in gamma can be thought of as an index of overall arousal or activation in that cortical area as a result of work being done in the mind (Jensen et al., 2007).

Furthermore, gamma has been shown to be highly context-dependent and cannot be classified simply as good or bad purely based on an increase or decrease in activity (Fitzgerald & Watson, 2018). Interestingly, individuals with ASC exhibit excessive gamma activity (Lawson, 2013), which challenges

the idea that increased gamma levels always correlate with normal brain function. As seen in the study conducted by Madhavan et al. (2015), gamma activity exhibits both an increase and decrease during different stages of a normal learning process. This suggests that gamma activity alone should not be used as a definitive diagnostic measure. In the current research examined the change in gamma in the control and treatment group were examined while they used the Neurocycle in a planned and guided way over time to intentionally form new habits that would lead to healthier lifestyles and mental well-being.

Biological Factors Impact in Habit Formation and Automaticity

Telomeres are a protective casing at the end of a DNA strand (Epel, 2009). Each time a cell divides, it loses some of its telomeres and an enzyme called telomerase can replenish it; however, chronic unmanaged stress and cortisol exposure decrease the supply of telomerase (Epel et al., 2004). When the telomere becomes too diminished, the cell often dies or becomes proinflammatory (Yegorov et al., 2020). Both chronic and perceived stress, or self-reported measures of unmanaged stress, have been linked to shorter telomeres (Cawthon et al., 2003; Lin & Epel, 2022; Rentscher et al., 2020). Existing research demonstrates that changing lifestyle behaviors and mindful meditation practices can influence telomere length (Epel, 2009).

The literature in this field has focused predominantly on changes in the telomerase activity because it was believed that changes in telomere length took months or even years to change, which is longer than the typical length of mindful meditation and lifestyle interventions for mental well-being (Conklin et al., 2018). However, more recent studies demonstrate that deliberate lifestyle changes such as exercise, diet, and mindful meditation can lead to an increase in telomere length over shorter periods of approximately 3 weeks to 4 months corresponding with the timing of habit formation and automaticity (Alda et al., 2016; Conklin et al., 2015; Epel, 2012; Shen et al., 2020; Wang et al., 2017). The research further suggests that the duration and intensity of a given intervention play an important role on the impact of telomere length (Carlson et al., 2015; Lengacher et al., 2014; Pines, 2013).

Carlson et al. (2015) and Conklin et al. (2015) found that telomere length declined in their control groups but stayed the same in the intervention groups, suggesting the potential protective effect of mindfulness practices, such as meditation and the intentional implementation of lifestyle habits, on telomere length. Therefore, attempting to expand on this research, our current study examined the change in telomere length in the control and treatment group while they used the Neurocycle in a mindful, planned, and guided way over time, specifically daily over 9 weeks, to intentionally form new habits that would lead to healthier lifestyles and mental well-being.

Prolactin, a neuropeptide that promotes physiological responses related to reproduction, stress adaptation, neurogenesis, and neuroprotection, has been shown to play a role in the attenuation of the hypothalamic-pituitary-aderenal (HPA) axis, helping the brain and body to adapt to chronic stress (Lennartsson & Jonsdottir, 2011; Levine & Muneyyirci-Delale, 2018; Torner, 2016). Unmanaged stress leads to an imbalance in prolactin, which in turn can result in reduced neurogenesis and reduced stress modulation, impacting mental health (Elgellaie et al., 2021; Kumar, 2019; Torner, 2016). However, there is a scarcity of research showing that intervention changes prolactin levels, though there are a few studies in the meditation literature where mindful lifestyle changes like meditation have been shown to improve prolactin levels (Nagendra, 2022). Additionally, some research demonstrates that passive coping increases prolactin whereas active coping leads to lowering or unchanged prolactin levels (Theorell, 1992). Our current research examined the change in prolactin in the control and treatment group as they used the Neurocycle in a mindful, planned, and guided way over 9 weeks to intentionally form new habits that would lead to healthier lifestyles and mental well-being.

The Need for a Psychoneurobiological Approach in Automaticity and Habit Formation

With the current global mental health crisis (World Health Organization [WHO], 2022), clinicians, researchers, public health experts, and individuals alike have increasingly realized that effective, affordable, empowering, and sustainable mental health interventions are critically needed. Specifically, Gardner and Lally (2018), Lewis et al. (2021), and Harvey et al. (2020) have underscored the need for researchers to contribute to the investigation and improved effectiveness of mental health interventions by incorporating the science of habit formation and automaticity into their design. Research on how to use planned, guided, and mindful approaches to deconstruct a disruptive habit and mindfully reconstruct and reconceptualize a new useful habit as a lifestyle would clearly benefit an

individual's mental health (Mantzios & Giannou, 2019).

This current pilot study seeks to contribute to the field's developing knowledge of habit formation and automaticity as something that can be deliberately and mindfully learned, through a planned and guided approach over a specified time frame, to facilitate lasting and impactful management of mental health challenges. Thus, this research contributes to the understanding of how to improve mental health intervention and achieve sustainable outcomes. Additionally, by using a psychoneurobiological approach within a longitudinal study, we are gaining insight into the amount of practice that is likely to be needed to form a habit that leads to improved and sustainable mental health changes. It is also important to acknowledge the complexity of these changes in the neurological and biological aspects of the human in response to the challenges of life (Vage et al., 2023), underscoring this need for a psychoneurobiological approach.

To achieve this, the study herein evaluated an evidence-based treatment protocol, the Neurocycle hosted on the Neurocycle app. With the ever-growing rise of technology influencing our everyday lives, it is not only convenient but essential to create accessible, technological interventions for mental health that promote well-being and sustainable changes (Figueroa & Aguilera, 2020; Hollis et al., 2015; Lattie et al., 2022; Philippe et al., 2022; Schueller et al., 2013). Furthermore, Singh and colleagues (2022) encourage the use of digital technology as an additional factor for improving mental health interventions in terms of ease of accessibility and use, thereby empowering an individual to manage their mental health. Answering this call, we implemented the Neurocycle app as a planned and guided process that models how to optimize the science of habit formation and automaticity in mental health interventions. The Neurocycle has been evaluated as an evidence-based intervention for mental health in clinical trials, using a psychoneurobiological approach, assessing participants' psychosocial reports of mental health wellness, energy patterns in the brain, and hematological measures (Leaf, Turner, Wasserman, et al., 2023).

The following hypotheses are being tested:

- H1: There will be positive change in the subjects' psychological well-being after their completion of the Neurocycle program, as measured by psychometric assessments of the Leaf Mind Management (LMM) Autonomy and Toxic Thoughts subscales and the Patient Health Questionnaire (PHQ-9) scale.
- H2: There will be a change in subjects' neurophysiological functioning as measured by gamma activity during and following the Neurocycle system.
- H3: There will be positive change in the subjects' biophysical anxiety symptoms after the completion of the Neurocycle program, as measured by blood serum for prolactin levels and telomeres length analysis.

Altogether, this psychoneurobiological approach will provide the more detailed neurophysiological data called for by Newson and Thiagarajan (2019) via mapping of the psychological, neurological, and biological identifiers of complex mental health behaviors as they become automatized into mindful habits and how this process relates to changes in the psychological aspects, gamma neural activity, and biological changes in telomeres and prolactin.

Materials and Methods

Based on the detailed methods previously described, we present a summary of the materials and methods herein (Leaf, Turner, Wasserman, et al., 2023).

Study Design

A double-blind randomized clinical trial (RCT) pilot study was selected, and the study design, instruments, and protocol were approved by the Sterling Institutional Review Board (approval ID no. 7281-RPTurner). A total of 14 participants were recruited based on the power analysis of convenience sampling; a priori power analysis was conducted, and the necessary sample size was verified as 12. An additional two participants were included for potential attrition during the study period. To ensure that participants met the recruitment criteria of preexisting anxiety and/or depression, the research team recruited a total initial pool of 30 recruits in a prescreening phase. To select the 14 participants from the initial 30 recruits, inclusion and exclusion criteria were applied. After the final 14 participants were selected, they were provided with an informed consent and randomly assigned to the treatment group (n = 7), the Neurocycle, or the control group (n = 7), which received no special attention beyond the standard of care of their physician. During the study, attrition occurred following baseline measurements in both groups (control: attrition of n = 1, for a final total of n = 6; treatment: attrition of n = 2, for a final total of

n = 5). Attrition bias was avoided by removing their entire profiles from the final samples for analysis.

Materials

The intervention utilized the Neurocycle program hosted on the Neurocycle app. The Neurocycle (Leaf, 1997, 2021) is a 63-day mind-directed self-help mental health program, in which participants are directed by daily audio and video recordings through the five-step Neurocycle process of Gather Awareness, Reflect, Write, Recheck, and Active Reach; these steps provide a scientifically validated framework for participants to reconceptualize and take control of their mental health through mind-management, fostering development in the required skills to actualize the benefits of mindfulness: self-regulation, resilience, reconceptualization, and exposure (Shapiro et al., 2006).

Measurements, Instruments, and Data Collection

The psychological effects of the Neurocycle were measured by the LMM scale and validated with the Hospital Anxiety and Depression Scale, Anxiety and Depression subscales (HADS-A and HADS-D; Bjelland et al., 2022), as well as the BBC Subjective Well-Being Scale (BSC; Pontin et al., 2013). The neurophysiological effects of the Neurocycle were assessed using surface qEEG functional analysis. The psychological and neurophysiological effects were then verified in bloodwork analysis that measured the participants' prolactin levels, which are known to increase alongside stress, anxiety, and depression (Lennartsson & Jonsdottir, 2011; Levine & Muneyyirci-Delale, 2018; Torner, 2016). This tripartite approach addresses the lack of multimethod approaches in the field of electroencephalography (Newson & Thiagarajan, 2019) and is intended to help provide additional insight into resting-state gamma activity and how it is interpreted in the context of therapeutic intervention. The assessments were administered across six distinct time periods: preintervention (day 1), on days 7, 14, 21, and 42, and during postintervention on day 63. The schedule of assessment administration is provided in Table 1 below, and descriptions of each assessment phase are fully described in a previous article (Leaf, Turner, Wasserman, et al., 2023).

Table 1

Implementation Schedule for Measures of Interest to This Paper

Measure	Prescreen	Day 1	Day 7	Day 14	Day 21	Day 42	Day 63	3-Month Follow-Up
Clinical Anxiety (HAM-A)	X							
Clinical Depression (HAM-D)	X							
Psychological Effects (BBC-SWB)		X	X	X	X	X	X	X
Self-Report Anxiety & Depression (HADS-A & HADS-D)		X	X	X	X	X	X	X
Patient Health Questionnaire (PHQ-9)		X	X	X	X	X	X	X
Awareness, Autonomy, and Toxic Thoughts Subscales (LMM)		X	X	X	X	X	X	X
Neurophysiological Effects (qEEG)		X			X		X	
Bloodwork (Prolactin and Telomeres)		X			X		X	

Neurophysiological Assessment

Participants underwent three qEEG sessions for neuroimaging analysis on days 1, 21, and 63. Participants' qEEG was recorded for 10 min with their eyes open and another 10 min with their eyes closed. Only low gamma band (30–120 Hz) data are reported on in this paper.

Psychological Assessment

Self-assessment of psychometric indicators was taken by participants during all six key stages of the intervention's administration: days 1, 7, 14, 21, 42, and 63. The primary assessment tool implemented was the LMM scale. Improvements in stress and anxiety can be measured by increases in the Autonomy, Awareness, and Empowerment subscales alongside decreases in the Toxic Thoughts, Toxic Stress, and Barriers subscales. In

this paper, data on the Awareness, Autonomy, and Toxic Thoughts subscales are reported. To triangulate and validate the LMM assessment in this study, traditional measures of anxiety, stress, and depression were also administered, including the PHQ-9, a depression module, which scores each of the nine DSM-IV criteria as "0" (*not at all*) to "3" (*nearly every day*).

Biological Assessment

Participants were sampled for blood-measured prolactin levels and telomere length. Elevated prolactin levels and decreased telomere length are known to be associated with an individual's elevated stress and anxiety levels and the direct neurotoxic effects (Aghayan et al., 2020; Chung et al., 2017; Epel, 2009; Epel et al., 2004; Mayer et al., 2023). During the preintervention on day 1, after the initial phase of the intervention on day 21, and postintervention on day 63, given that this sulphurated amino acid is responsible for mediating methylation, which is critical for nervous system balance and health (Kennedy, 2016), blood amino acid analysis for prolactin levels was then performed by a contracted lab and reported to the researchers as follows: normal range: 5–15 mcmol/L; moderately elevated range: 15–30 mcmol/L; intermediately elevated range: 30–100 mcmol/L; and severely elevated range: < 100 mcmol/L (Haldeman-Englert et al., 2022).

The qEEG study descriptions are presented in a previous article (Leaf, Turner, Wasserman, et al., 2023). Relative power was calculated for each frequency band relative to the total power in the 0.5–120 Hz range. Further, relative power was used for analysis to allow direct comparison from one subject to another, controlling for interpersonal differences in overall EEG amplitude. In this study, all-electrode-averaged eyes-open (EO) and eyes-closed (EC) global average gamma relative power (30–120 Hz), low gamma relative power (30–49.9 Hz), high gamma relative power (50–120 Hz), and EO frontal low gamma relative power (30–49.9 Hz; averaged over the three frontal electrode sites; F3, Fz, and F4) were analyzed.

Analysis

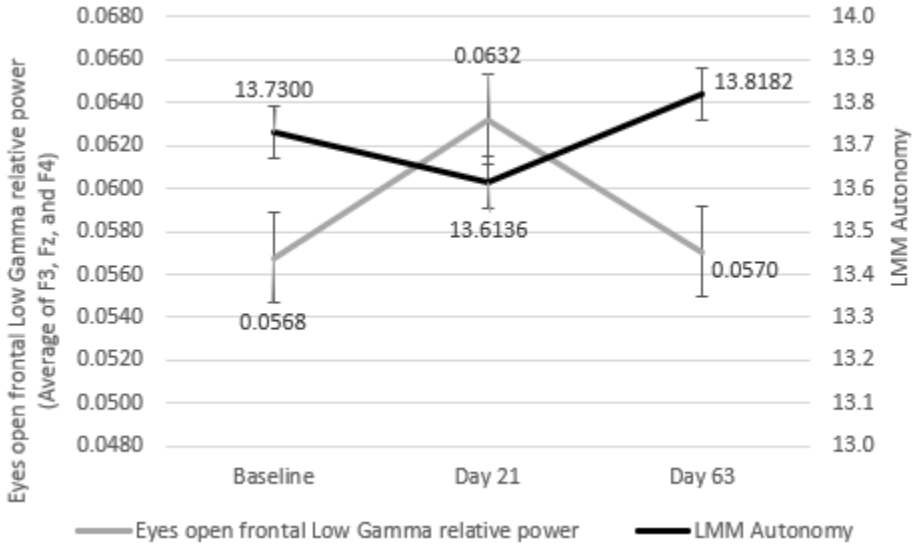
The data gathered from the qEEG, bloodwork, and psychometric assessments were analyzed altogether using IBM SPSS v27. The study analysis is presented in a previous article (Leaf, Turner, Wasserman, et al., 2023). In this study, we analyzed global average gamma (low = 30–49.9 Hz; high = 50–120 Hz) relative power and frontal low gamma (30–49.9 Hz; averaged over the three frontal electrode sites; F3, Fz, and F4) relative power in both the EO and EC conditions. To examine the specific hypotheses outlined in this paper, linear multiple regression models and simple regressions were conducted to examine the relationships among the specific variables as nonparametric correlations (ρ) to assess potential relationships. The alpha (α) level for this pilot study was set at 0.10.

Results

Overall Gamma Change and Psychological Relationship

EO frontal low gamma relative power (average of F3, Fz, and F4) increased from day 1 to day 21 (t = 1.35, p = .104) followed by a significant decrease from day 21 to 63, t = 1.75, p = .055 (Figure 1). The overall change in EO frontal low gamma relative power over the course of the entire study, from day 1 to 63, correlated significantly with change in the LMM Autonomy subscale, ρ = 0.575, p = .065.

Figure 1. *EO Frontal Low Gamma Relative Power and LMM Autonomy*.



Note. EO frontal low gamma relative power from baseline to day 21 all subject average, t = 1.35, p = .104, and day 21 to 63, t = 1.75, p = .055 and LMM Autonomy from days 1 to 63, ρ = 0.575, p = .065. Error bars are standard error.

A linear regression model showed that the stress (PHQ-9 scale) at baseline was a significant predictor and accounted for 34.5% of the variance of EO frontal low gamma relative power changes from day 1 to day 63, F = 4.73, R^2 = .345, beta coefficient (standardized) = .587, p = .058.

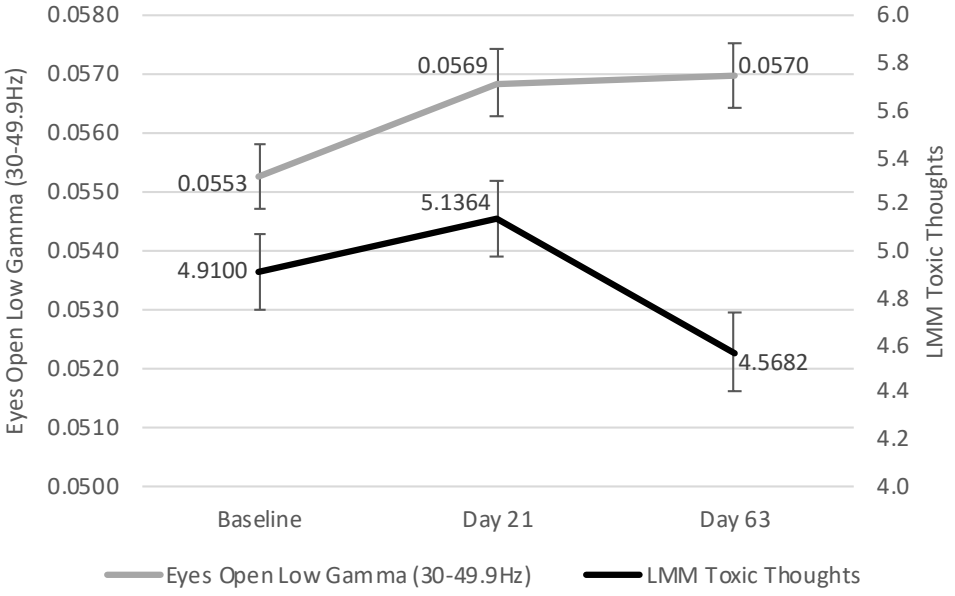
Stress levels, as measured by the PHQ-9 at baseline, were significantly correlated with the LMM Autonomy subscale (ρ = −0.635, p = .036) and the LMM Toxic Thoughts subscale (ρ = 0.703, p = .016). Scores on the LMM Autonomy subscales need to increase to show improvement; scores on the LMM Toxic Thoughts subscale needs to decrease to show improvement.

Similar to LMM scale validation results from another study (Leaf, Turner, Paulson, et al., in press), the LMM Autonomy subscale is significantly correlated to LMM Awareness (ρ = 0.538, p = .088) and LMM Toxic Thoughts (ρ = −0.507, p = .097). Scores on the LMM Autonomy and Awareness subscales need to increase to show improvement; scores on the LMM Toxic Thoughts subscale needs to decrease to show improvement.

Over the course of the study from day 1 to 63, EO global average low gamma (30–50 Hz) increased and scores on the LMM Toxic Thoughts subscale decreased, ρ = −0.669, p = .024 (Figure 2).

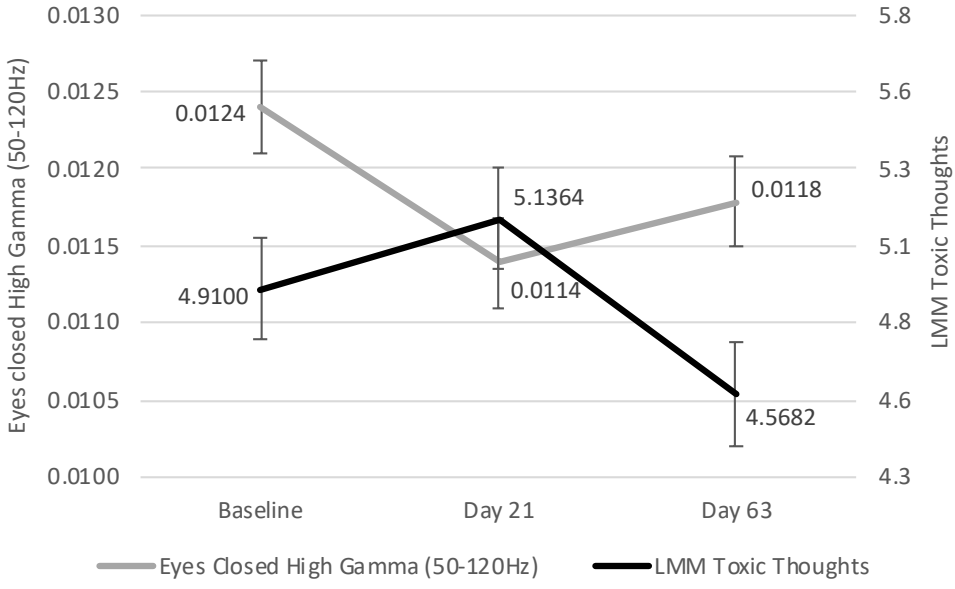
Over the course of the study, there was an inverse relationship between EC global average high gamma and the LMM Toxic Thoughts scores which was significant from baseline to day 63, ρ = −0.758, p = .007. We observed an inverse relationship between an increase of the Toxic Thought subscale from day 1 to day 21 and decreasing EC global average high gamma (50–120 Hz), both measures reverse trajectory at the 21-day inflection point (Figure 3).

Figure 2. *EO Global Average Low Gamma Relative Power and LMM Toxic Thoughts*.



Note. EO global average low gamma (30–49.9 Hz) and LMM Toxic Thoughts subscale scores. Total change from day 1 to 63 in EO global average low gamma were significantly correlated with LMM Toxic Thoughts subscale scores from day 1 to 63, $\rho = -0.669$, $p = .024$. Error bars are standard error.

Figure 3. *EO Global Average High Gamma Relative Power and LMM Toxic Thoughts*.



Note. EC global average high gamma (50–120 Hz) and LMM Toxic Thoughts subscale scores change from baseline to day 63, $\rho = -0.758$, $p = .007$. Error bars are standard error.

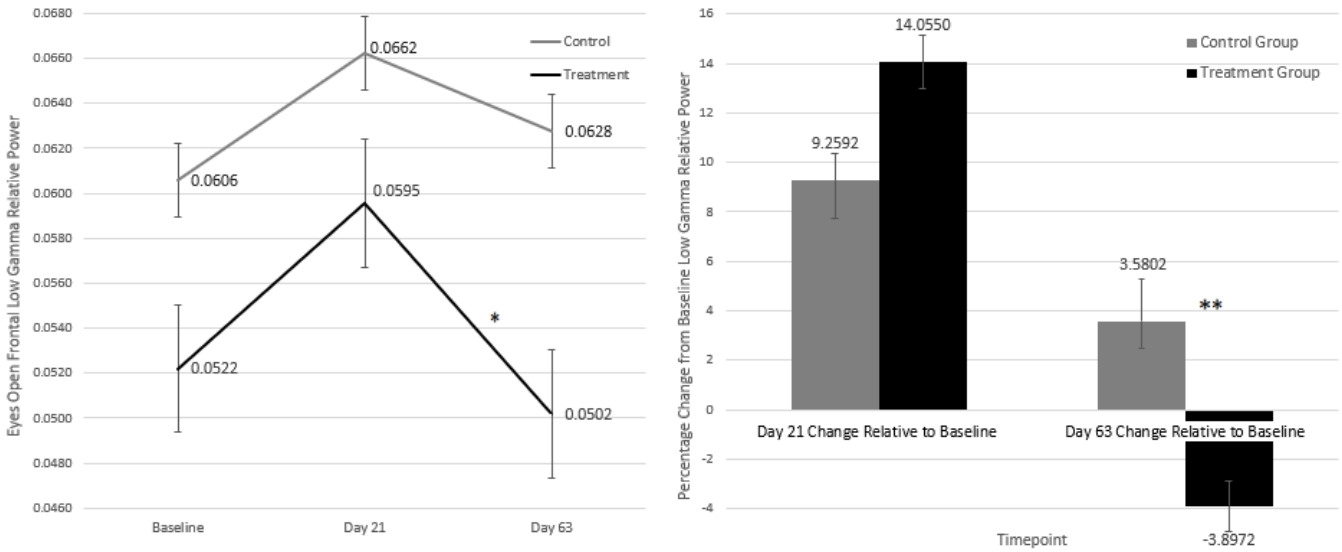
Overall Gamma Change and Biological Relationships

A linear regression model showed that the prolactin change from day 1 to 63 was a significant predictor and accounted for 65.2% of the variance of EO frontal low gamma relative power changes from day 1 to day 63, F = 16.86, R^2 = .652, beta coefficient (standardized) = .807, p = .003.

Group Differences and Psychological Relationships

Results revealed that while both the control and treatment group increased in EO frontal low gamma relative power change from baseline to day 21 and then decreased from day 21 to 63 EO frontal low gamma relative power change, the treatment group had significant change from day 21 to day 63, t = 1.85, p = .069 (Figure 4, left). Examination of the group differences on the percentage change relative to baseline revealed that the treatment group had decreased EO frontal low gamma relative power change relative to baseline while the control group had increased EO frontal low gamma relative power change relative to baseline (Figure 4, right), t = 1.38, p = .097.

Figure 4. *EO Frontal Low Gamma Relative Power and Percentage Change*.



Note. EO frontal low gamma relative power change from baseline to day 21 and day 63 for the treatment and control groups. EO frontal low gamma relative power percentage change from baseline to day 21 and baseline to day 63 for the treatment and control groups. Significant difference, (left) treatment group, day 21 to day 63, t = 1.85, p = .069; (right) control vs. treatment group day 63 to baseline, t = 1.38, p = .097. Error bars are standard error.

Results also revealed that the control group and treatment group had similar awareness scores at day 1, t = .242, p = .407; however, by day 63, the treatment group had significantly greater awareness scores than the control group, t = 1.74, p = .058 (Figure 5). Analysis showed that the awareness score of the treatment group significantly increased from day 1 to day 63, t = 2.24, p = .045, while the control group awareness score did not significantly change over the course of the study, t = .045, p = .084.

Looking towards the end of the 63-day program, for subjects in the treatment group who completed the 3-month follow-up LMM measures (n = 5), there was a significant correlation between EO frontal gamma relative power on day 63 of the study and their LMM Autonomy and LMM Awareness subscale scores at that same timepoint, ρ = 0.894, p = .041, which persisted through to the 3-month follow-up, ρ = 0.894, p = .041.

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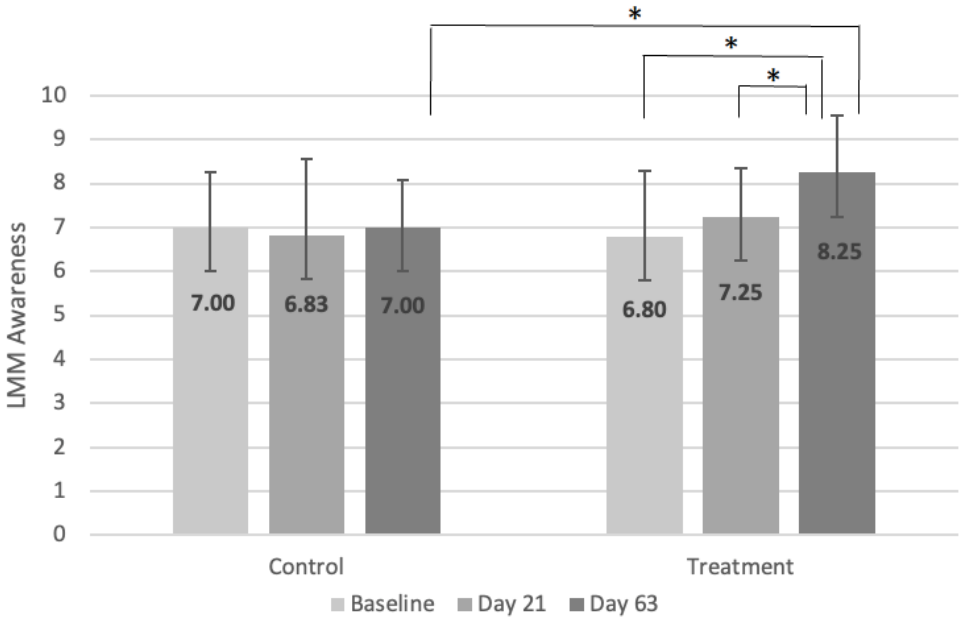
Figure 5. *Leaf Mind Manaement Awareness*.



Note. Leaf Mind Management Awareness subscale from baseline to day 63 for the treatment and control groups. *Significant difference, control vs. treatment group, t = 1.74, p = .058; treatment group: day 1 to day 63, t = 2.24, p = .045; treatment group: day 21 to day 63, t = 2.29, p = .042. Error bars are one standard deviation.

We also observed a significant correlation between the overall decrease in EO global low gamma between days 21 and 63 and scores on the LMM Empowerment and Life Satisfaction subscale on day 63, ρ = −0.975, p = .005. This correlation also persisted through to the 3-month follow-up LMM scores, ρ = −0.975, p = .005. A similar pattern of inverse correlation was observed in the change in EC global average gamma from day 21 to 63 and LMM Autonomy and Awareness subscales on both day 63 and 3-month follow-up, ρ = −0.894, p = 0.041.

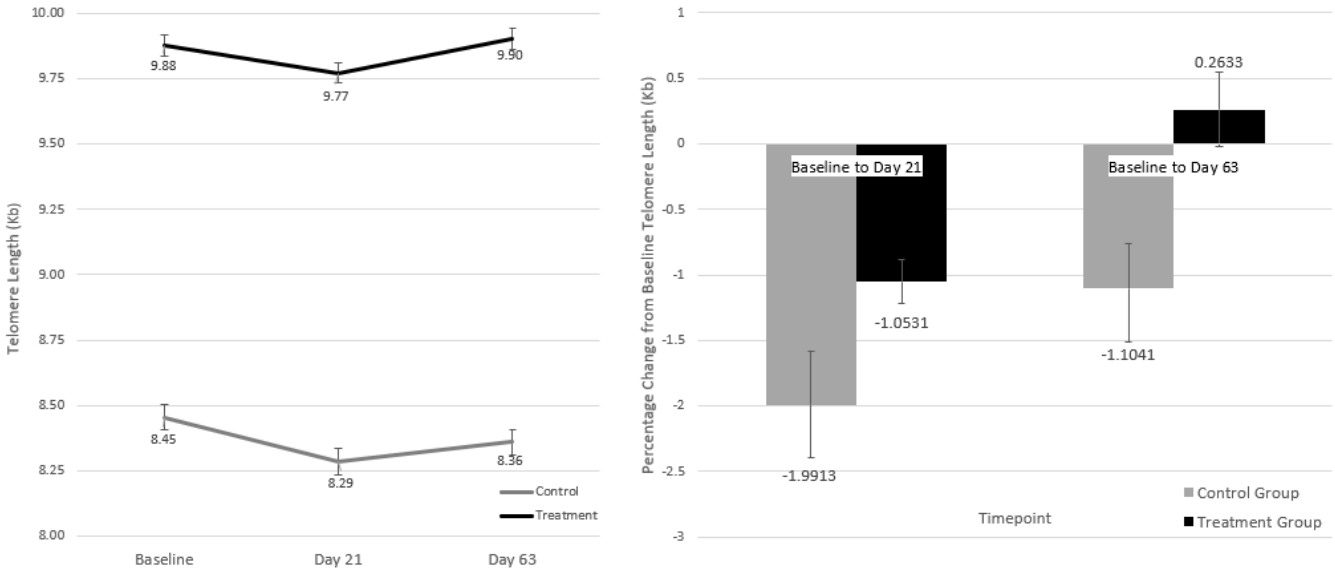
Group Differences and Biological Relationships

Telomere length decreased from day 1 to day 21 for both the treatment (−1.05%) and control (−1.99%) groups, although the decrease was less for the treatment group than the control group (Figure 6). Telomere length increased from day 21 to day 63 for both groups; however, the control group did not reach their baseline telomere length (−1.10%), while the treatment group exceeded their baseline telomere length (+0.26%), t = 1.62, p = .069.

Due to low sample sizes in the pilot study, multivariate correlational analyses by group were not possible; however, there are corresponding relationships of percent change of telomere length and improved LMM Toxic Thoughts scores from baseline to day 63 of telomere length and overall gamma relative power (30–120 Hz) during the EO condition, ρ = 0.670, p = .024, as well as percent change from baseline to day 63 of telomere length and improved LMM Toxic Thoughts scores, ρ = .560, p = .073 (see Figure 7).

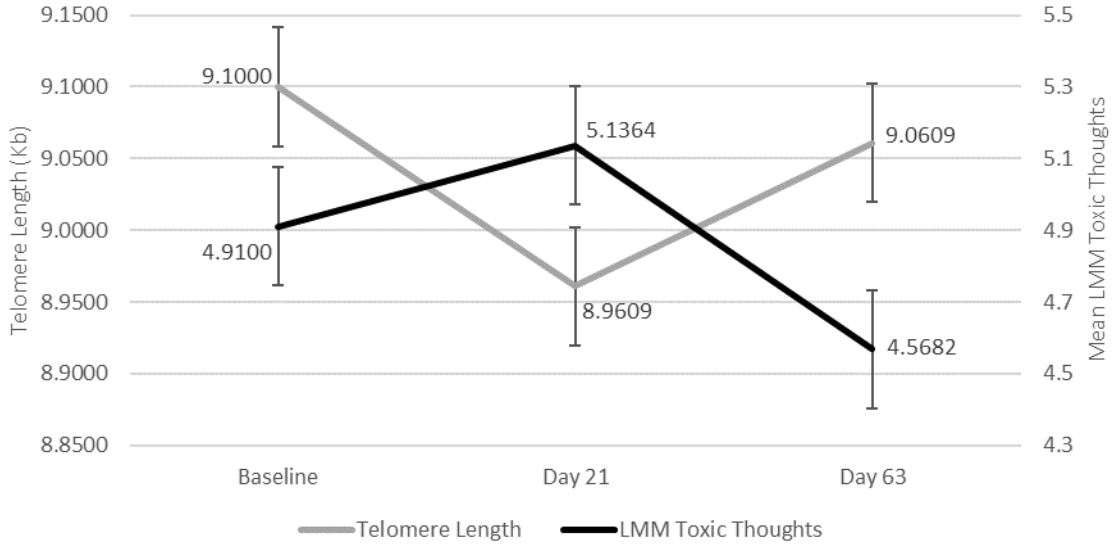
Percent change from baseline to day 21 telomere length was significantly correlated with percent change from baseline to day 21 for prolactin, ρ = 0.584, p = .059, indicating that greater change in telomere length was related to greater change in prolactin. In addition, percent change from baseline to day 63 in overall gamma (30–120 Hz) during the EO condition were significantly correlated with improved LMM Toxic Thoughts scores, ρ = .724, p = .012.

Figure 6. *Telomere Length and Percentage Change*.



Note. Telomere length; percentage change from baseline to day 21 and baseline to day 63 for the treatment (t = 1.62, p = .069) and control groups. Error bars are standard error.

Figure 7. *Telomere Length and LMM Toxic Thoughts*.



Note. Telomere Length (Kb) and LMM Toxic Thoughts subscale scores change from day 1 to 63, ρ = 0.560, p = .07. Error bars are standard error.

Discussion

Understanding the process of habit formation and automaticity is needed to contribute to creating interventions for mental health treatments that seek to create more sustainable change (Harvey et al., 2020). Even though a major focus of habit research has been on simple repetition of cue-response-reward sequences, the literature calls for a more mindful view, as well as the application of habit formation and automaticity into the design and implementation of evidence-based mental health intervention (Mergelsberg et al., 2021; Gardner et al., 2012). We have attempted to address this need through the current research by examining the effectiveness of a 9-week planned and guided intervention informed by the science of habit formation and automaticity using a psychoneurobiological approach. In the current study we used an app called the Neurocycle, a technology-based mental health intervention, as a tool for promoting habit formation and automaticity while working through mental health struggles (Leaf, Turner, Wasserman, et al., 2023). In a growing technological age, and after a global pandemic where there was so much isolation between people and fewer face-to-face interactions, technological interventions for mental health issues have vast potential to provide accessible and affordable mental health care. The present study further serves to study the effectiveness of said technology, as called for in current research (Aguilera, 2015; Jameel et al., 2022; Lattie et al., 2022; Naslund et al., 2017; Stawarz et al., 2015; Taylor et al., 2020).

We observed a pattern of change in the data over the course of the 9 weeks (63 days) time frame of the Neurocycle that integrates with the common consensus of how long it takes to build effective and useful habits that could have a positive impact on the mental health of an individual, whichh is around 8–12 weeks (Armitage, 2005; Gardner et al., 2012; Lally et al., 2010; van der Weiden, 2020). In this study, on a psychological level, we observed significantly improved increases in awareness and autonomy and decreased toxic thoughts. On a neurological level, we observed that this was reflected by frontal gamma following a pattern of increasing while active change and learning were taking place between days 1–21, and then decreasing between days 21–63. This potentially shows that habit formation is taking place and being wired into the brain, creating neural networks and demonstrating the learning process that leads to automaticity and habit formation. We also found correlated positive changes in the biological components (prolactin and telomeres). This psychoneurobiological approach helps to provide the more detailed neurophysiological data called for by Newson and Thiagarajan (2019) through a blending of the psychological, neurological, and biological identifiers of automaticity and habit formation.

Psychological Changes

Overall gamma changes and multiphasic pattern of habit formation and automaticity were found to be correlated with the psychological measures on the LMM scale. A change in EO frontal low gamma over the course of the entire study was related to a greater change in the Autonomy subscale of the LMM, with an inflection point occurring at day 21, followed by a change of direction from day 21 to day 63. These results indicate that a greater change in frontal low gamma relative power was related to a greater change in autonomy. This time course (day 21 to day 63) corresponds with the decrease in low gamma that Madhavan et al. (2015) recorded in frontal regions, suggesting that the mindful conscious part of the initiation and goal setting of the habit formation process may be frontally based.

Additionally, as EO global average low gamma increased over the course of the study from day 1 to day 63, scores on the LMM Toxic Thoughts subscale decreased, once again with an inflection point occurring at day 21, with the same change of direction from day 21 to day 63, which was also the pattern seen with the frontal low gamma. It is not surprising to see an increase in toxic thoughts while participants were prompted to become aware of the problem they had chosen to address because this involves active and deliberate learning and change as an individual becomes more aware and mindful of their issue, which is associated with the increase in low gamma globally (Leaf, Paulson, et al., 2023). Then at the inflection point of 21 days, toxic thoughts decrease along with the decrease in the slope of increase of low gamma.

These results may suggest that global low gamma relative power may be related to the initial awareness of facing and dealing with the toxic issue followed by stabilization after the inflection point. This may represent a measure of mindful cognitive effort working towards their goal. Both the treatment and control groups could be experiencing and benefiting from the “therapeutic alliance” (Alldredge et al., 2021), since they are both receiving the standard of care from the physician. Additionally, they were aware of being in a study to help manage mental health and were therefore motivated to initially face and deal with their issues (Benedetti,

2013; Munnangi et al., 2022), which could account for the increase in frontal low gamma.

Throughout the duration of the study, EC global average high gamma and the LMM Toxic Thoughts scores were inversely related (Figure 3). These results indicate that as one increases the other decreases and vice versa. These changes also occurred in a phasic pattern on a shorter timescale with a decrease in EC global average high gamma from day 1 to day 21 as the toxic thoughts increased, with an inflection point at day 21, and then from day 21 to day 63, where the global high gamma increased and the toxic thoughts decreased. This interpretation is supported by a similar trajectory of activation in EO relative beta power (Leaf, Turner, Wasserman, et al., 2023). These results suggest that as EC high gamma increased, over the second phase of the Neurocycle, toxic thoughts decreased. There is a delicate balance of resources in the brain, and the results demonstrated gamma modulating alongside correlation with changes in psychology among several different measures.

An overall gamma change was also found to be correlated with the psychological measures on the PHQ-9. The PHQ-9 stress scale at day 1 was a significant predictor of low gamma relative power changes from day 1 to day 63, if the study was a significant predictor of the patterns of change in frontal low gamma relative power. This is a foreseeable result of beginning to work on changing a toxic thought, which has implications for the initiation and consistency of working through the issue, pushing past the struggle. This could indicate an overall level of severity dictating how much of a change is yet to be made. Participants' stress levels at baseline, as measured by the PHQ-9, were also significantly correlated with LMM Autonomy and Toxic Thoughts subscales at baseline. These results indicate that at baseline, higher levels of stress, as measured by the PHQ-9, were related to lower scores on autonomy and higher scores on toxic thoughts on day 1. This potentially indicated that the worse a participant's starting point is, the more frontal engagement they still experience at day 63, which could be an indicator of the level of complexity of the issue that they are working on and suggests the potential benefit of another Neurocycle. Multiple sequential Neurocycles may prove beneficial for individuals dealing with complex mental health issues.

Group Differences in Psychological Measures

The LMM scale is uniquely situated to measure and help sustain the development of mindfulness awareness into a cognitive practice that involves self-regulation to form new habits and automatize them. This involves the initiation of the intervention to the learning and eventual stabilization of the new habits that have a consistent impact on well-being (Leaf, Turner, Paulson, et al., in press). The results of this automaticity are supported by the psychological component as part of the psychoneurobiological approach used in the study (Leaf, Turner, Wasserman, et al., 2023).

The current study revealed that the control group and treatment group had similar scores on the Awareness subscale of the LMM, from day 1 to 21; however, by day 63, the treatment group had significantly greater awareness scores than the control group (Figure 5). Analyses showed that the Awareness score of the treatment group significantly increased from day 1 to day 63, while the control group's awareness score did not significantly change over the course of the study. This reveals another important facet of automaticity and habit formation: that increased awareness leads to planned and guided practice, without which automaticity of a new effectual habits may not occur. Instead, the established destructive habit will persist, as was seen in the control group and prior literature (Fleig et al., 2013, Gardner, 2014).

Awareness is an essential component of self-regulation, and self-regulation is a significant skill for mental health given its profound impact on people's everyday struggles (Diamond, 2013; McCelland et al., 2015). Self-regulation is one of the mediating factors for well-being outcomes (Leaf, Turner, Paulson, et al., in press). Self-regulation is a critical factor in habit formation and automaticity that will change behavior irrespective of the context (Frazier et al., 2021). On a psychological level, this may represent the cognitive effort of identifying, disrupting, deconstructing, reconstructing, and reconceptualizing toxic thoughts involved in the process of doing the Neurocycle daily over the 63 days to improve mental health. The persisting LMM scores in the treatment group at 3-month follow-up indicate that the subjects maintained their psychological changes past the end of the program. Further investigations will include tracking of physiology past the end of the Neurocycle to investigate the long-term trajectories of how these measures interact with the psychology of Neurocyclists.

Neurophysiological Change

EO frontal low gamma increased from day 1 to day 21, peaked at day 21, followed by a significant decrease from day 21 to 63. EO global average low gamma (30–50 Hz) increased over the course of the study from day 1 to 63, but slowed down at day 21 after which the slope of the increase decreased. EC global high gamma (50–120 Hz) decreased from day 1 to day 21, then increased from day 21 to day 63. We observed a nonlinear trajectory of change in the qEEG gamma metrics. This supports the concept that the process of changing complex mental behaviors is not linear and requires a greater degree of investigation in the temporal domain in order to more fully describe the patterns and associations between the measured variables. The nonlinear nature of these changes supports the concept of gamma as a "goldilocks frequency" that has differing stable states of ideal activity depending on individual contextual factors and is interpreted differently depending on the source of gamma in the cortex.

Group Differences in Neurophysiological Measures

Results suggest that EO frontal low gamma increased from baseline to day 21 and decreased from day 21 to day 63 in both the treatment and control groups. However, the treatment group had a significant change from day 21 to day 63 (Figure 4), demonstrating the automaticity pattern with the peak at day 21 and the change of direction thereafter. Examination of percentage change from day 63 relative to baseline revealed that EO frontal low gamma relative power decreased in the treatment group and increased in the control group (Figure 4).

The decreased activity in frontal low gamma in the treatment group may represent that less deliberate intentional work is needed to manage the intrusive thought than was required in the initial 21 days, the first phase, where active deconstruction of the root cause and reconceptualization and reconstruction of the new thought was being carried out. The second phase, days 21 to 63, was a practice phase to stabilize and automatize the thought into a habit that will manifest as behavior change impacting mental health in a positive way. It is also possible that a modification in effective habit formation was happening at around the 21-day point and that this level of intense type focus was no longer needed as the person moved into a practice stage of stabilization of the new pattern. A simple comparison elucidating this is learning to ride a bicycle, drive a car, or play a musical instrument. Initially there is intensive deliberate intentional work to learn the "how to," after which one is able to ride the bike, drive the car, or play the musical instrument automatically. In this study, improved self-regulation of an experience that was challenging the person's mental health is the new habit that is forming. The automaticity component shows up in the decreased deliberate intentional conscious work needed and the shift to a stabilization of the new thought pattern.

In the control group, we observed a different pattern. They became aware of their problem thought through the interaction and interviews during the study but didn't have a treatment plan to deal with this, which could be the reason why their frontal low gamma increased from baseline to day 63. The data support the concept that awareness alone is not sufficient for mental health change.

Biological Change

There is an overall correlation between the decrease in global gamma relative power (30–120 Hz) in the EO condition from day 1 to 63 and the change in telomere length over that same time period. It is critical, however, to analyze this finding in the context of whether or not the subjects were in the treatment or control conditions. Both groups saw decreases in telomere length from day 1 to 21 of the study (Figure 7); however, while the control group made a small rebound in telomere length from day 21 to 63 of the study, those in the treatment group had increased telomere length from day 21 to 63 and increased in average telomere length from the beginning to the end of the Neurocycle that approached statistical significance.

The hard work being done over the first 21 days is mentally challenging and can increase stress in the process of gaining insight into the cause of the mental health issues being worked on. This is supported by the telomeres shortening in both groups, which can be likened to having surgery where you must be cut first to then be healed. The improved telomere length in the treatment group aligns with the improved mental health management reported in the second phase from days 21–63 of the intervention where automaticity of the new reconceptualized behavior is in the process of developing.

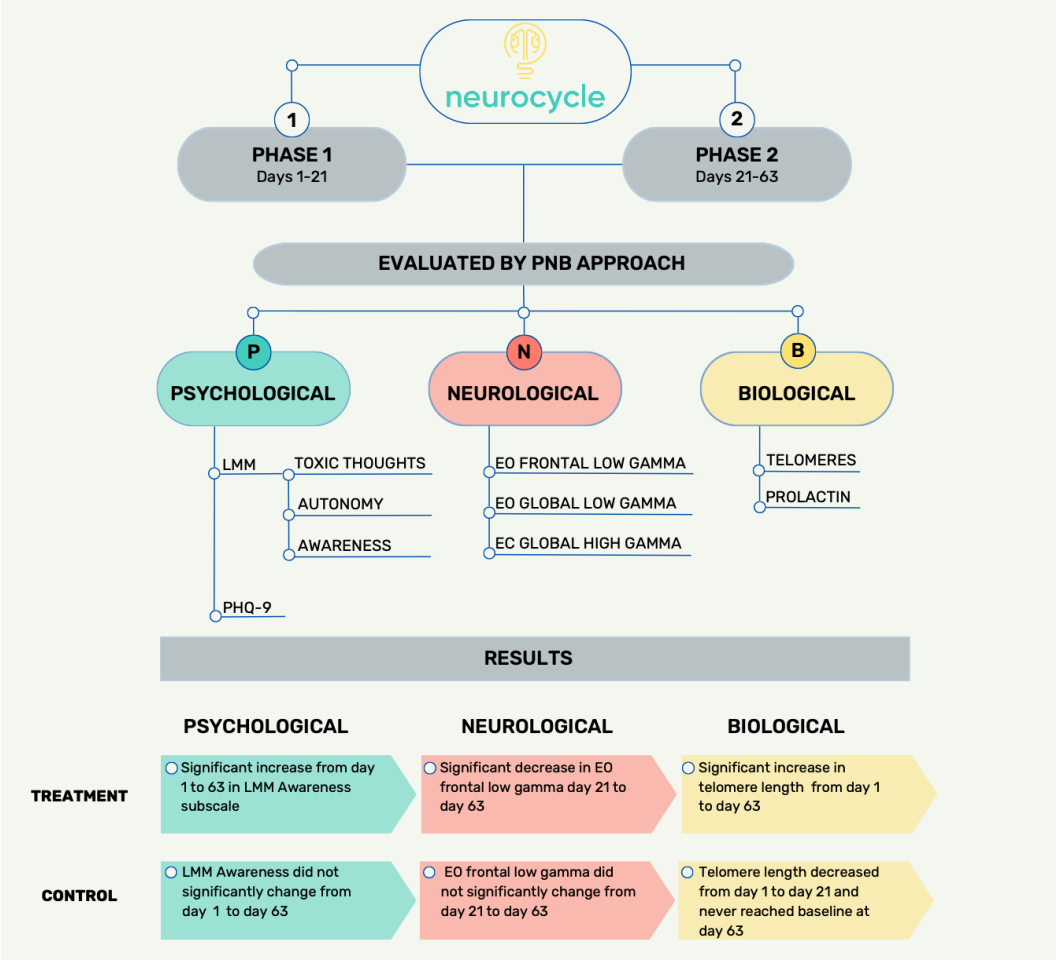
Likewise, the change in prolactin from day 1 to day 63 was a significant predictor of frontal low gamma relative power changes over the same time span. Prolactin is a versatile hormone that has been associated with adaptation to stress and neurogenesis, and it has been shown to help alter neural circuits to help the individual cope with stress (Torner, 2016). It would be improper, however, to

interpret the associated increase in gamma as also being therefore beneficial by association. Instead, we propose that gamma is likely representative of an overall arousal level, or index of local cortical activity, and needs to be interpreted based on context. As discussed in the introduction, gamma activity, like most other brain activity, can be maladaptive in either a hyper- or hypoactive manner (Barry et al., 2010; Lawson, 2013; Roh et al., 2016). The ideal level of activity is a constantly moving target range dependent on a myriad of individual factors and contexts.

Group Differences in Biological Measures

Group differences revealed a smaller decrease in telomere length from day 1 to day 21 in the treatment group. The treatment group was working within a deliberate and guided treatment protocol to reconstruct the new patterns of behaviors and emotions and perspectives, versus the control group which had no specific guidance; therefore, the stressors experienced by both groups were experienced differently, either as the eustress of planning to address challenges or merely bringing up stressors without providing a plan to address them. From day 21 to day 63, both groups exhibited an increase in telomere length; however, the control group never recovered to their baseline length, while the treatment group surpassed their baseline telomere length. We recorded in this biological measure, the pattern of the peak at day 21, followed by changes from day 21 to day 63. Furthermore, within the treatment group, our results showed a correlation between the percent change from baseline to day 63 in overall gamma relative power (30–120 Hz) and telomere length during the EO condition. Similarly, the percentage change from baseline to day 63 in telomere length and improved LMM Toxic Thought scores were also related (Figure 8).

Figure 8. *The Psycho-Neuro-Biological (PNB) Impact of the Neurocycle*.



Note. Gamma, prolactin, telomeres, and psychosocial measurements.

These results suggest a positive correlation between a greater change in telomere length, greater overall gamma change, and improved LMM Toxic Thoughts scores in the same automaticity pattern. From baseline to day 21, percent change in telomere length was also significantly correlated with the percent change in prolactin, indicating that greater change in telomere length was related to greater change in prolactin, with both following the automaticity pattern. Additionally, during the EO condition, the percentage change from day 1 to day 63 in overall gamma (30–120 Hz) was significantly correlated with improved LMM Toxic Thoughts. These results suggest a positive correlation between improved LMM Toxic Thoughts and a greater change in overall gamma activity. It would therefore appear that chronic stress management using the Neurocycle was also reflected in the biological results, which is supported by the literature (Epel, 2009, 2012; Epel et al., 2004) Further research is needed to confirm these results.

Conclusion

Integrating the Psycho-Neuro-Biological to Inform Automaticity and Habit Formation

The brain has evolved to process and encode sensory information and cognitive processes in a manner that utilizes a minimal amount of effort and energy, both biologically and cognitively speaking. Unfortunately, the most effective and energy-efficient way of solving problems is often not the most psychologically healthy solution. It is possible that for some situations, the most energy-efficient solution is not just a nonideal one but could be maladaptive in the long run. An individual can alleviate the exposure to a stressor by suppressing or simply removing oneself from the situation, but this is often unrealistic. Therefore, a more effortful process of discovering why the stressor initiated that strong response and going through a process of self-discovery and reconceptualization are needed to move past that stressor. This requires a great deal more cognitive, emotional, and biological energy to complete; however, it has the potential to provide a more healthy, long-term, solution to that stressor. The present pilot study was conducted to assess the efficacy of the Neurocycle as providing such a planned and guided system to foster effective and sustainable habit formation and the automaticity of complex mental health issues of participants as measured using a psychoneurobiological approach.

Neurophysiological changes were observed as an indicator of improved complex mental health wellness through improved psychosocial state as indicated by decreased LMM Toxic Thoughts, increased autonomy scores, and decreased PHQ-9 stress scores. Neurological and mental health improvement were validated with the measurement of changed gamma levels as correlated with improved self-regulation on the LMM, decreased prolactin blood levels, and increased telomere length from day 21 to day 63, coinciding with decreased self-reporting of symptoms of stress and anxiety. The correlation of these results provides novel support for the connection between gamma as a goldilocks frequency and automaticity and habit formation. Gamma can be too low or too high and is interpreted based on source location (gamma is representative of communication between higher level cortices). Thus, depending on which cortical areas you are talking about, the increase or decrease in gamma can be thought of as an index of overall arousal or activation in that cortical area, expending effort. Furthermore, the automatization effect of habit formation appears to involve frontal low gamma increasing from days 1–21 and then pivoting and decreasing to day 63 to a greater extent for the treatment versus the control group. This potentially shows the hard work being done in days 1–21 as the person is embracing, deconstructing, and reconstructing the issue resulting in low gamma increasing frontally, then calming down as the individual starts to practice using the new habit to stabilize it. The global low gamma is potentially showing that, as the new habit is developing from day 1 to day 21, and then stabilizing from day 21 to day 63, the whole brain gets involved in this complex organic growth-oriented process of the new habit being practiced. Additionally, this could possibly be evidence of complex activity in the nonconscious mind that needs to happen outside of conscious awareness in order to stabilize an effective habit that will be helpful and useful to the individual. The therapeutic alliance effect was evidenced in the significant improvement in awareness and empowerment in the control group over the course of the 63 days.

As this was a pilot study done on a small, nondiverse population, it has limitations. Future research should confirm these relationships with larger data sets and longitudinal studies to understand how to incorporate the science of habit formation and automaticity in improving mental health intervention.

Author Declarations

As an owner of Switch on Your Brain and the Neurocycle, Dr. Caroline Leaf receives financial benefits from royalties for the intellectual property

that is subject to evaluation or improvement through the research presented here. Concerns over financial interest were addressed by the double-blind research design and involvement of an independent third-party research consulting firm. There are no conflicts of interest or grant support to disclose.

References

Aarts, H., & Dijksterhuis, A. (2000). Habits as knowledge structures: Automaticity in goal-directed behavior. *Journal of Personality and Social Psychology, 78*(1), 53–63. https://doi.org/10.1037/0022-3514.78.1.53

Aghayan, S. S, Farajzadeh, A., Bagheri-Hosseinabadi, Z., Fadaei, H., Yarmohammadi, M., &. Jafarisani, M. (2020). Elevated homocysteine, as a biomarker of cardiac injury, in panic disorder patients due to oxidative stress. *Brain and Behavior, 10*(12), e01851. https://doi.org/10.1002/brb3.1851

Aguilera, A. (2015). Digital technology and mental health interventions: Opportunities and challenges. *Arbor, 191*(771), a210. http://doi.org/10.3989/arbor.2015.771n1012

Alda, M., Puebla-Guedea, M., Rodero, B., Demarzo, M., Montero-Marin, J., Roca, M., & Garcia-Campayo, J. (2016). Zen meditation, length of telomeres, and the role of experiential avoidance and compassion. *Mindfulness, 7*, 651–659. https://doi.org/10.1007/s12671-016-0500-5

Alldredge, C. T., Burlingame, G. M., Yang, C. & Rosendahl, J. (2021). Alliance in group therapy: A meta-analysis. *Group Dynamics: Theory, Research, and Practice, 25*(1), 13–28. https://doi.org/10.1037/gdn0000135

Allom, V., Mullan, B., Smith, E., Hay, P., & Raman, J. (2018). Breaking bad habits by improving executive function in individuals with obesity. *BMC Public Health, 18*(1), Article 505. https://doi.org/10.1186/s12889-018-5392-y

Ariyasinghe, S. K., & Arachchige, B. J. H. (2020). The intervention of mindfulness on behavioral change for achieving goals. *International Journal of Scientific and Research Publications, 10* (10), 209–215. http://doi.org/10.29322/IJSRP.10.10.2020.p10631

Armitage, C. J. (2005). Can the theory of planned behavior predict the maintenance of physical activity? *Health Psychology, 24*(3), 235–245. https://doi.org/10.1037/0278-6133.24.3.235

Barry, R. J., Clarke, A. R., Hajos, M., McCarthy, R., Selikowitz, M., & Dupuy, F. E. (2010). Resting-state EEG gamma activity in children with attention-deficit/hyperactivity disorder. Clinical *Neurophysiology, 121*(11), 1871–1877. https://doi.org/10.1016/j.clinph.2010.04.022

Benedetti, F. (2013). Placebo and the new physiology of the doctor-patient relationship. *Physiological Reviews, 93*(3), 1207–1246. https://doi.org/10.1152/physrev.00043.2012

Bjelland, I., Dahl, A. A., Haug, T. T., & Neckelmann, D. (2002). The validity of the Hospital Anxiety and Depression Scale: An updated literature review. *Journal of Psychosomatic Research, 52*(2), 69–77. https://doi.org/10.1016/S0022-3999(01)00296-3

Carden, L., & Wood, W. (2018). Habit formation and change. *Current Opinion in Behavioral Sciences, 20*, 117–122. https://doi.org/10.1016/j.cobeha.2017.12.009

Carlson, L. E., Beattie, T. L., Giese-Davis, J., Faris, P., Tamagawa, R., Fick, L. J., Degelman, E. S., & Speca, M. (2015). Mindfulness-based cancer recovery and supportive-expressive therapy maintain telomere length relative to controls in distressed breast cancer survivors. *Cancer, 121*(3), 476–484. https://doi.org/10.1002/cncr.29063

Casey, M.-B., Smart, K. M., Segurado, R., Hearty, C., Gopal, H., Lowry, D., Flanagan, D., McCracken, L., & Doody, C. (2022). Exercise combined with Acceptance and Commitment Therapy compared with a standalone supervised exercise programme for adults with chronic pain: A randomised controlled trial. *Pain, 163*(6), 1158–1171. https://doi.org/10.1097/j.pain.0000000000002487

Cawthon, R. M., Smith, K. R., O'Brien, E., Sivatchenko, A., & Kerber, R. A. (2003). Association between telomere length in blood and mortality in people aged 60 years or older. *The Lancet, 361*(9355), 393–395. https://doi.org/10.1016/S0140-6736(03)12384-7

Chung, K.-H., Chiou, H.-Y., & Chen, Y.-H. (2017). Associations between serum homocysteine levels and anxiety and depression among children and adolescents in Taiwan. *Scientific Reports, 7*(1), Article 8330. https://doi.org/10.1038/s41598-017-08568-9

Conklin, Q. A., King, B. G., Zanesco, A. P., Lin, J., Hamidi, A. B., Pokorny, J. J., Álvarez-López, M. J., Cosín-Tomás, M., Huang, C., Kaliman, P., Epel, E. S., & Saron, C. D. (2018). Insight meditation and telomere biology: The effects of intensive retreat and the moderating role of personality. *Brain, Behavior, and Immunity, 70*, 233–245. https://doi.org/10.1016/j.bbi.2018.03.003

Conklin, Q., King, B., Zanesco, A., Pokorny, J., Hamidi, A., Lin, J., Epel, E., Blackburn, E., & Saron, C. (2015). Telomere lengthening after three weeks of an intensive meditation retreat. *Psychoneuroendocrinology, 61*, 26–27. https://doi.org/10.1016/j.psyneuen.2015.07.462

Diamond, A. (2013). Executive functions. *Annual Review of Psychology, 64*, 135–168. https://doi.org/10.1146/annurev-psych-113011-143750

Dovis, S., Van der Oord, S., Wiers, R. W., & Prins, P. J. M. (2015). Improving executive functioning in children with ADHD: Training multiple executive functions within the context of a computer game. A randomized double-blind placebo controlled trial. *PLoS ONE, 10*(4), Article e0121651. https://doi.org/10.1371/journal.pone.0121651

Elgellaie, A., Larkin, T., Kaelle, J., Mills, J., & Thomas, S. (2021). Plasma prolactin is higher in major depressive disorder and females, and associated with anxiety, hostility, somatization, psychotic symptoms and heart rate. *Comprehensive Psychoneuroendocrinology, 6*, 100049. https://doi.org/10.1016/j.cpnec.2021.100049

Epel, E. S. (2009). Telomeres in a life-span perspective: A new "psychobiomarker"? *Current Directions in Psychological Science, 18*(1), 6–10. https://doi.org/10.1111/j.1467-8721.2009.01596.x

Epel, E. S. (2012). How "reversible" is telomeric aging? *Cancer Prevention Research, 5*(10), 1163–1168. https://doi.org/10.1158/1940-6207.CAPR-12-0370

Epel, E. S., Blackburn, E. H., Lin, J., Dhabhar, F. S., Adler, N. E., Morrow, J. D., & Cawthon, R. M. (2004). Accelerated telomere shortening in response to life stress. *Proceedings of the National Academy of Sciences (PNAS), 101*(49), 17312–17315. https://doi.org/10.1073/pnas.0407162101

Figueroa, C. A., & Aguilera, A. (2020). The need for a mental health technology revolution in the COVID-19 pandemic. *Frontiers in Psychiatry, 11*, 523. https://doi.org/10.3389/fpsyt.2020.00523

Fiorella, L. (2020). The science of habit and its implications for student learning and well-being. *Educational Psychology Review, 32*, 603–625. https://doi.org/10.1007/s10648-020-09525-1

Fitzgerald, P. J., & Watson, B. O. (2018). Gamma oscillations as a biomarker for major depression: An emerging topic. *Translational Psychiatry, 8*(1), Article 177. https://doi.org/10.1038/s41398-018-0239-y

Fleig, L., Pomp, S., Parschau, L., Barz, M., Lange, D., Schwarzer, R., & Lippke, S. (2013). From intentions via planning and behavior to physical exercise habits. *Psychology of Sport and Exercise, 14*(5), 632–639. https://doi.org/10.1016/j.psychsport.2013.03.006

Frazier, L. D., Schwartz, B. L., & Metcalfe, J. (2021). The MAPS model of self-regulation: Integrating metacognition, agency, and possible selves. *Metacognition and Learning, 16*(2), 297–318. https://doi.org/10.1007/s11409-020-09255-3

Gardner, B. (2012). Habit as automaticity, not frequency. *The European Health Psychologist, 14*, 32–36.

Gardner, B. (2014). A review and analysis of the use of 'habit' in understanding, predicting and influencing health-related behaviour. *Health Psychology Review, 9*(3), 277–295. https://doi.org/10.1080/17437199.2013.876238

Gardner, B., & Lally, P. (2018). Modelling habit formation and its determinants. In B. Verplanken (Ed.), *The psychology of habit* (pp. 207–229). Springer, Cham. https://doi.org/10.1007/978-3-319-97529-0_12

Gardner, B., Lally, P., & Wardle, J. (2012). Making health habitual: The psychology of 'habit-formation' and general practice. *The British Journal of General Practice, 62*(605), 664–666. https://doi.org/10.3399/bjgp12X659466

Greeson, J. M., Zarrin, H., Smoski, M. J., Brantley, J. G., Lynch, T. R., Webber, D. M., Hall, M. H., Suarez, E. C., & Wolever, R. Q. (2018). Mindfulness meditation targets transdiagnostic symptoms implicated in stress-related disorders: Understanding relationships between changes in mindfulness, sleep quality, and physical symptoms. *Evidence-based Complementary and Alternative Medicine, 2018*, Article 4505191. https://doi.org/10.1155/2018/4505191

Haldeman-Englert, C., Turley, R., & Novick, T. (2022). Homocysteine. In *Health Encyclopedia*. New York, NY: University of Rochester Medical Center.

Harvey, A. G., Callaway, C. A., Zieve, G. G., Gumport, N. B., & Armstrong, C. C. (2020, July 21). Applying the science of habit formation to evidence-based psychological treatment: Improving outcomes for mental illness. https://doi.org/10.31234/osf.io/qma4f

Harvey, A. G., Callaway, C. A., Zieve, G. G., Gumport, N. B., & Armstrong, C. C. (2022). Applying the science of habit formation to evidence-based psychological treatments for mental illness. *Perspectives on Psychological Science, 17*(2), 572–589. https://doi.org/10.1177/1745691621995752

Henry, L. A., & Bettenay, C. (2010). The assessment of executive functioning in children. *Child and Adolescent Mental Health, 15*(2), 110–119. https://doi.org/10.1111/j.1475-3588.2010.00557.x

Hima, C. S., Asheeta, A., Chithra, C., N., Sandhya, M. J. N., & Fathima Beevi, U. (2020). A review on brainwave therapy. *World Journal of Pharmaceutical Sciences, 8*(11), 59–66. https://www.wjpsonline.com/index.php/wjps/article/view/review-brainwave-therapy

Hollis, C., Morriss, R., Martin, J., Amani, S., Cotton, R., Denis, M., & Lewis, S. (2015). Technological innovations in mental healthcare: Harnessing the digital revolution. *The British Journal of Psychiatry, 206*(4), 263–265. https://doi.org/10.1192/bjp.bp.113.142612

Howard, M. W., Rizzuto, D. S., Caplan, J. B., Madsen, J. R., Lisman, J., Aschenbrenner-Scheibe, R., Schulze-Bonhage, A., & Kahana, M. J. (2003). Gamma oscillations correlate with working memory load in humans. *Cerebral Cortex, 13*(12), 1369–1374. https://doi.org/10.1093/cercor/bhg084

Hussam, R. N., Rabbani, A., Reggiani, G., & Rigol, N. (2017). Habit formation and rational addiction: A field experiment in handwashing. *Social Science Research Network*. https://doi.org/10.2139/ssrn.3040729

Jameel, L., Valmaggia, L., Barnes, G., & Cella, M. (2022). mHealth technology to assess, monitor and treat daily functioning difficulties in people with severe mental illness: A systematic review. *Journal of Psychiatric Research, 145*, 35–49. https://doi.org/10.1016 /j.jpsychires.2021.11.033

Jensen, O., Kaiser, J., & Lachaux, J.-P. (2007). Human gamma-frequency oscillations associated with attention and memory. *Trends in Neurosciences, 30*(7), 317–324. https://doi.org/10.1016/j.tins.2007.05.001

Jokisch, D., & Jensen, O. (2007). Modulation of gamma and alpha activity during a working memory task engaging the dorsal or ventral stream. *The Journal of Neuroscience, 27*(12), 3244–3251. https://doi.org/10.1523/jneurosci.5399-06.2007

Judah, G., Gardner, B., & Aunger, R. (2013). Forming a flossing habit: An exploratory study of the psychological determinants of habit formation. *British Journal of Health Psychology, 18*(2), 338–353. https://doi.org/10.1111/j.2044-8287.2012.02086.x

Kabat-Zinn, J. (1994). Wherever you go, there you are: Mindfulness meditation in everyday life. Hyperion.

Kazdin, A. E. (2018). *Innovations in psychosocial interventions and their delivery: Leveraging cutting-edge science to improve the world's mental health*. Oxford University Press. https://doi.org/10.1093/med-psych/9780190463281.001.0001

Keller, J., Kwasnicka, D., Klaiber, P., Sichert, L., Lally, P., & Fleig, L. (2021). Habit formation following routine-based versus time-based cue planning: A randomized controlled trial. *British Journal of Health Psychology, 26*(3), 807–824. https://doi.org/10.1111/bjhp.12504

Kennedy, D. O. (2016). B vitamins and the brain: Mechanisms, dose and efficacy—A review. *Nutrients, 8*(2), 68. https://doi.org/10.3390/nu8020068

Kohn, R., Saxena, S., Levav, I., & Saraceno, B. (2004). The treatment gap in mental health care. *Bulletin of the World Health Organization, 82*(11), 858–866.

Kumar, A., Gupta, R. C., Arora, M., Sharma, R., Kumar, D., & Kashmir, J. (2019). Assessment of serum TSH and prolactin levels among patients with major depressive disorder. *International Journal of Research and Analytical Reviews, 6*(1), 266–270. https://ijrar.org/papers/IJRAR19J2228.pdf

Lachman, S. J. (1997). Learning is a process: Toward an improved definition of learning. *The Journal of Psychology, 131*(5), 477–480. https://doi.org/10.1080/00223989709603535

Lally, P., & Gardner, B. (2013). Promoting habit formation. *Health Psychology Review, 7*(Suppl. 1), S137–S158. https://doi.org/10.1080/17437199.2011.603640

Lally, P., van Jaarsveld, C. H. M., Potts, H. W. W., & Wardle, J. (2010). How are habits formed: Modeling habit formation in the real world. *European Journal of Social Psychology, 40*(6), 998–1009. https://doi.org/10.1002/ejsp.674

Lally, P., Wardle, J., & Gardner, B. (2011). Experiences of habit formation: A qualitative study. *Psychology, Health & Medicine, 16*(4), 484–489. https://doi.org/10.1080/13548506.2011.555774

Langer, E. J. (1989). Minding matters: The consequences of mindlessness-mindfulness. In L. Berkowitz (Ed.), *Advances in experimental social psychology* (vol. 22, pp. 137–173). Academic Press. https://doi.org/10.1016/S0065-2601(08)60307-X

Lattie, E. G., Stiles-Shields, C., & Graham, A. K. (2022). An overview of and recommendations for more accessible digital mental health services. *Nature Reviews Psychology, 1*, 87–100. https://doi.org/10.1038/s44159-021-00003-1

Lawson, W. (2013). Autism spectrum conditions: The pathophysiological basis for inattention and the New Diagnostic and Statistical Manual of Mental Disorders (DSM-V). *OA Autism, 1*(1). https://doi.org/10.13172/2052-7810-1-1-343

Leaf, C. M. (1997). The mind-mapping approach: A model and framework for geodesic learning (Doctoral dissertation, University of Pretoria). UPSpace. http://hdl.handle.net/2263/24323

Leaf, C. (2021). *Cleaning up your mental mess: 5 simple, scientifically proven steps to reduce anxiety, stress, and toxic thinking*. Baker Books.

Leaf, C. M., Louw, B., & Uys, I. C. (1997). The development of a model for geodesic learning: The geodesic information processing model. *South African Journal of Communication Disorders, 44*(1), 53-70.

Leaf, C., Paulson, R. M., & Lynch, G. L. (2023). Mindfulness extended into mind-management: A new model and measurement tool for teacher mindfulness training, Manuscript submitted for publication.

Leaf, C. M, Turner, R. P., Paulson, R. M., Lynch, G. L., Leaf, A. (in press). Psychometric testing of a new instrument for assessing individual's mindfulness, mediating abilities, and well-being outcomes: The Leaf Mind Management (LMM) Scale. *Current Psychology*.

Leaf, C. M., Turner, R. P., Wasserman, C. S., Paulson, R. M., Kopooshian, N., Lynch, G. Z., & Leaf, A. (2023). Psycho-neuro-biological correlates of beta Aactivity. *NeuroRegulation, 10*(1), 11–20. https://doi.org/10.15540/nr.10.1.11

Lengacher, C. A., Reich, R. R., Kip, K. E., Barta, M., Ramesar, S., Paterson, C. L., Moscoso, M. S., Carranza, I., Budhrani, P. H., Kim, S. J., Park, H. Y., Jacobsen, P. B., Schell, M. J., Jim, H. S. L., Post-White, J., Farias, J. R., & Park, J. Y. (2014). Influence of mindfulness-based stress reduction (MBSR) on telomerase activity in women with breast cancer (BC). *Biological Research for Nursing, 16*(4), 438–447. https://doi.org/10.1177/1099800413519495

Lennartsson, A.-K., & Jonsdottir, I. H. (2011). Prolactin in response to acute psychosocial stress in healthy men and women. *Psychoneuroendocrinology, 36*(10), 1530–1539. https://doi.org/10.1016/j.psyneuen.2011.04.007

Levine, S., & Muneyyirci-Delale, O. (2018). Stress-induced hyperprolactinemia: Pathophysiology and clinical approach. *Obstetrics and Gynecology International, 2018*, Article 9253083. https://doi.org/10.1155/2018/9253083

Lewis, R., Liu, Y., Groh, M., & Picard, R. (2021). Habit formation dynamics: Finding factors associated with building strong mindfulness habits. In C. Stephanidis, M. Antona, & S. Ntoa (Eds.), *Human-Computer Interaction (HCI) International 2021 Posters, Communications in Computer and Information Science* (vol. 1421, pp. 348–356). Springer, Cham. https://doi.org/10.1007/978-3-030-78645-8_44

Li, X., Jing, Z., Hu, B., & Sun, S. (2016). An EEG-based study on coherence and brain networks in mild depression cognitive process. 2016 IEEE International Conference on Bioinformatics and Biomedicine (BIBM), Shenzhen, China, 1275–1282. https://doi.org/10.1109/BIBM.2016.7822702

Lin, J., & Epel, E. (2022). Stress and telomere shortening: Insights from cellular mechanisms. *Ageing Research Reviews, 73*, 101507. https://doi.org/10.1016/j.arr.2021.101507

Liu, F., Zhang, Z., Liu, S., & Zhang, N. (2021). Examining the effects of brief mindfulness training on athletes' flow: The mediating role of resilience. *Evidence-based Complementary and Alternative Medicine, 2021*, Article 6633658. https://doi.org/10.1155/2021/6633658

Maddux, J. E. (1997). Habit, health, and happiness. *Journal of Sport and Exercise Psychology, 19*(4), 331–346. https://doi.org/10.1123/jsep.19.4.331

Maddux, J. E., & DuCharme, K. A. (1997). Behavioral intentions in theories of health behavior. In D. S. Gochman (Ed.), *Handbook of health behavior research 1: Personal and social determinants* (pp. 133–151). Plenum Press.

Madhavan, R., Millman, D., Tang, H., Crone, N. E., Lenz, F. A., Tierney, T. S., Madsen, J. R., Kreiman, G. & Anderson, W. S. (2015). Decrease in gamma-band activity tracks sequence learning. *Frontiers in Systems Neuroscience, 8*, 222. https://doi.org/10.3389/fnsys.2014.00222

Mainy, N., Kahane, P., Minotti, L., Hoffmann, D., Bertrand, O., & Lachaux, J.-P. (2007). Neural correlates of consolidation in working memory. *Human Brain Mapping, 28*(3), 183–193. https://doi.org/10.1002/hbm.20264

Maltz, M. (1960). Psycho-cybernetics. New York, NY: Prentice-Hall, Inc.

Mantzios, M., & Giannou, K. (2019). A real-world application of short mindfulness-based practices: a review and reflection of the literature and a practical proposition for an effortless mindful lifestyle. *American Journal of Lifestyle Medicine, 13*(6), 520–525. https://doi.org/10.1177/1559827618772036

Mayer, S. E., Guan, J., Lin, J., Hamlat, E., Parker, J. E., Brownell, K., Price, C., Mujahid, M., Tomiyama, A. J., Slavich., G. M., Laraia, B. A., & Epel, E. S. (2023). Intergenerational effects of maternal lifetime stressor exposure on offspring telomere length in Black and White women. *Psychological Medicine, 53*(13), 6171–6182. https://doi.org/10.1017/S0033291722003397

McClelland, M. M., Geldhof, G. J., Cameron, C. E., & Wanless, S. B. (2015). Development and self-regulation. In R. M. Lerner (Ed.), *Handbook of Child Psychology and Developmental Science* (pp. 1–43). https://doi.org/10.1002/9781118963418.childpsy114

Mergelsberg, E. L. P., Mullan, B. A., Allom, V., & Scott, A. (2021). An intervention designed to investigate habit formation in a novel health behaviour. *Psychology & Health, 36*(4), 405–426. https://doi.org/10.1080/08870446.2020.1779272

Mitchell, A. D., Martin, L. E., Baldwin, A. S., & Levens, S. M. (2021). Mindfulness-informed guided imagery to target physical activity: A mixed method feasibility and acceptability pilot study. *Frontiers in Psychology, 12*, Article 742989. https://doi.org/10.3389/fpsyg.2021.742989

Munnangi, S., Sundjaja, J. H., Singh, K., Dua, A., & Angus, L. D. (2022). Placebo effect. In *StatPearls*. StatPearls Publishing.

Nagendra, R. P., Sathyaprabha, T. N., & Kutty, B. M. (2022). Enhanced dehydroepiandrosterone levels are positively correlated with N3 sleep stage in long-term mindfulness meditation practitioners. *Sleep Science, 15*(2), 179–187. https://doi.org/10.5935/1984-0063.20220039

Naslund, J. A., Aschbrenner, K. A., Kim, S. J., McHugo, G. J., Unützer, J., Bartels, S. J., & Marsch, L. A. (2017). Health behavior models for informing digital technology interventions for individuals with mental illness. *Psychiatric Rehabilitation Journal, 40*(3), 325–335. https://doi.org/10.1037/prj0000246

Neal, D. T., & Wood, W. (2009). Automaticity in situ and in the lab: The nature of habit in daily life. In E. Morsella, J. A. Bargh, & P. M. Gollwitzer (Eds.), *Oxford handbook of human action* (pp. 442–456). Oxford University Press.

Newson, J. J., & Thiagarajan, T. C. (2019). EEG frequency bands in psychiatric disorders: A review of resting state studies. *Frontiers in Human Neuroscience, 12*, 521. https://doi.org/10.3389/fnhum.2018.00521

Noda, Y., Zomorrodi, R., Saeki, T., Rajji, T. K., Blumberger, D. M., Daskalakis, Z. J., & Nakamura, M. (2017). Resting-state EEG gamma power and theta–gamma coupling enhancement following high-frequency left dorsolateral prefrontal rTMS in patients with depression. *Clinical Neurophysiology, 128*(3), 424–432. https://doi.org/10.1016/j.clinph.2016.12.023

Oathes, D. J., Ray, W. J., Yamasaki, A. S., Borkovec, T. D., Castonguay, L. G., Newman, M. G., & Nitschke, J. (2008). Worry, generalized anxiety disorder, and emotion: Evidence from the EEG gamma band. *Biological Psychology, 79*(2), 165–170. https://doi.org/10.1016/j.biopsycho.2008.04.005

Orbell, S., & Verplanken, B. (2010). The automatic component of habit in health behavior: Habit as cue-contingent automaticity. *Health Psychology, 29*(4), 374–383. https://doi.org/10.1037/a0019596

Patel, V., Goel, D. S., & Desai, R. (2009). Scaling up services for mental and neurological disorders in low-resource settings. *International Health, 1*(1), 37–44. https://doi.org/10.1016/j.inhe.2009.02.002

Philippe, T. J., Sikder, N., Jackson, A., Koblanski, M. E., Liow, E., Pilarinos, A., & Vasarhelyi, K. (2022). Digital health interventions for delivery of mental health care: Systematic

and comprehensive meta-review. *JMIR Mental Health, 9*(5), e35159. https://doi.org/10.2196/35159

Pines, A. (2013). Telomere length and telomerase activity in the context of menopause. *Climacteric, 16*(6), 629–631. https://doi.org/10.3109/13697137.2013.812603

Pontin, E., Schwannauer, M., Tai, S., & Kinderman, P. A. (2013). A UK validation of a general measure of subjective well-being: The modified BBC subjective well-being scale (BBC-SWB). *Health and Quality of Life Outcomes, 11*(1), Article 150. https://doi.org/10.1186/1477-7525-11-150

Raja-Khan, N., Agito, K., Shah, J., Stetter, C. M., Gustafson, T. S., Socolow, H., Kunselman, A. R., Reibel, D. K., & Legro, R. S. (2017). Mindfulness-based stress reduction in women with overweight or obesity: A randomized clinical trial. *Obesity 25*(8), 1349–1359. https://doi.org/10.1002/oby.21910

Rentscher, K. E., Carroll, J. E., & Mitchell, C. (2020). Psychosocial stressors and telomere length: A current review of the science. *Annual Review of Public Health, 41*, 223–245. https://doi.org/10.1146/annurev-publhealth-040119-094239

Robinson, L., Arden, M. A., Dawson, S., Walters, S. J., Wildman, M. J., & Stevenson, M. (2022). A machine-learning assisted review of the use of habit formation in medication adherence interventions for long-term conditions. *Health Psychology Review, 18*(1), 1–23. https://doi.org/10.1080/17437199.2022.2034516

Roh, S.-C., Park, E.-J., Shim, M., & Lee, S.-H. (2016). EEG beta and low gamma power correlates with inattention in patients with major depressive disorder. *Journal of Affective Disorders, 204*, 124–130. https://doi.org/10.1016/j.jad.2016.06.033

Rothman, A. J., Sheeran, P., & Wood, W. (2009). Reflective and automatic processes in the initiation and maintenance of dietary change. *Annals of Behavioral Medicine, 38*(Suppl. 1), S4–S17. https://doi.org/10.1007/s12160-009-9118-3

Schueller, S. M., Muñoz, R. F., & Mohr, D. C. (2013). Realizing the potential of behavioral intervention technologies. *Current Directions in Psychological Science, 22*(6), 478–483. https://doi.org/10.1177/0963721413495872

Shapiro, S. L., Carlson, L. E., Astin, J. A., & Freedman, B. (2006). Mechanisms of mindfulness. *Journal of Clinical Psychology, 62*(3), 373–386. https://doi.org/10.1002/jclp.20237

Sheeran, P. (2001). Intention–behavior relations: A conceptual and empirical review. In W. Stroebe and M. Hewstone (Eds.), *European Review of Social Psychology* (vol. 12, pp. 1–36). https://doi.org/10.1002/0470013478.ch1

Shen, H., Chen, M., & Cui, D. (2020). Biological mechanism study of meditation and its application in mental disorders. *General Psychiatry, 33*(4), e100214. https://doi.org/10.1136/gpsych-2020-100214

Singh, V., Kumar, A., & Gupta, S. (2022). *Mental health prevention and promotion—A narrative review. Frontiers in Psychiatry, 13*, Article 898009. https://doi.org/10.3389/fpsyt.2022.898009

Smith, K. S., & Graybiel, A. M. (2022). Habit formation. *Dialogues in Clinical Neuroscience, 18*(1), 33–43. https://doi.org/10.31887/DCNS.2016.18.1/ksmith

Sniehotta, F. F. (2009). Towards a theory of intentional behaviour change: Plans, planning, and self-regulation. *British Journal of Health Psychology, 14*(2), 261–273. https://doi.org/10.1348/135910708X389042

Sniehotta, F. F., & Presseau, J. (2012). The habitual use of the Self-report Habit Index. *Annals of Behavioral Medicine, 43*(1), 139–140. https://doi.org/10.1007/s12160-011-9305-x

Stawarz, K., Cox, A. L., & Blandford, A. (2015). Beyond self-tracking and reminders: Designing smartphone apps that support habit formation. *Proceedings of the 33rd Annual ACM Conference on Human Factors in Computing Systems*, 2653–2662. https://doi.org/10.1145/2702123.2702230

Stojanovic, M., Grund, A., & Fries, S. (2022). Context stability in habit building increases automaticity and goal attainment. *Frontiers in Psychology, 13*, Article 883795. https://doi.org/10.3389/fpsyg.2022.883795

Stone, J. Y., Mayberry, L. S., Clouse, K. & Mulvaney, S. (2023). The Role of Habit Formation and Automaticity in Diabetes Self-Management: Current Evidence and Future Applications. *Current Diabetes Reports, 23*(4), 43–58. https://doi.org/10.1007/s11892-023-01499-y

Tallon-Baudry, C., Bertrand, O., Peronnet, F., & Pernier, J. (1998). Induced γ-band activity during the delay of a visual short-term memory task in humans. *The Journal of Neuroscience, 18*(11), 4244–4254. https://doi.org/10.1523/jneurosci.18-11-04244.1998

Taylor, C. B., Fitzsimmons-Craft, E. E., & Graham, A. K. (2020). Digital technology can revolutionize mental health services delivery: The COVID-19 crisis as a catalyst for change. *International Journal of Eating Disorders, 53*(7), 1155–1157. https://doi.org/10.1002/eat.23300

Theorell, T. (1992). Prolactin—A hormone that mirrors passiveness in crisis situations. *Integrative Physiological and Behavioral Science, 27*(1), 32–38. https://doi.org/10.1007/BF02691090

Torner, L. (2016). Actions of prolactin in the brain: From physiological adaptations to stress and neurogenesis to psychopathology. *Frontiers in Endocrinology, 7*, 25. https://doi.org/10.3389/fendo.2016.00025

Trafimow, D. (2018). The automaticity of habitual behaviours: Inconvenient questions. In B. Verplanken (Ed.). The psychology of habit: Theory, mechanisms, change and context (pp. 379–395). Springer, Cham. https://doi.org/10.1007/978-3-319-97529-0_21

Vage, A., McCarron, E., & Hamilton, P. K. (2023). Biological testing during acute psychological stress: A hindrance or an opportunity? *Clinical Biochemistry, 114*, 11–17. https://doi.org/10.1016/j.clinbiochem.2023.01.005

van der Weiden, A., Benjamins, J., Gillebaart, M., Ybema, J. F., & de Ridder, D. (2020). How to form good habits? A longitudinal field study on the role of self-control in habit formation. *Frontiers in Psychology, 11*, Article 560. https://doi.org/10.3389/fpsyg.2020.00560

Verplanken, B. (2006). Beyond frequency: Habit as mental construct. *British Journal of Social Psychology, 45*(3), 639–656. https://doi.org/10.1348/014466605x49122

Verplanken, B. & Orbell, S. (2003). Reflections on past behavior: A self-report index of habit strength. *Journal of Applied Social Psychology, 33*(6), 1313–1330. https://doi.org/10.1111/j.1559-1816.2003.tb01951.x

Wang, X., Sundquist, K., Hedelius, A., Palmér, K., Memon, A. A., & Sundquist, J. (2017). Leukocyte telomere length and depression, anxiety and stress and adjustment disorders in primary health care patients. *BMC Psychiatry, 17*(1), Article 148. https://doi.org/10.1186/s12888-017-1308-0

Wespatat, V., Tennigkeit, F., & Singer, W. (2004). Phase sensitivity of synaptic modifications in oscillating cells of rat visual cortex. *The Journal of Neuroscience, 24*(41), 9067–9075. https://doi.org/10.1523/JNEUROSCI.2221-04.2004

Wong, R. S. K., How, P. N., & Cheong, J. P. G. (2022). The effectiveness of a mindfulness training program on selected psychological indices and sports performance of sub-elite squash athletes. *Frontiers in Psychology, 13*, Article 906729. https://doi.org/10.3389/fpsyg.2022.906729

Wood, W. (2017). Habit in personality and social psychology. *Personality and Social Psychology Review, 21*(4), 389–403. https://doi.org/10.1177/1088868317720362

Wood, W., & Neal, D. T. (2007). A new look at habits and the habit-goal interface. *Psychological Review, 114*(4), 843–863. https://pubmed.ncbi.nlm.nih.gov/17907866/

Wood, W., & Neal, D. T. (2009). The habitual consumer. *Journal of Consumer Psychology, 19*(4), 579–592. https://doi.org/10.1016/j.jcps.2009.08.003

Wood, W., & Rünger, D. (2016). Psychology of habit. Annual Review of Psychology, 67, 289–314. https://doi.org/10.1146/annurev-psych-122414-033417

World Health Organization [WHO]. (2022). World mental health report: Transforming mental health for all. https://www.who.int/publications/i/item/9789240049338

Yegorov, Y. E., Poznyak, A. V., Nikiforov, N. G., Sobenin, I. A., & Orekhov, A. N. (2020). The link between chronic stress and accelerated aging. *Biomedicines, 8*(7), 198. https://doi.org/10.3390/biomedicines8070198

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Investigation of Neopterin and Neurophysiological Measurements as Biomarkers of Anxiety and Stress

Rouxzan Cronje[1], Johanni Beukes[2], Andries Masenge[3], Peet du Toit[1], and Priyesh Bipath[1]*

[1]Department of Physiology, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa
[2]Mindset Neurofeedback, Lydiana, Pretoria, South Africa
[3]Department of Statistics, Faculty of Natural and Agricultural Sciences, University of Pretoria, Pretoria, South Africa

Abstract

The aim of this study was to investigate whether the inflammatory marker neopterin and certain neurophysiological measurements could be used as complementary markers for stress and anxiety symptoms as determined by the Depression, Anxiety, and Stress Scale (DASS-21) questionnaire. A cohort of 158 respondents completed the DASS-21 and biographical questionnaire which were used to stratify health sciences university students between Group A (*n* = 20), who had high levels of symptoms, and Group B (*n* = 20) who had normal levels of stress and anxiety. Neurophysiological measurements were taken from these participants, namely heart rate variability (HRV), blood pressure (BP), blood-volume pulse (BVP), electrodermal activity (EDA), and quantitative electroencephalography (qEEG). Each participant also donated a urine sample which was tested for neopterin concentration using an enzyme-linked immunosorbent assay (ELISA). Neopterin positively correlated with the stress and anxiety scores, while HRV and BVP were negatively correlated with these scores. In terms of qEEG, delta and hibeta wave activity increased in the left and frontal brain regions of participants with high mental health scores, whereas alpha wave activity decreased in these regions. High DASS scores were associated with elevated neopterin concentration and neurophysiological changes (brain waves, HRV, and BVP).

Keywords: anxiety; biomarkers; brainwaves; heart rate variability; inflammation; neopterin; stress

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***Address correspondence to**: Rouxzan Cronje, Department of Physiology, University of Pretoria, Private Bag X323, Gezina 0031, South Africa. Email: u17027617@tuks.co.za

Edited by:
Rex L. Cannon, PhD, Currents, Knoxville, Tennessee, USA

Reviewed by:
Rex L. Cannon, PhD, Currents, Knoxville, Tennessee, USA
Randall Lyle, PhD, Mount Mercy University, Cedar Rapids, Iowa, USA

Introduction

The number of people who suffer from mental health conditions is increasing. Between 1990 and 2019, cases of mental health disorders increased by 48% (Ferrari et al., 2022). Of these, the cases of anxiety disorders increased by nearly 50% and depressive disorders increased by 64% (Ferrari et al., 2022; Yang et al., 2021). Mental health conditions are among the most costly disorders in terms of projected healthcare expenditures needed to treat them (Tomlinson et al., 2009). Accordingly, the global economic impact of these conditions is estimated to be US$3–7 trillion each year (due to medical costs, disability, and lost productivity; Arias et al., 2022). Despite the pervasive and increasing effects of mental health, the medical resources, interventions, and funding allocated to treating them are not proportional to the actual burden. In many countries, less than 1% of government health expenditure goes towards mental health services, with the average expenditure being only 2.8% (Rajkumar, 2022; Saxena et al., 2003; Whiteford et al., 2013).

Not only is mental health a major concern globally but it is also of particular importance for medical students who have a high incidence of anxiety, depression, burnout, and mental health struggles (Dyrbye et al., 2005; Fares et al., 2016). Studies suggest that medical students often have higher levels of psychological distress than the general population, and their age-matched peers (Dyrbye et al., 2006; Goebert et al., 2009; Maser et al., 2019). This may have an adverse effect on academic performance, empathy, and the care of their

patients, as well as contribute to other negative professional and personal aspects (Dyrbye et al., 2010; Hojat et al., 2004; Thomas et al., 2007).

Stress, Anxiety, and Depression

Stress is commonly defined as the response to a real or perceived threat to homeostasis (Charmandari et al., 2005; Johnson et al., 2019; Smith & Vale, 2006). This response involves physiological, endocrine, and cognitive reactions, which aid in survival (Charmandari et al., 2005; Sapolsky et al., 2000). Although the stress response is a normal and healthy physiological process to help restore homeostasis, prolonged stress can become maladaptive and detrimental. Chronic stress is an important risk factor for the development of many disorders, including anxiety (Pêgo et al., 2010), depression (Kessler, 1997), and cardiovascular disease (CVD; Satyjeet et al., 2020).

Anxiety disorders are a considerable problem worldwide (Buist-Bouwman et al., 2006), and are characterized by excessive worry, fear, and other psychological and physiological alterations (American Psychiatric Association [APA], 2013; 2013; Steimer, 2002; Wilmer et al., 2021). Anxiety can interfere with quality of life, impacting health, emotion regulation, social and occupational function, and the ability to cope successfully with challenges (Steimer, 2002; Wilmer et al., 2021). Aberrations in neurotransmitters, stress hormones, and the autonomic nervous system (ANS) are thought to be involved in its pathophysiology (Bagdy, 1998; Crestani et al., 1999; Gass et al., 2001; Ho et al., 2020; Holwerda et al., 2018; Mitra & Sapolsky, 2008; Nutt & Malizia, 2001; Risbrough & Stein, 2006; Steimer, 2002; Tanaka et al., 2000; Teed et al., 2022; Weinstock, 2001). In addition to stress, genetic, environmental, and experiential factors also contribute to the risk of developing anxiety (Pêgo et al., 2010; Steimer, 2002).

Depression is characterized by feelings of sadness, emptiness, and/or irritability, which are accompanied by somatic and cognitive changes that significantly impact a person's capacity to function (APA, 2013). It should be noted that these symptoms are present every day and are distinguished from normal feelings of sadness or grief, which reduce in intensity over time (APA, 2013). There are many factors that contribute to the risk of developing depression in university students. These include confidence, personality, academic pressure, preexisting conditions, lifestyle choices, social support, and financial struggles (Mohammad, 2021). In addition to these, stress is also a risk factor for depression (Kessler, 1997; Raison & Miller, 2003).

DASS-21 Questionnaire

The Depression, Anxiety, and Stress Scale (DASS) was designed to measure mental health aspects on three scales. The Depression scale reflects self-esteem and motivation, while the Anxiety scale reflects feelings of fear, panic, and arousal. The third scale, Stress, measures tension, irritability, and difficulty relaxing (Lovibond & Lovibond, 1995). Each scale of the DASS assesses unique features of the three conditions, which reduces the overlapping or intercorrelation of the measurements, thus increasing the ability to distinguish between depression, anxiety, and stress. The short-form version of DASS, which consists of 21 questions (DASS-21), was used in this study. The DASS has been found to be a reliable and valid measure in both clinical and nonclinical samples (Akin & Çetin, 2007; Antony et al., 1998; Beaufort et al., 2017; Crawford & Henry, 2003; De Beurs et al., 2001; Dreyer et al., 2019; Henry & Crawford, 2005; Jiang et al., 2020; Tonsing, 2014; Tran et al., 2013).

The DASS questionnaire is a dimensional rather than a categorical measure. As such, it should not be used to diagnose participants into discrete categories proposed in classification systems such as the *Diagnostics and Statistical Manual of Mental Disorders*, but rather should be used as a screening tool to assess symptom severity.

Although mental health aspects can be determined through the administration of self-assessment questionnaires, suitable physiological measurements may be necessary to complement and substantiate the questionnaire facets surveyed. Adjunct physiological biomarkers may contribute to the scientific understanding of mental well-being and may be advantageous in improving the management thereof. For example, some but not all depressed patients present with elevated inflammation (Osimo et al., 2020), as such an inflammatory biomarker could be useful in identifying this subset of patients and thus prescribing an appropriate course of treatment.

The body of research investigating the links between mental health and inflammation is growing. Studies involving the effects of proinflammatory cytokines on the brain suggest that inflammation may have a pivotal role in the pathophysiology and symptom severity of stress, anxiety, and depression (Bankier et al., 2008; Bauer & Teixeira, 2019; Dowlati et al., 2010; Hoge et al., 2009; Osimo et al., 2020; Pace &

Miller, 2009; Pace et al., 2007; Valkanova et al., 2013; Von Känel et al., 2007).

Neopterin: A Biomarker of Inflammation

Neopterin is a molecule that forms part of the pteridine family. It is also known as 2-amino-4-hydroxy-(erythro-1,2,3-trihydroxypropyl)-pteridine (Hamerlinck, 1999). Neopterin is synthesized from guanosine-5′-triphosphate (GTP) and forms part of the tetrahydrobiopterin (BH4) synthetic pathway (Ghisoni et al., 2015).

The main source of neopterin in humans is monocytes and macrophages, which produce neopterin when stimulated by interferon-γ (IFNγ); a cytokine produced by immune cells (Huber et al., 1984). Activated T-lymphocytes, particularly Th1 cells, produce IFNγ which stimulates macrophages, resulting in the production of neopterin (Huber et al., 1984; Maggi et al., 1992). Therefore, neopterin is reflective of immune activation and considered to be a nonspecific biomarker of cell-mediated immunity because it reflects the production and effects of IFNγ, in addition to Th1 cell and macrophage activity (Berdowska & Zwirska-Korczala, 2001; Dunbar et al., 1992). As such, neopterin has been used as a marker of immune activation during inflammation in a broad range of conditions, including cancer (Berdowska & Zwirska-Korczala, 2001), CVD (Fuchs et al., 2009; Pacileo et al., 2007), and infectious diseases (Eisenhut, 2013).

Neopterin may provide a link between mental health and inflammation, as it could reflect one mechanism by which immune system activation can affect neurotransmitters (Klaus et al., 2021). In addition, neopterin levels have been found to change significantly during periods of psychological stress, suggesting a correlation between mental state and alterations in cell-mediated immunity (Dunbar et al., 1993). Furthermore, inflammation-induced stimulation of indoleamine 2,3-dioxygenase (IDO) and the kynurenine pathway can contribute to tryptophan depletion and decreased serotonin, which has been associated with depression (Albert et al., 2012; Maes et al., 1994; Müller & Schwarz, 2007; Myint et al., 2013; Myint & Kim, 2003; O'Connor et al., 2009) and anxiety (Bagdy, 1998; Blokland et al., 2002). This relates to neopterin as tryptophan depletion and increased kynurenine have been found to be correlated with neopterin (Brown et al., 1989; Maes et al., 1994). Despite the potential mental health effects, tryptophan depletion by the immune system is purposeful, as it can reduce microbial proliferation (Gao et al., 2020). Considering these findings, neopterin has potential to be an immunological marker for mental health conditions.

In terms of assessing immune activity, cytokines, such as IFNγ, can be measured. However, monitoring neopterin instead may be superior as it is biochemically inert and has a longer half-life. These properties allow neopterin to reach and stay in circulation, unlike other cytokines, which have a short half-life and may not reach circulation (Fuchs et al., 2009). Once in circulation, neopterin levels can be measured with ease due to its unchanged excretion by the kidneys (Berdowska & Zwirska-Korczala, 2001), allowing it to be quantified in the urine using validated assays such as an enzyme-linked immunosorbent assay (ELISA; Fuchs et al., 2009; Gieseg et al., 2018).

Measures of Autonomic Activity

Fluctuations between the dominance of the sympathetic and parasympathetic nervous system is part of normal and healthy responses to maintain homeostasis; however, when stress becomes chronic, an imbalance between these two systems can result in negative health outcomes. Namely, chronic stress and the imbalance of the ANS are implicated in the pathogenesis of anxiety and depression (Godoy et al., 2018). As such, measuring aspects of ANS activity and finding suitable biomarkers thereof may contribute to the management of mental health symptoms.

Heart rate variability (HRV) is a measure of ANS activity; it measures fluctuations in heartbeat intervals (Hourani et al., 2020). As stated by Shaffer and Ginsberg, “a healthy heart is not a metronome; the oscillations of a healthy heart are complex and constantly changing, which allow the cardiovascular system to rapidly adjust to sudden physical and psychological challenges to homeostasis” (Shaffer & Ginsberg, 2017). Therefore, HRV is indicative of ANS flexibility in response to stressors and can be used to assess the links between the stress response and neuropsychological parameters (Hourani et al., 2020). Abnormalities in HRV may serve as a biomarker for various mental health disorders and stress-related variables (Hourani et al., 2020; Shinba, 2017). For example, there is an association between reduced HRV and mental health conditions, such as anxiety and depression (Hourani et al., 2020; Schiweck et al., 2019). This is not entirely surprising given the high comorbidity observed between CVD and depression (Cohen et al., 2015). Conversely, higher HRV is associated with increased resilience, greater recovery from acute stressors, changes in cognitive performance

and emotional regulation, and less vulnerability to depressive-like states (Hourani et al., 2020). Due to this, HRV could serve as a measure of neuropsychological parameters and ANS activity. However, HRV should not be used as a single indicator or as a diagnosis.

Other measures of ANS activity include blood volume pulse (BVP) and electrodermal activity (EDA), which have been used as biomarkers of psychological arousal (Kushki et al., 2011) and emotional states such as depression (Sarchiapone et al., 2018). BVP is a measure of the volume of blood in the arteries, which is related to the constriction and dilation of the vessels (Sarchiapone et al., 2018). Greater vasoconstriction leads to lower volume of blood in the vessels, so BVP decreases. Greater vasodilation leads to a greater blood volume, so BVP increases. Therefore, BVP is reflective of ANS activity, as autonomic activation of adrenergic receptors on blood vessels can cause vasoconstriction (Gordan et al., 2015; Peper et al., 2007; Sarchiapone et al., 2018). Of relevance, ANS activity changes with emotions, thus an emotion like fear can lead to vasoconstriction (Kreibig, 2010).

Previous research using BVP as a biomarker found it to be useful in measuring anxiety levels, although it was more accurate when combined in a model with other physiological measures (Šalkevicius et al., 2019). Another study used BVP to create a model for short-term anxiety recognition (Handouzi et al., 2014). Little research has been done on the use of BVP as a biomarker, particularly in the area of mental health, thus warranting further investigation.

EDA (also known as skin conductance) depends on the electrical conductivity of the skin, which is altered by sweat levels. ANS activity affects the amount of sweat on the skin due to eccrine sweat glands having sympathetic innervation. Thus, EDA can be used to measure sympathetic activity of the ANS (Kushki et al., 2011; Sarchiapone et al., 2018). EDA has potential as a biomarker for mental health as studies have found electrodermal hypoactivity in depression. Thus, EDA can be useful in distinguishing depressive patients from healthy patients (Sarchiapone et al., 2018).

Blood pressure (BP) can also be used to assess ANS activity. For example, hypertension may be indicative of ANS abnormalities and imbalance (Edwards et al., 2011). In addition, chronic stress has been shown to increase heart rate and BP (Torpy et al., 2007). Given that many physiological systems influence BP, it clearly cannot be used in isolation as a single biomarker for mental health conditions. This warrants further studies for its link and usefulness when combined with other measures.

Quantitative Electroencephalography (qEEG)

Electroencephalography (EEG) is a medical imaging technique that measures the electrical activity of the brain (Rojas et al., 2018; Teplan, 2002).

The electrical currents detected by an EEG are referred to as brain waves which are measured from the peak of one wave to the peak of another (Teplan, 2002). There are four main categories of brain waves: delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), and beta (12–38 Hz). Different brain regions do not simultaneously produce the same frequency of brain waves, they produce varying amounts of each frequency. Therefore, signals between EEG electrodes consist of many waves that have differing characteristics (Teplan, 2002).

Different brainwaves are associated with different states. For example, when an individual's eyes are open, beta waves are usually dominant. When an individual is relaxed or drowsy, alpha activity rises. As an individual moves into a sleep state, lower frequency waves such as theta and delta increase (Teplan, 2002).

Quantitative EEG (qEEG) involves the digitalization of raw EEG measurements. Complex algorithms then allow for the creation of brain maps using EEG readings. These maps can be used to examine the power, amplitude, coherence, and lag phase of different brain waves. There are two types of power measured by qEEG: absolute power (the electrical power at each site of measurement) and relative power (the distribution of power at one site compared to other sites; Neurofeedback Alliance, 2021).

Quantification of EEG recordings may give further insight into mental health and potential markers. For example, qEEG allows the identification of abnormalities, such as frontal alpha asymmetries that are often observed in depressed patients (Kanda et al., 2009). A preliminary study also found that participants with higher activity in the right anterior of the brain reported a greater tendency to feel anxious a year later. Thus, right frontal EEG activity may act as a vulnerability marker and predict the future onset of anxiety symptoms (Blackhart et al., 2006). Other studies have also found greater relative right frontal EEG activity in those with

anxious or depressive symptoms (Blackhart et al., 2006).

Materials and Method

Study Design and Participants

This study was noninterventional, observational, and cross-sectional. The participants were students from the Faculty of Health Sciences at the University of Pretoria, South Africa, who were recruited online via a biographical questionnaire and the DASS-21.

A total of 158 respondents completed the online questionnaires. A cohort of 78 respondents met the inclusion requirements for physiological measurements. A total of 40 participants were recruited for the measurements and were divided into Group A (n = 20) and Group B (n = 20) based on their DASS questionnaire scores. Participants qualified for Group A if they scored Moderate, Severe, or Extremely Severe in the Anxiety and/or Stress categories of the DASS questionnaire. Participants qualified for Group B if they scored Normal or Mild on all three DASS categories.

Participants were not included if they did not sign informed consent, complete the questionnaires, and/or withdrew from the study at any time, thus not completing the measurements (qEEG, HRV, BP, BVP, EDA, and donate a urine sample), or did not have qualifying DASS scores. Other exclusion criteria included having epilepsy, use of recreational drugs, use of medication that may alter EEG readings (e.g., barbiturates, antidepressants, antipsychotics, antihypertensives), use of anti-inflammatory drugs, a chronic or recent infection, or an inflammatory disorder.

Institutional Review Board Statement

This study was conducted in accordance with the recommendations of the Research Ethics Committee at the University of Pretoria (210/2022) and with approval of the Dean of the Health Sciences Faculty. Furthermore, this study complied with the Declaration of Helsinki, and with South African privacy law. Participation was voluntary, and participants could withdraw at any time without any negative consequences. All data were stored only by using an anonymous ID for each participant and the data obtained were used solely for scientific purposes.

Measures

The electrodes for the qEEG were placed according to the 10–20 electrode placement protocol. The measurements from the 19 active electrodes were transferred to the qEEG Pro program (BrainMaster Technologies Inc., Bedford, OH). This program analyzed and compared the recordings to the qEEG Pro normative database.

HRV was measured using the Zephyr BioHarness and Ominisense software (Medtronic PLC, Midrand, South Africa). Further analysis was conducted using Kubios software (Kubious Oy, Kuopio, Finland). Eleven HRV parameters were investigated: mean HRV, mean RR, standard deviation of normal-to-normal (SDNN), root mean square of successive differences between normal heartbeats (RMSSD), low-frequency (LF) peak, high-frequency (HF) peak, LF power, HF power, LF/HF ratio, sympathetic nervous system (SNS) index, and parasympathetic nervous system (PNS) index (SD1 and SD2).

BVP and EDA were measured using the Infiniti Pro biofeedback apparatus (Thought Technology Ltd., Montreal, Canada), whereby sensors were placed on the fingers. BP was measured using an automated BP monitor (Clicks Retailers [Pty] Ltd., Woodstock, Cape Town).

The Demeditec ELISA kit (Demeditec Diagnostics GmbH, Kiel, Germany) was used for the determination of urine neopterin concentrations according to the manufacturer's protocol.

Statistical Analysis

Data was analyzed using IBM SPSS Statistics version 28.0.1.0 software. Spearman's Rank Correlation was used as the measure of association between two variables. The independent samples t-test was used to determine if there was a significant difference in means between Group A and B. For variables that did not have a normal distribution, the Mann-Whitney U test was also performed. A p-value of less than .05 was considered significant.

For variables that were not normally distributed, the median, interquartile range (IQR), and p-value for the Mann-Whitney U test were also reported. Normality was determined through having a Shapiro-Wilk p-value of less than .05. For variables where no median, IQR, or Mann-Whitney p-value is reported, normality was assumed.

Table 1

Comparison of Means Between Group A and B

	Group A	Group B		Group A	Group B	
	Mean ± SD		*t*-test *p*-value	Median (IQR)		M-W *p*-value
Demographics						
Year of Study	3.45 ± 1.90	4.00 ± 3.60		-	-	-
Age	22.35 ± 3.27	23.85 ± 3.60		-	-	-
DASS Scores						
Stress Score	24.10 ± 6.79	9.20 ± 5.09	<.001**	-	-	-
Anxiety Score	20.60 ± 8.03	4.65 ± 3.28	<.001**	20.00 (11.00)	4.00 (7.00)	<.001**
Depression Score	13.22 ± 7.87	5.20 ± 3.07	<.001**	12.00 (13.00)	6.00 (6.00)	<.001**
Neopterin						
Neopterin (µmol neopterin/ µmol creatinine)	33.81 ± 22.80	13.22 ± 10.52	<.001	31.40 (38.39)	10.47 (15.47)	.002**
Heart Rate Variability						
PNS Index	2.64 ± 1.09	2.12 ± 1.24	.171	-	-	-
SNS Index	−1.80 ± 0.63	−1.49 ± 0.84	.204	−1.83 (0.80)	−1.64 (1.38)	.242
Mean HRV	57.07 ± 15.36	74.21 ± 15.61	.002**	59.74 (27.14)	80.68 (33.54)	.001**
Mean RR (ms)	1381.33 ± 196.74	1259.49 ± 235.71	.084	-	-	-
SDNN (ms)	54.48 ± 12.42	63.91 ± 14.27	.032*	-	-	-
RMSDD (ms)	60.92 ± 15.51	67.15 ± 14.87	.202	-	-	-
Peak LF (Hz)	0.074 ± 0.038	0.066 ± 0.027	.430	0.05 (0.07)	0.06 (0.03)	.845
Peak HF (Hz)	0.186 ± 0.034	0.186 ± 0.022	.993	0.17 (0.04)	0.18 (0.04)	.614
LF Power (ms^2)	1601.71 ± 993.97	2031.41 ± 1306.90	.254	1013.15 (1895.61)	2142.80 (1876.49)	.351
HF Power (ms^2)	956.67 ± 644.01	1254.97 ± 643.07	.151	778.82 (983.69)	1036.40 (1045.70)	.149
LF/HF	1.79 ± 0.78	1.78 ± 1.18	.991	1.54 (1.15)	1.68 (2.03)	.940
SD1 (ms)	43.26 ± 11.02	47.69 ± 10.55	.202	-	-	-
SD2 (ms)	62.53 ± 14.66	75.97 ± 19.40	.018*	-	-	-
Blood Pressure						
Systolic BP (mmHg)	116.08 ± 8.45	121.43 ± 13.88	.149	-	-	-
Diastolic BP(mmHg)	81.30 ± 7.19	81.10 ± 7.98	.934	-	-	-
Blood-Volume Pulse						
Mean BVP Amplitude (%)	8.81 ± 4.18	11.84 ± 6.60	.091	-	-	-
Min BVP Amplitude (%)	3.57 ± 2.27	4.3 ± 2.28	.278	3.22 (3.64)	3.88 (3.69)	.267
Max BVP Amplitude (%)	19.90 ± 10.22	18.54 ± 10.02	.672	-	-	-
Mean BVP FFT Peak Frequency (Hz)	0.16 ± 0.07	0.13 ± 0.07	.240	-	-	-
Min BVP FFT Peak Frequency (Hz)	0.04 ± 0.06	0.04 ± 0.05	.775	0.02 (0.00)	0.02 (0.00)	.820
Max BVP FFT Peak Frequency (Hz)	0.28 ± 0.08	0.25 ± 0.08	.106	-	-	-
Electrodermal Activity						
Mean EDA (µSiemens)	1.15 ± 0.86	1.31 ± 1.18	.647	0.99 (1.64)	1.15 (1.18)	.988

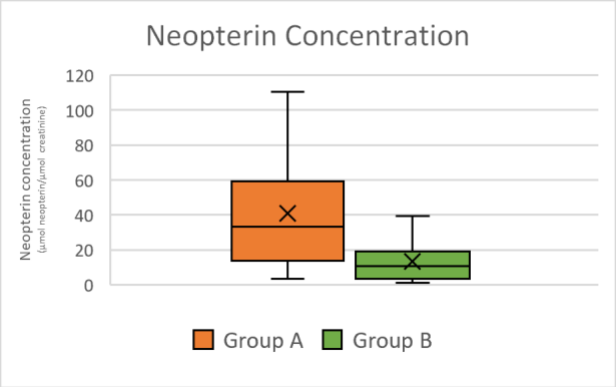
* = Difference in means is significant at the .05 level; ** = Difference in means is significant at the .01 level. The two-sided independent samples *t*-test was performed. *Df* = 38; *n* = 40; The nonparametric Mann-Whitney U test was also performed for variables that were not considered to be normally distributed (determined using the Shapiro-Wilk test).

Results

Group A consisted of 18 females and 2 males. Group B consisted of 12 females and 8 males. There was a significant difference between the DASS scores of the Group A and B (p < .001 for each category). For Group A, the mean scores were moderate for stress (24.10 ± 6.79), extremely severe for anxiety (20.60 ± 8.03), and mild/moderate for depression (13.22 ± 7.87). The mean scores for participants in Group B were Normal for the categories of stress (9.20 ± 5.09), anxiety (4.65 ± 3.28) and depression (5.20 ± 3.07). Group B had less variation in scores than Group A, as can be seen in Table 1.

There was a significant difference in the concentration of neopterin between Group A and B. Group A had a higher concentration of neopterin than Group B (33.81 ± 22.80, 95% CI [22.47, 45.15] vs. 13.22 ± 10.5, 95% CI [8.29, 18.14]; p < .001). The distributions can be seen in the neopterin boxplot (Figure 1).

Figure 1. *Boxplot of Neopterin Concentration*.



Note. The boxplot shows the concentrations of neopterin between the Group A (n = 20) and Group B (n = 20).

The mean values for the power of hibeta, beta, and theta at each electrode were not significantly different between the groups. Only frequencies and electrodes that showed a significant difference are shown in Table 2. None of the electrode positions in the theta, beta, or hibeta band showed a significant difference in mean.

Table 2

Comparison of Mean Power at Various Electrodes Between Group A and B

	Group A	Group B		Group A	Group B	
	Mean ± SD		*t*-test *p*-value	Median (IQR)		M-W *p*-value
Absolute Power						
Delta FP1	0.38 ± 0.48	−0.34 ± 0.72	.002**	-	-	-
Delta FP2	0.63 ± 0.68	−0.26 ± 0.73	<.001**	-	-	-
Relative Power						
Delta FP2	−1.39 ± 1.08	−2.73 ± 1.71	.005**	-	-	-
Delta Fz	−1.74 ± 2.11	−3.98 ± 3.75	.025*	−1.65 (2.80)	−4.15 (4.38)	.038*
Alpha FP1	−1.40 ± 1.37	−0.48 ± 1.53	.051	-	-	-
Alpha T3	−2.03 ± 1.09	−1.20 ± 1.29	.033*	-	-	-

* = Difference in means is significant at the .05 level; ** = Difference in means is significant at the .01 level. The two-sided independent samples *t*-test was performed. *Df* = 38; n = 40; The nonparametric Mann-Whitney U test was also performed for variables which were not considered to be normally distributed (determined using the Shapiro-Wilk test).

In terms of a difference in mean or correlation with DASS scores, the only notable electrodes were FP1, FP2, F7, F3, Fz, and T3, and the only notable frequencies were delta, alpha, and hibeta. No significant correlation or difference in mean was found at any of the other electrodes or frequencies (theta and beta). All notable correlations are presented in Table 3.

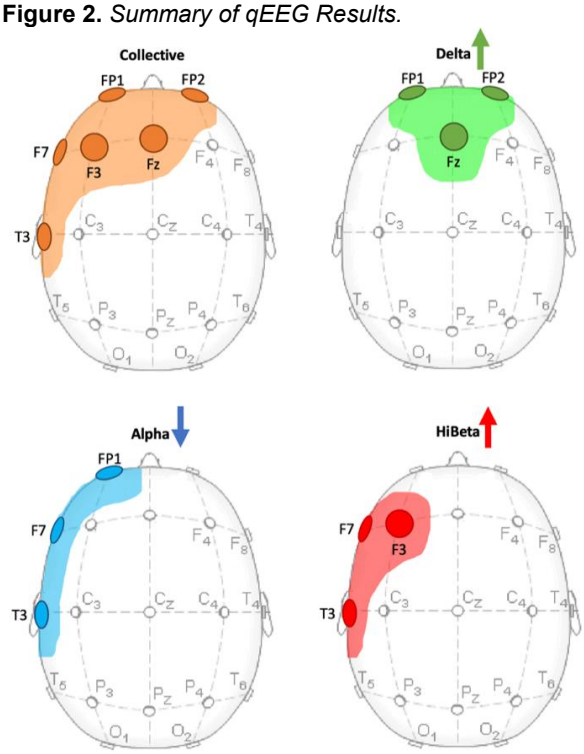
Table 3
Correlations Between Parameters.

	Spearman's Correlation Coefficient	*p*-value
Stress Score and:		
Anxiety Score	0.829	<.001**
Depression Score	0.732	<.001**
Neopterin	0.588	<.001**
Mean HRV	−0.433	.005**
FP1 Z-Delta Absolute Power	0.373	.027*
FP2 Z-Delta Absolute Power	0.344	.030*
T3 Z-Alpha Relative Power	−0.379	.016*
F3 Z-HiBeta Relative Power	0.323	.042*
T3 Z-HiBeta Relative Power	0.333	.036*
Anxiety Score and:		
Stress Score	0.823	<.001**
Depression Score	0.642	<.001**
Neopterin	0.426	.006**
Mean HRV	−0.365	.021*
Min BVP Amplitude	−0.366	.020*
Mean BVP Amplitude	−0.344	.030*
FP2 Z-Delta Absolute Power	0.374	.018*
F7 Z-Alpha Relative Power	−0.324	.042*
T3 Z-Alpha Relative Power	−0.399	.011*
F7 Z-HiBeta Relative Power	0.325	.041*
F3 Z-HiBeta Relative Power	0.359	.023*
Depression Score and:		
Stress Score	0.732	<.001**
Anxiety Score	0.642	<.001**
Neopterin	0.451	.003**
Age	−0.315	.048*
Mean HRV	−0.383	.015*
BVP Min Amplitude	−0.400	.011*
BVP Mean Amplitude	−0.368	.019*
BVP Max FFT Peak Frequency	0.387	.014*

Note. Only correlations that had $p < .05$ are presented.
* = Correlation is significant at the 0.05 level (2-tailed);
** = Correlation is significant at the 0.01 level (2-tailed).
BVP – blood-volume pulse; FFT – fast Fourier transform; HRV – heart rate variability; $n = 40$.

The significant results regarding the qEEG measures are summarized in Figure 2. The results suggest that delta power increased, alpha power decreased, and hibeta increased with stress and anxiety symptoms.

Figure 2. *Summary of qEEG Results.*



Note. Electrodes at which there was a significant correlation with DASS score or difference in mean were included. The first image (Collective, in orange) shows all the electrodes with a significant association. The inclusion of FP1 in the alpha frequency should be treated with caution given that the *p*-value for the difference in means was .051 and not $p < .05$.

Discussion

Subjectivity, misdiagnosis, and social stigma can interfere with the detection, prevention, and treatment of mental health problems (Forgione, 2018; Rössler, 2016; Wakefield, 2010). Therefore, more objective measures such as biomarkers are necessitated to aid in the identification and treatment of mental health disorders (García-Gutiérrez et al., 2020; Guest, 2017; Macaluso & Preskorn, 2012; Roffman, 2011). As the ANS is implicated in stress and anxiety (Chu et al., 2022; Godoy et al., 2018; Ho et al., 2020; Holwerda et al., 2018; Teed et al., 2022), biomarkers measuring ANS activity were investigated in this study, namely HRV, BP, BVP, EDA, and qEEG. Additionally, inflammation appears

to have a bidirectional relationship with stress and anxiety (Bauer & Teixeira, 2019; Hodes et al., 2015; Maes et al., 1998; Maydych, 2019; Silverman et al., 2005; Von Känel et al., 2007). Therefore, the inflammatory marker neopterin was also investigated as a possible biomarker of stress and anxiety scores. The study aimed to determine whether the aforementioned biomarkers could be used as complementary markers for stress and anxiety scores as determined by the DASS-21 questionnaire.

Neopterin

Neopterin concentration was found to be significantly higher in Group A, compared to Group B, and was positively correlated with scores for stress, anxiety, and depression. This is in line with other studies that found increased neopterin in depression (Dunbar et al., 1992; Klaus et al., 2021; Maes et al., 1994; Widner et al., 2002), PTSD (Atmaca et al., 2002), and psychological stress (Dunbar et al., 1993). Increased inflammatory markers have also been found in panic disorder (Hoge et al., 2009) and generalized anxiety disorder (Bankier et al., 2008). It should be noted that the neopterin concentrations found in the present study correlated with symptom severity and not diagnosed disorders.

Our results also support other studies that found inflammation to be connected to stress (Maydych, 2019; Raison et al., 2006), anxiety (Bankier et al., 2008; Hoge et al., 2009; Maydych, 2019; Vogelzangs et al., 2013), and depression (Dowlati et al., 2010; Inserra et al., 2019; Raison et al., 2006; Valkanova et al., 2013).

The exact nature of the association between neopterin and mental health symptom severity requires further research. However, macrophage activation, IFNγ, and oxidative stress may provide potential mechanisms, as neopterin is associated with the levels of these (Fuchs et al., 2009; Gieseg et al., 2018; Huber et al., 1984; Maes et al., 1998; Monteiro et al., 2016; Nathan, 1986). In addition, the aforementioned all contribute to or have been associated with mental health symptoms (Bouayed et al., 2009; Inserra et al., 2019; Monteiro et al., 2016; Salim, 2014). For example, macrophage infiltration into the brain can increase neuroinflammation, which contributes to anxiety and depression (Dunn, 2006; Haroon et al., 2012; Maes et al., 1992; Quagliato & Nardi, 2018; Raison et al., 2006; Reader et al., 2015; Torres-Platas et al., 2014; Wohleb et al., 2013). Neurotransmitter abnormalities due to IFNγ may also be involved, as this cytokine can impact levels of serotonin, dopamine, and glutamate by stimulating the activity of the enzymes IDO and GTP-cyclohydrolase I (Capuron & Castanon, 2016; Dantzer et al., 2008; Ghisoni et al., 2015; Lanser et al., 2020; Miller et al., 2009; Müller & Schwarz, 2007; Weiss et al., 1999), which can contribute to mental health disorders (Myint et al., 2013). Additionally, the absence of IFNγ in the hippocampus, a region involved in memory and learning, has positive neuronal effects. These neuroplastic changes have been associated with improved performance in learning and memory tasks (Monteiro et al., 2016), which is of particular importance in the context of university students. Therefore, IFNγ could be a therapeutic target for treating or preventing cognitive dysfunction associated with inflammation (Monteiro et al., 2016). Considering these factors, neopterin may provide a connection between inflammation and mental health by linking immune system activation and neurotransmitter abnormalities (Dunbar et al., 1992; Klaus et al., 2021). However, since neopterin can be influenced by other factors, it should not be used solely as a marker or to discriminate severity but should be combined with other mental health measures.

ANS Measures

The HRV results of certain indices were significantly lower in Group A. This is suggestive of having reduced ANS flexibility and resilience to stress (An et al., 2020) and that HRV is decreased among those with high mental health scores. Higher variability in heart rate has been associated with better health, self-regulation, adaptability, and resilience. Although the “normal” range for an individual is based on age and sex, it should be noted that females tend to have a higher mean heart rate, which means smaller NN intervals, and lower SDNN when compared to males. In addition, HRV time-domain measurements decrease with age (Shaffer & Ginsberg, 2017).

Lower SDNN and SD2 in Group A suggest increased SNS activity (or reduced PNS activity) in individuals with mental health struggles. This is supported by other studies that found increased sympathetic activity in depression (Singla et al., 2020) and anxiety (Holwerda et al., 2018), and reduced autonomic flexibility in patients with anxiety disorders (Hoehn-Saric & McLeod, 1988). Furthermore, it has been suggested that ANS imbalance is involved in the pathogenesis of anxiety and depression (Godoy et al., 2018).

Mean HRV correlated with stress, anxiety, and depression scores. This is supported by meta-analyses which also found that both anxiety disorders (Chalmers et al., 2014) and depression (Kemp et al., 2010) are associated with decreased HRV. HRV has been found to be even more reduced in patients with comorbid anxiety and depression (Kemp et al., 2012). Additionally, measures like RMSSD and HF reflect parasympathetic activity, and the present study only found differences in parameters that reflect sympathetic activity. Yet, neither the SNS Index nor LF/HF ratio was significantly higher in Group A, which would indicate sympathetic dominance (Shaffer & Ginsberg, 2017). Thus, the involvement of sympathetic and parasympathetic activity in HRV parameters and mental health needs to be further investigated.

In addition to being a potential marker for mental health, reduced HRV has also been associated with other negative health outcomes, such as diabetes and obesity (Karason et al., 1999; Kudat et al., 2006). More importantly, HRV has been associated with CVD and risk thereof, and as such HRV could be a predictor of CVD (Hillebrand et al., 2013; Kubota et al., 2017). This provides a link between mental disorders and the high rate of comorbid CVD observed, in that both anxiety and depression increase the risk of CVD. In fact, anxiety can be considered a predictor or early marker of CVD risk (Chalmers et al., 2014). Furthermore, comorbid anxiety and depression increase the risk of mortality and CVD by two to threefold (Vogelzangs et al., 2010). Given that CVD is the leading global cause of death (Roth et al., 2018), this relationship is important to note. Addressing mental health problems, particularly in student populations, not only impacts the present but may also help prevent future health problems.

The present study only found significant associations between mean HRV, SDNN, SD2, and mental health, which are inconsistent with previous findings. This highlights that there is some kind of relationship between HRV and mental health, but that further research is required. In addition, the relationship between sympathetic and parasympathetic balance in HRV parameters needs to be further investigated. Despite the discrepancies in the results between the present study and other studies, HRV should not be discounted as a viable biomarker as there is a large body of evidence to suggest otherwise.

In terms of BVP, minimum and mean BVP amplitude negatively correlated with the anxiety and depression scores, but not with the stress score. BVP decreases with increasing sympathetic activity, and increases with decreasing parasympathetic activity (Gordan et al., 2015; Peper et al., 2007; Sarchiapone et al., 2018). Therefore, the results of the present study suggest that BVP may decrease (and sympathetic activity may increase) as symptoms of anxiety and depression increase. This is supported by the correlations found with minimum BVP amplitude, which suggests that the lower the minimum value recorded, the greater the anxiety and depression scores. This is of interest considering that stress is usually more acute and is regularly associated with activation of the sympathetic activity, yet BVP only correlated with anxiety and depression scores and not stress.

The results from the present study suggest that BVP could be a potential biomarker for anxiety and depression scores. However, not much research has been done concerning BVP and mental health, thus further investigation is required.

qEEG Power

Of the 19 electrodes used in the EEG, six electrodes showed a significant association with the DASS scores. These electrodes resided in the frontal and left side of the brain, five of which were on the frontal lobe and the other one was located at the left midtemporal lobe. These findings suggest altered function in the prefrontal cortex, which is involved in emotion, cognitive function, and motivation (Perlstein et al., 2002).

The power of delta frequencies showed the greatest associations. The power of delta at the FP1, FP2, and Fz electrodes was significantly higher in Group A than in Group B. These electrodes measure activity from the left and right Brodmann area 10 and the left Brodmann area 8, respectively. The location of FP2 appears to be largely involved and could be a predictor of the severity of the symptoms, given that the absolute power of delta at FP2 had a significant positive correlation with both the stress score and the anxiety score. This is suggestive of delta power in the prefrontal cortex increasing as stress or anxiety symptoms increase, which might make focusing and performing tasks difficult as the FP1, FP2, and Fz electrodes are associated with executive function (e.g., planning, decision-making, working memory), self-regulation, regulation of emotions, and social behavior (Warner, 2013). Additionally, Brodmann area 8 includes the frontal eye field, which is involved in visual attention and control of eye movements; therefore, visual disturbances may also be present, exacerbating

feelings of detachment from the surroundings (Watanabe, 2017), due to higher delta activity (Sroykham & Wongsawat, 2019; Warner, 2013).

Significant associations were also found in the alpha frequency band. The relative power of alpha was significantly lower at the T3 electrode in Group A, and negatively correlated with stress and anxiety scores. As alpha waves are associated with alertness and relaxation, low alpha can be indicative of anxiety (Warner, 2013). The T3 electrode records activity from the left temporal lobe, which is usually the dominant side in most people. It is involved in memory, learning, perception, hearing, speech, and understanding language (Guy-Evans, 2021). Damage to this area can result in impaired memory, executive function, learning, speech and understanding thereof. Other effects include apathy, memory loss, and poor impulse control (Guy-Evans, 2021). Specifically, the T3 electrode records activity from Brodmann areas 41 and 42 which form part of the primary auditory cortex. This area is involved in speech perception, sound intensity, pitch, auditory working memory, and the processing of auditory information. There is sparse information on the effect of alpha oscillations in the auditory cortex; however, some research suggests that alpha waves are involved in selective auditory attention, speech processing, and tinnitus (Malekshahi et al., 2020; Schlee et al., 2014; Straußß et al., 2014). In relation to this, almost half of tinnitus patients also have a mental disorder, mostly anxiety and depression, which correlates with the severity of tinnitus symptoms (Pinto et al., 2014; Zöger et al., 2006).

In terms of both delta and alpha waves, a study found increased delta power and decreased alpha power in elderly patients with mild cognitive impairment (Sroykham & Wongsawat, 2019). Therefore, it could be interpreted that participants in the present study with high DASS scores, which were associated with increased delta and decreased alpha, might be suffering from cognitive impairment, a symptom of mental health struggles (Trivedi, 2006). An alternative interpretation is that changes in brain waves could help explain the cognitive impairment observed in patients with mental health problems. If cognitive impairment is related to the increased delta and decreased alpha, then this might negatively impact the academic performance of those with mental health symptoms; mental health struggles impact academic achievement (Awadalla et al., 2020; Eisenberg et al., 2009; Jamil et al., 2022; Vitasari et al., 2010; Wagner et al., 2022). However, caution should be exercised with these interpretations given the age difference between the present study and the study with elderly patients.

Hibeta was found to increase in the positions of F3 and T3 as the stress score increased, and hibeta increased in the positions of F3 and F7 as the anxiety score increased. Excess hibeta has been associated with being tense and anxious, and it can be indicative of inefficient frontal alpha activity in areas associated with emotional control (Warner, 2013). Considering that decreased alpha and increased hibeta were found at both the T3 and F7 positions in Group A, difficulties with emotional control could be associated with their mental health scores. Furthering this, decreased frontal alpha and increased hibeta is thought to be indicative of agitation, anxiety, feeling overwhelmed, and impulsivity (Warner, 2013). As there may be an inverse relation between alpha and hibeta, increased hibeta and concomitantly decreased alpha at T3 might produce alterations in auditory processing.

The F7 electrode measures activity from Brodmann area 47, which is in the orbitofrontal cortex. The function of this area involves motivation, social behavior, and emotional reactions. Interestingly, the orbitofrontal cortex has been implicated in disorders involving thinking, feeling, or fear, with altered activity during sadness, depression, and distress (Mayberg, 1997). In conjunction with F3, activity at F7 is thought to regulate engagement, mood, processing of positive emotions, and conscious awareness. Alterations in alpha and hibeta activity in these areas may be linked to aberrations in these processes in mental health conditions. Specifically, increased hibeta at the F3 electrode is thought to indicate that a patient is hiding emotions and feelings, although this effect occurs with a simultaneous increase at FP2 (Warner, 2013)

The activity at three electrodes (FP2, F3, and T3) correlated with both stress and anxiety scores, which suggests that these regions are involved in both stress and anxiety symptoms. This is supported by previous research which found that brain regions involved in anxiety, such as the prefrontal cortex, are also implicated in the stress response (Shin & Liberzon, 2010).

In summary, people with mental health struggles, particularly those with high stress and anxiety scores, might present with increased delta and hibeta, and decreased alpha activity, in the frontal and left side of the brain. Differences at the T3 and F7 locations occurred in more than one frequency,

which might be related to difficulties with attention, focus, cognition, emotional regulation, and visual and auditory processing. Therefore, delta, alpha, and hibeta frequencies could potentially be used as biomarkers for stress and anxiety scores.

Potential Biomarkers

The most promising biomarker in this study was neopterin concentration, as it showed a significant difference between Group A and B, and crucially neopterin showed a strong positive correlation with all three of the DASS score categories. Therefore, neopterin could be of use in aiding the measurement of stress, anxiety, and depression scores. An advantage of using neopterin as a biomarker is that it can be obtained simply and noninvasively via a urine sample.

There appears to be a negative relationship between mental health and HRV (mean HRV, SDNN, and SD2). Although the present study did not find the same associations in HRV parameters as other studies, HRV should not be discounted as a biomarker. More research is required to define the best parameters and ranges thereof that can be considered normal or at-risk. These definitions will need to produce consistent, reliable, and reproducible results. HRV may be a particularly important marker in students as it has been related to attention, emotional processing, and executive function (McCraty & Shaffer, 2015), which are important for university success.

Due to the number of frequencies and electrodes that showed a difference with DASS scores, qEEG could also be a viable biomarker. However, there are some factors to consider such as recordings can vary depending on the state of the individual and EEG can be quite sensitive. Further research is required to validate the findings of the present study and to verify changes in brain activity in relation to mental health scores and increase the validity of measuring such differences.

Limitations

The measurements in the present study were taken from one moment in time and may not reflect the average lives of the participants. The recording time was relatively short, and no follow-up measurements were taken at a later stage.

Other lifestyle factors were also not recorded, such as exercise, supplements, sleep, diet, and alcohol consumption. Participants were also not asked if they had participated in intense exercise on the day or if they had an upcoming academic assessment, which could have affected perceived anxiety.

All the biomarkers used in this study can be affected by biological factors other than mental health. Therefore, studies using such biomarkers should consider their results to be interpreted with caution and with professional psychological assistance.

Future Directions

Further investigation into the differences in neopterin, HRV, BVP, and qEEG parameters in comparison to mental health scores in different groups of students, different ages, and the differences between sex is required. Furthermore, studies that consider comorbidity and lifestyle should also be conducted to consolidate associations. Finally, studies that investigate the exact mechanisms that are involved are necessary to establish causation and not just correlation. With regard to neopterin, determining whether oxidative stress, IFNγ, macrophages, the neopterin molecule itself, or inflammation in general are the cause(s) of correlation with mental symptom severity, may aid in developing therapeutic targets.

Conclusion

Social stigma, together with misdiagnosis and subjectivity can interfere with the detection, prevention, and treatment of mental health issues. This study found that neopterin and certain neurophysiological measures could be used as complementary markers for stress and anxiety symptom scores as determined by the DASS-21 questionnaire.

Measurements such as HRV, BVP, qEEG, and neopterin may have potential to be used as biomarkers in conjunction with existing measures such as questionnaires. The inflammatory and noteworthy neurophysiological changes associated with increased stress and anxiety contribute to our understanding of mental health. Identifying physical changes associated with mental health conditions could be useful in the prevention, identification, and treatment of these struggles. This is prudent considering that anxiety is the leading mental health disorder, and that stress and anxiety are associated with inflammation, another major contributor to disease.

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Author Declaration

The authors declare no conflict of interest.

References

Akin, A., & Çetin, B. (2007). The Depression Anxiety and Stress Scale (DASS): The study of validity and reliability. *Kuram ve Uygulamada Egitim Bilimleri*, *7*(1), 260–268.

Albert, P. R., Benkelfat, C., & Descarries, L. (2012). The neurobiology of depression—revisiting the serotonin hypothesis. I. Cellular and molecular mechanisms. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *367*(1601), 2378–2381. https://doi.org/10.1098/rstb.2012.0190

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). https://doi.org/10.1176/appi.books.9780890425596

An, E., Nolty, A. A. T., Amano, S. S., Rizzo, A. A., Buckwalter, J. G., & Rensberger, J. (2020). Heart rate variability as an index of resilience. *Military Medicine*, *185*(3–4), 363–369. https://doi.org/10.1093/milmed/usz325

Antony, M., Bieling, P., Cox, B., Enns, M., & Swinson, R. (1998). Psychometric properties of the 42-item and 21-item versions of the Depression Anxiety Stress Scales in clinical groups and a community sample. *Psychological Assessment*, *10*(2), 176–181. https://doi.org/10.1037/1040-3590.10.2.176

Arias, D., Saxena, S., & Verguet, S. (2022). Quantifying the global burden of mental disorders and their economic value. *eClinicalMedicine*, *54*, Article 101675. https://doi.org/10.1016/j.eclinm.2022.101675

Atmaca, M., Kuloglu, M., Tezcan, E., Onal, S. I., & Ustundag, B. (2002). Neopterin levels and dexamethasone suppression test in posttraumatic stress disorder. *European Archives of Psychiatry and Clinical Neuroscience*, *252*(4), 161–165. https://doi.org/10.1007/s00406-002-0374-5

Awadalla, S., Davies, E. B., & Glazebrook, C. (2020). A longitudinal cohort study to explore the relationship between depression, anxiety and academic performance among Emirati university students. *BMC Psychiatry*, *20*(1), Article 448. https://doi.org/10.1186/s12888-020-02854-z

Bagdy, G. (1998). Serotonin, anxiety, and stress hormones: Focus on 5-HT receptor subtypes, species and gender differences[a]. *Annals of the New York Academy of Sciences*, *851*(1), 357–363. https://doi.org/10.1111/j.1749-6632.1998.tb09009.x

Bankier, B., Barajas, J., Martinez-Rumayor, A., & Januzzi, J. L. (2008). Association between C-reactive protein and generalized anxiety disorder in stable coronary heart disease patients. *European Heart Journal*, *29*(18), 2212–2217. https://doi.org/10.1093/eurheartj/ehn326

Bauer, M. E., & Teixeira, A. L. (2019). Inflammation in psychiatric disorders: What comes first? *Annals of the New York Academy of Sciences*, *1437*(1), 57–67. https://doi.org/10.1111/nyas.13712

Beaufort, I. N., De Weert-Van Oene, G. H., Buwalda, V. A. J., de Leeuw, J. R. J., & Goudriaan, A. E. (2017). The Depression, Anxiety and Stress Scale (DASS-21) as a screener for depression in substance use disorder inpatients: A pilot study. *European Addiction Research*, *23*(5), 260–268. https://doi.org/10.1159/000485182

Berdowska, A., & Zwirska-Korczala, K. (2001). Neopterin measurement in clinical diagnosis. *Journal of Clinical Pharmacy and Therapeutics*, *26*(5), 319–329. https://doi.org/10.1046/j.1365-2710.2001.00358.x

Blackhart, G. C., Minnix, J. A., & Kline, J. P. (2006). Can EEG asymmetry patterns predict future development of anxiety and depression?: A preliminary study. *Biological Psychology*, *72*(1), 46–50. https://doi.org/10.1016/j.biopsycho.2005.06.010

Blokland, A., Lieben, C., & Deutz, N. E. P. (2002). Anxiogenic and depressive-like effects, but no cognitive deficits, after repeated moderate tryptophan depletion in the rat. *Journal of Psychopharmacology*, *16*(1), 39–49. https://doi.org/10.1177/026988110201600112

Bouayed, J., Rammal, H., & Soulimani, R. (2009). Oxidative stress and anxiety: Relationship and cellular pathways. *Oxidative Medicine and Cellular Longevity*, *2*(2), 63–67. https://doi.org/10.4161/oxim.2.2.7944

Brown, R. R., Lee, C. M., Kohler, P. C., Hank, J. A., Storer, B. E., & Sondel, P. M. (1989). Altered tryptophan and neopterin metabolism in cancer patients treated with recombinant interleukin 21. *Cancer Research*, *49*(17), 4941–4944.

Buist–Bouwman, M. A., De Graaf, R., Vollebergh, W. A. M., Alonso, J., Bruffaerts, R., Ormel, J., & ESEMeD/MHEDEA 2000 Investigators (2006). Functional disability of mental disorders and comparison with physical disorders: A study among the general population of six European countries. *Acta Psychiatrica Scandinavica*, *113*(6), 492–500. https://doi.org/10.1111/j.1600-0447.2005.00684.x

Capuron, L., & Castanon, N. (2016). Role of inflammation in the development of neuropsychiatric symptom domains: Evidence and mechanisms. In R. Dantzer & L. Capuron (Eds.), *Inflammation-associated depression: Evidence, mechanisms and implications* (pp. 31–44). *Current topics in behavioral neurosciences* (vol. 31). Springer, Cham. https://doi.org/10.1007/7854_2016_14

Chalmers, J. A., Quintana, D. S., Abbott, M. J., & Kemp, A. H. (2014). Anxiety disorders are associated with reduced heart rate variability: A meta-analysis. *Frontiers in Psychiatry*, *5*, Article 80. https://doi.org/10.3389/fpsyt.2014.00080

Charmandari, E., Tsigos, C., & Chrousos, G. (2005). Endocrinology of the stress response. *Annual Review of Physiology*, *67*, 259–284. https://doi.org/10.1146/annurev.physiol.67.040403.120816

Chu, B., Marwaha, K., Sanvictores, T., & Ayers, D. (2022). Physiology, stress reaction. StatPearls. StatPearls Publishing.

Cohen, B. E., Edmondson, D., & Kronish, I. M. (2015). State of the art review: Depression, stress, anxiety, and cardiovascular disease. *American Journal of Hypertension*, *28*(11), 1295–1302. https://doi.org/10.1093/ajh/hpv047

Crawford, J. R., & Henry, J. D. (2003). The Depression Anxiety Stress Scales (DASS): Normative data and latent structure in a large non-clinical sample. *British Journal of Clinical Psychology*, *42*(2), 111–131. https://doi.org/10.1348/014466503321903544

Crestani, F., Lorez, M., Baer, K., Essrich, C., Benke, D., Laurent, J. P., Belzung, C., Fritschy, J. M., Lüscher, B., & Mohler, H. (1999). Decreased $GABA_A$-receptor clustering results in enhanced anxiety and a bias for threat cues. *Nature Neuroscience*, *2*(9), 833–839. https://doi.org/10.1038/12207

Dantzer, R., O'Connor, J. C., Freund, G. G., Johnson, R. W., & Kelley, K. W. (2008). From inflammation to sickness and depression: When the immune system subjugates the brain. *Nature Reviews Neuroscience*, *9*(1), 46–56. https://doi.org/10.1038/nrn2297

De Beurs, E., Van Dyck, R., Marquenie, Lange, A., & Blonk, R. (2001). De DASS: Een vragenlijst voor het meten van epressivee, angst en stress [The DASS: A questionnaire for the measurement of depression, anxiety, and stress]. *Gedragstherapie*, *34*(1), 35–53.

Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E. K., & Lanctôt, K. L. (2010). A meta-analysis of cytokines in major depression. *Biological Psychiatry*, *67*(5), 446–457. https://doi.org/10.1016/j.biopsych.2009.09.033

Dreyer, Z., Henn, C., & Hill, C. (2019). Validation of the Depression Anxiety Stress Scale-21 (DASS-21) in a non-clinical sample of South African working adults. *Journal of Psychology in Africa*, *29*(4), 346–353. https://doi.org/10.1080/14330237.2019.1647499

Dunbar, P. R., Hill, J., & Neale, T. J. (1993). Urinary neopterin quantification indicates altered cell-mediated immunity in healthy subjects under psychological stress. *Australian & New Zealand Journal of Psychiatry*, *27*(3), 495–501. https://doi.org/10.3109/00048679309075808

Dunbar, P. R., Hill, J., Neale, T. J., & Mellsop, G. W. (1992). Neopterin measurement provides evidence of altered cell-mediated immunity in patients with depression, but not with schizophrenia. *Psychological Medicine*, *22*(4), 1051–1057. https://doi.org/10.1017/s0033291700038629

Dunn, A. J. (2006). Effects of cytokines and infections on brain neurochemistry. *Clinical Neuroscience Research*, *6*(1–2), 52–68. https://doi.org/10.1016/j.cnr.2006.04.002

Dyrbye, L. N., Massie, F. S., Eacker, A., Harper, W., Power, D., Durning, S. J., Thomas, M. R., Moutier, C., Satele, D., Sloan, J., & Shanafelt, T. D. (2010). Relationship between burnout and professional conduct and attitudes among US medical students. *JAMA*, *304*(11), 1173–1180. https://doi.org/10.1001/jama.2010.1318

Dyrbye, L. N., Thomas, M. R., & Shanafelt, T. D. (2005). Medical student distress: Causes, consequences, and proposed solutions. *Mayo Clinic Proceedings*, *80*(12), 1613–1622. https://doi.org/10.4065/80.12.1613

Dyrbye, L. N., Thomas, M. R., & Shanafelt, T. D. (2006). Systematic review of depression, anxiety, and other indicators of psychological distress among U.S. and Canadian medical students. *Academic Medicine*, *81*(4), 354–373. https://doi.org/10.1097/00001888-200604000-00009

Edwards, K. M., Wilson, K. L., Sadja, J., Ziegler, M. G., & Mills, P. J. (2011). Effects on blood pressure and autonomic nervous system function of a 12-week exercise or exercise plus DASH-diet intervention in individuals with elevated blood pressure. *Acta Physiologica*, *203*(3), 343–350. https://doi.org/10.1111/j.1748-1716.2011.02329.x

Eisenberg, D., Golberstein, E., & Hunt, J. (2009). Mental Health and Academic Success in College. *The B. E. Journal of Economic Analysis & Policy*, *9*(1), Article 40. https://doi.org/10.2202 /1935-1682.2191

Eisenhut, M. (2013). Neopterin in diagnosis and monitoring of infectious diseases. *Journal of Biomarkers*, *2013*, Article 196432. https://doi.org/10.1155/2013/196432

Fares, J., Al Tabosh, H., Saadeddin, Z., El Mouhayyar, C., & Aridi, H. (2016). Stress, burnout and coping strategies in preclinical medical students. *North American Journal of Medical Sciences*, *8*(2), 75–81. https://doi.org/10.4103/1947-2714.177299

Ferrari, A. J., Santomauro, D. F., Mantilla Herrera, A. M., Shadid, J., Ashbaugh, C., Erskine, H. E., Charlson, F. J., Degenhardt, L., Scott, J. G., McGrath, J. J., Allebeck, P., Benjet, C., Breitborde, N. J. K., Brugha, T., Dai, X., Dandona, L., Dandona, R., Fischer, F., Haagsma, J. A., … Whiteford, H. A. (2022). Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. *The Lancet Psychiatry*, *9*(2), 137–150. https://doi.org/10.1016/S2215-0366(21)00395-3

Forgione, F. A. (2018). Diagnostic dissent: Experiences of perceived misdiagnosis and stigma in persons diagnosed with schizophrenia. *Journal of Humanistic Psychology*, *59*(1), 69–98. https://doi.org/10.1177/0022167818777151

Fuchs, D., Avanzas, P., Arroyo-Espliguero, R., Jenny, M., Consuegra-Sánchez, L., & Kaski, J. (2009). The role of neopterin in atherogenesis and cardiovascular risk assessment. *Current Medicinal Chemistry*, *16*, 4644–4653. https://doi.org/10.2174/092986709789878247

Gao, K., Mu, C.-L., Farzi, A., & Zhu, W.-Y. (2020). Tryptophan metabolism: A link between the gut microbiota and brain. *Advances in Nutrition*, *11*(3), 709–723. https://doi.org/10.1093/advances/nmz127

García-Gutiérrez, M. S., Navarrete, F., Sala, F., Gasparyan, A., Austrich-Olivares, A., & Manzanares, J. (2020). Biomarkers in psychiatry: Concept, definition, types and relevance to the clinical reality. *Frontiers in Psychiatry*, *11*, Article 432. https://doi.org/10.3389/fpsyt.2020.00432

Gass, P., Reichardt, H. M., Strekalova, T., Henn, F., & Tronche, F. (2001). Mice with targeted mutations of glucocorticoid and mineralocorticoid receptors: Models for depression and anxiety? *Physiology & Behavior*, *73*(5), 811–825. https://doi.org/10.1016/S0031-9384(01)00518-2

Ghisoni, K., de Paula Martins R., Barbeito, L., & Latini, A. (2015). Neopterin as a potential cytoprotective brain molecule. *Journal of Psychiatric Research*, *71*, 134–139. https://doi.org/10.1016/j.jpsychires.2015.10.003

Gieseg, S. P., Baxter-Parker, G., & Lindsay, A. (2018). Neopterin, inflammation, and oxidative stress: What could we be missing? *Antioxidants*, *7*(7), Article 80. https://doi.org/10.3390/antiox7070080

Godoy, L. D., Rossignoli, M. T., Delfino-Pereira, P., Garcia-Cairasco, N., & de Lima Umeoka, E. H. (2018). A comprehensive overview on stress neurobiology: Basic concepts and clinical implications. *Frontiers in Behavioral Neuroscience*, *12*, Article 127. https://doi.org/10.3389/fnbeh.2018.00127

Goebert, D., Thompson, D., Takeshita, J., Beach, C., Bryson, P., Ephgrave, K., Kent, A., Kunkel, M., Schechter, J., & Tate, J. (2009). Depressive symptoms in medical students and residents: A multischool study. *Academic Medicine*, *84*(2), 236–241. https://doi.org/10.1097/ACM.0b013e31819391bb

Gordan, R., Gwathmey, J. K., & Xie, L.-H. (2015). Autonomic and endocrine control of cardiovascular function. *World Journal of Cardiology*, *7*(4), 204–214. https://doi.org/10.4330/wjc.v7.i4.204

Guest, P. C. (2017). *Biomarkers and mental illness: It's not all in the mind*. Copernicus Books.

Guy-Evans, O. (2021, April 13). *Temporal lobe: Definition, functions, and location.* Simple Psychology. Retrieved January 22. www.simplypsychology.org/temporal-lobe.html

Hamerlinck, F. F. V. (1999). Neopterin: A review. *Experimental Dermatology*, *8*(3), 167–176. https://doi.org/10.1111/j.1600-0625.1999.tb00367.x

Handouzi, W., Maaoui, C., Pruski, A., & Moussaoui, A. (2014). Objective model assessment for short-term anxiety recognition from blood volume pulse signal. *Biomedical Signal Processing and Control*, *14*, 217–227. https://doi.org/10.1016/j.bspc.2014.07.008

Haroon, E., Raison, C. L., & Miller, A. H. (2012). Psychoneuroimmunology meets neuropsychopharmacology: Translational implications of the impact of inflammation on behavior. *Neuropsychopharmacology*, *37*(1), 137–162. https://doi.org/10.1038/npp.2011.205

Henry, J. D., & Crawford, J. R. (2005). The short-form version of the Depression Anxiety Stress Scales (DASS-21): Construct validity and normative data in a large non-clinical sample. *British Journal of Clinical Psychology*, *44*(2), 227–239. https://doi.org/10.1348/014466505X29657

Hillebrand, S., Gast, K. B., de Mutsert, R., Swenne, C. A., Jukema, J. W., Middeldorp, S., Rosendaal, F. R., & Dekkers, O. M. (2013). Heart rate variability and first cardiovascular event in populations without known cardiovascular disease: Meta-analysis and dose–response meta-regression. *EP Europace*, *15*(5), 742–749. https://doi.org/10.1093/europace/eus341

Ho, T. C., Pham, H. T., Miller, J. G., Kircanski, K., & Gotlib, I. H. (2020). Sympathetic nervous system dominance during stress recovery mediates associations between stress sensitivity

and social anxiety symptoms in female adolescents. *Development and Psychopathology*, *32*(5), 1914–1925. https://doi.org/10.1017/S0954579420001261

Hodes, G. E., Kana, V., Menard, C., Merad, M., & Russo, S. J. (2015). Neuroimmune mechanisms of depression. *Nature Neuroscience*, *18*(10), 1386–1393. https://doi.org/10.1038/nn.4113

Hoehn–Saric, R., & McLeod, D. R. (1988). The peripheral sympathetic nervous system. Its role in normal and pathologic anxiety. *Psychiatric Clinics of North America*, *11*(2), 375–386.

Hoge, E. A., Brandstetter, K., Moshier, S., Pollack, M. H., Wong, K. K., & Simon, N. M. (2009). Broad spectrum of cytokine abnormalities in panic disorder and posttraumatic stress disorder. *Depression and Anxiety*, *26*(5), 447–455. https://doi.org/10.1002/da.20564

Hojat, M., Mangione, S., Nasca, T. J., Rattner, S., Erdmann, J. B., Gonnella, J. S., & Magee, M. (2004). An empirical study of decline in empathy in medical school. *Medical Education*, *38*(9), 934–941. https://doi.org/10.1111/j.1365-2929.2004.01911.x

Holwerda, S. W., Luehrs, R. E., Gremaud, A. L., Wooldridge, N. A., Stroud, A. K., Fiedorowicz, J. G., Abboud, F. M., & Pierce, G. L. (2018). Relative burst amplitude of muscle sympathetic nerve activity is an indicator of altered sympathetic outflow in chronic anxiety. *Journal of Neurophysiology*, *120*(1), 11–22. https://doi.org/10.1152/jn.00064.2018

Hourani, L. L., Davila, M. I., Morgan, J., Meleth, S., Ramirez, D., Lewis, G., Kizakevich, P. N., Eckhoff, R., Morgan, T., Strange, L., Lane, M., Weimer, B., & Lewis, A. (2020). Mental health, stress, and resilience correlates of heart rate variability among military reservists, guardsmen, and first responders. *Physiology & Behavior*, *214*, Article 112734. https://doi.org/10.1016/j.physbeh.2019.112734

Huber, C., Batchelor, J. R., Fuchs, D., Hausen, A., Lang, A., Niederwieser, D., Reibnegger, G., Swetly, P., Troppmair, J., & Wachter, H. (1984). Immune response-associated production of neopterin. Release from macrophages primarily under control of interferon-gamma. *Journal of Experimental Medicine*, *160*(1), 310–316. https://doi.org/10.1084/jem.160.1.310

Inserra, A., Mastronardi, C. A., Rogers, G., Licinio, J., & Wong, M. L. (2019). Neuroimmunomodulation in major depressive disorder: Focus on caspase 1, inducible nitric oxide synthase, and interferon-gamma. *Molecular Neurobiology*, *56*(6), 4288–4305. https://doi.org/10.1007/s12035-018-1359-3

Jamil, H., Alakkari, M., Al-Mahini, M. S., Alsayid, M., & Al Jandali, O. (2022). The impact of anxiety and depression on academic performance: A cross-sectional study among medical students in Syria. *Avicenna Journal of Medicine*, *12*(3), 111–119. https://doi.org/10.1055/s-0042-1755181

Jiang, L.-C., Yan, Y.-J., Jin, Z.-S., Hu, M.-L., Wang, L., Song, Y., Li, N.-N., Su, J., Wu, D.-X., & Xiao, T. (2020). The Depression Anxiety Stress Scale-21 in Chinese hospital workers: Reliability, latent structure, and measurement invariance across genders. *Frontiers in Psychology*, *11*, Article 247. https://doi.org/10.3389/fpsyg.2020.00247

Johnson, J. D., Barnard, D. F., Kulp, A. C., & Mehta, D. M. (2019). Neuroendocrine regulation of brain cytokines after psychological stress. *Journal of the Endocrine Society*, *3*(7), 1302–1320. https://doi.org/10.1210/js.2019-00053

Kanda, P. A. M., Anghinah, R., Smidth, M. T., & Silva, J. M. (2009). The clinical use of quantitative EEG in cognitive disorders. *Dementia & Neuropsychologia*, *3*(3), 195–203. https://doi.org/10.1590/S1980-57642009DN30300004

Karason, K., Mølgaard, H., Wikstrand, J., & Sjöström, L. (1999). Heart rate variability in obesity and the effect of weight loss. *The American Journal of Cardiology*, *83*(8), 1242–1247. https://doi.org/10.1016/s0002-9149(99)00066-1

Kemp, A. H., Quintana, D. S., Felmingham, K. L., Matthews, S., & Jelinek, H. F. (2012). Depression, comorbid anxiety disorders, and heart rate variability in physically healthy, unmedicated patients: implications for cardiovascular risk. *PLoS ONE*, *7*(2), Article e30777. https://doi.org/10.1371/journal.pone.0030777

Kemp, A. H., Quintana, D. S., Gray, M. A., Felmingham, K. L., Brown, K., & Gatt, J. M. (2010). Impact of depression and antidepressant treatment on heart rate variability: A review and meta-analysis. *Biological Psychiatry*, *67*(11), 1067–1074. https://doi.org/10.1016/j.biopsych.2009.12.012

Kessler, R. C. (1997). The effects of stressful life events on depression. *Annual Review of Psychology*, *48*, 191–214. https://doi.org/10.1146/annurev.psych.48.1.191

Klaus, F., Guetter, K., Schlegel, R., Seifritz, E., Rassi, A., Thöny, B., Cathomas, F., & Kaiser, S. (2021). Peripheral biopterin and neopterin in schizophrenia and depression. *Psychiatry Research*, *297*, Article 113745. https://doi.org/10.1016/j.psychres.2021.113745

Kreibig, S. (2010). Autonomic nervous system activity in emotion: A review. *Biological Psychology*, *84*(3), 394–421. https://doi.org/10.1016/j.biopsycho.2010.03.010

Kubota, Y., Chen, L. Y., Whitsel, E. A., & Folsom, A. R. (2017). Heart rate variability and lifetime risk of cardiovascular disease: The atherosclerosis risk in communities study. *Annals of Epidemiology*, *27*(10), 619–625.e2. https://doi.org/10.1016/j.annepidem.2017.08.024

Kudat, H., Akkaya, V., Sozen, A. B., Salman, S., Demirel, S., Ozcan, M., Atilgan, D., Yilmaz, M. T., & Guven, O. (2006). Heart rate variability in diabetes patients. *Journal of International Medical Research*, *34*(3), 291–296. https://doi.org/10.1177/147323000603400308

Kushki, A., Fairley, J., Merja, S., King, G., & Chau, T. (2011). Comparison of blood volume pulse and skin conductance responses to mental and affective stimuli at different anatomical sites. *Physiological Measurement*, *32*(10), 1529–1539. https://doi.org/10.1088/0967-3334/32/10/002

Lanser, L., Kink, P., Egger, E. M., Willenbacher, W., Fuchs, D., Weiss, G., & Kurz, K. (2020). Inflammation-induced tryptophan breakdown is related with anemia, fatigue, and depression in cancer. *Frontiers in Immunology*, *11*, Article 249. https://doi.org/10.3389/fimmu.2020.00249

Lovibond, S. H., & Lovibond, P. F. (1995). *Manual for the depression anxiety stress scales* (2nd Ed.). Psychology Foundation of Australia.

Macaluso, M., & Preskorn, S. H. (2012). How biomarkers will change psychiatry: From clinical trials to practice. Part I: Introduction. *Journal of Psychiatric Practice*, *18*(2), 118–121. https://doi.org/10.1097/01.pra.0000413277.11091.25

Maes, M., Scharpé, S., Meltzer, H. Y., Okayli, G., Bosmans, E., D'Hondt, P., Vanden Bossche, B. V., & Cosyns, P. (1994). Increased neopterin and interferon-gamma secretion and lower availability of L-tryptophan in major depression: Further evidence for an immune response. *Psychiatry Research*, *54*(2), 143–160. https://doi.org/10.1016/0165-1781(94)90003-5

Maes, M., Song, C., Lin, A., De Jongh, R., Van Gastel, A., Kenis, G., Bosmans, E., De Meester, I., Benoy, I., Neels, H., Demedts, P., Janca, A., Scharpé, S., & Smith, R. S. (1998). The effects of psychological stress on humans: Increased production of pro-inflammatory cytokines and a Th1-like response in stress-induced anxiety. *Cytokine*, *10*(4), 313–318. https://doi.org/10.1006/cyto.1997.0290

Maes, M., Van der Planken, M., Stevens, W. J., Peeters, D., DeClerck, L. S., Bridts, C. H., Schotte, C., & Cosyns, P. (1992). Leukocytosis, monocytosis and neutrophilia: Hallmarks of severe depression. *Journal of Psychiatric Research*, *26*(2), 125–134. https://doi.org/10.1016/0022-3956(92)90004-8

Maggi, E., Parronchi, P., Manetti, R., Simonelli, C., Piccinni, M. P., Rugiu, F. S., De Carli, M., Ricci, M., & Romagnani, S. (1992). Reciprocal regulatory effects of IFN-gamma and IL-4

on the in vitro development of human Th1 and Th2 clones. *Journal of Immunology*, *148*(7), 2142–2147.

Malekshahi, A., Malekshahi, R., Czornik, M., Dax, J., Wolpert, S., Bauer, H., Braun, C., & Birbaumer, N. (2020). Real-time monitoring and regulating auditory cortex alpha activity in patients with chronic tinnitus. *Journal of Neural Engineering*, *17*(1), Article 016032. https://doi.org/10.1088/1741-2552/ab57d5

Maser, B., Danilewitz, M., Guérin, E., Findlay, L., & Frank, E. (2019). Medical student psychological distress and mental illness relative to the general population: A Canadian cross-sectional survey. *Academic Medicine*, *94*(11), 1781–1791. https://doi.org/10.1097/acm.0000000000002958

Mayberg, H. S. (1997). Limbic-cortical dysregulation: A proposed model of depression. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *9*(3), 471–481. https://doi.org/10.1176/jnp.9.3.471

Maydych, V. (2019). The interplay between stress, inflammation, and emotional attention: Relevance for depression. *Frontiers in Neuroscience*, *13*, Article 384. https://doi.org/10.3389/fnins.2019.00384

McCraty, R., & Shaffer, F. (2015). Heart rate variability: New perspectives on physiological mechanisms, assessment of self-regulatory capacity, and health risk. *Global Advances in Integrative Medicine and Health*, *4*(1), 46–61. https://doi.org/10.7453/gahmj.2014.073

Miller, A. H., Maletic, V., & Raison, C. L. (2009). Inflammation and its discontents: The role of cytokines in the pathophysiology of major depression. *Biological Psychiatry*, *65*(9), 732–741. https://doi.org/10.1016/j.biopsych.2008.11.029

Mitra, R., & Sapolsky, R. M. (2008). Acute corticosterone treatment is sufficient to induce anxiety and amygdaloid dendritic hypertrophy. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(14), 5573–5578. https://doi.org/10.1073/pnas.0705615105

Mohammad, M. (2021). Risk factors associated with stress, anxiety, and depression among university undergraduate students. *AIMS Public Health, 8*(1), 36–65. https://doi.org/10.3934/publichealth.2021004

Monteiro, S., Ferreira, F. M., Pinto, V., Roque, S., Morais, M., de Sá-Calçada, D., Mota, C., Correia-Neves, M., & Cerqueira, J. J. (2016). Absence of IFNγ promotes hippocampal plasticity and enhances cognitive performance. *Translational Psychiatry*, *6*(1), Article e707. https://doi.org/10.1038/tp.2015.194

Müller, N., & Schwarz, M. J. (2007). The immune-mediated alteration of serotonin and glutamate: Towards an integrated view of depression. *Molecular Psychiatry*, *12*(11), 988–1000. https://doi.org/10.1038/sj.mp.4002006

Myint, A. M., Bondy, B., Baghai, T. C., Eser, D., Nothdurfter, C., Schüle, C., Zill, P., Müller, N., Rupprecht, R., & Schwarz, M. J. (2013). Tryptophan metabolism and immunogenetics in major depression: A role for interferon-γ gene. *Brain, Behavior, and Immunity*, *31*, 128–133. https://doi.org/10.1016/j.bbi.2013.04.003

Myint, A. M., & Kim, Y. K. (2003). Cytokine–serotonin interaction through IDO: A neurodegeneration hypothesis of depression. *Medical Hypotheses*, *61*(5–6), 519–525. https://doi.org/10.1016/S0306-9877(03)00207-X

Nathan, C. F. (1986). Peroxide and pteridine: A hypothesis on the regulation of macrophage antimicrobial activity by interferon gamma. *Interferon*, *7*, 125–143.

Neurofeedback Alliance. (2021). *Understanding brain waves*. https://neurofeedbackalliance.org/understanding-brain-waves/

Nutt, D. J., & Malizia, A. L. (2001). New insights into the role of the $GABA_A$–benzodiazepine receptor in psychiatric disorder. *The British Journal of Psychiatry*, *179*(5), 390–396. https://doi.org/10.1192/bjp.179.5.390

O'Connor, J. C., Lawson, M. A., André, C., Moreau, M., Lestage, J., Castanon, N., Kelley, K. W., & Dantzer, R. (2009). Lipopolysaccharide-induced depressive-like behavior is mediated by indoleamine 2,3-dioxygenase activation in mice. *Molecular Psychiatry*, *14*(5), 511–522. https://doi.org/10.1038/sj.mp.4002148

Osimo, E. F., Pillinger, T., Rodriguez, I. M., Khandaker, G. M., Pariante, C. M., & Howes, O. D. (2020). Inflammatory markers in depression: A meta-analysis of mean differences and variability in 5,166 patients and 5,083 controls. *Brain Behavior, and Immunity*, *87*, 901–909. https://doi.org/10.1016/j.bbi.2020.02.010

Pace, T. W., & Miller, A. H. (2009). Cytokines and glucocorticoid receptor signaling. Relevance to major depression. *Annals of the New York Academy of Sciences*, *1179*(1), 86–105. https://doi.org/10.1111/j.1749-6632.2009.04984.x

Pace, T. W. W., Hu, F., & Miller, A. H. (2007). Cytokine-effects on glucocorticoid receptor function: Relevance to glucocorticoid resistance and the pathophysiology and treatment of major depression. *Brain, Behavior, and Immunity*, *21*(1), 9–19. https://doi.org/10.1016/j.bbi.2006.08.009

Pacileo, M., Cirillo, P., De Rosa, S., Ucci, G., Petrillo, G., Musto Dâ€™Amore, S., Sasso, L., Maietta, P., Spagnuolo, R., & Chiariello, M. (2007). The role of neopterin in cardiovascular disease. *Archivio Monaldi per Le Malattie Del Torace [Monaldi Archives for Chest Disease]*, *68*(2), 68–73. https://doi.org/10.4081/monaldi.2007.454

Pêgo, J. M., Sousa, J. C., Almeida, O. F., & Sousa, N. (2010). Stress and the neuroendocrinology of anxiety disorders. In M. B. Stein & T. Steckler (Eds.), *Behavioral neurobiology of anxiety and its treatment* (pp. 97–118). Springer Science + Business Media. https://doi.org/10.1007/7854_2009_13

Peper, E., Harvey, R., Lin, I.-M., Tylova, H., & Moss, D. (2007). Is there more to blood volume pulse than heart rate variability, respiratory sinus arrhythmia, and cardiorespiratory synchrony? *Biofeedback*, *35*, 54–61.

Perlstein, W. M., Elbert, T., & Stenger, V. A. (2002). Dissociation in human prefrontal cortex of affective influences on working memory-related activity. *Proceedings of the National Academy of Sciences*, *99*(3), 1736–1741. https://doi.org/10.1073/pnas.241650598

Pinto, P. C. L., Marcelos, C. M., Mezzasalma, M. A., Osterne, F. J. V., de Melo Tavares de Lima, M. A., & Nardi, A. E. (2014). Tinnitus and its association with psychiatric disorders: Systematic review. *The Journal of Laryngology & Otology*, *128*(8), 660–664. https://doi.org/10.1017/S0022215114001030

Quagliato, L. A., & Nardi, A. E. (2018). Cytokine alterations in panic disorder: A systematic review. *Journal of Affective Disorders*, *228*, 91–96. https://doi.org/10.1016/j.jad.2017.11.094

Raison, C. L., Capuron, L., & Miller, A. H. (2006). Cytokines sing the blues: Inflammation and the pathogenesis of depression. *Trends in Immunology*, *27*(1), 24–31. https://doi.org/10.1016/j.it.2005.11.006

Raison, C. L., & Miller, A. H. (2003). When not enough is too much: The role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. *The American Journal of Psychiatry*, *160*(9), 1554–1565. https://doi.org/10.1176/appi.ajp.160.9.1554

Rajkumar, R. P. (2022). The correlates of government expenditure on mental health services: An analysis of data from 78 countries and regions. *Cureus*, *14*(8), Article e28284. https://doi.org/10.7759/cureus.28284

Reader, B. F., Jarrett, B. L., McKim, D. B., Wohleb, E. S., Godbout, J. P., & Sheridan, J. F. (2015). Peripheral and central effects of repeated social defeat stress: Monocyte trafficking, microglial activation, and anxiety. *Neuroscience*, *289*, 429–442. https://doi.org/10.1016/j.neuroscience.2015.01.001

Risbrough, V. B., & Stein, M. B. (2006). Role of corticotropin releasing factor in anxiety disorders: A translational research

perspective. *Hormones and Behavior*, *50*(4), 550–561. https://doi.org/10.1016 /j.yhbeh.2006.06.019

Roffman, J. L. (2011). Biomarkers and personalized psychiatry. *Harvard Review of Psychiatry*, *19*(3), 99–101. https://doi.org /10.3109/10673229.2011.586547

Rojas, G. M., Alvarez, C., Montoya, C. E., de la Iglesia-Vayá, M., Cisternas, J. E., & Gálvez, M. (2018). Study of resting-state functional connectivity networks using EEG electrodes position as seed. *Frontiers in Neuroscience*, *12*, Article 235. https://doi.org/10.3389/fnins.2018.00235

Rössler, W. (2016). The stigma of mental disorders: A millennia-long history of social exclusion and prejudices. *EMBO Rep*, *17*(9), 1250–1253. https://doi.org/10.15252/embr.201643041

Roth, G. A., Abate, D., Abate, K. H., Abay, S. M., Abbafati, C., Abbasi, N., Abbastabar, H., Abd-Allah, F., Abdela, J., Abdelalim, A., Abdollahpour, I., Abdulkader, R. S., Abebe, H. T., Abebe, M., Abebe, Z., Abejie, A. N., Abera, S. F., Abil, O. Z., Abraha, H. N., ... Murray, C. J. L. (2018). Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: A systematic analysis for the Global Burden of Disease Study 2017. *Lancet*, *392*(10159), 1736–1788. https://doi.org /10.1016/S0140-6736(18)32203-7

Salim, S. (2014). Oxidative stress and psychological disorders. *Current Neuropharmacology*, *12*(2), 140–147. https://doi.org /10.2174/1570159x11666131120230309

Šalkevicius, J., Damaševičius, R., Maskeliunas, R., & Laukiene, I. (2019). Anxiety level recognition for virtual reality therapy system using physiological signals. *Electronics*, *8*(9), Article 1039. https://doi.org/10.3390/electronics8091039

Sapolsky, R. M., Romero, L. M., & Munck, A. U. (2000). How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocrine Reviews*, *21*(1), 55–89. https://doi.org/10.1210 /edrv.21.1.0389

Sarchiapone, M., Gramaglia, C., Iosue, M., Carli, V., Mandelli, L., Serretti, A., Marangon, D., & Zeppegno, P. (2018). The association between electrodermal activity (EDA), depression and suicidal behaviour: A systematic review and narrative synthesis. *BMC Psychiatry*, *18*(1), Article 22. https://doi.org /10.1186/s12888-017-1551-4

Satyjeet, F., Naz, S., Kumar, V., Aung, N. H., Bansari, K., Irfan, S., & Rizwan, A. (2020). Psychological stress as a risk factor for cardiovascular disease: A case-control study. *Cureus*, *12*(10), Article e10757. https://doi.org/10.7759/cureus.10757

Saxena, S., Sharan, P., & Saraceno, B. (2003). Budget and financing of mental health services: Baseline information on 89 countries from WH''s project atlas. *Journal of Mental Health Policy and Economics*, *6*(3), 135–143.

Schiweck, C., Piette, D., Berckmans, D., Claes, S., & Vrieze, E. (2019). Heart rate and high frequency heart rate variability during stress as biomarker for clinical depression. A systematic review. *Psychological Medicine*, *49*(2), 200–211. https://doi.org/10.1017/S0033291718001988

Schlee, W., Schecklmann, M., Lehner, A., Kreuzer, P. M., Vielsmeier, V., Poeppl, T. B., & Langguth, B. (2014). Reduced variability of auditory alpha activity in chronic tinnitus. *Neural Plasticity*, *2014*, Article 436146. https://doi.org/10.1155/2014 /436146

Shaffer, F., & Ginsberg, J. P. (2017). An overview of heart rate variability metrics and norms. *Frontiers in Public Health*, *5*, Article 258. https://doi.org/10.3389/fpubh.2017.00258

Shin, L. M., & Liberzon, I. (2010). The neurocircuitry of fear, stress, and anxiety disorders. *Neuropsychopharmacology*, *35*(1), 169–191. https://doi.org/10.1038/npp.2009.83

Shinba, T. (2017). Major depressive disorder and generalized anxiety disorder show different autonomic dysregulations revealed by heart-rate variability analysis in first-onset drug-naïve patients without comorbidity. *Psychiatry and Clinical Neurosciences*, *71*(2), 135–145. https://doi.org/10.1111 /pcn.12494

Silverman, M. N., Pearce, B. D., Biron, C. A., & Miller, A. H. (2005). Immune modulation of the hypothalamic-pituitary-adrenal (HPA) axis during viral infection. *Viral Immunology*, *18*(1), 41–78. https://doi.org/10.1089/vim.2005.18.41

Singla, S., Jhamb, S., Singh, K. D., & Kumar, A. (2020). Depression affects autonomic system of the body? Yes, it does! *Journal of Education and Health Promotion*, *9*, Article 217. https://doi.org/10.4103%2Fjehp.jehp_627_19

Smith, S. M., & Vale, W. W. (2006). The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress. *Dialogues in Clinical Neuroscience*, *8*(4), 383–395. https://doi.org/10.31887/DCNS.2006.8.4/ssmith

Sroykham, W., & Wongsawat, Y. (2019). Effects of brain activity, morning salivary cortisol, and emotion regulation on cognitive impairment in elderly people. *Medicine*, *98*(26), Article e16114. https://doi.org/10.1097 /md.0000000000016114

Steimer, T. (2002). The biology of fear- and anxiety-related behaviors. *Dialogues in Clinical Neuroscience*, *4*(3), 231–249. https://doi.org/10.31887/DCNS.2002.4.3/tsteimer

Strauß, A., Wöstmann, M., & Obleser, J. (2014). Cortical alpha oscillations as a tool for auditory selective inhibition. *Frontiers in Human Neuroscience*, *8*, Article 350. https://doi.org /10.3389/fnhum.2014.00350

Tanaka, M., Yoshida, M., Emoto, H., & Ishii, H. (2000). Noradrenaline systems in the hypothalamus, amygdala and locus coeruleus are involved in the provocation of anxiety: Basic studies. *European Journal of Pharmacology*, *405*(1–3), 397–406. https://doi.org/10.1016/S0014-2999(00)00569-0

Teed, A. R., Feinstein, J. S., Puhl, M., Lapidus, R. C., Upshaw, V., Kuplicki, R. T., Bodurka, J., Ajijola, O. A., Kaye, W. H., Thompson, W. K., Paulus, M. P., & Khalsa, S. S. (2022). Association of generalized anxiety disorder with autonomic hypersensitivity and blunted ventromedial prefrontal cortex activity during peripheral adrenergic stimulation: A randomized clinical trial. *JAMA Psychiatry*, *79*(4), 323–332. https://doi.org/10.1001/jamapsychiatry.2021.4225

Teplan, M. (2002). Fundamental of EEG measurement. *Measurement Science Review*, *2*(2), *1–11*.

Thomas, M. R., Dyrbye, L. N., Huntington, J. L., Lawson, K. L., Novotny, P. J., Sloan, J. A., & Shanafelt, T. D. (2007). How do distress and well-being relate to medical student empathy? A multicenter study. *Journal of General Internal Medicine*, *22*(2), 177–183. https://doi.org/10.1007/s11606-006-0039-6

Tomlinson, M., Grimsrud, A. T., Stein, D. J., Williams, D. R., & Myer, L. (2009). The epidemiology of major depression in South Africa: Results from the South African stress and health study. *South African Medical Journal*, *99*(5 Pt. 2), 367–373.

Tonsing, K. N. (2014). Psychometric properties and validation of Nepali version of the Depression Anxiety Stress Scales (DASS-21). *Asian Journal of Psychiatry*, *8*, 63–66. https://doi.org/10.1016/j.ajp.2013.11.001

Torpy, J. M., Lynm, C., & Glass, R. M. (2007). Chronic stress and the heart. *JAMA*, *298*(14), Article 1722. https://doi.org /10.1001/jama.298.14.1722

Torres-Platas, S. G., Cruceanu, C., Chen, G. G., Turecki, G., & Mechawar, N. (2014). Evidence for increased microglial priming and macrophage recruitment in the dorsal anterior cingulate white matter of depressed suicides. *Brain, Behavior, and Immunity*, *42*, 50–59. https://doi.org/10.1016 /j.bbi.2014.05.007

Tran, T. D., Tran, T., & Fisher, J. (2013). Validation of the depression anxiety stress scales (DASS) 21 as a screening instrument for depression and anxiety in a rural community-based cohort of northern Vietnamese women. *BMC Psychiatry*, *13*(1), Article 24. https://doi.org/10.1186/1471-244X-13-24

Trivedi, J. K. (2006). Cognitive deficits in psychiatric disorders: Current status. *Indian Journal of Psychiatry*, *48*(1), 10–20. https://doi.org/10.4103/0019-5545.31613

Valkanova, V., Ebmeier, K. P., & Allan, C. L. (2013). CRP, IL-6 and depression: A systematic review and meta-analysis of longitudinal studies. *Journal of Affective Disorders*, *150*(3), 736–744. https://doi.org/10.1016/j.jad.2013.06.004

Vitasari, P., Wahab, M. N. A., Othman, A., Herawan, T., & Sinnadurai, S. K. (2010). the relationship between study anxiety and academic performance among engineering students. *Procedia - Social and Behavioral Sciences*, *8*, 490–497. https://doi.org/10.1016/j.sbspro.2010.12.067

Vogelzangs, N., Beekman, A. T., de Jonge, P., & Penninx, B. W. (2013). Anxiety disorders and inflammation in a large adult cohort. *Translational Psychiatry*, *3*(4), Article e249. https://doi.org/10.1038/tp.2013.27

Vogelzangs, N., Seldenrijk, A., Beekman, A. T. F., van Hout, H. P. J., de Jonge, P., & Penninx, B. W. J. H. (2010). Cardiovascular disease in persons with depressive and anxiety disorders. *Journal of Affective Disorders*, *125*(1–3), 241–248. https://doi.org/10.1016/j.jad.2010.02.112

Von Känel, R., Hepp, U., Kraemer, B., Traber, R., Keel, M., Mica, L., & Schnyder, U. (2007). Evidence for low-grade systemic proinflammatory activity in patients with posttraumatic stress disorder. *Journal of Psychiatric Research*, *41*(9), 744–752. https://doi.org/10.1016/j.jpsychires.2006.06.009

Wagner, F., Wagner, R. G., Kolanisi, U., Makuapane, L. P., Masango, M., & Gómez-Olivé, F. X. (2022). The relationship between depression symptoms and academic performance among first-year undergraduate students at a South African university: A cross-sectional study. *BMC Public Health*, *22*(1), Article 2067. https://doi.org/10.1186/s12889-022-14517-7

Wakefield, J. C. (2010). Misdiagnosing normality: Psychiatry's failure to address the problem of false positive diagnoses of mental disorder in a changing professional environment. *Journal of Mental Health*, *19*(4), 337–351. https://doi.org/10.3109/09638237.2010.492418

Warner, S. (2013). *Cheat sheet for neurofeedback*. Stress Therapy Solutions. Retrieved January 23. https://stresstherapysolutions.com/uploads/STSCheatSheetoftheBrain.pdf

Watanabe, M. (2017). [Brodmann Areas 8 and 9 Including the Frontal Eye Field]. *Brain and Nerve*, *69*(4), 347–354. https://doi.org/10.11477/mf.1416200751

Weinstock, M. (2001). Alterations induced by gestational stress in brain morphology and behaviour of the offspring. *Progress in Neurobiology*, *65*(5), 427–451. https://doi.org/10.1016/s0301-0082(01)00018-1

Weiss, C., Murr, C., Zoller, H., Haun, M., Widner,B., Ludescher, C., & Fuchs, D. (1999). Modulation of neopterin formation and tryptophan degradation by Th1- and Th2-derived cytokines in human monocytic cells. *Clinical & Experimental Immunology*, *116*(3), 435–440. https://doi.org/10.1046/j.1365-2249.1999.00910.x

Whiteford, H. A., Degenhardt, L., Rehm, J., Baxter, A. J., Ferrari, A. J., Erskine, H. E., Charlson, F. J., Norman, R. E., Flaxman, A. D., Johns, N., Burstein, R., Murray, C. J. L., & Vos, T. (2013). Global burden of disease attributable to mental and substance use disorders: Findings from the Global Burden of Disease Study 2010. *Lancet*, *382*(9904), 1575–1586. https://doi.org/10.1016/S0140-6736(13)61611-6

Widner, B., Laich, A., Sperner-Unterweger, B., Ledochowski, M., & Fuchs, D. (2002). Neopterin production, tryptophan degradation, and mental depression—What is the link? *Brain Behavior and Immunity*, *16*(5), 590–595. https://doi.org/10.1016/S0889-1591(02)00006-5

Wilmer, M. T., Anderson, K., & Reynolds, M. (2021). Correlates of quality of life in anxiety disorders: Review of recent research. *Current Psychiatry Reports*, *23*(11), Article 77. https://doi.org/10.1007/s11920-021-01290-4

Wohleb, E. S., Powell, N. D., Godbout, J. P., & Sheridan, J. F. (2013). Stress-induced recruitment of bone marrow-derived monocytes to the brain promotes anxiety-like behavior. *Journal of Neuroscience*, *33*(34), 13820–13833. https://doi.org/10.1523/jneurosci.1671-13.2013

Yang, X., Fang, Y., Chen, H., Zhang, T., Yin, X., Man, J., Yang, L., & Lu, M. (2021). Global, regional and national burden of anxiety disorders from 1990 to 2019: Results from the Global Burden of Disease Study 2019. *Epidemiology and Psychiatric Sciences*, *30*, Article e36. https://doi.org/10.1017/s2045796021000275

Zöger, S., Svedlund, J., & Holgers, K.-M. (2006). Relationship between tinnitus severity and psychiatric disorders. *Psychosomatics*, *47*(4), 282–288. https://doi.org/10.1176/appi.psy.47.4.282

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Top-Level Managers' Psychophysical Recovery Investigated Through Different Psychophysiological Parameters Benefits From Training Based on Muscle Relaxation and Self-monitoring of HRV-Biofeedback

*Carlo Pruneti, Alice Fiduccia, and Sara Guidotti**

Clinical Psychology, Clinical Psychophysiology, and Clinical Neuropsychology Labs, Dept of Medicine and Surgery, University of Parma, Italy

Abstract

Objective. The present study aimed to verify whether training based on progressive muscle relaxation (PMR) and self-monitoring of heart rate variability biofeedback (HRV-BFB) could lead to a significant reduction of psychophysical stress among top-level managers, measured on different physiological parameters related to the stress response. **Methods.** Thirty-four top-level managers, after completing the Symptom Questionnaire (SQ), were subjected to a psychophysiological stress profile (PSP) to describe the psychophysiological activation (Skin Conductance, surface Electromyography, Heart Rate, and Peripheral Temperature were registered in three phases: baseline, stress, and recovery). Following the intervention with PMR and HRV-BFB, SQ and PSP were readministered. **Results.** A condition of psychophysical stress was detected through SQ and PSP in the total sample at T0. The intervention allowed participants to reduce their psychological symptoms. Furthermore, muscular tension and skin conductance levels were significantly lower in the recovery phase of the PSP administered at T1. Additionally, a reduction in the reactivity to stress was observed in the HR value postintervention. **Conclusion**. Combining PMR and HRV-BFB therapy can reduce distress symptoms and improve responses to stress. It's cost-effective and offers many benefits, making it a widely recommended intervention.

Keywords: top-level managers; stress response; progressive muscle relaxation; heart rate variability; biofeedback

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***Address correspondence to**: Sara Guidotti, PhD Student, Clinical Psychology, Clinical Psychophysiology, and Clinical Neuropsychology Labs, Dept of Medicine and Surgery, Via Volturno, 39 43126 Parma, Italy. Email: sara.guidotti@unipr.it

Edited by:
Rex L. Cannon, PhD, Currents, Knoxville, Tennessee, USA

Reviewed by:
Rex L. Cannon, PhD, Currents, Knoxville, Tennessee, USA
Randall Lyle, PhD, Mount Mercy University, Cedar Rapids, Iowa, USA

Introduction

Currently, mental health systems are facing challenges in addressing the increasingly high levels of stress within the population (Brinkmann et al., 2020). Stress is a complex phenomenon that occurs in response to physical or psychological threats, triggering psychological, behavioral, and physiological responses (Bali & Jaggi, 2015). If individuals do not recover sufficiently from stress, it can lead to significant risks to both physical and psychological health, and result in substantial economic costs for healthcare systems (Cooper & Dewe, 2008). Stressful situations can overload the autonomic state, causing an increase in heart rate (HR) and sweating (or skin conductance), as well as a reduction in peripheral temperature and higher levels of muscular tension (Jarczok et al., 2013).

Among the different potential sources of stress, work-related stress stands out from the most recent psychological and psychophysiological literature.

Work-related stress is considered a psychophysical response that occurs when job demands exceed employees' resources and abilities to cope with them or they clash excessively with this (National Institute for Occupational Safety and Health, 1999). The European Agreement on Stress at Work, dated October 8, 2004, defines it as a state characterized by discomfort, along with physical, psychological, and social dysfunctions, resulting from an individual's inability to meet performance expectations.

According to research (Skagert et al., 2012; Van Bogaert et al., 2014), top-level managers are particularly susceptible to work-related stress due to their high level of responsibility and the constantly evolving nature of their work (Barreto et al., 2022). This stress is further compounded in large organizations, where managers must navigate a highly competitive business sector while overseeing a large number of employees (Siegrist & Bollmann, 2023). Prolonged stress in the workplace can lead to burnout (Maslach, 1982), a syndrome characterized by exhaustion, job disaffection or cynicism, and reduced professional effectiveness.

Greater attention has been paid to the psychophysical health of workers following the European Agreement on Stress (2004) with the introduction of work-related stress risk assessment. For instance, in Italy, an adjustment to the European guidelines took place thanks to the Legislative Decree 81/2008. Consequently, the research line of Psychology of Work has enriched its literature and proposed interventions useful for the reduction of psychological distress related to the workplace. As a result, situations of chronic stress and psychophysiological activation were treated with intervention programs that were demonstrated to be useful in the management of anxious and somatic disorders (Lalanza et al., 2023). This led to the development of the Psychology of Work research line, which aims to reduce workplace-related psychological distress through various interventions such as Jacobson's progressive muscular relaxation (PMR) and biofeedback training (BFB). Studies show that these interventions are effective in managing anxious and somatic disorders. PMR has been proven to reduce anxiety, depression, sleep disturbances, chronic pain, and burnout levels (Golombek, 2001; Semerci et al., 2021). Meanwhile, BFB has shown promising results in improving autonomic imbalance, according to clinical psychophysiology studies (Dillon et al., 2016). More specifically, researchers are focusing their attention on the BFB based on heart rate variability (HRV). HRV is the variation in time between consecutive heartbeats (RR-intervals) and serves as a quantitative marker of autonomic balance and physiological stress (Malik et al., 1996). It consists of coupling and synchronizing the cardiac rhythm with the phases of respiration. Deep, regular breathing has been found to increase HR fluctuation and respiratory sinus arrhythmia, and it appears capable of optimizing the balance between sympathetic (SANS) and parasympathetic (PANS) systems (Russo et al., 2017). The two components of the autonomic nervous system (SANS and PANS) are also known as the fight-or-flight mechanism and the relaxation response, respectively (Hoareau et al., 2021; Jiménez Morgan & Molina Mora, 2017). Moreover, technological advances make it possible to make BFB-based projects increasingly usable thanks to portable medical devices that fall into the category of mHealth tools (Istepanian et al., 2004). Recent research by De Witte et al. (2019) and Schoenberg & David (2014) has revealed that wearable devices used for BFB (biofeedback) can significantly enhance the efficacy of psychological treatments for symptoms associated with psychophysiological hyperactivation. Numerous studies have demonstrated that HRV-BFB (heart rate variability biofeedback) has positive effects in alleviating symptoms of depression and anxiety (De Witte et al., 2019; Lehrer & Gevirtz, 2014; Saito et al., 2021; Schäfer et al., 2018). Additionally, psychological programs that incorporate HRV-BFB are effective in improving cardiac parameters (Lehrer & Gevirtz, 2014; Lehrer et al., 2000; Shaffer & Meehan, 2022). Despite these benefits, there is currently no research evaluating the impact of psychophysiological interventions on relaxation and other psychophysical parameters, while considering physiological parameters beyond those directly targeted. Generally, studies in the literature have assessed treatment efficacy using psychological tests (Goessl et al., 2017) or only one biofeedback parameter, such as HRV (Brinkmann et al., 2020).

After careful consideration of all factors, we determined it imperative to investigate the efficacy of an intervention incorporating Jacobson exercises and HRV-BFB. Our study aimed to examine the effects of this intervention on a range of psychophysiological parameters that reflect autonomic nervous system (ANS) activity in a cohort of high-level executives, with the ultimate goal of mitigating work-related stress.

Materials and Methods

Participants and Study Design

In this quasi-experimental study, 34 top managers were consecutively recruited from different multinational companies (i.e., TIM, an Italian telephone company; BNP Paribas, an international bank; Europcar, a car rental agency; eFM, a private import–export big company; Trenitalia, Italian public railway transportation; and Oracle, multinational IT company) with different locations in Italy by the Bloom (S.r.l., Rome) company. The subjects were recruited through e-mail contact by Bloom Company, and they were offered to book an in-person appointment. The 34 top managers who took part in the study were volunteers and provided informed consent before taking part in the protocol. Before administering the tests, the researchers provided information about the purpose of the study. A public presentation of the principal aims of the study and a personal individual interview was conducted. An idea of the purpose of the psychometric test administered was offered without specification of the single scale test. Once the subjects completed the administration, they were offered the option to book another appointment to receive a description of their results during a psychological interview that would be kept confidential. Criteria for inclusion in the study were age greater than 18 years old; completion of informed consent; no history of psychiatric and/or neurological syndromes (e.g., previous head trauma, epilepsy, etc.) and/or physical diseases (i.e., sensory disturbances of sight and/or hearing) that may limit the administration of the tests; and not on psychological/psychiatric or psychopharmacological treatment at the time of the recruitment. None of the participants reported previous knowledge of breathing and/or relaxation practices.

All data were handled under the ethical standards established in the 1964 Helsinki Declaration. Subjects' anonymity was preserved, and the data obtained were used solely for scientific purposes. All patient/personal identifiers have been removed or disguised so the patient/person(s) described are not identifiable and cannot be identified through the details of the story.

Measures

All of the participants underwent a psychological and psychophysiological assessment.

Psychopathological symptoms were assessed through the Symptom Questionnaire (SQ; Fava et al., 1983). It contains four scales based on the factorial analysis of the psychological symptoms of Anxiety (A), Depression (D), Somatization (S), and Hostility (H). Each scale can be divided into two subscales, one concerned with symptoms and the other with well-being, for a total of eight subscales. Therefore, each of the main scales includes items from both the symptoms and the well-being subscales. The clinical cutoff corresponds to four for all the scales of the test. The SQ was shown to have high sensitivity and specificity levels (80% and 76% in general practice, respectively; 86% and 74% in hospital medical wards; and 83% and 85% in emergency departments (Rucci et al., 1994). Such observations allowed this instrument to be particularly adequate, not only for the initial assessment of the patients' complex clinical profiles but also for a possible retest of the self-reported symptoms over time (Benasi et al., 2020). This test has weekly, daily, and hourly versions. For this research, the weekly version was used.

A psychophysiological stress profile (PSP; Fuller, 1979) structured in three phases was implemented. In the baseline phase (6 min), each patient was instructed to close his eyes and remain still and relaxed. In the stress phase (4 min), a mental arithmetic task (MAT) was presented to the participant. This task consisted of subtracting the number 13 from the number 1007 and continuing to subtract 13 from each successive result that was obtained. Lastly, in the recovery phase (6 min), the patient was instructed to relax again. The following parameters were continuously registered: surface frontal electromyography (sEMG), where the electrical potential was detected by means of two active electrodes placed 1 cm over the two eyebrows on the same line of the pupils and one reference electrode placed at the center of the front (2 cm of distance between poles); the skin conductance level-response (SCL-SCR), where a very low intensity electrical direct current was attained by means of two electrodes placed on the first and second finger of the nondominant hand; heart rate (HR), that consists of the detection of the electrical potential of cardiac muscle by the classic bipolar shunt for the electrocardiogram (ECG) with the possibility of calculation of inter-beat-interval (IBI) and all of the heart rate variability (HRV) data (e.g., high, very low, ultra-low and low frequencies); and peripheral temperature (PT), the peripheral body temperature recorded by a thermistor with a device placed on the thenar eminence of the nondominant hand. EMG and HR parameters were detected using surface disposable electrodes with 0.5 mm of active surface. For the SCL-SCR, two gold-plated electrodes were employed. For the PT, a

very sensitive electronic thermometer (capable of evaluating fluctuations in temperature of less than 0.1°C) was utilized. The employed technology device was the “psycholab VD 13” by SATEM, Rome, Italy. The Modulab was connected by an infrared cable to a PC and all the data were detected and processed by a PC soft VD 13SV VERSION 5.0 Works program software (by SATEM, Rome, Italy). Values are considered normal if they move within their respective normal ranges: 1.7–2.5 μV for sEMG; 2.2–6.0 μS for SCL; 60–90 bpm for HR; and 31–32 °C for PT (Cacioppo et al., 2007).

Assessment Procedure

The SQ was used as an outcome measure of the psychopathological symptoms and was administered before (T0) and after the PMR and BFB intervention (T1). In addition, the psychophysiological parameters of the PSP (sEMG, SCL-SCR, HR, and PT) were considered outcome measures to assess the benefit of the level of psychophysiological activation. A clinical psychologist who received a research fellow collected participants’ personal history and psychological and psychophysiological data.

Intervention Procedure

The intervention was carried out by two researchers and clinical psychologists. This phase was structured as follows: the study participants underwent 10 relaxation sessions with exercises based on Jacobson's progressive muscle relaxation (PMR). The sessions were weekly and lasted 45 min. The procedure consisted of contracting muscle groups (one at a time and then all together) for 5–7 s, followed by a 20-s relaxation time. The training included an alternation of tension and relaxation of the muscles of the legs, arms, abdomen, neck, and mouth based on the classic training proposed by Jacobson (McGuigan, 1978).

The BFB training was started following the three months of the 10 relaxation sessions with PMR. The researchers were trained to lead the BFB program by a professor of psychopathology and clinical psychophysiology who was an expert in the field over a month with four lectures and guided practical exercises. In turn, researchers trained the participants to do BFB exercises independently. In particular, the participants were provided with the Inner Balance, an HRV BFB device consisting of an ear clip (photoplethysmographic sensor), a signal transformer, and software for viewing HRV cardiac data on the smartphone in real time. This app allows monitoring the sympathovagal balance independently in the absence of the operator. Participants were asked to spend 15 min per day repeating the PMR exercises and monitoring their HRV using the Inner Balance app. The researchers downloaded the HeartMath App on participants' smartphones and demonstrated how to use it. HeartMath is an mHealth intervention that teaches people to increase awareness and management of their internal states by increasing HRV through a wearable sensor. The auditory and visual feedback that is provided to the subject corresponds with the heart rhythm coherence elaborated within the Inner Balance technology of the HeartMath Institute (McCraty, 2016). For instance, the irregular heart-rhythm pattern (incoherence) is typical of negative emotions such as anger or frustration, while the coherent heart-rhythm pattern is typically observed when an individual is experiencing sustained, positive emotions and appreciation.

> A coherent heart rhythm is defined as a relatively harmonic (sine-wave-like) signal with a very narrow, high-amplitude peak in the low-frequency region (typically around 0.1 Hz) of the power spectrum with no major peaks in the other bands. Coherence is assessed by identifying the maximum peak in the 0.04–0.26 Hz range of the HRV power spectrum, calculating the integral in a window 0.030 Hz wide, centered on the highest peak in that region, and then calculating the total power of the entire spectrum. The coherence ratio is formulated as Peak Power / (Total Power − Peak Power)^2 (McCraty & Shaffer, 2015).

People were instructed to do HRV-BFB at least twice per day for 5 min or once each day for 10 min, every day for the 60-day study period.

Statistical Analysis

All statistical analyses were performed using SPSS (Version 28.0.1.0; IBM Corp, Armonk, NY). Nonparametric statistical analyses were used in light of the small sample size of the sample. After descriptive statistics of the scores obtained from the total samples in the SQ scores and PSP values, the following statistics were performed: (1) comparisons between males and females on the sociodemographic characteristics (age, marital status, educational level) and the clinical features (psychological symptoms and psychophysiological activation) were calculated at baseline; (2) comparisons between the SQ scores and the PSP values obtained from the total sample at T0 and T1 were computed. The chi-square test was used for variables such as marital status and education whereas the Mann-Whitney U test was calculated for

age, SQ scores, and PSP values at T0, and the Wilcoxon signed-rank sum test was used for the paired difference analysis (T0-T1) for SQ scores and PSP values.

Results

Descriptive statistics of the sociodemographic variables clearly showed that males and females did not differ at baseline (Table 1).

Table 1

Comparisons of Sociodemographic Characteristics Between Males and Females at Baseline (T0)

Sociodemographic features	Male (n = 20)	Female (n = 14)	Total (n = 34)	U or χ^2	p
Age, *M* (*SD*)	47.95 (5.83)	46.57 (7.39)	47.38 (6.4)	$t(33) = -0.53$	n.s.
Marital status, *N* (%)				χ^2 (2, N = 34) = 5.24	n.s.
Married/cohabitant	19 (55.88%)	11 (32.35%)	30 (88.24%)		
Unmarried	0 (0%)	3 (8.82%)	3 (8.82%)		
Separated/divorced	1 (2.94%)	0 (0%)	1 (2.94%)		
Education Level, *N* (%)				χ^2 (1, N = 34) = 0.31	n.s.
High school	14 (41.18%)	11 (32.35%)	25 (73.50%)		
University/post-University	6 (17.65%)	3 (8.82%)	9 (26.50%)		

Not even considering the psychopathological symptoms, differences emerged between the two groups. However, both groups reported symptoms related to anxiety activation and irritable mood with somatic complaints above the threshold of significance (= 4). From the psychophysiological point of view, both samples appeared to be under psychophysical stress as both skin conductance and muscle tension values exceeded the upper limits of the typical values (6μS and 2.2μV, respectively; Table 2).

Table 2

Comparisons of Clinical Features Between Males and Females at Baseline (T0)

	Male (n = 20)		Female (n = 14)		Total (n = 34)			
	M	*SD*	*M*	*SD*	*M*	*SD*	U (33)	p
Symptom Questionnaire								
Anxiety	5.00	2.38	7.29	4.89	5.94	3.7	−1.34	n.s.
Depression	2.70	3.18	5.07	4.50	3.68	3.9	−1.95	n.s.
Somatization	5.10	3.95	7.86	5.52	6.24	4.8	−1.55	n.s.
Hostility	3.40	2.23	5.50	4.18	4.26	3.3	−1.36	n.s.
Psychophysiological Assessment								
Skin Conductance								
Baseline	11.03	7.04	7.86	6.09	9.81	7.34	−1.62	n.s.
Stress	17.62	10.21	13.91	7.51	16.19	9.30	−0.89	n.s.
Recovery	16.77	9.84	11.19	5.96	16.61	8.88	−1.74	n.s.

Table 2

Comparisons of Clinical Features Between Males and Females at Baseline (T0)

	Male (n = 20)		Female (n = 14)		Total (n = 34)			
	M	*SD*	*M*	*SD*	*M*	*SD*	*U* (33)	*p*
Surface Electromygraphy								
Baseline	3.94	1.57	3.47	1.05	3.76	1.22	−1.22	n.s.
Stress	4.79	1.58	5.73	1.95	5.16	1.76	−0.95	n.s.
Recovery	3.86	1.46	4.28	1.19	4.02	1.36	−1.01	n.s.
Heart Rate								
Baseline	74.27	9.55	75.12	8.66	74.60	9.08	−0.77	n.s.
Stress	86.50	15.34	84.21	12.23	85.62	14.05	−0.43	n.s.
Recovery	74.07	11.33	74.46	9.31	74.22	10.43	−0.59	n.s.
Peripheral Temperature								
Baseline	32.21	1.57	32.43	1.24	32.30	1.43	−0.30	n.s.
Stress	31.82	1.91	32.36	1.59	32.03	1.79	−0.55	n.s.
Recovery	31.69	1.70	32.00	1.32	31.81	1.55	−0.41	n.s.

Subsequently, a clinical-psychological and clinical-psychophysiological reevaluation was performed after the intervention. A significant reduction in psychopathological symptoms was observed. In particular, anxious activation, somatic complaints, and mood alterations were within the normal range at T1 and significantly reduced from baseline. Furthermore, a decrease in the level of skin conductance and muscle tension was observed in the recovery phase of the psychophysiological stress profile. In addition, a lower reactivity to stress was described by looking at the cardiac parameter of HR. No differences emerged regarding peripheral temperature (Table 3).

Table 3

Comparison Between Pre–post SQ Scores and Psychophysiological Stress Profile Values of the Total Sample (n = 34)

	T0		T1			
	M	*SD*	*M*	*SD*	*Z* (33)	*p*
Symptom Questionnaire						
Anxiety	5.94	3.7	2.84	2.34	−4.23	< .001
Depression	3.68	3.9	1.65	1.06	−4.25	< .001
Somatization	6.24	4.8	3.65	3.49	−3.32	< .01
Hostility	4.26	3.3	1.77	1.94	−2.98	< .001

Table 3

Comparison Between Pre–post SQ Scores and Psychophysiological Stress Profile Values of the Total Sample (n = 34)

	T0		T1			
	M	*SD*	*M*	*SD*	*Z* (33)	*p*
Psychophysiological Assessment						
Skin Conductance						
Baseline	7.34	−1.62	9.43	7.92	−0.88	n.s.
Stress	9.30	−0.89	15.89	10.78	−1.39	n.s.
Recovery	8.88	−1.74	12.67	9.71	−2.57	< .01
Surface Electromygraphy						
Baseline	1.22	−1.22	3.56	1.70	−0.72	n.s.
Stress	1.76	−0.95	5.07	2.28	−0.36	n.s.
Recovery	1.36	−1.01	2.67	1.28	−3.52	< .001
Heart Rate						
Baseline	9.08	−0.77	72.74	10.89	−0.77	n.s.
Stress	14.05	−0.43	79.20	13.36	−2.21	< .05
Recovery	10.43	−0.59	71.36	13.15	−1.06	n.s.
Peripheral Temperature						
Baseline	1.43	−0.30	32.51	1.81	−0.59	n.s.
Stress	1.79	−0.55	32.21	2.06	−0.23	n.s.
Recovery	1.55	−0.41	32.35	2.25	−1.44	n.s.

Discussion

This study aimed to investigate the efficacy of an intervention utilizing PMR and HRV-BFB on a group of high-ranking executives. The sample was well-diversified across gender, age, marital status, and educational attainment, with no significant gender differences noted. Participants reported experiencing anxious activation with accompanying somatic complaints, which was consistent across both groups. Furthermore, the psychological symptoms as measured by the SQ exceeded the clinical threshold for both groups, and the psychophysiological evaluation of skin conductance and muscle tension revealed values beyond the expected range. These results support prior research indicating the presence of stress-related symptoms among top-level managers (Siegrist & Bollmann, 2023; Skagert et al., 2012; Van Bogaert et al., 2014), suggesting that all participants experienced a state of psychophysical stress.

As a part of validating the proposed intervention's effectiveness, pre–post treatment comparisons were conducted. The participants benefited from the intervention, reporting decreased distress at baseline in terms of psychopathological symptoms. The clinical scales' scores, including anxiety, depression, somatizations, and hostility, were in the normal range at T1, similar to other interventional studies (Ferendiuk et al., 2019; Ghorbannejad et al., 2022; McGuigan, 1978). The training exercises proposed at the beginning of the training resulted in better muscle relaxation skills, which was reflected in lower levels of muscle tension and skin conductance observed during the recovery phase. The majority of physiological parameters showed improvement in the psychophysiological assessment. A generalization across multiple psychophysiological parameters was observed, except for the peripheral temperature parameter, which remained unchanged. The HRV-BFB training restored ANS balance globally, generating benefits that affect the whole

organism. This training can activate the modulatory function of the reflexes that control the two branches of the ANS, SANS and PANS. The results of this study support the idea that HRV-BFB allows balancing the ANS and confirms the evidence of benefits in several clinical contexts (Chrousos & Boschiero, 2019; Reneau, 2020; Windthorst et al., 2017; Zucker et al., 2009). The benefits can be measured on several parameters connected to the complex system involved in the stress response. The findings of this study are consistent with the literature, which shows no evident changes in the short term for the thermoregulation processes measured within a brief psychophysiological evaluation (Bregman & McAllister, 1983).

To summarize, individuals who exhibit a lower reactivity to stress, which is indicated by the HR parameter, and a better psychophysical recovery, which can be observed with the sEMG and SCR values, tend to have a better stress response (Cannon, 1932; Selye, 1950). This was demonstrated in a study where subjects were evaluated and reevaluated using a PSP that simulates stress. By doing this, researchers were able to elicit and monitor the stress response and found that these individuals had learned to recover their psychophysical balance after experiencing stress.

Based on our initial findings, it appears that further studies are necessary to corroborate our results and address the limitations of our study. A more structured methodology, such as a randomized controlled trial, coupled with a larger sample size and the inclusion of a control group, would enable us to conduct more sophisticated statistical analyses and analyze the main effect of the intervention while controlling for confounding variables such as gender and specific temperamental traits. Our study found that the combined use of PMR and HRV-BFB did not yield conclusive evidence as to which technique is more effective in reducing work-related stress. However, our research's strength lies in its integrated treatment approach, which has provided participants with muscle relaxation exercises that they can perform independently with minimal operator costs. We utilized the HeartMath app for HRV-BFB to promote self-monitoring and equip participants with stress management skills that foster independence from the operator. Furthermore, we found it beneficial to reevaluate participants using parameters that are not under conscious control, such as psychophysiological values. Questionnaire responses may be subject to social desirability, whereas ANS activity evaluation is free from simulation. In conclusion, research indicates that cardiac coherence induction techniques are effective in managing stress in individuals with anxiety, insomnia, hypertension, and other conditions, as well as in high-risk situations as a preventive measure (Alabdulgader, 2012).

Conclusion

Despite some limitations, this study's findings are significant and have important clinical implications. The research aimed to assess the effectiveness of a PMR and HRV-BFB intervention on high-level managers. The results demonstrate that this intervention enhanced the emotional self-regulation skills of the participants, as evidenced by the differences in various physiological parameters before and after the intervention. Specifically, participants showed lower HR levels under stress, and their skin conductance levels and muscular tension significantly decreased during the recovery phase, indicating better management of stress-induced emotions.

Overall, the study suggests that 10 guided PMR sessions and 2 months of HRV-BFB using a smartphone can effectively reduce work-related stress symptoms. This research also highlights the importance of examining both subjective and objective aspects of psychophysical well-being. Further research is necessary to validate these findings and determine the most appropriate methods for monitoring the treatment's effectiveness. These findings could pave the way for more widespread use of clinical psychological and psychophysiological assessments.

Author Disclosures

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References

Alabdulgader, A. A. (2012). Coherence: A novel nonpharmacological modality for lowering blood pressure in hypertensive patients. *Global Advances in Integrative Medicine and Health, 1*(2), 56–64. https://doi.org/10.7453/gahmj.2012.1.2.011

Bali, A., & Jaggi, A. S. (2015). Clinical experimental stress studies: Methods and assessment. *Reviews in the Neurosciences, 26*(5), 555–579. https://doi.org/10.1515/revneuro-2015-0004

Barreto, M. F. C., Galdino, M. J. Q., Fernandes, F. G., Martins, J. T., Marziale, M. H. P., & Haddad, M. d. C. F. L. (2022). Workaholism and burnout among stricto sensu graduate professors. *Revista de Saúde Pública, 56*, Article 48. https://doi.org/10.11606/s1518-8787.2022056003883

Benasi, G., Fava, G. A., & Rafanelli, C. (2020). Kellner's Symptom Questionnaire, a highly sensitive patient-reported outcome measure: Systematic review of clinimetric properties. *Psychotherapy and Psychosomatics, 89*(2), 74–89. https://doi.org/10.1159/000506110

Bregman, N. J., & McAllister, H. A. (1983). Constraints on the Yerkes-Dodson law in skin temperature biofeedback. *International Journal of Neuroscience, 21*(3–4), 183–189. https://doi.org/10.3109/00207458308986137

Brinkmann, A. E., Press, S. A., Helmert, E., Hautzinger, M., Khazan, I., & Vagedes, J. (2020). Comparing effectiveness of HRV-biofeedback and mindfulness for workplace stress reduction: A randomized controlled trial. *Applied Psychophysiology and Biofeedback, 45*(4), 307–322. https://doi.org/10.1007/s10484-020-09477-w

Cacioppo, J. T., Tassinary, L. G., & Berntson, G. G. (Eds.). (2007). *Handbook of psychophysiology* (3rd ed.). Cambridge University Press. https://doi.org/10.1017/CBO9780511546396

Cannon, W. B. (1932). *The wisdom of the body*. W. W. Norton & Co.

Chrousos, G. P., & Boschiero, D. (2019). Clinical validation of a non-invasive electrodermal biofeedback device useful for reducing chronic perceived pain and systemic inflammation. *Hormones, 18*(2), 207–213. https://doi.org/10.1007/s42000-019-00098-5

Cooper, C., & Dewe, P. (2008). Well-being—Absenteeism, presenteeism, costs and challenges. *Occupational Medicine, 58*(8), 522–524. https://doi.org/10.1093/occmed/kqn124

De Witte, N. A. J., Buyck, I., & Van Daele, T. (2019). Combining biofeedback with stress management interventions: A systematic review of physiological and psychological effects. *Applied Psychophysiology and Biofeedback, 44*(2), 71–82. https://doi.org/10.1007/s10484-018-09427-7

Dillon, D. G., Gurdasani, D., Riha, J., Ekoru, K., Asiki, G., Mayanja, B. N., Levitt, N. S., Crowther, N. J., Nyirenda, M., Njelekela, M., Ramaiya, K., Nyan, O., Adewole, O. O., Anastos, K., Azzoni, L., Boom, W. H., Compostella, C., Dave, J. A., Dawood, H., Erikstrup, C., … Sandhu, M. S. (2013). Association of HIV and ART with cardiometabolic traits in sub-Saharan Africa: A systematic review and meta-analysis. *International Journal of Epidemiology, 42*(6), 1754–1771. https://doi.org/10.1093/ije/dyt198

Fava, G. A., Kellner, R., Perini, G. I., Fava, M., Michelacci, L., Munari, F., Evangelisti, L. P., Grandi, S., Bernardi, M., & Mastrogiacomo, I. (1983). Italian validation of the Symptom Rating Test (SRT) and Symptom Questionnaire (SQ). *The Canadian Journal of Psychiatry. La Revue Canadienne de Psychiatrie, 28*(2), 117–123. https://doi.org/10.1177/070674378302800208

Ferendiuk, E., Biegańska, J. M., Kazana, P., & Pihut, M. (2019). Progressive muscle relaxation according to Jacobson in treatment of the patients with temporomandibular joint disorders. *Folia Medica Cracoviensia, 59*(3), 113–122. https://doi.org/10.24425/fmc.2019.131140

Fuller, G. D. (1979). Biofeedback methods and procedures in clinical practice. San Francisco, CA: Biofeedback Press.

Ghorbannejad, S., Mehdizadeh Tourzani, Z., Kabir, K., & Yazdkhasti, M. (2022). The effectiveness of Jacobson's progressive muscle relaxation technique on maternal, fetal and neonatal outcomes in women with non-severe preeclampsia: A randomized clinical trial. *Heliyon, 8*(6), e09709. https://doi.org/10.1016/j.heliyon.2022.e09709

Goessl, V. C., Curtiss, J. E., & Hofmann, S. G. (2017). The effect of heart rate variability biofeedback training on stress and anxiety: A meta-analysis. *Psychological Medicine, 47*(15), 2578–2586. https://doi.org/10.1017/S0033291717001003

Golombek, U. (2001). Progressive Muskelentspannung nach Jacobson in einer psychiatrisch-psychotherapeutischen Abteilung - empirische Ergebnisse [Progressive muscle relaxation (PMR) according to Jacobson in a department of psychiatry and psychotherapy - empirical results]. *Psychiatrische Praxis, 28*(8), 402–404. https://doi.org/10.1055/s-2001-18615

Hoareau, V., Godin, C., Dutheil, F., & Trousselard, M. (2021). The effect of stress management programs on physiological and psychological components of stress: The influence of baseline physiological state. *Applied Psychophysiology and Biofeedback, 46*(3), 243–250. https://doi.org/10.1007/s10484-021-09508-0

Istepanian, R. S. H., Jovanov, E., & Zhang, Y. T. (2004). Introduction to the special section on M-Health: Beyond seamless mobility and global wireless health-care connectivity. *IEEE Transactions on Information Technology in Biomedicine, 8*(4), 405–414. https://doi.org/10.1109/titb.2004.840019

Jarczok, M. N., Jarczok, M., Mauss, D., Koenig, J., Li, J., Herr, R. M., & Thayer, J. F. (2013). Autonomic nervous system activity and workplace stressors—A systematic review. *Neuroscience and Biobehavioral Reviews, 37*(8), 1810–1823. https://doi.org/10.1016/j.neubiorev.2013.07.004

Jiménez Morgan, S., & Molina Mora, J. A. (2017). Effect of heart rate variability biofeedback on sport performance, a systematic review. *Applied Psychophysiology and Biofeedback, 42*(3), 235–245. https://doi.org/10.1007/s10484-017-9364-2

Lalanza, J. F., Lorente, S., Bullich, R., García, C., Losilla, J.-M., & Capdevila, L. (2023). Methods for heart rate variability biofeedback (HRVB): A systematic review and guidelines. *Applied Psychophysiology and Biofeedback, 48*, 275–297. https://doi.org/10.1007/s10484-023-09582-6

Lehrer, P. M., & Gevirtz, R. (2014). Heart rate variability biofeedback: How and why does it work? Frontiers in Psychology, 5, 756. https://doi.org/10.3389/fpsyg.2014.00756

Lehrer, P. M., Vaschillo, E., & Vaschillo, B. (2000). Resonant frequency biofeedback training to increase cardiac variability: Rationale and manual for training. *Applied Psychophysiology and Biofeedback, 25*(3), 177–191. https://doi.org/10.1023/a:1009554825745

Malik, M., Bigger, J. T., Camm, A. J., Kleiger, R. E., Malliani, A., Moss, A. J., & Schwartz, P. J. (1996). Heart rate variability: Standards of measurement, physiological interpretation, and clinical use. *European Heart Journal, 17*(3), 354–381. http://doi.org/10.1093/oxfordjournals.eurheartj.a014868

Maslach, C. (1982). *Burnout: The cost of caring*. Englewood Cliffs, NJ: Prentice-Hall.

McGuigan, F. J. (1978). Interview with Edmund Jacobson. *Biofeedback and Self-regulation, 3*(3), 287–300. https://doi.org/10.1007/BF00999297

McCraty, R. (2016). Science of the heart, Volume 2: Exploring the role of the heart in human performance. HeartMath Institute.

McCraty, R., & Shaffer, F. (2015). Heart rate variability: New perspectives on physiological mechanisms, assessment of self-regulatory capacity, and health risk. *Global Advances in Integrative Medicine and Health, 4*(1), 46–61. https://doi.org/10.7453/gahmj.2014.073

National Institute for Occupational Safety and Health (NIOSH). (1999). *Stress at Work*. Centers for Disease Control and Prevention, U. S. Department of Health and Human Services. Publication No. 99-101, 26.

Reneau, M. (2020). Heart rate variability biofeedback to treat fibromyalgia: An integrative literature review. *Pain Management Nursing, 21*(3), 225–232. https://doi.org/10.1016/j.pmn.2019.08.001

Rucci, P., De Marco, P., & Bivi, R. (1994). Il Symptom Questionnaire come strumento di screening nei contesti sanitari di base. *Epidemiology and Psychiatric Sciences*. *Epidemiologia E Psichiatria Sociale, 3*(1), 31–37. https://doi.org/10.1017/S1121189X00009295

Russo, M. A., Santarelli, D. M., & O'Rourke, D. (2017). The physiological effects of slow breathing in the healthy human. *Breathe, 13*(4), 298–309. https://doi.org/10.1183/20734735.009817

Saito, R., Sawamura, D., Yoshida, K., & Sakai, S. (2021). Relationship between the proficiency level and anxiety-reducing effect in a one-time heart rate variability biofeedback: A randomized controlled trial. *Medicine, 100*(45), Article e27742. https://doi.org/10.1097/MD.0000000000027742

Schäfer, S. K., Ihmig, F. R., Lara H., K. A., Neurohr, F., Kiefer, S., Staginnus, M., Lass-Hennemann, J., & Michael, T. (2018). Effects of heart rate variability biofeedback during exposure to fear-provoking stimuli within spider-fearful individuals: Study protocol for a randomized controlled trial. *Trials, 19*(1), Article 184. https://doi.org/10.1186/s13063-018-2554-2

Schoenberg, P. L. A., & David, A. S. (2014). Biofeedback for psychiatric disorders: A systematic review. *Applied Psychophysiology and Biofeedback, 39*(2), 109–135. https://doi.org/10.1007/s10484-014-9246-9

Selye, H. A. (1950). Stress and the general adaptation syndrome. *British Medical Journal, 1*(4667), 1383–1392. https://doi.org/10.1136/bmj.1.4667.1383

Semerci, R., Öztürk, G., Akgün Kostak, M., Elmas, S., İhsan Danacı, A., & Musbeg, S. (2021). The effect of progressive muscle relaxation exercises on compassion satisfaction, burnout, and compassion fatigue of nurse managers. *Perspectives in Psychiatric Care, 57*(3), 1250–1256. https://doi.org/10.1111/ppc.12681

Shaffer, F., & Meehan, Z. M. (2022). An undergraduate program with heart: Thirty years of Truman HRV research. *Applied Psychophysiology and Biofeedback, 47*(4), 317–326. https://doi.org/10.1007/s10484-022-09543-5

Siegrist, J., & Bollmann, U. (2023). Promoting good and sustainable work in occupational health education. *Occupational Medicine, 73*(2), 61–65. https://doi.org/10.1093/occmed/kqac018

Skagert, K., Dellve, L., & Ahlborg, G. (2012). A prospective study of managers' turnover and health in a healthcare organization. *Journal of Nursing Management, 20*(7), 889–899. https://doi.org/10.1111/j.1365-2834.2011.01347.x

Van Bogaert, P., Adriaenssens, J., Dilles, T., Martens, D., Van Rompaey, B., & Timmermans, O. (2014). Impact of role-, job- and organizational characteristics on Nursing Unit Managers' work related stress and well-being. *Journal of Advanced Nursing, 70*(11), 2622–2633. https://doi.org/10.1111/jan.12449

Windthorst, P., Mazurak, N., Kuske, M., Hipp, A., Giel, K. E., Enck, P., Nieß, A., Zipfel, S., & Teufel, M. (2017). Heart rate variability biofeedback therapy and graded exercise training in management of chronic fatigue syndrome: An exploratory pilot study. *Journal of Psychosomatic Research, 93*, 6–13. https://doi.org/10.1016/j.jpsychores.2016.11.014

Zucker, T. L., Samuelson, K. W., Muench, F., Greenberg, M. A., & Gevirtz, R. N. (2009). The effects of respiratory sinus arrhythmia biofeedback on heart rate variability and posttraumatic stress disorder symptoms: A pilot study. *Applied Psychophysiology and Biofeedback, 34*(2), 135–143. https://doi.org/10.1007/s10484-009-9085-2

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Validation and Application of a Factorial Model of Attention in Attention-Deficit/Hyperactivity Disorder

María Agudo Juan[1], Rubén Pérez-Elvira[1,2], Marina Wobbeking[2], and Bogdan Neamtu[3,4,5]*

[1]Laboratory of Neuropsychophysiology, NEPSA Rehabilitación Neurológica, Salamanca, Spain
[2] Pontifical University of Salamanca, Salamanca, Spain
[3] Medicine Faculty, Lucian Blaga University, Sibiu, Romania
[4] Research Department (Ceforaten), Sibiu Pediatric Hospital, Sibiu, Romania
[5] Faculty of Engineering, Lucian Blaga University, Sibiu, Romania

Abstract

Background. Attentional processes and executive functions have been essential elements in the study of attention-deficit/hyperactivity disorder (ADHD). This research aims to validate Ríos Lago and Muñoz-Céspedes (2004) factorial model of attention in ADHD and to investigate the attentional and executive alterations that occur in ADHD according to this model. **Method**. A total of 40 participants, aged between 7 and 16 years, took part in the study. The sample included 20 ADHD patients and 20 control subjects who participated as volunteers. **Results**. The factors identified through principal component analysis accounted for 78.81% of the variance in the data. Four factors were found, consistent with Ríos Lago and Muñoz-Céspedes' model, based on the factor loadings and following neuropsychological criteria. **Conclusions**. The results supported the replicability of the proposed attentional model in ADHD. They demonstrated the presence of specific alterations in individuals with ADHD, as predicted by the model.

Keywords: ADHD; factorial model of attention; neuropsychological testing

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***Address correspondence to:** Marina Wobbeking, Facultad de Psicología, Universidad Pontificia de Salamanca, C/ Compañía, 5 37002, Salamanca, Spain. Email: mwobbekingsa@upsa.es

Edited by:
Rex L. Cannon, PhD, Currents, Knoxville, Tennessee, USA

Reviewed by:
Rex L. Cannon, PhD, Currents, Knoxville, Tennessee, USA
Mark S. Jones, DMin, University of Texas at San Antonio, San Antonio, Texas, USA

Attention-deficit/hyperactivity disorder (ADHD) has been associated with deficits in attentional processes and executive functions. This disorder begins in childhood and has been defined as a sustained pattern of inattention, hyperactivity, and impulsivity behaviors that must be maintained for a sufficient period of time and usually appears before the age of 12 years (Piñón et al., 2019). ADHD has been considered a problem of behavioral self-regulation. In contrast, in the past decades it was defined not only as a behavioral disorder but also as a learning disorder, explained as deficits in cognitive functions that manifest themselves in disruptive behaviors (García-Nonell & Rigau-Ratera, 2015). According to the *Diagnostic and Statistical Manual of Mental Disorders*, it shows three clinical presentations: inattentive, hyperactive/impulsive, and combined inattentive and hyperactive-impulsive (5th ed.; DSM-5; American Psychiatric Association [APA], 2013).

As noted, one of the affected processes in ADHD is attention. Mellado et al. (2013) state that attention is understood as a control mechanism, which activates the necessary processes to perfect the processing of information and inhibit stimuli that could create interference, ensuring perceptual processing of sensory messages relevant to the goal set and an equally adequate execution of relevant actions to achieve it, in addition to being linked to motivational mechanisms. Therefore, it is a precondition for cognition and indispensable for affective behavior and the survival of the human being itself (Sales, 2016). Attention is composed of different types of processes and systems, within which are situated processes aimed at creating and maintaining an adequate state of alertness, guidance systems

aimed at the selection of relevant information from sensory input, and processes that are to a greater extent related to the control and monitoring of attentional resources (Fan, et al., 2002; Rodríguez-Blanco et al., 2017; Stuss, 2006). One of the most interesting attentional models is the one developed by Ríos, Periáñez and Muñoz-Céspedes (2004), who have based their model on a series of response patterns in different psychometric tests and factor analysis to elucidate the underlying attentional mechanisms for performance in these tests. Factor analysis represents a strong, satisfactory, and relatively common tool to study which underlying constructs are represented in different tests and which are responsible for the variance of a group of items in an independent test or in a battery (Agelink van Rentergem et al., 2020; Santos et al., 2015; Spikman et al., 2001; Ustárroz et al., 2012).

Thus, they proposed a model that studies four factors (Table 1), based on factor analysis applied to the results of patients with traumatic brain injury and normal subjects in some classic attention tests (Stroop; Trail Making Test; Wisconsin Card Sorting Test; Ríos Lago et al., 2008).

Table 1
Factors in Attention Measures

High-level Processes	Low-level Processes
Control	Speed of Information Processing
Interference Control	
Cognitive Flexibility	
Working Memory	

Ríos et al. (2004) attention factorial model.

Components of Care

The components of care according to this model are described below.

Speed of Processing. It is the amount of information that can be processed per unit of time (Spikman et al., 2001). As it has been highlighted, it is more a substrate on which attention develops than an attentional component. Although it is not an attentional process per se, it is closely related to attention and can affect attentional performance, such that if attention is not fast it may not fully fulfill its adaptive function.

Attentional Control. Three components are grouped under this denomination.

- **Cognitive Flexibility**. It is the ability to shift the focus of attention from one scheme of action to a different one and modify behavior in response to changes in the environment.
- **Operative Memory**. This is the ability to maintain information that has been experienced in previous instants, or information retrieved from long-term memory, and which is no longer available in the environment, also implying the ability to manipulate this information (Ríos Lago et al., 2008). Likewise, the ability to change the attentional focus would depend on working memory (Baddeley, 2001).
- **Control of Interference**. One of the most consistent findings in the work on attention, this factor shows the ability to control the tendency of overlearned automatic responses and distractions from irrelevant stimuli (Klenberg et al., 2001; Pineda Salazar et al., 2000).

Consequently, in order to perform attentional tasks, both components, speed and control, would be necessary. These components reflect two characteristics of the tasks: time pressure and structure, respectively. If the task is highly structured, the amount of control required will be minimal, the main factor being the processing speed. If, on the contrary, the task has little organization, the control required for its performance will be the maximum, since it cannot be solved with routine responses and will require interference control, cognitive flexibility, and working memory (Ríos Lago et al., 2008).

Our objectives with this study are 1) validation of the Factorial Model of Attention by Ríos Lago and Muñoz-Céspedes (2004) in ADHD, assuming the hypothesis that the factorial analysis will reveal four factors equivalent to those of the Ríos et al. (2004) model, and 2) to verify the attentional and executive impairments that occur in ADHD, according to the model by Ríos Lago and Muñoz-Céspedes (2004), in order to differentiate which tests or scores better distinguish between healthy subjects and controls.

Methods

Subjects

Data for this study were obtained from a sample of 40 subjects, aged 7 to 16 years. The sample included 20 ADHD patients and 20 healthy controls who participated as volunteers. The clinical subjects

were referred by the Guidance and Behavior Team of the Junta de Castilla y León, after requesting their participation in this study. The inclusion criteria for participation in this study were as follows:

- **Clinical Group**. Diagnosis of ADHD (following the ADHD coordination protocol of the Junta de Castilla y León), drug control (withdrawal 24 hours before the application of the tests) under the supervision of the neurologist and acceptance by the parents, age between 7–16 years, and no other medical complications or psychiatric disorders. The parents signed an informed consent for their children to participate in the study.
- **Control Group**. Same age criteria as the clinical group and no medical complication or psychiatric alteration.

The ethics committee of our affiliated research institution (Research and Telemedicine Center for Neurological Diseases in Children—the CEFORATEN project) approved the study with the following authorization number: ECN 6227/23. We complied with all the ethical standards asserted in the Declaration of Helsinki in the study's design.

Instruments

Neuropsychological factors and tests included:

- **Speed of Processing**. For this component, test or subtest scores involving speed or time pressure were used, such as the Trail Making Test (TMT), Letters and Numbers (LN), Symbol Search (BS) and Number Key (CN) of the WISC-IV, Stroop P, Stroop PC, and Brief Test of Attention (BTA). The TMT is a neuropsychological instrument widely used as an indicator of processing speed (Sánchez-Cubillo et al., 2009). Both parts A and B require speed in execution, with time being a decisive aspect in the performance of the task. CN and BS are part of the Processing Speed index of the WISC-IV. In both, the subject is under time pressure, since they have to perform the task in a certain amount of time—speed playing a primordial role for the correct performance of the task. In other tests such as LN or BTA (total), although time measures are not taken and they are not considered processing speed tests, these are tasks where the rate of stimulus presentation is not controlled by the patient but by the examiner. The task has a standard rate and not one appropriate for each patient, so there is some implicit time pressure (Ríos et al., 2004). Likewise, the Stroop test requires an adequate processing speed for its correct performance.
- **Cognitive Flexibility**. For this factor we used the Wisconsin Card Sorting Test (WCST) hits, perseverative errors and perseverative responses and the TMT B/A score (Ríos et al., 2004). The WCST has been one of the most widely used tests in the attentional switching paradigm, both in clinical and research contexts (Periáñez et al., 2004). The WCST also reflects skills related to cognitive flexibility that are not measured by other prefrontal tests (Barceló et al., 2000). Perseverative responses would reflect inflexibility in shifting attentional focus to another set (Ríos et al., 2004; Greve et al., 1999), on the contrary, the percentage of successes in the test is related to the ability to shift attentional focus (Ríos et al., 2004). As for the TMT B/A ratio, it reflects alternating attention, which also implies the ability to shift attention from one sequence to another; in this score the influence of processing speed is eliminated (Ríos et al., 2004) and the influences of visuoperceptual and working memory demands are minimized, thus obtaining a relatively purer indicator of control (Sánchez-Cubillo et al., 2009).
- **Operative Memory**. This factor consisted of scores related to information maintenance and manipulation; that is, LN, BTA Total, set loss, and nonperseverative errors on the WCST (Ríos et al., 2004). The LN score is clearly related to working memory processes, being a working memory index of the WISC-IV (Wechsler, 2007). The BTA score reflects, among other things, the ability to mentally manipulate numerical information that is not already present while attending to a series of items being presented (Ríos et al., 2004). Several factors underlie the performance of the WCST, so not only are its scores indicative of Cognitive Flexibility but its performance would also involve working memory (Brauer et al., 1998; Ríos et al., 2004). Although there has been some confusion about whether working memory is involved in the performance of the TMT, Kortte et al. (2002) found that neither part A nor part B was related to the maintenance of information.
- **Control of Interference**. This factor included two Stroop test scores (Stroop PC and Interference), the TMT B/A ratio and the

Paced Auditory Serial Addition Test score (PASAT, in this case 3); the Stroop PC and Stroop Interference scores suggest that there is a cognitive process that controls the tendency of automatic responses. In the PASAT, the presence of interference control is evident since it is necessary for the subject to inhibit the responses that they offer in order to correctly attend to the list of numbers that is presented to them audibly (Ríos et al., 2004). The score extracted from the B/A ratio of the TMT implies an attentional shift that is composed of a change of focus to another point of attention and, in addition, of an inhibition or control component (Arbuthnott & Frank, 2000; Ríos et al., 2004). This inhibition component would therefore be an important element of control (Mecklinger et al., 1999).

In addition, the finger-tapping test (FTT; Enokizono et al., 2022) was applied as a measure of motor speed.

Procedure

To collect the data, each participant was invited to the NEPSA Neurological Rehabilitation Clinic (Salamanca). The subjects in the clinical group had not taken medication in the previous 24 hours. All subjects were evaluated after their parents' signed consent and the subsequent return of a report with their performance in these tests.

First, a form was collected that included their demographic variables (sex, age, date of birth, group, and contact data). The tests were applied in an office under the same conditions, with the following order: Digits and Number Key (CN) from the WISC-IV, Stroop test, Wisconsin Card Sorting Test (WCST), Brief Test of Attention (BTA), Trail Making Test (TMT), Paced Auditory Serial Addition Test (PASAT), finger-tapping test (FTT), Letters and Numbers (LN) and Symbol Search (BS) from the WISC-IV. Despite alternating between manipulative and verbal tests, there seemed to be no influence of the order of application of these tests on test performance, according to Ríos Lago and Muñoz-Céspedes (2004). The rules of each test were explained, making sure that all participants understood what had to be done in each test. The duration of the tests ranged from 50 to 75 min. Optionally, the possibility of an intellectual capacity assessment on another day was offered to all those who were interested, subsequent to the attention assessment. The data were coded in an Excel spreadsheet for later analysis.

Data Analysis

All analyses were performed using SPSS version 25.0 software, except for the effect size, which was obtained using the Cohen's *d* calculator of the University of Colorado (https://www.uccs.edu/lbecker/). The statistical analyses performed were as follows:

For objective 1, the possibility of obtaining a factorial structure of the utilized scores was studied by considering the results of two tests, Kaiser-Meyer-Olkin (KMO) and Bartlett's sphericity. Afterward, a principal component analysis was conducted. Varimax rotation method used with Kaiser normalization.

For objective 2, the Shapiro-Wilk test of normality was performed to assess the fit of each score to a normal distribution. Subsequently, a mean difference test was applied using either the parametric Student's *t*-test for normally distributed scores or the nonparametric Mann-Whitney U test for nonnormally distributed scores. Cohen's *d* was used to calculate effect sizes.

Results

The results obtained from the aforementioned analysis are presented below.

No significant differences were found between groups with respect to age (Table 2).

In regard to objective 1, as shown in Table 3, both assumptions, factorial structure and relationship between variables, are met.

Table 2
ADHD and Control Groups Ages

	ADHD	Control	U Mann-Whitney	*p*
Age	*M* = 129.85 *DT* = 33.14 *N* = 20	*M* = 137.75 *DT* = 35.01 *N* = 20	177.5	.547

Table 3
KMO and Bartlett Tests

KMO	Bartlett's Sphericity		
	Approx. Chi-squared	gl	Sig.
.687	630.419	105	.000

The principal component analysis yielded a grouping into four factors that explained 78.81% of the variance (Table 4). Table 5 shows, marked in bold, the scores that loaded for each factor.

In regard to objective 2, we further present the results for each test.

In the Stroop test, only the Interference score of the control group was normally distributed, so the Mann-Whitney U test was chosen to study their mean differences. Significant differences were found in all scores (Stroop P: U = 90, p = .002, d = 1.228; Stroop C: U = 92, p = .003, d = 1.014; Stroop PC: U = 111, p = .015, d = 0.966) except for the Interference score (Stroop Interference: U = 152, p = .194, d = 0.460). However, for the latter data, the effect size was medium, compared to the acceptable effect size for the other scores of the same test. The clinical group was significantly worse than the control in Word, Color, and Word-Color scores.

Table 4
Explained Variance

Component	Percentage of variance per factor	Percentage of cumulative variance
1 Speed of Processing	46.498	46.498
2 Cognitive Flexibility	16.152	62.650
3 Operative Memory	8.702	71.352
4 Control of Interference	7.461	78.813

Table 5
Rotated Component Array

	Components			
	1	2	3	4
ST-P	**.874**	−.099	−.138	−.208
TMT-A	**−.883**	.050	.150	.050
TMT-B	**−.678**	.141	.210	**.617**
ST-PC	**.954**	.031	−.050	−.135
CL-A	**.719**	.061	.167	−.300
BS	**.732**	.188	.139	−.317
LN-T	**.597**	−.124	**−.559**	−.287
BTA-T	**.751**	−.229	−.230	.026
WCST % Perseverative Errors	−.205	**.582**	**.513**	−.084
WCST % Conceptual Level	.035	**−.973**	−.117	−.056
TMT B/A	−.143	.101	.166	**.899**
WCST Set Loss	.067	-.061	**.828**	.158
WCST % Nonperseverative Errors	.130	**.893**	−.177	.134
ST-INT	**.848**	.134	−.006	.058
PASAT Correct Responses	**.715**	−.121	**−.496**	−.051

Note. Extraction method: Principal component analysis. Rotation method: Varimax with Kaiser normalization. The rotation has converged in six iterations.

As for the WISC-IV Number Key subtest, a normal distribution was found in the correct scores, but not in the errors made. Therefore, the *t* and *U* statistics were applied respectively. Significant differences were found in correct scores (t = 3.285, p = .002, d = 1.039), however, the clinical group did not make more errors (U = 170, p = .429, d = 0.454), with a moderate effect size.

In Digits, we found a total score that was significantly worse in the clinical group with respect to the control group (U = 81, p = .001, d = 0.979), obtaining a large effect size.

The mean difference in the BTA total score showed that the clinical group scored significantly higher than the control (t = 2.523, p = .016, d = 0.799). A mean effect size was obtained for this test.

TMT, a significant difference between groups was obtained in the B score (U = 95, p = .004, d = 0.839) with a large effect size, and in the B/A speed free score (U = 90.5, p = .002, d = 1.059), also with a large effect size.

The clinical group also scored significantly worse on the Letters and Numbers subtest (U = 93.5, p = .003, d = 1.029), with a large effect size.

In the Symbol Search subtest, the clinical group scored significantly worse than the control group (U = 121, p = .033, d = 0.724) although, again, they did not make more errors than the control group (U = 171.5, p = .445, d = 0.154). This last finding should be taken with caution due to the small effect size obtained.

Motor speed, as measured by FTT, was not found to be different between groups (U = 144, p = .134, d = 0.336), although a small effect size was obtained.

No significant differences were found in any PASAT score (Hits: U = 129.5, p = .056, d = 0.583; Omissions: U = 160, p = .289, d = 0.487; Errors: U = 172, p = .461, d = 0.147). The clinical group, again, did not make more errors, but similarly a low effect size was found for this score.

No significant differences were found in any WCST score between the groups (Number of attempts: U = 174, p = .495, d = 0.201; Number of categories: U = 165.5, p = .355, d = 0.358; % Hits: U = 195, p = .904, d = 0.140; % Errors: U = 186.5, p = .718, d = 0.193; % Perseverative Errors: U = 167, p = .383, d = 0.306; % Nonperseverative Errors: U = 188, p = .758, d = 0.121; Perseverative %RR: U = 173.5, p = .478, d = 0.226; % Conceptual Level: U = 184, p = .678, d = 0.236; Set loss: U = 181, p = .620, d = 0.200), although the low effect size obtained for each of the scores must be taken into account.

The clinical group performed worse on the Working Memory Index than the control (U = 86.4, p = .002, d = 1.072), achieving a large effect size.

As for the Processing Speed Index, there was no significant difference between groups (U = 150.5, p = .183, d = 0.519), with a moderate effect size.

Discussion

The factors found after principal component analysis were able to explain 78.81% of the variance of the data. Four factors were found, as in the Ríos et al. model, which, due to the scores that loaded on each of the factors (Table 5), and according to neuropsychological criteria, were similar to those presented in the work of Ríos et al. (2004).

Key Factors

1 Speed of Processing. The first factor included scores where processing speed or time pressure is present in test performance. In this factor, we loaded scores such as CL and BS which, although they may involve other functions or subfunctions for their performance, have processing speed as their main construct and in fact constitute the two main tests for the calculation of the WISC-IV Processing Speed Index. In addition, other tests carry time pressure explicitly, such as the Stroop subtests, or those of the TMT, or implicitly, such as LN, BTA, and PASAT, where time pressure is exerted by stimulus presentation ratio (1 item/1s or 1 item/3s, for example). The B/A ratio of the TMT did not saturate in this factor, probably because it is an a posteriori calculation where the influence of speed is precisely isolated.

2 Cognitive Flexibility. The second factor was composed of WCST scores, where cognitive flexibility, the ability to shift the focus of attention from one task to another, is a mandatory skill. Thus, the percentage of perseverative errors shows the inability to leave the focus of attention from one stimulus source and switch to another when demands dictate it. Similarly, the percentage of successes is a measure of the effective ability to shift focus when required. The percentage of nonperseverative errors would, like the previous score, be related to the ability to be flexible; a higher

number of nonperseverative errors (as opposed to perseverative errors) would inform us that the subject's problem is not in flexibility but in other issues related to a test as complex as the WCST.

3 Operative Memory. The third factor includes scores that have in common some relationship to working memory. LN is a core test of the WISC-IV Working Memory Index, as well as there is sufficient literature support for the influence of WCST on working memory (Monchi et al., 2001). The PASAT clearly includes the ability to mentally retain information and operate with it, so it is not surprising that it is also one of the saturating scores in this factor.

4 Control of Interference. The fourth factor is exclusively configured by the TMT-B and TMT-B/A scores. Although these scores also saturate in flexibility, they do so here without the presence of other components of flexibility (such as the WCST scores), and studies show that in addition to a focus-shifting ability component, a prior focus inhibition component is necessary in the performance of this test (Houghton & Tipper, 1996; Mecklinger et al., 1999). It is not surprising that the Stroop interference subtest does not appear here; the sample size may have contributed to its undetectability as an element of this factor.

The results for objective 1 are compatible with accepting that the Ríos et al. model is replicable, fulfilled in a sample of children and adolescents, made up of both healthy controls and subjects with ADHD. In this study, we found a factorial structure underlying the tests used, a relationship between them and four principal components that are highly coincident with those proposed by Ríos et al. (2004).

As for objective 2, to study attentional disturbances in ADHD following the Ríos et al. model and to be able to decide which scores are more representative to differentiate between controls and ADHD, our data showed that subjects with ADHD performed significantly lower than controls in Stroop P, Stroop C, Stroop, PC, CL, Digits, BTA-t, TMT-B, TMT-B/A, LN, BS, and the Working Memory Index of the WISC-IV. These battery scores would therefore be more appropriate to distinguish subjects with ADHD from those without ADHD. If we consider the four factors of the model by the scores that make up each one of them, *4 Control of Interference* was affected 100% in ADHD, followed by *1 Speed of Processing*, affected 81.8%, after which *3 Operative Memory* was affected 25%. *2 Cognitive Flexibility* was not affected.

On the other hand, it should be noted that in those tests where errors were computed (CL and BS) no differences were found between the ADHD group and the control group. Errors in these tests can be of omission and commission; That is, for lack of response to the item or for responding in an inadequate way to the item. Both issues closely relate to the interference control; however, neither of these two tests appeared among the constituent of the interference factor, which could mean that the low performance of the ADHD group subjects in these tests is explained precisely by the alteration in the processing speed. Nor did subjects with ADHD perform worse compared to controls on the FTT, which could rule out motor slowing as a cause of poor performance on time-pressure tests involving paper and pencil.

Our study contributes to a better understanding of the underlying cognitive impairments in ADHD and provides valuable insights for clinical assessment and intervention. The factorial model of attention, validated in this study, offers a comprehensive framework for assessing and characterizing attentional deficits in individuals with ADHD. On the other hand, it is important to highlight that the study had a small sample size, which could be a potential source of bias in the results and their interpretations.

Future research should continue to explore the applicability of this factorial model in larger and more diverse samples to enhance its generalizability. Additionally, investigating the relationships between the identified factors and other relevant clinical variables may provide further insights into the complexity of ADHD and guide targeted interventions.

Conclusions

In conclusion, our study aimed to validate and apply the mentioned factorial model of attention in ADHD. The results provided strong support for the replicability of the model proposed by Ríos et al (2004). The identified factors were able to explain a significant portion (78.81%) of the variance in the data.

The factorial analysis revealed four distinct factors that closely aligned with the Ríos et al. model. These factors included Speed of Processing, Cognitive Flexibility, Operative Memory, and Control of Interference.

Furthermore, our findings demonstrated significant differences between individuals with ADHD and

healthy controls in various tests, confirming the utility of using these tests in ADHD detection. Scores in tests such as Stroop, WCST, LN, and the Working Memory Index of the WISC-IV consistently differentiated between the two groups.

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References

Agelink van Rentergem, J. A., de Vent, N. R., Schmand, B. A., Murre, J. M. J., Staaks, J. P. C., ANDI Consortium, & Huizenga, H. M. (2020). The factor structure of cognitive functioning in cognitively healthy participants: A meta-analysis and meta-analysis of individual participant data. *Neuropsychology Review, 30*(1), 51–96. https://doi.org/10.1007/s11065-019-09423-6

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). https://doi.org/10.1176/appi.books.9780890425596

Arbuthnott, K., & Frank, J. (2000). Trail making test, part b as a measure of executive control: Validation using a set-switching paradigm. *Journal of Clinical and Experimental Neuropsychology, 22*(4), 518–528. https://doi.org/10.1076/1380-3395(200008)22:4;1-0;FT518

Baddeley, A. D. (2001). Is working memory still working? *American Psychologist, 56*(11), 851–864. https://doi.org/10.1037/0003-066X.56.11.851

Barceló, F., Muñoz-Céspedes, J. M., Pozo, M. A., & Rubia, F. J. (2000). Attentional set shifting modulates the target p3b response in the Wisconsin Card Sorting Test. *Neuropsychologia, 38*(10), 1342-1355. https://doi.org/10.1016/S0028-3932(00)00046-4

Brauer, K., Pontón, M. O., Gorsuch, R. L., González, J. J., & Miller, B. L. (1998). Factor analysis of four measures of prefrontal lobe functioning. *Archives of Clinical Neuropsychology, 13*(7), 585–595.

Enokizono, T., Ohto, T., Tanaka, M., Maruo, K., Mizuguchi, T., Sano, Y., Kandori, A., & Takada, H. (2022). Boys with attention-deficit/hyperactivity disorder perform wider and fewer finger tapping than typically developing boys – Peer comparisons and the effects of methylphenidate from an exploratory perspective. *Brain & Development, 44*(3), 189–195. https://doi.org/10.1016/j.braindev.2021.11.002

Fan, J., McCandliss, B. D., Sommer, T., Raz, A., & Posner, M. I. (2002). Testing the efficiency and independence of attentional networks. *Journal of Cognitive Neuroscience, 14*(3), 340–347. https://doi.org/10.1162/089892902317361886

García-Nonell, K., & Rigau-Ratera, E. (2015). Trastorno de déficit de atención/hiperactividad. In A. Enseñat Cantallops, M. T. Roig Rovira, & A. García Molina (Eds.), *Neuropsicología pediátrica* (pp. 139–161). Editorial Síntesis: España

Greve, K. W., Bianchini, K. J., Hartley, S. M., & Adams, D. (1999). The Wisconsin Card Sorting Test in stroke rehabilitation: Factor structure and relationship to outcome. *Archives of Clinical Neuropsychology, 14*(6), 497–509. https://doi.org/10.1093/arclin/14.6.497

Houghton, G., & Tipper, S. P. (1996). Inhibitory mechanisms of neural and cognitive control: Applications to selective attention and sequential action. *Brain and Cognition, 30*(1), 20–43. https://doi.org/10.1006/brcg.1996.0003

Klenberg, L., Korkman, M., & Lahti-Nuuttila, P. (2001). Differential development of attention and executive functions in 3- to 12-year-old Finnish children. *Developmental Neuropsychology, 20*(1), 407–428. https://doi.org/10.1207/S15326942DN2001_6

Kortte, K. B., Horner, M. D., & Windham, W. K. (2002). The Trail Making Test, part b: Cognitive flexibility or ability to maintain set? *Applied Neuropsychology, 9*(2), 106–109. https://doi.org/10.1207/S15324826AN0902_5

Mecklinger, A., Von Cramon, D. Y., Springer, A., & Cramon, G. M.-V. (1999). Executive control functions in task switching: Evidence from brain injured patients. *Journal of Clinical and Experimental Neuropsychology, 21*(5), 606–619. https://doi.org/10.1076/jcen.21.5.606.873

Mellado, M. B., Martínez, L. N., & Tello, F. P. H. (2013). Procesos atencionales implicados en el trastorno por déficit atencional con hiperactividad (TDAH). *Convergencia Educativa*, (2), 9–19. https://core.ac.uk/download/pdf/19775027.pdf

Monchi, O., Petrides, M., Petre, V., Worsley, K., & Dagher, A. (2001). Wisconsin card sorting revisited: Distinct neural circuits participating in different stages of the task identified by event-related functional magnetic resonance imaging. *The Journal of Neuroscience, 21*(19), 7733–7741. https://doi.org/10.1523/jneurosci.21-19-07733.2001

Periáñez, J. A., Maestú, F., Barceló, F., Fernández, A., Amo, C., & Ortiz-Alonso, T. (2004). Spatiotemporal brain dynamics during preparatory set shifting: MEG evidence. *NeuroImage, 21*(2), 687–695. https://doi.org/10.1016/j.neuroimage.2003.10.008

Pineda Salazar, D. A., Merchán Morales, V., Rosselli, M., & Ardila, A. (2000). Estructura factorial de la función ejecutiva en estudiantes universitarios jóvenes. *Revista de Neurología, 31*(12), 1112–1118. https://doi.org/10.33588/rn.3112.2000417

Piñón, A., Carballido, E., Vázquez, E., Fernande, S., Gutiérrez, O., & Spuch, C. (2019). Rendimiento neuropsicológico de niños y niñas con trastorno por déficit de atención e hiperactividad (TDAH). *Cuadernos de Neuropsicología/Panamerican Journal of Neuropsychology, 13*(1), 116–131.

Ríos Lago, M., & Muñoz-Céspedes, J. M. (2004). La atención y el control ejecutivo después de un traumatismo craneoencefálico. Madrid: Editorial Mapfre.

Ríos, M., Periáñez, J. A., & Muñoz-Céspedes, J. M. (2004). Attentional control and slowness of information processing after severe traumatic brain injury. *Brain Injury, 18*(3), 257–272. https://doi.org/10.1080/02699050310001617442

Ríos Lago, M., Periáñez, J. A., & Rodriguez, J. M. (2008). Neuropsicología de la atención. In J. Tirapu, M. Ríos Lago, & F. Maestu (Eds.), *Manual de neuropsicología* (pp. 151–188). Viguera Editores.

Rodríguez-Blanco, L., Lubrini, G., Vidal-Mariño, C., & Ríos-Lago, M. (2017). Eficacia de la rehabilitación cognitiva de la atención, funciones ejecutivas y memoria operativa en los trastornos psicóticos. Revisión sistemática. *Actas Españolas de Psiquiatría, 45*(4), 167–178.

Sales, G, A. (2016). *Fronteras entre el Deterioro Cognitivo Leve y personas mayores sanas*. [Tesis doctoral]. Universidad de Valencia, Valencia.

Sánchez-Cubillo, I., Periáñez, J. A., Adrover-Roig, D., Rodríguez-Sánchez, J. M., Ríos-Lago, M., Tirapu, J., & Barceló, F. (2009). Construct validity of the Trail Making Test: Role of task-switching, working memory, inhibition/interference control, and visuomotor abilities. *Journal of the International Neuropsychological Society, 15*, 438–450. https://doi.org/10.1017/S1355617709090626

Santos, N. C., Costa, P. S., Amorim, L., Moreira, P. S., Cunha, P., Cotter, J., & Sousa, N. (2015). Exploring the factor structure of neurocognitive measures in older individuals. *PLoS ONE, 10*(4), Article e0124229. https://doi.org/10.1371/journal.pone.0124229

Spikman, J. M., Kiers, H. A. L., Deelman, B. G., & van Zomeren, A. H. (2001). Construct validity of concepts of attention in healthy controls and patients with CHI. *Brain and Cognition, 47*(3), 446–460. https://doi.org/10.1006/brcg.2001.1320

Stuss, D. T. (2006). Frontal lobes and attention: Processes and networks, fractionation and integration. *Journal of the International Neuropsychological Society, 12*(2), 261–271. https://doi.org/10.1017/S1355617706060358

Ustárroz, J. T., Molina, A. G., Lario, P. L., García, A. V., & Lago, M. R. (2012). Corteza prefrontal, funciones ejecutivas y regulación de la conducta. Neuropsicología de la corteza prefrontal y las funciones ejecutivas, 116.

Wechsler, D. (2007). *Manual de aplicación y corrección* (WISC-IV). Madrid, Tea Ediciones.

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Effect of Attention on Prestimulus Neural Noise

Anoop Basavanahalli Jagadeesh[1], Sandeep Maruthy[2], and Ajith Kumar U[2]*

[1]Auditory Neuroscience Laboratory, Department of Communication Sciences and Disorders, Northwestern University, Evanston, Illinois, USA
[2]Department of Audiology, All India Institute of Speech and Hearing, Mysuru, India

Abstract

Attending to a target sound increases the number of cortical resources allotted towards processing the target stimuli, leading to larger response amplitudes for the cortical auditory evoked potentials (CAEPs). However, the effect of attention on the neural noise, as well its definition, is still not clear. Having defined neural noise as the neural activity immediately preceding a stimulus, we aimed to explore the effects of attention on the prestimulus activity when measured using CAEPs. Using a 256-channel montage, we compared the global RMS amplitudes of the prestimulus (PreRMS), poststimulus (PostRMS), and the difference between PostRMS and PreRMS (DiffRMS) measured under active attention and passive attention conditions. Paired *t*-tests revealed a significant attention-related increase in the amplitudes of all three measures. We suppose that the attention-related excitation of target-relevant cortical pathways as well as the inhibition of target-irrelevant mechanisms, in combination, resulted in an increase in the overall neural activity in the three measures. Higher prestimulus activity can, therefore, be used as an objective index of attention and is likely to indicate anticipatory cortical preparation. Our results further validate the supposition that prestimulus activity is not merely neural noise, but indicates the neurophysiological activity associated with complex sensory and/or cognitive functions.

Keywords: cortical auditory evoked potentials; attention; neural noise; prestimulus; anticipatory; RMS

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***Address correspondence to**: Anoop Basavanahalli Jagadeesh, Auditory Neuroscience Laboratory, Department of Communication Sciences and Disorders, Northwestern University, 2240 Campus Dr., Evanston, IL 60208, USA. Email: anoop.basavanhalli.jagadee@northwestern.edu; anoop2187@gmail.com

Edited by:
Rex L. Cannon, PhD, Currents, Knoxville, Tennessee, USA

Reviewed by:
Rex L. Cannon, PhD, Currents, Knoxville, Tennessee, USA
Wesley D. Center, PhD, Liberty University, Lynchburg, Virginia, USA

Introduction

Paying attention to the target stimulus while recording cortical auditory evoked potentials (CAEPs) is known to alter the characteristics of CAEPs and can result in shorter latencies (Alho, 1992; Hillyard et al., 1973) and/or larger amplitudes (Getzmann et al., 2017; Zendel et al., 2016; Zhang et al., 2016). Additionally, studies that assessed the effects of attention on brain wave (alpha, beta, gamma, and/or delta) oscillations (Debener et al., 2003; Foxe & Snyder, 2011; Horton et al., 2013) and degree of cortical entrainment (Fuglsang et al., 2017; Olguin et al., 2018) also have found significant attention-related changes—mostly showing stronger or enhanced responses. In concordance with the "Gain Theory" of attention (Hillyard et al., 1973), these effects are often attributed to the increased activity of cortical generators corresponding to the allocation of additional cortical resources towards processing the target stimuli (Bennet et al., 2012; Sussman et al., 2005; Zhang et al., 2016). It is proposed that attention (specifically, selective attention) acts as a gating mechanism which works by inhibiting the unattended stimuli and enhancing the responses to attended stimuli (Foxe & Snyder, 2011).

In addition to such enhancements, attention is also suggested to improve the perception of the attended stimuli by increasing the response strength for the attended stimuli and reducing the "neural noise" in the brain (Luck et al., 1997; Nandy et al., 2019). However, the method to calculate and define neural

noise is variable across studies. While some studies have measured neural noise as the variability in intertrial response consistency (Dwyer et al., 2022; Haigh, 2018), others have measured it as the brain activity unrelated to stimulus in the prestimulus time period (Krizman, Bonacina, et al., 2021; Krizman, Lindley, et al., 2020). For our current study, we prefer to define and calculate the neural noise based on the strength and amplitude of the prestimulus neural activity, as this is a more physiologically appropriate metric. Intertrial response consistency, at a physiological level, is a measure of the time (or frequency)-based consistency of occurrence of an expected neural activity, such as a negative or positive "peak" associated with the onset of stimuli. Additionally, this measure is likely to be affected or modulated by the concurrent brain activity in response to the stimuli presented. It is therefore more a measure of neural "jitter" rather than that of noise in the brain. Prestimulus activity, on the other hand, is largely devoid of concurrent stimulus-evoked activity and more likely a measure of spontaneous neural activity (similar to the spontaneous firing rate of a large number of individual neurons measured at the scalp). Attention-related modulation of neural spiking has already been implicated in the visual modality (Luck et al., 1997). Therefore, we chose to use the prestimulus activity to measure the effects of attention on neural noise.

When measured using an event-related potential (ERP) approach, prestimulus activity is the brain activity that occurs in the gap between two successive stimulus presentations (assuming the stimulus presentation paradigm has already accounted for the time taken for the brain activity to return to its baseline levels). This prestimulus (baseline) activity was previously considered to be a metric of the contamination of the response by nonneural sources such as muscular activity, electrical noise, etc. Therefore, prior studies have used it as an index of the quality of response recording (Musacchia et al., 2006; Russo et al., 2004).

However, other studies suggest that the prestimulus activity reflects cortical or neural dynamics associated with various brain functions (Alhanbali et al., 2022; Harris et al., 2018; Kayser et al., 2016; Rahn & Basar, 1993). For example, Bastiaansen and Brunia (2001) presented evidence of anticipatory attention-related changes in brainwave activity, particularly in the frequencies around 10 Hz. Studies have also suggested that the prestimulus cortical activity is likely to reflect complex neural processing associated with task performance or attention (Alhanbali et al., 2022; Henry et al., 2017; Mathewson et al., 2009; McNair et al., 2019). In addition to such immediate online changes, evidence suggests that neural noise is also shaped by life experiences. For example, studies have shown that neural noise is significantly lesser in athletes, compared to nonathletes (Krizman et al., 2020), while an impoverished brain (due to underexposure to linguistically and cognitively stimulating conditions—a consequence of lower socioeconomic status) is shown to be significantly noisier than those with sufficient linguistic and cognitive stimulation (Skoe et al., 2013).

These studies show that the prestimulus neural activity provides an index of the global neurocortical functioning associated with a task at hand. Given this supposition, a need arises to study how neural noise is affected by cognitive tasks such as attention. Previous studies have shown that prestimulus brainwave activity, especially alpha activity, is modulated by attention (Alhanbali et al., 2022; Fellinger et al., 2011; Henry et al., 2017; McNair et al., 2019). However, such approaches using specific brain wave activities provide a very restricted view of the cortical activity, largely limited to a few cortical regions, despite using multichannel EEG recordings. When measured with a high-density EEG recording, prestimulus neural activity, on the other hand, provides a more broadband metric of how a larger number of brain regions work in unison. Therefore, in the current study, we aimed to explore the effects of active attention on prestimulus (and the consequent poststimulus) neural activity. Specifically, we measured and compared the root-mean-square (RMS) amplitudes of the prestimulus (PreRMS) activity of the Global Field Power (GFP) when CAEPs were recorded in either active or passive attention conditions using a high-density EEG system. The GFP characterizes the combined contemporaneous activity of all the electrodes across the epoch (Lehmann & Skrandies, 1980), and hence is well suited for the purposes of our study. When appropriate care is taken to record and analyze the EEG, the PreRMS in ERPs has been suggested to be primarily "neural," and not related to the nonbrain activity such as muscular or electrode-related (impedance) artifacts (Krizman et al., 2021). Hence, PreRMS could be utilized to study brain-related activity prior to stimulus presentation, and we predict evident attention-related changes in the PreRMS measure.

We also explored the effects of attention on the RMS activity in the poststimulus (PostRMS) time

periods as well as the difference between the PreRMS and PostRMS activity (DiffRMS). The PostRMS measure will provide information regarding the overall increased neurocortical activity in the poststimulus time period, a fact that is commonly reported in previous literature (Alho, 1992; Getzmann et al., 2017; Hillyard et al., 1973). The DiffRMS measure, on the other hand, has commonly been considered a measure of the response signal-to-noise ratio (SNR). Given the previous literature's support that prestimulus activity can and does reflect complex neurocognitive mechanisms (at least the preparation stages of such mechanisms), it is our opinion that the DiffRMS is not a straightforward measure of SNR, at least at the cortical level. Therefore, we intend to explore the possible attention-related changes in this measure. We hypothesize that the systematic differences in the three metrics under the two attention conditions likely provide newer insights into the attention-related changes in the cortical processing of sounds.

Method

Participants

A total of 26 volunteers (10 females, 16 males) in the age range of 18 to 30 years (mean age = 23.15 years) participated in the study. All participants had normal hearing thresholds (better than 15 dB HL) in the octave frequencies between 0.25–8 kHz, normal middle ear (Type 'A' tympanogram with the presence of acoustic reflexes) and normal outer hair cell functioning between 1–6 kHz (TEOAE amplitude of more than 3 dB). Ensuring "normal" peripheral hearing was an essential control mechanism since literature has reported neural hyperactivity in the central auditory system in the face of damage to the peripheral hearing mechanism (Zhao et al., 2016). A detailed history, taken before the commencement of the testing, ensured no relevant history of any otological, neurological, psychological, and/or speech-language deficits. All participants passed the Screening Checklist for Auditory Processing in Adults (SCAP-A; Vaidyanath & Yathiraj, 2014) and were right-handed as evaluated using the Edinburgh Handedness Inventory (Oldfield, 1971). Further, all participants were native speakers of the Kannada language (a language spoken in the South Indian state of Karnataka) and had at least 12 years of formal education with English as the medium of instruction. They signed informed consents before the testing, for their participation in the study. The experimental procedures were reviewed and approved by the Ethics Committee of the All India Institute of Speech and Hearing, Mysuru (Ref No: Ph.D/AUD-2/2016-17).

Stimuli

Stimuli consisted of four meaningful bisyllabic words—*gadi*, *gade*, *gaja*, and *ganya*—in the Kannada language. The first syllable was the same in all the words, while only the second syllable differed. The participants could recognize the words only after listening to the second syllable, which ensured that the participants paid attention to the complete word. These words were spoken by a native female speaker in a neutral tone and were recorded using a unidirectional microphone kept at 5 cm from the mouth. The recorded samples were digitally stored having a sampling frequency of 44,100 Hz. Although four different stimuli were included in the experiment, only the word *gadi* was considered as the target word. The other three words were used only as distractor words.

Recording ERPs

The ERP recordings were carried out in a sound-treated and electrically shielded double-room setup with noise levels within the prescribed standards (American National Standards Institute, 1999). The participants were seated in a comfortable reclining chair. Raw EEGs were recorded from each participant using a 256-channel EGI Geodesic sensor net (EGI, Inc., Eugene, OR) connected to a GES-400 amplifier. The electrode impedance was ensured to be below 50 kΩ (Ferree et al., 2001). Further, the impedances across all electrodes were measured at the end of EEG recordings which confirmed that the impedances did not fall below the 50 kΩ limit. This ensured that there were no spurious electrode-related noises in the recorded raw EEG. The EEG was recorded at a sampling frequency of 1000 Hz with Cz as the reference.

Using the E-Prime 2.0 (Psychology Software Tools, Inc., Sharpsburg, PA) software, the stimuli were presented binaurally at 70 dB SPL using ER-3A (Etymotic Research Inc., Elk Grove Village, IL) insert receivers. The interstimulus interval (onset-to-onset) was 3 s (jitter of 0.3 s). A total of 100 stimuli were presented, such that the four words were presented randomly with a probability of 0.7, 0.1, 0.1, and 0.1. The target stimulus *gadi* was presented with a probability of 0.7 (70 presentations) while the three distractor stimuli (*gade*, *gaja*, and *ganya*) were presented with a probability of 0.1 each (10 presentations each).

The responses were recorded under two attention conditions—Passive and Active. In the passive attention condition, the responses were recorded while the participants ignored the stimuli and watched a muted close-captioned video. In the

active attention condition, the participants were instructed to press appropriate buttons on a numerical keypad (1 for *gadi*, 2 for *gade*, 3 for *gaja*, and 4 for *ganya*) as soon as they recognized the words. The responses were always recorded first in the passive attention condition and then in the active attention condition to ensure no subconscious bias towards the target stimuli in the passive attention condition.

Preprocessing and Analyses of the EEG

The raw EEG obtained from each participant was exported from Net Station 4 to EEGLAB Version 14.1.1 (Delorme & Makeig, 2004) using Matlab. Continuous raw EEG from each participant was downsampled to 256 Hz, filtered between 1 Hz and 30 Hz, visually inspected for bad data (and removed, if any), screened for line interferences using the Cleanline plugin, interpolated (removed bad channels) using a spherical spline interpolation method, and rereferenced to the "common average." The rereferenced data was subjected to Independent Component Analyses (ICA; Infomax) with a Principal Component Analysis option of 64. ICA was used to reject "nonbrain" responses such as eye blinks, ocular movements, heartbeat, muscular artifacts, etc. Cleaned data was then epoched between −1000 ms (prestimulus) and 2000 ms (poststimulus). Any epochs exceeding ± 50 μV were rejected, and only the clean sweeps were averaged to obtain separate waveforms for the active and passive attention conditions.

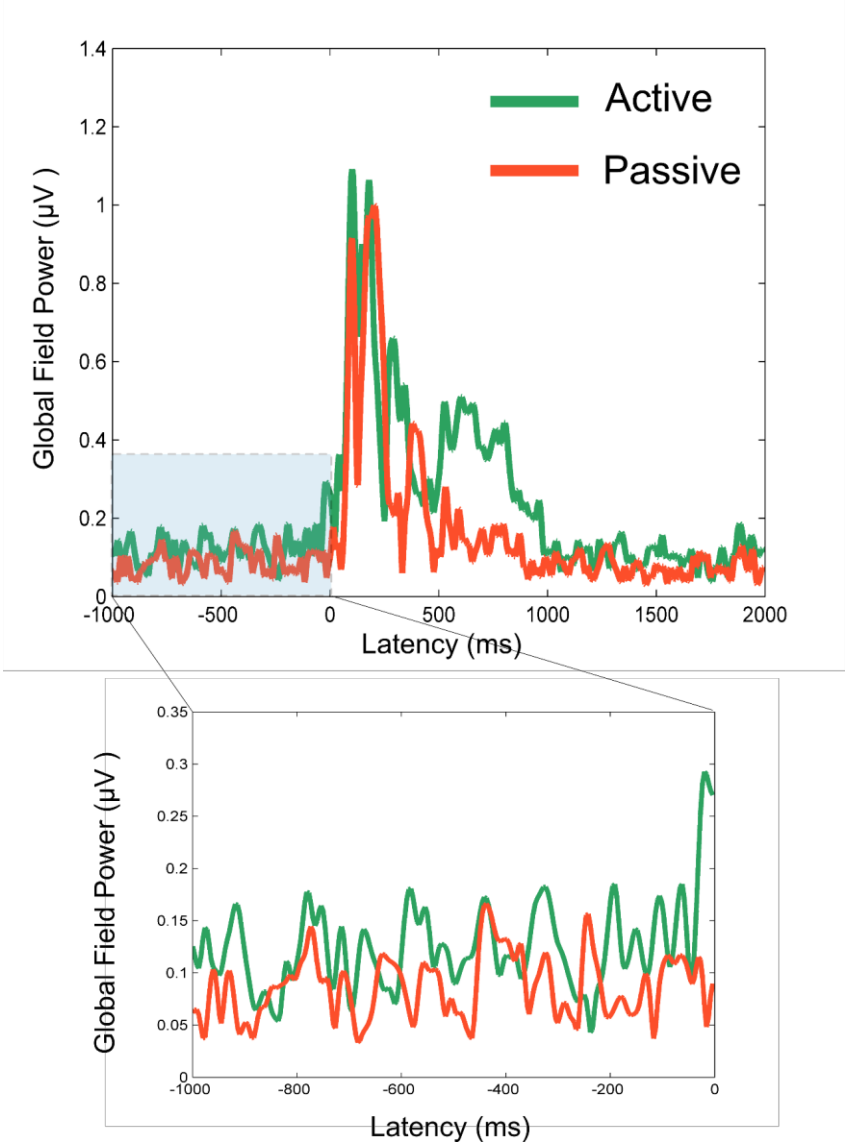
Calculation of Prestimulus and Poststimulus RMS, and Difference Measures

The RMS amplitudes of the PreRMS and PostRMS time regions were calculated on the GFP waveforms. The GFP characterizes the combined contemporaneous activity of all the electrodes across the epoch (Lehmann & Skrandies, 1980). It is obtained by calculating the standard deviation across all electrodes and channels as a function of time. Because of this property, GFP is always positive and hence was specifically used to calculate the RMS amplitudes. Separate GFP waveforms were obtained for the two attention conditions for all participants. The PreRMS was obtained, for each participant, by using the RMS function in Matlab for the time period between −1000–0 ms (with reference to the trigger). Similarly, the PostRMS was calculated for the time period between 0–1000 ms (with reference to the trigger). Finally, the DiffRMS was calculated as the difference between PostRMS and PreRMS. Figure 1 shows the mean GFPs of the passive and active attention conditions, with a zoomed-in view of the prestimulus time period.

Results

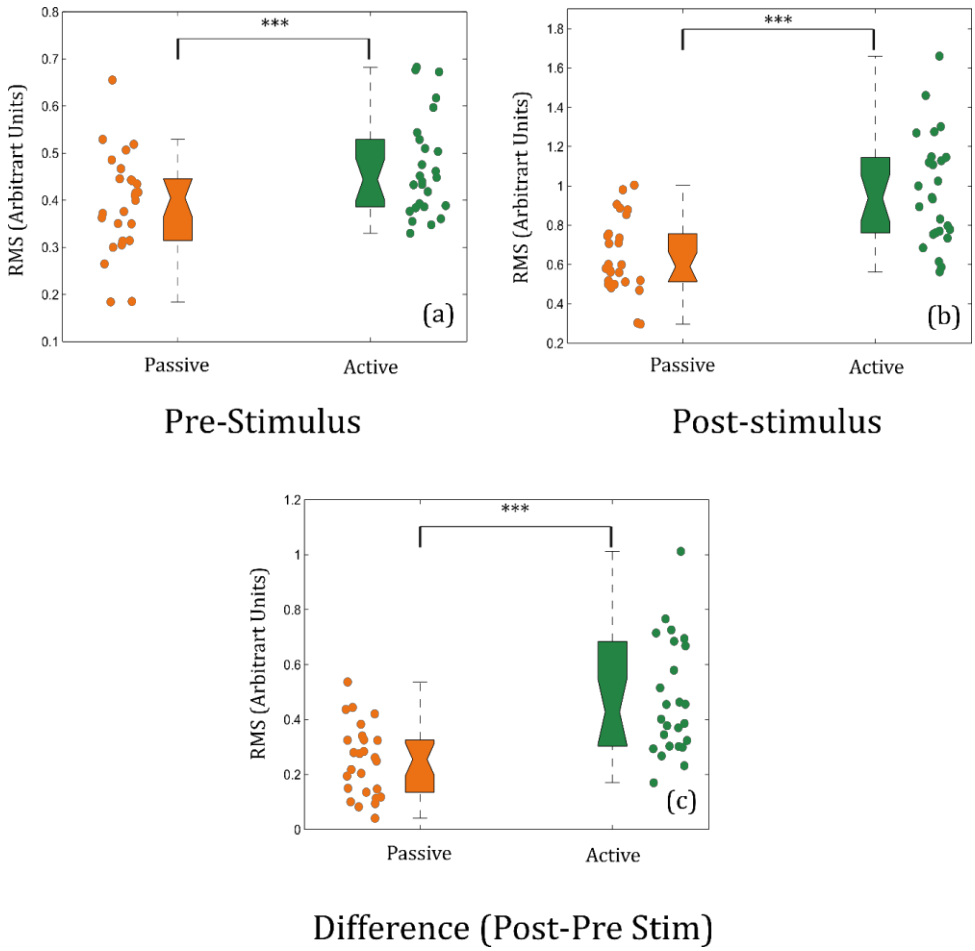
The JASP (version 0.8.5.1) statistical package (The JASP Team, 2017) was used to statistically analyze the data. Figure 2 (panels a, b, and c) shows the individual and the median RMS amplitudes in the two attention conditions for the three measures (PreRMS, PostRMS, and DiffRMS, respectively). The results showed that the active attention condition had higher (median) RMS amplitudes for the PreRMS (panel a), PostRMS (panel b) as well as the DiffRMS (panel c) metrics, compared to the passive attention condition. Paired-samples *t*-test showed significant differences between active and passive attention conditions for the PreRMS [$t(25) = 3.686$, $p = .001$, $d = 0.723$], PostRMS [$t(25) = 6.047$, $p < .001$, $d = 1.257$], as well as DiffRMS [$t(25) = 4.572$, $p < .001$, $d = 0.879$] metrics.

Figure 1. *Mean Global Field Power (GFP) Waveforms of the Active (Green Trace) and Passive (Orange Trace) Attention Conditions.*



Note. The prestimulus time period (shaded region) is zoomed-in (inset figure below) for better visualization of the differences between the two attention conditions.

Figure 2. *Comparison of RMS Amplitudes Between Active (Green Color) and Passive (Orange Color) for the Prestimulus (PreRMS; Panel A), Poststimulus (PostRMS; Panel B), and Difference (DiffRMS; Panel C) Activities*.



Note. The filled green dots in each of the panels represent the individual data points of the different participants for the Active attention condition. The filled orange dots represent the individual data for the Passive attention condition. The box plots to the right of the individual data plots (green boxes for Active, and orange boxes for Passive) show the median (thick black line) and the quartiles (thinner black lines) for the corresponding conditions. The distribution plots to the right show the data distribution for the active (pink color) and passive (blue color) attention conditions for each of the RMS metrics.

Discussion

In the current study, we explored the attention-related changes in the neural noise as measured using the prestimulus RMS amplitudes of CAEPs. Specifically, we calculated and compared three RMS measures—PreRMS, PostRMS, and DiffRMS—measured between two attention conditions—active and passive attention. Results showed a statistically significant increase in all three RMS amplitudes for the active attention condition compared to the passive attention condition.

Previous studies have already shown significant brain wave activity in the prestimulus time period when the target is attended to. These studies have shown changes in the prestimulus activity such as event-related desynchronization (ERD) in anticipation of stimuli (Bastiaansen & Brunia, 2001; Pfurtscheller & Da Silva, 2011) and stronger alpha activity (Alhanbali et al., 2022; Fellinger et al., 2011), etc. when attention (or similar cognitive functions) is involved in the task. Increased cortical brain wave activity, especially increased alpha power, has been positively associated with better cognitive (including attention) function (Klimesch et al., 2007). However,

using alpha power restricts the response activity to a narrow band of frequencies, typically between 8–12 Hz. In our study, we have used a much broader range of frequencies to extract the GFPs, a global measure of the activity from all electrodes employed for the study. Hence, we believe that this measure provides an orthogonal metric of understanding the neural activity, compared to the narrowband measures such as alpha power. However, the stronger prestimulus brain wave activity (such as increased alpha), even in a smaller range of frequencies, associated with attention is likely represented as increased PreRMS amplitudes observed in the active attention condition of the current study.

Pfurtscheller and Da Silva (2011) propose a “cortical idling” hypothesis (Pfurtscheller & Da Silva, 2011; Pfurtscheller et al., 1996). According to this hypothesis, activity in cortical areas (brain waves) changes such that the regions involved in (or related to) the task at hand undergoes a time-locked desynchronization (ERD). On the other hand, the cortical areas that are not directly related to the task at hand are put into an idling state—an increase in brain wave activity or synchrony (event-related synchrony). It appears that when the brain anticipates an incoming stimulus, especially one that it needs to specifically attend to, it puts a greater emphasis on idling the task-irrelevant brain activity (inhibitory or suppressive action) to improve the perception of the attended task-relevant stimulus. This activity, likely, is represented as an increase in the preRMS amplitude, as observed in the active attention conditions of our study. Irrespective of the increase or decrease in brain wave synchronization, however, there is greater overall brain activity associated with paying attention to the task-relevant stimulus, which can be observed as higher preRMS amplitude. In other words, preRMS can be considered a global index of attention.

Another aspect of the PreRMS measure is the possible association with the neurophysiological processes related to anticipatory attention. Anticipatory attention is proposed to manifest itself as increased cortical activity in the neurophysiological responses (Bastiaansen & Brunia, 2001). Bastiaansen and Brunia (2001) suggest that the increased cortical activation is probably due to an enhanced thalamocortical transfer in the relevant modality. This increased activity would then serve in “presetting” the neurophysiological processes necessary for the fast and efficient processing of the impending sensory input. Additionally, it is even shown that attention increases the neural firing rate in the prestimulus time periods (Luck et al., 1997). Luck et al. (1997) reported an increase in neural firing rate by 42% (an increase from 10.1 spikes/s to 14.4 spikes/s) when attention was directed towards the target. Therefore, increased PreRMS could also be thought of as an indicator of anticipatory attention.

The results of the study also showed that active attention resulted in significantly higher PostRMS amplitudes compared to the passive attention condition. The presence of high RMS EEG activity in the poststimulus time periods is expected. Multiple studies have shown increased peak (N1 and/or P2) amplitudes when the target stimulus was paid attention (Folyi et al., 2012; Harris et al., 2012; Mast & Watson, 1968; Zhang et al., 2016). A straightforward translation of this observation would be higher RMS amplitudes in the entire poststimulus time period.

The higher DiffRMS amplitudes observed in our study for the active attention condition, compared to the passive attention condition, is an interesting one. This observation is in spite of a significant increase in the preRMS amplitudes in the active attention condition. To the best of our knowledge, no previous study has evaluated the effects of attention on the SNR (DiffRMS) amplitudes (difference in RMS activity between poststimulus and prestimulus time periods). However, Fellinger et al. (2011) have demonstrated evidence of the magnitude of prestimulus alpha wave activity influencing the amplitude of the poststimulus P1 peak. They suggest that the absolute amplitude of the P1 peak is based on a complex interaction of the prestimulus and poststimulus activity. On similar lines, the PreRMS in the active attention condition could cause increased PostRMS amplitudes, resulting in larger DiffRMS amplitudes. It appears that attending to the target stimulus can help offset the increased prestimulus activity (noise according to traditional views) by increasing the activity in the poststimulus activity (signal), thereby ensuring that the resultant SNR is still more than sufficient to reveal clean and robust CAEPs.

Conclusion

In the current study, we aimed to observe the effects of attention on the neural noise as measured using the prestimulus EEG (RMS) activity. By measuring CAEPs in response to speech tokens, under active and passive attention conditions, we show that the prestimulus activity (as well as the poststimulus activity and the difference between the poststimulus

and prestimulus activity) was significantly larger when the participants attended to the target stimulus. Higher prestimulus amplitude, subsequently, resulted in an attention-related enhancement in the poststimulus response amplitudes. The prestimulus neural noise can, therefore, be used as an objective index of attention, especially in anticipation of an upcoming target sound. The results provide further evidence to the assumption that prestimulus activity is not merely noise, but indicates the neurophysiological activity associated with complex sensory and/or cognitive functions.

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Author Disclosure

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References

Alhanbali, S., Munro, K. J., Dawes, P., Perugia, E., & Millman, R. E. (2022). Associations between pre-stimulus alpha power, hearing level and performance in a digits-in-noise task. *International Journal of Audiology, 61*(3), 197–204. https://doi.org/10.1080/14992027.2021.1899314

Alho, K. (1992). Selective attention in auditory processing as reflected by event-related brain potentials. *Psychophysiology, 29*(3), 247–263. https://doi.org/10.1111/j.1469-8986.1992.tb01695.x

American National Standards Institute. (1999). Maximum permissible ambient noise levels for audiometric test rooms (ANSI S3.1-1999).

Bastiaansen, M. C. M., & Brunia, C. H. M. (2001). Anticipatory attention: An event-related desynchronization approach. *International Journal of Psychophysiology, 43*(1), 91–107. https://doi.org/10.1016/S0167-8760(01)00181-7

Bennet, K. O., Billings, C. J., Molis, M. R., & Leek, M. R. (2012). Neural encoding and perception of speech signals in informational masking. *Ear Hear, 32*(2), 231–238. https://doi.org/10.1097/AUD.0b013e31823173fd

Debener, S., Herrmann, C. S., Kranczioch, C., Gembris, D., & Engel, A. K. (2003). Top-down attentional processing enhances auditory evoked gamma band activity. *NeuroReport, 14*(5), 683–686. https://doi.org/10.1097/00001756-200304150-00005

Delorme, A., & Makeig, S. (2004). EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics. *Journal of Neuroscience Methods, 134*(1), 9–21. https://doi.org/10.1016/j.jneumeth.2003.10.009

Dwyer, P., Vukusic, S., Williams, Z. J., Saron, C. D., & Rivera, S. M. (2022). "Neural noise" in auditory responses in young autistic and neurotypical children. *Journal of Autism and Developmental Disorders, 54*, 642–661 https://doi.org/10.1007/s10803-022-05797-4

Fellinger, R., Klimesch, W., Gruber, W., Freunberger, R., & Doppelmayr, M. (2011). Pre-stimulus alpha phase-alignment predicts P1-amplitude. *Brain Research Bulletin, 85*(6), 417–423. https://doi.org/10.1016/j.brainresbull.2011.03.025

Ferree, T. C., Luu, P., Russell, G. S., & Tucker, D. M. (2001). Scalp electrode impedance, infection risk, and EEG data quality. *Clinical Neurophysiology, 112*(3), 536–544. https://doi.org/10.1016/S1388-2457(00)00533-2

Folyi, T., Fehér, B., & Horváth, J. (2012). Stimulus-focused attention speeds up auditory processing. *International Journal of Psychophysiology, 84*(2), 155–163. https://doi.org/10.1016/j.ijpsycho.2012.02.001

Foxe, J. J., & Snyder, A. C. (2011). The role of alpha-band brain oscillations as a sensory suppression mechanism during selective attention. *Frontiers in Psychology, 2*, Article 154. https://doi.org/10.3389/fpsyg.2011.00154

Fuglsang, S. A., Dau, T., & Hjortkjær, J. (2017). Noise-robust cortical tracking of attended speech in real-world acoustic scenes. *NeuroImage, 156*, 435–444. https://doi.org/10.1016/j.neuroimage.2017.04.026

Getzmann, S., Jasny, J., & Falkenstein, M. (2017). Switching of auditory attention in "cocktail-party" listening: ERP evidence of cueing effects in younger and older adults. *Brain and Cognition, 111*, 1–12. https://doi.org/10.1016/j.bandc.2016.09.006

Haigh, S. M. (2018). Variable sensory perception in autism. *European Journal of Neuroscience, 47*(6), 602–609. https://doi.org/10.1111/ejn.13601

Harris, A. M., Dux, P. E., & Mattingley, J. B. (2018). Detecting unattended stimuli depends on the phase of prestimulus neural oscillations. *The Journal of Neuroscience, 38*(12), 3092–3101. https://doi.org/10.1523/JNEUROSCI.3006-17.2018

Harris, K. C., Wilson, S., Eckert, M. A., & Dubno, J. R. (2012). Human evoked cortical activity to silent gaps in noise. *Ear & Hearing, 33*(3), 330–339. https://doi.org/10.1097/AUD.0b013e31823fb585

Henry, M. J., Herrmann, B., Kunke, D., & Obleser, J. (2017). Aging affects the balance of neural entrainment and top-down neural modulation in the listening brain. *Nature Communications, 8*, Article 15801. https://doi.org/10.1038/ncomms15801

Hillyard, S. A., Hink, R. F., Schwent, V. L., & Picton, T. W. (1973). Electrical signs of selective attention in the human brain. *Science, 182*(4108), 177–180. https://doi.org/10.1126/science.182.4108.177

Horton, C., D'Zmura, M., & Srinivasan, R. (2013). Suppression of competing speech through entrainment of cortical oscillations. *Journal of Neurophysiology, 109*(12), 3082–3093. https://doi.org/10.1152/jn.01026.2012

Kayser, S. J., McNair, S. W., & Kayser, C. (2016). Prestimulus influences on auditory perception from sensory representations and decision processes. *Proceedings of the National Academy of Sciences, 113*(17), 4842–4847. https://doi.org/10.1073/pnas.1524087113

Klimesch, W., Sauseng, P., & Hanslmayr, S. (2007). EEG alpha oscillations: The inhibition-timing hypothesis. *Brain Research Reviews, 53*(1), 63–88. https://doi.org/10.1016/j.brainresrev.2006.06.003

Krizman, J., Bonacina, S., Otto-Meyer, R., & Kraus, N. (2021). Non-stimulus-evoked activity as a measure of neural noise in the frequency-following response. *Journal of Neuroscience Methods, 362*, Article 109290. https://doi.org/10.1016/j.jneumeth.2021.109290

Krizman, J., Lindley, T., Bonacina, S., Colegrove, D., White-Schwoch, T., & Kraus, N. (2020). Play sports for a quieter brain: Evidence from Division I collegiate athletes. *Sports Health, 12*(2), 154–158. https://doi.org/10.1177/1941738119892275

Lehmann, D., & Skrandies, W. (1980). Reference-free identification of components of checkerboard-evoked multichannel potential fields. *Electroencephalography and Clinical Neurophysiology, 48*(6), 609–621. https://doi.org/10.1016/0013-4694(80)90419-8

Luck, S. J., Chelazzi, L., Hillyard, S. A., & Desimone, R. (1997). Neural mechanisms of spatial selective attention in areas v1, v2, and v4 of macaque visual cortex. *Journal of Neurophysiology, 77*(1), 24–42. https://doi.org/10.1152/jn.1997.77.1.24

Mast, T., & Watson, C. (1968). Attention and auditory evoked responses to low-detectability signals. *Perception & Psychophysics, 4*(4), 237–240. https://doi.org/10.3758/BF03206309

Mathewson, K. E., Gratton, G., Fabiani, M., Beck, D. M., & Ro, T. (2009). To see or not to see: Prestimulus alpha phase predicts visual awareness. *The Journal of Neuroscience, 29*(9), 2725–2732. https://doi.org/10.1523/jneurosci.3963-08.2009

McNair, S. W., Kayser, S. J., & Kayser, C. (2019). Consistent pre-stimulus influences on auditory perception across the lifespan. *NeuroImage, 186*, 22–32. https://doi.org/10.1016/j.neuroimage.2018.10.085

Musacchia, G., Sams, M., Nicol, T., & Kraus, N. (2006). Seeing speech affects acoustic information processing in the human brainstem. *Experimental Brain Research, 168*(1–2), 1–10. https://doi.org/10.1007/s00221-005-0071-5

Nandy, A., Nassi, J. J., Jadi, M. P., & Reynolds, J. (2019). Optogenetically induced low-frequency correlations impair perception. *ELife, 8*, Article e35123. https://doi.org/10.7554/eLife.35123

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia, 9*(1), 97–113. https://doi.org/10.1016/0028-3932(71)90067-4

Olguin, A., Bekinschtein, T. A., & Bozic, M. (2018). Neural encoding of attended continuous speech under different types of interference. *Journal of Cognitive Neuroscience, 30*(11), 1606–1619. https://doi.org/10.1162/jocn_a_01303

Pfurtscheller, G., & Da Silva, F. L. (2011). EEG-event-related desynchronization (ERD) and event-related synchronization. In D. L. Schomer, & F. L. Da Silva (Eds.), *Niedermeyer's Electroencephalography - Basic principles, clinical applications and related fields* (6th ed., pp. 935–948). Kluwer/Lippincott Williams & Wilkins.

Pfurtscheller, G., Stancák, A., & Neuper, Ch. (1996). Event-related synchronization (ERS) in the alpha band — an electrophysiological correlate of cortical idling: A review. *International Journal of Psychophysiology, 24*(1–2), 39–46. https://doi.org/10.1016/S0167-8760(96)00066-9

Rahn, E., & Başar, E. (1993). Prestimulus EEG-activity strongly influences the auditory evoked vertex response: A new method for selective averaging. *International Journal of Neuroscience, 69*(1–4), 207–220. https://doi.org/10.3109/00207459309003331

Russo, N., Nicol, T., Musacchia, G., & Kraus, N. (2004). Brainstem responses to speech syllables. *Clinical Neurophysiology, 115*(9), 2021–2030. https://doi.org/10.1016/j.clinph.2004.04.003

Skoe, E., Krizman, J., & Kraus, N. (2013). The impoverished brain: Disparities in maternal education affect the neural response to sound. *Journal of Neuroscience, 33*(44), 17221–17231. https://doi.org/10.1523/JNEUROSCI.2102-13.2013

Sussman, E. S., Bregman, A. S., Wang, W. J., & Khan, F. J. (2005). Attentional modulation of electrophysiological activity in auditory cortex for unattended sounds within multistream auditory environments. *Cognitive, Affective & Behavioral Neuroscience, 5*(1), 93–110. https://doi.org/10.3758/CABN.5.1.93

The JASP Team. (2017). JASP (Version 0.8.5.1). [Computer Software].

Vaidyanath, R., & Yathiraj, A. (2014). Screening checklist for auditory processing in adults (SCAP-A): Development and preliminary findings. *Journal of Hearing Science, 4*(1), 27–37. https://doi.org/10.17430/890788

Zendel, B. R., de Boysson, C., Mellah, S., Démonet, J. F., & Belleville, S. (2016). The impact of attentional training on event-related potentials in older adults. *Neurobiology of Aging, 47*, 10–22. https://doi.org/10.1016/j.neurobiolaging.2016.06.023

Zhang, C., Arnott, S. R., Rabaglia, C., Avivi-Reich, M., Qi, J., Wu, X., Li, L., & Schneider, B. A. (2016). Attentional modulation of informational masking on early cortical representations of speech signals. *Hearing Research, 331*, 119–130. https://doi.org/10.1016/j.heares.2015.11.002

Zhao, Y., Song, Q., Li, X., & Li, C. (2016). Neural hyperactivity of the central auditory system in response to peripheral damage. *Neural Plasticity, 2016*, Article 2162105. https://doi.org/10.1155/2016/2162105

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The Age-Specific Impact of Alpha-Wave Binaural Acoustic Stimulation on Motor-Learning Aptitude

Mahla Azizzadeh Herozi[1], Ali-Mohammad Kamali[2,3], Fatemeh Shamsi[2], and Mohammad Nami[4]*

[1]Department of Clinical Psychology, School of Education and Psychology, Shiraz University, Shiraz, Iran
[2]Department of Neuroscience, School of Advanced Medical Sciences and Technologies, Shiraz University of Medical Sciences, Shiraz, Iran
[3]Iranian Neuroscience Society-Fars Chapter, DANA Brain Health Institute, Shiraz, Iran
[4]Cognitive Neuropsychology Unit, Department of Social Sciences, Faculty of Communication, Arts, and Science, Canadian University Dubai, Dubai, UAE

Abstract

There are some reports on the impact of binaural acoustic beat (BAB) training on motor learning. The current study aimed to explain the possible influences of alpha BAB on motor learning in young and older adult individuals. To this end, 26 male participants were assigned to four parallel groups: two alpha BAB groups (young, older adults) and two control groups (young, older adults). The alpha BAB groups received alpha BAB for 30 min, whereas examinees in the control groups just wore headphones without listening to any music over the experiment period. The digital mirror-tracing task was employed to examine the subjects' motor performance simultaneously with quantitative electroencephalography and after the intervention. In the mirror-tracing task, a significant decrease in the number of errors was found only for the older adults who received alpha BAB. Meanwhile, the reaction time decreased significantly in the young Alpha BAB group. Alpha BAB was associated with a notable increase in alpha current source density dynamics in the young subjects and enhanced beta, high beta oscillations, and gamma power in the older adults. Our findings suggest that alpha BAB might improve motor performance in older adults and young individuals through different patterns.

Keywords: motor learning; alpha binaural acoustic beats; EEG power; mirror-tracing task

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***Address correspondence to**: Mohammad Nami, Assistant Professor of Cognitive Neuropsychology and Neuroscience at the Department of Social Sciences, Canadian University Dubai, City Walk, Dubai, United Arab Emirates. Email: mohammad.nami@cud.ac.ae

Edited by:
Rex L. Cannon, PhD, Currents, Knoxville, Tennessee, USA

Reviewed by:
Rex L. Cannon, PhD, Currents, Knoxville, Tennessee, USA
Randall Lyle, PhD, Mount Mercy University, Cedar Rapids, Iowa, USA

Introduction

Motor learning is essential for processing most activities in daily living. Motor aptitude is also found to be involved in social skills and professional requirements (Haar et al., 2020). Several cortical and subcortical brain areas are known to be implicated in motor learning, including the primary motor cortex (M1), the supplementary motor area (SMA), the premotor cortex (PMC), the cerebellum (C) the cingulate cortex (CC), and basal ganglia (Halsband & Lange, 2006; Hardwick et al., 2013).

There have been few studies investigating neuromodulation or any intervention to preserve or enhance motor learning capacity across the lifespan (Maceira-Elvira et al., 2020; Wang, Xiao, et al., 2021). In previous studies, objective assessments using some behavioral or motor tasks demonstrated learning capacity decline in the older adults (Frolov et al., 2020; Nieborowska et al., 2019), which could be partly attributed to the normal aging process (Iturralde & Torres-Oviedo, 2018; King et al., 2013; Roig et al., 2014).

To either improve or empower cognitive or neurobehavioral aptitude, there are three different approaches to neuromodulation including the noninvasive, minimally invasive, and invasive interventions. Minimally invasive interventional methods, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS), involve surface-level interventions, minimizing the risk of complications. On the other hand, noninvasive techniques are mostly diagnostic or investigational. For instance, quantitative electroencephalography (qEEG) and functional magnetic resonance imaging (fMRI) offer a window into brain activity without physical penetration, enhancing safety but sacrificing some precision. Invasive procedures, exemplified by deep brain stimulation (DBS) and intracranial electroencephalography (iEEG), provide a more targeted and continuous modulation of neural circuits but come with increased surgical risks.

In recent years, several forms of minimally invasive brain stimulation techniques such as repetitive transcranial magnetic stimulation (rTMS; Taga et al., 2019), tDCS (Rivera-Urbina et al., 2022), and binaural acoustic beat (BAB; Ross & Lopez, 2020) have been investigated as attractive nonpharmaceutical alternatives to improve or empower motor processes in patients and healthy subjects, respectively.

BAB is a minimally invasive neuromodulation method in which the brainwaves can be altered through acoustic wave training differentially delivered to both ears. In BAB, two sinusoidal waves (tones) are presented to each ear separately with different frequencies which may range from 1 to 60 Hz (Oster, 1973; Perrott & Nelson, 1969). Objective findings have postulated that this process causes a third illusory tone in the brain with a frequency that is equivalent to the difference between the two presented tones, called BAB (Chaieb et al., 2015).

The BAB training is shown to help individuals to boost creativity (Ortiz et al., 2008), relieve stress and anxiety (Norhazman et al., 2014; Young et al., 2014), modify moods (Chaieb et al., 2015; Wahbeh et al., 2007) and even alleviate some symptoms and disorders such as tinnitus (Ibarra-Zarate et al., 2022), depression (Sung et al., 2017), and anxiety (Kraus & Porubanová, 2015) through a subjective sense of perceived calmness, self-awareness, and neurocognitive agility which have partly been investigated through objective findings in several research works (Coffey et al., 2019; Garcia-Argibay et al., 2019a, 2019b; Haar et al., 2020; Huang & Charyton, 2008; Mammarella et al., 2007; Perez et al., 2020; Tarr et al., 2014).

Alpha wave is regarded as the dominant human brainwave in resting state (Halgren et al., 2019) and is found to be related to fundamental cognitive functions (Klimesch, 2012). The alpha activity has also been demonstrated to play a central role motor performance (Ghasemian et al., 2016) and learning (Schubert et al., 2021).

While being innately generated by the brain, alpha waves can simultaneously be induced in the brain by external stimuli such as BAB (Gao et al., 2014).

Some earlier reports have highlighted the effects of alpha BAB in clinical populations and healthy individuals (Beauchene et al., 2017; Goodin et al., 2012). The effect of BAB on enhancing memory function through increased alpha waves has been studied in older individuals with neurocognitive disorders such as Alzheimer's (Calomeni et al., 2017) and Parkinson's disease (Gálvez et al., 2018) and also in healthy subjects (Benwell et al., 2019). However, to our best knowledge, the possible effects of BAB on motor learning and motor task performance and its possible efficacy in remediating age-related decline in motor function have not been systematically examined yet. Therefore, the purpose of the current study was to investigate the possible effects of alpha BAB on motor learning and motor performance in younger and older populations using a motor task and concurrent qEEG recording. Considering the inconclusive evidence on the research question and the empirical nature of the present work, we hypothesized that alpha BAB might improve motor learning and ideomotor performance in our studied young and older adult populations as compared to the control peers who did not receive the BAB intervention.

Materials and Methods

Participants

Twenty-six right-handed participants including 12 older males with an age range of 55–70 years (mean age = 62 ± 5/64) and 14 young males with an age range of 20–30 years (mean age = 24 ± 2/51) were randomly assigned to four parallel groups. There were two experimental groups (young, older adults) and two control groups (young, older adults) in this double-blinded, controlled randomized study. The experimental groups (i.e., alpha BAB treated), received alpha wave BAB as described in an earlier report (Garcia-Argibay et al., 2019b). The control

groups received no intervention during the study session while wearing the headphone.

All participants were examined by a medical neuroscientist for mental disorders, learning disabilities, hearing problems, or difficulty performing new motor tasks and they were confirmed to be in proper neurocognitive health status.

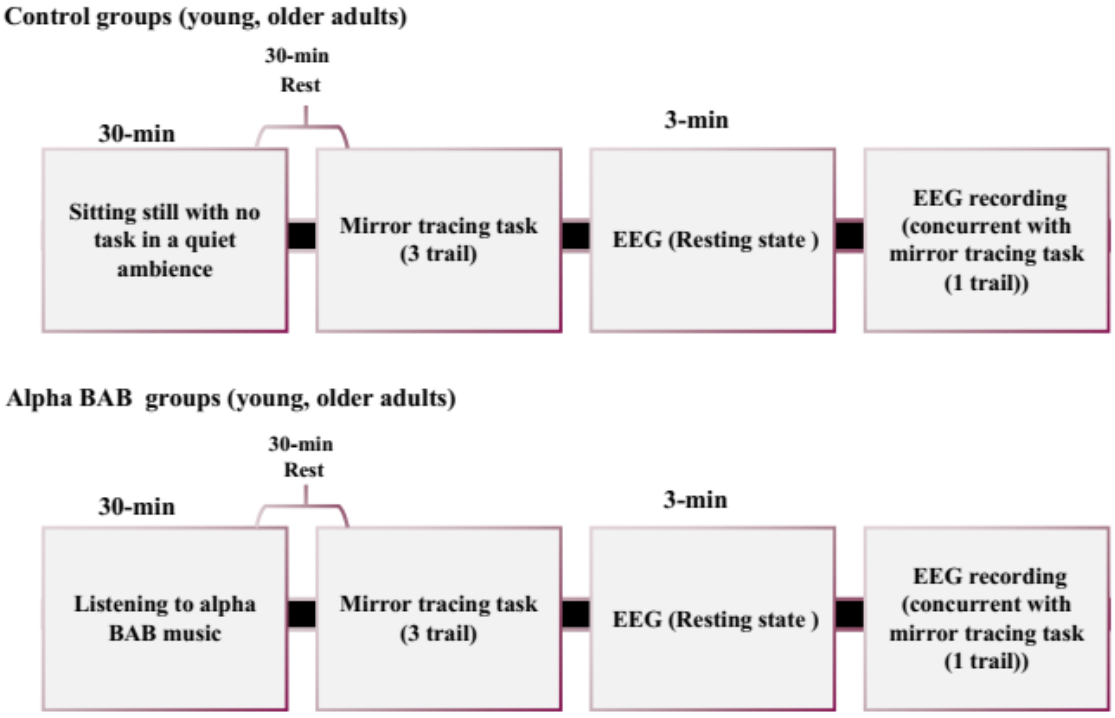
The study was approved by the Ethics Committee of the Shiraz University of Medical Science (Institutional review board approval code: 26819). All participants read and signed the informed consent for the research procedure. The entire procedure was done at the Neuroscience Laboratory (Brain, Cognition and Behavior Unit) at the School of Advanced Medical Sciences and Technologies, SUMS.

Participants were asked not to exercise, smoke, or use alcohol or medications 24 hours before the test.

Study Design

In a quiet room, the participants sat on a comfortable chair located 80–100 cm away from the computer screen. They were required to be relaxed and minimize their movement as much as possible. Before the experiment, the volume gain of alpha BAB was set at 60% by the participants through the headphones (MDR-XB450AP). The alpha BAB groups (young and older adults) were instructed to relax and listen carefully to the alpha BAB through headphones for 30 min. The control groups placed headphones on their heads for the same time without alpha BAB. The participants were asked to keep their eyes closed during the experiment. All participants (alpha BAB, control) rested for 30 min. After that, they performed mirror-tracing tasks three times. A 3-min eyes-open resting-state EEG was recorded. After that, the mirror-tracing task was performed for the fourth time. Figure 1 demonstrates the study protocol.

Figure 1. *The Study Procedures for the Alpha BAB and Control Groups (Young and Older Adults)*.



Note. The alpha BAB groups (young and older adults) received alpha BAB for 30 min. After a 30-min rest, the mirror-tracing task (three trials) was performed. Then, resting-state EEG was recorded for 3 min. Later, the mirror-tracing task (one trial) was performed simultaneously with EEG recording. The control groups (young and older adults) just wore headphones without listening to any sound while their other experiments were identical to the alpha BAB groups.

Motor Learning Assessment (Mirror-Tracing Task)

The digital mirror-tracing task was used to evaluate motor learning through visual-motor interaction (Desmottes et al., 2017). All subjects performed the mirror-tracing task (RT - 912 – T, Sina Psychology, Tehran, Iran). In this task, subjects were asked to move a stylus with their right hand to trace the brass star while they were allowed to look only at the reflection of their right hand in a mirror (Gabrieli et al., 1993). A digital timer and error recorder were attached to the metal stylus for recording both the task time and the number of errors. When the stylus came out of the star and touched the star borders it complemented an electrical circuit and an error was recorded. The star track was 6 mm wide. This task was performed four times, and the number of errors and task time were recorded as an index for assessing motor learning aptitude.

Alpha BAB Stimulation

To induce an alpha binaural beat at a frequency of 10 Hz, a tone of 220 Hz was presented to one ear and a tone of 230 Hz was presented to the other ear in accordance with Kraus and Probanova's protocol (Kraus & Porubanová, 2015).

In this regard, the Alpha frequency was produced by Audacity software (version 2.2) and Adobe Audition CC (version 2017).

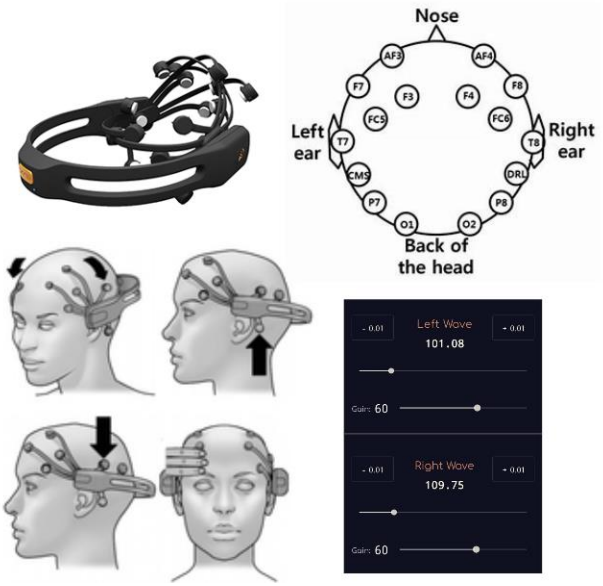
EEG Recording

Several methods can be used to measure motor learning and control, one of which is electroencephalography (EEG), also known as the neural technique (Beik et al., 2020). In fact, EEG is a good tool to analyze neural correlates for both simple and complex movements in humans (Bradford et al., 2016; Pfurtscheller et al., 2003).

The EEG data were recorded using the Epoc+ EEG headset (Emotiv, USA) which included 16 wet saline electrodes and two reference electrodes, providing 14 EEG channels. According to the international 10-20 system, a total of 14 electrodes were placed on the skin surface in the following locations (Yu & Sim, 2016): AF3, F3, F7, FC5, T7, P7, O1, O2, P8, T8, FC6, F4, F8, AF4 to record the five well-known frequency bands, namely theta (4–8 Hz) alpha (8–12 Hz), low beta (12–16 Hz), high beta (16–25 Hz) and gamma (25–45 Hz; see Figure 2).

In this study, reference electrodes (CMS/DRL) were placed on P3 and P4. The quality of the EEG signal was checked using the Test Bench software. The collected raw data were processed offline using NeuroGuide software (v. 3.0.2 2001-2018 Applied Neuroscience Inc. USA). Artifacts such as eye movements, motion or muscle artifacts were detected and removed by an EEG expert. Based on the NeuroGuide qEEG normative database, fast Fourier transform (FFT) was used to compute the absolute power.

Figure 2. *Emotive Headset Sensors Placement and Fitting (Left Panel), 16 Channel qEEG Montage and Alpha BAB (8.67 Hz), 60% Gain Setup (Right Panel).*



Statistical Analysis

All statistical tests were performed with GraphPad Prism (GraphPad Software Inc., San Diego, CA, USA) and the SPSS statistical package (Version 26.0.0, Copyright IBM, 2018). Descriptive statistics were computed for each group. The Kolmogorov-Smirnov test was used to investigate the normal distribution of data. To analyze the differences between control groups (young and older adults) and alpha BAB groups (young and older adults), a series of independent sample *t*-tests were run for the data with normal distribution and homogeneity of variance.

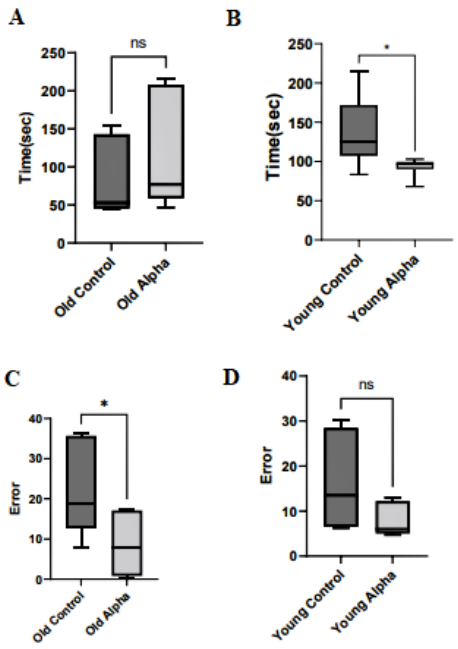
The differences between alpha BAB groups (young and older adults) and control groups (young and older adults) were evaluated by calculating the mean ± the standard error of the mean, for several parameters, including the number of errors and task time in the mirror-tracing task. An independent sample *t*-test was conducted to compare qEEG data in alpha BAB groups (young, older adults) and control groups (young, older adults); $p < .05$ was considered statistically significant.

Results

Motor Learning Assessment (Mirror-Tracing Task)

The results in the control and alpha BAB groups of older adult individuals showed no significant difference in the task time (p = .407; Figure 3, A) while there was a statistically significant difference in the task time between the young individuals in the control and alpha BAB (p = .015) groups (Figure 3, B). There was a significant difference between both groups in older adult individuals in the number of errors (p = .042; Figure 3, C) but there was no significant difference in terms of the number of errors in young individuals between the control and alpha BAB groups (p = .06; Figure 3, D).

Figure 3. *Box Plots Illustrate the Average of Each Task Time and the Number of Errors in the Mirror-Tracing Task in the Control Groups (Young, Older Adults) and the Alpha BAB Groups (Young, Older Adults).*



Note. Panel A shows no significant difference in task time between the control and alpha BAB groups of the older adult participants (p > .05). Panel B demonstrates the difference in task time between the control and alpha BAB groups of young individuals (p < .05). Panel C indicates the difference in the number of errors between the control and alpha BAB groups in the older adult participants (p < .05). Panel D displays no significant difference in the number of errors between the young control and alpha BAB groups (p > .05).

* significant difference between the groups p < .05
ns nonsignificant difference between the groups p > .05

EEG Absolute Power

The results revealed a statistically significant difference in the absolute power between the older adults control group and the older adults alpha BAB group (Figure 4, A). Electrical neural imaging data in the older adult subjects who received and did not receive alpha BAB confirmed the special and spectral distribution of beta and high beta in bilateral frontocentral cortical regions while this has been localized in the left frontocentral cortical zone for the gamma frequency band. However, in the young groups, our result showed a statistically significant difference in the absolute power of theta, alpha and beta frequency bands (p < .01) (Figure 4, B).

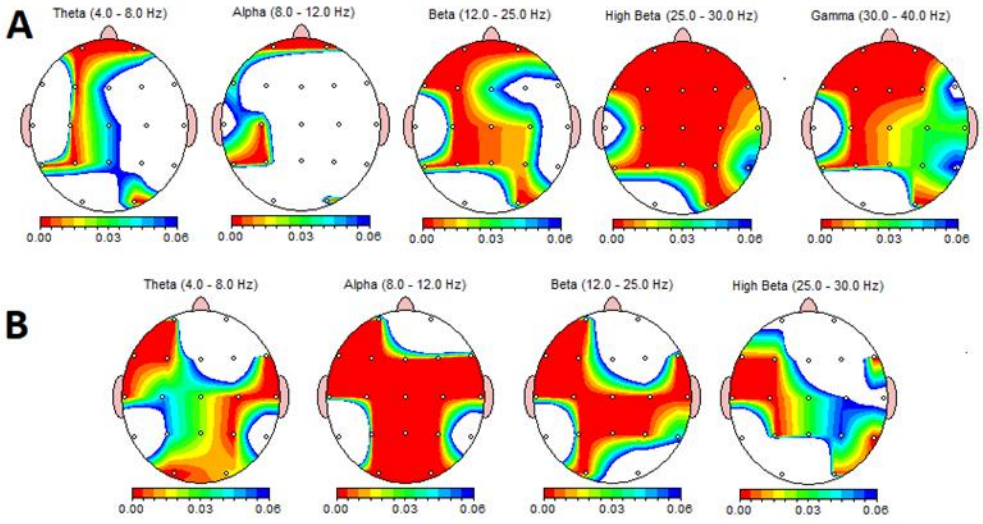
Discussion

The effect of alpha BAB on the distribution and amplitude of the alpha frequency band in the premotor and motor cortex as well as its impact on the process of motor learning has not been systematically evaluated so far. Our study was an attempt to investigate the possible impacts of alpha BAB on the neural dynamics of alpha oscillation within the motor cortices and motor performance in both older and young individuals. Our results demonstrated that the older adult subjects who received alpha BAB had a significantly lower number of errors upon performing mirror-tracing tasks compared to their age-matched control group. Meanwhile, the task performance time by older adult subjects did not differ between the alpha BAB group and the control group.

On the other hand, our study investigated the impact of alpha BAB and motor performance amongst young individuals. Although no significant difference was observed between the young group receiving alpha BAB and their controls in the number of errors in the mirror-tracing task, the intervention resulted in a notable or statistically significant difference concerning task performance time in young individuals. In other words, it took less time for the young individuals who received alpha BAB to perform the mirror-tracing task as compared to the young individuals who did not receive alpha BAB.

Regarding the effect of Alpha BAB on the number of errors in the mirror tracing between the age groups, a reduced number of errors in both older and young individuals receiving Alpha BAB compared to their age-match control suggests a potential positive effect of Alpha BAB training on motor learning; however, the reduction was just statistically significant in the older adult group.

Figure 4. *QEEG Topographical Spectral Brain Maps.*



Note. FFT absolute power independent *t*-test (*p*-value) results across spectra during motor learning tasks in older adult groups (A; control and alpha BAB) and young groups (B; control and alpha BAB). Colors indicate the significance level.

Features including time and precision, are the two main indicators that define motor aptitude (Shekar et al., 2018).

Our motor learning results were in line with the findings that we observed in concurrent EEG recording during mirror-tracing task administration. According to our EEG results, despite its high beta and theta oscillation performance, alpha BAB caused a significant gain in alpha dynamics in young people. The spectral distribution of alpha and low beta bands in frontocentral cortical hubs is consistent with an improved motor sequential planning, which has already been observed in the alpha BAB-treated young subjects. Yet, this has not been the case for theta and high beta frequency bands. A denser EEG array and further statistical analysis on different features and parameters across frequency spectra may shed further light on the possible involvement of cortical, and subcortical neural structures, which justify and improve motor performance speed, which was observed in young individuals who received alpha BAB.

Alpha BAB in the older adult subjects resulted in an enhanced current source density at beta, high beta oscillations, and bilateral frontocentral derivation. Interestingly, the increased gamma power has been localized in the left frontocentral cortical region, which is responsible for right-hand dexterity.

Our brain mapping results demonstrated an increased current source density in frontocentral derivations in young individuals who received alpha BAB. Meanwhile, this has not been the case in the frontopolar and occipital parietal areas. Given the fact that inferior frontal and frontocentral derivations are the cortical areas corresponding to supplementary and association motor cortices, enhanced alpha BAB in those areas (supplementary motor area [SMA] and cingulate motor area [CMA]) are proposed to result in improved motor sequential planning.

One of the main key parameters which correlate with motor sequential planning is the time to perform a motor task (Shekar et al., 2018). Mirror-tracing test is a task that requires both attention and performance speed (Woodard & Fairbrother, 2020).

Alpha BAB was found to improve the performance speed. Given the improved performance speed, it might be expected that motor sequential planning is positively affected and that in turn corresponds to an increased current source density gain (CSD) in supplementary SMA and CMA cortical/subcortical structures. The reason why alpha BAB has resulted in the CSD and a special distribution of not only beta and high beta but even faster frequencies, including gamma in bilateral frontocentral and left frontocentral cortical regions, respectively, has not

been up to our expectations. We were expecting to observe enhanced alpha dynamics upon alpha BAB either in both young and older adult subjects. Nonetheless, while we observed an improved distribution of alpha in frontocentral and bilateral inferior frontal cortical areas, this has not been the case for the alpha frequency band in the older adult group. Instead, we have observed a significant increase in the neural dynamics of higher frequency bands, including beta, high beta, and gamma, which corresponds to motor aptitude.

Elder individuals completed the mirror-tracing task with fewer errors following alpha BAB, which suggests better motor aptitude; this is partly related to the function of the primary motor cortex rather than supplementary motor areas. Taking these findings together, it might be speculated that alpha BAB might at least partly impact the dynamics of the neural oscillations and the motor performance outcome amongst the people who were submitted to the mirror-tracing task. Interestingly, the time to perform the mirror-tracing task was mostly affected by alpha BAB in young individuals, whereas no change in the task performance time was observed in older adult subjects after alpha BAB intervention.

The significance of maintenance and improvement of motor learning and related motor aptitude is emphasized in specific populations whose daily life or job-related responsibilities involve motor skills (Haar et al., 2020). Motor skill is normally considered a dynamic change that occurs throughout life by motor learning (Hadders-Algra, 2010) based on neuroplasticity (Dayan & Cohen, 2011) and rewiring within the neural networks (Askim et al., 2009; Wang, Fan, et al., 2013) that control the speed, precision, and aptitude of motor performance (Kitago & Krakauer, 2013).

Earlier studies have indicated that motor learning and planning might get impaired as we age (Frolov et al., 2020; Grose & Mamo, 2012; Nieborowska et al., 2019; Solcà et al., 2016) which might be at least partly due to the possible impairments of neuroplasticity and neurodynamic changes over time (Park & Bischof, 2013; Seidler et al., 2010). The previously published body of scientific evidence suggests that the motor learning impairment or decrease in the learning capacity of motor skills in older adult individuals who have not been trained for motor skills over time might be due to neurodegenerative changes. (Gale et al., 2018; Newson & Kemps, 2005; Wang, Zhang, et al., 2019; Wenk et al., 1989). Previous studies have shown that essential tremors can decline motor learning in older adults (Bermejo-Pareja et al., 2007; Collins et al., 2017; Raethjen et al., 2007). In addition, loss of skeletal muscle and decline in physical activity contribute to impaired motor learning in older adult subjects (Clark, 2019; Hunter et al., 2016). Several studies have reported that the motor performance of older individuals declines more pronouncedly as their task difficulty increases (Bangert et al., 2010; Smith et al., 1999)

Neural entrainment and synchronization of the specific type of neural oscillation within the distinct frequency band in premotor and motor areas has been a central indicator in the process of motor learning (Buzsáki & Draguhn, 2004; Schnitzler & Gross, 2005; Varela et al., 2001). To enhance the capacity of the special and spectral distribution of alpha band in the specific premotor and motor areas, one hypothesis has been the application of neural entrainment through the use of the BAB (Solcà et al., 2016). Some studies have employed BAB as a neural modulatory approach to enhance the special distribution of a distinct frequency and amplitude or power of that frequency within functional cortical hubs (Draganova et al., 2008; Grose & Mamo, 2012; Pratt et al., 2009, 2010), which involves motor performance that might in some way retain implications for a specific indistinct population of individuals who need to employ even more precise, sophisticated, and fine motor skills, including professional athletes (Ross & Lopez, 2020).

The use of alpha BAB has been tested in some studies (Ecsy et al., 2017; Munro & Searchfield, 2019; Shekar et al., 2018). The present report generally suggests that alpha entrainment might partly help remediation of the neural dynamics which correspond to sequential motor planning and motor aptitude in young and older adult populations, respectively. As such, according to our findings, using the alpha BAB could at least be considered as an auxiliary neuromodulation approach to empower motor skills in people who require further motor learning.

The extension of this line of research, together with our findings, might have implications for those who are involved with critical motor responsibilities in their jobs and personal life. Those might include people who need to have maximal precision, reaction time, performance speed, motor learning and the responsibilities they are involved in. Examples might be surgeons, professional athletes, industrial workers who deal with sophisticated machinery, defense personnel, artists, or other creative people.

Conclusion

The present report suggests that alpha entrainment may partly help young and older adult populations improve their neural dynamics which correspond to sequential motor planning and motor aptitude. Considering the effect of the alpha BAB on motor learning, the intervention might enhance motor skills in people who require further motor learning.

Further research needs to be pursued to extend other imaging or neuromodulation modalities further to what we examined here. The idea whether concurrent use of BAB and minimally invasive brain stimulation, including TMS, tDCS, and more specifically, tACS (transcriptional alternating current stimulation) might presumably add value to the level of motor learning in terms of precision, processing speed, reaction time, and performance speed needs further evaluation.

Author Declarations

Authors confirm that they have thoroughly read and approved the manuscript in question. We have ensured that there are no issues or conflicts that could impede the publication process. Furthermore, authors affirm that the outcome of this work has not been influenced by any internal or external factors, including financial considerations.

In addition, authors have diligently reviewed and adhered to all intellectual property guidelines and regulations. The authors followed the ethical principles and guidelines for research and publication with utmost care and diligence.

References

Askim, T., Indredavik, B., Vangberg, T., & Håberg, A. (2009). Motor network changes associated with successful motor skill relearning after acute ischemic stroke: A longitudinal functional magnetic resonance imaging study. *Neurorehabilitation and Neural Repair, 23*(3), 295–304. https://doi.org/10.1177/1545968308322840

Bangert, A. S., Reuter-Lorenz, P. A., Walsh, C. M., Schachter, A. B., & Seidler, R. D. (2010). Bimanual coordination and aging: Neurobehavioral implications. *Neuropsychologia, 48*(4), 1165–1170. https://doi.org/10.1016 /j.neuropsychologia.2009.11.013

Beauchene, C., Abaid, N., Moran, R., Diana, R. A., & Leonessa, A. (2017). The effect of binaural beats on verbal working memory and cortical connectivity. *Journal of Neural Engineering, 14*(2), Article 026014. https://doi.org/10.1088 /1741-2552/aa5d67

Beik, M., Taheri, H., Saberi Kakhki, A., & Ghoshuni, M. (2020). Neural mechanisms of the contextual interference effect and parameter similarity on motor learning in older adults: An EEG study. *Frontiers in Aging Neuroscience, 12*, Article 173. https://doi.org/10.3389/fnagi.2020.00173

Benwell, C. S. Y., London, R. E., Tagliabue, C. F., Veniero, D., Gross, J., Keitel, C., & Thut, G. (2019). Frequency and power of human alpha oscillations drift systematically with time-on-task. *NeuroImage, 192*, 101–114. https://doi.org/10.1016 /j.neuroimage.2019.02.067

Bermejo-Pareja, F., Louis, E. D., & Benito-León, J. (2007). Risk of incident dementia in essential tremor: A population-based study. *Movement Disorders, 22*(11), 1573–1580. https://doi.org/10.1002/mds.21553

Bradford, J. C., Lukos, J. R., & Ferris, D. P. (2016). Electrocortical activity distinguishes between uphill and level walking in humans. *Journal of Neurophysiology, 115*(2), 958–966. https://doi.org/10.1152/jn.00089.2015

Buzsáki, G., & Draguhn, A. (2004). Neuronal oscillations in cortical networks. *Science, 304*(5679), 1926–1929. https://doi.org/10.1126/science.1099745

Calomeni, M. R., da Silva, V. F., Velasques, B. B., Feijó, O. G., Bittencourt, J. M., & de Souza E. Silva, A. P. (2017). Modulatory effect of association of brain stimulation by light and binaural beats in specific brain waves. *Clinical Practice & Epidemiology in Mental Health, 13*, 134–144. https://doi.org /10.2174 /1745017901713010134

Chaieb, L., Wilpert, E. C., Reber, T. P., & Fell, J. (2015). Auditory beat stimulation and its effects on cognition and mood states. *Frontiers in Psychiatry, 6*, Article 70. https://doi.org/10.3389 /fpsyt.2015.00070

Clark, B. C. (2019). Neuromuscular changes with aging and sarcopenia. *The Journal of Frailty & Aging, 8*(1), 7–9. https://doi.org/10.14283/jfa.2018.35

Coffey, E. B., Nicol, T., White-Schwoch, T., Chandrasekaran, B., Krizman, J., Skoe, E., Zatorre, R. J., & Kraus, N. (2019). Evolving perspectives on the sources of the frequency-following response. *Nature Communications, 10*(1), Article 5036. https://doi.org/10.1038%2Fs41467-019-13003-w

Collins, K., Rohl, B., Morgan, S., Huey, E. D., Louis, E. D., & Cosentino, S. (2017). Mild cognitive impairment subtypes in a cohort of elderly essential tremor cases. *Journal of the International Neuropsychological Society, 23*(5), 390–399. https://doi.org/10.1017%2FS1355617717000170

Dayan, E., & Cohen, L. G. (2011). Neuroplasticity subserving motor skill learning. *Neuron, 72*(3), 443–454. https://doi.org /10.1016/j.neuron.2011.10.008

Desmottes, L., Maillart, C., & Meulemans, T. (2017). Mirror-drawing skill in children with specific language impairment: Improving generalization by incorporating variability into the practice session. *Child Neuropsychology, 23*(4), 463–482. https://doi.org/10.1080/09297049.2016.1170797

Draganova, R., Ross, B., Wollbrink, A., & Pantev, C. (2008). Cortical steady-state responses to central and peripheral auditory beats. *Cerebral Cortex, 18*(5), 1193–1200. https://doi.org/10.1093/cercor/bhm153

Ecsy, K., Jones, A. K. P., & Brown, C. A. (2017). Alpha-range visual and auditory stimulation reduces the perception of pain. *European Journal of Pain, 21*(3), 562–572. https://doi.org /10.1002/ejp.960

Frolov, N. S., Pitsik, E. N., Maksimenko, V. A., Grubov, V. V., Kiselev, A. R., Wang, Z., & Hramov, A. E. (2020). Age-related slowing down in the motor initiation in elderly adults. *PLoS ONE, 15*(9), Article e0233942. https://doi.org/10.1371 /journal.pone.0233942

Gabrieli, J. D., Corkin, S., Mickel, S. F., & Growdon, J. H. (1993). Intact acquisition and long-term retention of mirror-tracing skill in Alzheimer's disease and in global amnesia. *Behavioral Neuroscience, 107*(6), 899–910. https://doi.org/10.1037 /0735-7044.107.6.899

Gale, S. A., Acar, D., & Daffner, K. R. (2018). Dementia. *The American Journal of Medicine, 131*(10), 1161–1169. https://doi.org/10.1016 /j.amjmed.2018.01.022

Gálvez, G., Recuero, M., Canuet, L., & Del-Pozo, F. (2018). Short-term effects of binaural beats on EEG power, functional connectivity, cognition, gait and anxiety in Parkinson's

disease. *International Journal of Neural Systems, 28*(05), Article 1750055. https://doi.org/10.1142/s0129065717500551

Gao, X., Cao, H., Ming, D., Qi, H., Wang, X., Wang, X., Chen, R., & Zhou, P. (2014). Analysis of EEG activity in response to binaural beats with different frequencies. *International Journal of Psychophysiology, 94*(3), 399–406. https://doi.org/10.1016/j.ijpsycho.2014.10.010

Garcia-Argibay, M., Santed, M. A., & Reales, J. M. (2019a). Binaural auditory beats affect long-term memory. *Psychological Research, 83*(6), 1124–1136. https://doi.org/10.1007/s00426-017-0959-2

Garcia-Argibay, M., Santed, M. A., & Reales, J. M. (2019b). Efficacy of binaural auditory beats in cognition, anxiety, and pain perception: A meta-analysis. *Psychological Research, 83*(2), 357–372. https://doi.org/10.1007/s00426-018-1066-8

Ghasemian, M., Taheri, H., Kakhki, A. S., & Ghoshuni, M. (2016). The effect of alpha neurofeedback training on motor skill acquisition. *Biosciences Biotechnology Research Asia, 13*(3), 1651–1656. https://doi.org/10.13005/bbra/2313

Goodin, P., Ciorciari, J., Baker, K., Carrey, A.-M., Harper, M., & Kaufman, J. (2012). A high-density EEG investigation into steady state binaural beat stimulation. *PLoS ONE, 7*(4), Article e34789. https://doi.org/10.1371/journal.pone.0034789

Grose, J. H., & Mamo, S. K. (2012). Electrophysiological measurement of binaural beats: Effects of primary tone frequency and observer age. *Ear and Hearing, 33*(2), 187–194. https://doi.org/10.1097/AUD.0b013e318230bbbd

Haar, S., van Assel, C. M., & Faisal, A. A. (2020). Motor learning in real-world pool billiards. *Scientific Reports, 10*(1), Article 20046. https://doi.org/10.1038/s41598-020-76805-9

Hadders-Algra, M. (2010). Variation and variability: Key words in human motor development. *Physical Therapy, 90*(12), 1823–1837 https://doi.org/10.2522/ptj.20100006

Halgren, M., Ulbert, I., Bastuji, H., Fabó, D., Erőss, L., Rey, M., Devinsky, O., Doyle, W. K., Mak-McCully, R., Halgren, E., Wittner, L., Chauvel, P., Heit, G., Eskandar, E., Mandell, A., & Cash, S. S. (2019). The generation and propagation of the human alpha rhythm. *Proceedings of the National Academy of Sciences, 116*(47), 23772–23782. https://doi.org/10.1073/pnas.1913092116

Halsband, U., & Lange, R. K. (2006). Motor learning in man: A review of functional and clinical studies. *Journal of Physiology-Paris, 99*(4–6), 414–424. https://doi.org/10.1016/j.jphysparis.2006.03.007

Hardwick, R. M., Rottschy, C., Miall, R. C., & Eickhoff, S. B. (2013). A quantitative meta-analysis and review of motor learning in the human brain. *NeuroImage, 67*, 283–297. https://doi.org/10.1016/j.neuroimage.2012.11.020

Huang, T. L., & Charyton, C. (2008). A comprehensive review of the psychological effects of brainwave entrainment. *Alternative Therapies in Health and Medicine, 14*(5), 38–50.

Hunter, S. K., Pereira, H. M., & Keenan, K. G. (2016). The aging neuromuscular system and motor performance. *Journal of Applied Physiology, 121*(4), 982–995. https://doi.org/10.1152/japplphysiol.00475.2016

Ibarra-Zarate, D. I., Naal-Ruiz, N. E., & Alonso-Valerdi, L. M. (2022). Binaural sound therapy for tinnitus treatment: A psychometric and neurophysiological evaluation. *American Journal of Otolaryngology, 43*(1), Article 103248. https://doi.org/10.1016/j.amjoto.2021.103248

Iturralde, P. A., & Torres-Oviedo, G. (2018). The adaptation of muscle activity during split-belt walking reveals age-dependent decline of motor learning. *bioRxiv,* Article 372359. https://doi.org/10.1101/372359

King, B. R., Fogel, S. M., Albouy, G., & Doyon, J. (2013). Neural correlates of the age-related changes in motor sequence learning and motor adaptation in older adults. *Frontiers In Human Neuroscience, 7*, Article 142. https://doi.org/10.3389/fnhum.2013.00142

Kitago, T., & Krakauer, J. W. (2013). Motor learning principles for neurorehabilitation. *Handbook Of Clinical Neurology, 110*, 93–103. https://doi.org/10.1016/b978-0-444-52901-5.00008-3

Klimesch, W. (2012). Alpha-band oscillations, attention, and controlled access to stored information. *Trends In Cognitive Sciences, 16*(12), 606–617. https://doi.org/10.1016/j.tics.2012.10.007

Kraus, J., & Porubanová, M. (2015). The effect of binaural beats on working memory capacity. *Studia Psychologica, 57*(2), 135. https://doi.org/10.21909/sp.2015.02.689

Maceira-Elvira, P., Popa, T., Schmid, A.-C., & Hummel, F. C. (2020). Feasibility of home-based, self-applied transcranial direct current stimulation to enhance motor learning in middle-aged and older adults. *Brain Stimulation, 13*(1), 247–249. https://doi.org/10.1016/j.brs.2019.08.014

Mammarella, N., Fairfield, B., & Cornoldi, C. (2007). Does music enhance cognitive performance in healthy older adults? The Vivaldi effect. *Aging Clinical and Experimental Research, 19*(5), 394–399. https://doi.org/10.1007/bf03324720

Munro, B. A., & Searchfield, G. D. (2019). The short-term effects of recorded ocean sound with and without alpha frequency binaural beats on tinnitus perception. *Complementary Therapies in Medicine, 44*, 291–295. https://doi.org/10.1016/j.ctim.2019.05.005

Newson, R. S., & Kemps, E. B. (2005). General lifestyle activities as a predictor of current cognition and cognitive change in older adults: A cross-sectional and longitudinal examination. *The Journals of Gerontology Series B, 60*(3), P113–P120. https://doi.org/10.1093/geronb/60.3.p113

Nieborowska, V., Lau, S.-T., Campos, J., Pichora-Fuller, M. K., Novak, A., & Li, K. Z. (2019). Effects of age on dual-task walking while listening. *Journal Of Motor Behavior, 51*(4), 416–427. https://doi.org/10.1080/00222895.2018.1498318

Norhazman, H., Zaini, N. M., Taib, M., Jailani, R., & Omar, H. (2014). The investigation of alpha frontal energy asymmetry on normal and stress subjects after listening to the binaural beats 10 Hz. Paper presented at the *2014 IEEE 10th International Colloquium on Signal Processing and its Applications* (pp. 246–250). Kuala Lumpur, Malaysia. https://doi.org/10.1109/CSPA.2014.6805758

Ortiz, T., Martínez, A., Fernández, A., Maestu, F., Campo, P., Hornero, R., Escudero, J., Poch, J. (2008). Efecto de la estimulación auditiva a una frecuencia de 5 Hz en la memoria verbal. *Actas Espanolas de Psiquiatria, 36*(6), 307–313.

Oster, G. (1973). Auditory beats in the brain. *Scientific American, 229*(4), 94–103. https://doi.org/10.1038/scientificamerican1073-94

Park, D. C., & Bischof, G. N. (2013). The aging mind: Neuroplasticity in response to cognitive training. *Dialogues in Clinical Neuroscience, 15*(1), 109–119. https://doi.org/10.31887/DCNS.2013.15.1/park

Perez, H. D. O., Dumas, G., & Lehmann, A. (2020). Binaural Beats through the auditory pathway: From brainstem to connectivity patterns. *Eneuro, 7*(2), Article ENEURO.0232. https://doi.org/10.1523 /ENEURO.0232-19.2020

Perrott, D. R., & Nelson, M. A. (1969). Limits for the detection of binaural beats. *The Journal of the Acoustical Society of America, 46*(6B), 1477–1481. https://doi.org/10.1121/1.1911890

Pfurtscheller, G., Woertz, M., Supp, G., & Lopes da Silva, F. H. (2003). Early onset of post-movement beta electroencephalogram synchronization in the supplementary motor area during self-paced finger movement in man. *Neuroscience Letters, 339*(2), 111–114. https://doi.org/10.1016/s0304-3940(02)01479-9

Pratt, H., Starr, A., Michalewski, H. J., Dimitrijevic, A., Bleich, N., & Mittelman, N. (2009). Cortical evoked potentials to an auditory illusion: Binaural beats. *Clinical Neurophysiology, 120*(8), 1514–1524. https://doi.org/10.1016/j.clinph.2009.06.014

Pratt, H., Starr, A., Michalewski, H. J., Dimitrijevic, A., Bleich, N., & Mittelman, N. (2010). A comparison of auditory evoked potentials to acoustic beats and to binaural beats. *Hearing Research, 262*(1–2), 34–44. https://doi.org/10.1016 /j.heares.2010.01.013

Raethjen, J., Govindan, R., Kopper, F., Muthuraman, M., & Deuschl, G. (2007). Cortical involvement in the generation of essential tremor. *Journal of Neurophysiology, 97*(5), 3219–3228. https://doi.org/10.1152/jn.00477.2006

Rivera-Urbina, G. N., Molero-Chamizo, A., & Nitsche, M. A. (2022). Discernible effects of tDCS over the primary motor and posterior parietal cortex on different stages of motor learning. *Brain Structure and Function, 227*, 1115–1131. https://doi.org/10.1007/s00429-021-02451-0

Roig, M., Ritterband-Rosenbaum, A., Lundbye-Jensen, J., & Nielsen, J. B. (2014). Aging increases the susceptibility to motor memory interference and reduces off-line gains in motor skill learning. *Neurobiology of Aging, 35*(8), 1892–1900. https://doi.org/10.1016/j.neurobiolaging.2014.02.022

Ross, B., & Lopez, M. D. (2020). 40-Hz Binaural beats enhance training to mitigate the attentional blink. *Scientific Reports, 10*(1), Article 7002. https://doi.org/10.1038/s41598-020-63980-y

Schnitzler, A., & Gross, J. (2005). Normal and pathological oscillatory communication in the brain. *Nature Reviews Neuroscience, 6*(4), 285–296. https://doi.org/10.1038/nrn1650

Schubert, C., Dabbagh, A., Classen, J., Krämer, U. M., & Tzvi, E. (2021). Alpha oscillations modulate premotor-cerebellar connectivity in motor learning: Insights from transcranial alternating current stimulation. *NeuroImage, 241*, Article 118410. https://doi.org/10.1016/j.neuroimage.2021.118410

Seidler, R. D., Bernard, J. A., Burutolu, T. B., Fling, B. W., Gordon, M. T., Gwin, J. T., Kwak, Y., & Lipps, D. B. (2010). Motor control and aging: Links to age-related brain structural, functional, and biochemical effects. *Neuroscience & Biobehavioral Reviews, 34*(5), 721–733. https://doi.org /10.1016/j.neubiorev.2009.10.005

Shekar, L., Suryavanshi, C. A., & Nayak, K. R. (2018). Effect of alpha and gamma binaural beats on reaction time and short-term memory. *National Journal of Physiology, Pharmacy and Pharmacology, 8*(6), 829–833. https://doi.org/10.5455 /njppp.2018.8.1246506022018

Smith, C. D., Umberger, G. H., Manning, E. L., Slevin, J. T., Wekstein, D. R., Schmitt, F. A., Markesbery, W. R., Zhang, Z., Gerhardt, G. A., Kryscio, R. J., & Gash, D. M. (1999). Critical decline in fine motor hand movements in human aging. *Neurology, 53*(7), 1458. https://doi.org/10.1212 /wnl.53.7.1458

Solcà, M., Mottaz, A., & Guggisberg, A. G. (2016). Binaural beats increase interhemispheric alpha-band coherence between auditory cortices. *Hearing Research, 332*, 233–237. https://doi.org/10.1016/j.heares.2015.09.011

Sung, H.-C., Lee, W.-L., Li, H.-M., Lin, C.-Y., Wu, Y.-Z., Wang, J.-J., & Li, T.-L. (2017). Familiar music listening with binaural beats for older people with depressive symptoms in retirement homes. *Neuropsychiatry, 7*(4), 347–353. https://doi.org/10.4172/Neuropsychiatry.1000221

Taga, M., Curci, A., Lacal, I., & Turner, D. (2019). The N100 TEP as a neural predictor of motor learning: A TMS-EEG study. *Brain Stimulation, 12*(2), 445–446. https://doi.org/10.1016 /j.brs.2018.12.445

Tarr, B., Launay, J., & Dunbar, R. I. (2014). Music and social bonding: "self-other" merging and neurohormonal mechanisms. *Frontiers in Psychology, 5*, Article 1096. https://doi.org/10.3389 /fpsyg.2014.01096

Varela, F., Lachaux, J.-P., Rodriguez, E., & Martinerie, J. (2001). The brainweb: Phase synchronization and large-scale integration. *Nature Reviews Neuroscience, 2*(4), 229–239. https://doi.org/10.1038/35067550

Wahbeh, H., Calabrese, C., & Zwickey, H. (2007). Binaural beat technology in humans: A pilot study to assess psychologic and physiologic effects. *The Journal of Alternative and Complementary Medicine, 13*(1), 25–32. https://doi.org /10.1089/acm.2006.6196

Wang, B., Fan, Y., Lu, M., Li, S., Song, Z., Peng, X., Zhang, R., Lin, Q., He, Y., Wang, J., & Huang, R. (2013). Brain anatomical networks in world class gymnasts: A DTI tractography study. *NeuroImage, 65*, 476–487. https://doi.org /10.1016/j.neuroimage.2012.10.007

Wang, B., Xiao, S., Yu, C., Zhou, J., & Fu, W. (2021). Effects of transcranial direct current stimulation combined with physical training on the excitability of the motor cortex, physical performance, and motor learning: A systematic review. *Frontiers in Neuroscience, 15*, Article 336. https://doi.org/10.3389 /fnins.2021.648354

Wang, L., Zhang, Y., Zhang, J., Sang, L., Li, P., Yan, R., Qiu, M., & Liu, C. (2019). Aging changes effective connectivity of motor networks during motor execution and motor imagery. *Frontiers in Aging Neuroscience, 11*, Article 312. https://doi.org /10.3389/fnagi.2019.00312

Wenk, G. L., Pierce, D. J., Struble, R. G., Price, D. L., & Cork, L. C. (1989). Age-related changes in multiple neurotransmitter systems in the monkey brain. *Neurobiology of Aging, 10*(1), 11–19. https://doi.org/10.1016/S0197-4580(89)80005-3

Woodard, K. F., & Fairbrother, J. T. (2020). Cognitive loading during and after continuous task execution alters the effects of self-controlled knowledge of results. *Frontiers in Psychology, 11*, Article 1046. https://doi.org/10.3389 /fpsyg.2020.01046

Young, C.-W., Tsai, C.-Y., Zheng, S.-R., Wang, L.-P., Chen, H.-W., & Ay, C. (2014). Investigate the effect of EEG for relaxation using binaural beats. In *Proceedings of the 7th International Symposium on Machinery and Mechatronics for Agriculture and Biosystems Engineering (ISMAB)*. Yilan, Taiwan. https://doi.org/10.2196/resprot.4251

Yu, J.-H., & Sim, K.-B. (2016). Classification of color imagination using Emotiv EPOC and event-related potential in electroencephalogram. *Optik, 127*(20), 9711–9718. https://doi.org/10.1016/j.ijleo.2016.07.074

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NeuroRegulation

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Trauma-Informed Neurofeedback for Law Enforcement Occupational and Organizational Stress

James R. Spears[1], Devon E. Romero[1], Katherine McVay[2], and Emily Surratt[1]*

[1]University of Texas at San Antonio, Department of Counseling, San Antonio, Texas, USA
[2]Texas A&M University-Corpus Christi, Corpus Christi, Texas, USA

Abstract

Occupational and organizational stressors impact workplace performance and contribute to mental health concerns among law enforcement officers. Although literature focuses on identifying the degree of relationship that these two factors have within this specific profession, studies offer limited solutions for decreasing associated symptoms relating to stressors. Implementing an intervention that acknowledges law enforcement factors such as psychological and physiological concerns, workplace culture, and mental health stereotypes could significantly impact both those that serve within this career as well as the community. In this article, we explore the use of trauma-informed neurofeedback a therapeutic intervention for the treatment of occupational and organizational stressors commonly experienced by law enforcement officers. We also present recommendations for clinical practice and research.

Keywords: law enforcement; occupational stress; organizational stress; neurofeedback

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***Address correspondence to**: James R. Spears, University of Texas at San Antonio, Department of Counseling, 501 W. Cesar E. Chavez, San Antonio, TX 78207, USA. Email: james.spears@utsa.edu

Edited by:
Rex L. Cannon, PhD, Currents, Knoxville, Tennessee, USA

Reviewed by:
Rex L. Cannon, PhD, Currents, Knoxville, Tennessee, USA
Randall Lyle, PhD, Mount Mercy University, Cedar Rapids, Iowa, USA

Neurofeedback for Law Enforcement Occupational and Organizational Stress

Law enforcement officers undertake an occupational position that requires psychological and physiological wellness (Violanti, 2021). The profession encompasses the potential for repeated exposure to traumatic situations and affiliated mental health consequences (Tovar, 2011). In tandem with subjection to dangerous situations, law enforcement officers must uphold high standards of ethical behavior while simultaneously navigating public scrutiny (Bishopp et al., 2016). Unsurprisingly, these professionals are likely to suffer from mental health concerns due to the combination of occupational and organizational stressors associated with their profession. For instance, law enforcement officers commonly encounter a variety of stress-related situations such as motor vehicle accidents, witnessing violent deaths, and altercations with perpetrators (Arnetz et al., 2009; Marmar et al., 2006) while also handling day-to-day aspects including job structure, departmental hierarchies, and administrative pressure (Dabney et al., 2013). Further, since 2020, law enforcement officers have also experienced the aftereffects associated with civil unrest and the COVID-19 pandemic (Violanti, 2021).

In the book *The Siege: Mental Health and the Police,* Violanti (2021) stated, “there are mental health crises in police work and an urgent need to resolve these crises” (p. 3). Counselors and other mental health professionals are in a unique position to provide services to these professionals and do so in a way that is accessible for those who may be hesitant to seek assistance (Hakik & Langlois, 2020). In this article, we propose utilizing a trauma-informed approach to neurofeedback when assisting law enforcement officers with mental health concerns. Through this lens, we consider how neurofeedback attends to law enforcement occupational and organizational stressors, workplace culture, traditional reluctance to seeking

out mental health services, and recommendations for clinical practice. Furthermore, this article aims to provide meaningful content promoting career retention, mental health services, and future research that advocate for law enforcement officers.

Occupational and Organizational Stressors in Law Enforcement

Researchers have explored causations for negative psychological and physiological concerns among the law enforcement population such as occupational burnout (Burke, 2017; Martinussen et al., 2007), poor decision-making (Nieuwenhuys et al., 2012), performance (Reynolds et al., 2018; Shane, 2010), and the onset of mental illness (Carlan & Nored, 2008). In addition, several studies have explored the connection that geography (Husain, 2020), professional roles (Dabney et al., 2013), and work-family conflict (Griffin & Sun, 2018) have with unfavorable employment outcomes. Although literature concludes the need to further explore additional avenues, researchers generally propose occupational and organizational stressors as two broad themes contributing to these unwanted issues (Soomro & Yanos, 2019). Occupational stressors depict environmental elements (e.g., community interactions, public perception, exposure to dangerous situations), while organizational stressors characterize facets relating to the institutional portion of the career (e.g., departmental structure, interactions with supervisors, job promotions, disciplinary actions; Dabney et al., 2013).

Due to the nature of their work, law enforcement officers are exposed to both occupational and organizational stressors repeatedly throughout their careers. These stressors can lead to the onset of physical, behavioral, and mental health concerns. Researchers have documented negative physical symptoms in this population as increased rates of diabetes, cardiac complications, and obesity (Trombka et al., 2021), while articulating police misconduct (e.g., unnecessary force) as a behavioral repercussion to unattended occupational and organizational stressors. Relating to mental health, in their meta-analysis, Syed et al. (2020) found the most common mental health problems among law enforcement officers were depression, posttraumatic stress disorder (PTSD), generalized anxiety disorder, suicidal ideation, and alcohol use. To emphasize this finding, a study conducted by Jetelina et al. (2020) discovered that out of the 434 participating officers from Dallas-Fort Worth, Texas, 54 (12%) reported a lifetime mental health diagnosis of depression, anxiety, or PTSD. An additional 114 (26%) officers without a lifetime mental illness diagnosis had positive screening results for current mental illness symptoms representative of depression, anxiety, PTSD, and/or suicidal ideation or self-harm. Of those reporting a lifetime diagnosis or positive screening results for a current mental illness, PTSD was the most reported mental health concern, followed by depression and anxiety (Jetelina et al., 2020).

Ongoing exposure to occupational and organizational stressors provides a unique challenge when working with the law enforcement population (Lawson et al., 2022). It is worth noting that while a presenting concern for the treatment of an officer may be PTSD, depression, or anxiety stemming from repeated exposure to occupational stressors, these symptoms may be compounded or exacerbated by organizational stressors such as unsupportive supervisors, policies, and procedures (Kohan & Mazmanian, 2003; Molnar et al., 2017). In fact, in addition to the onset of adverse mental health symptoms, researchers have also identified that occupational and organizational stressors influence burnout (Burke, 2017), negative perceptions to workplace fairness (Kohan & Mazmanian, 2003; Wolfe & Nix, 2017), and police misconduct (Bishopp et al., 2016). The events following 2020 have only exacerbated this phenomenon. Based on their review of historical trends following the HIV epidemic and terrorist attacks of September 11, 2002, researchers such as Stogner et al. (2020) theorized an increased experience of work-related stressors (e.g., resource shortages, loss of personnel, economic uncertainty) as a result of COVID-19. Treatment modalities for stress and other mental health concerns for law enforcement officers must be flexible to reflect the demands and stressors each officer may face regardless of cultural or departmental dynamics (Padilla, 2020).

Of particular interest to this article, law enforcement officers are exposed to trauma routinely, both directly and indirectly as vicarious trauma, making PTSD and stress-related symptoms one of the more concerning mental health issues in this field (Hakik & Langlois, 2020). PTSD and trauma-related symptoms are the outward expression of an internal rewiring of neural networks and damages to behavioral and emotional areas of the brain (Bremner, 2006). Areas such as the prefrontal cortex (behavior), hippocampus (memory), and the amygdala (emotion) undergo changes when a person is exposed to trauma and the underlying changes are responsible for the cognitive-affective

dysfunctional symptoms observed in PTSD clients (Harnett et al., 2020). These brain alterations create ongoing symptoms that might negatively express themselves in an officer's job performance, leading to a lack of ability to cope with ongoing work-related stressors.

A Barrier to Care: Mental Health Stigma in Law Enforcement

Law enforcement officer training is a rigorous and daunting process. It entails breaking down an individual's identity to rebuild professional characteristics such as independence and self-reliance (Wester et al., 2010). A trainee learns that the loss of emotional control could risk their career (Karaffa & Koch, 2016), implicitly encouraging the suppression of their mental health concerns. Although officer training constructs internal protective barriers that safeguard against high-risk and dangerous occupational events, the preparation traditionally supports workplace stigmas surrounding mental health (Karaffa & Koch, 2016). Additionally, because this career also emphasizes colleague protection and rapport (Loftus, 2010; Wester et al., 2010), law enforcement professionals have been found to view seeking outside help with distrust as it promotes the concept of an officer's inability to protect another professional in an escalating situation (Soomro & Yanos, 2019). This increases the possibility of having an officer who struggles with either a mental health illness or stress related to the job to deny their condition, oppose assistance, silently struggle until retirement (Hakik & Langlois, 2020), or retire early (Police Executive Research Forum, 2021).

Efforts for Treatment

Given the negative mental health implications that occupational and organizational stressors have on officers, their families, those they serve, and their organizations (Burke, 2017; Griffin & Sun, 2018; Hakik & Langlois, 2020), therapeutic interventions that address these concerns are needed. In fact, the United States Congress unanimously signed the Law Enforcement Mental Health and Wellness Act (LEMHWA; 2018) into law in 2018, acknowledging the need for mental health resources and interventions for law enforcement officers. A review of literature indicates that researchers continue to examine stress management and resilience strategies as main avenues for reducing law enforcement mental health concerns while improving work performance (Christopher et al., 2016; Grupe et al., 2021).

Rooted in psychological frameworks (i.e., cognitive-behavioral, mindfulness-based resilience, motivational interviewing), these approaches employ techniques that ask individuals to gain deeper intrapersonal awareness through identifying and recognizing signs of stress (Grupe et al., 2021), participating in guided meditation and imagery exercises (Christopher et al., 2016), integrating coping strategies (Eddy et al., 2021), and engaging in group mental health support programs (Hohner, 2017). These research initiatives reveal promising results. For instance, Christopher et al. (2016) constructed a mindfulness-based resilience training program for 43 United States officers that contained various common mindfulness practices, such as body scanning, mindful movement, and walking meditations. The focus of the study was to equip participants with strategies to manage occupational and organizational stressors. During an 8-week period, officers attended weekly sessions that intentionally adapted common language and understandings found within this population. Results were significant in attending to a variety of symptoms including burnout, emotional regulation, mental health, personal awareness, and perceived stress (Christopher et al., 2016). Similarly, Grupe et al. (2021) developed a comparable program but included a 5-month follow-up for the 30 participants. Measured relative to the pretest data, results continued to reveal improvements in PTSD, burnout, anxiety, and sleep quality (Grupe et al., 2021).

Unfortunately, despite the positive outcomes of utilizing stress management and mindfulness-based interventions with law enforcement personnel, one substantial limitation remains. Noted in their qualitative study, Eddy et al. (2021) found that although participants relayed improvement in interpersonal and intrapersonal functioning following mindfulness-based resilience training, participants also disclosed that ingrained professional stigmas might deter professionals from participating. This limitation is congruent with past law enforcement literature suggesting officers might view stress management and resilience strategies as abstruse or mundane (Anderson et al., 1995) as well as incongruent with workplace culture (Waters & Ussery, 2007). Thus, a therapeutic intervention that acknowledges occupational culture and mental health stigma while simultaneously advocating for the wellness and safety of law enforcement members is warranted.

Trauma-Informed Neurofeedback for Law Enforcement Officers

Unlike traditional talk therapy or mindfulness-based training, both of which prioritize emotional awareness, neurofeedback provides a noninvasive and nonverbal way to focus on neural activity and brain regulation. This form of treatment has proven to be successful in treating disorders and symptoms that are resistant to traditional therapy options (Demos, 2019). Although empirical research on mindfulness-based interventions reveals promising results (e.g., Christopher et al., 2016; Eddy et al., 2021; Grupe et al., 2021), neurofeedback training recognizes these studies' limitations by informing clients of the psychophysiological relationship between unconscious brain activity and mental health symptoms while being sensitive to any ingrained stereotypes and stigmas surrounding mental illness. Building upon the success of officer mindfulness-based research, individuals participating in neurofeedback are encouraged to take an active, independent role by becoming aware of their ability to regulate brain activity correlating with their presenting concerns. This type of client involvement complements law enforcement characteristics of independence and self-reliance as it stimulates individual learning and performance. Additionally, in this facet of neural-specific psychoeducation, individuals begin to not only understand the relationship between neurobiological activity and mental health diagnoses but client acceptance, empathy, and engagement in symptom-related strategic thinking are also promoted (Erk, 2000; Russell-Chapin, 2016).

In conjunction with the recommendations above, it is the belief of the authors that use of trauma-informed neurofeedback for law enforcement officers seeking mental health assistance can be a way to both destigmatize and reframe their fear of being perceived as unreliable by proactively attending to concerns. Research alludes to the helpfulness of utilizing a trauma-informed approach with police officers (Raver & McElheran, 2022). In this section, we present the use of neurofeedback and a trauma-informed framework for addressing the mental health concerns precipitated or exacerbated by the everyday work of law enforcement officers.

Neurofeedback for Occupational and Organizational Stressors

Police officers are routinely exposed to stressors and trauma in the course of their work, and the likelihood of developing PTSD or other related problems can increase as the exposure factors and stressors increase (Bishopp et al., 2019; Maguen et al., 2009). In addition, researchers have noted brain structural differences in individuals exposed to continued traumatic events which have been found to be correlated with symptomatology (Baldaçara et al., 2017; Bremner, 2006). To date, research literature regarding professions exposed to trauma and the professional fields themselves are reactive rather than proactive in implementing preventative measures (Lawson et al., 2022). Given that individuals in this field are susceptible to continued stressful situations and have an increased chance of developing a mental health illness, the deficit of preventive mental health options necessitates the need for accessible, evidence-based treatment options that address current mental health disorders while also building resilience.

Fortunately, research continues to provide evidence that neurofeedback offers therapeutic results by conditioning and working directly with brain wave activity. Neurofeedback uses operant conditioning principles which allow the client to train and control their brain. Its ability to target unhealthy neural pathways and reroute the signals into a healthy functioning network allows it to focus on the originating source of the symptoms rather than treating the surface indicators. Neurofeedback research has been conducted for a variety of mental health concerns, including PTSD (Romero et al., 2020; van der Kolk et al., 2016), anxiety (Gregory et al., 2020, 2023), and stress (Balconi et al., 2018; Hafeez et al., 2019). Utilizing neurofeedback both as a preemptive measure and as a posttraumatic-exposure therapy tool could also allow for faster recovery and long-term success rates.

Although scholars have studied the use of biofeedback, a self-regulation tool that empowers an individual to change physiological activity for the purposes of improving health and performance (Association for Applied Psychophysiology and Biofeedback [AAPB], 2008), this literature has primarily focused on performance enhancement strategies including physiological stress regulation (Brammer et al., 2021) and shooting performance (Gong et al., 2020). Currently, there is a lack of literature studying the impact neurofeedback has on members of the law enforcement population. Utilizing this form of neuro-informed counseling with law enforcement professionals might aid in decreasing certain symptomology developed from common occupational and organizational stressors. We identified several trends in the literature with implications for treatment and further research. In the following sections, we provide considerations

from the literature for training focused on the anterior prefrontal cortex, alpha and asymmetry training, and utilizing individualized neurofeedback protocols to address functional and structural brain changes resulting from exposure to traumatic experiences.

Implications for Prefrontal Cortex Training. Because law enforcement officers encounter ongoing occupational and organizational stressors, examining avenues that improve cognitive functioning in relation to anxiety, stress, and depression is warranted. The prefrontal cortex, located at the anterior-most portion of the frontal lobe, assists with executive and social-emotional functioning as it communicates with other cerebral structures (e.g., amygdala) to regulate thoughts, emotions, and behaviors (Demos, 2019). Specifically, the prefrontal cortex inhibits amygdala activity (top-down processing) to encourage appropriate responses to environmental stimuli (Demos, 2019). However, researchers continue to document that prolonged exposure to stress decreases the prefrontal cortex's ability to hinder inappropriate impulses resulting in increased emotional dysregulation, poor decision-making, and other mental health concerns (Arnsten et al., 2015; Rauch et al., 2006).

In an effort to understand the impact of trauma on the prefrontal cortex of law enforcement personnel, Kaldewaij et al. (2021) conducted a quasi-experimental, pre-post study design in which 185 police recruits participated in an emotional action control task that activated the anterior prefrontal cortex. Using functional magnetic resonance imaging (fMRI) to record neural activity and activation, the researchers tasked participants to maneuver a joystick depending on a specific positive or negative stimulus. Results indicated that improved emotional control and resiliency to posttraumatic stress symptoms were predicted when activating the anterior prefrontal cortex (Kaldewaij et al., 2021).

Neurofeedback training is another avenue shown to activate the prefrontal cortex while simultaneously conditioning a more desired and rational response to environmental factors. Although neurofeedback researchers have seen success in downregulating the amygdala at electrode sites outside of the frontal lobe (Keynan et al., 2019), other researchers articulate that training along the anterior dorsal (Fz), ventral (Fpz), or right prefrontal cortex (Fp2) might increase social behaviors and an overall sense of well-being (Demos, 2019). Further, other researchers examining the benefits of frontal neurofeedback training demonstrate positive results in alleviating depressive and anxiety symptoms when training frontal alpha asymmetry (Mennella et al., 2017) or cerebral areas located at either the left (Takamura et al., 2020) or right (Yu et al., 2021) dorsolateral prefrontal cortex. Due to the consequential relationship between the prefrontal cortex and reoccurring stress, clinicians integrating neurofeedback with law enforcement officers should consider alterations in frontal lobe activity when deciding on an efficacious training protocol.

Implications for Alpha Training and Frontal Alpha Asymmetry Training. Of particular interest for this population, scholars have identified a positive trend in improving PTSD indicators, anxiety, and related symptoms by training alpha brainwave activity (e.g., Gregory et al., 2020; Mennella et al., 2017; Wang et al., 2019). Professionals correlate alpha oscillations with "internal reflection, brain synchrony, and peak performance," (Demos, 2019, p. 25) as well as "meditation or a deep sense of inner calm" (p. 215). Further, research continues to demonstrate that while there is a positive correlation between these traits and the default mode network (Jann et al., 2009), alpha activity is reduced in the default mode network for individuals with PTSD (Clancy et al., 2020). Thus, several studies have examined the relationship between alpha training and decreasing PTSD symptoms (Nicholson et al., 2020; van der Kolk et al., 2016). For example, Romero et al. (2020) utilized van der Kolk's et al. (2016) PTSD neurofeedback protocol of decreasing 2–6 Hz and 22–36 Hz while increasing 10–13 Hz at sites T4 (active) and P4 (reference). Participants included 21 individuals who presented with primary trauma symptoms. Following a minimum of 15 biweekly 30-min neurofeedback sessions, the researchers discovered that participants showed statistically significant improvements in various areas including hyperarousal, avoidance, severity and frequency, identity diffusion, susceptibility to influence, and affect skill deficits (Romero et al., 2020).

Additionally, our review of the literature resulted in the identification of another form of alpha training with implications for the treatment of law enforcement officers. Frontal alpha asymmetry training, originally theorized by Davidson (1992), accounts for the differences in left (positive emotions and approach motivation) and right (avoidance and negative emotions) frontal region alpha power and their association with emotional reactivity and temperament. Neurofeedback researchers have aimed to use this training approach to decrease

anxiety and depressive symptoms (Choi et al., 2010; Mennella et al., 2017; Peeters et al., 2014). For instance, Mennella et al. (2017) provided neurofeedback training to 32 female participants divided equally into two experimental groups who either received training to increase frontal alpha asymmetry or mid-frontal alpha activity. After conducting five sessions, results supported a significant increase in alpha asymmetry compared to the active control group. Additionally, individuals who participated in the asymmetry group demonstrated a significant increase in resting alpha power at site F4, inferring a decrease in anxiety and negative affect (Mennella et al., 2017).

Results from studies such as these emphasize the potential use of alpha neurofeedback training and alpha asymmetry training to decrease PTSD and stress related symptoms commonly experienced by the law enforcement population. Similar to the recommendation of Fragedakis and Toriello (2014) related to utilizing neurofeedback for combat-related to PTSD, it is our recommendation that clinicians and researchers consider alpha and alpha asymmetry training when developing neurofeedback treatment plans for law enforcement officers. Integrating informed, empirically based neurofeedback protocols for officers can decrease maladaptive symptoms and the potential onset of comorbid concerns such as substance use (Hammond, 2007; Othmer & Othmer, 2009).

Implications for Individualized Treatment Protocols. Researchers have long demonstrated that exposure to traumatic experiences and subsequent PTSD-related symptoms can lead to neurobiological dysregulation and brain structural and functional differences (Bremner et al., 2006; Shucard et al., 2012). Despite inconsistencies in reported findings, commonly reported neuroanatomical abnormalities consist of reduced volume in the hippocampus (Karl et al., 2006; Starcevic et al., 2014), anterior cingulate cortex, and amygdala (Lyoo et al., 2011; Starcevic et al., 2014; Xiao et al., 2022) and alterations in cortical thickness in frontal and temporal areas (Bing et al., 2013; Geuze et al., 2008; Xiao et al., 2022). Several studies have explored this phenomenon with law enforcement officers (e.g., Baldaçara et al. 2017; Lindauer et al., 2004; Shucard et al., 2012). For instance, a neuroimaging study completed by Lindauer et al. (2004) found decreased total and left hippocampal volumes in trauma-exposed officers. Additionally, Baldaçara et al. (2017) documented a reduction of prefrontal thickness in military police officers with PTSD. Relatedly, Shucard et al. (2012) identified a greater likelihood that police officers' frequent exposure to traumatic events increased PTSD symptomatology and reduced brain structure volume. Together, this information supports the notion that individuals do not always experience exposure to stress and trauma the same in terms of symptomatology or structural and functional differences (Setroikromo et al., 2020). Thus, to acknowledge the array of diverse neurological presentations of a single mental health concern (e.g., PTSD, depression, anxiety, stress), our recommendation for improving brain function when structural differences are a concern is to utilize individualized neurofeedback protocols informed by quantitative electroencephalography (qEEG; Gregory et al., 2020, 2023). Prior to beginning neurofeedback treatment, the use of a qEEG can help identify an individual's standard brainwave patterns and the areas that would benefit from neurofeedback training. Utilizing qEEG assists clinicians in determining efficacious routes of treatment relating to an individual's specific cortical dysfunctions with presenting mental health symptomologies (Wigton & Krigbaum, 2015).

A Trauma-informed Framework

Due to the complex nature of their work with navigating diverse stressors, law enforcement officers often experience trauma and are exposed to traumatic situations. Trauma is the result of violence, loss, disaster, abuse, neglect, or otherwise harmful situations individuals are subjected to experience (SAMHSA, 2014). Trauma-informed care is the practice of staff awareness of trauma, the impact of services in use with trauma, and the incorporation of the knowledge around trauma into current practices (Hopper et al., 2010). The Substance Abuse and Mental Health Services Administration (SAMHSA), identified six core tenets to the informed approach including (a) safety; (b) trustworthiness and transparency; (c) peer support; (d) collaboration and mutuality; (e) empowerment, voice, and choice; and (f) cultural, historical, and gender issues. Each of these principles promotes rapport building and personal success to the trauma. Furthermore, several of the tenets can be associated with certain values and aspects found in the career of law enforcement such as safety, trustworthiness, peer support, and collaboration which encompass officer camaraderie and protecting one another. Understanding how these different principles align with law enforcement policies and values will provide counselors the ability to not only relate to this career mindset but incorporate a trauma-informed approach that increases well-being among law enforcement officers and their perceptions of trauma.

With trauma being perceived differently by every person, trauma-informed care considers the factors of the event, an individual's experience of the event, and the effect it has on the person (SAMHSA, 2014). Accompanied by law enforcement occupational demands, the individual perception an officer has concerning certain experiences might influence their sensitivity to trauma. Therefore, preventative measures have been taken by operating a trauma-informed framework with this population. Several studies have been conducted with the utilization of police officers using a trauma-informed framework when responding to victims (Lathan et al., 2019; Rich, 2019). However, limited research is shown on trauma-informed practices when working with police officers. For instance, Raver and McElheran (2022), propose several ways to incorporate a trauma-informed approach to reduce police misconduct and violence. We suggest an organizational change in trauma-informed approaches by police leadership and supervisors. Additionally, the authors advise to not use a "one size fits all" approach when training others on understanding trauma. Finally, we recommend a change in approach to the system by leaders in varying levels of police organization. We encourage having leaders learn more about trauma and building the skills to help other employees with traumatic events (Raver & McElheran, 2022). It is also our recommendation that clinicians utilize a trauma-informed framework when working with law enforcement.

Discussion and Implications for Future Research

We sought to present trauma-informed neurofeedback as a means to prevent and treat the mental health concerns often experienced by law enforcement officers. We synthesized previous literature which identified neurofeedback as a means to decrease symptoms such as anxiety (e.g., Gregory et al., 2020) and PTSD (e.g., Romero et al., 2020; 2023) while also recognizing the hesitation of law enforcement officers engaging in traditional mental health care (Jetelina et al., 2020). From our review of the literature, we discovered that researchers cited neurofeedback protocols that trained the prefrontal cortex (e.g., Kaldewaij et al., 2021; Takamura et al., 2020; Yu et al., 2021), alpha amplitude (e.g., Romero et al., 2020; van der Kolk, 2016), alpha asymmetry (e.g., Mennella et al., 2017), or utilized qEEG results to develop an individualized neurofeedback protocol as successful in decreasing negative symptoms often experienced by officers.

Although presented separately, we suggest that clinicians and researchers consider all the presented recommendations when creating neurofeedback treatment protocols. For instance, resources permitting, we suggest qEEG-informed individualized protocols as a standard for treatment planning, as each client will present with their own unique concerns and cortical presentations. When reviewing qEEG reports, clinicians may also consider the existing body of literature that identifies the significance of alpha and interhemisphere synchronicity for stress and trauma-related symptomology.

Further, when developing treatment protocols, we emphasize the need for communication with the client about their personal and occupational needs. Clinicians must consider the potential impact of alleviating adverse symptoms that protect officers while out in the community. For instance, heightened vigilance is often necessary as law enforcement job requirements demand repeated exposure to dangerous environments or situations. While mental health professionals regard hypervigilance as a presenting mental health phenotype, it would be dangerous and potentially unethical for clinicians to conduct brain modulation training without knowing possible risk factors for this occupational population. Through this lens, we emphasize caution be taken and encourage one to conceptualize presenting concerns and treatment planning with the unique needs of these professionals. It may be advantageous for the clinician to periodically check in to assess if the training protocol is having the desired effects and is not interfering with their ability to execute work-related tasks.

Finally, this article primarily focused on the occurrence of PTSD and stress-related symptoms in law enforcement officers and the use of trauma-informed neurofeedback for treatment purposes. It is important for counselors to be aware of the high rates of anxiety and depression with this population. We recommend future researchers to explore and consider the diverse array of mental health implications that often accompany the law enforcement career path. We also suggest researchers examine the presentation of officers across various units (e.g., homicide, Special Weapons and Tactics [SWAT]) such as using qEEG software to inform individual and group biomarkers or develop neurofeedback treatment plans.

Conclusion

While there is a surplus of literature recognizing the negative repercussions of occupational and organizational stressors, there continues to be a lack of research proposing techniques that encourage officer well-being. Clinicians using therapeutic interventions must be mindful of the distinct components found within the profession, including exposure to dangerous and traumatic events, training competencies, and workplace stigmas. Building from previous mindfulness-based interventions, neurofeedback could greatly benefit those serving in this occupation in that this form of biofeedback attends to these components. Because neurofeedback encourages client self-regulation, officers can take an active, independent role in their improvement. Additionally, utilizing a trauma-informed framework builds upon neurofeedback by supporting client well-being through trustworthiness, collaboration, and empowerment. By providing these services, counselors are encouraging officers to reframe their beliefs surrounding seeking mental health and advocating for their needs. In conclusion, the hope of integrating neurofeedback with a trauma-informed framework as a normalized, therapeutic intervention would provide preventative and holistic care as well as promote the well-being of the officer, the profession as a whole, and the communities being served.

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References

Anderson, W., Swenson, D., & Clay, D. (1995). *Stress management for law enforcement officers*. Prentice Hall.

Arnetz, B. B., Nevedal, D. C., Lumley, M. A., Backman, L., & Lublin, A. (2009). Trauma resilience training for police: Psychophysiological and performance effects. *Journal of Police and Criminal Psychology, 24*(1), 1–9. https://doi.org/10.1007/s11896-008-9030-y

Arnsten, A. F., Raskind, M. A., Taylor, F. B., & Connor, D. F. (2015). The effects of stress exposure on prefrontal cortex: Translating basic research into successful treatments for post-traumatic stress disorder. *Neurobiology of Stress*, *1*, 89–99. https://doi.org/10.1016/j.ynstr.2014.10.002

Association for Applied Psychophysiology and Biofeedback [AAPB]. (2008). https://aapb.org/

Balconi, F., Fronda, G., & Crivelli, D. (2018). Effects of technology-mediated mindfulness practice on stress: Psychophysiological and self-report measures. *Stress, 22(2)*, 200–209. https://doi.org/10.1080/10253890.2018.1531845

Baldaçara, L., Araújo, C., Assunção, I., Da Silva, I., & Jackowski, A. P. (2017). Reduction of prefrontal thickness in military police officers with post-traumatic stress disorder. *Archives of Clinical Psychiatry, 44*(4), 94–98. https://doi.org/10.1590/0101-60830000000128

Bing, X., Ming-Guo, Q., Ye, Z., Jing-Na, Z., Min, L., Han, C., Yu, Z., Jia-jia, Z., Jian, W. Wei, C., Han-jian, D., & Shao-xiang, Z. (2013). Alterations in the cortical thickness and the amplitude of low-frequency fluctuation in patients with post-traumatic stress disorder. *Brain Research,* 1490, 225–232. https://doi.org/10.1016/j.brainres.2012.10.048

Bishopp, S. A., Piquero, N. L., Worrall, J. L., & Piquero, A. R. (2019). Negative affective responses to stress among urban police officers: A general strain theory approach. *Deviant Behavior*, *40*(6), 635–654. https://doi.org/10.1080/01639625.2018.1436568

Bishopp, S. A., Worrall, J., & Piquero, N. L. (2016). General strain and police misconduct: The role of organizational influence. *Policing: An International Journal of Police Strategies & Management, 39*(4), 635–651. https://doi.org/10.1108/PIJPSM-10-2015-0122

Brammer, J. C., van Peer, J. M., Michela, A., van Rooij, M. M. J. W., Oostenveld, R., Klumpers, F., Dorrestijn, W., Granic, I., & Roelofs, K. (2021). Breathing biofeedback for police officers in a stressful virtual environment: Challenges and opportunities. *Frontiers in Psychology, 12*, Article 586553. https://doi.org/10.3389/fpsyg.2021.586553

Bremner, J. D. (2006). Traumatic stress: Effects on the brain. *Dialogues in Clinical Neuroscience, 8*(4), 445–461. https://doi.org /10.31887/DCNS.2006.8.4/jbremner

Burke, R. J. (2017). Burnout in police work. In R. J. Burke (Ed.), *Stress in policing: Sources, consequences, and interventions* (pp. 154–169). Routledge.

Carlan, P. E., & Nored, L. S. (2008). An examination of officer stress: Should police departments implement mandatory counseling? *Journal of Police and Criminal Psychology, 23*(1), 8–15. https://doi.org/10.1007/s11896-008-9015-x

Choi, S. W., Chi, S. E., Chung, S. Y., Kim, J. W., Ahn, C. Y., & Kim, H. T. (2010). Is alpha wave neurofeedback effective with randomized clinical trials in depression? A pilot study. *Neuropsychobiology*, *63*(1), 43–51. https://doi.org/10.1159/000322290

Christopher, M. S., Goerling, R. J., Rogers, B. S., Hunsinger, M., Baron, G., Bergman, A. L., & Zava, D. T. (2016). A pilot study evaluating the effectiveness of a mindfulness-based intervention on cortisol awakening response and health outcomes among law enforcement officers. *Journal of Police and Criminal Psychology, 31*(1), 15–28. https://doi.org/10.1007/s11896-015-9161-x

Clancy, K. J., Andrzejewski, J. A., Simon, J., Ding, M., Schmidt, N. B., & Li, W. (2020). Posttraumatic stress disorder is associated with α dysrhythmia across the visual cortex and the default mode network. *eNeuro*, *7*(4), Article ENEURO.0053-20.2020. https://doi.org/10.1523/ENEURO.0053-20.2020

Dabney, D. A., Copes, H., Tewksbury, R., & Hawk-Tourtelot, S. R. (2013). A qualitative assessment of stress perceptions among members of a homicide unit. *Justice Quarterly*, *30*(5), 811–836. https://doi.org/10.1080/07418825.2011.633542

Davidson, R. J. (1992). Anterior cerebral asymmetry and the nature of emotion. *Brain and Cognition*, *20*(1), 125–151. https://doi.org/10.1016/0278-2626(92)90065-t

Demos, J. N. (2019). *Getting started with EEG neurofeedback*. W. W. Norton & Company.

Eddy, A., Bergman, A. L., Kaplan, J., Goerling, R. J., & Christopher, M. S. (2021). A qualitative investigation of the experience of mindfulness training among police officers. *Journal of Police and Criminal Psychology, 36*(1), 63–71. https://doi.org /10.1007/s11896-019-09340-7

Erk, R. R. (2000). Five frameworks for increasing understanding and effective treatment of attention-deficit/hyperactivity disorder: Predominately inattentive type. *Journal of Counseling & Development, 78*(4), 389–399. https://doi.org/10.1002/j.1556-6676.2000.tb01922.x

Fragedakis, T. M., & Toriello, P. (2014). The development and experience of combat-related PTSD: A demand for neurofeedback as an effective form of treatment. *Journal of Counseling & Development, 92*(4), 481–488. https://doi.org/10.1002/j.1556-6676.2014.00174.x

Geuze, E., Westenberg, H. G., Heinecke, A., de Kloet, C. S., Goebel, R., & Vermetten, E. (2008). Thinner prefrontal cortex in veterans with posttraumatic stress disorder. *NeuroImage, 41*(3), 675–681. https://doi.org/10.1016/j.neuroimage.2008.03.007

Gong, A., Nan, W., Yin, E., Jiang, C., & Fu, Y. (2020). Efficacy, trainability, and neuroplasticity of SMR vs. alpha rhythm shooting performance neurofeedback training. *Frontiers in Human Neuroscience, 14*, Article 94. https://doi.org/10.3389/fnhum.2020.00094

Gregory, J. C., Romero, D. E., & Jones, M. S. (2020). Predictors of neurofeedback outcomes following qEEG individualized protocols for anxiety. *NeuroRegulation, 7*(1), 18–25. https://doi.org/10.15540/nr.7.1.18

Gregory, J. C., Romero, D., & Jones, M. (2023). Exploring single-case research design with individualized anxiety-based neurofeedback protocols and session data. *NeuroRegulation, 10*(3), 159–169. https://doi.org/10.15540/nr.10.3.159

Griffin, J. D., & Sun, I. Y. (2018). Do work-family conflict and resiliency mediate police stress and burnout: A study of state police officers. *American Journal of Criminal Justice*, *43*(2), 354–370. https://doi.org/10.1007/s12103-017-9401-y

Grupe, D. W., McGehee, C., Smith, C., Francis, A. D., Mumford, J. A., & Davidson, R. J. (2021). Mindfulness training reduces PTSD symptoms and improves stress-related health outcomes in police officers. *Journal of Police and Criminal Psychology, 36*, 72–85. https://doi.org/10.1007/s11896-019-09351-4

Hafeez, A. (2019). Investigating neurofeedback protocols for stress mitigation: A comparative analysis of different stimulus contents. *IEEE Access, 7*, 141021–141035. https://doi.org/10.1109/access.2019.2944202

Hakik, L. & Langlois, K. (2020). "To serve and protect their mental health": The effects of police occupational culture on police officers mental health. *Salus Journal, 8(2)*, 117–151.

Hammond, D. C. (2007). What is neurofeedback? *Journal of Neurotherapy, 10*(4), 25–26. https://doi.org/10.1300/J184v10n04_04

Harnett, N. G., Goodman, A. M., & Knight, D. C. (2020). PTSD-related neuroimaging abnormalities in brain function, structure, and biochemistry. *Experimental Neurology, 330,* Article 113331. https://doi.org/10.1016/j.expneurol.2020.113331

Hohner, C. (2017). *'The environment says it's okay': The tension between peer support and police culture* [Doctoral dissertation, The University of Western Ontario (Canada)]. Electronic Thesis and Dissertation Repository.

Hopper, E., Bassuk, E., & Olivet, J. (2010). Shelter from the storm: trauma-informed care in homelessness services settings. *The Open Health Services and Policy Journal, 3*, 80–100. https://doi.org/10.2174/1874924001003020080

Husain, W. (2020). Depression, anxiety, and stress among urban and rural police officers. *Journal of Police and Criminal Psychology, 35*, 443–447. https://doi.org/10.1007/s11896-019-09358-x

Jann, K., Dierks, T., Boesch, C., Kottlow, M., Strik, W., & Koenig, T. (2009). BOLD correlates of EEG alpha phase-locking and the fMRI default mode network. *NeuroImage*, *45*(3), 903–916. https://doi.org/10.1016/j.neuroimage.2009.01.001

Jetelina, K. K., Molsberry, R. J., Gonzalez, J. R., Beauchamp, A. M., & Hall, T. (2020). Prevalence of mental illness and mental health care use among police officers. *JAMA Network Open, 3*(10), Article e2019658. https://doi.org/10.1001/jamanetworkopen.2020.19658

Kaldewaij, R., Koch, S. B. J., Hashemi, M. M., Zhang, W., Klumpers, F., & Roelofs, K. (2021). Anterior prefrontal brain activity during emotion control predicts resilience to post-traumatic stress symptoms. *Nature Human Behaviour*, *5*, 1055–1064. https://doi.org/10.1038/s41562-021-01055-2

Karaffa, K. M., & Koch, J. M. (2016). Stigma, pluralistic ignorance, and attitudes toward seeking mental health services among police officers. *Criminal Justice and Behavior*, *43*(6), 759–777. https://doi.org/10.1177/0093854815613103

Karl, A., Schaefer, M., Malta, L. S., Dörfel, D., Rohleder, N., & Werner, A. (2006). A meta-analysis of structural brain abnormalities in PTSD. *Neuroscience & Biobehavioral Reviews*, *30*(7), 1004–1031. https://doi.org/10.1016/j.neubiorev.2006.03.004

Keynan, J. N., Cohen, A., Jackont, G., Green, N., Goldway, N., Davidov, A., Meir-Hasson, Y., Raz, G., Intrator, N., Fruchter, E., Ginat, K., Laska, E., Cavazza, M., & Hendler, T. (2019). Electrical fingerprint of the amygdala guides neurofeedback training for stress resilience. *Nature Human Behaviour, 3*(1), 63–73. https://doi.org/10.1038/s41562-018-0484-3

Kohan, A. & Mazmanian, D. (2003). Police work, burnout, and pro-organizational behavior: A consideration of daily work experiences. *Criminal Justice and Behavior, 30*(5), 559–583. https://doi.org/10.1177/0093854803254432

Lathan, E., Langhinrichsen-Rohling, J., Duncan, J., & Stefurak, J. "Tres." (2019). The promise initiative: Promoting a trauma-informed police response to sexual assault in a mid-size southern community. *Journal of Community Psychology*, *47*(7), 1733–1749. https://doi.org/10.1002/jcop.22223

Law Enforcement Mental Health and Wellness Act, S 867, 115th Cong., 163 Cong. Rec. 2955 (2018) (enacted). https://www.congress.gov/congressional-record/volume-163/issue-84/senate-section/article/S2955-2

Lawson, S. G., Wolfe, S. E., Rojek, J. & Alpert, G. P. (2022). Occupational stress and attitudes toward misconduct in law enforcement: The moderating role of organizational justice, *Police Practice and Research, 23*(1), 95–110, https://doi.org/10.1080/15614263.2021.1946395

Lindauer, J. L. R., Vliegler, E.-J., Jalink, M., Carlier, I. V. E., Majoie, C. B. L. M., den Heetan, G. J., & Gersons, B. (2004). Smaller hippocampal volume in Dutch police officers with posttraumatic stress disorder. *Biological Psychiatry, 56*, 356–363. https://doi.org/10.1016/j.biopsych.2004.05.021

Loftus, B. (2010). Police occupational culture: Classic themes, altered times. *Policing and Society, 20(1)*, 1–20. https://doi.org /10.1080/10439460903281547

Lyoo, I. K., Kim, J. E., Yoon, S. J., Hwang, J., Bae, S., & Kim, D. J. (2011). The neurobiological role of the dorsolateral prefrontal cortex in recovery from trauma: Longitudinal brain imaging study among survivors of the South Korean subway disaster. *Archives of General Psychiatry*, *68*(7), 701–713. https://doi.org/10.1001/archgenpsychiatry.2011.70

Maguen, S., Metzler, T. J., McCaslin, S. E., Inslicht, S. S., Henn-Haase, C., Neylan, T. C., & Marmar, C. R. (2009). Routine work environment stress and PTSD symptoms in police officers. *The Journal of Nervous and Mental Disease, 197*(10), 754–760. https://doi.org/10.1097/NMD.0b013e3181b975f8

Marmar, C. R., McCaslin, S. E., Metzler, T. J., Best, S., Weiss, D. S., Fagan, J., Liberman, A., Pole, N., Otte, C., Yehuda, R., Mohr, D., & Neylan, T. (2006). Predictors of posttraumatic stress in police and other first responders. *Annals of the New York Academy of Sciences, 1071*(1), 1–18. https://doi.org/10.1196/annals.1364.001

Martinussen, M., Richardsen, A. M., & Burke, R. J. (2007). Job demands, job resources, and burnout among police officers. *Journal of Criminal Justice*, *35*(3), 239–249. https://doi.org/10.1016/j.jcrimjus.2007.03.001

Mennella, R., Patron, E., & Palomba, D. (2017). Frontal alpha asymmetry neurofeedback for the reduction of negative affect

and anxiety. *Behaviour Research and Therapy*, *92*, 32–40. https://doi.org/10.1016/j.brat.2017.02.002

Molnar, B. E., Sprang, G., Killian, K. D., Gottfried, R., Emery, V., & Bride, B. E. (2017). Advancing science and practice for vicarious traumatization/secondary traumatic stress: A research agenda. *Traumatology, 23*(2), 129–142. https://doi.org/10.1037/trm0000122

Nicholson, A. A., Harricharan, S., Densmore, M., Neufeld, R. W. J., Ros, T., McKinnon, M. C., Frewen, P. A., Théberge, J., Jetly, R., Pedlar, D., & Lanius, R. A. (2020). Classifying heterogeneous presentations of PTSD via the default mode, central executive, and salience networks with machine learning. *NeuroImage: Clinical*, *27*, Article 102262. https://doi.org /10.1016/j.nicl.2020.102262

Nieuwenhuys, A., Savelsbergh, G. J. P., & Oudejans, R. R. D. (2012). Shoot or don't shoot? Why police officers are more inclined to shoot when they are anxious. *Emotion, 12*(4), 827–833. https://doi.org/10.1037/a0025699

Othmer, S., & Othmer, S. F. (2009). Post traumatic stress disorder—The neurofeedback remedy. *Biofeedback, 37*(1), 24–31. https://doi.org/10.5298/1081-5937-37.1.24

Padilla, K. E. (2020). Sources and severity of stress in a Southwestern police department. *Occupational Medicine, 70*(2), 131–134. https://doi.org/10.1093/occmed/kqaa018

Peeters, F., Oehlen, M., Ronner, J., van Os, J., & Lousberg, R. (2014). Neurofeedback as a treatment for major depressive disorder–a pilot study. *PLoS ONE*, *9*(3), Article e91837. https://doi.org/10.1371/journal.pone.0091837

Police Executive Research Forum. (2021). PERF special report. https://www.policeforum.org/workforcesurveyjune2021

Rauch, S. L., Shin, L. M., & Phelps, E. A. (2006). Neurocircuitry models of posttraumatic stress disorder and extinction: Human neuroimaging research—past, present, and future. *Biological Psychiatry*, *60*(4), 376–382. https://doi.org/10.1016 /j.biopsych.2006.06.004

Raver, J., & McElheran, M. (2022). A trauma-informed approach is needed to reduce police misconduct. *Industrial and Organizational Psychology, 15*(4), 583–587. https://doi.org /10.1017/iop.2022.82

Reynolds, P. D., Fitzgerald, B. A., & Hicks, J. (2018). The expendables: A qualitative study of police officers' response to organizational injustice. *Police Quarterly*, *21*(1), 3–29. https://doi.org/10.1177/1098611117731558

Rich, K. (2019). Trauma-informed police responses to rape victims. *Journal of Aggression, Maltreatment & Trauma*, *28*(4), 463–480. https://doi.org/10.1080 /10926771.2018.1540448

Romero, D. E., Anderson, A., Gregory, J. C., Potts, C. A., Jackson, A., Spears, J. R., Jones, M. S., & Speedlin, S. (2020). Using neurofeedback to lower PTSD symptoms. *NeuroRegulation, 7*(3), 99–106. https://doi.org/10.15540 /nr.7.3.99

Russell-Chapin, L. A. (2016). Integrating neurocounseling into the counseling profession: An introduction. *Journal of Mental Health Counseling*, *38*(2), 93–102. https://doi.org/10.17744 /mehc.38.2.01

Setroikromo, S. N. W., Bauduin, S. E. E. C., Reesen, J. E., van der Werff, S. J. A., Smit, A. S., Vermetten, E., & van der Wee, N. J. A. (2020). Cortical thickness in Dutch police officers: An examination of factors associated with resilience. *Journal of Traumatic Stress, 33*(2), 181–189. https://doi.org/10.1002 /jts.22494

Shane, J. W. (2010). Organizational stressors and police performance. *Journal of Criminal Justice, 38*(4), 807–818. https://doi.org/10.1016/j.jcrimjus.2010.05.008

Shucard, J. L., Cox, J., Shucard, D. W., Fetter, H., Chung, C., Ramasamy, D., & Violanti, J. (2012). Symptoms of posttraumatic stress disorder and exposure to traumatic stressors are related to brain structural volumes and behavioral measures of affective stimulus processing in police officers. *Psychiatry Research: Neuroimaging, 204*(1), 25–31. https://doi.org/10.1016/j.pscychresns.2012.04.006

Soomro, S. & Yanos, P. T. (2019). Predictors of mental health stigma among police officers: The role of trauma and PTSD. *Journal of Police and Criminal Psychology, 34(2)*, 175–183. https://doi.org/10.1007/s11896-018-9285-x

Starcevic, A., Postic, S., Radojicic, Z., Starcevic, B., Milovanovic, S., Ilankovic, A., Dimitrijevic, I., Damjanovic, A., Aksić, M., & Radonjic, V. (2014). Volumetric analysis of amygdala, hippocampus, and prefrontal cortex in therapy-naïve PTSD participants. *BioMed Research International, 2014*, Article 968495. http://dx.doi.org/10.1155/2014/968495

Stogner, J., Miller, B. L., & McLean, K. (2020). Police stress, mental health, and resiliency during the COVID-19 Pandemic. *American Journal of Criminal Justice, 45*, 718–730. https://doi.org/10.1007/s12103-020-09548-y

Substance Abuse and Mental Health Services Administration [SAMHSA]. (2014). SAMHSA's concept of trauma and guidance for a trauma-informed approach. *HHS Publication No. (SMA) 14-4884*. Substance Abuse and Mental Health Services Administration.

Syed, S., Ashwick, R., Schlosser, M., Jones, R., Rowe, S., & Billings, J. (2020). Global prevalence and risk factors for mental health problems in police personnel: A systematic review and meta-analysis. *Occupational & Environmental Medicine, 77*, 737–747. https://doi.org/10.1136/oemed-2020-106498

Takamura, M., Okamoto, Y., Shibasaki, C., Yoshino, A., Okada, G., Ichikawa, N., & Yamawaki, S. (2020). Antidepressive effect of left dorsolateral prefrontal cortex neurofeedback in patients with major depressive disorder: A preliminary report. *Journal of Affective Disorders, 271*, 224–227. https://doi.org /10.1016/j.jad.2020.03.080

Tovar, L. A. (2011). Vicarious traumatization and spirituality in law enforcement. *FBI Law Enforcement Bulletin, 80*(7), 16–21.

Trombka, M., Demarzo, M., Campos, D., Antonio, S. B., Cicuto, K., Walcher, A. L., García-Campayo, J., Schuman-Olivier, Z., & Rocha, N. S. (2021). Mindfulness training improves quality of life and reduces depression and anxiety symptoms among police officers: Results from the POLICE study—a multicenter randomized controlled trial. *Frontiers in Psychiatry*, 12, Article 624876. https://doi.org/10.3389/fpsyt.2021.624876

Van der Kolk, B. A., Hodgdon, H., Gapen, M., Musicaro, R., Suvak, M. K., Hamlin, E., & Spinazzola, J. (2016). A randomized controlled study of neurofeedback for chronic PTSD. *PLoS ONE, 11(12),* Article e0166752. https://doi.org /10.1371%2Fjournal.pone.0166752

Violanti, J. (2021). *Occupation under Siege: Resolving Mental Health Crises in Police Work*. Charles C. Thomas Publisher.

Wang, S.-Y., Lin, I.-M, Fan, S.-Y., Tsai, Y.-C., Yen, C.-F., Yeh, Y.-C., Huang, M.-F., Lee, Y., Chiu, N.-M., Hung, C.-F., Wang, P.-W., Liu, T.-L., & Lin, H.-C. (2019). The effects of alpha asymmetry and high-beta down-training neurofeedback for patients with the major depressive disorder and anxiety symptoms. *Journal of Active Disorders*, *257*, 287–296. https://doi.org/10.1016/j.jad.2019.07.026

Waters, J. A., & Ussery, W. (2007). Police stress: History, contributing factors, symptoms, and interventions. *Policing: An International Journal of Police Strategies & Management*, *30*(2), 169–188.

Wester, S. R., Arndt, D., Sedivy, S. K., & Arndt, L. (2010). Male police officers and stigma associated with counseling: The role of anticipated risks, anticipated benefits and gender role conflict. *Psychology of Men & Masculinity, 11(4)*, 286–302. https://doi.org/10.1037/a0019108

Wigton, N. L., & Krigbaum, G. (2015). A review of qEEG-guided neurofeedback. *NeuroRegulation*, *2*(3), 149–155. https://doi.org/10.15540/nr.2.3.149

Wolfe, S. E., & Nix, J. (2017). Police officers' trust in their agency: Does self-legitimacy protect against supervisor procedural

injustice? *Criminal Justice and Behavior, 44*(5), 717–732. https://doi.org/10.1177/0093854816671753

Xiao, S., Yang, Z., Su, T., Gong, J., Huang, L., & Wang, Y. (2022). Functional and structural brain abnormalities in posttraumatic stress disorder: A multimodal meta-analysis of neuroimaging studies. *Journal of Psychiatric Research, 155*, 153–162. https://doi.org/10.1016/j.jpsychires.2022.08.010

Yu, L., Long, Q., Tang, Y., Yin, S., Chen, Z., Zhu, C., & Chen, A. (2021). Improving emotion regulation through real-time neurofeedback training on the right dorsolateral prefrontal cortex: Evidence from behavioral and brain network analyses. *Frontiers in Human Neuroscience, 15*, Article 620342. https://doi.org/10.3389/fnhum.2021.620342

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A Critical Review of: *Double-Blind Placebo-Controlled Randomized Clinical Trial of Neurofeedback for Attention-Deficit/Hyperactivity Disorder With 13-Month Follow-Up*

Gary J. Schummer[1] and Tristan Sguigna[2]*

[1]Clinical Director (Retired), ADD Treatment Center, Torrance, California, USA
[2]Former Senior Technician, ADD Treatment Center, Torrance, California, USA

Abstract

Attention-deficit/hyperactivity disorder (ADHD) is a common neurobehavioral condition affecting children and adolescents impairing academic success, self-esteem, and social interactions. Since there is no cure for ADHD, the public relies on researchers to provide an honest and objective evaluation of treatment options to help those with ADHD manage the disorder. The public's expectation was thwarted when a study was published in the Journal of the American Academy of Child & Adolescent Psychiatry (JAACAP) titled *Double-Blind Placebo-Controlled Randomized Clinical Trial of Neurofeedback for Attention-Deficit/Hyperactivity Disorder with 13-Month Follow-Up* (Arnold et al., 2021). The principal investigator and lead author was L. Eugene Arnold, MD, who referred to his coauthors as a collaborative team. The National Institute of Mental Health funded the study with a $2 million grant. This critical review of Arnold et al. examines various aspects of the study to help us understand why the findings and stated conclusion of the study deviated from a substantial body of research and clinical evidence demonstrating the effectiveness of NFB for treating ADHD.

Keywords: call for retraction; neurofeedback; pharmaceutical biasing

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***Address correspondence to**: Gary Schummer, PhD, 3030 N. Redwood Dr., Palm Springs, CA 92262-2086, USA. Email: gjschummer@cs.com

Edited by:
Rex L. Cannon, PhD, Currents, Knoxville, Tennessee, USA

Reviewed by:
Rex L. Cannon, PhD, Currents, Knoxville, Tennessee, USA
Randall Lyle, PhD, Mount Mercy University, Cedar Rapids, Iowa, USA

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common neurobehavioral condition affecting children and adolescents impairing academic success, self-esteem, and social interactions. Since there is no cure for ADHD, the public relies on researchers to provide an honest and objective evaluation of treatment options to help those with ADHD manage the disorder. The public's expectation was thwarted when a study was published in the Journal of the American Academy of Child & Adolescent Psychiatry (JAACAP) in August 2021, titled *Double-Blind Placebo-Controlled Randomized Clinical Trial of Neurofeedback for Attention-Deficit/Hyperactivity Disorder with 13-Month Follow-Up* [Hereafter, abbreviated as "study" or "Arnold et al."]. The study intended to evaluate neurofeedback as a treatment for ADHD over a 13-month period. The principal investigator and lead author was L. Eugene Arnold, MD, along with a team of coauthors collectively known as the Neurofeedback Collaborative Group. The study may be accessed in the JAACAP, 2021-07-01, Volume 60, Issue 7, pages 841–855. This study was supported by a $2 million grant from the National Institute of Mental Health (NIMH) #R01-MH100144, by Ohio State University College of Medicine Endowment, and by a Clinical and Translational Science award 8UL18TR000090-05 from the National Center for Translational Sciences. Clinical Trials Identifier: NCT02251743, date of registration: 9/17/2014. The paper is available here:

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The Neurofeedback Collaborative Group was cited as coauthors and comprised of the following:

> Martijn Arns, PhD; Justin Barterian, PhD; Rachel Bergman, BA; Sarah Black, PhD; C. Keith Conners, PhD (deceased); Shea Connor, BS; Sudeshna Dasgupta, MD; Roger deBeus, PhD; Teryll Higgins, MA; Laurence Hirshberg, PhD; Jill A. Hollway, PhD; Cynthia Kerson, PhD; Howard Lightstone, B; Nicholas Lofthouse, PhD; Joel Lubar, PhD; Keith McBurnett, PhD; Vincent Monastra, PhD; Kristin Buchan-Page, BA; Xueliang (Jeff) Pan, PhD; Robert Rice, PhD; Michelle E. Roley-Roberts, PhD; Rachel Rhodes, MLAS; Constance Schrader, PhD; Yubo (Jeremy) Tan, MS, MBBS; Craig E. Williams, MD.

Neurofeedback training (NFB) is one of several types of biofeedback, all of which are predicated on the operant conditioning paradigm, wherein spontaneous activity increases when reinforcement is provided. In the specific case of NFB treatment of ADHD, an electroencephalographic (EEG) device is used to continually analyze the child's brainwaves. This device provides auditory and visual signals or rewards within 250 ms of the moment the child's brain shifts into an EEG pattern that is known to correlate with a more attentive state. When these transient moments of heightened alertness are paired with the reward signals, the child learns how to better self-regulate their attention. As the child receives this training, their ability to sustain attention improves and ADHD symptoms decrease.

This critique examines various aspects of the study to help us understand why the findings and stated conclusion of the study deviated from a substantial body of research and clinical evidence demonstrating the effectiveness of NFB for treating ADHD. In addition to identifying errors in the study's design, methodology, and data analysis, information gathered from interviewing several authors revealed deeper issues compromising the reliability and validity of the conclusions. One author described personal surreptitious communication between the authors of the study and a journal editor that indicated the JAACAP journal would publish the study *if* the conclusion stated that NFB was no better than a placebo. In direct contradiction to core ethical principles, the manuscript was subsequently manipulated to conform with the journal editor's predetermined outcome.

Lexchin along with other concerned scientists (2003) have compiled substantial evidence demonstrating that sponsorship of research by the pharmaceutical industry compromises the outcome and quality of research studies. Although investigators are ethically required to disclose conflicts of interest, this fails to reveal the degree to which said conflict impacted the research. This study by Arnold et al. is a prime example of how current ethical requirements fail to reveal critical information. The sheer number of methodological errors alone, not to mention the coercion by editors at JAACAP, demonstrates that incentives to disparage NFB, influenced the evolution and publication of this study to a greater extent than the ethical requirement to provide research that is free of conflicts of interest. Those controlling the authorship and publishing of this study abused their credentialed authority and now must follow ethical requirements to disclose the errors and retract the study. When those who conduct research admit and correct errors, the very nature of scientific inquiry is strengthened along with the public's trust in the conclusions offered by research studies. For future researchers, an admission and retraction of this study will demonstrate the critical nature for adopting strategies to minimize the impact of conflicts of interest by fostering transparency and accountability in their research practices.

Part I. Neurofeedback History

Before discussing specific issues in the study, it is important to understand that the efficacy of NFB treatment for ADHD has already been repeatedly demonstrated. In the 1950s, Kamiya (1968, 1969, 2011) demonstrated successful operant conditioning of the alpha frequency (8–12 Hz). Sterman (1969, 1972, 1974, 2000) completed a series of exemplary studies characterized by rigorous research designs and transparent methodology allowing publication in top-tier scientific journals and replication at independent laboratories. In the 1960s, Sterman conducted research on medication-resistant epilepsy using NFB to increase an EEG frequency called the sensorimotor rhythm (12–15 Hz). This training allowed epileptics to significantly reduce the frequency, intensity, and duration of seizure incidents lasting for many months and even years. Sterman's work with human and animal subjects demonstrated cross-species conditioning thus eliminating any suggestion that the effects produced by NFB might be due to placebo or bias. Lubar et al. (1995) and Zuberer et al. (2015) conducted studies demonstrating the effectiveness of NFB as a treatment for ADHD. Many others contributed to this early efficacy research verifying that NFB was safe

and effective to improve functional abilities for a wide range of physiological and psychogenic disorders.

Part II. Acceptance of Neurofeedback

For the purposes of this critique, *detractor* will be used as a general term to refer to those having direct or indirect ties, are paid by, or receive tangible benefit(s) from their association with the pharmaceutical industry, including, but not limited to, pharmaceutical company employees, members of their Boards of Director, major stockholders, agents such as pharmaceutical company consultants, collaborators, biomedical researchers funded by the industry, and physicians who "have a monopoly over the prescription trade by virtue of their licenses to practice" (Idzik, 1965).

Detractors have created and spread many false beliefs regarding NFB. One such false belief is that key decision-makers at the NIMH have been unwilling to fund NFB studies because they question the legitimacy of NFB. The real reason this major source of funding for research is hesitant to fund NFB research is because the efficacy of NFB has already been scientifically demonstrated. The funding priority of the NIMH, as their mission statement indicates, is to investigate *new* treatments that build upon our knowledge base (see https://www.nih.gov/about-nih/what-we-do/mission-goals).

NFB is not a new treatment, therefore allocating funding to assess efficacy is duplicative and unwarranted. Detractors disregard the fact that NFB has an extensive history of acceptance as a medical procedure illustrated by these selected examples:

a) In 1978, the Current Procedural Terminology (CPT) committee, under the auspices of the American Medical Association, acknowledged that NFB met or exceeded requirements for efficacy and assigned treatment codes indicating it was a legitimate intervention eligible for reimbursement by health insurance companies (https://www.ama-assn.org/amaone/cpt-current-procedural-terminology).
b) In 1976, the U.S. Food and Drug Administration began regulating NFB instruments as Class II medical devices indicating they were safe and effective tools for treatment (https://www.accessdata.fda.gov/cdrh_docs/pdf14/K143031.pdf).
c) The International Society for Neurofeedback (ISNR) supplies the public with a downloadable bibliography of NFB studies. In the section covering NFB research treatment of ADHD (pp. 3–12), the bibliography identifies over 130 studies showing NFB is an efficacious treatment for ADHD as both a standalone treatment or part of a multimodal regimen. In addition, ISNR estimates there are over 15,000 clinicians worldwide using this technology (https://isnr.org/wp-content/uploads/2019/07/download.pdf).
d) Another professional organization, the Applied Psychophysiology and Biofeedback Society (AAPB), recently released the 4th edition of a book titled, "Evidence-Based Practice in Biofeedback & Neurofeedback" (Khazan et al., 2023). Chapter 6 focuses on NFB and ADHD (pp. 121–135) and cites over 40 highly credible studies that were peer-reviewed. Based on the strength of this research, the authors and AAPB determined that the research on NFB for ADHD earned their highest determination of effectiveness: Level 5 – Efficacious and Specific.
e) NFB has been evaluated by various regulatory authorities and is recognized as within the "scope of practice" for psychologists, psychiatrists, physical therapists, nurses, occupational therapists, social workers, and family therapists, among others.
f) NFB developed from well-established foundational studies that have continued to support the growth of the field. The neurofeedback field continues to be supported by ongoing research projects, professional organizations, a dedicated peer-reviewed journal, and a certification program for new providers.
g) Data Bridge Market Research analyzes trends and predicts that the global market for NFB will be USD 1,908 million by 2029 (https://www.databridgemarketresearch.com/reports/global-neurofeedback-market).

Despite these facts and optimistic projections, as this critique discusses, the pharmaceutical industry and detractors who benefit from their association with this industry have a long history of unfairly targeting NFB. This abuse of the public's trust is directly related to the fact that, when people choose nondrug treatments rather than drug therapy, the profit margin of the pharmaceutical industry diminishes. Detractors do more than simply ignore

the mountain of NFB research or write articles to dissuade the public from NFB treatment. Over time, their fear of this intervention has effectively marginalized the entire neurofeedback field. This critique provides evidence that methods and data were manipulated to draw false conclusions that advance the narrative that NFB treatment of ADHD has yet to prove itself as an efficacious treatment. While the neurofeedback field is receptive to legitimate research-based challenges and constructive criticism, these must be scientifically based and take into consideration conclusions derived from previous research and prevailing standards of care. Deviating from ethical scientific procedures undermines the search for evidence-based interventions and unfairly deprives the public of effective treatment options.

Part III. Documenting Errors, Notifying the Authors and the Editor of JAACAP

After the publication of this study, an ad hoc committee of experts in the neurofeedback field gathered to review the study. The committee included Lori Ellison, Henry Harbin, Joy Lunt, Lori Russell-Chapin, Gary Schummer, and Mark Trullinger. The committee identified the list of significant errors (see Part IV below) that severely compromised the study's integrity. Taken together, these errors make any meaningful interpretation of the study's data impossible and prevent the study from being determinative of the efficacy of NFB. Additionally, a "Letter to the Editor" titled *Erroneous Science* in Arnold et al. (2021) was sent to the Editor-In-Chief of JAACAP pointing out the errors. Consistent with ethical standards, the Letter urged the Journal to retract the study and provide an explanation of the nature and extent of the errors. Although the authors appeared to agree with the validity of the errors, to the best of our knowledge, none have asked the Journal to retract the study. Interestingly, the ad hoc committee received a response regarding the Letter from the Editor-in-Chief of the JAACAP stating that he considered the documented concerns but was unwilling to share it with his fellow editors. He ended his response paradoxically and shamelessly stating that our Letter did not meet the journal's standards for publication.

After the errors were made known to the primary authors in the meeting, some of the authors indicated they had not been apprised of the issues. Perhaps this is due to the fact that the study's collaborators were responsible for nonoverlapping aspects of the study and not all were involved in writing the manuscript. As indicated in the support material for the study, tasks were assigned as follows:

> ***Conceptualization***. Arnold, Arns, deBeus, Hirshberg, Hollway, Kerson, Lubar, McBurnett, Monastra; **Data Curation**: Arns, deBeus, Lightstone, Monastra, Buchan-Page, Pan, Rice, Tan; **Formal Analysis**: Arnold, Arns, Black, Conners, Dasgupta, deBeus, Hollway, Kerson, Lofthouse, Monastra, Buchan-Page, Pan, Rice, Roley-Roberts, Rhodes, Schrader, Tan, Williams; **Funding Acquisition**: Arnold; **Investigation:** Arnold, Black, Connor, Dasgupta, deBeus, Kerson, McBurnett, Monastra, Pan, Roley-Roberts; **Methodology**: Arnold, Arns, Barterian, Bergman, Black, Conners, Connor, Dasgupta, deBeus, Higgins, Hirshberg, Hollway, Kerson, Lofthouse, Lubar, Monastra; **Project Administration**: Arnold, Barterian, Bergman, Connor, deBeus, Higgins, Hollway, Kerson, Monastra, Buchan-Page, Roley-Roberts; **Resources**: Arnold, Connor, deBeus, Kerson, Lightstone, Monastra, Buchan-Page, Pan, Tan; **Software**: Lightstone; **Supervision**: Arnold, Barterian, Black, deBeus, Hollway, Kerson, Rhodes, Schrader, Williams; **Validation:** Arnold, Arns, Barterian, Black, deBeus, Hollway, Kerson, Monastra, Buchan-Page, Rhodes, Williams; **Visualization**: Arnold, Arns, Connor, deBeus, Pan, Tan**; Writing – original draft**: Arnold, Arns, deBeus; **Writing – review and editing**: Kerson, Monastra, Pan, Roley-Roberts (https://www.jaacap.org/article/S0890-8567(20)31358-7/fulltext - articleInformation).

Part IV. Errors in Arnold et al. (2021)

Error 1: Hypothesizing After Results Are Known. Abbreviated *HARKing*, Kerr (1998) stated this involves deceptively modifying a study's primary hypothesis after the results are analyzed. HARKing obscures valuable aspects of the truth and engenders a range of issues. Originally, the authors had preregistered a specific primary outcome hypothesis, which they later altered *after* analyzing the results. This shift in hypothesis compromises the integrity of the study and introduces misleading elements into the analysis. The authors of this study stated the following preregistered primary outcome hypothesis:

> Children randomly assigned to NFB will, when assessed in an unmedicated state, show a significantly greater reduction of inattentive ADHD symptoms rated by parents and teachers than those assigned to double-blind placebo sham treatment of equal duration, intensity, involvement, and appearance.

By definition, a sham placebo is designed to have no real effect. However, in this study, the sham placebo *did* show a real effect. The authors stated:

> The control improvement appears comparable to the longer, more intensive MTA behavioral treatment. What this improvement is due to requires further research, but the 13-month durability suggests more than a placebo response.

Therefore, critical data required by the primary hypothesis could not be calculated. Rather than truthfully stating this fact, the authors changed their preregistered primary outcome hypothesis by removing the words *placebo sham* when they presented their conclusion. The authors stated:

> In summary, the primary outcome failed to show a significant advantage of NFB over the control treatment.

Experts well-versed in HARKing have stated that this error typically arises from either investigator incompetence or a deliberate intent to mislead readers into perceiving the study as credible. In this context, the authors knowingly misrepresented the truth or concealed a material fact for reasons we can only speculate. The choice by the Editor of JAACP to publish the manuscript without identifying and insisting this error be corrected is duplicitous and raises questions about the journal's oversight and commitment to maintaining research integrity.

Error 2: There Was No Valid Placebo Sham Control Group. The "control" group was given EEG feedback acquired from subjects of similar ages who were not part of the study. Additionally, this group was provided with real-time electromyographic (muscle tension level) feedback (EMG). EMG feedback was given when a fluctuation in muscle tension was detected. Participants received visual and auditory cues that guided them into a more relaxed state typically associated with lowering muscle tension. Notably, Barth et al. (2017) found that EMG feedback *alone* leads to a reduction in ADHD symptoms, particularly the hyperactivity component. EMG researchers suggest that decreasing muscle tension facilitates the reallocation of physiological resources so attention can be better regulated. Not knowing the literature regarding the impact of EMG biofeedback on ADHD is another indication of the sophomoric approach Arnold et al. (2021) took to conducting this study. Additionally, participants in both the control and treatment groups received guidance about the significance of sleep and nutrition, with a specific emphasis on the importance of breakfast, and were provided with a list of recommended breakfast foods. During each session, all participants were queried about their daily food intake and sleep duration. Given the implementation of these interventions, one could reasonably anticipate that the control group would also exhibit a learning effect, which manifested as a 59% improvement compared to a 67% improvement in the treatment group. The control group therefore did not serve as a true control as they were given an intervention known to directly impact attentional factors. The study's control group was actually an alternative treatment group, and the principal investigators should have been aware of this prior to finalizing the study's method. Lacking a true control group, the title, data analysis, and manuscript should have been corrected to indicate this fact.

Error 3: Type III Error or P-Hacking. The integrity of research findings and their ethical interpretation demand thorough consideration of all possible factors influencing outcomes, particularly when such conclusions impact medical treatments and patients' well-being. Diligent researchers and journal reviewers exercise caution to avoid the Type III error, a misjudgment characterized by rejecting the null hypothesis for an incorrect rationale. Trullinger et al. (2019) indicated that this error occurs when researchers repeatedly select data or apply statistical analyses until nonsignificant results become significant. Astonishingly, the authors of the study, and even more notably, the panel of editors at JAACP, permitted the authors to reach a conclusion that brain-wave-contingent reinforcement was ineffective simply based on the absence of a statistically significant disparity between the treatment and control groups in the EEG domain. This approach highlights a fundamental misinterpretation of statistical significance, overlooking the broader context and potential nuances within the data and was essentially dishonest. Such an oversight calls into question both the methodological rigor of those who analyzed the data and the scrutiny expected from the editorial review process. From the study:

> From baseline to treatment end the primary outcome showed significant (p < .0001) improvement for both NFB (d = 1.51) and control (d = 1.47) but did not show a significant difference between them.

Left unexamined was the very plausible scenario wherein the improvement observed with the control group was not without cause. After all, the "sham treatment" the authors referred to as the control group produced positive results akin to those observed in the NFB group. Of primary importance,

but completely disregarded in the manuscript, the control condition exhibited effectiveness comparable to established treatments for ADHD, including stimulant medication and behavior therapy, as per the primary outcome measure. Consequently, the control condition cannot be cavalierly deemed as inert or a mere placebo. A more scientifically and ethically sound conclusion would be to acknowledge that significant inferences regarding the efficacy of NFB cannot be drawn from this study due to the absence of one of the conditions necessary to conduct a viable double-blind placebo-controlled randomized clinical trial (RCT); that is, the control group must meet the criteria for a neutral placebo. The study's conclusion, as presented, inaccurately portrayed the data. The authors, out of ignorance or deliberate deceit, set this fact aside and presented to the public a false conclusion. Failing to rectify this is not only irresponsible but also ethically indefensible.

Error 4: "False No-Effect" Error. The analysis was not conducted to ascertain whether conditioned theta-beta ratio (TBR) training played a mediating role in driving symptom improvements across both the control and treatment groups. The authors stated:

> Categorically, based on the simple slope direction (up or down), the percentage of TBR "learners" was 59% for controls (9% greater than the 50% expected by chance in the dichotomous classification, p = .22) and 67% for NFB (17% greater than expected by chance, p = .003).

The erroneous assumption of a 50% random chance for TBR learning resulted in a misleading situation where a statistically significant difference between NFB and random chance emerged, rather than between the control and random chance. Additionally, hypothesis testing within this study's data may not accurately determine specificity due to the near-identical number of participants reported as having achieved TBR learning in both the NFB and control groups. This misstep led to the authors committing a "False no-effect" error, as discussed by Head et al. (2015). Experts state that this error can only be attributed to either the researchers' incompetence or deliberate deception. Ethical researchers are careful to avoid this error by employing readily accessible statistical techniques developed to identify this issue thereby allowing investigators to accurately test their hypotheses. Had the authors and/or the editorial staff at JAACAP chosen to identify this error and utilize appropriate corrective measures, the impact of this error would have been mitigated allowing the study to present somewhat more accurate findings.

Error 5: The Authors Stated There Was Only One Deviation From the Registered Protocol, Which Was Dishonest and Deceptive. The authors stated:

> The TBR inclusion threshold was changed from 5.0 (~1.5 *SD* above norms for 6- to 11-year-olds) in the registration protocol to 4.5 (~1.2 *SD* above norms) to increase sample representativeness, *the only change from the registered protocol*. [emphasis added]

The assertion in this statement is inaccurate. In addition, it is the second instance where the authors diverged from their initially preregistered protocol. While it is commendable that the authors acknowledged this deviation from the original design, it prompts one to question why they chose to acknowledge this relatively minor deviation while neglecting to address a major deviation concerning the study's most pivotal aspect—altering the criteria necessary to reach a conclusion. The authors doubled down on this ethical violation by explicitly stating that this deviation represented "the only change," misleading readers into presuming that no other departures from the preregistered protocol existed throughout the study. This selective acknowledgment misguides readers by creating an impression of transparency while concealing more significant deviations from the original protocol. The impact of the author's failure to honestly address all deviations and their implications cannot be overstated. Honest and full transparency, qualities this study lacks, is crucial for maintaining the credibility and reliability of the research process.

Error 6: The Misapplication of the TBR. The authors claimed that the core element of the treatment group was the behaviorally conditioned alteration in the TBR. However, unwarranted assumptions about random changes in the TBR resulted in a misinterpretation of the sham group's efficacy, erroneously suggesting similar outcomes to the treatment group. The evaluation of learning rates for the TBR followed the methodology established by Monastra et al. (2005), having a documented test-retest reliability of 96%. This high reliability indicates that only 4% of participants should exhibit changes due to random chance. Surprisingly, the present study's analysis diverged from this established research on TBR test-retest reliability by assuming that learning would occur in 50% of participants purely due to random chance, without clear justification. Furthermore, employing the TBR as either a dependent variable or considering it as a

possible underlying mechanism of action was a substantial error. Although some research studies have indicated decreases in the TBR following NFB, other research by Janssen et al. (2017) contradicted this finding. Despite studies showcasing significant reductions in ADHD symptoms, Bakhshayesh et al. (2011) and Gevensleben et al. (2009) observed that some participants who improved showed no significant changes in the TBR. In addition, Ogrim and Hestad (2013) noted the persistence of "remarkably stable" power measures in both theta and beta frequencies after 30 sessions of NFB. Given the variance in findings and the lack of a consensus within the scientific community that decreasing the TBR indicates effective NFB, using the TBR in the context of this study was naïve, lacking both scientific validity and reliability.

Error 7: The Focus on the TBR Overlooked More Scientifically Viable Alternatives. The decision to focus on the TBR as a key measure of training indicated that the authors assumed ADHD is a disorder stemming from a frequency imbalance. A much more popular theory, but equally controversial, suggests ADHD is caused by an imbalance of neurotransmitters. Both theories lack scientific validation and have been criticized in the literature. While identifying EEG subtypes based on frequency-specific phenotypic expressions has been shown to have diagnostic utility, there is no consensus among experts that this EEG metric is the best or even a good way to account for all possible expressions of ADHD. A competing theory suggested by clinical data indicates that problems with ADHD are more likely an instability in the vigilance network rather than an issue involving an imbalance in certain frequencies. Since an overarching principle of every NFB session is that this training *always* reinforces neural stability, no matter what frequency bands are trained or where the electrodes are placed, there is significantly more justification to consider metrics that indicate a correlation with NFB. Similar to Sterman's work with epileptics, NFB clinicians have found that the best EEG metrics showing a consistent positive correlation with a reduction in ADHD symptoms are those assessing neural stability. Among the many measures, the most reliable metric in our clinical work has been the coefficient of variation, a statistical measure used to express the relative variability of a dataset. This metric is also known as normalized root-mean-square deviation (NRMSD), Percent RMS, or relative standard deviation (RSD). It is a standardized measure of dispersion of a probability distribution or frequency distribution and is defined as the ratio of the standard deviation (σ) to the mean (μ) or its absolute value, often expressed as a percentage. Of note, the software used in this study calculates the standard deviation for each period of NFB for the treatment group. However, the authors ignored this readily available measure, choosing instead to employ the TBR, a measure lacking validity and reliability.

Error 8: The Training Interval Was Not Consistent With the Best Practice Model. Beginning with the earliest research, it has been consistently understood that the training interval represents a critical consideration in effectively implementing any operant conditioning paradigm. The level of attention an individual devotes to a signal as well as the impact that signal may have on the individual in any environment directly correlates with their capacity to extract crucial information from that signal. The evolution of best practice guidelines within the neurofeedback field is consistent with operant conditioning research and stems from clinical experience. Similar to determining the ideal dosage of medication, the training interval is highly significant in determining the success or failure of NFB. The spacing between training sessions becomes more determinative of the success when treating younger children or at the beginning of treatment. Additional considerations impacting the training session interval involve the severity of ADHD symptoms or if daily events in the child's life are complicated by varying social, mental, or emotional issues. These issues impact clinical recommendations for the spacing of treatment intervals. Generally, we find that treatment outcomes are optimal when the participant or their parent commits to engage in a minimum of three spaced NFB sessions per week *consistently*. Participants undergoing fewer than three sessions weekly tend to experience less favorable outcomes or require a greater number of sessions to achieve maximum benefit from NFB. However, the methodology employed in this study did not require participants to consistently adhere to the three-sessions-per-week guideline. Instead, participants were allowed to attend sessions that yielded them an *average* of three sessions per week. Notably, the authors we interviewed disclosed that certain participants in the treatment group went up to 2 weeks without training. In clinical settings, fewer sessions, especially during the initial stages of treatment, results in significant slowing in progress and, with longer treatment intervals, there is often a substantial regression in progress. The noncompliance of participants or their parents with this critical recommendation sometimes leads them to say the NFB was not effective. This is why some experts in this field have said, "When NFB

fails, it has more to do with factors outside the therapist's control than it does the NFB." In the context of this study, allowing participants to have extended no-training intervals was an avoidable methodological error that undoubtedly compromised the effectiveness of NFB on the treatment group.

***Error 9*: *The Fixed Protocol for Training That Changes on a Fixed Schedule Was Not Reasonable or Optimal*.** The information provided in the text of this study is not transparent on the schedule of NFB, but according to the authors interviewed, a fixed protocol was utilized for training frequencies that changed every five sessions. This signifies a noteworthy deviation from established best practice guidelines. Such a fixed protocol, particularly one with a five-session interval, could potentially introduce inadequate spacing for effective reinforcement, especially for younger children who often require more immediate and frequent rewards. Moreover, considering the nature of ADHD treatment, the training is more effective if the interface of the participant with the instrument is more interactive. A characteristic of ADHD is the difficulty individuals with this condition face in terms of delaying gratification. This inability to defer immediate rewards in favor of longer-term goals contributes to challenges in impulse control, attention regulation, and behavioral self-regulation. This characteristic underscores the complex nature of ADHD and further emphasizes the importance of tailoring treatment approaches to accommodate the age, maturity level, degree of impairment, and specific cognitive and behavioral profiles of those who present for NFB. Furthermore, the conventional process during the initial 3 min of a session involves the NFB device calibrating itself to align with the participant's real-time EEG activity. Subsequently, this calibration is utilized during the session to determine thresholds for providing the feedback rewards. When a more adaptive protocol is used, more focused attention results empowering the child to experience enhanced self-regulation of their attention. The study's adherence to a fixed protocol, without considering the nuances of individuals with ADHD ignores the benefits associated with more fluid and interactive reinforcement schedule. This negatively impacted the treatment group's ability to learn self-regulation of attention.

***Error 10: Placement of the Active Sensor, a Critical Piece of Information, Was Omitted*.** For a study to be ethically reviewed, comprehended, and replicated, ethical guidelines mandate transparent communication of critical information, particularly concerning the methods employed. In clear violation of this principle, the study omitted critically important details regarding the precise placement of active electrodes on each participant. Additionally, a cogent rationale for selecting the specific electrode placements is absent. The process by which these determinations were reached remains enigmatic even to certain authors we interviewed. Typically, NFB involves selecting the optimal electrode placement based on a quantitative EEG (qEEG) assessment and a comprehensive clinical interview. The qEEG is a sensitive diagnostic assessment tool commonly used in clinical settings, neuroscience research, and in fields such as neurofeedback, psychology, neurology, and psychiatry to gain insights into brain function and help to identify potential neurological issues. This software-based application mathematically processes digitally recorded EEG to highlight specific waveform components that transforms the EEG into a format or domain that allows exploration of relevant information and examining the data in a variety of montages which can highlight impairments. In addition, associating numerical results with EEG data facilitates subsequent review, most importantly, allowing the comparison of a participant's data with an age-matched database. For purposes of NFB, the information provided by the qEEG is interpreted by a trained clinician and integrated along with clinical data into an individualized treatment plan. Practitioners are expected to be capable of justifying their chosen electrode placements based on these criteria. It follows that researchers should adhere to, at minimum, this same standard. The extent to which this study deviated from this established best practice guidelines is undisclosed, but any deviation without robust scientific justification is untenable. The lack of transparency in this aspect of the study raises concerns about the overall rigor and integrity of the research process, and by extension, the reliability of the conclusions drawn from the study.

***Error 11: The Study Makes It Clear the qEEG Was Used Diagnostically While Other Protocol Determinative Information Was Disregarded*.** To be eligible for inclusion in the study, each participant's qEEG assessment confirmed the presence of an ADHD phenotype characterized by excessive theta and deficient beta activity. Beyond this baseline criterion, best practice guidelines and clinical expertise have evolved that direct NFB providers to seek convergent validity by utilizing information from several databases. These data in conjunction with data derived from a comprehensive clinical interview are used to inform the optimal NFB protocol. Although the low beta, high theta phenotype may accurately categorize this subtype,

the precise frequency ranges for each participant differs. For example, some might exhibit excessive activity in the 3–7 Hz range, while others could display excesses in the 4–9 Hz range. The qEEG assessments identify the ideal inhibit frequency range for each participant and, when this, more tailored, range is incorporated into the NFB treatment protocol, it significantly impacts the degree and rate of improvement and, of course, the overall success of the treatment. However, in the context of an RCT, we must assume all participants were provided feedback based on a fixed bandwidth. This approach was abandoned years ago in favor of using tailored inhibits; training using tailored inhibits results in a significantly more effective treatment. Explicit information about the choice of inhibit frequency and the failure to provide a robust scientific rationale for their selection is a departure from best practice procedures and ethical research guidelines. This, no doubt, had a negative impact on the NFB treatment group.

Error 12: The Lack of Proper Training for the Technicians. Technicians must be thoroughly trained in proper electrode placement; how to obtain a viable, stable, and reliable EEG signal; how to ensure proper functioning of the amplifier, hardware, and software; and how to optimize participant engagement. Two authors of the study who were well-versed in NFB procedures independently disclosed that the technicians lacked even the most basic skills necessary to fulfill this role. They readily discussed the following: the lack of consistency in how technicians addressed problems that arose during sessions, including solving problematic software or hardware issues and how to proceed or even recognize when, for example, an electrode becomes unseated during a session, or when excessive muscle artifact obliterates the EEG that will later be analyzed and considered an important datapoint. Discrepancies among technicians extended to various aspects, such as differing responses to session interruptions and troubleshooting problems related to the equipment. NFB technicians are expected to do much more than ensure the computer and NFB instrument are functioning properly. Equally significant, technicians were inadequately trained in effectively interacting with participants, which is particularly crucial for minors with ADHD, who are not known for having patience and typically do not respond well to corrective measures. For instance, children with ADHD, particularly after a 6-hour school day, will exhibit fatigue that is often characterized by limited tolerance for remedial or insensitive interactions. Although they may feign attentiveness, they are adept at disengaging from prescribed tasks out of boredom or spite if they perceive their technician is treating them unfairly or is placing unreasonable demands on them. These factors would markedly influence the EEG data used for analysis and undoubtedly had a dramatic impact on the overall treatment outcome. Technicians in this study were neither certified nor provided the *minimum* 6 weeks of training considered necessary in clinical settings. They lacked the skills to properly resolve technical issues and, even more importantly, they lacked interpersonal training to effectively manage ADHD children and adolescents. It was reported the technicians improved as the study proceeded; however, this lack of consistency throughout the course of the study would have impacted the quality and reliability of the data. The lack of proper technician training had implications for the integrity of the data, the ultimate effectiveness of the treatment, the generalizability of the results, and the validity and reliability of the study's conclusions.

Error 13: The Study's Primary Outcome Measure Lacked Ecological Validity. According to standards of scientific inquiry, this study should be reported as a failed trial since the anticipated group differences that were hypothesized did not materialize for the primary outcome measure, as stated. However, scientific reporting standards also necessitate considering the possibility that the primary outcome measure lacked validity in accurately measuring changes related to ADHD. Clinically, it is quite common to see a reduced need for medication during and post-NFB, which is likely attributed to enhanced self-regulation of attention. Interestingly, this study did identify significant differences in the NFB group after 13 months, along with a notably higher rate of remission, as reported in the study (40% in the treatment group compared to 19% in the control group). Curiously, this outcome was overlooked and not presented because the reduction in medication was not designated as a primary outcome measure. Overlooking this common and expected result from NFB centers worldwide shows a lack of sophistication and understanding of how this treatment impacts children and adolescents who use medication to treat their ADHD. Indeed, this finding should have been reported as it raises questions about the ecological validity of statistically significant changes observed in the primary outcome measure. It is likely that the primary outcome measure might not have been sensitive or valid enough to gauge changes in ADHD symptoms. Therefore, it is essential to consider the possibility that statistical significance on the primary outcome measure may not equate to clinical significance.

This is a common consideration in various neurological and neuropsychological disorders. In essence, the divergence between the NFB and control conditions may have held clinical significance even if statistical significance was not achieved in the criterion measure. This underscores the need for a more thorough and inclusive interpretation of results, a recognition that clinical significance holds distinct value from statistical significance in related neurophysiological data. In addition, it indicates that the principal investigators had a less than adequate understanding of how NFB interacts with the use of medications.

Error 14: Including Dual-Diagnosis Participants Confounded the Results. Dual-diagnosis participants have complex clinical profiles. By definition, this unnecessarily introduced confounding variables that affected the accuracy and generalizability of the study's findings. Writing in the Journal of the American Medical Association, Plana-Ripoll et al. (2019) noted that the presence of comorbid disorders alongside ADHD considerably complicates treatment outcomes. The inclusion criteria stipulated the requirement for ADHD to be present, but neither the inclusion nor exclusion criteria specified that ADHD must be the participant's primary disorder. This study allowed participants with primary diagnoses other than ADHD to enroll, as long as they met the criteria for ADHD. Dual-diagnosis individuals often require specialized and integrated treatments to address their issues comprehensively. Had the authors avoided this complexity and minimized confounding influences, the study would have offered a clearer evaluation of the specific impact of NFB on ADHD symptoms and been more generalizable to this group. There exists no sound justification for including participants whose primary concern was not ADHD in a study with this level of funding and support.

Error 15: Failing to Control for Medication Severely Confounds the Results. It is inexplicable and unjustifiable to fail to either control the use of ADHD medication or exclude those who are medicated. The fact that medications chemically produce the same results as the treatment being evaluated should have been enough to convince investigators to exclude medicated participants. In addition, medications are known to alter the EEG, a key measure that was used to evaluate the efficacy of NFB in this study. The degree to which medications impact a particular individual's ability to focus attention varies idiosyncratically depending on multiple factors that make it extremely difficult to control. It is difficult, if not impossible, to accurately apportion changes in these primary measures to the medication or the NFB. Random assignment cannot account for the wide diversity of effects seen with the use of medication as illustrated in this partial list of medication-related issues:

a) Although there are only two major groups of ADHD medications, the stimulants and nonstimulants, within these groups are many medications, all of which have unique EEG profiles, dosing instructions, and duration of effects.
b) There is no dosing formula that can be tracked, such as milligrams per pound of body weight as the dose a child is prescribed varies not only with body mass but also the severity of the disorder.
c) A feature of ADHD is being forgetful making inconsistent medication use difficult to track.
d) Medication has a wide variety of idiosyncratic expressions and side effects as the blood level of the medication increases, peaks, and is removed from the body through metabolism.
e) Likewise, there is a wide variety of distinctive social and emotional differences when blood levels are either increasing or decreasing from medication use.
f) Although the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; DSM-5; American Psychiatric Association [APA], 2013)] no longer differentiates between ADD and ADHD, the presence or absence of hyperactivity impacts medications that are prescribed and how NFB sessions are conducted.
g) Research shows that when a child is treated with NFB, the need for medication decreases or is eliminated. As the course of NFB progresses, to minimize the possibility that the child experiences medication overdose symptoms, typically a child undergoing NFB is periodically reevaluated by the prescribing physician who will adjust the medication appropriately. This becomes an ethical issue that must be properly addressed in a study utilizing NFB if medication use is not eliminated or controlled.

NFB teaches the participant to self-regulate their attention; therefore, the presence of medication impacts the child's capacity to glean meaningful learning from their interaction with the NFB instrument. Clinically, we see that if a child remains on stimulant medication during NFB, they typically require extending the overall number of sessions

before positive effects are observed. In some cases, stimulant usage can make it impossible for the child to show any improvement. Had the participants not been medicated, the study would have been better focused and yielded a more valid and reliable evaluation of the impact of NFB on the targeted population. Given the substantial prevalence of ADHD, we must conclude that there exists no sound justification for including medicated ADHD participants in a study with this level of funding and support.

> **Note**. While it may be argued that the RCT design accounts for issues such as co-occurring conditions and medications because the effects are randomly distributed and, theoretically, they statistically cancel out over a series of imaginary experiments. However, given the *extremely* wide diversity in how these confounds manifest, the decision not to exclude these individuals means any causality attributed to the treatment could come from imbalances in these confounding issues.

Error 16: Treatment Fidelity Was Inadequate and Unfeasible. The absence of an on-site expert during the sessions who was proficient in all aspects of proper NFB treatment application posed a significant concern in the reliability of each session. The study's method section stated:

> All trainers/technicians received initial reliability training and weekly phone consultations from Dr. Vincent Monastra, who reviewed 287 randomly selected videotapes of treatment sessions and visited each site yearly to observe treatment in person.

The acquisition of skills necessary to promptly address the challenges that invariably arise during NFB demands a substantial investment of time. It is imperative to address problems as they emerge during sessions, rather than addressing them in annual visits by an expert or a weekly phone conversation. If supervision were conducted in such a manner in a clinical setting, it would be considered substantially below the standard of care, inadequate, and negligent. Conversations with the authors revealed a consensus on the gravity of this oversight. Having an expert on site who possesses comprehensive proficiency in all facets of the treatment help to ensure that sessions are conducted with optimal consistency, quality, and effectiveness. Disregarding this crucial "best-practice" guideline represents a notable shortcoming that undoubtedly had a detrimental impact on the validity and reliability of the study's published results.

Error 17: Creating a Valid "Sham" Condition for NFB Has Never Been Demonstrated. Since each time a researcher claims to have created a valid sham, their study concludes that NFB is no more effective than a placebo, it is reasonable to question the neutrality of the ostensible sham condition itself rather than questioning the efficacy of NFB. Researchers have speculated the degree to which NFB's effectiveness is rooted exclusively in the operant conditioning model. Some experts suggest NFB may be more aligned with skill acquisition. This alternate perspective could potentially clarify the elusive search for robust neuromarkers that correlate with positive responses to NFB. Considering the evolution of the human brain, it is evident that natural selection has molded our brain's development to be highly attuned to both conscious and subconscious signals within our environment. As the brain functions as the central control center for an intricate and interconnected system, it is exceedingly unlikely that a sham condition could ever be devised in which physiological input occurs without influencing the distributed attention neural network. Given the challenges in developing a valid placebo equivalent akin to the placebo used in drug studies, a better alternative would be to utilize research designs that do not require this condition (West, 2008). If the authors had a better understanding of the shortcomings of the sham control paradigm in assessing NFB, they might have considered employing more innovative and suitable research designs to more accurately assess the efficacy of NFB.

Error 18: The RCT Study Design Is Not <u>Feasible</u> to Evaluate Neurofeedback Efficacy. The choice by Arnold et al. (2021) to employ the research design known as the double-blind placebo-controlled RCT to evaluate the efficacy of NFB was inappropriate. Despite RCT's "gold standard" reputation, experts state the special status for RCTs is unwarranted and depends on many factors. As Páez et al. (2022) and Shean (2014) have discussed, there are many common and effective treatments, including NFB, that cannot be properly evaluated using the RCT. Surgery, physical therapy, psychotherapy, evaluating diet/exercise programs, novel therapies, or treatments for rare conditions are a few interventions where the RCT research design would be inappropriate to demonstrate efficacy. The imposition of this requirement and its acceptance by the neurofeedback field has been somewhat successful at dismissing the significance of the myriad of past studies that consistently demonstrated the efficacy of NFB. Those studies employed experimental designs such as controlled

trials, ABA design, cross-sectional and longitudinal research, case and observational studies, and meta-analyses. These designs are scientifically valid and, in the opinion of many scholars, are more appropriate research designs to demonstrate the efficacy of NFB. Deaton and Cartwright (2018) explained how the role of RCTs in scientific investigation has been exaggerated. They also point out that RCT's reputation as the gold standard for uncovering truth may even be harmful when, for example, it undermines the obligation of scientific investigation to reconcile RCT's results with other evidence in a process of cumulative understanding. In summary, here are a few selected explanations cited by experts explaining why the RCT design is inappropriate for NFB research:

a) Complexity and individualization make creating a standardized placebo condition that adequately mimics active NFB intervention difficult. NFB is highly individualized and tailored. Therefore, treatment-specific protocols are based on the patient's unique expression of a disorder and their desired goals.
b) Blinding Difficulties – As Lang and Stroup (2020) have pointed out, true blinding is so unhelpful and misleading that researchers should stop using it. In the context of this study, one cannot create a placebo condition that effectively masks the real-time feedback or mimics the changes in brainwave activity associated with the active treatment.
c) Lack of Suitable Sham Control – Finding an analogous placebo or sham control for NFB that convincingly replicates the experience of receiving real-time brainwave feedback is very difficult and simply providing random or irrelevant feedback does not effectively mimic the active NFB intervention.
d) Placebo-controlled studies raise ethical concerns – If NFB is an established and potentially beneficial treatment for several conditions. Therefore, many ethicists contend that withholding the active treatment from participants in the placebo group is not ethically justifiable.
e) RCTs are expensive, time-consuming, and require at least 100 or more, preferably 300 participants.
f) Given this study's target population were children and adolescents with ADHD who often have at least one ADHD parent, the probability of compliance with all requirements of the RCT for the duration of time required is, by definition, extremely low.

Of particular note, the technician's responsibility encompasses real-time observation of both the participant and their raw EEG displayed on their monitor. Achieving true blinding is impossible since the technician can seamlessly correlate the participant's movements with their real-time physiological data (EEG) being displayed on the technician monitor. This is an intrinsic limitation compromising every NFB study that purports to employ a double-blind design, including this study. Mandating this condition creates a conundrum for the technician; that is, the integrity of the double-blind design is inevitably compromised when the technician is adequately fulfilling their role. The investigators of this study should have been aware of this problem and chosen a more appropriate research design that acknowledges the unique challenges of NFB while maintaining scientific rigor.

Error 19: The Double-Blind Study Design Is Not Necessary to Evaluate Neurofeedback Efficacy. To conduct an objective study on the application of NFB to treat ADHD, the most meaningful metric to investigate is the degree to which the treatment impacts ADHD symptoms and the durability of the effects. It is worth noting that drug studies, in their evaluations of efficacy, typically do not rely on an array of physiological measures nor are they required to identify the underlying mechanism of action. Instead, they employ relatively straightforward symptom checklists or simple computerized test to assess attentional factors. Since a significant reduction in the disruptive symptoms of ADHD suffices for determining the effectiveness of medications, the same criterion should apply to assessing the efficacy of NFB. Regrettably, in this study, there was insufficient emphasis placed on validated ADHD symptom reduction metrics.

Part V. The Authors and Journal Editor Colluded to Modify the Data

In a stunning and troubling disclosure, an author divulged to two members of the ad hoc committee that, as the manuscript was being reviewed, editors from the JAACAP contacted the authors to communicate their willingness to publish the manuscript on the condition that the conclusion stated that neurofeedback was no more effective than the placebo. This revelation raised serious concerns about the study's credibility and the integrity of the journal publication process. It also highlighted the extent to which some medical journals go to protect their interests and the existing status quo. The pressure exerted by the journal on the authors meets the definition of coercion and was

the immediate catalyst for the manipulation of data and the presentation of an invalid and deceptive conclusion. However, this behavior by the JAACAP and the willingness of the authors to change their original results illustrates larger contextual factors that have historically targeted nondrug treatments that threaten the financial interests of the pharmaceutical industry and medication prescribers.

Part VI. Conflicts of Interest Compromise Research Integrity

The expectation that an individual will act in ways that benefit their self-interest aligns with disclosures exposing financial ties between vocal critics of NFB and the pharmaceutical industry. Given that these critics influence patient treatments and research funding decisions, the field of neurofeedback faces persistent criticism that precludes fair competition in the healthcare marketplace. Ethical guidelines prioritize treatments that are most effective, least toxic, and have the fewest side effects. If gatekeepers and key decision-makers were to acknowledge the safety and efficacy of NFB, it would likely become the primary treatment for ADHD, replacing drugs as the first-line option. In such a scenario, drug therapy would be reserved for those who either prefer taking medications or fail a trial of NFB.

Given that the authors were apprised of the issues discussed above and to date have taken no action to retract or publicly correct these issues, we are left to speculate and offer opinions as to why the study so egregiously departed from ethical research standards and delivered to the public a contrived and deceptive conclusion. There are three possible explanations for this: incompetence, negligence, or the deliberate intent to deceive. The NIMH carefully screens potential investigators to ensure competency and approves grants to those professionals who possess the highest academic credentials and have demonstrated a history of cautiously overseeing large research projects. Given this rigorous screening procedure, it is unlikely the key investigators of the study were incompetent or negligent. Combining competence with the collusion described above, there is only one rational explanation for this deception—the authors knew exactly what they were doing and made the conscious decision to compromise their ethical responsibility.

The problematic issues identified in this critique could have been avoided were it not for bias, conflicts of interest, and a willingness to pervert the scientific method. Over 10 years before the publication of this study, our office and several other NFB experts were recruited to advise Dr. Arnold on relevant issues regarding the study's design and methods. At that time, the limitations of the RCT research design and the problems associated with developing a blinded placebo-sham condition were discussed. In addition, it was suggested that Dr. Arnold speak with a spectrum of NFB providers and incorporate best practice recommendations derived from their clinical experience into the methods used. Best practice guidelines reflect the most current practices NFB providers have found to help ensure positive treatment outcomes.

In addition, there was a team of coauthors identified as collaborators in the study some of whom were themselves experts in NFB, having many decades of experience. The authors we interviewed stated that each collaborator was assigned responsibility for a specific aspect of the study however there was little opportunity to offer input or suggestions to Dr. Arnold once the methods were determined and the study commenced. Lastly, if there were any gaps in knowledge or competence, Dr. Arnold had access to funds from a $2 million grant to hire experts or consultants as necessary. Had the principal investigator been willing to draw from the wealth of knowledge and resources at his disposal, this research could have met the highest standards of research, garnered widespread respect, and been considered a landmark study. Sadly, the compelling body of evidence outlined in this critique strongly indicates that this study should be retracted and its conclusion ignored.

In his role as the principal investigator, Dr. Arnold was responsible for ensuring the integrity of this research project. Given the breadth of his experience and the availability of NFB experts, he must have been cognizant of the issues negatively impacting the validity and reliability of the study as it unfolded. Considering that many of these issues were brought to his attention long before initiating participant enrollment, and again after the study was published, his decision to do nothing speaks volumes in terms of his commitment to the integrity of the project and to science, in general. This study serves as a reminder of the multifaceted dynamics that can impact scientific research, ranging from biases in authors and journal editors to powerful background forces that offer scientists benefits that would not otherwise be available to them. The benefits flow when researchers align their conclusions with corporate interests. The author's collusion with the publishing journal resulted in a predetermined, although nonscientific, outcome that

frustrates, in particular, the public's ability to discern the best treatment for loved ones with ADHD and harms those who would otherwise have benefited from honest, unbiased research.

To illustrate the duplicity in medication research for ADHD, consider the fact that Dr. Arnold was the principal investigator in an earlier and much larger $17.7 million NIMH-funded study conducted at the University of Buffalo titled Multimodal Treatment of Attention Deficit Hyperactivity Disorder (MTA, 1999). This study compared stimulant medication to behavioral interventions. One conclusion from this study demonstrated that medications had an initial positive effect on ADHD that diminished after 1–2 years. Once the effects of medication lessened, the data indicated behavior therapy became more effective than medications to manage ADHD symptoms. This breakdown in the widely believed fiction that stimulant medications are the only legitimate treatment of ADHD had to be explained and the 3-year follow-up to this study did just that (Jensen et al., 2007). Whereas one might think the diminished response to medication might be due to increased tolerance or adverse drug reactions, which occurs with other drugs. However, the follow-up study blamed the less-than-optimal effects of the medication on poor adherence and persistence of the participants taking the medication. This later study stated, "Precise knowledge of the actual extent of adherence and persistence as well as an understanding of what factors predict treatment adherence has remained somewhat elusive" (Jensen et al., 2007). This suggests that if the participants had simply continued to take the stimulant medication, the results would have shown the superiority of medications. Apparently, to understand any of the reasons why children and adolescents often stop taking stimulants proves to be too "elusive" for the researchers to consider.

The degree to which the MTA study influenced Dr. Arnold's decisions concerning the present study would be pure speculation. However, we know that the prestige and academic acclaim resulting from being a principal investigator overseeing the present study that uses the gold standard of research designs and being funded by the NIMH, coupled with the veneer of legitimacy provided by publication in the flagship journal of psychiatry, the American Academy of Child and Adolescent Psychiatry, was sufficient to convince Dr. Arnold to alter his findings such that they "coincidentally" and unethically aligned with the goals of the pharmaceutical industry and the prescribing community.

Part VII. Uncovering Conflicts of Interest

The very nature of the scientific method separates fact from fiction in order to discern truth. Since research will positively impact some interests and negatively impact others, considering which groups benefit and which are hurt is a reasonable way to assess the degree to which biases and conflicts of interest influence an investigator's conclusions. If NFB efficacy is acknowledged as a treatment for ADHD, the field of psychiatry and the pharmaceutical industry have the most to lose. Although the actual percentage of income child and adolescent psychiatrists derive from diagnosing and treating ADHD varies depending on the focus of individual practices, given the growing numbers of children who are being prescribed an ever-widening formulary of powerful psychotropic drugs to treat ADHD (Watson et al., 2014), it is fair to say that a significant portion of their income is derived from prescribing drugs to treat ADHD. Experts are legitimately concerned that, according to the Centers for Disease Control and Prevention, 1 in 6 children aged 2–8 years have been prescribed at least one medication to treat a behavioral or mental health condition. DEA data shows that in 1 year (2020–2021), the amount of prescription amphetamines, such as Adderall, that were sold in the U.S. jumped by 1.5 tons. More than 41 million prescriptions for amphetamines were filled in 2020—an almost 16% increase over 2019. Alan Schwarz's book, *ADHD Nation: Children, Doctors, Big Pharma, and the Making of an American Epidemic* (2017) paints many industry-funded ADHD "opinion leaders" in an unflattering light and sees their influence as malicious:

> Psychiatry journals teemed with more than a thousand studies on ADHD conducted by pharma-sponsored scientists. The Food and Drug Administration relied upon them when green-lighting medications as safe and effective. Their findings served as the backbone for the lectures that drug companies' key opinion leaders delivered on world tours. The whirlwind created a self-affirming circle of science, one that quashed all dissent.

"The direct-to-consumer model, supported by the pharmaceutical industry, is an inappropriate, potentially dangerous model," warned Crowley et al. (2021), who authored a 2021 research paper that examined the role of profit in the U.S. healthcare system. In a fact-checked, well-referenced, and widely cited article titled, *Big Pharma's Role in Clinical Trials*, Michelle Llamas (2021) discussed a review conducted by the Washington Post of 73 studies of new drugs that were published in The

New England Journal of Medicine. Of those 73 studies, a pharmaceutical company funded 60 of them, 50 had drug-company employees among the authors, and 37 lead researchers had accepted money from a drug company. Given these recent trends, the public should be extremely cautious when considering research that evaluates new or novel treatments, especially nondrug treatments, when the research is conducted by investigators who benefit directly or indirectly from their association with the pharmaceutical industry.

Disclosures for all authors may be found here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7904968/

The principal investigator for this study, L. Eugene Arnold, MD, stated he is a child and adolescent psychiatrist. According to the disclosure cited above, Dr. Arnold has received research funding from Shire, Supernus, Otsuka, Roche/Genentech, and Young Living, has consulted with Children and Adults with Attention-Deficit/Hyperactivity Disorder (CHADD), Pfizer, and Waypoint, and has been on advisory boards for Ironshore, Novartis, Otsuka, Pfizer, Roche, and Shire (a Takeda company). In addition, Dr. Arnold has received research funding from five pharmaceutical companies, consulted with groups that have historically been extremely critical of NFB and served on the advisory boards for six pharmaceutical companies.

Jureidini and McHenry (2011) disclosed the fact that the Journal of the American Academy of Child and Adolescent Psychiatry has a history of having been criticized for failing to uphold the scientific standards of clinical research by not retracting fraudulent research. Additionally, they indicated that the JAACAP downplayed a trial's negative results in a study sponsored by, and ghostwritten on behalf of, SmithKline Beecham (now GlaxoSmithKline). JAACAP editors declined to retract the article, arguing that the negative results are available in the article, and therefore there were insufficient grounds for retraction. This claim is disputed on the basis that primary and secondary outcomes for efficacy were manipulated and safety results were obscured or omitted.

H. Edmund Pigott (2010, 2011, 2015) spent over a decade documenting a parallel scandal that occurred in a series of NIMH-funded studies published in the *American Journal of Psychiatry*, the *Journal of Clinical Psychopharmacology,* and *Psychological Medicine,* known as the STAR*D study that cost taxpayers $35 million. Pigott presented irrefutable evidence that these industry-supported studies failed to provide an accurate assessment of psychiatric drugs purported to treat depression. Similar to Arnold et al. (2021) the research design used in their clinical trials was biased. Authoring articles in several journals, Pigott exposed how STAR*D investigators manipulated data, minimized adverse events, and failed to report negative effects. The conclusion the STAR*D authors deceptively reported was a cumulative remission rate of depression was 67% when, if the study protocol had been correctly followed, would have only been 35%. Rather than adhere to ethical guidelines and retract the study, the journal editors doubled down on their fraud falsely accusing Pigott and colleagues of being methodologically flawed and having created the problems they documented (https://www.madinamerica.com/2023/12/stard-authors-double-down-fraud/).

There is enough direct and circumstantial evidence to reasonably conclude that there are no ethical barriers and no limit to the number of human lives the pharmaceutical industry is willing to sacrifice to increase the sale of drugs. In addition, there appears to be no shortage of “researchers” who benefit from the sale of drugs and are willing to abandon their oath to “first, do no harm” to advance the sale of drugs. Publishing studies that deceive the public, helps to ensure that the supremacy of drug therapy remains unchallenged. History shows that those who attempt to demonstrate efficacy for nondrug treatments will be rebuffed, disregarded, and forced to confront numerous artificial barriers.

Part VIII. The Impact of This Study

This study’s conclusion has been publicly distributed, widely repeated, and weaponized in statements and articles written usually by psychiatrists or others who benefit from the sale of drugs to treat ADHD. The detrimental effects on the public perception of NFB and the reputation of researchers and providers in the neurofeedback field have been profound. Health insurance companies rely on published research, such as this study, to make coverage decisions. Currently, this study is perceived as authoritative; therefore, the conclusion is cited by adjusters to deny coverage or reimbursement for NFB services. We have spoken with prospective and current neurofeedback providers who have reevaluated their decision to enter or continue in this field. It is possible that, if this study is not retracted, the Current Procedural Terminology (CPT) committee could cite this study to withdraw treatment codes effectively disallowing

providers to receive insurance reimbursement for offering NFB services.

Carlat Publishing claims to be a respected distributor of unbiased psychiatric education. They issued a report on April 1, 2023, stating that, based on the Arnold et al. (2021) study, they do not "recommend referring patients to this expensive treatment until studies show clearer benefit." (https://www.thecarlatreport.com/articles/4357-testing-neurofeedback-for-adhd). A scathing editorial in the American Journal of Psychiatry also referenced Arnold et al. (2021). The author James McGough (2022), a psychiatrist, "coincidentally" served on the Board for Sunovion Pharmaceuticals and was a consultant for Eli Lilly, Takeda, and Tris Pharma. With little understanding of the issues involved in studying NFB, he sarcastically titled his editorial, *Neurofeedback for ADHD: Time to Call It Quits?* As he could not reasonably critique the early NFB studies, McGough glosses over them. Ironically, all the issues he identifies as problematic in more recent NFB research applies to Arnold et al. (2021), including poorly described outcome measures, the use of too few metrics measuring improvement, positive outcomes being attributed to nonspecific effects, and, to no one's surprise, the studies failed to find statistically significant benefits comparing NFB treatment groups to sham-control groups. Naively unaware of his hubris and hypocrisy, McGough writes, "In evaluating these studies, one should be aware of methodological concerns as well as the possibility of financial conflicts of interest."

Arnold et al. (2021) published a flawed conclusion that has had detrimental effects on the parents of minors with ADHD who no longer have valid and reliable information upon which to make an informed decision regarding treatments. Those damaged the most by this study are the children and adolescents who would likely have received lifelong benefits from NFB had the study been conducted properly and its conclusion been ethically sound. If this study is allowed to go unchallenged and is not retracted, money from a variety of entrenched interests will likely continue to undermine NFB along with other treatments that are perceived to negatively impact drug manufacturers due to these interests profiting from treating illness, not curing or preventing illness. If nothing is done to force the retraction of this study, NFB may cease to exist as a treatment option. The choice to do something to support the retraction of this abysmal study or to remain silent about it being published as legitimate research is not social or academic, it is a moral choice.

Part IX. Ethical Considerations

The mission statement for the NIMH calls for the "urgent study and integration of novel brain-based innovative therapies that integrate advances in technology." A major issue impeding the realization of this statement is exemplified in the study criticized here. Those invested in the pharmacological "status quo" are powerfully entrenched and resist the advancement of all technologically-based neuromodulatory interventions such as NFB. Even in the face of overwhelming evidence that NFB is helpful in the treatment of a wide variety of disorders, produces far fewer side effects than medications, has durable results, and is less costly over the long term than drug therapy, recent studies led by medical doctors, including the present study, continue to disparage NFB.

Current ethical guidelines require researchers to disclose all conflicts of interest. However, this guideline does not reveal the most relevant ethical issue—to what extent did the author's conflict of interest impact their research. We are left to surmise this by examining patterns of behavior among researchers or groups they affiliate, or by scrutinizing the implications of their research conclusions; that is, who benefits from their research. Because of this limitation, ethicists have recommended that future guidelines direct researchers to abstain from research projects if there is even the possibility that their conflict could skew the results. At the very least, those having any conflict of interest should never be principal investigators. Forward-thinking ethics such as this are discussed on the Integrity website at https://h2020integrity.eu/integrity/. Considering the issues revealed in this critique, it should be obvious that no one with a direct or indirect association with the pharmaceutical industry can be trusted to fairly evaluate any nondrug treatment.

We would be remiss to overlook the harm done to society when pseudoscientists allow personal biases and conflicts of interest to direct their work. According to a recent survey conducted by Pew Research Center (2022), the percentage of adults in the U.S. who say they have a great deal of confidence in medical scientists to act in the best interests of the public dropped from 40% to 29% *in only the past year*. Almost daily, the news reminds us of unprecedented challenges that, if not dealt with quickly and comprehensively, could end the existence of our species. There is a direct relationship between the degree to which researchers adhere to sound scientific principles and the public's capacity to invest their trust in research

conclusions. Studies that manipulate data to draw false conclusions not only fail to add anything of value to our knowledge base but, more significantly, they erode the public's trust in the scientific method—unarguably humanity's most reliable tool to forge a positive and healthy future.

Part X. Summary

To conform with research ethics, the authors of Arnold et al. (2021) and the editors of JAACAP are urged, once again, to consider the issues in this critique and take responsibility to explain how these errors occurred and retract the study. We fully expect the editors of JAACAP to be argumentative and hostile to any call for retraction and try to blame anyone but themselves for this travesty. Perhaps the main author, Dr. Arnold will decide to issue the call to retract. If not, the team of coauthors, designated the Neurofeedback Collaborative Group, should be aware that each author shares joint responsibility for the study's lack of integrity. At the point an author becomes aware of the issues delineated in this critique, they are ethically required to initiate a formal retraction request to the Editor-In-Chief of JAACAP, even if they were not directly responsible for the errors. Although authorship of a retracted study may have negative implications, given the degree this study departed from ethical guidelines, the failure to call for retraction will likely be viewed by colleagues as being on the wrong side of this issue.

For years, detractors of NFB have shown themselves to be puppets of the pharmaceutical industry by demanding that NFB must, once again, prove it is an effective treatment. However, these detractors insist that the only path for NFB to be considered evidence-based is by employing the RCT research design—which is as inappropriate as it is impossible. The best research design to test a hypothesis depends on what is being measured and what the measure is to be used for. Any presumption that the RCT is the best method to test the efficacy of NFB requires an argument strong enough to lead to a consensus among researchers. Not only is there no such consensus, but experts in NFB have repeatedly stated viable reasons the RCT design is inappropriate. The insistence that NFB be held to a standard that cannot possibly be met is a no-win situation for this treatment. This study and its publication in JAACAP play a major role in supporting the false narrative that detractors continue to repeat; that is, "Studies show NFB is not an effective treatment." Although the information in this critique challenges the validity and reliability of the study, until the authors publicly demand the study be retracted, it will be considered as authoritative and assumed by most people to be legitimate research. By citing the inaccurate and deceptive conclusion in the study, detractors can falsely claim to have evidence that NFB fails to meet efficacy standards. The deceptive conclusion in the Arnold et al. (2021) study confuses the public and impedes NFB from fairly competing in the healthcare marketplace. As long as detractors of NFB are successful, other novel nondrug treatments will likely find the path to efficacy blocked, leaving drug therapy as the treatment of choice for most problems—which conveniently allows those in power to retain their exalted status and the pharmaceutical industry to continue receiving record profits.

It is unfortunate to have to remind scientists and healthcare providers that it is incumbent upon them to be honest and ethical. The main feelings expressed by the authors we interviewed as well as many NFB providers regarding this study were confusion and profound sadness. Particularly clinicians were confused because the study's conclusion stands in stark contrast to their experience of providing life-changing positive benefits every day to their patients. Many expressed sadness at having wasted precious resources on a meaningless study that does nothing except further erode public confidence in therapeutic research. This study should dispel any illusion that the experts and doctors we consult will provide us with unbiased recommendations since their recommendations are often based on biased studies. The public has a right to be informed regarding the degree to which biases or conflicts of interest skewed data and compromised the validity and reliability of any study they rely on to make treatment decisions. Concerning Arnold et al. (2021), our tax dollars paid "scientists" who had an agenda—meaning they were no longer engaged in research. They were, in fact, playing an exceedingly dangerous game that ultimately deceived the public and undermined the credibility of scientific investigation. By marginalizing NFB, the profits of the financial elite are protected at the expense of the public's health and safety, not to mention robbing ADHD children and adolescents of the opportunity to receive the lifelong benefits of NFB. The only way to help ensure that the information upon which we base healthcare decisions is true and correct is to accept some measure of personal responsibility to expose unethical research and demand the authors and Journal publicly admit and correct their errors. The deceptive methods and misguided motivations that masqueraded as legitimate research in Arnold et al.

(2021) sadly mischaracterized the efficacy of NFB—this must be corrected.

Author Disclosure

The authors of this critique have no current or future relevant or material financial interest in the research described in this paper. The authors further affirm that the information expressed herein is true and correct to the best of our knowledge. The opinions expressed are those of the authors and do not necessarily reflect those of the ISNR or the journal *NeuroRegulation*. Some information cited in this paper came from confidential sources and will not be disclosed. The First Amendment encompasses the right of journalists to maintain the confidentiality of their source. In addition, the Inter-American Declaration of Principles on Freedom of Expression, Principle 8, states "every social communicator has the right to keep his/her source of information, notes, personal and professional archives confidential."

References

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). https://doi.org/10.1176/appi.books.9780890425596

Arnold, L. E., Arns, M., Barterian, J., Bergman, R., Black, S., Conners, C. K., Connor, S., Dasgupta, S., deBeus, R., Higgins, T., Hirshberg, L., Hollway, J. A., Kerson, C., Lightstone, H., Lofthouse, N., Lubar, J., McBurnett, K., Monastra, V., Buchan-Page, K., ... Williams, C. E. (2021). Double-blind placebo-controlled randomized clinical trial of neurofeedback for attention-deficit/hyperactivity disorder with 13-month follow-up. *Journal of the American Academy of Child & Adolescent Psychiatry*, *60*(7), 841–855. https://doi.org/10.1016%2Fj.jaac.2020.07.906

Bakhshayesh, A. R., Hänsch, S., Wyschkon, A., Rezai, M. J., & Esser, G. (2011). Neurofeedback in ADHD: A single-blind randomized controlled trial. *European Child & Adolescent Psychiatry*, *20*, 481–491. https://doi.org/10.1007/s00787-011-0208-y

Barth, B., Mayer, K., Strehl, U., Fallgatter, A. J., & Ehlis, A.-C. (2017). EMG biofeedback training in adult attention-deficit/hyperactivity disorder: An active (control) training? *Behavioural Brain Research*, *329*, 58–66. https://doi.org/10.1016/j.bbr.2017.04.021

Crowley, R., Atiq, O., Hilden, D., & Health and Public Policy Committee of the American College of Physicians (2021). Financial profit in medicine: A position paper from the American college of physicians. *Annals of Internal Medicine, 174*(10), 1447–1449. https://doi.org/10.7326/M21-1178

Deaton, A., & Cartwright, N. (2018). Understanding and misunderstanding randomized controlled trials. *Social Science & Medicine, 210*, 2–21. https://doi.org/10.1016/j.socscimed.2017.12.005

Gevensleben, H., Holl, B., Albrecht, B., Schlamp, D., Kratz, O., Studer, P., Wangler, S., Rothenberger, A., Moll, G. H., & Heinrich, H. (2009). Distinct EEG effects related to neurofeedback training in children with ADHD: A randomized controlled trial. *International Journal of Psychophysiology*, *74*(2), 149–157. https://doi.org/10.1016/j.ijpsycho.2009.08.005

Head, M. L., Holman, L., Lanfear, R., Kahn, A. T., & Jennions, M. D. (2015). The extent and consequences of p-hacking in science. *PLoS Biology, 13*(3), Article e1002106. https://doi.org /10.1371/journal.pbio.1002106

Idzik, M. F. (1965). *Physician ownership in pharmacies*. Notre Dame Law Review. http://scholarship.law.nd.edu/ndlr/vol41/iss1/4?utm_source=scholarship.law.nd.edu%2Fndlr%2Fvol41%2Fiss1%2F4&utm_medium=PDF&utm_campaign=PDFCoverPages

Janssen, T. W., Bink, M., Weeda, W. D., Geladé, K., van Mourik, R., Maras, A., & Oosterlaan, J. (2017). Learning curves of theta/beta neurofeedback in children with ADHD. *European Child & Adolescent Psychiatry*, *26*, 573–582. https://doi.org/10.1007/s00787-016-0920-8

Jensen, P. S., Arnold, L. E., Swanson, J. M., Vitiello, B., Abikoff, H. B., Greenhill, L. L., Hechtman, L., Hinshaw, S. P., Pelham, W. E., Wells, K. C., Conners, C. K., Elliott, G. R., Epstein, J. N., Hoza, B., March, J. S., Molina, B. S. G., Newcorn, J. H., Severe, J. B., Wigal, T., … Hur, K. (2007). 3-year follow-up of the NIMH MTA study. *Journal of the American Academy of Child & Adolescent Psychiatry, 46*(8), 989–1002. https://doi.org/10.1097/CHI.0b013e3180686d48

Jureidini, J. N., & McHenry L. B. (2011). Conflicted medical journals and the failure of trust. *Accountability in Research, 18*(1), 45–54. https://doi.org/10.1080/08989621.2011.542683

Kamiya, J. (1968). Conscious control of brain waves. *Psychology Today, 1*, 56–60. https://doi.org/10.1037/e400092009-006

Kamiya, J. (1969). Operant control of the EEG alpha rhythm and some of its reported effects on consciousness. In C. T. Tart (Ed.), *Altered states of consciousness.* Wiley.

Kamiya, J. (2011). The first communications about operant conditioning of the EEG. *Journal of Neurotherapy, 15*(1), 65–73. https://doi.org/10.1080/10874208.2011.545764

Kerr, N. L. (1998). HARKing: Hypothesizing after the results are known. *Personality and Social Psychology Review*, *2*(3), 196–217. https://doi.org/10.1207/s15327957pspr0203_4

Khazan, I., Shaffer, F., Moss, D., Lyle, R., & Rosenthal, S. (Eds.) (2023). *Evidence-Based practice in biofeedback & neurofeedback* (4th Ed). Association for Applied Psychophysiology and Biofeedback.

Lang, T. A., & Stroup, D. F. (2020). Who knew? The misleading specificity of “double-blind” and what to do about it. *Trials, 21*, Article 697. https://doi.org/10.1186/s13063-020-04607-5

Lexchin, J., Bero, L. A., Djulbegovic, B., & Clark, O. (2003). Pharmaceutical industry sponsorship and research outcome and quality: Systematic review. *BMJ, 326*(7400), 1167–1170. https://doi.org/10.1136/bmj.326.7400.1167

Llamas, M. (2021). *Big pharma’s role in clinical trials*. Drugwatch. https://www.drugwatch.com/featured/clinical-trials-and-hidden-data

Lubar, J. F., Swartwood, M. O., Swartwood, J. N., & O'Donnell, P. H. (1995). Evaluation of the effectiveness of EEG neurofeedback training for ADHD in a clinical setting as measured by changes in T.O.V.A. scores, behavioral ratings, and WISC-R performance. *Biofeedback and Self-Regulation, 20*, 83–99. https://doi.org/10.1007/BF01712768

McGough, J. J. (2022). Neurofeedback for ADHD: Time to call it quits? *The American Journal of Psychiatry*, *179*(12), 888–889. https://doi.org/10.1176/appi.ajp.20220861

Monastra, V. J., Lynn, S., Linden, M., Lubar, J. F., Gruzelier, J., & La Vaque, T. J. (2005). Electroencephalographic biofeedback in the treatment of attention-deficit/hyperactivity disorder. *Applied Psychophysiology and Biofeedback, 30*(2), 95–114. https://doi.org/10.1007/s10484-005-4305-x

MTA Cooperative Group. (1999). A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. *Arch Gen Psychiatry, 56*(12), 1073–1086. https://doi.org/10.1001/archpsyc.56.12.1073

Ogrim, G., & Hestad, K. A. (2013). Effects of neurofeedback versus stimulant medication in attention-deficit/hyperactivity disorder: A randomized pilot study. *Journal of Child and*

Adolescent Psychopharmacology, *23*(7), 448–457. https://doi.org/10.1089/cap.2012.0090

Páez, A., Rovers, M., Hutchison, K., Rogers, W., Vasey, B., & McCulloch, P. (2022). Beyond the RCT: When are randomized trials unnecessary for new therapeutic devices, and what should we do instead? *Annals of Surgery*, *275*(2), 324–331. https://doi.org/10.1097/SLA.0000000000005053

Pew Research Center. (2022). *Public confidence in scientists and medical scientists has declined over the last year*. https://www.pewresearch.org/science/2022/02/15/americans-trust-in-scientists-other-groups-declines/ps_22-02-15_trust-declines_00-01/

Pigott, H. E. (2011). STAR*D: A tale and trail of bias. *Ethical Human Psychology and Psychiatry, 13*(1), 6–28. https://doi.org/10.1891/1559-4343.13.1.6

Pigott, H. E. (2015). The STAR*D trial: It is time to reexamine the clinical beliefs that guide the treatment of major depression. *The Canadian Journal of Psychiatry, 60*(1), 9–13. https://doi.org/10.1177/070674371506000104

Pigott, H. E., Leventhal, A. M., Alter, G. S., & Boren, J. J. (2010). Efficacy and effectiveness of antidepressants: Current status of research. *Psychotherapy and Psychosomatics, 79*(5), 267–279. https://doi.org/10.1159/000318293

Plana-Ripoll, O., Pedersen, C. B., Holtz, Y., Benros, M. E., Dalsgaard, S., de Jonge, P., Fan, C. C., Degenhardt, L., Ganna, A., Greve, A. N., Gunn, J., Iburg, K. M., Kessing, L. V., Lee, B. K., Lim, C. C. W., Mors, O., Nordentoft, M., Prior, A., Roest, A. M., … McGrath, J. J. (2019). Exploring comorbidity within mental disorders among a Danish national population. *JAMA Psychiatry*, *76*(3), 259–270. https://doi.org/10.1001/jamapsychiatry.2018.3658

Schwarz, A. (2017). *ADHD nation: Children, doctors, big pharma, and the making of an American epidemic*. Scribner/Simon & Schuster.

Shean, G. (2014). Limitations of randomized control designs in psychotherapy research. *Advances in Psychiatry*, *2014*, Article 561452. https://doi.org/10.1155/2014/561452

Sterman, M. B. (2000). Basic concepts and clinical findings in the treatment of seizure disorders with EEG operant conditioning. *Clinical EEG and Neuroscience*, *31*(1), 45–55. https://doi.org/10.1177/155005940003100111

Sterman, M. B., & Friar, L. (1972). Suppression of seizures in an epileptic following sensorimotor EEG feedback training. *Electroencephalography and Clinical Neurophysiology, 33*(1), 89–95. https://doi.org/10.1016/0013-4694(72)90028-4

Sterman, M. B., MacDonald, L. R., & Stone, R. K. (1974). Biofeedback training of the sensorimotor EEG rhythm in man: Effects on epilepsy. *Epilepsia 15*(3), 395–416. https://doi.org/10.1111/j.1528-1157.1974.tb04016.x

Sterman, M. B., Wyrwicka, W., & Roth, S. R. (1969). Electrophysiological correlates and neural substrates of alimentary behavior in the cat. *Annals of the New York Academy of Sciences, 157*(2), 723–739. https://doi.org/10.1111/j.1749-6632.1969.tb12916.x

Trullinger, M., Novian, A., Russell-Chapin, L., & Pradhan, D. (2019). Perspectives on type III statistical errors: Exaggerating the effects of placebo in neurofeedback. *NeuroRegulation*, *6*(1), 38–38. https://doi.org/10.15540/nr.6.1.38

Watson, G. L., Arcona, A. P., Antonuccio, D. O., & Healy, D. (2014). Shooting the messenger: The case of ADHD. *Journal of Contemporary Psychotherapy, 44*(1), 43–52. https://doi.org/10.1007/s10879-013-9244-x

West, S. G., Duan, N., Pequegnat, W., Gaist, P., Des Jarlais, D. C., Holtgrave, D., Szapocznik, J., Fishbein, M., Rapkin, B., Clatts, M., & Mullen, M. (2008). Alternatives to the randomized controlled trial. *American Journal of Public Health, 98*(8), 1359–1366. https://doi.org/10.2105/AJPH.2007.124446

Zuberer, A., Brandeis, D., & Drechsler, R. (2015). Are treatment effects of neurofeedback training in children with ADHD related to the successful regulation of brain activity? A review on the learning of regulation of brain activity and a contribution to the discussion on specificity. *Frontiers in Human Neuroscience, 9*, Article 135. https://doi.org/10.3389/fnhum.2015.00135

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