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Automated Detection of Cognitive Performance and Resilience Changes in Former Professional American Football Players Following the Administration of a Hemp Extract

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Abstract

Introduction. In high-contact sport athletes, repetitive head trauma might be linked to permanent brain damage. In particular, findings in professional American football players indicate that brain injury is often associated with long-term cognitive slowing. In this context, hemp extracts might have beneficial effects.

Methods. Forty-two former professional American football players were recruited (age = 49.6 ± 9.8 years). Before or immediately after the oral administration of a THC-free hemp extract, the following measures were acquired: 1) the median theta/beta ratio and posterior peak alpha frequency (PAF) during resting state; 2) P200 and P300b latencies as well as reaction times (RT) during performance of a Go/NoGo task.

Results. After treatment, a smaller median theta/beta ratio ($p < .01$) was detected. An onset latency reduction was also found for the P200 ($p < .01$) and P300b ($p < .05$) measures, which was accompanied by smaller RT variances ($p < .05$). Finally, a positive correlation between RT measures and P300b latencies was found only after treatment.

Conclusion. The administration of THC-free hemp extracts in former professional high-impact athletes might have beneficial effects on both cognitive performance and emotion regulation. Also, recent technological advances in EEG detection and analysis could play an important role in the management of patients with sport-related brain injuries.

Keywords: sports concussion; American football; EEG; ERP; CBD; CBG

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Introduction

Neurobiological Abnormalities in Former Professional American Football Players

In recent years, studies with contact sport athletes (including American football, ice hockey, soccer, baseball, rugby, boxing, and wrestling) have provided support for early findings indicating a link between repetitive head trauma and the risk for permanent brain damage (Changa et al., 2018; Ling et al., 2015; McKee et al., 2018). Emerging evidence suggests that retired professional players of American football often exhibit mild cognitive impairment (Guskiewicz et al., 2005; Randolph et al., 2013), neuroimaging abnormalities (Hart et al., 2013; Strain et al., 2013) and reduced neuronal

energy metabolism (Alosco, Tripodis, Rowland, et al., 2020), disproportionately to their age. Key insights are also offered by studies with this population suggesting Alzheimer's-like changes in the brain, such as increased microglial activation associated with higher t-tau concentrations in the cerebral spinal fluid (Alosco, Tripodis, Fritts, et al., 2018). Postmortem studies have also shown perivascular deposition of abnormal phosphorylated tau (p-tau) in neurons and astroglia at the base of cortical sulci (Manley et al., 2017).

Neuroprotective Properties of Endocannabinoids

In recent years, astrocytes have gained considerable interest as a potential target for pharmacological interventions and, while more research is needed to understand how their activity can be differentially manipulated (Ridet et al., 1997), a number of candidate molecules and systems have been proposed as targets for astrocyte-mediated neuroregulation or neuroprotection. Accumulating evidence indicates that cannabinoids, including phytocannabinoids (naturally found in plants of the genus *Cannabaceae*), endocannabinoids, and also synthetic ligands can modulate gliosis reactivity and exert neuromodulatory, anti-inflammatory, and neuroprotective effects in the brain (Navarrete et al., 2014; Stella, 2010; Vázquez et al., 2015; Walter & Stella, 2004).

The endogenous cannabinoid system consists of two Gi/o-coupled cannabinoid receptors anchored in the plasma membrane (CB1 and CB2), their endogenous ligands [N-arachidonoylethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG)] and specific synthesis or degradation enzymatic complexes (Lu & Mackie, 2016). Remarkably, the CB2 receptor density detected in microglia and astrocytes has been found to be increased in neuroinflammatory conditions (Benito et al., 2005; Cassano et al., 2017), in parallel with greater levels of endocannabinoids (Panikashvili et al., 2001; Shohami et al., 2011), which might provide support for the involvement of the cannabinoid system in brain pathology or recovery.

Preparations derived from *Cannabis sativa* are a source of a wide variety of cannabinoid chemicals with differential affinities for CB1 and CB2 receptors. In particular, the psychoactive compound Δ9-tetrahydrocannabinol (THC) as well as the nonpsychoactive cannabidiol (CBD) and cannabigerol (CBG) have been receiving growing attention from the scientific community in recent years. While these preparations have shown to have neuroprotective and antineuroinflammatory effects, only THC has affinity for CB1 and CB2 receptors, although its neuroprotective effects are likely to be driven by CB1 mediated mechanisms (Gómez del Pulgar et al., 2002; Molina-Holgado et al., 2002). However, concerns have been raised about the clinical use of THC because of the deleterious effects on cognitive functions linked to the activation of CB1 receptors (Borgan et al., 2019).

While it is less clear how CBD induces its neuroprotective effects, there is common agreement that its mechanism of action does not involve the recruitment of either CB1 or CB2 receptors, and there is evidence indicating that it indirectly influences the endocannabinoid system through its affinity for transient receptor potential vanilloid-1 (TRPV1) receptors (Muller et al., 2018), which are thought to play a role in the transmission of nociceptive impulses along pain pathways (Immke & Gavva, 2006). Further, increasing preclinical evidence demonstrates that CBD provides neuroprotection against acute and chronic brain injury (Campos et al., 2016; Fernández-Ruiz et al., 2013; Hayakawa et al., 2010), most likely exerting its modulatory effects on astrocyte activity (Kozela et al., 2017).

In many ways, CBG exhibits pharmacological characteristics that fall between Δ9-THC and CBD. Like Δ9-THC, CBG activates CB1 and CB2 receptors but with much lower affinity (Cascio et al., 2010; Navarro, Varani, Lillo, et al., 2020; Navarro, Varani, Reyes-Resina, et al., 2018; Pertwee, 2008; Pollastro et al., 2011; Rosenthaler et al., 2014). On the other hand, CBD and CBG exert comparable activity at six transient receptor potential cation channels (TRPA1, TRPV1, TRPV2, TRPV3, TRPV4, and TRPM8; De Petrocellis, Ligresti, et al., 2011; De Petrocellis, Orlando, et al., 2012; Muller et al., 2018; Pollastro et al., 2011). Importantly, CBG also has high affinity for the α_2-adrenoceptor (Cascio et al., 2010), which supports its beneficial effects on cognitive functions (Arnsten, 2010) and suggests that it might as well have antihypertensive, sedative, and analgesic properties (Ernsberger et al., 1990; Gertler et al., 2001; Hunter et al., 1997).

While there is evidence that both CBG and CBD modulate 5-HT1A receptor activity, antagonistic effects have been reported for CBG, while CBD has been found to exert indirect stimulation (Cascio et al., 2010; Rock, Bolognini, et al., 2012; Rock, Goodwin, et al., 2011; Russo et al., 2005). The modulatory effects of CBD on 5-HT1A receptor activity have been suggested to stimulate neuroprotective mechanisms that prevent cellular

apoptosis, suggesting a role for this cannabinoid in the treatment of neurodegenerative diseases (Echeverry et al., 2021).

Finally, it has been proposed that *Cannabis* extracts should also include naturally occurring terpenoids to obtain optimal standardized synergistic compositions and improve clinical outcomes. Recognized as safe by the U.S. Food and Drug Administration (FDA) and other regulatory agencies, terpenoids are fragrant essential oils that bind neurotransmitter receptors, muscle and neuronal ion channels, G-protein receptors, enzymes, cell membranes, and second messenger systems (Bowles, 2003; Husnu Can Baser & Buchbauer, 2015; Russo, 2011). They display unique therapeutic effects that could meaningfully contribute to the "entourage effects" of *Cannabis*-based medicinal extracts that may enhance the effects of cannabinoids on migraine, headache, pain, inflammation, anxiety, and depression (Baron, 2018; Lorenzetti et al., 1991).

EEG Anomalies in Traumatic Brain Injury

Several studies indicate that following traumatic brain injury (TBI) patients may exhibit cognitive deficits and also a variety of psychiatric symptoms, including affective disorders, substance abuse, psychosis, and personality changes (Jorge et al., 2005; E. Kim et al., 2007; Pelegrín-Valero et al., 2001; Sachdev et al., 2001; van Reekum et al., 2000; Zeilig et al., 1996).

Over the last two decades, studies using electrophysiological methods have significantly gained further insight into the mechanisms that underpin cognitive slowing in individuals with TBI. While rapidly evolving neuroanatomical imaging techniques have improved anatomical resolution in the quantification of the tissue loss associated with TBI, recent technological advances in electroencephalogram (EEG) data acquisition and analysis have allowed researchers to investigate neural activity with gradually greater sensitivity and higher temporal resolution. This has contributed to unveil functional abnormalities and brain-behavior relationships that could not be reliably identified in this clinical population using neuroimaging methods (Levine et al., 2006). In this context, a range of resting-state EEG measures and event-related potentials (ERPs) recorded during performance of behavioral tasks offer valuable insights into cognitive processes, and numerous studies have demonstrated that they can also be used to detect neuropathology.

There is general agreement that the alpha frequency in the EEG is an indicator of cognitive and memory performance (Klimesch, 1999). However, interindividual and age-related fluctuations of spectral boundaries in this frequency band can make the interpretation of spectral analysis problematic (Klimesch, 1999). A suggested approach to more accurately define individualized alpha frequency boundaries is to compute the average frequency of the highest power between 6 and 13 Hz across all the electrodes of the EEG montage (Angelakis, Lubar, & Stathopoulou, 2004). The result is called peak alpha frequency (PAF), which has been found to be a highly heritable physiological feature (Grandy et al., 2013; Posthuma et al., 2001; Smit et al., 2006) that typically increases throughout the first 20 years of life, starts slowing from age 40 (Aurlien et al., 2004; Bazanova & Vernon, 2014; Chiang et al., 2011) and is reduced in patients with TBI (Angelakis, Lubar, Stathopoulou, & Kounios, 2004) when compared with healthy controls.

Moreover, the ratio between the average EEG magnitude in the frequency bands theta (4–8 Hz) and beta (13–25 Hz), namely the theta/beta ratio, has been proposed as a resting-state measure of attention, logical thinking, concentration, memory, and emotional regulation (Clarke et al., 2001; Markiewcz, 2017). Increased frontal midline theta power and reduction of frontal beta power have been demonstrated to correlate with executive attention impairment in TBI subjects (Shah et al., 2017), a pattern that could reflect reduced excitatory synaptic activity in the medial frontal neuronal population (McWilliams & Schmitter-Edgecombe, 2008). Importantly, a decrease of the theta/beta ratio can be associated with improvements in both cognitive performance (Marlats et al., 2019) and emotion regulation (Sari et al., 2016).

One of the most observed impairments associated with brain injury is the reduction of cognitive processing speed (Ferraro, 1996; Mathias et al., 2004; Mathias & Wheaton, 2007), which has been associated with diffuse axonal damage and altered interhemispheric functional connectivity (Felmingham et al., 2004). Patients with brain injury are over 1.5 times slower than healthy controls, as measured by reaction time (RT) in a range of cognitive tasks (Ferraro, 1996). However, since RTs are70ffectted by both perceptual and motor execution processes, more specific measures are needed to identify the origins of processing speed deficits during task performance. In this regard, ERP research has revealed important differences between TBI patients and healthy persons. Specifically, the P300 measure (a positive going

deflection appearing in the EEG 250–500 ms after the attendance of rare target stimuli; Polich, 2007) has been shown to be a highly sensitive measure of cortical synaptic transmission deficits. The P300 deflection consists of two components: 1) a P3a component appearing in the EEG 250–280 ms after stimulus presentation, thought to originate from stimulus-driven frontal attention mechanisms during task processing and 2) a P3b component, with peak latency falling in the 250–500 ms time window after stimulus presentation, originating in the temporal-parietal region and thought to be associated with attention and subsequent memory processing (Polich, 2007). Importantly, these components can show significant changes even in mild cases of TBI or even in asymptomatic patients with history of sports concussion (Baillargeon et al., 2012; Moore et al., 2017; Thériault et al., 2009). The P200 (a positive deflection in the EEG waveform that peaks between 150 and 275 ms after stimulus onset) has also been shown to offer highly valuable insights on cognitive processes. It is thought to reflect the modulation of attention by nontarget stimuli and stimulus classification (Key et al., 2005). Reduction of P200 Go/NoGo amplitude has been linked to slower RTs and reduced accuracy in stimulus classification (Hampton & Weber-Fox, 2008).

Finally, emotional responses are also altered in TBI patients (Tateno et al., 2003, 2004), which has been proposed to be linked to the reduced ability of the anterior prefrontal cortex to regulate orbitofrontal activity (Ghajar & Ivry, 2008; Rule et al., 2002). Interestingly, in Go/NoGo tasks, patients with TBI make more errors than healthy controls, and patients with faster RTs exhibit greater level of alpha power synchronization over the fronto-central midline region, suggesting prefrontal down-regulation (Garavan et al., 2002).

State-of-the-Art Technological Innovations Allow to Automatically Detect EEG Markers of Cognitive Functions and Drug Response

Since its first discovery (Collura, 1993), EEG technology has dramatically evolved, allowing for gradually more accurate and reliable measurements of electrophysiological activity in the brain, which has significantly contributed to numerous scientific breakthroughs and to the development of highly sophisticated clinical applications (Borck, 2005).

State-of-the-art EEG machines today allow not only for resting-state, region-specific spectral analysis of the EEG but also for the automatic detection of a wide range of ERPs elicited during performance in well-established behavioral tasks (Miranda et al., 2019).

Made gradually more accessible to researchers and clinicians, modern EEG detection and analysis technology offers the opportunity to carry out accurate diagnoses and also evaluate or monitor the effects of pharmacological interventions. This has opened new avenues in psychopharmacology, contributing to the development of biomarkers that can help clinicians make more informed decisions and more reliable predictions of treatment outcomes.

In this context, while preliminary research suggests that nonpsychoactive cannabinoids might induce modulatory effects on EEG power (Alvarez et al., 2008), more research is needed to establish their effects on specific EEG markers of cognitive performance.

With this in mind, the aim of the present study was twofold: 1) to investigate the effects of orally given cannabidiol (CBD) and cannabigenol (CBG) on both resting-state EEG and ERP markers of cognitive performance in former professional American football players with a history of head injury, and 2) to demonstrate the ability of the computerized electroencephalograph BrainView NeuralScan Pro to automatically detect and measure posttreatment changes in target metrics.

Materials and Methods

Participant Recruitment and Demographics

Male former professional American football players were approached for enrollment, and those who consented to participate in the study were interviewed up to a week before the experimental session would take place (also depending on the participant's availability). During the interviews, the experimenter offered information on the study, providing a short introduction on EEG, the metrics that would be computed and analyzed before and after the administration of the experimental protocol, and the nature of the supplements to be administered.

Participants were selected if they had normal or corrected-to-normal vision and no current or history of neurological or psychiatric conditions, alcohol dependence, or drug misuse. Next, all the interviewed subjects who met the inclusion criteria were asked to sign consent to participation.

The interview process culminated with the recruitment of 42 participants (age = 49.6 ± 9.8

years). Other than age, no other demographic information could be acquired, to comply with the personal conduct policy of their former professional association. All data acquisition was carried out in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki, in two different locations and times, namely the Marriott Conference Center in Allen, TX (777 Waters Creek Blvd) between January 17–19, 2020, and the Hyatt Regency Hotel in Miami, FL (400 SE 2nd Ave) between January 27–30, 2020.

EEG Data Acquisition

Continuous EEG (0.5–40 Hz bandpass; notch filter: 60 Hz) was acquired from 19 AgAgCL scalp-electrodes during resting state or task performance using the FDA-cleared BrainView NeuralScan Pro workstation (Medeia Inc., Santa Barbara, CA; https://www.brainview.com), consisting of a 21-channel EEG cap (using distance ratios consistent with the 10–20 System) and a 21-channel EEG amplifier (input impedance > 200 MΩ; common mode rejection ratio > 110 dB at 10 Hz, kept consistent across all participants) controlled by EEG data acquisition software recording at a sampling rate of 500 Hz.

At the time of recording, the ground electrode was located at Cz and the reference electrode at Pz. All recordings took place in a quiet room while the participants were seated in comfortable chairs that provided adequate support for the neck and shoulder muscles.

Spontaneous EEG (acquired at rest for 5 min while the participants' eyes were open or closed) and ERPs elicited during performance of a visual Go/NoGo task were acquired before and immediately after the oral administration of 1 ml of the hemp extract FOCUS (Sacred Ally, Missoula, MT), containing 11.3 mg cannabidiol (CBD) and 0.6 mg cannabigerol (CBG), sonicated into 20–30 nm liposomes (batch ID: PMB-FOCUS-FIN1.024; certificate number: 011020SR001; certificate of analysis prepared by PrimeMyBody, LLC, Carrolton, TX; Table 1).

Go/NoGo Task

Participants were presented with a series of blue circles (standard stimuli) appearing on the center of a white computer monitor and were asked to press a button (Go) only when a bigger circle of the same color (deviant stimulus) was randomly shown (duration of each stimulus: 400 ms; interval between each stimulus: 3000 ms; total task duration: approximately 6 minutes). The task included 110 trials, with approximately 72 deviant stimuli (65.45% of total trials).

Table 1
The Tested Sample of FOCUS, Analyzed by Liquid Chromatography-Mass Spectrometry, LC-MS for Plant-Based Cannabinoids.

ID	Conc. (mg/ml)
D-9 THC	0.0
CBD	11.307
CBG	0.611
β-Caryophyllene	4.401
Geraniol	2.722
Limonene	4.164
Linalool	1.342
Myrcene	0.602
Humulene	0.571
Terpinolene	0.333

All collected data were compared to laboratory certified reference standards at known concentrations. Compounds present in traces (< 0.15 mg/ml) or not detected (≤ 0.001 ng/ml) are not shown on the table. Modified after the original report by PrimeMyBody (ID: PMB-FOCUS-FIN1.024; Certificate number: 011020SR001). Abbreviations: D-9 THC = tetrahydrocannabinol; CBD = cannabidiol; CBG = cannabigerol.

EEG Signal Processing

Offline, the data were filtered between 1–50 Hz with a notch filter set at 60 Hz, while no change was applied to the sampling rate (500 Hz). Next, individual EEG files were automatically edited to remove non-EEG artifacts (blinks, pulse artifact, MR gradient artifact, ballisto-cardiogram, and bad blocks) using the built-in custom scripts and functions available in Brainview NeuralScan Pro (Fast Fourier Transform, Wavelet, and Independent Component Analysis; Al-Fahoum & Al-Fraihat, 2014; Iriarte et al., 2003; Jiang et al., 2019). The cleaned-up data were then used to compute absolute power in 4 different frequency bands: delta (1–4 Hz), theta (5–7 Hz), alpha (8–14 Hz), and beta (15–30 Hz).

To extract ERPs, continuous EEG was automatically segmented by BrainView into 1200 ms epochs including activity recorded 200 ms before stimulus to 1000 ms after stimulus, and baseline corrected by subtracting the mean amplitude of the prestimulus signal. Epochs with EEG or EOG amplitudes exceeding 100 μV were removed and the average

peak latencies of target components were computed for each subject.

Resting-State EEG, ERP, and Behavioral Measures

The median of the ratio between theta and beta absolute power detected from all electrodes at rest during an eyes-open condition was automatically computed by BrainView NeuralScan Pro. The PAF during an eyes-closed condition was also obtained by automatically computing the median frequency of the highest power in the 8–14 Hz frequency range at the O1 electrode site.

During performance of the Go/NoGo task, ERP onset latencies were acquired for the measures P200 (100–175 ms) recorded at O1 (Kothari et al., 2016) and P300b (370–390 ms) recorded at T5 (Polich, 2007). Also, RTs were acquired and RT variances computed.

Statistical Analysis

Statistical analysis was performed to test for before/after treatment changes, as measured by the selected resting state EEG (theta/beta ratio and PAF) and ERP (P200 and P300b latencies) measures. To do so, we first applied a Shapiro-Wilk test (Shapiro & Wilk, 1965) to all measures in order to verify whether values were normally distributed. Since only the data relative to the P300b and theta/beta ratio measures were found not to be normally distributed, we explored within-group differences for all measures using a nonparametric Wilcoxon signed-rank test (Whitley & Ball, 2002).

Moreover, a Pearson correlation was used to investigate the relationship between EEG/ERP measures and RTs or RT variances. For each statistical analysis, the significance threshold was set at 0.05 and, for each measure, the mean ± standard deviation (*SD*) was reported. All statistical analyses were performed using custom code based on python libraries (ADD).

Results

Theta/Beta Ratio

The median theta/beta ratio was reduced after treatment (before treatment = 0.71 ± 0.18; after treatment = 0.65 ± 0.20; $p < .01$; Figure 1, Table 2).

PAF

After treatment, there was no change in average posterior PAF (before treatment = 9.4 ± 1.3, after treatment = 9.5 ± 1.2, Figure 1, Table 2).

P200 and P300b

The average P200 latency was found to be shorter after treatment (before treatment = 212 ± 50.8; after treatment = 179 ± 55.7, $p < .01$). Similarly, the median P300b latency was shorter after treatment (before treatment = 370.95 ± 59.50; after treatment = 341.31 ± 58.31, $p < .05$, Figure 1, Table 2).

RT

There was no difference between the average RTs recorded during performance in the Go/NoGo task before and after treatment (before treatment = 526.26 ± 108.45; after treatment = 516.00 ± 103.64). However, a before/after treatment difference was found for the average RT variances (before treatment = 17.7 ± 11.7; after treatment = 14.5 ± 12.7; $Z = -2.07$, $p < .05$,). These results are shown in Figure 2 and summarized in Table 2.

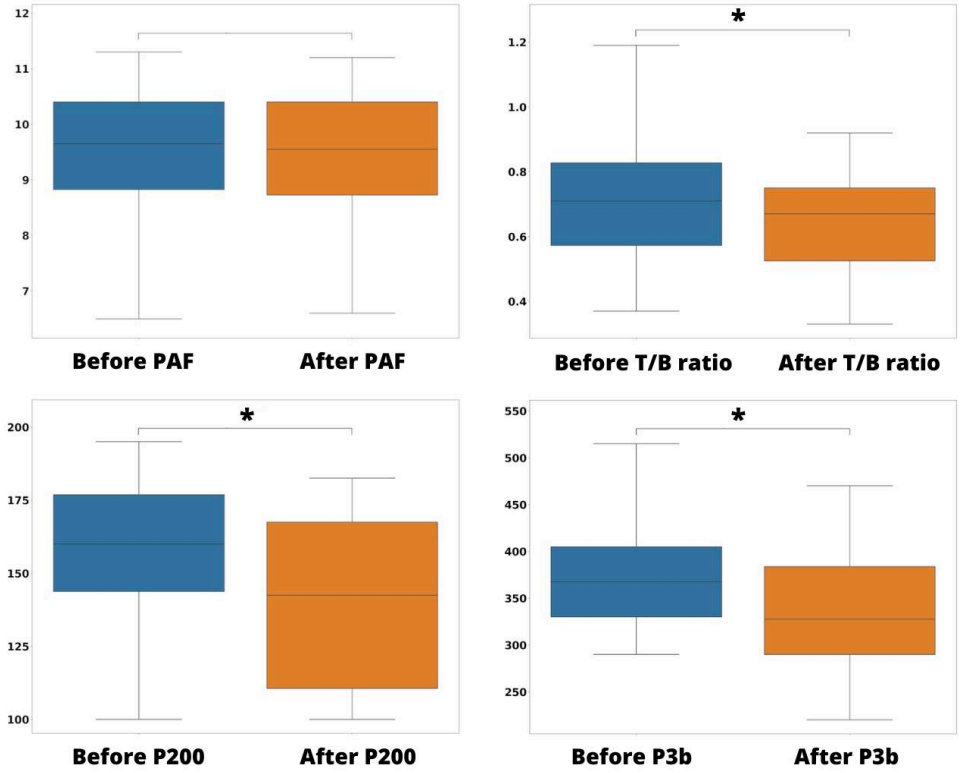
Table 2

Changes (Mean ± Standard Deviation) of Resting State (Eyes Open) Electroencephalogram, Event-related Potentials and Reaction Times Recorded During Performance of a Go/NoGo Task Before and After the Administration of FOCUS.

EEG/ERP	Before	After	*p*
Theta/beta ratio (RS – eyes open)	0.71 ± 0.18	0.65 ± 0.20	< .01
PAF (RS – eyes closed)	9.4 ± 1.3	9.5 ± 1.2	n.s.
P200	212 ± 50.8	179 ± 55.7	< .01
P300b	370.95 ± 59.50	341.31 ± 58.31	< .05
Reaction Time			
Speed	526.26 ± 108.45	516.00 ± 103.64	n.s
Variance	17.7 ± 11.7	14.5 ± 12.7	< .05

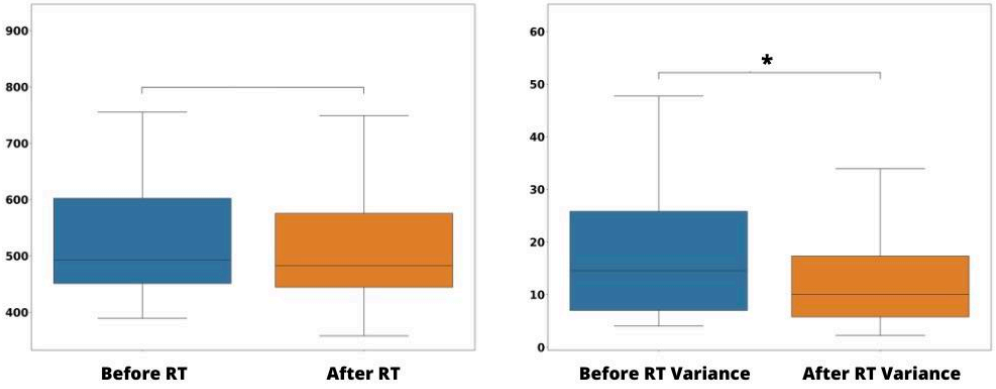
Abbreviations: EEG = electroencephalogram; ERP = event-related potentials; RS = resting state; PAF = peak alpha frequency.

Figure 1. *Resting State (Eyes Open) EEG and ERP Differences Before and After the Administration of FOCUS*.



Note. Asterisks indicate statistical significance. Abbreviations: PAF = posterior alpha frequency; T/B = theta/beta.

Figure 2. *Reaction Times and Reaction Time Variance (Go/NoGo Task) Differences Before and After the Administration of FOCUS.*

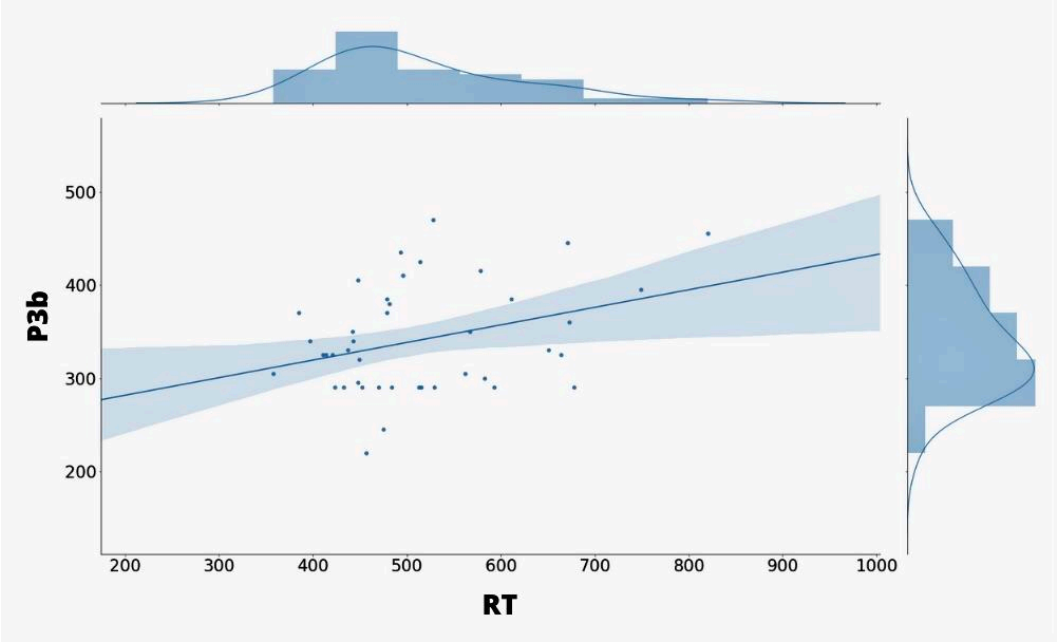


Note. Asterisk indicates statistical significance. Abbreviations: RT = reaction time.

Correlations Between RT and EEG/ERP Measures

A positive correlation (Figure 3) was found between P300b latencies and RTs after treatment (r = 0.34, p < .05). No other correlation was found before or after treatment.

Figure 3. *Correlation Between P3b Latencies and Reaction Times After the Administration of FOCUS.*



Note. Abbreviations: RT = reaction time.

Discussion

The present study found that the administration of the hemp extract FOCUS induced a number of changes in the EEG of former professional American football players and might add to previous evidence indicating that manipulations of the endocannabinoid system could contribute to ameliorate TBI pathology (Schurman & Lichtman, 2017). While we could not exactly determine which of the compounds in the preparation drove the observed resting-state EEG changes, we nonetheless confirmed the ability of a *Cannabis* extract to induce beneficial effects on brain activity in the absence of THC.

The present study also provides further support for the use of well-established EEG and ERP measures of cognitive performance, as detected by the FDA-cleared BrainView NeuralScan Pro workstation, in adult individuals with a history of head injury associated with a high-impact sport (Clark & Guskiewicz, 2016), suggesting that regular automated EEG-based assessments might contribute to reveal subclinical functional anomalies in this population and also assist clinicians in regular drug response evaluations.

The decrease in the theta/beta ratio we found after treatment during resting state suggests improved cognitive performance and emotion regulation (Gomes & Damborská, 2017; Papathanasiou et al., 2018). The interplay of cognitive functions and emotion is of particular relevance in TBI, with particular respect of its role in modulating the reductions in attentional control that may be found in this clinical population (Ríos et al., 2004), which could in turn affect their resilience to stress (Yao & Hsieh, 2019). Importantly, it has been reported that the administration of noradrenaline or dopamine agonists normalizes the theta/beta ratio (Clarke et al., 2003; Schutter & Van Honk, 2005). Given the evidence suggesting that both CBD and CBG might indirectly affect noradrenergic or dopaminergic transmission in the brain through the inhibition of CB1/CB2 receptors (Szabo & Schlicker, 2005) or selectively modulating gene expression (Gugliandolo et al., 2020), our results might suggest the ability of FOCUS to affect these mechanisms and future research should investigate the neurochemical substrates and pathways involved in region-specific slow versus fast wave EEG power regulation, in normal conditions and also in populations with a history of head injury.

Our results might also add to previous pilot findings in healthy subjects suggesting some beneficial effects of THC-free hemp extracts on both autonomic nervous system regulation and brain function (Gugliandolo et al., 2020), although our participants exhibited no change in a measure of

alpha activity (PAF). While more research is still required to more confidently determine the differential effects of hemp extracts on resting-state EEG rhythms, the present study might suggest a treatment resistant frequency-specific anomaly in the participant cohort we investigated. Interestingly, while little or no research has explored the differential effects of endocannabinoid receptor modulation on resting-state alpha EEG frequency, there is evidence indicating that increases in PAF associated with improved cognitive performance can be achieved through learning-based interventions (Angelakis et al., 2007; Dobrakowski & Lebecka, 2020). This remarks the ability of targeted EEG-based assessments to provide valuable feedback on treatment efficacy, also suggesting that EEG data acquisition and analysis platforms like BrainView NeuralScan Pro may easily automate this process, offering clinicians the opportunity to devise appropriate protocols on the basis of objectively and reliably measured biomarkers.

We also detected changes in ERP latencies after treatment. In particular, the P200 latency reduction suggests an improvement in attention and stimulus classification (Key et al., 2005), which have been found to be linked to TBI (Gomes & Damborská, 2017; Papathanasiou et al., 2018. Reduced latency was also found for the P300b response, suggesting an improvement in stimulus evaluation and classification speed (Duncan-Johnson & Donchin, 1982; Kutas et al., 1977), previously found to be altered in individuals with sports concussion (Baillargeon et al., 2012). Again, given the evidence indicating that *Cannabis* users and persons administered with THC exhibit prolonged latencies of multiple ERPs, including the P300 component (Roser et al., 2008; van Tricht et al., 2013), our results remark the importance of using only low-concentration or THC-free hemp extracts, and also strengthen the importance of regular ERP investigations in high-contact athletes, even when conventional neuropsychological tests reveal little or no cognitive slowing (Gosselin et al., 2012). Importantly, while we found no posttreatment difference in response speed, the reduced RT variability suggests improved cognitive performance (Gorus et al., 2008). Also, the correlation between RTs and P3b latencies might reflect greater association between stimulus processing time and expectancy, perhaps resulting from an improved response strategy in relation to the nature of the task (Duncan-Johnson & Donchin, 1980).

Finally, “entourage effects” due to the terpenoids present in the FOCUS preparation cannot be ruled out, given the evidence indicating the ability of these natural compounds to induce EEG changes. For example, quantitative EEG research with healthy persons suggests that changes in resting-state EEG detected after the inhalation of the essential oil *Abies koreana* (Jeong et al., 2007) may contribute to the enhancement of relaxation and alertness/attention states (Seo et al., 2016). Importantly, α-pinene, one of the major components of *Abies koreana*, has shown to have acetylcholinesterase inhibitory activity with associated memory enhancement (K. Kim et al., 2006). Of note, limonene highly influences the human autonomic nervous system and mental conditions (Heuberger et al., 2001), and recent pilot research has shown that the inhalation of a *Cannabis sativa* extract containing 35 different essential oils induced a reduction of diastolic blood pressure, an increase in heart rate, and an increase in skin temperature (Gulluni et al., 2018). Also, the analysis of resting-state EEG in the same participants showed generalized and region-specific shifts in slow versus fast frequency power, which were associated with greater self-rated relaxation and calmness.

Further research in larger sample sizes is needed to evaluate the differential effects of nonpsychoactive endocannabinoids and terpenes on both resting-state EEG and ERP measures of brain activity.

Limitations

While the present study revealed a number of important EEG changes in the population examined, a number of limitations must be remarked.

Unfortunately, given the necessary restrictions imposed by personal privacy guidelines, we could not gather any further demographic information (other than age and sex) on participants, or even use standard psychiatric questionnaires to acquire data on their cognitive abilities and emotional state. Also, it was not possible to access the medical history of any of the participants recruited, including information on the number and nature of the concussion episodes reported throughout their career, past and current medication, or any other officially diagnosed neurological and/or psychiatric conditions. Importantly, in assuming that all participants had a history of brain injury, we could not control for symptom heterogeneity and severity.

Conclusions

The present study suggests that the administration of the hemp extract FOCUS in former professional American football athletes induced a number of key changes in both resting state EEG and ERP measures. We found that the theta/beta ratio, a measure that is thought to reflect the interplay between cognitive performance and emotion regulation, was decreased immediately after the administration of the preparation, suggesting improved resilience. Additionally, our ERP results suggest an improvement in attention and information processing speed. Further research is needed to investigate the long-term effects of the FOCUS preparation in a similar cohort and to also explore its suitability in other clinical populations.

Finally, we also confirmed the ability of BrainView NeuralScan Pro to detect the above-mentioned changes, suggesting its suitability for day-to-day drug response monitoring in patients with sport-related brain injuries.

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Author Disclosures

Dr. Ruan is the Science and Safety Advisor for PrimeMyBody, clinical advisor for BrainView NeuralScan Pro, and CEO of the Texas Center for Lifestyle Medicine. Dr. Amico regularly provides neuroscience consultancy to Medeia Inc. Mr. Danev is the founder and CEO of Medeia Inc.

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Investigating the Relationship Between Resting-state EEG Frontoparietal Coherence, Visuospatial Ability, and Motor Skill Acquisition: A Retrospective Analysis

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Abstract

Introduction: Visuospatial ability may explain individual differences in the extent of motor skill learning. This study tested whether frontoparietal functional connectivity at rest, measured by resting-state electroencephalography (EEG) coherence, is related to both visuospatial performance and motor skill acquisition (an early stage of motor learning). **Methods:** Across 21 participants, the following data were retrospectively analyzed: 2-min eyes-closed resting-state EEG, the Visuospatial/Constructional Index score from the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), and five practice trials of a functional motor task. Right frontoparietal coherence in the alpha band (8–12 Hz) was computed with imaginary coherence (IC) between electrodes F4 and P4, with ICs from left and midline electrodes included as negative controls. **Results:** F4–P4 alpha IC was highly correlated with the RBANS Visuospatial/Constructional Index, while left and midline alpha ICs were not. However, there was no correlation between right frontoparietal alpha IC with skill acquisition. **Conclusion:** This study supports that right frontoparietal IC is positively related with visuospatial function, yet the limited dose of motor practice (five trials) in the retrospective dataset was not inherently designed to investigate motor skill acquisition per se. However, results show proof of concept for developing right frontoparietal alpha IC-based neurofeedback applications for visuospatial training.

Keywords: visuospatial function; EEG; imaginary coherence; motor learning

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Introduction

The process of motor skill learning has widespread implications across motor rehabilitation, sports, surgical training, and brain–computer interface control. However, some individuals learn slower than others with the same amount of practice, or not at all (e.g., Brooks et al., 1995). Recently, we have demonstrated that individual differences in the extent of motor skill learning can be explained by variation in visuospatial ability, such that better visuospatial scores correlate with more skill retention (Lingo VanGilder, Hengge, et al., 2018; Lingo VanGilder, Lohse, et al., 2021; Regan et al., 2021; Wang et al., 2020).

A potential underlying mechanism may be the degree of connectivity between right frontoparietal network, which may be critical for the interaction between motor learning and visuospatial processes. Frontoparietal neural structures, such as the superior longitudinal fasciculus, have been shown to underlie skilled motor performance (Steele et al., 2012), and both cognitive and visuomotor control (Brandes-Aitken et al., 2019). Further, neuropsychological findings suggest that many visuospatial processes are specialized to the right

parietal cortex (Corbetta et al., 2000; Foxe et al., 2003). Based on the structural findings, this study aimed to test whether functional connectivity between right frontal and parietal regions at rest, measured by resting-state electroencephalography (EEG) coherence, is related to both visuospatial function and motor skill acquisition, which is an early stage of motor learning. EEG coherence is a correlation measure based on the frequency spectrum, which measures the degree of synchronization between oscillations of different neuronal ensembles underlying any two scalp electrodes (Nunez & Srinivasan, 2009). Recent studies have suggested that resting-state EEG coherence is linked to motor learning (Wu, Knapp, et al., 2018; Wu, Srinivasan, et al., 2014; Zhou et al., 2018). Coherence in the alpha band (8–12 Hz) is of particular interest in this study, because higher alpha power has been linked with improved performance in a spatial rotation task (Zoefel et al., 2011), while resting-state EEG coherence of the motor network in the mu (11–14 Hz) frequency band may also predict motor skill acquisition (i.e., within-session changes; Wu, Srinivasan, et al., 2014).

Methods

Experimental Design

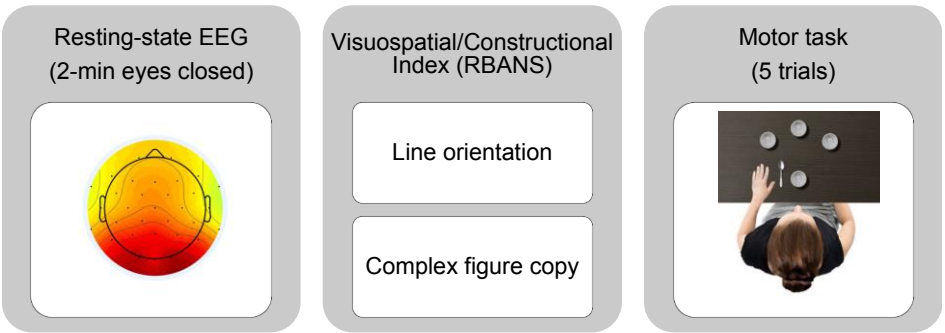
This study utilized an existing dataset (Pathania et al., 2022). The original data collection was approved by the University of Utah Institutional Review Board (IRB), in which participants provided informed consent prior to study enrollment. This retrospective analysis was approved by the Arizona State University IRB.

The dataset contained data from 21 healthy younger adults (aged 23.29 ± 3.47 years, 10 females). Eyes-closed resting-state EEG data was recorded for 2 min prior to completing the RBANS test battery and five trials of a functional motor task, as illustrated in Figure 1. More detail about the EEG data collection and processing is provided below. Visuospatial ability was measured using the Visuospatial /Constructional Index of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph et al., 1998), which was scored according to the test manual.

Motor Task

As described previously (Lingo VanGilder, Hengge, et al., 2018; Lingo VanGilder, Lohse, et al., 2021; Regan et al., 2021; Wang et al., 2020), the functional motor task in this study involves reaching and fine motor control. Briefly, the experimental apparatus is comprised of four plastic cups adhered to a board; three of the cups are “target” cups that are located radially around a center “home” cup that is aligned with the participant’s midline (Figure 1, right panel). The participant must use a standard plastic spoon with their nondominant hand to acquire two beans at a time from the home cup and transport them to one of the target cups. The participants are instructed to transport the beans first to the target cup located ipsilateral to the participant’s nondominant hand. They then scoop two more beans from the home cup and transport them to the middle target cup, then another two beans to the contralateral cup. The home cup contains 30 beans, resulting in 15 total reaches (five target cycles) per trial. Trial time is the measure of performance for each trial, which is the elapsed time from when the participant picks up the spoon until the last of the beans are deposited into the last target cup. In this dataset, participants completed five training trials only.

Figure 1. *Experimental protocol.*



Modeling Motor Skill Acquisition

To quantify motor skill acquisition, trial time data (in seconds) from each individual were fit with a linear model[1]:

$$Trial\ Time_i = A_i - B_i t \quad (1)$$

where *t* is trial number, *A* intercept term, and *B* the slope term. Individual participant was specified as *i*. Initial performance was estimated with *A*, where smaller *A* values indicates better initial performance. The rate of improvement was estimated with *B*, where larger *B* values indicates a faster rate of improvement.

EEG Acquisition and Preprocessing

Scalp EEG was collected from 32 electrodes of a 64-channel EEG cap housing a Brain Vision actiCAP system (Brain Products GmbH, Gilching, Germany), labeled in accord with an extended International 10–20 system (Oostenveld & Praamstra, 2001) and amplified and digitized using a BrainAmp DC amplifier (Brain Products GmbH, Gilching, Germany) and BrainVision Recorder software (Brain Products GmbH, Gilching, Germany). Eyes-closed resting-state EEG data were collected for 2 min. Data were online referenced to the right earlobe, and the ground electrode was placed on the left earlobe. Sampling rate was 1000 Hz. Preprocessing was done via the EEGLAB toolbox (Delorme & Makeig, 2004) and the ZapLine package (de Cheveigné, 2020) in MATLAB. Continuous data were high-passed at 1 Hz with a zero-phase noncausal window sinc FIR filter (EEGLAB function “pop_eegfiltnew”), which had a filter order of 3300 and a cutoff of 0.5 Hz at 6 dB.

As the current dataset contains heavy line noise, ZapLine was used to remove line for its superiority in specifically cleaning 60 Hz noise while preserving signals at other frequencies (de Cheveigné, 2020). Faulty channels and data segments with heavy muscle artifacts were manually rejected. Channels whose power spectrum did not demonstrate 1/f decline or with power less than other channels were removed. This resulted in 1.94 ± 1.24 removed channels for each participant, mostly temporal electrodes (T7, T8, TP9 & TP10, 83.9%) and FT electrodes (FT9 & FT10, 9.7%). The continuous data were then visually inspected to reject segments with spatially widespread muscle artifact. This resulted in average data length of 107.63 ± 8.61 s for the sample. Following data rejection, data were then submitted to an infomax ICA (Delorme et al., 2007). The validity of ICA artifact removal (e.g., eye movement artifact, muscle artifact) has been tested via numerous publications (Delorme et al., 2007; Hoffmann & Falkenstein, 2008; Plöchl et al., 2012) and recommended by consensus guidelines (Keil et al., 2014). In one paper (Plöchl et al., 2012), comparing ICA-identified artifacts with real eye tracking data, the authors concluded that rejecting ICs from the data resulted in complete removal or significant reduction of the eye and eyelid movement artifacts, while leaving the relevant signal emerging from neural sources intact. Furthermore, previous research that inspired this study (Wu, Knapp, et al., 2018; Wu, Srinivasan, et al., 2014) have used ICA analysis along with visual inspection. Therefore, this study utilized ICA as recommended by guidelines and to be consistent in preprocessing methods with similar studies. ICLabel (Pion-Tonachini et al., 2019) was used to identify and remove independent component(s) with eye artifacts and muscle artifacts. Any IC components with eye and muscle artifacts over 90% probability as identified by ICLabel were removed. On average, 2.3 ± 1.5 independent components were removed from the sample. After ICA artifact correction, rejected channels were interpolated with spherical splines interpolation (Perrin et al., 1989). Data were then segmented into nonoverlapping 1-s epochs.

Lastly, to appropriately perform electrode-level connectivity with EEG, the preprocessed data (scalp potentials) were submitted to a reference-free surface Laplacian algorithm to mitigate volume conduction (Kayser & Tenke, 2015). The surface Laplacian is a current source density measure that estimates the spatial second derivatives of scalp EEG potentials as an approximation for the amplitudes of underlying current generators (Tenke & Kayser, 2012). Due to the nature of taking derivatives, the EEG data at this point were reference free. A spline Surface Laplacian was used with default flexibility (*m* = 4) and regularization (lambda = 10− 5) parameters (Cohen, 2015; Perrin et al., 1989). The Surface Laplacian step was completed in MATLAB with code from Cohen (2014).

EEG Coherence

Imaginary coherence (IC) was chosen as the primary coherence measure because it avoids inflated and artifacted coherence values caused by volume conduction, and thus provides a robust estimate of EEG connectivity (Nolte et al., 2004). IC was estimated with the frequency spectrum, and

[1] A mixed-effect model was not used here because it failed to capture the individual variabilities for the slope term (B). That is, the random effect of slope is zero for all subjects when the data were fit with a mixed-effect linear model.

reflects the amount of phase synchronization between two time series. However, IC only measures time-lagged synchronizations by taking only the imaginary part of the complex cross-power spectrum of the two EEG signals (see Equation 3). IC was computed using customized codes in MATLAB as described in the following paragraphs.

Laplacian-referenced, preprocessed 1-s data segments were submitted to Fourier transforms using the MATLAB *fft* function and normalized by segment length to yield Fourier coefficients. No windowing function was used. Frequency resolution was 1 Hz. The Fourier coefficients were then used to calculate auto- and cross-power spectra via Welch's method:

$$S_{xy}(f_n) = \frac{2}{K} \sum_{k=1}^{K} X_k(f_n) Y_k^*(f_n) \quad n = 1, 2, \ldots, \frac{N}{2} - 1 \quad (2)$$

where n stands for the index of frequencies after the Fourier transform, N is the total number of time points for each segment, k indicates the index of segments, and K the total number of segments. $X_k(f_n)$ is the complex Fourier coefficients of time series $x(t)$ at frequency f_n, whereas $Y_k^*(f_n)$ is the conjugated complex Fourier coefficients of time series $y(t)$ at frequency f_n. The notation and definition for S_{xy} is consistent with that from Nunez (Nunez & Srinivasan, 2009) in which a factor of two of only the positive frequencies (as the corresponding negative frequencies have the same Fourier coefficients) was included and the DC signal (f = 0) and Nyquist frequency (f = N/2) were omitted.

Thus, the cross-power spectrum Sxy between signals x and y was estimated from the average of individual power spectra of all segments. This estimation can increase signal-to-noise ratio and, therefore, obtains robust estimates (Nunez & Srinivasan, 2009). When the two signals are the same, $x(t) = y(t)$, the complex-valued cross spectrum S_{xy} is reduced to a real-valued auto spectrum for that signal, noted as S_{xx}.

IC is calculated with the magnitude of the imaginary part of cross-power spectrum normalized by the square root of both auto power spectra (Nolte et al., 2004):

$$IC_{xy} = \frac{Im\left(S_{xy}(f_n)\right)}{\sqrt{S_{xx}(f_n) S_{yy}(f_n)}} \quad n = 1, 2, \ldots, \frac{N}{2} - 1 \quad (3)$$

where Im denotes taking the imaginary part of the complex cross spectrum. IC reflects the level of consistency of the phase difference between two channels of interest and is valued from 0 to 1. A higher IC value indicates that the two channels are more connected. By definition, the IC between a channel and itself is zero, because there is no time-lagged coherence. Thus, IC avoids inflated and artifacted coherence values caused by volume conduction, and can provide a robust estimate of EEG connectivity. Based on Zoefel et al. (2011), only the alpha band was examined in this study.

Statistical Analysis

Brain-behavior correlations between coherence and motor or visuospatial variables were tested with bivariate correlation. All bivariate correlation analyses were tested using Spearman Rank correlation. Significance level was set to 0.05. Multiple comparisons were not adjusted for to minimize the potential of rejecting true positives in this proof-of-concept study with a relatively small sample size. Instead, statistics are reported comprehensively for all analyses, including those for null results.

Results

Data from 21 participants were analyzed. One participant was excluded for missing motor performance data and four participants were excluded due to substantial artifacts in the EEG data (neither alpha peaks in power spectra nor not following typical 1/f shape). This resulted in a final sample of 15 participants (8 females; age 22.73 ± 2.69 years old).

On average, motor performance improved from the first trial to the fifth trial by a reduction of 9.15 ± 4.77 in trial time, $t(14) = 7.42$, $p < .001$, 95% CI [6.50, 11.79] seconds. The distribution of trial times is presented in Figure 2, showing that motor performance improved across participants with considerable individual variability. Individual model fits (Figure 3) demonstrated an average intercept of 52.05 ± 5.97 s for baseline performance, and an average slope of 1.80 ± 1.30 for rate of improvement over trials. Modeled baseline performance and slope were correlated ($r = 0.78$, $p < .001$).

Right Frontoparietal Imaginary Coherence Did Not Correlate with Motor Variables

Right frontoparietal (F4-P4) imaginary coherence, the primary coherence measure of interest, did not correlate with the modeled initial performance ($p = .271$) or the rate of improvement ($p = .474$)

Figure 2. *Progression of motor performance over five trials.*

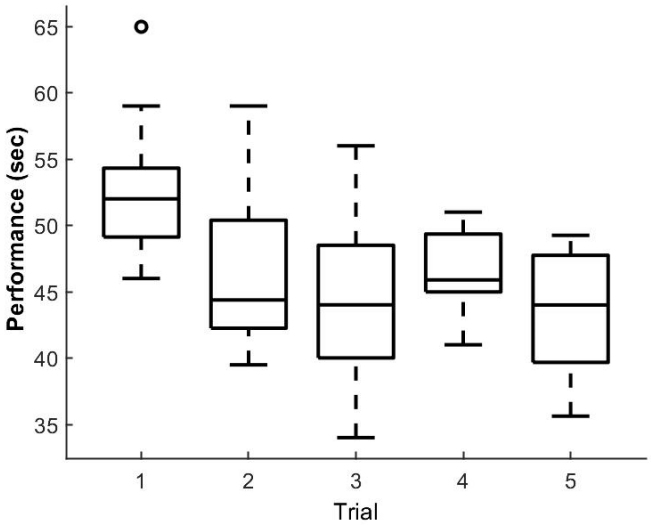
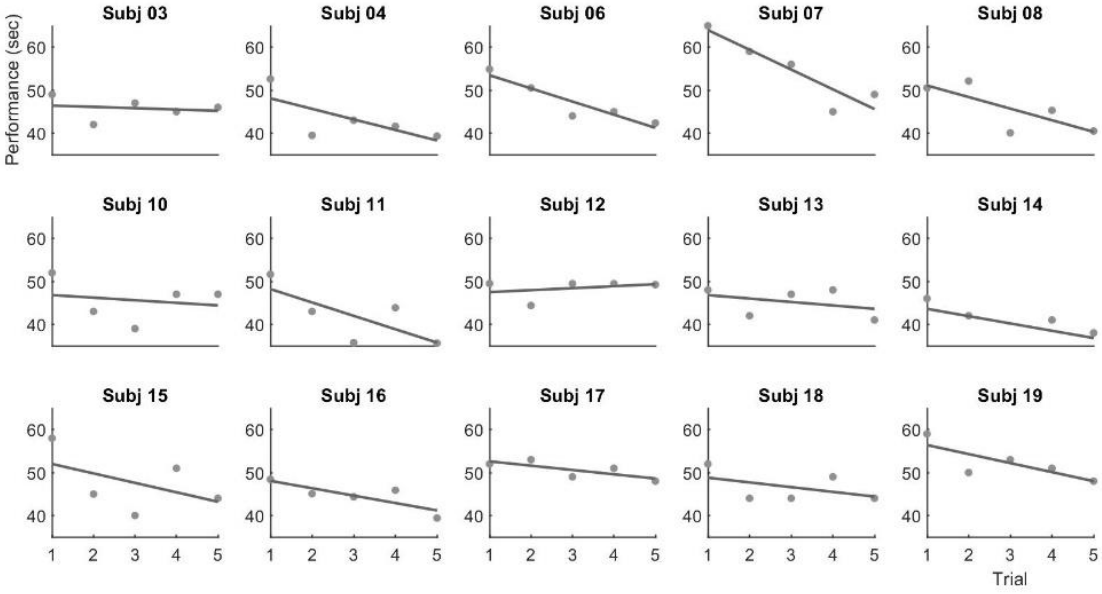
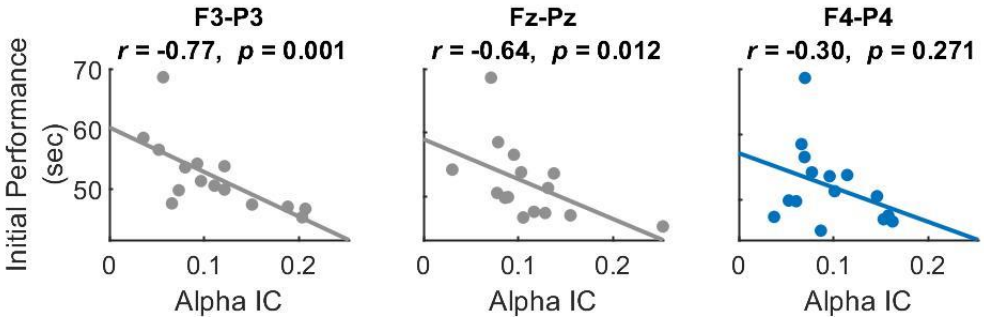


Figure 3. *Individual model fits for motor performance over five trials.*



On the contrary, initial motor performance was strongly correlated with both control imaginary coherence measures (Figure 4, middle and right column). Left frontoparietal (F3-P3) imaginary coherence correlated with initial motor performance (r = −0.77, p = .001). Midline frontoparietal (Fz-Pz) imaginary coherence also correlated with initial performance (r = −0.64, p = .012). Although two control ICs also demonstrated correlations with rate of improvement (r = −0.51, p = .052 for left imaginary coherence; and r = −0.52, p = .051 for midline imaginary coherence), this relationship was driven by the innate relationship between initial performance and rate of learning. When follow-up regression analyses used both IC and baseline performance to predict rate of improvement, IC was no longer correlated to the rate of improvement (p = .812 for left IC, p = .712 for midline IC) while baseline performance was (beta = 0.74, p = .019; and beta = 0.83, p = .005 for the two models separately).

Figure 4. *Relationship between frontoparietal alpha ICs and initial motor performance.*

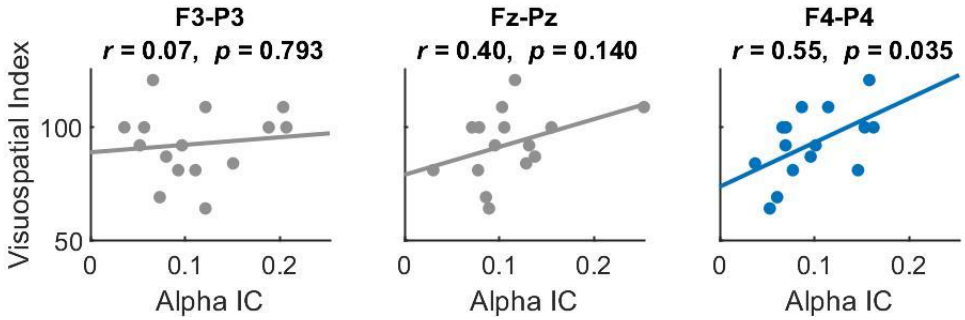


Note. Color blue indicates the analysis between the right frontoparietal coherence (primary IC measure) and motor performance. Color grey indicates control analyses with left and midline frontoparietal coherence.

Right Frontoparietal Imaginary Coherence Correlated with RBANS Visuospatial Index

Spearman Rank correlation revealed that right frontoparietal (F4-P4) alpha IC correlated with the RBANS Visuospatial Index (r = 0.55, p = .035; Figure 5 left column). Control analyses using left (F3-P3) and midline (Fz-Pz) alpha IC did not reveal any correlations between ICs and the RBANS Visuospatial Index (all ps > .140; Figure 5 middle and right column).

Figure 5. *Relationship between frontoparietal alpha ICs and Visuospatial Index.*



Note. Color blue indicates the analysis between the right frontoparietal coherence (primary IC measure) and visuospatial performance. Color grey indicates control analyses with left and midline frontoparietal coherence.

Discussion

This study tested whether right frontoparietal EEG resting-state connectivity was associated with visuospatial function (measured as the RBANS Visuospatial/Constructional Index) and motor skill acquisition. F4-P4 alpha IC, measured at rest with eyes closed, was highly correlated with the RBANS Visuospatial/Constructional Index, while left and midline alpha ICs were not. In terms of motor skill acquisition, F4-P4 IC did not correlate with motor skill acquisition (measured as within-session rate of improvement), nor with baseline motor performance. However, F3-P3 and Fz-Pz IC were highly correlated with baseline motor performance. No IC measure correlated with rate of improvement (i.e., how quickly motor performance improved).

Current results indicate that the right frontoparietal coherence, not left or midline coherence, is highly correlated with visuospatial function. This study extends previous structural neuropsychological findings that frontoparietal networks underlie visuospatial function (Brandes-Aitken et al., 2019; Corbetta et al., 2000; Foxe et al., 2003; Steele et al., 2012) by showing that functional connectivity at rest

between right frontal and parietal cortical regions also predicts visuospatial function. This study provides support that the link between alpha coherence and visuospatial function could be causal. Rizk et al. (2013) showed that continuous theta-burst stimulation (cTBS, which is thought to be inhibitory) to the right posterior parietal cortex reduced visuospatial attention and induced neglect-like behavior, with fewer cumulative fixations in the leftward direction (selective-focused attention was not considered in this cited study); the same cTBS stimulation to the right frontal eye field did not show the same effect. After right posterior parietal cortex cTBS stimulation, alpha coherence between the parietal stimulation site and other cortical regions decreased, suggesting that right frontoparietal coherence may be an important visuospatial biomarker with clinical implications. For example, F4-P4 alpha coherence (8–12 Hz) could be a therapeutic target in neurofeedback training for patients with visuospatial deficits, in which they could learn to self-regulate the coherence signal directly and potentially improve visuospatial function. Neurofeedback approaches that provide feedback of dynamic brain networks (such as coherence signals) are considered to be more effective in achieving neural regulation than those providing signals from one single brain region (Sitaram et al., 2017). The feasibility and efficacy of alpha imaginary coherence neurofeedback has been demonstrated previously (Mottaz, Corbet, et al., 2018; Mottaz, Solcà, et al., 2015). Alpha coherence can be successfully modulated via neurofeedback (Mottaz, Solcà, et al., 2015) and upregulating alpha coherence between the motor cortex and the rest of the cortical regions can improve motor performance after stroke (Mottaz, Corbet, et al., 2018). Given the prevalence of visuospatial deficits following stroke (Jokinen et al., 2015; Jongbloed, 1986) and in preclinical Alzheimer's disease (Caselli et al., 2020; Johnson et al., 2009), there is a clinical need for effective visuospatial training paradigms. Results from the current study warrant follow-up studies that directly test the feasibility of a frontoparietal alpha neurofeedback intervention for improving visuospatial function.

Contrary to the hypothesis, this study did not find a correlation between right frontoparietal alpha IC with motor skill acquisition, or baseline motor performance. One potential reason for this could be the limited dose of motor practice (only five trials) in this retrospective dataset, which was not inherently designed to investigate motor skill acquisition per se. In previous studies using the same motor task, visuospatial function correlated with 1-month motor retention after 50 or more trials of practice (Lingo VanGilder, Lohse, et al., 2021), as well as with 1-week retention after at least 10 trials of practice (Lingo VanGilder, Hengge, et al., 2018; Schaefer & Duff, 2017). The dose of practice in the current dataset may be too small to accurately evaluate motor skill acquisition and the learning process, but future studies are needed to test whether right frontoparietal coherence correlates with skill acquisition over a larger training dose, as suggested by the multisession motor training paradigm reported in Zhou et al. (2018).

This study did, however, identify a relationship between left and midline frontoparietal coherence with baseline motor performance. This is particularly provocative since 14 out of 15 participants used their left (nondominant) hand on the motor task, for whom the dominant (left) cortex is the ipsilateral cortex. Other studies have demonstrated that the alpha coherence in the left, but not right, hemisphere was related to visuomotor learning (Manuel et al., 2018) and motor skill acquisition (Wu, Srinivasan, et al., 2014) when using the right (dominant) hand. Moreover, alpha and beta coherence between left M1 and the rest of the cortical regions predicts motor skill acquisition (Wu, Srinivasan, et al., 2014; Zhou et al., 2018). Because this dataset used in the current study did not include any dominant hand motor data, we cannot directly test whether our data are consistent with these previous studies. However, our data do suggest a left parietal specialization for motor planning regardless of which effector is used, consistent with Kumar et al. (2020).

We acknowledge that the current study only focused on a single EEG frequency band (the alpha band). This was because this retrospective dataset included substantial artifacts that contaminated the beta band even after rigorous preprocessing (described in Methods), preventing the analyses of the beta frequency. Beta-band oscillations are strong sensorimotor rhythms (Hari & Salmelin, 1997; Jensen et al., 2005) that have been shown to predict performance both during task and at rest. Beta coherence at rest may also play a role in predicting motor learning. Wu, Srinivasan, et al. (2014) found that beta coherence from M1 to other parts of the brain predicted motor learning in high accuracy, while alpha coherence demonstrated a weaker correlation. It is worth pointing out that Wu, Srinivasan, et al. (2014) also showed that left premotor-parietal beta coherence was not related to motor learning. In further support of the beta frequency band, beta coherence can predict training-related behavioral gains in stroke patients

(Zhou et al., 2018) and beta oscillations at rest were confined to sensorimotor cortex, inferior parietal lobes, as well as the dorsolateral prefrontal cortex (Hillebrand et al., 2012). These findings suggest that frontoparietal beta coherence should be investigated as a biomarker for motor learning in future studies.

In conclusion, this retrospective analysis used imaginary coherence in the alpha frequency band to measure frontoparietal functional connectivity with EEG, and demonstrated that right frontoparietal connectivity is positively related with visuospatial function. This finding has implications for developing right frontoparietal alpha IC-based neurofeedback applications for improving visuospatial function, which could be used on its own as a form of cognitive training, or as a concurrent therapy to motor rehabilitation that would benefit slow- or nonlearners. Future studies are needed to test the relationship between alpha IC and motor learning with more extensive motor training.

Author Declarations

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Reduce Anxiety

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Abstract

More than half of college students self-report some kind of anxiety and depression. This study reports how a university course that incorporated structured self-experience practices may reduce symptoms of self-reported anxiety associated with college stress and strain. Ninety-eight college Junior and Senior students were enrolled in a Holistic Health class that focused on "whole-person" Holistic Health curriculum and included the exploration of psychobiology of stress, the role of posture, and the psychophysiology of respiration. The class included daily self-practices of awareness of stress, muscle relaxation, diaphragmatic breathing, and posture awareness. The students were instructed to apply these techniques whenever they become aware of, or experienced, sensations of stress or dysfunctional breathing during the day. After 5 weeks of practice, the students self-reported a 73% reduction in anxiety, 68% reduction in stress, 27% reduction in neck and shoulder discomfort, 26% reduction in abdominal discomfort; 18% of abdominal discomfort and 16% reduction in menstrual cramps. We recommend that schools incorporated a "whole-persons" self-care approach within their curriculum to teach students skills to prevent and reduce anxiety and stress and that therapists teach these skill before beginning bio/neurofeedback.

Keywords: anxiety; respiration; stress management; breathing; posture

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More than half of college students now self-report some kind of anxiety (Coakley et al., 2021). Before the COVID-19 pandemic nearly one-third of students had or developed moderate or severe anxiety or depression while being at college (Adams et al., 2021). The pandemic accelerated a trend of increasing anxiety that was already occurring. "The prevalence of major depressive disorder among graduate and professional students is two times higher in 2020 compared to 2019 and the prevalence of generalized anxiety disorder is 1.5 times higher than in 2019" as reported by Chirikov et al. (2020) from the UC Berkeley SERU Consortium Reports.

In an anonymous survey during the first day of a spring semester class, 59% of the students reported feeling tired, dreading their day, being distracted, lacking mental clarity, and having difficulty concentrating. Unsurprisingly, these are some of the same symptoms corresponding with the prevalence of anxiety and depression from other types of stress and strain observed in college students as reported by Beiter et al. (2015).

The increase in symptoms of stress and strain, such as in anxiety, has both short- and long-term performance and health consequences. Severe anxiety reduces cognitive functioning and is a risk factor for early dementia many years after students leave college (Bierman et al., 2005; Richmond-Rakerd et al., 2022). Chronic severe anxiety also increases the risk many kinds of comorbid health issues, such as asthma, arthritis, back or neck problems, chronic headaches, diabetes, heart disease, hypertension, pain, obesity, and ulcers (Bhattacharya et al., 2014; Kang et al., 2017).

The most commonly used medical treatment approaches for anxiety are various pharmaceutical

drugs (Kaczkurkin & Foa, 2015). These anti-anxiety drugs are sedative medications (e.g., benzodiazepines; Bushnell et al., 2017). Unfortunately, side effects of sedating medications like benzodiazepines include drowsiness, irritability, dizziness, memory and attention problems, and physical dependence (Crane, 2013; Peppin et al., 2020; Shader & Greenblatt, 1993; Shri, 2012). Note that the most typical uses for sedating medications are for issues relating to anxiety and insomnia (Table 1).

Table 1

Typical Uses for Sedating Medications (Arranged Alphabetically by Trade Name)

Trade Name	Duration	Generic Name	Typical Use Depending on Dose
Ativan	Longer	Lorazepam	Anxiety, Seizures, Anesthesia
Centrax	Longer	Prazepam	Anxiety, Insomnia
Dalamane	Shorter	Flurazepam	Insomnia
Doral	Longer	Quazepam	Insomnia, Anxiety
Halcion	Shorter	Triazolam	Insomnia
Klonopin	Longer	Clonazepam	Seizures, Panic
Librium	Longer	Chlordiasepoxide	Anxiety, Alcohol Withdrawal
ProSom	Shorter	Estazolam	Insomnia
Restoril	Shorter	Temazepam	Insomnia
Serex	Longer	Oxazepam	Anxiety, Insomnia
Tranxene	Longer	Clorazepate	Anxiety, Insomnia, Seizures
Valium	Longer	Diazepam	Anxiety, Seizures, Anesthesia, Restless Leg
Versed	Shorter	Midazolam	Anesthesia
Xanax	Longer	Alprazolam	Anxiety

Sedating medications (benzodiazepines) are restricted under the Controlled Substances Act under Schedule IV. The most common prescription medications for anxiety are trade named Valium, Xanax, Halcion (short acting), Ativan, and Klonopin. Benzodiazepines may have toxic or fatal interactions when combined with alcohol, barbiturates, and other nonbenzodiazepine/ nonbarbiturate sleeping pills such as Zolpidem (Ambien), Eszopicione (Lunesta), Zopicione (Somnol), and Zaleplon (Sonata).

Because benzodiazepine medications work by enhancing the effects of a neurotransmitter that slows down nervous system excitability and regulation of muscle tone (e.g., Gamma-Amino Butyric Acid or GABA; Toossi et al., 2017), it is plausible that many behavioral techniques that influence anxiety may also influence regulation of neurotransmitters that slow down regulation of muscle tone and nervous system excitability (Bandelow et al., 2015).

The most commonly used nonmedical treatment approaches for anxiety are cognitive-behavioral therapy (CBT) techniques based upon the assumption that anxiety is primarily a disorder in thinking, which then influence the symptoms and behaviors associated with anxiety (Marker & Norton, 2018; Smits et al., 2008). In an oversimplification, the primary treatment intervention by CBT practitioners focuses on changing thoughts which co-occur with behaviors and physical measures of psychophysiology.

Prior research (cf. Peper, Harvey, & Hamiel, 2019) suggests transforming “hopeless, helpless, depressive” thoughts into “empowering” thoughts has enhanced efficacy when a person first shifts to an upright posture, and then begins slow diaphragmatic breathing, before finally reframing their hopeless, helpless, or negative thoughts into empowering or positive thoughts. Participants were able to reframe stressful memories much more easily when in an upright posture compared to a slouched posture. Those who incorporated posture-plus-reframing reported a relevant reduction in negative thoughts and self-reported anxiety compared to those with no posture change while attempting to reframe their thoughts. Whereas the relationship between postural changes (e.g., power

poses) and hormones associated with dominance or submission (e.g., testosterone levels) is still under investigation (Körner & Schütz, 2020; Metzler & Grèzes, 2019), it has been proposed that power poses, such as those poses practiced in various yoga traditions, may act on the body by enhancing the inhibitory neurotransmitter GABA (Streeter et al., 2018). As suggested by Peper, Harvey, and Lin (2019), as well as Streeter et al. (2020), behavioral strategies that enhance attention, influence posture, as well as regulate breathing, all have a positive effect on emotions and behaviors.

Simplifying a complex relationship between mechanisms involving GABA, testosterone, and anxiety behaviors can be difficult; however, regulation of GABA has been associated with lowered anxiety in humans and animals (e.g., Lowery-Gionta et al., 2018; Smith et al., 2017; Thayer, 2006). There are strategies to reduce anxiety that focus on breathing and posture change. At the same time, there are many other factors that may contribute the onset or maintenance of anxiety such as social isolation, economic insecurity, etc. In addition, low glucose levels can increase irritability and may lower the threshold of experiencing anxiety or impulsive behavior (Barr et al., 2019; Bushman et al., 2014). This is often labeled as being “hangry” (MacCormack & Lindquist, 2019). Thus, changing a high glycemic diet to a low glycemic diet may reduce the somatic discomfort (which can be interpreted as anxiety) triggered by low glucose levels. In addition, people are also sitting more and more in front of screens. In this position, they tend to breathe quicker and more shallowly in their chest.

Shallow, rapid breathing tends to reduce the partial pressure of carbon dioxide (pCO2) which has normal values between 35 and 45 mmHg. Reduced pCO2 contributes to subclinical hyperventilation, which could be interpreted as a symptom of anxiety (Du Pasquier et al., 2020**;** Lum, 1981; Wilhelm et al., 2001). Experimentally, the body sensations that co-occur with experiences of anxiety can be evoked by instructing a person to sequentially exhale about 70% of their inhaled air, continuously for 30 seconds. After 30 seconds, participants report a significant increase in self-reported anxiety (Peper & MacHose, 1993). During the period of the COVID-19 pandemic—when college students spent many hours sitting in front of a computer screen, shallow breathing and having hopeless, helpless thoughts from the pandemic—all cofactors that contribute to the self-reported increased in anxiety symptoms.

To reduce symptoms related to anxiety and discomfort in college students, McGrady and Moss (2013) suggested that self-regulation and stress management approaches could be offering as the initial treatment and teaching strategy in health care, instead of first offering medication. Another useful approach to reduce sympathetic arousal and optimize health in college students is breathing awareness and retraining as described by Gilbert (2003).

The purpose of this report is to describe how a university course curriculum that incorporated structured self-experience practices may reduce symptoms of self-reported anxiety associated with college stress and strain (Peper et al., 2016). For several decades starting in 1976, up to 180 undergraduates have enrolled in a three-unit Holistic Health class on stress management and self-healing (Peper et al., 2014). Students in the class are assigned self-healing projects using techniques that focus on awareness of stress, dynamic regeneration, stress reduction imagery for healing, and other behavioral change techniques adapted from the book, *Make Health Happen* (Peper et al., 2002). At the end of the semester, 4 out of 5 students (82%) self-reported that they were “mostly successful” in achieving their self-healing goals. Students consistently reported achieving positive benefits such as increasing physical fitness; improving diets; reducing symptoms of anxiety, depression, and pain; eliminating eczema; and even reducing substance abuse (Bier et al., 2005; Peper et al., 2003; Peper et al., 2014). This survey explores the change in self-reported anxiety, stress and other somatic symptoms after practicing a “whole-person” Holistic Health stress management program that included the exploration of psychobiology of stress, the role of posture, psychophysiology of respiration, and daily self-practices.

Method

Participants

Ninety-eight college junior and senior students enrolled in a Holistic Health class were in the experimental group, and 12 college juniors and seniors from another class served as controls. As a report about an effort to improve the quality of a classroom activity, this report of findings was exempted from Institutional Review Board oversight.

Procedure

Students were enrolled in a Holistic Health class that focused on the psychobiology of stress, the role of

posture, and the psychophysiology of respiration. For 5 weeks, the class included didactic presentations along with guidance for daily self-practice in paced-breathing and posture awareness while sitting or using a computer.

Didactic Lecture Content. Didactic class presentations on the psychophysiology of stress included how mind emotions impact the body, how the body affects mind and emotions, and how posture impacts health (Sapolsky, 2004). It included discussions about the physiology of breathing and how a constricted waist tends to cause the person to breathe more in their chest (the cause of neurasthemia) and how the fight/flight response may trigger chest breathing, breath holding, or shallow breathing.

The lectures include short experiential practices the body–mind connections such as imagining a lemon to increase salivation, the effect of slouched versus erect posture on evoking positive/empowering or hopeless/helpless/powerless/defeated thoughts, and the effect of sequential 70% exhalation for 30 s on increasing anxiety (Peper et al., 2002; Peper et al., 2017; Peper & MacHose, 1993; Tsai, Peper, & Lin, 2016).

Daily Self-Practice. Students were assigned daily self-practices focusing on skill mastery (e.g., gradually building to 20 min of practices daily) and implementing the skills during their daily life. Students recorded their experiences after their practice. At the end of the week, they reviewed their own log and summarized their observations (benefits, difficulties), then met in small groups to discuss their experiences and extract common themes. These daily practices included:

- Awareness of stress by monitoring their reactions to daily stressors.
- Dynamic relaxation for 20 min per day and then observing and inhibiting a bracing pattern during the day.
- Changing “energy drain and energy gains.” Students observed what events reduced or increased their subjective energy and were instructed to implement changes in their behavior to decrease events that reduced their energy and increase behaviors that increased their energy.
- Creating a “memory of wholeness,” which consisted of relaxing and then recalling and evoking a past memory when they felt healthy and well.
- Practicing effortless breathing. Students practiced slow diaphragmatic abdominal breathing at approximately a six breaths-per-minute pace, for 10–20 minutes per day. Even more importantly, each time they become aware during the day of dysfunctional breathing pattern (e.g., breath-holding, shallow chest breathing, or gasping), they would change to an erect power posture and shift to slower diaphragmatic breathing.

After 5 weeks, students filled out an anonymous survey in which they rated the change in anxiety and other symptoms as compared to the beginning of the semester. The control group filled out the same questionnaire.

Results

It will come as no surprise that the majority of students reported improvement. 73% reported a reduction in anxiety, and 68% reported a reduction in stress. In addition, they reported decreases in their symptoms of stress, neck and shoulder, abdominal discomfort, headaches, irritable bowel or acid reflux, and menstrual cramps, as shown in Figure 1.

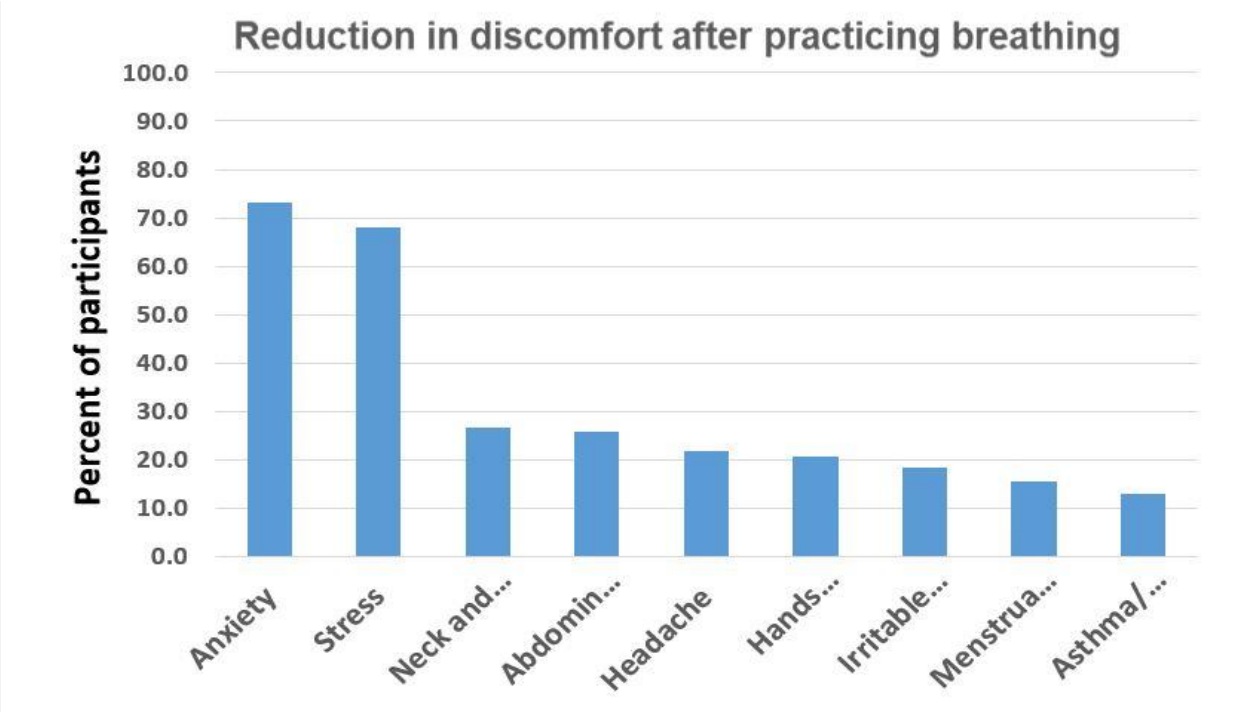
The control group did not report a decrease in symptoms; instead, they reported a slight increase in anxiety, stress, and somatic symptoms. In addition, although not assessed on the symptom questionnaire, most students anecdotally reported an increase in mental clarity and concentration that improved their study habits.

As one student noted: “Now that I breathe properly, I have less mental fog and feel less overwhelmed and more relaxed. My shoulders don’t feel tense, and my muscles are not as achy at the end of the day.”

Discussion

Almost all students were surprised how beneficial these easily learned practices were to reduce their symptoms of anxiety along with other symptoms of depression, stresses, and strains, while other students not in this class informally reported an increase in anxiety and somatic symptoms. Arguably the most important skill students learned was to interrupt their individual stress responses throughout the day, including shifting to diaphragmatic breathing. The more they practiced during the day, more benefits they reported in reducing their

Figure 1. Self-report of Decrease in Symptoms After Practice Integrated Stress Management and Diaphragmatic Breathing.



symptoms. In summary, the major factors that contributed to the students' improvement were:

- Learning through self-mastery as an education approach versus clinical treatment.
- Generalizing the skill into daily life and activities. Practicing the skill during the day in which the cue of a stress reaction triggered the person to shift to an upright position and breathe slowly, which would reduce their sympathetic activation.
- Interrupting escalating sympathetic arousal. Responding with an intervention by the participant performing an active task that reduced the sense of being overwhelmed and unable to cope.
- Redirecting attention and thoughts away from the anxiety trigger to a positive task of diaphragmatic breathing.
- Increasing heart rate variability through slower breathing which enhanced sympathetic parasympathetic balance.
- Reducing subclinical hyperventilation by breathing slower and thereby increasing pC02.
- Increasing social support by meeting in small groups. The class discussion group normalized the anxiety experiences.
- Providing hope. The class lectures and assigned readings and videos provide hope, since students read case reports and watched videos of other students who had had reversed their chronic disorders such as irritable bowel disease, acid reflux, and psoriasis with behavioral interventions.

Although the study lacked a systematic control group and is only based upon self-report (e.g., correlated symptoms), this approach represents an economical nonpharmaceutical approach to reduce anxiety. The stress management strategies referred to may not resolve anxiety for everyone. By practicing and implementing these skills the moment the student comes aware of, or experiences symptoms of stress (sloughing shallow breathing or breath holding, neck and shoulder tension, etc.), they reduce the development of symptoms and enhance health. Nevertheless, we recommend that schools implement this nonpharmacological educational approach into the classroom to reduce anxiety and stress-related disorders and have

therapists teach this approach first before beginning bio/neurofeedback.

To quote another student, “I noticed that breathing helped tremendously with my anxiety. I was able to feel okay without having that dreadful feeling stay in my chest, and I felt it escape in my exhales. I also felt that I was able to breathe deeper and relax better altogether. It was therapeutic—I felt more present, aware, and energized.”

Author Disclosure

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Limited Visual Working Memory Capacity in Children with Dyslexia: An ERP Study

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Abstract

Some researchers suggest that deficits in attention and working memory influence the development of dyslexia, whereas others propose that these deficits are more likely due to reduced global processing speed. The current study aimed to investigate behavioral performance in children with dyslexia compared to typically developing controls on two tasks: a visual oddball task for attention and an *n*-back task for working memory. We measured P300 event-related potentials (ERP) amplitude and latency for both tasks. Our results demonstrated reduced behavioral accuracy and P300 amplitude for the children with dyslexia compared to their typically developing peers in both the *n*-back and visual oddball tasks. We also found no differences in response time or P300 latency between these groups on either task. These findings support the idea that children with dyslexia experience deficits in cognitive processes related to working memory and attention, but do not exhibit decreased global processing speed on these tasks.

Keywords: working memory; *n*-back; oddball; dyslexia; P300 event-related potentials (ERP)

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Introduction

The ability to process and integrate text in reading is a critical skill that enables one to be successful in an academic setting (Savolainen et al., 2008; Taraban, Kerr, et al., 2004; Taraban, Rynearson, et al., 2000). Deficits in these reading abilities contribute to several negative outcomes, including poor academic achievement (Bergey et al., 2017; Chevalier et al., 2017; Snow & Strucker, 1999) and interference in career performances (Adelman & Vogel, 1990; Morris & Turnbull, 2007). Given the increased prevalence of reading disabilities in the population (Lewis, 1999; Newman et al., 2011), it is critical to further understand the neurocognitive factors related to reading difficulties.

Dyslexia, defined as a learning disorder associated with reading difficulties (Snowling & Hulme, 2012; Vellutino et al., 2004), has received considerable attention. Despite displaying adequate levels of intelligence (Tanaka et al., 2011), individuals with dyslexia experience difficulties in decoding text during reading (Snowling & Melby-Lervåg, 2016) and processing speech (Ziegler & Goswami, 2005). While it is believed that cognitive deficits likely influence the development of dyslexia (Singleton, 2002), the specific nature of which cognitive factors and how they predict impairments associated with dyslexia is still widely debated. For example, while the role of phonology-related deficits (e.g., dysfunctional verbal and auditory processes) are well documented in individuals with dyslexia (Chan, 2018; Richardson et al., 2004; Szenkovits et al., 2016), others have highlighted the role of

maladaptive nonverbal cognitive processes, such as decreased speed of attentional engagement and disengagement (Facoetti et al., 2008), a lower visual attention span (Bosse et al., 2007; Heiervang & Hugdahl, 2003), and impaired visual working memory (VWM) processes (Albano et al., 2016; Gathercole et al., 2006; Menghini et al., 2011; Pennington, 2008; Smith-Spark & Fisk, 2007; Swanson, 1994). This suggests the importance of further investigations on attention and working memory processes to better understand the nature of cognitive deficits associated with dyslexia.

Attention allows one to prioritize information that may be necessary for the completion of task-relevant goals by allocating cognitive resources necessary for greater processing of specific stimuli (Corbetta & Shulman, 2002). Enhanced processing of these stimuli leads to the subsequent transfer of this information into working memory (Awh et al., 2006). Working memory is a limited-capacity system that supports the temporary storage and manipulation of information (Cowan, 2010, 2017). The multifaceted nature of this system requires information held in working memory to be updated, revised, and replaced with newer and more relevant information (Monsell, 1996). Efficient working memory functioning is necessary for the completion of complex cognitive tasks, such as learning and reading processing. As such, individuals diagnosed with a variety of reading disorders, such as dyslexia, commonly demonstrate deficits in working memory (Brandenburg et al., 2015; Pickering, 2012; Schuchardt et al., 2008; Swanson & Alloway, 2012; Swanson et al., 2009; Vellutino et al., 2004; Wagner & Muse, 2006). Therefore, deficits in attentional and working memory related processes may contribute to the deficits observed in dyslexia.

Visual components of working memory are believed to contribute to reading processes (Magliano et al., 2016). In addition, reading and VWM processes require the engagement of overlapping brain structures responsible for multifaceted visual sensory processes, including selective attention (Mayer et al., 2007; Awh & Jonides, 2001), that enable efficient reading performance (Baddeley et al., 2019, Gathercole et al., 2006). Other evidence for the association between VWM and reading abilities can be seen by work demonstrating that reading skill training yielded increased VWM capacity (Shiran & Breznitz, 2011). Ultimately, these studies provide evidence suggesting that reduced VWM abilities may impact reading abilities, and thus contribute to the development of dyslexia.

Deficits in reading abilities in individuals with dyslexia may be maintained by a decreased storage of VWM resources necessary to complete current goal-directed tasks (Coady & Evans, 2008; Hoffman & Gillam, 2004). This reduction in VWM capacity may be caused by inefficient attentional allocation towards task-relevant information (Daucourt et al., 2019). For example, prior work has indicated that deficits in visual attention may play a role in the development of dyslexia (Saksida et al., 2016; Vidyasagar & Pammer, 2010). Thus, it is possible these individuals may experience attentional deficits, resulting in decreased storage of task-relevant information in VWM, negatively impacting overall reading performance.

Alternatively, there is a viewpoint suggesting that decreased processing speed leads to deficits in attention and working memory (Kail & Salthouse, 1994), which may result in reading disabilities. As such, it can be argued that individuals with dyslexia demonstrate cognitive inefficiency relative to their typically developing counterparts. Several other studies have reported slower reaction time for children with dyslexia compared to their peers in terms of different cognitive processing, such as phonological and orthographical processing (Breznitz, 2003, 2006), implicit learning tasks and consolidation (van der Kleij et al., 2019), visual naming (Wolf, & Bowers, 1999), and processing speed of working memory (Shiran & Breznitz, 2011). Therefore, while it is clear that individuals with dyslexia experience impairments in attention and VWM, the nature of how these processes are impacted remains unclear.

The use of electrophysiological markers may provide a useful avenue for unwrapping the association between deficits in attention and working memory processes, and the impact this has on reading disabilities (Luck, 2005). Specifically, the measurement of event-related potentials (ERP), obtained through electroencephalography (EEG) recordings, enables us to address both the speed of processing as well as fundamental underlying neurocognitive characteristics of VWM. One ERP component, the P300, has received considerable attention regarding its relationship with working memory (Brouwer et al., 2012; Christensen et al., 2012; Shiran & Breznitz, 2011) and attentional processes (Polich, 2007; Taroyan et al., 2007). Polich (2007) proposed that P300 amplitude reflects both attentional allocation towards novel or rare stimuli, and context-updating in working memory. Specifically, this positive-going ERP is often observed across various working memory paradigms

involved with the storage and maintenance of information, such as the *n*-back task, and tasks that assess attentional allocation and working memory updating, such as the visual oddball task (VOT).

The current study aimed to investigate the behavioral and neural correlates underlying both attention and VWM processes in children with dyslexia compared to typically developing controls. Specifically, we examined behavioral performance, reflected by accuracy and response times, and P300 amplitude and latency on a VWM task (*n*–back) and a visual attention task (visual oddball task). Enhanced P300 amplitude is believed to reflect the level of working memory load in the *n*-back paradigm, with larger magnitudes indicating a higher load of WM (Brouwer et al., 2012), while greater P300 on the VOT has been associated with increased attentional processing of a novel and infrequent stimulus (Polich, 2007). Prior work has also revealed decreased amplitude and increased latency of the P300 in individuals with dyslexia on an attentional task (Taroyan et al., 2007). We sought to examine which of the two perspectives (i.e., WM deficit in dyslexia vs. the global processing speed deficit in dyslexia) would explain the observed behavioral and ERP data better. The attention/WM deficit account offered the following two hypotheses. First, children with dyslexia compared to typically developing controls would exhibit lower levels of P300 amplitude and accuracy for the *n*-back task due to their lower VWM capacity, as seen in previous work (Evans et al., 2011). Second, children with dyslexia would demonstrate lower P300 amplitude and accuracy for the visual oddball task, due to their deficit in attentional allocation towards novel or rare stimuli, and context-updating in WMM. Alternatively, the global processing deficit account would offer the hypothesis that children with dyslexia would primarily show a slower reaction time and longer P300 latencies on both the visual oddball and *n*-back tasks regardless of accuracy, given their deficits in global speed of information processing.

Methods

Participants

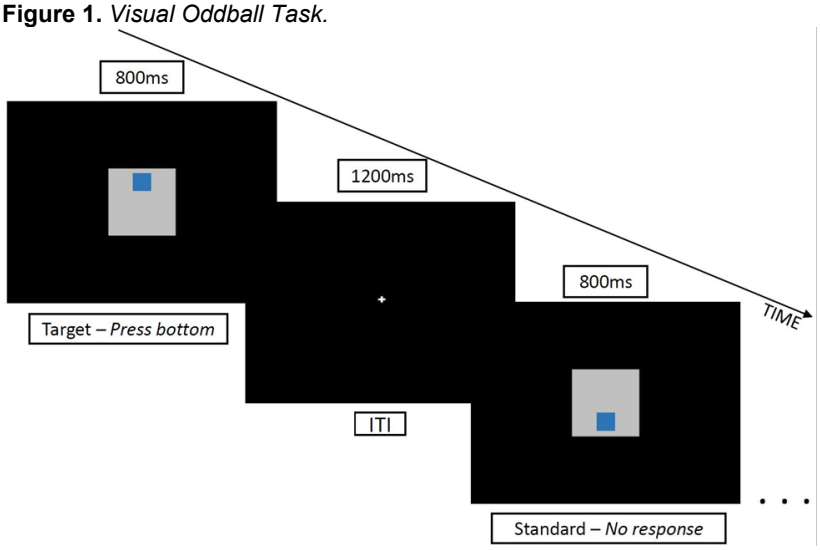
Fifty-five children (38 males) aged 7 to 12 (mean age = 8.73, *SD* = 1.62) years were recruited for this study: 32 (mean age = 8.25, *SD* = 1.61) were evaluated as presenting dyslexia (DYS) and 23 (mean age = 9.21, *SD* = 1.65) were considered as typically developing children (TDC). These children were recruited from a larger group of participants that were involved in ongoing studies in a psychological clinic in Tehran, Iran. Criteria for placement in the DYS group involved scoring two standard deviations below the mean in the Reading and Dyslexia Scale (Kormi-Nouri et al., 2012; Shokoohi-Yekta et al., 2014), currently undergoing dyslexia treatments at schools or the psychology clinic, and receiving a reading problems diagnosis with on-site psychologists at the clinic. Children in the TDC group were free from psychological or learning disabilities based on parent reports, and in-person psychological interviews conducted by on-site psychologists at the psychology clinic. Both groups of children were age-matched, and were within the average range of nonverbal IQ measured by the Raven Colored Progressive Matrices (DYS_M = 96.46, *SD* = 9.47; TDC_M = 101.73, *SD* = 12.83; Raven, 1977). Statistical analysis found no significant group difference in terms of nonverbal IQ ($p > 0.09$). Parents reported that none of the children received medication prior to the experimental session. All children had normal hearing and vision, were right-handed, and were native Persian speakers. Written consents were obtained prior to the study participation from parents and verbally from the children.

Procedure and Materials

Children completed a VOT and visual 1-back task (V1-Back) while EEG recordings were obtained. Children were seated 50 cm away from an LCD monitor used to present both tasks.

The VOT Task. The VOT is commonly used in EEG experiments to study neural responses to novel stimuli and updating of WM, usually reflected by the P300 ERP component (Polich, 2007). In this task, blue square stimuli were presented within a 10 cm by 10 cm gray field located at the center of black background. These squares would present at either the top (rare stimuli) or bottom (frequent stimuli) of the gray field for a short period of 800 ms with a 1200 ms intertrial intervals. The task constituted one block of 200 trials, with 160 frequent trials (80%) and 40 rare trials (20%). Children were instructed to respond as quickly as possible by pressing the spacebar to the frequent stimuli and withholding a response to rare stimuli (Figure 1).

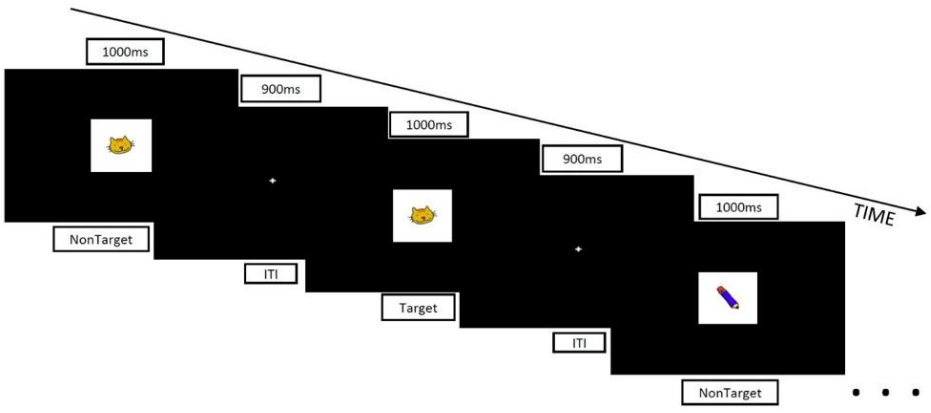
Figure 1. *Visual Oddball Task.*



Note. Children were instructed to respond as quickly as possible by pressing the spacebar to the target stimuli and withhold a response to standard stimuli.

The V1-Back Task. The *n*-back task is used to investigate the maintenance and manipulation of information in WM (e.g., Meegan et al., 2004; Ragland et al., 2002). Watter et al. (2001) have shown that P300 amplitude increased as a function of N. The V1-Back task of this study consisted of 80 trials, with up to eight different cartoon stimuli (e.g., baseball, book, fish) presented individually (1000 ms) followed by a fixation cross (900 ms). A pseudorandom presentation algorithm was administrated to present the stimuli so that each stimulus had the same probability of being a target in a sequence of two trials across the task. Children were required to press the spacebar if an item shown in a given trial was the same item presented one trial prior (Figure 2).

Figure 2. *Visual 1-Back Task.*



Note. Children were required to press the spacebar if an object shown in a given trial was the same item presented one trial prior.

Electroencephalography Data Acquisition and Processing

Electroencephalographic (EEG) data were recorded using a Mitsar EEG device (Mitsar Co. LTD, Russia) with a 21 Ag/AgCl electrode fitted nylon cap with the following sites according to the 10–20 International System of Electrodes (Fp1/Fp2, F3/F4, C3/C4, P3/P4, O1/O2, F7/F8, T3/T4, T5, T6, Fz, Cz, Pz).

The average value of (A1+A2) / 2 left (A1) and right (A2) ear lobe electrodes served as the reference for all channels during online recording. Impedances were kept below 5KΩ, and a 250-Hz sampling rate with a notch filter (50 Hz) was used. Electrooculography (EOG) electrodes were placed 1 cm to the left and right of the external canthi for horizontal eye movements, and an electrode under the right eye referenced to the left earlobe was used for vertical eye movements.

EEG data were cleaned and preprocessed using EEGLAB (Delorme & Makeig, 2004), and ERPLAB (Lopez-Calderon & Luck, 2014), and WinEEG software (Mitsar Co. LTD, Russia). An offline filter with a Butterworth bandpass of 0.1–50 Hz was applied prior to removal of excessive data as well as eye blink artifacts using Independent Component Analysis (ICA) methodology. A time window of −200 to 800 ms from the onset of the stimuli was segmented from the continuous EEG data with a 200 ms baseline correction applied to each bin. As recommend by Luck (2014), the segmented data was subjected to horizontal and vertical EOG artifact rejection procedures (VEOG exceeding +/− 70 μV; HEOG exceeding +/− 40 μV). Twelve subjects were removed from further analyses due to technical issues (6), and a higher percentage (> 30%) of rejected trials (6). Following artifact rejection, an average of four (2%) trials from the VOT and two (2.5%) trials from the V1-Back task were removed due to excessive movements or eye blinks.

P300

The P300 component has been shown to reflect WM load in the *n*-back paradigm (e.g., different *n*-back load; Brouwer et al., 2012; Christensen et al., 2012; Evans et al., 2011, Watter et al., 2001), and greater attentional processing of rare stimuli in oddball tasks (Polich, 2007). As such, we investigated the P300 component in both the VOT and V1-Back. P300 values were quantified as the mean amplitude between 350–500 ms for V1-Back and 450–600 ms for VOT following the onset of stimuli in both tasks (Lotfi et al., 2020). We examined P300 activity from central midline (Cz electrode; Sokhadze et al., 2017) for the VOT task, and parietal midline (Pz electrode; Evans et al., 2011; Polich, 2007) for the V1-Back.

Results

Behavioral Outcomes

SPSS and R software packages were used to conduct statistical analyses. Data cleaning and handling of missing data (< 5%) was done using multivariate imputations by chained equations via MICE package of R software (van Buuren & Groothuis-Oudshoorn, 2011). In order to account for individual differences (Muthén & Curran, 1997), the data were examined using ANCOVAs with age and nonverbal IQ as covariates, and with Group (DYS or TDC) as a between-subjects factor. We examined percentage of accuracy, error rate, and reaction time (RT) as well as P300 amplitude and latency in both tasks between groups.

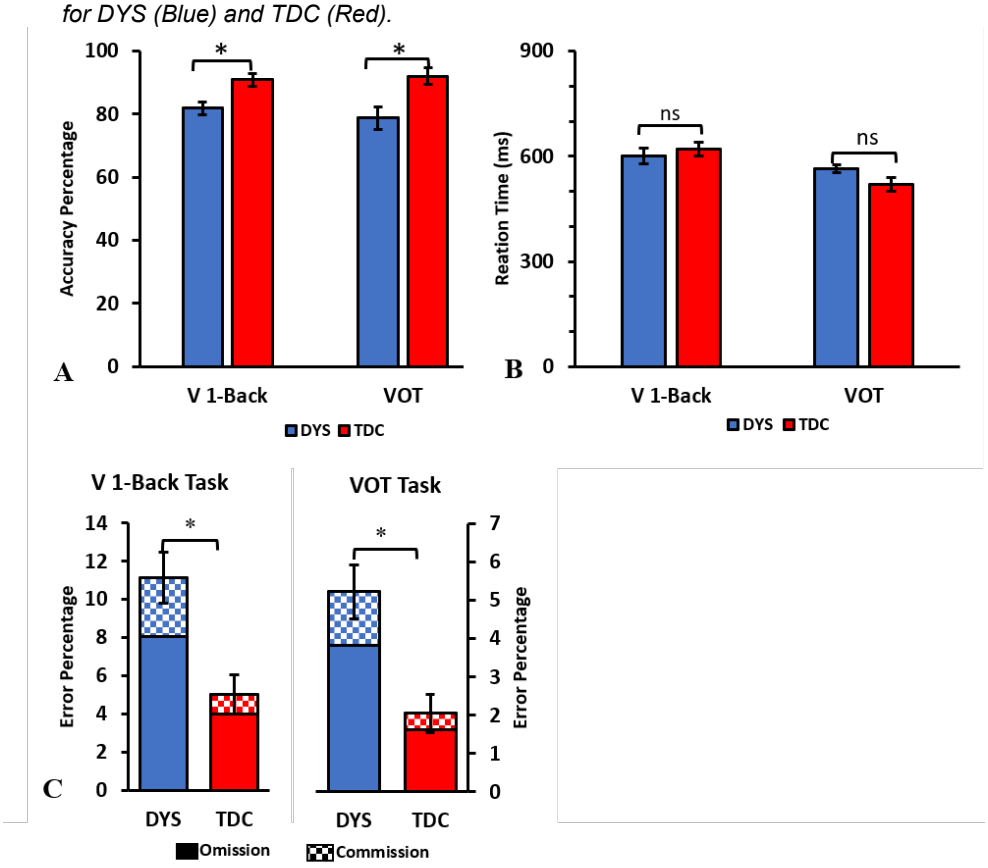
Accuracy in Behavioral Performance. On the V1-Back task, the TDC group showed a significantly higher level of accuracy than the DYS group, $F(1, 51) = 6.29$, $p < 0.05$, ηp2 = 0.11 (Figure 3A). Consistently, a similar ANCOVA yielded a significant group difference with large effect size for the VOT, $F(1, 51) = 6.34$, $p < 0.05$, ηp2 = 0.11 (Figure 3A), indicating that the TDC group demonstrated a significantly higher level of accuracy on VOT compared to the DYS group.

Reaction Time on the Behavioral Tasks. In terms of reaction time for both tasks, there were no significant group differences; V1-Back: $F(1, 51) = 1.34$, $p = 0.25$; VOT: $F(1, 51) = 0.87$, $p = .35$; Figure 3B. Further, ANCOVAs examining commission error rate revealed that the DYS group showed significantly larger commission error rates compared to the TDC group on both tasks; V1-Back: $F(1, 51) = 4.61$, $p < 0.05$, ηp2 = 0.08; VOT: $F(1, 51) = 4.80$, $p < 0.05$, ηp2 = 0.09; Figure 3C. A similar analysis showed that the DYS group showed greater omission errors in the V1-Back, $F(1, 51) = 4.71$, $p < 0.05$, ηp2 = 0.08, but no group differences were observed in the VOT, $F(1, 51) = 2.18$, $p = 1.46$, ηp2 = 0.04.

ERP Analyses

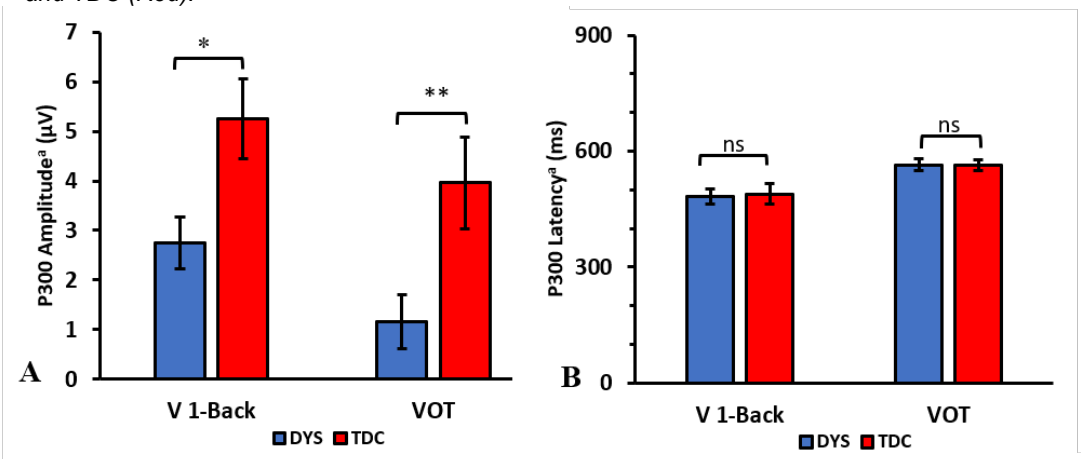
P300 Amplitude. We examined the P300 amplitude at the onset of correct target trials for the V1-Back task at the Pz electrode, and at the onset of infrequent trials for the VOT at the Cz electrode. We conducted two separate ANCOVAs to compare these variables between the DYS and TDC groups. We observed group differences across both tasks, with the TDC group showing a significant larger P300 amplitude on both the V1-Back and VOT tasks, respectively; V1-Back: $F(1, 34) = 5.11$, $p < 0.05$, ηp2= 0.13; VOT: $F(1, 39) = 5.01$, $p < 0.05$, ηp2= 0.11; Figures 4A and 5. This indicates that the TDC group had a significantly larger P300 amplitude in processing of target trials on both VOT and V1-Back tasks when compared to the DYS group. Additionally, we examined the correlation between the P3 amplitude and the accuracy of the V1-Back task between the two groups. Results showed a

Figure 3. *Accuracy and Error Percentages (A & B) and RT (C) in V1-Back and VOT for DYS (Blue) and TDC (Red).*



Note. *p < 0.05; DYS = Dyslexic Group; TDC = Typically Developing Children; VOT = Visual Oddball Task; Error bars represent SEM; as = approach significance; Checkered pattern = Omission errors; Solid color = Commission errors.

Figure 4. *P3 Amplitude (A) & Latency (B) of Target Trials in V1-Back and VOT for DYS (Blue) and TDC (Red).*

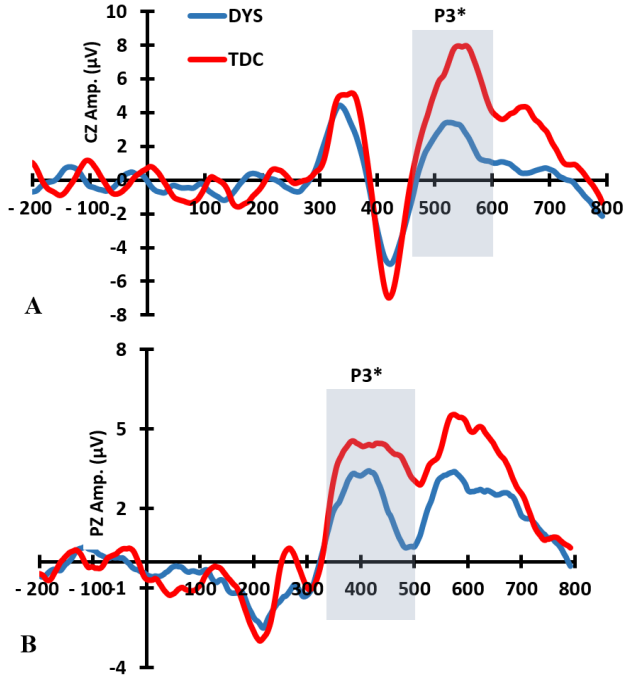


Note. *p < 0.05; **p < 0.01; DYS = Dyslexic Group; TDC = Typically Developing Children; VOT = Visual Oddball Task; [a]P3 amplitude and latency are obtained from Pz electrode for V1-back and Cz electrode for VOT. Error bars represent SEM.

significant correlation between them, $r(43) = 0.46$, $p < 0.05$ (see Figure 6), which indicates that the amount of P300 amplitude deflection was positively associated with the rate of correct responses on the V-1Back task, however, we did not observe such a correlation between the behavioral performance and P300 amplitude for the VOT task, $r(42) = 0.128$, $p = 0.49$.

P300 Latency. We applied a similar analysis for P300 latency processing of target trials for both tasks separately. The results demonstrated that there were no group differences in P300 latency across both tasks; V1-Back: $F(1, 34) = 0.23$, $p = 0.63$; VOT: $F(1, 39) = 0.02$, $p = 0.87$; Figure 4B.

Figure 5. *Average ERPs of Target Trials of VOT (A) andV1-Back (B) for DYS (Blue) and TDC (Red).*

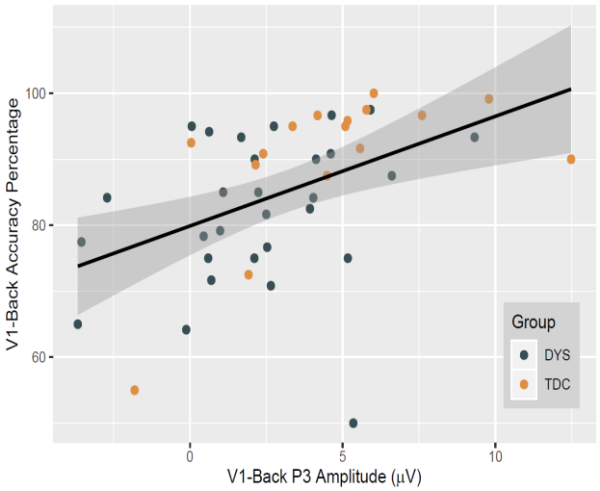


Note. *$p < 0.05$; DYS = dyslexic group; TDC = typically developing children; VOT = visual oddball task; P3 amplitude are obtained from Pz electrode for V1-Back and Cz electrode for VOT.

Discussion

Prior work has shown that when compared to their typically developing peers, children with reading problems exhibit a limited, dysfunctional phonological loop efficacy in WM performance (Pickering & Gathercole, 2001; Swanson & Howell,

Figure 6. *The Correlation Plot Between the P3 Amplitude (y-axis) and the Accuracy Percentage (x-axis) of the V1-Back Task Across Both Groups.*



Note. This indicates that V1-Back accuracy is positively associated with V1-Back amplitude ($r = 0.46$, $p < 0.05$).

2001; Swanson et al., 2009). Nonetheless, there is a paucity of developmental EEG studies examining the role of visual WM capacity, attentional processing (e.g., attention allocation, inhibition control), and global processing speed of information for children with dyslexia compared to their typically developing peers. Here we investigated behavioral performance and P300 amplitude reflecting VWM and attentional processing in children with dyslexia compared to typically developing counterparts on two well-established VWM and attention tasks (V1-Back and VOT) to address this gap in the literature.

In line with the WM deficit account, we found that children with dyslexia demonstrated lower VWM accuracy compared to typically developing controls on the V1-Back task. This suggests that these children exhibit behavioral deficits in maintaining visual information in WM. These results are consistent with others who have also shown that individuals with dyslexia exhibit impaired WM processes at the behavioral level (Albano et al., 2016; Brandenburg et al., 2015; Gathercole et al., 2006; Menghini et al., 2011; Pennington, 2008; Pickering, 2012; Schuchardt et al., 2008; Smith-Spark & Fisk, 2007; Swanson, 1994; Swanson et al., 2009; Vellutino et al., 2004; Wagner & Muse, 2006). It is possible that these deficits contribute to the development of reading difficulties experienced by children with dyslexia (Singleton, 2002), and serve as a potential risk factor for decreased academic

performance commonly observed in this population (Bergey et al., 2017; Chevalier et al., 2017; Snow & Strucker, 1999). Similar to V1-Back accuracy, we found significant group differences in accuracy between children with dyslexia and typically developing controls on the VOT, suggesting that attentional allocation to novel stimuli and updating in WM is attenuated in children with dyslexia compared to typically developing individuals. This finding complements the work of others who have also found attentional deficits in individuals with dyslexia (Bosse et al., 2007; Facoetti et al., 2008; Heiervang & Hugdahl, 2003; Saksida et al., 2016; Vidyasagar & Pammer, 2010). Taken together, our results suggest that children with dyslexia experience behavioral deficits on tasks including attentional allocation, working memory maintenance, and working memory updating.

Despite the differences in accuracy in the V1-Back and VOT, we did not observe any differences in response time between children with dyslexia and typically developing controls in these tasks. This finding is consistent with others who also failed to observe impaired response times in individuals with dyslexia (Evans et al., 2011), but others have reported contrasting results (Kail & Salthouse, 1994; Miller et al., 2006; Shiran & Breznitz, 2011). It is possible that the nature of the VWM and attention tasks we implemented were not sensitive enough to reflect difficulty in information processing speed that children with dyslexia might experience. Alternatively, in line with the work of others (McVay & Kane, 2012), it is likely that the cognitive impairment observed in individuals with dyslexia is more likely to impact the actual WM processes more so than the global processing speed. Overall, our behavioral results suggest that for children with dyslexia, impaired processing speed is unlikely to be the primary underlying deficit, when compared to their typically developing peers on VWM and attention tasks.

In complement with our null response time differences, we also failed to observe any significant discrepancies in P300 latency on both the V1-Back and VOT between children with dyslexia and typically developing controls. While this finding is consistent with existing data (Evans et al., 2011), it is inconsistent with others' work regarding global processing speed (Kail & Salthouse, 1994; Fawcett et al., 1993; Maciejewska et al., 2013; Miller et al., 2006; Ortiz et al., 1990; Taroyan et al., 2007). One possibility for the discrepancy between our results and others regarding latency is due to the use of age as a covariate, given that prior work suggests age strongly influences P300 latency (Papagiannopoulou & Lagopoulos, 2017; van Dinteren et al., 2014). Therefore, we interpret the lack of group difference in the P300 latency, in addition to our null differences in response time, as further supporting the notion that children with dyslexia maintain global processing speed of information to the same degree as their peers at both the behavioral and neural level.

Consistent with our hypotheses concerning P300 amplitude, we observed reduced P300 amplitudes on both the V1-Back and VOT in children with dyslexia compared to typically developing controls. This complements prior reports showing reduced P300 amplitudes in children with reading-related impairments (Evans et al., 2011; Papagiannopoulou & Lagopoulos, 2017; Taroyan et al., 2007). Regarding the reduced accuracy in the V1-Back task, it is likely that these individuals fail to maintain information in WM, resulting in decreased behavioral outcomes. This impairment in VWM load maintenance may impact the ability to process words and letters in WM for individuals with dyslexia. Given that WM impacts functions involving multifaceted visual sensory processing, such as reading letters and words, this may suggest that individuals with dyslexia experience abnormal development of visual representation, recognition and recall of words and letters. Therefore, automatic reading fluency is not achieved, rendering sematic impairment (Giovagnoli et al., 2016). In line with this hypothesis, more recent findings of Shiran and Breznitz (2011) and Lotfi et al. (2020) have emphasized the relationship between a larger VWM capacity and reading skill improvement among dyslexic individuals, suggesting the pivotal role these processes have in impacting these individuals' performance. They argued that WM deficits in individuals with dyslexia go beyond verbal processing and can rather stem from visuospatial subsystem of the WM. This suggests that exercising WM might consequently improve the quality of reading. In line with this position, using specifically designed computerized cognitive training to target the recall span and the efficiency of visuospatial processing within WM, these researchers showed their training resulted in a significant improvement in decoding, reading rate, and comprehension of dyslexic readers (Shiran & Breznitz, 2011; Lotfi et al., 2020).

We also observed reduced P300 amplitude on rare trials on the VOT for children with dyslexia compared to their typically developing peers. Our results are consistent with others who also observed decreased

P300 on VOT (Papagiannopoulou & Lagopoulos, 2017). It is not surprising that this reduced P300 amplitude was also associated with a reduced behavioral accuracy for dyslexic children on this task. Given that P300 amplitude is believed to reflect WM updating and attentional allocation towards novel stimuli (Polich, 2007), this finding may reflect deficits in these processes for children with dyslexia compared to typically developing peers. This finding also supplements the reduced accuracy observed in these individuals for the VOT.

Overall, our results are consistent with previous studies showing limited VWM and visual attentional processes for dyslexic children both at the behavioral level (i.e., reduced accuracy) as well as underlying neural signatures (i.e., P300 amplitude), resulting in more impaired processing of stimuli. Although we did not observe a significant response time (i.e., processing speed) difference between the DYS and TDC groups in V1-Back task, it is unclear whether this would be the case if the difficulty of *n*-back task increased (namely 2-back, 3-back) which requires larger WM capacity to maintain and manipulate items. Particularly, Evans et al. (2011) reported that children with language impairments showed significant reaction time deficiency when the load of WM increased (Evans et al., 2011). Therefore, it may be the case that incorporating more challenging tasks results in greater discrepancies in performance between children with dyslexia and their typically developing peers.

Additionally, it may be possible that this reduced P300 amplitude may not merely stem from a limited WM capacity, and could represent a broader developmentally dysfunctional visual system. Numerous studies have shown that developmental dyslexia is associated with a number of broad visual-perceptual abnormalities in low spatial and high temporal frequencies (Stein, 2001), visual perception of low contrast (Stein, 2001), and eye-movement anomalies (Dusek et al., 2011; Quercia et al., 2013). Nevertheless, there is evidence showing an increase of the P300 amplitude as a function of age among typically developing children. Therefore, it is likely that the reduced P300 of children with dyslexia might change as they enter later stages of their visual development trajectory (van Dinteren et al., 2014). It is also possible that the reduced P300 for children with dyslexia was due to other compensatory effortful brain mechanisms such as exploiting mental rehearsal strategies. This is quite unlikely though, given that countless studies have reported deficits in lexical encoding and retrieval for dyslexic children compared to their typically developing counterpart. We failed to observe a significant RT and P300 latency difference for both tasks. If this was true, this compensatory mechanism should have rendered slower RT and longer P300 latencies (van Dinteren et al., 2014). Third, we found a strong positive correlation between the magnitude of P300 and the WM capacity of V1-Back task, suggesting the possibility that the P300 amplitude deflection is modulated by the WM capacity.

This study is not without limitations. First, our V1-Back WM task was not capable of distinguishing between encoding or maintenance properties of WM. It may be that this reduced P300 reflects attenuated cognitive resources to encode or maintain degraded memoranda primarily due to resources being used to inhibit extraneous information to enter WM. In fact, our results show that the DYS group showed significantly higher rates of commission errors in both V1-Back and VOT tasks, attesting to some forms of inhibitory deficits in dyslexic children (Savage et al., 2006). Nonetheless, Huettel and McCarthy (2004) reported that VOT is associated with higher activation of the dorsolateral prefrontal cortex (dlPFC; i.e., thought to contribute to P300 magnitude), which regulates encoding, updating and activation of context-appropriate behavior, and maintaining WM. Given the lower accuracies and reduced P300 amplitudes observed for both tasks, one may infer that children with dyslexia might experience constraints on encoding, updating, and maintenance of WM. Therefore, we suggest that future studies investigate the incorporation of a WM task that distinctively taps into these properties of WM while capturing underlying neurophysiological signatures to increase validity and reliability of the result. As mentioned earlier (Evans et al., 2011), children with dyslexia might use covert compensatory effortful mechanism to offset their behavioral WM deficiencies, resulting in null findings between behavioral performance of dyslexic and typically developing children (Evans et al., 2011).

In conclusion, an abundance of evidence has highlighted impaired academic performance in individuals with reading disorders, such as dyslexia (Bergey et al., 2017; Chevalier et al., 2017; Snow & Strucker, 1999). Researchers (Albano et al., 2016; Bosse et al., 2007; Brandenburg et al., 2015; Facoetti et al., 2008; Gathercole et al., 2006; Heiervang & Hugdahl, 2003; Menghini et al., 2011; Pennington, 2008; Pickering, 2012; Schuchardt et al., 2008; Smith-Spark & Fisk, 2007; Swanson, 1994; Swanson et al., 2009; Vellutino et al., 2004; Wagner & Muse, 2006) have suggested that these

deficits may be the result of impairments in WM and attentional processes, or a more broad global processing speed impairment. Our results suggest that children with dyslexia exhibit both behavioral and neural deficits on tasks requiring WM maintenance, reflected by reduced accuracy and P300 amplitude for the *n*-back task. In addition, we identified behavioral and neural deficits in WM updating and attentional allocation processes, seen by reduced accuracy and P300 amplitude on the VOT. Finally, we found no evidence for impairments in global processing speed of information for children with dyslexia compared to their typically developing peers. These findings, using EEG, further support the notion that individuals with dyslexia, particularly children, exhibit deficits in cognitive processes related to WM and attention.

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Author Disclosure

The authors report no conflict of interest.

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Book Review – *Interpersonal Neurobiology and Clinical Practice*

by Daniel J. Siegel, Allan N. Schore, and Louis Cozolino. W. W. Norton & Company, New York, NY, 2021, 368 pages, ISBN: 978-0-393-71457-9.

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This is a review of the consilient book *Interpersonal Neurobiology and Clinical Practice* by Siegel et al., released at the end of 2021. The book is both an accessible and complex consilient demonstration of the principles and integration of Interpersonal Neurobiology (IPNB) with some new material on the influence of COVID-19 and moving mental healthcare into virtual spaces.

Like the theory of IPNB, Siegel et al.'s latest addition to the Norton Interpersonal Neurobiology Series is a glowing example of consilience at work. The voices found within the chapters are familiar and known to those who have read the collection. Each chapter is unique, and each author's voice, frame, and knowledge are clear. As a whole, this book holds the collective theoretical frame of IPNB, a consilience of voice.

As IPNB is a complex conceptualization of human development, these summaries are too complex to serve as an introduction to those who are not already familiar, while at the same time being too basic for those who are. However, the three chapters mentioned do provide sufficient new information to make reading worthwhile.

Chapter 4, written by Porges, is a polyvagal take on COVID-19 and our nervous system. In a clear Porges voice, it outlines and highlights the direct correlation between his work and our new reality. He gives voice to what many have felt during the past two years and what we may have seen as clinicians but have not yet been able to give a name to; the effects on the body of isolation, chronic stress, and unknown disease that affects our neurology. The clinical pieces come in the polyvagal understanding of coregulation and how we do that in the virtual space. "We need to embrace the virtual world of communication with our knowledge of the cures that our nervous system craves. To accomplish this, we need to become more accomplished at sharing feeling moments and not just syntax while in video conferences" (pg. 81)."

Chapter 10, written by Morgan, addresses the role of connection in addiction recovery in a time of social distancing. If you have not read Morgan's "Addiction, Attachment, Trauma, and Recovery," I would highly recommend you do. In this chapter, Morgan explores if connection is the healing power and force in treatment and addiction recovery and how we can accomplish this in a time of isolation, disconnection, stigma, and toxic environment. Morgan addresses the "upstream factors, that is, the social-ecological adversities and create an addiction enhanced environments" (pg. 245). He ends the chapter with positive signs, further changes, and sustainable changes. On a personal note, I think Morgan's voice is one of the warmest and most gentle voices to read in the IPNB series.

Chapter 12 is written by Hughes. He addresses the work of synchronizing states of the emotion of a family's system in working in telehealth. This chapter may be less of interest to the neuromodulation purest. However, a fundamental tenet of IPNB is that most brain development and function are derived from familial relationships. Therefore, it would likely serve even the hardcore neuroscientist to have some sense of family systems. Hughes provides a case example of a family, including a transcript of

fundamental interactions, and discusses the critical research on infant development of emotions and states. He describes the PACE (playfulness, acceptance, curiosity, empathy) conceptualization and reflection of the therapeutic power. He provides clear points in a summary of how this case was "influenced by key aspects of synchronized infant–parent interactions." Like the other chapters before, the novelty and power are not the theoretical frameworks but the inclusion of the teletherapy aspect, addressing and highlighting novel movement into this new shared space of online therapy.

Overall, this book is full of the powerhouse voices of IPNB, and it is more accessible than deep dives into each author's literature or foundational books. If you are an avid reader of the IPNB Norton Series, there is little new information, but there is a quality summary of those unique theories in IPNB. The integration of COVID, telehealth, and our neurology is a helpful starting conceptualization for those doing clinical work and supporting this new formation of our world. This book may be challenging for those new to IPNB and its prolific authors, but it may also spark interest in taking on those deep dives.

Author Declaration

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