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Aim and Scope

NeuroRegulation is a peer-reviewed journal providing an integrated, multidisciplinary perspective on clinically relevant research, treatment, and public policy for neurofeedback, neuroregulation, and neurotherapy. The journal reviews important findings in clinical neurotherapy, biofeedback, and electroencephalography for use in assessing baselines and outcomes of various procedures. The journal draws from expertise inside and outside of the International Society for Neurofeedback and Research to deliver material which integrates the diverse aspects of the field. Instructions for submissions and Author Guidelines can be found on the journal website (http://www.neuroregulation.org).

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Welcome to *NeuroRegulation* Volume 4, Issue 3–4.

We wish to thank all students, researchers, and clinicians that submitted and presented at this year's annual conference in Connecticut. It was a pleasure to hear the presentations, and we encourage presenters to submit their data to *NeuroRegulation*.

In the current issue authors utilize a variety of novel techniques and report interesting findings. Erik Peper and Richard Harvey discuss the implications of indirect treatment effects in placebo-controlled clinical trials. Connie McReynolds, Jodi Bell, and Tina Lincourt discuss data concerning neurofeedback techniques in veterans with posttraumatic stress disorder (PTSD). Mark Zinn, Marcie Zinn, and Leonard Jason present data examining small-world analytics of EEG connectivity in Chronic Fatigue Syndrome (CFS). Finally, we provide selected abstracts from the proceedings of the 2017 conference for the International Society for Neurofeedback and Research (ISNR).

NeuroRegulation thanks these authors for their valuable contributions to the scientific literature for neurofeedback and quantitative EEG. We strive for high quality and interesting empirical topics. We encourage the members of ISNR and other biofeedback and neuroscience disciplines to consider publishing with us. It is important to stress that publication of case reports is always useful in furthering the advancement of an intervention for both clinical and normative functioning. Thus, we encourage all individuals practicing neurofeedback to submit case studies! We thank you for reading *NeuroRegulation*!

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NeuroRegulation

The Fallacy of the Placebo-controlled Clinical Trials: Are Positive Outcomes the Result of "Indirect" Treatment Effects?

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Abstract

This paper argues that placebo effects have a larger influence on clinical trial outcomes than purported treatment effects, raising questions about the size of effects currently attributed to clinical treatments. Placebo-controlled clinical trials usually do not include an "active" placebo and thus the clinical outcome could be due to the placebo responses to nontherapeutic side effects of the treatment. For this paper, an active placebo includes substances or procedures that permit attribution of a physiological effect such as a B-vitamin that safely causes flushing, or a very low, subtherapeutic dose of a medication, as well as a biofeedback training procedure that safely trains physiological responses other than the target response. The paper also discusses the positive outcome of a sham treatment procedure (e.g., not actually doing the proposed treatment) in contrast to the nocebo effect (e.g., a worse or negative outcome associated with unintended effects of the treatment procedure). This paper emphasizes exercising caution when interpreting results from clinical trials using pharmaceutical or surgical treatments. The paper discusses possible mechanisms underlying the acceptance of treatment procedures which later have been shown to be ineffective or harmful, and highlights the importance of incorporating active placebo procedures to address any covert treatment side effects induced by placebo response. Finally, the authors suggest that clinical trials of bio/neurofeedback treatments carefully consider the important and consequential influences of placebos when designing studies or interpreting the results of trial outcomes.

Keywords: placebo; nocebo; active placebo; clinical trials; depression

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When research studies report that randomized placebo-controlled clinical trials are proof that pharmaceutical, surgical, or other bio/neurofeedback treatments are effective, the positive outcomes need to be questioned. For example, the positive findings, even in placebo-controlled trials, may be due to the indirect or "nondirected" placebo responses attributable to treatment side effects that include: the postsurgical discomfort which signals to the patient that the procedure was successful, or a dry mouth and constipation that were caused by the antidepressant medication, which signals to the person that the trial medication or procedure-related medication is working (Bell, Rear, Cunningham, Dawnay, & Yellon, 2014; Stewart-Williams & Podd, 2004). It is possible that the placebo response to treatment side effects (e.g., physical discomfort, dry mouth, or constipation) explains why some medical and psychopharmacology studies are not replicable (Leichsenring et al, 2017; Shader, 2017). Most placebo-controlled studies only control for the placebo effect with a "passive" or inert placebo

group versus an "active" placebo control group (Shader, 2017). This paper provides an overview of the concepts of placebo and nocebo, explores the impact placebo and nocebo, discusses the importance of an active placebo, and suggests questions to ask about the benefits of procedures which could be more attributed to placebo rather than to treatment effects.

What Is a Placebo?

The term *placebo* originates from the Latin for "I shall please" and *nocebo* for "I shall harm" (Bok, 2013). A placebo outcome is associated with the belief that a therapeutic technique or procedure will be beneficial (Haanstra et al., 2015; Moerman & Jonas, 2002). Rather than a simple definition such as "a placebo is a sugar pill," there is a more nuanced definition referring to the "placebo and nocebo processes" where beliefs are formed about the extent to which any benefits or harms are attributable to or are the result of a treatment procedure (Sellaro et al., 2015).

Typically, statements about placebo begin something like: "A placebo is defined as a sham medication, treatment, or procedure inducing, promulgating, or resulting in positive effects caused by nonspecific treatment ingredients." To generalize, a placebo is a medication, treatment, or procedure that supports a placebo belief or learned expectancy leading to a physical, behavioral, or psychological effect called a placebo effect. Placebo effects are illustrated in the following two examples:

> (1) Treatment of headaches. Eight hundred thirty-five women who regularly used analgesics for headache were randomly assigned to one of four groups (Branthwaite & Cooper, 1981). One group received aspirin labeled with a widely advertised brand name ("one of the most popular" analgesics in the United Kingdom that had been "widely available for many years and supported by extensive advertising"). The other groups received the same aspirin in a plain package, placebo marked with the same widely advertised brand name, or unmarked placebo.

The results of the Branthwaite and Cooper (1981) study showed that the branded aspirin worked better than unbranded aspirin, which worked better than branded placebo, which worked better than unbranded placebo. Namely, among 435 headaches reported by branded placebo users, 64% were reported as improved 1 hour after pill administration compared with only 45% of the 410 headaches reported as improved among the unbranded placebo users.

> (2) Treatment for pain reduction. When pain patients are administered pain medication via a needle injection by the nurse versus an automated infusion where the patient does not know that the medication is given, they experience doubling of the pain relief, presumably because the nurse influenced their belief that the treatment would have beneficial effects by reducing pain (Benedetti, 2007; Colloca & Benedetti, 2005).

In summary, Benedetti (2007) and Colloca and Benedetti (2005) each found the more dramatic the placebo procedure, the more confident the purported practitioner, and the more prevailing the cultural beliefs of the patient and practitioner that "help is on the way," the more likely it will be that the patient will benefit. A dramatized example of how the placebo response can be optimized is shown in the Derren Brown BBC video *Fear and Faith Placebo* (nlptechniques, 2013).

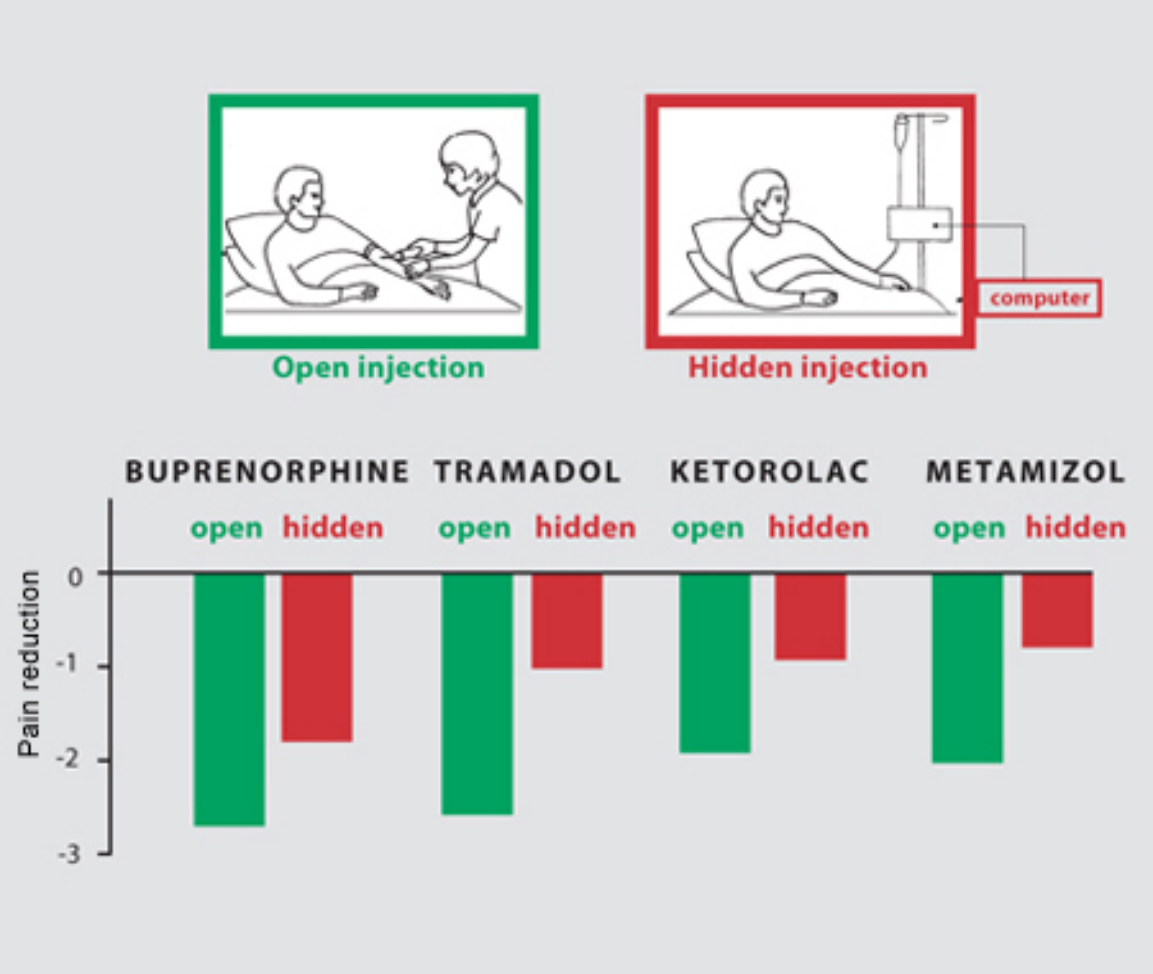

Figure 1. An open injection is compared to a hidden injection of one of four painkillers. An open injection is performed by a doctor in full view of the patient, whereas a hidden injection is carried out by a computer with the patient completely unaware that a medication is being administered. In all cases, a hidden injection is less effective than an open one. (Benedetti, 2007; Colloca & Benedetti, 2005).

What Is a Nocebo?

A nocebo refers to a noxious effect resulting in a nonhealing process of the body. A nocebo effect, treatment, or procedure induces negative expectations and beliefs that the treatment or procedure will be harmful. A nocebo treatment or procedure leads to the perception that the treatment or procedure will have a negative outcome in a way that actively influences the results of exposure to the treatment or procedure. As a result of the nocebo beliefs, the symptoms become worse (Colloca & Finniss, 2012). A common example of a nocebo effect is associated "white coat hypertension" when blood pressure increases after seeing the physician's white coat and believes that something unpleasant may occur during their treatment (Planès, Villier & Mallaret, 2016). The nocebo response occurs when the person gets worse because they now believe that a treatment could be harmful. For instance, when students are given instructions that placing a small electric, possibly undetectable current through their head will have no permanent harm but could result in a minor headache, more than two thirds of the students experience a headache, even though no actual electric current was passed through their head (Schweiger & Parducci, 1981). The symptoms were caused by the nocebo effect, the belief or expectancy (nocebo response) associated with the procedure of placing electrodes on their head.

Similarly, preoperative anxiety is correlated with increased postsurgical pain and discomfort (Vaughn, Wichowski, & Bosworth, 2007). Thus, one role of the healthcare professional is to use positive, reassuring communication to reduce the

preoperative anxiety. For example, when anesthesiologists before surgery simply describe all the possible problems that could occur, without providing a context that the problems are unlikely, some patients have more postoperative complications compared to when anesthesiologists share that they are required by law to describe the possible complications; however, they expect this specific situation to work out well (Cohen, 2014; Rosendahl, Koranyi, Jacob, Zech, & Hansen, 2016; Ruan & Kaye, 2016). Healing is promoted when patients feel safe; the task of the health provider is to support an experience of safety and trust.

Anecdotally, numerous clients have reported experiencing nocebo effects when they share with their physician that they are receiving treatments using traditional Chinese herbs and acupuncture, or bio/neurofeedback. Their doctor may imply verbally or nonverbally, "you are wasting your time and money." Nocebo communications are much more powerful than placebo communications, and nocebo suggestion has been called Western medicine's "voodoo curse" (Brabant, 2016; Dispenza, 2014; Lucas & Booth, 2014). The negative (nocebo) or positive (placebo) phrasing of patient communication influences treatment or procedure outcomes. For example, placebo benefits will more likely occur when the practitioner states or implies: "If you do the treatment (e.g., surgery, medication, bio/neurofeedback therapy), then there is hope that you will get better." On the other hand, nocebo effects will more likely occur when the practitioner states or implies: "If you do not do the treatment then you will stay the same, get significantly worse, or possibly even die." Careful consideration must go into the phrasing of patient communications in order to avoid unwanted nocebo consequences.

Nocebo communications may also be the result of a practitioner fear of litigation such as being sued for malpractice (Johnston, Wester & Sartwelle, 2016). For example, a patient with end-stage cancer may be encouraged to continue the standard medical procedures even though continuing those treatments is unlikely to prolong life: The continuation of treatment implies that there is hope even though the treatment may not provide a known benefit and may in fact lead to complications and an earlier death compared to stopping treatment.

If the patient dies, the medical staff as well as family and friends may then say, "We did everything we could have done." On the other hand, if a practitioner encourages the patient to choose an alternative medication, treatment, or procedure which is not the current "standard of care" and then the patient dies, the medical community, family, and friends may say, "The practitioner was a quack and caused the death." This unspoken fear may prevent practitioners from suggesting alternative treatments. The same fear may also prevent patients from participating in a placebo-controlled study for fear that a placebo administration and not the "real" (i.e., legally safe) treatment will be linked to poor outcome or even a death (Johnston, Wester, & Sartwelle, 2016).

Cautionary Tales

The following are but a few of the many treatments that were initially widely accepted as effective, only to be proven harmful or ineffective in subsequent investigations:

- **Bloodletting.** A bloodletting treatment for various illnesses which was logically consistent with the humoral theory of medicine in the 18th and 19th century may have contributed to the death of numerous patients (Greenstone, 2010).
- **Intensive psychological debriefing** (e.g., emotional "flooding"). A flooding treatment after trauma event was recommended as the treatment to reduce PTSD; however, flooding increased PTSD (Bisson, Jenkins, Alexander, & Bannister, 1997; Mayou, Ehlers, & Hobbs, 2000).
- **Thalidomide.** A medical remedy for sleeplessness and morning sickness for pregnant women lead to an epidemic of congenital abnormalities (Carey et al., 2017; McBride, 1961).
- **Anti-anxiety medication.** An anxiolytic treatment for panic attacks unfortunately increased panic attacks during medication withdrawal when compared to a placebo which had no withdrawal effects (Ballenger et al., 1988; Brown et al., 2016; Johnson, Federici, & Shekhar, 2014; Pecknold, Swinson, Kuch, & Lewis, 1988; Salzman & Shader, 2015).
- **Hormone replacement therapy (HRT).** A treatment for menopausal women to reduce menopausal symptoms seemed to reduce the risk of breast cancer; however, instead HRT was shown to increase the risk of breast cancer (Zbuk & Anand, 2012).
- **Vineberg procedure.** A procedure (Vineberg & Miller, 1951) in which the internal mammary artery was ligated by surgery for the treatment of angina pectoralis. Cobb, Thomas, Dillard,

Merendino, and Bruce (1959) showed that a double-blind (placebo-controlled) sham/mock surgery was equally effective as a real surgery; thus, the Vineberg procedure was abandoned (Beecher, 1961).

- **Arthroscopic knee surgery.** A surgery of the knee for people with osteoarthritis that uses a biomechanical approach to remove microscopic or macroscopic fragments of calcium phosphate crystals associated with synovitis (Felson & Buckwalter, 2002); however, there are no benefits in long-term follow-up for patients receiving surgery as compared to physical therapy (Brignardello-Petersen et al., 2017; Kirkley et al., 2008; Monk et al., 2017). More importantly, when the arthroscopic surgery outcomes were compared with a sham/mock surgery, there was no difference in outcome (Moseley et al., 2002).
- **Reducing dietary fat.** Despite "fat causes heart disease; therefore, eat a low-fat diet," recent studies have shown that low-fat diets were often very high in simple carbohydrates and much more harmful to the patients (Taubes, 2016).

Future treatment procedures may capitalize on the beneficial effects of placebo responses observed during placebo-controlled trials. A few examples include:

- **Bypass surgery.** Ornish et al. (1990; 1998), van Dixhoorn and White (2005), and others have shown that lifestyle changes appear more effective than traditional coronary surgery treatments (Pischke, Scherwitz, Weidner, & Ornish, 2009). The only way to test whether bypass surgery treatments are effective is to test against a sham/mock surgery group which for ethical reasons has not yet been done.
- **Annual mammogram screening.** Autier, Boniol, Gavin, and Vatten (2011) and Nelson et al. (2009) studied healthy women receiving routine mammography which may have unintentionally caused an excessive number of treatment and surgical interventions due to excessive x-ray exposure. Possibly screening of healthy women is not predictive of reduced incidence of breast cancers and may be less related to reducing breast cancer death rates when compared to other factors. In countries where screening did not occur until much later breast cancer deaths also decreased as compared to countries that started screening early (Autier et al., 2011; Nelson et al., 2009).
- **Treatment of depression.** An antidepressant medication for mild to moderate depression may be less effective compared to a treatment of exercise and behavior therapy which appear as, if not more, effective (Babyak et al., 2000; Hallgren et al., 2016).

Pharmaceutical Marketing Practices and Placebo Effects

Many of the benefits claimed by pharmaceutical companies for successfully treating depression, insomnia, or anxiety may be due to the placebo response evoked by changes in body sensations (e.g., "a flushing experience means the treatment or procedure is working") that are attributed to the "effectiveness" of the medication or medical treatment procedures. For example, selective serotonin reuptake inhibitors (SSRI) antidepressant medications such as Paxil or Prozac have side effects within hours compared to therapeutic effects that reportedly take at least one or two weeks to have an effect. Patients may report almost immediate benefits from Prozac, as reported by the many published research studies; however, as a cynical observation, many of those studies are funded by pharmaceutical companies. It is not clear that the therapeutic benefits are due to Prozac's purported direct mechanism of action or rather due to indirect effects associated with priming a belief that Prozac will be an effective medication (Kirsch & Sapirstein, 1998; Mayberg et al., 2002; Mora, Nestoriuc, & Rief, 2011). A similar example occurs with the purported benefits of Zoloft, an anti-depressant, that may be due solely to the placebo response associated with medication side effects which according to the Drugwatch website typically "decrease after the first or second week of use and include: nausea, diarrhea, weight loss or gain, increased sweating, dizziness, sleepiness or insomnia, tremor, dry mouth, headache, restlessness, suicidal thoughts, and sexual dysfunction" (Llamas, 2017).

When independent researchers (e.g., not funded by pharmaceutical companies) reanalyzed research data from published or unpublished studies, they often found that a treatment medication was no more effective than placebo for the treatment of mild and moderate depression, both within the first week or two of administration, as well as at long-term follow-up (Doering, Rief, & Petrie, 2014; Kirsch, 2014; Kirsch & Sapirstein, 1998; Mayberg et al.,

2002). Even though antidepressant medications such as Prozac may be no more effective than a placebo treatment, medications such as Prozac allow the pharmaceutic industry to post global sales in 2013 of $23.8 billion dollars for mental health medications, with tens of millions of pill prescriptions for antidepressant medications annually (Lindsley, 2015).

When pharmaceutical companies fully report both positive and negative results of medication studies, the positive data becomes much less favorable when the negative side effects from medications are included. For example, SmithKline Beecham's Study 329 data was reanalyzed by Le Noury et al. (2015) to compare the safety of paroxetine and imipramine which are SSRIs with placebo in the treatment of adolescents with unipolar major depression. The results showed that there was no significant difference in outcome between the medications and the placebos. Sadly, there were clinically significant increases in harms, including suicidal ideation, suicidal behavior, and other serious adverse events in the paroxetine group as well as cardiovascular problems in the imipramine group. In 2012, GlaxoSmithKline pleaded guilty and paid a $3 billion fine to resolve fraud allegations and failure to fully report safety data (U.S. Department of Justice, 2012).

How Come the Medical Procedures were Initially Accepted?

Medical interventions and procedures make rational sense, and any initial positive outcome is enhanced by "confirmation bias" when we "detect, attend to, and recall circumstances that confirm prior beliefs" (Kassin, Dror, & Kukucka, 2013; Schwarz & Büchel, 2015). Simply stated, when patients, researchers, and clinicians observe any—even minimal—positive physical, behavioral, or psychological effects of a treatment or procedure, it confirms their clinical bias that the treatment procedures were a success. The patient "improved" in the expected way. Eventually the treatment procedure becomes accepted and adopted by others.

Later when the results are "confirmed" by randomized, placebo-controlled trials, the procedures gain even more credibility. The patients' positive benefits are given as proof that the particular procedures "as described" was instrumental to cause the associated positive benefits. However, association is not causation (Bollen & Diamantopoulos, 2017; Bollen & Pearl, 2013). When clinical trials use inert placebo, the treatment will perform relatively better than when compared to an active placebo (Howick, 2017; Howick et al., 2013; Roose, Rutherford, Wall & Thase, 2016). Other factors that impact the reporting of predominantly positive findings are that:

- Scientific journals are biased to publish positive findings and tend not to publish negative findings (Every-Palmer et al., 2014; Franco et al., 2014).
- Researchers tend to publish positive findings; since, they may not receive follow-up grants if they report negative findings (Ioannidis, 2005).
- Lack of long-term follow-up and assessment of negative side effects of procedures are absent.
- Undue industry pressure and funding influence the outcome and publication of the research (Friedman & Friedman, 2016; Stamatakis, Weiler, & Ioannidis, 2013).
- Profit incentive to continue the practices (financial loss aversion) since the privatized medical industry's major goal is increasing shareholder value.

Once a procedure is believed to be effective, it is very challenging to stop the practice from becoming standardized even when later the positive outcomes are shown to be attributable more to a placebo response. For example, arthroscopic surgery for degenerative knee problems continues to be practiced at a cost of 3 billion dollars a year. Obvious questions are raised: If a positive outcome is mostly attributable to a placebo response, what is the harm, and why continue the medical or surgical procedure? Is it ethical to try new procedures once the patient believes the initial procedure is effective because a "positive outcome" occurred? Some answers may be found by exploring components of the placebo response.

Components of the Placebo Response

Before accepting whether any benefits are the result of the planned procedure, clinicians need to assess the following components of a placebo response and then document:

- The causally "direct" overt effect of the medication, surgery, or other treatment procedure such as the direct effects of both planned placebo (positive, encouraging) instructions, procedures, or substances used as a control.
- The causally "indirect" covert effects of the medication, surgery, or other treatment

procedure such as the unplanned effects the treatment procedures have on patients.
- The causally direct or indirect, overt or covert placebo effects attributable to the "side effects" of surgery; medication (e.g., discomfort, dry mouth, or even sitting still for an hour during biofeedback training) which evokes somatic changes that the person experiences and then attributes the outcome to the intervention.
- The overt or covert nocebo communication effects (e.g., "voodoo" instruction/ communication) about what would happen when the participant does not partake in the recommended treatment procedure.

The Importance of Active Placebo

It is impossible to separate direct and indirect, overt and covert components unless the study design includes an active placebo procedure. An active placebo is a procedure that induces psychophysiological effects, yet offers no obvious, causally direct therapeutic benefit. For example, Pollan (2015) primed student volunteers with a communication that if they experience a "skin flushing" then they may be experiencing the effects of a hallucinogenic substance, with the result that many reported a "psychedelic trip" even when they only received niacin (e.g., vitamin B3). Similarly, Lee (2015) primed student athletes with a communication that if they experience increased heart rate then they may have received an athletic performance-enhancing substance, with the result that many had observable athletic performance improvements when they only received a mild dose of caffeine. Another example was shown when study participants had improvements in "attentional performance" even though EEG biofeedback sensors were positioned over irrelevant anatomical locations (Bjørkedal, 2016; Jensen, Bielefeldt, & Hróbjartsson, 2017; Vollebregt, van Dongen-Boomsma, Buitelaar, & Slaats-Willemse, 2014).

During surgical procedures, an active placebo control would be a sham/mock surgery in which the patient would undergo the same medical procedure (e.g., external surgery incision) without continuing some internal surgical procedure (Jonas et al., 2015). In numerous cases of accepted surgery, such as the Vineberg procedure (Vineburg & Miller, 1951) for angina, or arthroscopic knee surgery for treating osteoarthritis, the clinical benefits of a sham/mock surgery were just as successful as the actual surgery. Similar studies suggest the clinical benefits were solely (or primarily) due directly to the placebo response (Beecher, 1961; Cobb et al., 1959; Moseley et al., 2002).

The Hidden Placebo in Study Designs

Many research studies employ a placebo control, however what is less typical is a double-blind study using an active placebo (Enck, Bingel, Schedlowski, & Rief, 2013). Unfortunately, a typical placebo-controlled study design is problematic for identifying the direct and indirect (covert) placebo effects that occur within the study as shown in Figure 1.

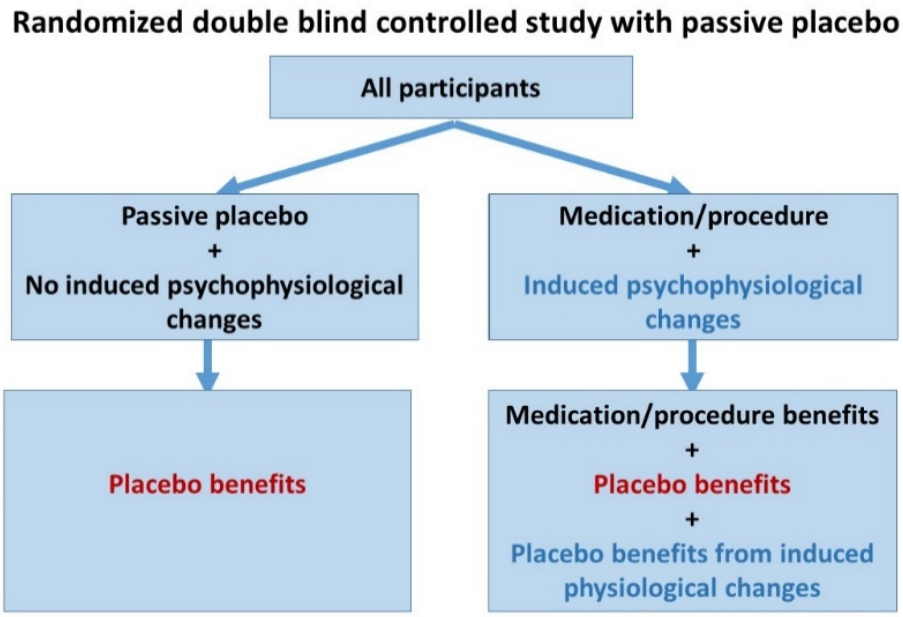

Figure 1. Normal (passive) placebo control group controls and experimental group. What is not assessed are placebo benefits induced by the medication/treatment induced side effects.

With a passive placebo, there is no way to know if the observed benefits are from the medication/ medical procedure or from the placebo/self-healing response triggered by the medication/medical procedure. The only way to know if the treatment is actually beneficial is to use an active placebo instead of a passive placebo. The active placebo triggers observed and felt body changes which do not affect the actual illness. A study design using an active placebo arm is shown in Figure 2.

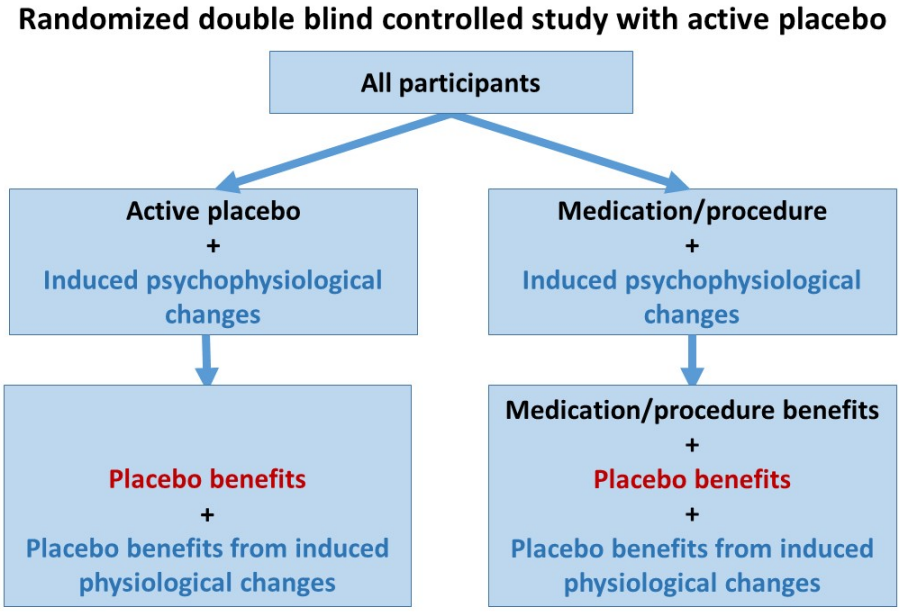

Figure 2. Active placebo control group controls for the normal placebo benefits plus those placebo benefits induced by the medication/treatment-induced side effects.

The implications of an active placebo may suggest that numerous treatments may not be as successful as claimed and may be one of the major factors why so many medical and psychological studies cannot be replicated.

Questions to Ask Before Agreeing on the Procedure or Medication

A quick way to ask whether a medication or medical treatment benefit is the result of placebo components is with the following questions:

> (1) Are there successful self-care or behavioral approaches that have demonstrated success? When successful treatments are reported, then questions are raised whether pharmaceutical or surgical outcomes are also attributable to the result of placebo effects. On the other hand, if there a no successful self-care approaches, then the benefits may be more due to the therapeutic effect of a surgical procedure or medication.
>
> (2) Has the procedure been compared to an active placebo control? If not, then it is possible that the results could be attributed to a placebo response.

What are the long-term benefits and complication rates of the medication, treatment, or procedure? When benefits are low and risks of the procedure are high, explore the risks associated with "watchful waiting" (Colloca, Pine, Ernst, Miller, & Grillon, 2016; Thomas, Williams, Sharma, Chaudry, & Bellamy, 2014).

Finally, interventions reflect the biases of the clinicians; therefore, more objective approaches to determining the fitness and appropriateness of the intervention may take trial-and-error over many variations of the interventions. To quote or paraphrase the work of Taleb (2012) from his book *Antifragile: Things That Gain from Disorder:*

- Over millions of years through natural selection, whatever increased reproductive fitness predominates; thus, it is unlikely we can do better than natural selection with technology.
- Nature produces ongoing experiments to improve reproductive fitness. As Taleb (2012) points out:

  > It was an insult to Mother Nature to override her programmed reactions unless we have a good reason to do so, backed by proper empirical testing to show that we humans can do better; the burden of evidence falls on us humans.

- How can we improve health with some simple procedure or medication when nature has experimented for millions of years? It is unlikely that we can do anything to improve fitness.
- Nature had to have tinkered through selection in inverse proportion to the rarity of the condition.
- Of the hundred and twenty thousand medications available today, none make a person better. For example, steroid substances may enhance athletic performance; however, they can reduce sperm production, increase aggression, heart attacks, or strokes, and may result in gynecomastia.
- If the patient is near healthy, then Mother Nature should be the doctor (e.g., eating well, avoiding stress, and getting lots of good rest should cure colds).
- If the patient is close to death, all speculative treatments should be encouraged—no holds barred.

Summary

All observed outcomes result from a combination of overt and covert, direct and indirect, specific and nonspecific effects of a medication, treatment, or procedure, including placebo components.

Because medications, treatments, or procedures may have both placebo and nocebo components, those medications, treatments, or procedures should only be recommended when they significantly improve the health of the patient more than an active placebo treatment group and not merely a passive placebo group. Unfortunately, most clinical studies that include pharmaceuticals or surgery do not test their medication or surgery against an active placebo. Sadly, the FDA does not require a standard of double-blind, active placebo controls for studies, which may work to support "Big Pharma" to maximize profits.

Fortunately, the design of active placebo-controlled studies is very possible for anyone interested in comparing the effectiveness of medications, treatments, and procedures in various settings, from hospitals and clinics to university classrooms and individual homes.

Finally, the benefits of the treatment must significantly outweigh any risks of negative treatment side effects. Short-term treatment benefits need to be balanced by any long-term benefits. Unfortunately, short-term benefits may lead to significant, long-term harm such as in the use of some medications (e.g., sleep medications, opioid pain killers) that result in chronic dependency and which lead to a significant increase in morbidity and mortality of many kinds. Using active placebo procedures have far less damaging side effects compared to many pharmaceutical interventions. Furthermore, bio/neurofeedback procedures are built on operant conditioning principles, which facilitate active learning techniques that have few, short-lived side effects compared to many long-lived pharmaceutical side effects (Luctkar-Flude, Groll, & Tyerman, 2017; Rogel et al., 2015).

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NeuroRegulation

Neurofeedback: A Noninvasive Treatment for Symptoms of Posttraumatic Stress Disorder in Veterans

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Abstract

This paper discusses positive therapeutic gains made with veterans whose primary treatment for posttraumatic stress disorder (PTSD) was artifact corrected neurofeedback. Assessments completed after both 20 and 40 half-hour sessions of treatment identified significant improvements for both auditory and visual attention using the IVA-2 and significant improvements in well-being based on the General Well-Being Scale (GWBS). It was discovered that neurofeedback impacted individuals' overall auditory attention and IVA-2 global auditory test scores significantly improved after both 20 ($p < .007$, Cohen's $d = 0.5$) and 40 training sessions ($p < .0001$, Cohen's $d = 0.8$). Veterans were found to have significant enhancements in auditory vigilance ($p < .03$), processing speed ($p < .0009$) and focus ($p < .01$). The IVA-2 global measure of visual attention was also found to show significant improvements after 20 sessions ($p < .004$, Cohen's $d = 0.5$) and after 40 sessions ($p < .06$, Cohen's $d = 0.4$). Specific improvements in visual processing speed ($p < .04$) and focus ($p < .02$) were identified after 40 sessions. Ratings of well-being significantly improved after treatment ($p < .001$, Cohen's $d = 0.8$) with 84% of the veterans improving five points or more on the GWBS. Improvements in well-being were found to be significantly correlated with increases in veterans' overall auditory attention ($r = .44$, $p < .03$) and auditory processing speed ($r = .57$, $p < .005$).

Keywords: veterans; posttraumatic stress disorder; PTSD; well-being; IVA-2; CPT; GWBS; attention; artifact corrected; neurofeedback; EEG biofeedback

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Introduction

One in five veterans returning from Iraq and Afghanistan conflicts have been identified as experiencing symptoms of posttraumatic stress disorder (PTSD; RAND, 2008). PTSD indicators can include behavioral, psychological, mood, and sleep symptoms, along with an emotional detachment, or unwanted or intrusive thoughts (NIMH, 2016). Specific symptoms include agitation, irritability, hostility, hypervigilance, self-destructive behavior, social isolation, flashbacks, fear, severe anxiety, or mistrust (American Psychiatric Association, 2013). Moreover, mood indicators can comprise a loss of interest or pleasure in activities, guilt, or loneliness, while sleep dysfunction can involve insomnia or nightmares. Additional symptoms of PTSD include informational processing dysregulation with impairments in attention and working memory (Karl, Malta, & Maercker, 2006; Mirsky, Anthony, Duncan,

Ahearn, & Kellam, 1991; Vasterling et al., 2002), excessive reactivity to trauma-related cues (Buckley, Blanchard, & Neill, 2000), and physiological responses that trigger the "fight-flight" response (Benson, 1975).

Traditional treatments for PTSD symptoms include pharmacotherapy and/or talk therapy; however, both common approaches have some realistic limitations. Specifically, pharmacotherapy addresses general symptoms but, unfortunately, can have a wide variety of medication side effects and, frequently, does not correct the underlying cause (van der Kolk et al., 2016). Similarly, conventional talk therapy for PTSD, while helpful for some individuals (Breuer & Freud, 1966), has been found not to be effective with others (Atkinson, 1999; Bisson, Roberts, Andrew, Cooper & Lewis, 2013; Bradley, Greene, Russ, Dutra, & Westen, 2005; Demos 2005; NICE, 2005; van der Kolk et al., 2016; Wylie, 2004). The use of traditional talk therapy often focuses on encouraging the person to emotionally recall the traumatic event and even to reexperience it somatically in an effort to reprocess the trauma and relieve its ongoing effects and symptoms. In contrast, the use of neurofeedback treatment avoids the potential triggering of painful experiences pertaining to the traumatic event (Reiter, Andersen, & Carlsson, 2016; van der Kolk et al. 2016) and instead helps the individual by enhancing their ability to be focused, attentive, and aware in the present moment. Through the use of neurofeedback, the person is able to release the painful experience without reliving the trauma as a means of exorcising it (Robbins, 2000).

It has been advanced that talk therapy may not be very effective for some individuals because the recall of traumatic events can easily initiate the activation of the brain's limbic circuits and provoke a strong emotional reaction that can potentially diminish the functioning of the left frontal lobe for self-regulation (Baum, 1997; Demos, 2005; Thompson & Thompson, 2003; van der Kolk, McFarlane, & Weisaeth, 1996; Wylie, 2004). Further, it is believed that for some veterans talk therapy triggers a strong physiological response to past emotional trauma, subsequently diminishing the effectiveness of the talk therapy approach (Benson, 1975; Demos, 2005).

Since it is recognized that memories of a traumatic event can activate the limbic system and be countertherapeutic for a number of veterans (Baum, 1997; van der Kolk et al., 1996; Wylie, 2004), then a viable alternative for the treatment of PTSD is to consider neurofeedback. By using neurofeedback training to decrease activation levels in the limbic system and enhance the self-regulatory capabilities of the frontal lobe system, veterans can experience PTSD symptoms while in a relaxed, focused mental state and use the frontal lobe's ability to process, resolve, and release the traumatic experience (Robbins, 2000; White & Richards, 2009). A key premise of neurofeedback training is that it is structured to improve cognitive flexibility, physical and mental relaxation, along with greater inner awareness, that can enhance an individual's emotional self-control skills thereby enabling the person to gradually process and release the conditioned reaction to past emotional events (Mason & Brownback, 2001).

Neurofeedback therapy, or EEG biofeedback, has been widely used for more than 30 years. During this time, it has gained recognition as an acceptable approach for treating conditions ranging from Attention-Deficit/Hyperactivity Disorders (ADHD) to anxiety, depression, sleep disorders, and learning disabilities (Hammond, 2011). Neurofeedback works by helping individuals learn to become more aware and sensitive to their emotional and mental states in order to develop better self-regulation, self-awareness, and attention control, thus allowing for individuals to slowly and safely experience traumatic memories in order to process and decondition their impact without becoming overwhelmed (Demos, 2005; Othmer & Othmer, 2009). While the initial stage of the neurofeedback therapeutic process for PTSD is to facilitate the development of a calm and stable mental state, the next phase is to permit the brain to access and to resolve the emotional expression of underlying traumas through deconditioning of emotional reactions that previously occurred whenever they spontaneously arose or were triggered by environmental stimuli (Robbins, 2000).

Neurofeedback has been found in research studies to be clinically effective and comparable in outcome measures to other recognized types of treatments for individuals who experience the symptoms of PTSD (Peniston & Kulkosky, 1991; van der Kolk et al., 2016). Weaknesses involving sustained attention have been identified previously in individuals with PTSD (Sachinvala et al., 2000), and documented specifically in veterans with PTSD (Vasterling, Brailey, Constans & Sutker, 1998; Vasterling et al., 2002; Uddo, Vasterling, Brailey, & Sutker, 1993), making the use of neurofeedback particularly beneficial in treating the attentional dysfunction, which is often prevalent in PTSD

populations. Neurofeedback can be conceptualized as utilizing the brain's inherent capability of neuroplasticity that allows individuals to become aware of the faint cues of their EEG neural activity. By attending to the feedback provided, individuals learn to control and direct their brain activity in order to cultivate a more harmonious and balanced mental state (Budzynski, 1999; Demos, 2005; Nunez, 1981; Othmer & Othmer, 2009; Speckmann & Elger, 1987; White & Richards, 2009). The changes resulting from neurofeedback have been found to result in long-term changes and positive outcomes (Budzynski, 1999; Demos, 2005; Othmer & Othmer, 2009).

The training process involves placing EEG sensors over selected brain regions on the scalp and ears to measure the amplitude of the electrical activity of the brain's neuronal network. The individual's brainwave patterns are quantified and then displayed on a computer screen in a meaningful manner using both visual and auditory feedback. The therapist develops a treatment plan, which can consist of 20 to 40 training sessions lasting about thirty minutes each, and establishes therapeutic goals that are specific for each person's needs. Both visual and auditory game-like feedback is utilized to reinforce the achievement of training goals.

The purpose of this retroactive study was to evaluate the clinical effectiveness of the neurofeedback treatment for the 20 veterans who presented with a variety of PTSD symptoms including anxiety, panic attacks, concentration difficulties, sleep disorders, depression, and memory concerns. It was hypothesized that the Integrated Visual and Auditory Continuous Performance Test – Version 2 (IVA-2 CPT) global measures of visual and auditory attention (VAQ and AAQ scale scores, respectively) would show a significant improvement after both 20 and 40 sessions of treatment. A second hypothesis was that the ratings of well-being measured by the General Well-Being Scale (GWBS) would significantly increase after 40 sessions were completed. Since five statistical tests were planned and neurofeedback training was expected based on past studies to positively affect attention and well-being, a one-tail alpha level was set to $p < .02$ based on the Bonferroni correction with adjustments for the initial mean correlation between all test scales. Additional analyses were planned to examine the relationship between improvements in IVA-2 measures of attention and the GWBS ratings of well-being in order to explore in detail the specific aspects of attentional functioning that changed after veterans completed 20 and 40 neurofeedback sessions and whether or not improvements in attention led to increases in veterans' feelings of well-being.

Methods

Participants

Neurofeedback treatment was provided for 20 U.S. military veterans (16 males, 4 females). The average age of the veterans at the time of testing was 46 years old (± 1 *SD* = 17.7). The self-reported primary diagnoses of these veterans included PTSD (65%), ADHD (15%), Major Depression (10%), Generalized Anxiety (5%), and Learning Disability (5%). The participants for this study were randomly drawn from an archival database of a sample of veterans who had previously received neurofeedback training. Individualized neurofeedback training was provided within a university-based clinic setting. Veterans were not compensated to participate in the neurofeedback training. The funding agency provided support for neurofeedback services to be delivered as a clinical intervention rather than as a study of a specific neurofeedback protocol. This study was approved by the California State University San Bernardino Internal Review Board. Participants were provided with an informed consent process.

Measurements

The IVA-2 CPT has been found to be a valid and reliable measure of both visual and auditory attention functioning in both children and adults and provides both global and primary measures of attentional functioning. The normative sample, with approximately equal numbers of males and females, included 1,700 individuals ages 6 to 96 (Maddux, 2010). The scales on the IVA-2 have a mean of 100 and a standard deviation of 15. The IVA-2 global measures of attention used in this study are the Visual Attention Quotient (VAQ) and the Auditory Attention Quotient (AAQ). The VAQ is a global measure of attention that is comprised of three primary visual scales: Vigilance, Speed, and Focus. Vigilance measures errors of omission, and Speed provides a measure response time to visual test targets. Focus is a measure of the variability of response time to visual test targets. The AAQ has the exact same components and differs in that it assesses auditory test responses to the same primary measures of attention (Sandford & Sandford 2015). Moreover, the IVA-2 has been demonstrated to be valid for adults with neurological insults such as traumatic brain injury (TBI; Tinius, 2003).

The GWBS is an 18-item questionnaire that is a self-report rating scale that measures a person's general sense of well-being. It incorporates six subscales of well-being including measures of anxiety, positive well-being, depression, vitality, general health, and self-control. The GWBS has been found to be both a valid and reliable measure of well-being for several ethnic minority groups including young Caucasian males (Fazio, 1977) along with Japanese (Nakayama, Toyoda, Ohno, Yoshiike, & Futagami, 2000), Mexican-American (Poston et al., 1998), and African-American populations (Taylor et al., 2003).

Test Procedure

Every veteran was administered and completed the IVA-2 CPT and the GWBS before beginning their first neurofeedback session. Testing was individually administered and scored in accordance with test procedures. There were a few individuals who were not able to validly respond to either visual or auditory IVA-2 test stimuli due to their extreme deficits in attentional functioning. In these cases, their "invalid scores" for IVA-2 were scored as zero in accordance with the test interpretive procedures (Sandford & Sandford, 2015). After the completion of 20 and again after 40 neurofeedback sessions, the IVA-2 test was readministered. Twenty veterans completed 20 neurofeedback sessions and 19 completed an additional 20 sessions. One individual dropped out due to scheduling conflicts after completing 20 sessions. Following the last neurofeedback session, the GWBS rating scale was administered for the second time. IVA-2 data was analyzed comparing baseline test scores and the scores obtained after both 20 and 40 sessions were completed. The GWBS rating scale score analysis compared pretraining baseline scores to scores obtained after 40 sessions of treatment.

Neurofeedback Treatment Protocols

An individualized neurofeedback training plan was developed for each participant and clinically modified as necessary. Therapeutic goals focused on improving attentional functioning and reducing any identified mental stress related to the symptoms of depression and anxiety. Training was completed using the SmartMind 3 artifact corrected neurofeedback system with a two-channel EEG station (BrainTrain, Inc., North Chesterfield, VA) which continuously filters out frequently occurring, very brief EMG artifacts in real time without interrupting the training program. Neurofeedback exercises were provided in game-like format that utilized both visual and auditory reinforcement, as well as graphs and numerical scores to provide positive reinforcement. The first step in the training session was to collect an individual's baseline EEG data in order to determine *Z*-Score feedback goals for each individual. Based on each individual's performance, they were provided clinically relevant feedback and adjustments were made to the training protocol to optimize their performance. All EEG data was automatically recorded.

Results

Since five main tests were required to answer the hypotheses of this study, the alpha level was determined to be .02 using a Bonferroni correction adjusted for the pretreatment correlation of the measures used (r = .46). All *t*-tests were one-tail measures given that it was expected based on past research studies that neurofeedback would result in positive changes in attention and emotional self-regulation. Given that the normative mean quotient score of the IVA-2 test is 100 and its standard deviation is 15, any increase of eight or more quotient score points (i.e., greater than one half of a standard deviation) is considered clinically significant. This section will first address the main hypotheses. Next, more specific IVA-2 component measures of auditory and visual attention will be examined in an exploratory analysis with the alpha level set to .10 in order to explore more in-depth any changes in attention and their relationship to improvements in well-being.

In order to evaluate whether or not neurofeedback training improves auditory and visual attention, paired sample *t*-tests were computed comparing pretreatment IVA-2 AAQ and VAQ quotient test scores with each individual's IVA-2 test scores after completing 20 and then 40 sessions. As indicated in Table 1, veterans (N = 20) significantly increased their AAQ score after 20 sessions of treatment from a mean of 83 (Mildly Impaired) to 96 (Average), a 13-point increase, $t(19) = -2.68$, $p < .007$, Cohen's d = 0.5. AAQ scores were also found to be significantly higher after 40 treatment sessions (see Table 2, N = 19) and increased from 82 to 100, an 18-point improvement, $t(18) = -4.53$, $p < .0001$, Cohen's d = 0.8.

Table 1
Paired Sample t*-tests comparing mean IVA-2 Quotient scale scores at Baseline and after veterans (N = 20) completed 20 neurofeedback training sessions.*

IVA-2 Attention Scales	Baseline (*N* = 20)	20 Sessions	Q Score Change	Pooled SD	Sig.	Cohen's *d*
Auditory Attention Quotient	83	96	13	24	0.007	0.5
Auditory Vigilance	88	97	9	28	0.15	n.a.
Auditory Speed	84	100	16	22	0.002	0.7
Auditory Focus	91	94	3	17	0.21	n.a.
Visual Attention Quotient	84	96	12	27	0.004	0.5
Visual Vigilance	86	94	8	28	0.08	0.3
Visual Speed	92	103	13	22	0.03	0.5
Visual Focus	84	96	12	26	0.007	0.5

Table 2
Paired Sample t*-tests comparing mean IVA-2 Quotient scale scores at Baseline and after veterans (N = 19) completed 40 neurofeedback training sessions.*

IVA-2 Attention Scales	Baseline (*N* = 19)	40 Sessions	Q Score Change	Pooled SD	Sig.	Cohen's *d*
Auditory Attention Quotient	82	100	18	24	0.0001	0.8
Auditory Vigilance	87	100	13	27	0.03	0.5
Auditory Speed	82	102	20	23	0.0009	0.9
Auditory Focus	91	97	6	14	0.01	0.5
Visual Attention Quotient	84	95	11	31	0.06	0.4
Visual Vigilance	87	90	3	35	0.37	n.a.
Visual Speed	90	102	12	22	0.04	0.5
Visual Focus	83	97	14	25	0.02	0.6

In Figure 1, the continued improvement in auditory attention from 20 to 40 sessions that was significant can be viewed, $t(18) = -1.83$, $p < .04$, Cohen's $d = 0.2$. The IVA-2 VAQ test scores significantly increased 12 points after 20 sessions, $t(19) = -2.99$, $p < .004$, Cohen's $d = 0.5$; and 11 points after 40 sessions, $t(18) = -1.64$, $p < .06$, Cohen's $d = 0.4$. Unlike AAQ scores, VAQ measures were not found to significantly change after an additional 20 training sessions as seen in Figure 1. Thus, these test results support the hypothesis that neurofeedback training led to a significant improvement in global measures of both auditory and visual attention.

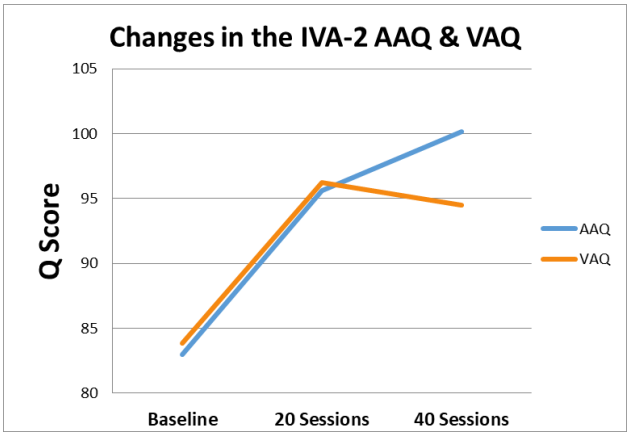

Figure 1. Changes in the IVA-2 Auditory Attention (AAQ) and Visual Attention (VAQ) standard Q scale scores after 20 and 40 sessions of neurofeedback.

An examination of the changes in AAQ and VAQ on a clinical basis was completed to further explore and predict the potential benefit of neurofeedback on an individual basis. In order to do so, a positive or negative change in IVA-2 quotient scale scores of eight or more was considered clinically significant. After 20 sessions, 80% of the veterans improved in either AAQ or VAQ scores by eight points or more and for 40 sessions the treatment success rate was 74%. IVA-2 testing after 20 sessions found that 15% did not improve or declined (greater than eight points) in either AAQ or VAQ scores, and at 40 sessions, 10% still did not show any change in their attentional functioning. Only one person, or 5% of the veterans at 20 sessions, decreased significantly in his VAQ score and had no meaningful change in AAQ indicating that he was more impaired in visual attention when evaluated for the second time. At 40 sessions, three individuals performed significantly more poorly in respect to visual attention and had no improvement or decrement in their auditory attention. In general terms, these results indicate that it is reasonable to expect that about four out of five veterans will significantly benefit from neurofeedback training, but that about 1 out of 10 will actually decline (eight or more points) in their visual attention without any compensating improvement in their auditory attention.

Changes in self-reports of well-being were assessed by comparing the initial scores on the GWBS with rating scores obtained after 40 sessions of treatment were completed using a paired sample *t*-test.

Table 3

Paired Sample t*-Test comparing the GWBS Well-Being rating scale scores at Baseline and after veterans (N = 19) completing 40 neurofeedback training sessions.*

GWBS Well-Being Rating Scale	Baseline (*N* = 19)	40 Sessions	Q Score Change	Pooled SD	Sig.	Cohen's *d*
GWBS Rating Scale Score	58	72	14	24	0.001	0.8

As can be seen in Table 3, the GWBS rating scale scores significantly improved 14 points from 58 to 72, $t(18) = -3.55$, $p < .001$, Cohen's $d = 0.8$. A positive change of five points or more in the GWBS total score was found for 84% of the participants. The changes are graphed in Figure 2.

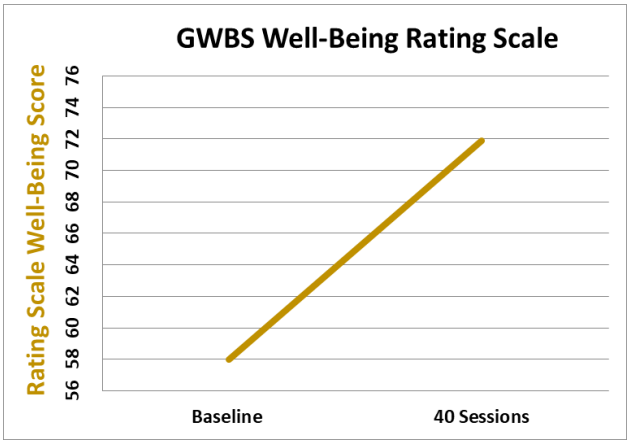

Figure 2. Changes in the General Well-Being Scale (GWBS) after veterans completed 40 neurofeedback sessions.

The GWBS has three primary interpretive categories for labeling a person's score: Severe Distress (0–60), Moderate Distress (61–72) and Positive Well-being (73–110). Initially, 79% of the individuals in this study, who completed it, rated themselves as either experiencing severe or moderate distress and 21% reported having scores reflective of positive well-being which they maintained during this study. Distress was defined as an "inner personal state" with elevated feelings of anxiety and depression combined with limited reports of good general health, vitality, positive well-being, and the ability for self-control (Dupuy, 1977). To evaluate the clinical effects of treatment changes, significant improvements in well-being were defined as a change from a more impaired level of distress to less impaired using the category labels provided above from the test manual. Of the 15 individuals who were identified as having either severe or moderate levels of distress prior to treatment, nine (60%) significantly improved in their well-being and seven of these nine veterans (78%) rated themselves as having a positive state of well-being after completing treatment. One veteran became clinically worse (7%) and the five individuals (33%) did not change in their ratings of well-being. These results show that neurofeedback is likely to help 6 out of 10 veterans

improve their general well-being and that about 5 out of these 6 individuals who have severe to moderate levels of distress prior to treatment are likely to return to a healthy state of positive well-being after neurofeedback.

In Table 4, the correlations between the GWBS rating scores and the IVA-2 global and primary measures of auditory and visual attention completed after treatment are reported. The question of interest was whether or not improvements in either auditory or visual attention contributed to increases in an individual's feelings of well-being. Prior to any treatment, the correlations between the first GWBS rating scale scores and the IVA-2 CPT test scores were examined and no significant correlations were found. After neurofeedback treatment, a significant correlation of .44 ($p < .03$) was found for the global AAQ, which consists of the Vigilance, Speed and Focus primary scale scores. The auditory Speed scale, which is a measure of the discriminatory response time to the IVA-2 targets (i.e., click if you hear the number one), was found to have a significant correlation of .57 ($p < .005$) with the GWBS. No significant correlations were identified for any IVA-2 visual scale.

Table 4
Correlations of the IVA-2 Attention Scales and the GWBS After Veterans Completed 40 Sessions of Neurofeedback Training.

IVA Attention Scales	GWBS Rating Scores	Sig.
Auditory Attention Quotient (AAQ)	**0.44**	0.03
Auditory Vigilance	0.28	n.s.
Auditory Speed	**0.57**	0.005
Auditory Focus	0.28	n.s.
Visual Attention Quotient (VAQ)	0.17	n.s.
Visual Vigilance	0.14	n.s.
Visual Speed	0.16	n.s.
Visual Focus	0.00	n.s.

Tables 1 and 2 are useful in that they show that prior to treatment (i.e., baseline) the mean attention scale scores for both auditory and visual were in what is labeled as a mild impairment. After neurofeedback treatment was completed, all global and primary IVA-2 scale scores fell for the most part in the middle of the Average range. After 20 sessions, the four measures of visual attention appeared to reach a maximum level of improvement and continued training did not seem to lead to any further changes in visual attention with mean scale scores remaining well within the average range and effect sizes essentially being equivalent. In contrast, continued neurofeedback training did seem to strengthen the attention skills of participants. To support this conclusion, it can be seen that the total Q score change after 20 more training sessions for the four auditory scales increased by 16 points (39%). In addition, the effect size after 20 sessions was medium for two scales and nil for the other two scales, because those two scales did not significantly improve. But after 40 sessions, all four auditory scales were found to significantly improve and the effect sizes were identified to be large for both AAQ and Speed scales and medium for Vigilance and Focus. It is interesting to note that the only two significant correlations between the IVA-2 scales and the GWBS discussed above were the AAQ and Speed scales, which after 40 sessions showed large effect sizes.

Given this study was archival, EEG protocols were individualized and modified as determined appropriate by the clinicians working with the veterans. Consequently, any statistical analysis on a group basis in order to examine possible EEG learning effects was not possible due to the fact that the clinically selected training protocols varied and were modified by clinicians during the course of the treatment in order to maximize the learning process for each individual. The agency providing support for these neurofeedback services did so with the understanding that services were provided on an individualized basis and not as a research study to evaluate a specific fixed neurofeedback training protocol.

Discussion

The positive benefits of neurofeedback as a therapeutic intervention for helping reduce PTSD symptomatology have been reported in a number of studies discussed above (Othmer & Othmer, 2009; Peniston & Kulkosky, 1991; van der Kolk et al. 2016). This study specifically identified that artifact corrected neurofeedback, which works by filtering out the contamination that continually results from naturally occurring EMG artifacts such as eye blinks, eye movements and facial activity, significantly improved both auditory and visual attention as measured by the IVA-2. As a group, these individuals initially presented with mild attentional impairments. After 20 half-hour treatment sessions, both their auditory and visual attention abilities were

normalized with standardized scale scores falling in the middle of the average range and effect sizes in the medium range.

While this study utilized archival data and there was no control group to control for possible test practice effects, the IVA-2 is an objective measure of attention which controls for practice effects in both its simplistic design (i.e., the test rule is to click if you see or hear the number one) and in its pretest instruction phase, which includes specific opportunities for individuals to practice the test before taking it. The reliability study in the test manual found that on retesting subjects did not significantly change by more than three to four points in either direction (Sandford & Sandford, 2015). Thus, any group increases in IVA-2 quotient scores greater than three to four points can be validly interpreted as a result of an active treatment and not due to practice effects. In this study, it was found that 20 additional neurofeedback sessions led specifically to the significant enhancement of auditory attention as evidenced by the greater effect sizes observed and the significant increase in the AAQ from 20 to 40 sessions (see Tables 1 and 2). While visual attention significantly improved after 20 sessions, no further improvements in visual scores were observed after training continued for an additional 20 sessions. Thus, the first hypothesis of this study that neurofeedback would significantly improve both auditory and visual attention was confirmed and effect sizes were large for the enhancement of auditory attention and medium in respect to visual attention. Given that the effects of neurofeedback for individuals with PTSD resulted in a greater enhancement of auditory than visual attention leads to the recommendation that the assessment of the effects of neurofeedback will need to include both auditory and visual measures of attention.

Given the nature of their missions, U.S. military veterans are subjected to exceptionally traumatic events. These traumatic events can result in an ongoing inner state of severe to moderate distress stemming from the numerous symptoms of PTSD. Consequently, any treatment to help reduce the emotional dysregulation and promote a greater sense of well-being will need to use an assessment tool like the GWBS to evaluate treatment effects. In this study, significant improvements in well-being were achieved which showed a large effect size after 40 sessions of neurofeedback were completed. While the lack of a control group in this study limits the conclusion that neurofeedback was the primary causal factor for the observed improvement in well-being, the discovery that the global measure of AAQ and specifically discriminatory auditory response time (i.e., the auditory Speed scale) were significantly correlated with ratings of well-being after 40 sessions of neurofeedback, but not prior to training, lends support to the validity of neurofeedback being the key factor in the improvements observed in well-being. This conclusion is further strengthened by the fact that the greatest size effects were found for the AAQ and auditory Speed scales after treatment was completed. This suggests that neurofeedback led to improvements in well-being in a specific way. Increases in auditory attention may help improve listening skills and an individual's ability to engage more effectively in verbal and, thus, social communication. When an individual can be a better listener and can understand what others are verbally communicating, then both positive social interaction and social feedback from others is more likely to occur leading to greater inner feelings of well-being. This reasoning would need to be further explored in additional studies by measuring improvements in social interaction, listening skills, and the ability to better process auditory information. The second hypothesis that neurofeedback would lead to significant increases in well-being for individuals with PTSD was supported by these results, along with indications that the mechanism may at least in part relate to improvements specifically in auditory attention and auditory processing speed.

Identifying multimodal approaches to treat PTSD creates opportunities for optimal patient care. Further research needs to explore the potential for neurofeedback to be used in combination with cognitive behavioral therapy and other interventions that have been found to improve the emotional and behavioral functioning and coping skills for individuals experiencing symptoms of PTSD. If the person's attentional functioning can be restored to premorbid levels along with an increase in feelings of well-being, then other therapeutic interventions may synergistically combine to maximize clinically targeted goals in less time. In general, given that clients often have varied responses and outcomes to different treatment approaches, a comprehensive and multifaceted treatment approach is called for in order to develop new and more clinically efficacious treatment strategies for PTSD. Neurofeedback offers the potential as an alternative treatment approach that is gradually becoming more widely accepted by many mental health care professionals and warrants institutional and governmental support for new research specifically with veterans who have PTSD based on the results of this study and

numerous others. Providing neurofeedback to veterans with PTSD who have not been successfully treated with other approaches including medication, provides a means to improve attention, can help reduce abnormal symptomology, improve the person's well-being, increase their ability to tolerate stress, and enable them to develop new skill sets in combination with other evidence-based treatment methods.

This research finding further substantiates the value and benefit of utilizing this new artifact corrected type of neurofeedback in the treatment of veterans with PTSD and warrants further research as a neurofeedback intervention. This study found that neurofeedback helped 4 out of 5 participants clinically improve their auditory and visual attention in only 20 sessions. In this study, initially 8 out of 10 veterans were found to be experiencing severe to moderate levels of distress. After receiving neurofeedback treatment without any supportive counseling or coaching, 60% of them reported significant clinical improvements in well-being. Thus, the benefits of neurofeedback showed its potential to help veterans improve their psychosocial functioning in ways that generalize to benefit them in everyday life situations.

In interpreting the results of this study, certain limitations were considered. Unquestionably, its archival nature was a primary drawback. Unfortunately, a comprehensive diagnostic intake was not possible due to funding limitations. It would be best to utilize the criterion specified in the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) in order to accurately diagnose PTSD and differentiate it from other mental disorders. It would also be useful to clarify a veteran's relevant history pertaining to their trauma experiences given that a large number of the individuals participating in this study pilot had been exposed to battlefield trauma at various times, but the length of time between trauma exposure and its severity was unknown. Future research exploring the benefits of neurofeedback in the treatment of the effects of PTSD would benefit from the use of standardized clinical interviews as part of the intake process. In addition, the systematic garnering of symptomatology in more detail is warranted along with comprehensive pre- and post-neuropsychological testing in order to evaluate the benefits of neurofeedback in more depth. Six-month and one-year follow-up evaluations to determine the long-term effects of neurofeedback treatment are also components recommended for consideration for future studies in this field. The inclusion of the above additions to future research will help elucidate both the benefits and underlying mechanisms whereby neurofeedback protocols can be evaluated and enhanced to improve their clinical impact. As such, prospective studies will provide a more reliable method of assessing the efficacy of neurofeedback on PTSD symptomology.

While this archival research was not designed to evaluate learning effects, the evaluation and demonstration of individuals' learned control of brainwave activity is an important issue which needs to be addressed in future research. Thus, research specifically designed to measure learning effects respective to the targeted EEG frequencies trained is recommended. However, in order to evaluate learning effects this type of study would require that all participants in the study receive training that used the same standardized treatment protocol for each person. Any clinical modifications to meet a person's specific needs would not be permitted. Consequently, participants would need to be clearly informed that the requirements of the research design are such that the neurofeedback training protocol will not be modified during training and, hence, will not be clinically adjusted to meet an individual's specific needs.

Conclusion

U.S. military veterans have historically experienced combat-related PTSD. Neurofeedback is becoming more widely used to treat a variety of psychiatric disorders and as such has been used by our clinic to treat veterans experiencing symptoms of PTSD. The results of this study supported the hypothesis that neurofeedback would significantly improve both auditory and visual attention of veterans with PTSD symptomatology. The veterans' improvement in their auditory and visual attention scores revealed that 8 out of 10 of them achieved clinically relevant improvements after only 20 half-hour treatment sessions. The treatment effect sizes of medium to large for this artifact corrected neurofeedback also served to support the clinical efficacy of this type of neurofeedback in improving attention.

A second hypothesis that neurofeedback treatment would significantly improve ratings of well-being was also supported by significant increases in the GWBS rating scales, as well as the large size effect found for this improvement. Only after treatment was completed did the enhancement observed in auditory attention and auditory processing speed correlate with the GWBS rating scores of well-being. The large effect size of the improvement in well-

being was believed to be attributable to the significant improvements in auditory attention and speed. These two aspects of attention were conceptualized as improving listening and verbal communication skills and, thus, suggested an underlying mechanism for how neurofeedback improves positive well-being. Overall, 60% of veterans who were initially experiencing severe to moderate levels of distress were identified to have clinically improved as a result of neurofeedback treatment in their well-being and the majority of them (78%) were reporting positive levels of well-being after completing treatment. The overall findings of this study support that artifact corrected neurofeedback is a clinically efficacious intervention that helps normalize the mild attentional impairments symptomatic of PTSD and that these specific improvements in auditory attention and processing speed are likely to contribute to better verbal communication skills and enhancing more positive feelings of well-being.

Author Note

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NeuroRegulation

Small-World Network Analysis of Cortical Connectivity in Chronic Fatigue Syndrome Using Quantitative EEG

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Abstract

The aim of this study was to explore the relationship between complex brain networks in people with Chronic Fatigue Syndrome (CFS) and neurocognitive impairment. Quantitative EEG (qEEG) recordings were taken from 14 people with CFS and 15 healthy controls (HCs) during an eye-closed resting condition. Exact low resolution electromagnetic tomography (eLORETA) was used to estimate cortical sources and perform a functional connectivity analysis. The graph theory approach was used to characterize network representations for each participant and derive the "small-worldness" index, a measure of the overall homeostatic balance between local and long-distance connectedness. Results showed that small-worldness for the delta band was significantly lower for patients with CFS compared to HCs. In addition, delta small-worldness was negatively associated with neurocognitive impairment scores on the DePaul Symptom Questionnaire (DSQ). Finally, delta small-worldness indicated a greater risk of complex brain network inefficiency for the CFS group. These results suggest that CFS pathology may be functionally disruptive to small-world networks. In turn, small-world characteristics might serve as a neurophysiological indicator for confirming a biological basis of cognitive symptoms, treatment outcome, and neurophysiological status of people with CFS.

Keywords: chronic fatigue syndrome; myalgic encephalomyelitis; qEEG; eLORETA; electrical neuroimaging; lagged coherence; functional connectivity; graph theory; complex networks; small-world

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Chronic fatigue syndrome (CFS) is a complex multi-system disease characterized by unexplained persistent or relapsing fatigue, post-exertional malaise, flu-like symptoms, and neurocognitive impairments not relieved by rest and worsened by physical or mental activity (Carruthers et al., 2003; Fukuda et al., 1994). Neurocognitive impairment is a hallmark symptom in CFS (Jason, Zinn, & Zinn, 2015) and one of the primary factors involved in the etiology of the condition (Johnson, DeLuca, & Natelson, 1996). Approximately 90% of patients with CFS report having cognitive symptoms, anecdotally referred to in the clinic as "brain fog," profoundly affecting health and quality of life (Grafman et al., 1993; Hopkins & Jackson, 2006; Komaroff & Buchwald, 1991; Ocon, 2013). A meta-analysis found cognitive deficits in CFS pertaining to memory, attention, and information processing speed, particularly during sustained working memory tasks (Cockshell & Mathias, 2010). In addition, patients have been shown to have slower reaction times in many studies (Busichio, Tiersky, DeLuca, & Natelson, 2004; Constant et al., 2011; Majer et al., 2008; Thomas & Smith, 2009; Van Den Eede et al., 2011), particularly under conditions of increasing task complexity (Dobbs, Dobbs, & Kiss, 2001). DeLuca, Johnson, and Natelson (1994) proposed that most memory deficits seen in patients are due to slower information processing rather than impairment in storage/retrieval mechanisms.

Functional MRI studies have observed that patients with CFS show signs of brain compensation in response to verbal working memory tasks (Cook, O'Connor, Lange, & Steffener, 2007; Lange et al., 2005). This suggests that dynamic reorganization of brain network topology in CFS with subsequent reductions in neural efficiency could be contributing to cognitive impairment indirectly. Thus, examining changes in overall brain information processing speed and neural efficiency factors in CFS may elucidate the relationship between cortical dysregulation and cognitive symptoms.

Knowledge of general principles of self-organization in real-word systems has prompted a paradigm shift in neuroscience away from localization of brain responses toward a deeper understanding of brain connectivity influences on information processing efficiency (Sporns, 2013). In the past decade, graph theoretical analysis has been increasingly used in neuroscience as a framework for understanding how dynamic processes are involved in the emergence of cognition and behavior (Menon, 2012; Stam, 2014). This approach has a number of distinct advantages which allow researchers to: 1) quantify and model a wide range of varying network attributes, 2) characterize the balance of local and global trade-offs that operate within systems, 3) examine weakened elements of the system and compensatory dynamics responding to pathological processes, and 4) simultaneously account for relationships between all the network elements and a given cognitive function (Rubinov & Sporns, 2010). In this sense, the application of graph theoretical analysis can extend our understanding of the key aspects of brain function in patients with CFS.

Complex networks are ubiquitous to the real world (e.g., social networks, airline routes, power grids, protein networks; Watts & Strogatz, 1998), and the brain itself is a complex network comprised of many subnetworks of distributed brain regions which instigate even the most basic behaviors (Deco, Jirsa, & Friston, 2012; Sepulcre, 2014; Stam, 2010). The coordinated activity within complex networks of the brain gives rise to fundamental aspects of neurocognitive domains involving attention, perception, memory, language, and motor processing (van den Heuvel & Sporns, 2013; Wig, Schlaggar, & Petersen, 2011). A homeostatic balance exists within complex brain networks between random neuronal growth processes and activity-dependent modification of those processes (Minati, Varotto, D'Incerti, Panzica, & Chan, 2013). This state of affairs can be explained in terms of parsimony; there is a continual drive in the system to negotiate trade-offs to the costs involved in supporting and to create adaptively valuable functional connectivity (Bullmore & Sporns, 2012). The number of connections in the system is relegated by wiring cost (biological energy and materials), and there are evolutionary reasons for keeping the demand for long distance connections, which are more “expensive,” to a minimum (Stam, 2010). Peculiar trade-offs in the topological properties of complex brain networks can therefore serve as a marker for specific neurobiological adaptions to the CFS condition, modeling disease course and spread, aberrant plasticity, indexing overall information processing efficiency—all of which could aid clinical diagnosis of patients and even identify clinical subtypes (Crossley et al., 2014).

The “small-world” network model was introduced in a landmark study by Watts and Strogatz (1998) demonstrating for the first time that small-world properties exist in central nervous systems. The topology of small-world networks is characterized by high clustering (segregation) and short path lengths (integration), representing a homeostatic balance between local and global processing in order to satisfy opposing demands which maximize processing speed at minimal neurobiological energy cost (Sporns & Honey, 2006). *Segregation* refers to the tendency of nearest neighbor elements to cluster together, whereas *integration* refers to the amount of interconnectedness and efficient information exchange within the entire network. The *clustering coefficient* is a measure of functional segregation or local connectedness, whereas the *characteristic path length* is a measure of functional integration describing global, large-scale activity and coactivation of neuronal populations within the network (Telesford, Simpson, Burdette, Hayasaka, & Laurienti, 2011). The clustering coefficient and the characteristic path length constitute properties of the small-world network model. Taken together, they are an indicator of *small-worldness*, an index representing the suitable balance between functional integration and segregation of dynamic system organization (Humphries & Gurney, 2008; Stam, 2010; Thatcher, 2016; van Straaten & Stam, 2013).

Kim et al. (2015) demonstrated small-world abnormality in CFS using resting-state fMRI to examine a sample of 18 women with CFS and 18 age-matched female controls. They assessed *global efficiency*, the inverse of the mean shortest characteristic path length, relating to the functional efficiency of information flow between any two nodes in the network. They also assessed *local efficiency*

which quantifies the fault tolerance of the network proportional to the clustering coefficient (Bassett & Bullmore, 2006). They found that global efficiency (integration) was lower in CFS compared to the HC group, while there were no differences in local efficiency (segregation). Increased demand for long distance connections in CFS suggests there is an added wiring expense for compensatory systems which negatively affects global efficiency of the network information processing. The degree of perturbation to small-world dynamics was linked to the amount of neurocognitive impairment in patients and brain processes found to be compromised reflected an underlying disturbance to small-world propensity. However, these investigators did not examine small-worldness, an overall indicator of optimal brain functioning and neural efficiency and neurocognitive impairment (e.g., memory, attention, slow thought, etc.) may represent a combination of pathology in the overall small-worldness measure with the concomitant overt behavioral changes in CFS.

Quantitative electroencephalography (qEEG) involves numeric analysis of local field potentials resulting from the summation of neuronal electrical activity that arises from the cell bodies and associated dendrites of large populations of synchronously active cortical pyramidal neurons (Niedermeyer & Lopes da Silva, 2005). The electrical currents are dependent on the integrity of the neural sodium/potassium and calcium ion pumps, reflecting metabolic activity and rendering qEEG a useful tool for quantifying and exploring electrophysiological correlates of both normal and abnormal neurological function (Thatcher, 2016). The frequency, phase, and amplitude of band-limited EEG oscillations relates to the specific information processing taking place at different spatiotemporal scales at any given moment (Le Van Quyen, 2011). Higher order cognitive processes appear to call upon even more temporal precision for sustained neuronal activity between neuronal populations (Nunez, Srinivasan, & Fields, 2015). Temporal resolution of qEEG on a millisecond timescale allows fine-grained detection of subtle differences in speed and efficiency within the relay of information flow via cooperative sequencing of oscillatory patterns and their phase differences (Buzsáki & Freeman, 2015; Steriade, 2005; Thatcher, North, & Biver, 2008). This is important given that even the most basic cognitive processes depend on precise timing of phase relationships in the brain occurring through large populations of spontaneously synchronized neurons communicating among distributed brain regions (Buzsáki, 2006; Sauseng & Klimesch, 2008; Steriade & Paré, 2006).

Tomographic EEG methods (electrical neuroimaging) use inverse methods to accurately map current source density in a three-diminensional brain volume, allowing the ability to visualize EEG abnormality in deeper brain structures (Grech et al., 2008; Thatcher, 2016). A growing number of studies are using electrical neuroimaging methods to elucidate information processing in the brain and small-world network organization in response to neurological conditions including epilepsy (Adebimpe, Aarabi, Bourel-Ponchel, Mahmoudzadeh, & Wallois, 2016; Vecchio, Miraglia, Curcio, Della Marca, et al., 2015), multiple sclerosis (Vecchio et al., 2017), and Alzheimer's disease (Hata et al., 2016; Vecchio, Miraglia, Curcio, Altavilla, et al., 2015; Vecchio et al., 2016). A comprehensive review on the role of electrical neuroimaging techniques for studying the brain in CFS can be found in Jason, Zinn, et al. (2015).

Using low resolution electromagnetic tomography (LORETA) to investigate 17 monozygotic twins with one twin with CFS vs. one healthy co-twin, Sherlin et al. (2007) showed that twins affected with CFS had increased delta sources in the left uncus and parahippocampal gyrus, deeper structures of the limbic system. Sherlin et al. also found higher theta sources in the cingulate gyrus and right superior-frontal gyrus. Using eLORETA (where "e" stands for exact), Zinn et al. (2014) found significantly elevated delta sources in a widespread portion of the frontal lobe and limbic lobe as well as decreased beta sources in the parietal lobe bilaterally. Higher delta sources were also associated with the reduced motivation scores on the Multidimensional Fatigue Inventory, a measure of fatigue severity commonly used in CFS studies. Increased delta in limbic structures is consistent with the findings of Sherlin et al., and rhythmic alterations in these regions could be indicators of blunted emotional processing in CFS possibly related to reduced motivation and attentional difficulties. Interestingly, symptoms manifested by brain pathology within the medial prefrontal cortex, anterior cingulate, and orbitofrontal cortex are largely undetected by most traditional neuropsychological tests (Koziol & Budding, 2009). Finally, using a Beamformer source analysis method, Flor-Henry, Lind, and Koles (2010) found sources that were globally reduced in the alpha and beta bands in those with CFS (delta band was not examined). Together, the various qEEG and tomographic EEG investigations mentioned here

demonstrate a relationship between EEG and CFS which lay the foundations for this study.

Zinn, Zinn, and Jason (2016) performed eLORETA functional connectivity analysis in CFS to examine three fundamental neurocognitive networks based on Menon's triple network model of brain pathology (Menon, 2011). This model posits there are three primary large-scale brain networks that operate dynamically to regulate shifts in arousal, attention, and general access to cognitive abilities. It includes the central executive network, salience network, and the default mode network and predicts that aberrant activity within any one of these networks will significantly impact the other two networks resulting in pathological states. Using lagged phase synchronization (Pascual-Marqui, 2007a), hypoconnectivity was found in the delta and alpha frequency bands between nodes for all three networks in the group with CFS in comparison to health controls. This finding is consistent with several functional connectivity studies using magnetic resonance which reported decreased connectivity involving key nodes of the salience network (Boissoneault et al., 2016; Gay et al., 2016; Wortinger et al., 2016). Disruptions to the salience network could underlie primary cognitive symptoms in CFS involving attention to internal/external events and adaptive engagement of systems responsible for processing of working memory and executive control. The above findings show that functional connectivity approaches including electrical neuroimaging methods are promising avenues for studying brain dysfunction in CFS.

The present study addressed the question of whether fundamental neurobiological relationships and adaptions could underlie cognitive symptoms in CFS. Our primary hypothesis was that patient networks would show deviations from normal in small-world network characteristics as measured by the small-worldness index, thus demonstrating a pathological imbalance affecting network efficiency and information processing due to the trade-offs associated with adaptive reconfiguration of network topology in CFS. Using graph theoretical analysis of small-world networks with eLORETA connectivity data was used for exploring the linkage of brain topology with cognitive impairments that are commonly associated with CFS (John, 2005; van Straaten & Stam, 2013). Secondly, changes in the small-worldness index were hypothesized to be associated with subjective levels of cognitive impairment due to maladaptive reconfigurations in network topology needed for supporting efficient brain processing in patients with CFS. Lastly, the small-worldness index was tested as a way to look at risk in patients with CFS compared to HC participants. At the present time, there is no physiological marker that represents risk for neurocognitive impairment in patients with CFS. Having an accurate method for identifying risk of cognitive impairment in CFS would help establish the utility for this approach for identifying epidemiological factors relating to patient health.

Method

Participants

The participants in this investigation were 29 adults (14 individuals with CFS, 15 HCs) ranging in age from 20 to 80 years old and the mean age was 43.97 years (*SD* = 20.32). The effects of age were statistically adjusted since the mean age between groups was significantly different and physiological aging is a significant factor within the EEG (Kirk, 2013; Rossini, Rossi, Babiloni, & Polich, 2007; Vysata et al., 2014). All participants visited the Center for Community Research at DePaul University to have their EEG recorded. The participants with CFS all met the Fukuda criteria (Fukuda et al., 1994) and they had been diagnosed with CFS by their physician. No participants were taking medications that would affect the EEG. This study was approved by the Institutional Review Board at DePaul University in Chicago.

Procedure

Eyes-closed, resting state EEG data for each participant was recorded for 5 min from 19 electrode locations (Fp1, Fp2, F3, F4, F7, F8, Fz, C3, C4, Cz, P3, P4, Pz, T3, T4, T5, T6, O1, and O2) positioned on the scalp according to the international 10/20 system using standardized electrode caps (Jurcak, Tsuzuki, & Dan, 2007) with a linked-ears reference. During cap preparation, impedances for all electrode sites were measured and brought to within 5 kΩ. Once cap preparation was completed, participants were shown their raw EEG signals and trained to minimize artifact by relaxing muscles in their forehead, jaws, and face to the best of their ability while they observed corresponding changes in the raw EEG. The data collection apparatus involved Neuroguide qEEG signal processing software (Version 2.8.7, 2016) together with the BrainMaster Discovery 24 (Bedford, OH) qEEG acquisition module, which allows up to 19 channels of EEG signals to be recorded simultaneously at 256 Hz.

During the EEG recording session, each participant was seated upright in a comfortable chair in a room that was well lit. Participants were given instructions to relax to the best of their ability while keeping their

eyes closed until the recording session has ended. EEG data were acquired at a 256 Hz sampling rate and filtered offline between 1 and 40 Hz. Artifact removal procedures were as follows: 1) visual inspection and manual deletion of visible artifact by an EEG technician; 2) automated *Z*-score artifact removal using rejection algorithms built into Neuroguide set for high sensitivity at two standard deviations for immediate exclusion of EEG segments with eye movement, muscle, and drowsiness artifact; and 3) second visual inspection and manual deletion of the artifact by an EEG technician. Since this study was directed toward understanding changes in phase relationships of the original time-series data, independent components analysis (ICA) was not performed. ICA/regression procedures intended to remove artifact actually produce distortion of phase relationships between channels by reconstructing the EEG time series. This methodological problem, which essentially invalidates the EEG data, has been empirically proven in several studies (Castellanos & Makarov, 2006; Kierkels, van Boxtel, & Vogten, 2006; Wallstrom, Kass, Miller, Cohn, & Fox, 2004). The EEG segments that were included for analysis showed greater than 95% split-half reliability and greater than 90% test–retest reliability coefficients instantaneously computed by Neuroguide, and each record had a minimum total edit time of at least 1 minute. For each participant, the artifact-free data were then fragmented into 2-sec EEG segments. Due to theoretical considerations, all analyses were limited to the delta (1–3 Hz), alpha-1 (8–10 Hz), and alpha-2 (10–12 Hz) frequency bands. Each frequency band provides an added layer of physiological significance to brain function.

Materials

All participants completed the DePaul Symptom Questionnaire (DSQ; Jason, So, Brown, Sunnquist, & Evans, 2015), and data for the DSQ were collected and managed using the Research Electronic Data Capture (REDCap) hosted at DePaul University (Harris et al., 2009). The DSQ is a self-report instrument that measures 54 symptoms related to criteria specified in the CDC criteria (Fukuda et al., 1994), the Canadian Criteria for ME/CFS (Carruthers et al., 2003), and the CFS International Consensus Criteria (Carruthers et al., 2011). For each symptom item, respondents are asked to separately rate the frequency and severity over the last 6 months on a 5-point Likert scale (0 = none of the time, 1 = a little of the time, 2 = about half the time, 3 = most of the time, and 4 = all of the time). The DSQ has good test–retest reliability with Pearson's correlation coefficients above 0.70 and test–retest correlations for classified symptom categories (fatigue, post-exertional malaise, neurocognitive, and autonomic) at 0.80 or higher (Jason, So, et al., 2015). Results of factor analysis on the DSQ support at least three distinct symptom factors: 1) post-exertional malaise, 2) neurocognitive dysfunction, and 3) neuroendocrine/autonomic /immune dysfunction (Jason, Sunnquist, et al., 2015). Murdock et al. (2016), an independent group using the DSQ, found that it demonstrated excellent internal reliability and that among patient-reported symptom measures it optimally differentiated between patients and controls. The cognitive variable of this proposal was the aggregate average of nine items that fall under the neurocognitive dysfunction factor: problems remembering things, difficulty paying attention for a long period of time, difficulty with word finding or expressing thoughts, difficulty understanding things, only able to focus on one thing at a time, unable to focus vision attention, slowness of thought, absentmindedness or forgetfulness, and loss of depth perception (Jason, Sunnquist, et al., 2015).

Functional connectivity was analyzed using coherence, a measure of the consistency of phase differences in the time-series corresponding to different spatial locations (Lehmann, Faber, Gianotti, Kochi, & Pascual-Marqui, 2006; Pascual-Marqui, 2007a, 2007b). Coherence is interpreted as an indicator of "connectivity" which quantifies the degree to which phase differences remain stable over time either between electrode sites, when measured at the scalp when using surface EEG (Buzsáki & Watson, 2012; Klimesch, Freunberger, Sauseng, & Gruber, 2008; Thatcher, 2016), or between two brain regions, in the case of eLORETA (Pascual-Marqui et al., 2011). An advantage of eLORETA is that it uses lagged coherence, a specialized measure of functional connectivity that controls for physiological artifact by removing zero-lag contributions from volume conduction and spatial blurring effects (Pascual-Marqui, 2007a, 2007c). Functional connectivity analyses of coherence was conducted using the LORETA-KEY software package (Pascual-Marqui, 2015). This software is freely provided for download by the KEY Institute for Brain-Mind Research at http://www.uzh.ch/keyinst /loreta.htm. eLORETA is based on the stereotactic space provided by the Montreal Neurological Institute (MNI) template and offers a highly accurate estimate of the intracortical current source density within a three-dimensional cortical volume consisting of 6,239 voxels of unambiguous grey matter at 5 mm^3 spatial resolution. Complete mathematical details of this inverse solution are provided in

Pascual-Marqui et al. (2011). To obtain a topographic view of the whole cortex, coordinates were computed for 42 separate Brodmann areas (BAs: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13, 17, 18, 19 20, 21, 22, 23, 24, 25, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47) for the left and right hemispheres (84 total ROIs) using a single voxel to define each ROI centroid. Given that eLORETA has low spatial resolution based on the spatial smoothness assumption, the single center voxel is considered an accurate representation of activity within the ROI while minimizing the possibility of signal contamination from neighboring ROIs.

eLORETA lagged coherence was then calculated for all 84 ROIs for each participant, generating text files with output containing a separate weighted 84 x 84 coherence matrix for each frequency band. The coherence matrix contains the entire set of network connections whereby each cell has a value representing the magnitude of the statistical correlation (coherence) between any pair of nodes. In each coherence matrix, the table rows and columns represent the ROIs and the cell values represent the coherence magnitude of dependency between each pair of ROIs. Figure 1 illustrates the workflow for all the analyses that were implemented in this study.

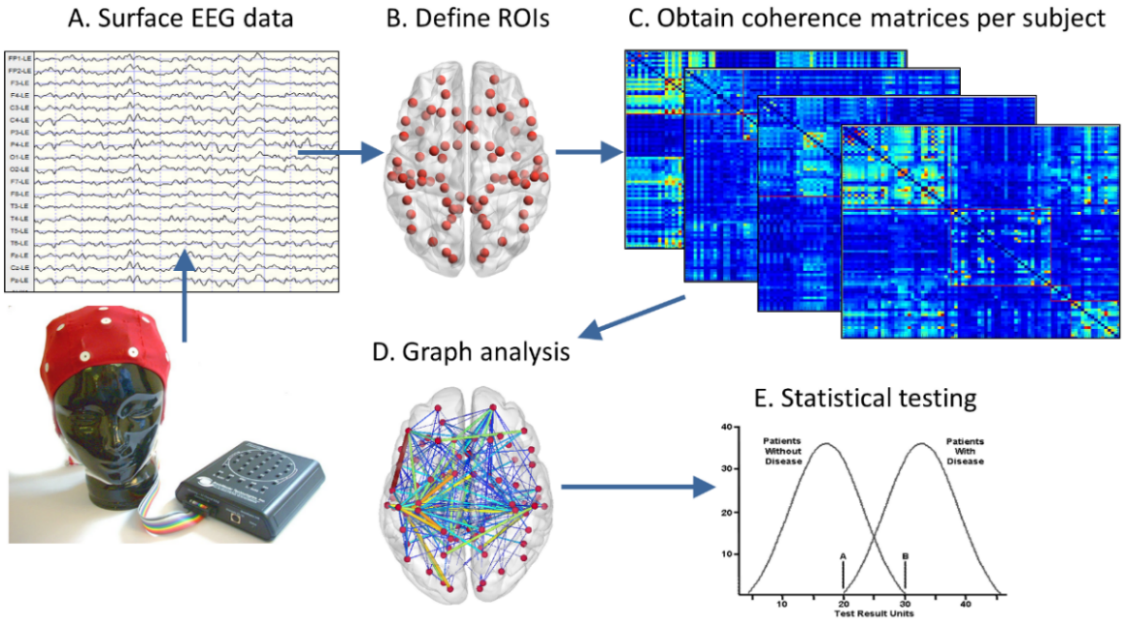

Figure 1. The workflow of all analyses in this thesis summarized as an overview.

Graph Theoretical Analysis

The coherence matrix for each frequency band for each participant was subjected to graph theoretical analysis using the MATLAB Brain Connectivity Toolbox (BCT; Rubinov & Sporns, 2010). The BCT has functions that take into account the weighted undirected strength or magnitude of all the network connections. Descriptions and code for the mathematical functions in the BCT are freely available for download at https://sites.google.com /site/bctnet/. BCT functions were applied to each participant's coherence matrix to calculate small-world characteristics. The weighted *clustering coefficient* around a given node varies from 0 to 1 and is quantified by the number of triangles formed by that node and its neighboring nodes. The weighted *characteristic path length* is defined as the average shortest weighted path between two given nodes using the sum of the individual weighted lengths. Path lengths with conversions based on values of the coherence matrix were stored separately as a distance matrix with sequences of edges that connect nodes indirectly to form neural paths. The path length values in the distance matrix are not physical distances, but instead they represent the degree of topological separation between any two given nodes (Rubinov & Sporns, 2010). The GraphVar toolbox in Matlab (Kruschwitz,

List, Waller, Rubinov, & Walter, 2015) was used to calculate *small-worldness*, which is the ratio between the clustering coefficient and characteristic path length compared to their values for equivalent randomly generated graphs (Humphries & Gurney, 2008). The small-worldness index variable (SW) was computed using $C_{sw} = (Cw/Cw_{rand})/(Lw/Lw_{rand})$ as a comparative marker of efficient brain functioning for each participant.

Statistical Analysis

The graph theory output that was produced using BCT functions in MATLAB was subsequently imported to SPSS version 23 for conducting further statistical analyses. The data were screened for outliers, missing data, skewness, and kurtosis in meeting the assumptions for parametric statistics. Continuous variables were log-transformed to meet the assumption of Gaussianity.

Results

Demographic characteristics by study group and descriptives of key study variables are shown in Tables 1 and 2. Most patients with CFS were older than HCs and the potential confound of age was controlled for in all models. Given that some secondary outcomes were considered corresponding to the study hypotheses, this study is considered exploratory, and the *p* values considered descriptive. All data were evaluated with tests which were two-sided at the .05 level of significance.

Table 1

Demographic and Clinical Data.

		14 CFS	15 HCs		All 29 Participants	
Age (years)* Mean (*SD*)		57.71 (15.15)		31.13 (15.63)		43.97 (20.32)
Sex	11	Female	11	Female	22	Female
	3	Male	4	Male	7	Male
Handedness	14	Right	14	Right	28	Right
	0	Left	1	Left	1	Left
Education	1	Partial college	2	Partial college	3	Partial college
	6	College	8	College	14	College
	7	Graduate	5	Graduate	12	Graduate
Ethnicity	14	White	14	White	28	White
			1	Latino	1	Latino
DSQ Cognitive Composite score* Mean (*SD*)		2.87 (.10)		1.25 (.04)		2.03 (.10)

* $p < .01$

Table 2

Means and Confidence Intervals for Small-worldness Indices by Experimental Group.

		Small-world delta	Small-world alpha-1	Small-world alpha-2
Group	*N*	*M (CI)*	*M (CI)*	*M (CI)*
HC	15	.89 (.85–.92)	.79 (.76–.83)	.84 (.80–.88)
CFS	14	.82 (.78–.85)	.78 (.74–.82)	.79 (.76–.82)

The primary outcome of interest was to determine whether small-world network values deviate from normal in a sample of patients with CFS. Analysis of Variance (ANOVA) was conducted to assess whether networks of patients with CFS deviated significantly from those of HCs, adjusting for age. We first identified statistically significant ANOVA values in an overall test, $F(2, 80) = 4.915$, $p = .029$, which indicated a significantly lower small-worldness index *z*-value for patients with CFS ($M = -.181$, $SD = 1.047$) than HCs ($M = .164$, $SD = .950$). To identify the differences between small-worldness within each frequency band in this study, follow-up tests were conducted with the Bonferroni correction for multiple comparisons. These estimates identified SW delta as statistically different between patients with CFS and HCs, $p = .014$; however, the SW alpha-1 and

SW alpha-2 were not significant between both groups (p = .622 for alpha-1; p = .099 for alpha-2; Figure 2). Within the HC group, a significant difference was found between SW delta and SW alpha-1 (p = .001), but not between SW delta and SW alpha-2 (p = .177). Within the CFS group, however, there was no significant difference between any SW frequency bands (p = .355).

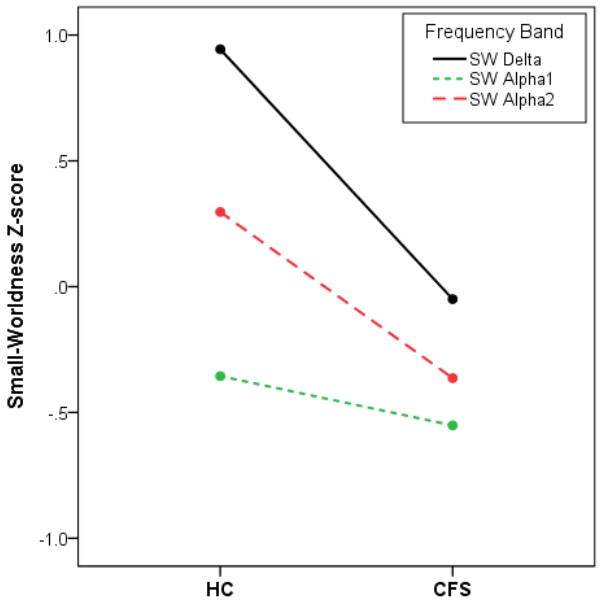

Figure 2. Small-worldness results of group comparisons by frequency band. The CFS group was 1 SD lower than the HC group for SW delta (p = .014).

Next, hierarchical regression techniques were used to determine the linear relationship of small-world network organization (measured by SW delta, SW alpha-1, and SW alpha-2 combined) with neurocognitive impairment. Two models were fit for estimating this relationship, age-adjusted, and found that small-worldness significantly predicted the neurocognitive impairment scores, $F(2, 84)$ = 53.482, p = .000, adjusted R^2 = .550 for model 1 and $F(2, 83)$ = 122.546, p = .000, adjusted R^2 = .809. These strong effect sizes suggest that deviations from small-worldness affect neurocognitive impairment. For model 2 in particular, 80.9% of neurocognitive impairment was predicted by the combination of small-worldness, experimental group, and age (Figure 3).

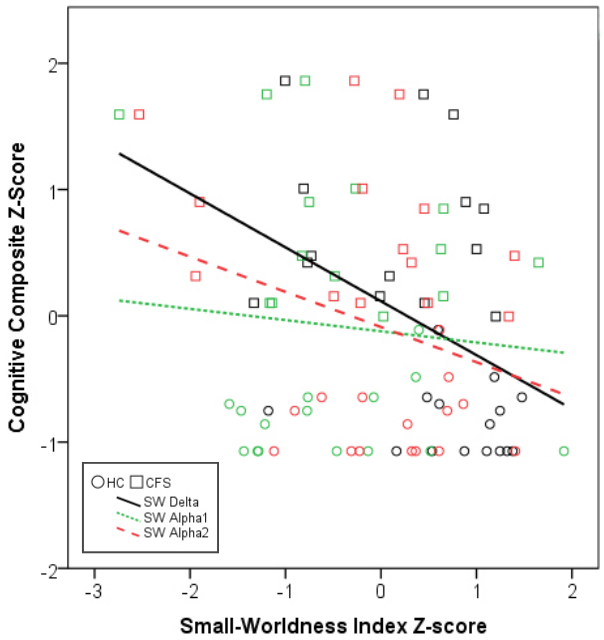

Figure 3. Small-worldness results of regression analysis by frequency band.

Our third outcome of interest was the development of prediction models to estimate odds ratios and 95% CIs for patients with CFS in SW delta, SW alpha-1, and SW alpha-2. Fixed-effects multinomial logistic regression allowed us to appropriately model the relationship between group membership and small-world effects at each frequency band. All models were adjusted for the potential confounder of age. To estimate differences between patients with CFS in our study cohort, the deviated small-world values (small-worldness index variable) in the fixed-effects logistic regression model were associated with increased risk in CFS of SW delta (OR 1.425; 95% CI: 0.500–3.75) but not for SW alpha-1 (OR 0.702; 95% CI: 0.310–1.590) or SW alpha-2 (OR 0.786; 95% CI: 0.386–1.601). According to this data set, the group with CFS was 1.425 times as likely to have deviations from normal in small-worldness in the delta frequency band but not in the alpha-1 or alpha-2 band. The overall regression model was significant at p = .05.

Discussion

To our knowledge, this is the first study to evaluate an association between small-world characteristics and cognitive symptoms reported in CFS. These findings of functional connectivity alterations suggest the importance of applying graph theory to connectome-scale analysis of network topology to detect subtle disruptions incurred by CFS sequelae.

Neurocognitive impairment, as measured by the DSQ cognitive composite score, was negatively associated with small-worldness index for the delta band under observation. Group-level differences were also found, but only for small-worldness in the delta band. Finally, the risk of having small-worldness deviations in the delta band is increasingly greater in CFS.

Small-world models of the brain systems explore the balance between high clustering of local systems with short path lengths of global systems; these attributes are considered to be vital to the efficiency of information processing within neurocognitive networks (Menon, 2012; Rubinov & Sporns, 2010). This model emphasizes the morphological adaptations (e.g., changes in axonal diameter, white matter pathways, conduction velocities, and energy transport mechanisms) governed by trade-offs within components and compensation necessary for maintaining the multiscale spatial-temporal patterns for which the brain operates. Differences in neural resource allocation in CFS were reported in three fMRI studies investigating compensatory responses to cognitive tasks (Caseras et al., 2006; Cook et al., 2007; Lange et al., 2005). The findings of our study explain these differences in terms of peculiarities to these trade-offs with subsequent weakness to small-worldness structure that could account for loss of cognitive function in people with CFS.

Secondarily, it was found that small-worldness in the delta band accounted for the greatest amount of variance in cognitive composite scores for the hierarchical regression model equation. Delta is a slow oscillation that plays a key role in the dynamic coordination of large-scale cortical networks and modulation of faster rhythms through cross-frequency coupling (Buzsáki & Freeman, 2015). In the case of inflammatory disorders of the CNS, the most prominent change in large-scale network dynamics is the occurrence of cortical slowing (e.g., delta activity) during the waking state (Westmoreland, 2005). Furthermore, delta cortical slowing can result from a decrease in the afferent drive due to white matter or subcortical lesions to deep midline areas (Gloor, Ball, & Schaul, 1977; Schaul, Gloor, & Gotman, 1981). Finding abnormal small-worldness in delta suggests there may be some similarities between CFS and Alzheimer's disease (Babiloni et al., 2013; Hata et al., 2016), multiple sclerosis (Babiloni et al., 2016), and Parkinson's disease (Babiloni et al., 2011), where abnormal delta sources have been detected.

This is the first study to measure small-world properties in CFS in terms of the small-worldness index. Using resting-state fMRI data, Kim et al. (2015) found that functional integration (global efficiency) was decreased in CFS and disruption to global efficiency suggests that, with fewer biologically "expensive" long distance connections, added burden is being placed on the system for satisfying opposing demands. The "costs" to chronically reduced functional integration in CFS include: 1) a lowered ability to rapidly combine specialized information from distributed brain regions, 2) slowed information processing speed due to compensatory responses, and 3) a generalized impairment to domains of cognitive function. However, our study found differences using the small-worldness index as a ratio of individual small-world properties (clustering and path lengths), a measure of both global and local properties which are salient in CFS depending on frequency band. This underscores the need for considering a combination of graph theory metrics for a more comprehensive examination of CFS.

There are some limitations in the present study. The results of this study should be interpreted with caution due to small sample size. Although significant deviations in the reported small-worldness phenomena were found in people with CFS, neurological disorders are invariably associated with diffuse network changes. However, it was beyond the scope of this study to report the individual nodes, hub, and modules that may be involved in suboptimal information processing efficiency and prone to failure in CFS. Although the outcome of brain function following individual hub failure would likely go beyond discrete local regions, future research could explore a more comprehensive inspection of hub strength, distribution, and participation within modular structures to identify ROIs that serve as potential targets for treatment. As another limitation of this study, the examination of small-world differences was kept within the delta, apha-1, and alpha-2 frequency bands. Frequency-dependent changes to cortical arrangements occurring in other frequency bands (e.g., theta, beta) could also be explored. Finally, insignificant findings in alpha-1 and alpha-2 could reflect a deficiency in the diagnostic criteria for CFS, a deficiency in the coherence-based measure itself, a problem with the way the ROIs were defined, and/or unexplored levels of complex network analysis using other graph theory metrics. Functional connectivity EEG markers associated with neurocognitive impairment and small-worldness

in different frequency bands should be verified in future studies.

Conclusions

The present findings support the concept that small-worldness is altered in CFS. This has important implications for this field of study. For example, system-dependent coupling of oscillations has fundamental importance to CNS function and may be strongly influenced by delays in conduction velocity and myelin plasticity. Changes to white matter have been reported in CFS (Puri et al., 2012), also associated with clinical measures (Barnden et al., 2011), and a severity-dependent increase in myelination has also been found (Barnden, Crouch, Kwiatek, Burnet, & Del Fante, 2015). Disruption to white matter could explain the relationship between abnormal eLORETA coherence patterns over large-scale complex systems in CFS. Furthermore, the linkage between cognitive symptoms and small-worldness demonstrates the fundamental importance of timing, stability, and adaptation of complex systems to CFS which could be related to findings of neuroinflammation in patients (Nakatomi et al., 2014). Understanding the network dynamics of CFS in terms of eLORETA coherence is an important way of comprehending compensatory mechanisms and could serve as a practical tool for investigating large-scale loss of cognitive function related to adaptive reconfiguration of brain networks. There is a need for future research that models the activity-dependent modifications of brain connectivity in CFS with disruption to neurocognitive processes.

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NeuroRegulation

Proceedings of the 2017 ISNR Conference: Keynotes, Invited, and Student Award Presentations

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KEYNOTE PRESENTATIONS

Functional Neuroimaging as a Window into Human Brain Function: Applications to Better Understand and Optimize Neuromodulatory Therapies

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Functional brain imaging has opened a window into brain function in humans and has significantly enhanced our understanding of neural function and connectivity supporting aversive symptom states. Our research has shown that the brain is composed of multiple primary sensory and associative networks that activate and deactivate over time as distinct assemblies. These networks can become blurred when chronic, recurring activation of network nodes is maintained. For example, recurring, spontaneous pain in a distinct body area brings saliency to specific somatosensory and nociceptive input, blurring the Salience Network (SLN) and somatotopically-distinct subregions of the Somatomotor Network (SMN). Additionally, catastrophizing about pain activates the Posterior Cingulate Cortex (PCC) and brings saliency to ruminative thought, blurring SLN and default mode network (DMN). Functional MRI brain connectivity metrics can be used to evaluate objective brain-based markers that track with clinical pain. Applications include objective markers of disease for drug and non-pharmacological/behavioral intervention trials, baseline predictor of response, and targets for neurofeedback.

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Impact of Childhood Maltreatment on Brain Development and the Critical Importance of Distinguishing Between Maltreated and Non-Maltreated Diagnostic Subtypes

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Childhood adversity is the most important preventable risk factor for mood, anxiety, personality, substance abuse, and psychotic disorders. Recent studies suggest that clinical sequelae may stem, at least in part, from enduring effects on brain development. Research will be reviewed highlighting the effects of childhood abuse on EEG coherence and the development of the hippocampus, white matter tracts, and cortical regions. Evidence will be presented identifying sensitive periods when specific brain regions are most vulnerable and unique effects of difference types of abuse on sensory systems and pathways that convey the adverse experience. These findings will be placed into context illustrating how exposure to abuse affects multiple components of the brain circuit responsible for threat detection and also affects the network architecture of the brain. Finally, the case will be made that maltreated and non-maltreated individuals with the same primary DSM diagnosis differ clinically, neurobiologically, and genetically. We refer to the disorder in the maltreated cohort as an *ecophenotype* and show that it is associated with earlier age of onset, more severe course, more comorbid diagnoses, and poorer response to first-line treatments. Recognition of this distinction may be of paramount importance in effectively identifying appropriate interventions with neurofeedback emerging as a key modality for treating individuals with the ecophenotype.

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The Evolution of Quantitative EEG: A Perfect Storm

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The historical evolution of QEEG will be explored with emphasis on significant steps its development. The following will be highlighted: 1) Early steps in quantification that pave the way, including normative equations (John et al., 1980), source localization (Pascual-Marqui, Esslen, Kochi, & Lehman, 2002), and Default Mode Network (Buckner, Andrews-Hanna, & Schacter, 2008); 2) QEEG treatment predictive biomarkers, including cognitive decline (Jelic et al., 2000; Prichep et al., 2006) and OCD (Dohrmann, Stengler, Jahn, & Olbrich, 2017); 3) QEEG as a surrogate for advanced neuroimaging, including TBI (Hanley et al., 2017) and chronic pain (Prichep et al., 2017). Impact of the “perfect storm” represented by advances over the last decade in technology, signal processing, and machine learning classification methodologies will be discussed in this context.

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INVITED PRESENTATIONS

Early Detection and Treatment of Attention Deficits in Preterm Infants

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This study described the application of a scale for evaluation and treatment of early attention deficits in infants, the "Infant Scale of Selective Attention" (EEAS). It is well known that attention deficit begins in infancy and adversely affects individuals throughout life; thus, the challenge is to find ways to diagnose and treat it early in life, during infancy, to try to prevent children from developing attention-deficit/hyperactivity disorder. EEAS measures the infant's overall ability to detect, locate, track, and respond selectively to visual and auditory stimuli. Also, an intervention program was designed to stimulate attention in infants with delayed attention. This program was applied daily, from 3 to 8 months corrected age. Monthly behavioral measures from 3 to 8 months and event-related potentials (ERP) recordings for a two-tone oddball paradigm were collected in 10 full-term and 21 preterm infants with white matter injury and attention deficits. Eleven preterm infants participated in the attention stimulation program (experimental group) and 10 did not (control group). The behavioral study showed that the experimental group had a faster rate of improvement in attention than the control group. ERPs showed that deviant stimuli were automatically detected and could involuntarily capture attention but only in the healthy and treated groups.

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Functional Neuromarkers for Psychiatry and Neurology: Defining Brain Dysfunctions and Constructing Protocols of Neuromodulation

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The paper describes a recently emerged methodology of extracting functional neuromarkers from spontaneous multichannel EEG, event-related de/synchronization, and event-related potentials (ERP). The methodology includes methods of blind source separation for artifact correcting and extracting latent (hidden) components from resting-state EEG and from event-related potentials, methods for constructing normative and patient databases, for comparing the extracted individual parameters with the normative data, as well for pre-post comparison. The high test–retest reliability of neuromarkers, the high level of specificity and sensitivity for defining dysfunctions in ADHD, schizophrenia, OCD, autism, depression, and dementia are described. Application of the methodology for predicting clinical outcome in response to pharmacological medication, for constructing protocols of neurofeedback, tDCS (transcranial Direct Current Stimulation) and TMS (transcranial magnetic stimulation) in clinical population is presented.

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STUDENT AWARD WINNERS – PLENARY PRESENTATIONS

Is A/T Neurofeedback Training (NFT) a Successful Treatment Method for Women with Moderate to Severe Trait Anxiety: A Clinical Trial and Methodological Considerations

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Since the late 1960s neurofeedback (NFT) has been used to treat adult individuals with anxiety disorders. Yet most related, evidence-based research studies

were conducted between the mid-1970s and late 1990s. Therefore, NFT as an efficacious treatment for anxiety problems remains unclear. The literature research discloses that of few studies, most used sample sizes 10 subjects or less per experimental or control group, results have been mixed, and the U.S. NIH's National Center for Complementary and Integrative Health (NCCIH) at this time does not endorse NFT as an efficacious treatment for anxiety problems.

In the present study 27 women between (age range = 19–67) with moderate to high trait anxiety were randomly assigned to either experimental or control condition, and received either 10 sessions of A/T NFT to up-regulate Theta (5–7 Hz) and Alpha power (8–11 Hz) or received ten 25-min sessions of alternately up- and down-regulating beta (15–19 Hz) and hibeta (20–24 Hz), respectively, at the Pz location, while getting auditory and visual feedback. Activation/Deactivation was assessed before and after each session via the Activation Deactivation Adjective Checklist (AD-ACL) list. Pre- and post-EEGs, anxiety (BAI, STAI, GAD-7), treatment expectancy, locus of control, and a variety of qualitative measures such as cognitive strategies, treatment group belief, and best times and worst times of day for learning were assessed.

Preliminary results using growth curve modeling (GCM using lmer), as well as traditional 2x2 and 2x3 ANOVAs and regression statistical analyses, indicate that both participants of experimental (EG) and control groups (CG) were able to successfully up-regulate their theta and alpha power, as well as the T/A ratio during the course of a session as well as over the course of the 10 treatment sessions. Self-perceived anxiety as measured by the two of the three anxiety measures went down significantly. No significant difference between EG and CG could be observed.

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STUDENT AWARD WINNERS – POSTER PRESENTATIONS

The Effect of Slow Breathing Training on Electroencephalogram

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Background. Previous studies have confirmed that slow breathing training not only improves heart rate variability and autonomic activation but also increases subjective relaxation feeling and reduces negative emotions. The purpose of this study was to explore the effect of slow breathing training on electroencephalogram (EEG).

Methods. Fifty-three healthy participants were randomly assigned to slow breathing group (n = 27; mean age was 25.30 ± 6.86 years; 3 male and 24 female) and control group (n = 26; mean age was 31.23 ± 14.77 years; 7 male and 19 female). Participants in the slow breathing group received 60-min weekly training for 4 weeks between pre- and posttest. The control group only received pre- and posttest. All participants received 5-min resting EEG measurement with eyes-opened at Fz, Cz, and Pz by using BrainAvatar (BrainMaster Technologies, Inc., Bedford, OH) at pre- and posttest. The EEG was analyzed in the following bandpass: delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), total beta (12–32 Hz), beta1 (12–15 Hz), beta2 (15–22 Hz), beta3 (22–28 Hz), and beta4 (28–32 Hz). The change in scores of pre- and posttest EEG were compared between two groups.

Results. There was no significant difference between slow breathing group and control group in age (t = 1.86, p = .71) and gender ($\chi 2$ = 2.16, p = .14). Significant group * time interaction effects were found at pre- and posttest between two groups at Fz on beta2, $F(1, 51) = 7.09$, $p < .05$; beta3, $F(1, 51) = 6.90$, $p < .05$; and beta4, $F(1, 51) = 4.71$, $p < .05$. The post-hoc comparison showed a trend to decrease beta activity in the slow breathing group, while increasing beta activity in the control group. Moreover, there were significant differences between two groups on change scores at Fz of beta2, $t(51) = 2.66$, $p < .05$; beta3, $t(51) = 2.63$, $p < .05$; and beta4, $t(51) = 2.17$, $p < .05$. However, there was no significant interaction effect on beta1 at Fz, as well as no significant interaction effect on EEG index at Cz and Pz.

Conclusion. This study confirmed that slow breathing training is a useful intervention protocol in decreasing cortical arousal at frontal area.

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The Effects of Personalized EEG-Neurofeedback in College Students with ADHD

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Background. Several neurophysiological subtypes based on EEG biomarkers have been identified in ADHD (Johnstone, Gunkelman, & Lunt, 2005). However, most studies investigating the efficacy of neurofeedback as a treatment for ADHD use a uniform treatment protocol without taking into account individual EEG biomarkers (Arns, de Ridder, Strehl, Breteler, & Coenen, 2009). A recent pilot study suggests that personalizing neurofeedback protocols to individual EEG biomarkers of ADHD might lead to increased specificity and efficacy of treatment (Arns, Drinkenburg, & Leon Kenemans, 2012). Hence, this preliminary study aims to investigate the effects of personalized EEG-neurofeedback in a population of college students with ADHD.

Methods. Eighty college students with a diagnosis of ADHD received personalized EEG-neurofeedback training (NFT) two times a week over a period of 4 months. Half of the participants was randomly assigned to the experimental condition. The other half was placed on a waiting list to serve as a control group and received treatment later. Resting-state EEG signals were recorded to evaluate overall brain activity pre- and posttraining and to determine individual EEG biomarkers for selection of personalized treatment protocol. ADHD behavioral symptoms were assessed pre- and posttraining using the Conners' Adult ADHD Rating Scale–Self-Report: Long Version (CAARS–S:L) and the IVA-2.

Results. The expected result is that a significant change will be observed in subjects trained in EEG neurofeedback, both in brain activation patterns and at the behavioral level. More specifically, normalization of targeted resting brain waves is expected in the experimental group. Changes in neural activity in the experimental group is also predicted to be correlated with improvements in ADHD symptoms.

Conclusion. This preliminary study will demonstrate the feasibility of personalizing neurofeedback protocols to individual EEG biomarkers of ADHD and the efficacy of neurofeedback as a treatment for ADHD. On a broader level, it will allow for a better understanding of the impact of neurofeedback training on neural and behavioral correlates of ADHD.

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The Differences Between Frontal Alpha Asymmetry Among Healthy Participants and Patients with Major Depressive Disorder

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Background. Previous studies indicated that frontal alpha asymmetry (FAA) is a potential biomarker for major depressive disorder (MDD). However, some results did not support the FAA. The purpose of this study was to examine the electroencephalogram (EEG) difference among healthy participants and patients with MDD patients whom with and without FAA.

Methods. Ninety-five healthy participants and 73 patients with MDD were recruited. Five minutes resting EEG with eyes-closed was measured at frontal (F3, F4) and midline (Fz, Cz, Pz) by BrainAvatar (BrainMaster Technologies, Inc., Bedford, OH). The EEG singles were analyzed into the following bands: delta (1–4 Hz), low theta (4–6 Hz), high theta (6–8 Hz), total theta (4–8 Hz), low alpha (8–10 Hz), high alpha (10–12 Hz), total alpha (8–12 Hz), low beta (12–20 Hz), high beta (20–32 Hz), and total beta (12–32 Hz). FAA score was calculated by log(F4 alpha) − log(F3 alpha). FAA score higher than 0 refers F4 alpha is higher than F3 alpha (FAA+); on the other hand, FAA score lower than 0 refers F4 alpha is lower than F3 alpha (FAA−). Participants were divided into one of four groups based on their FAA score: healthy control with FAA+ (H+ group), healthy control with FAA− (H− group), MDD with FAA+ (M+ group), and MDD with FAA− (M− group).

Results. No significant difference between four groups on age, $F(3, 168) = 0.43$, $p = .73$, and sex, $\chi^2 = 2.60$, $p = .46$. Significant differences were found between four groups on total theta and high beta, the post hoc comparison found that M+ and M− group had lower total theta at Fz and Cz compared with H− group ($F = 3.76$, $p = .012$; and $F = 3.85$, $p = .011$, respectively). M− group had higher high beta at Fz, F3, F4, and Cz compared with H− group ($F = 4.58$, $p = .004$; $F = 5.34$, $p = .002$; $F = 4.53$, $p = .004$; and $F = 4.32$, $p = .006$, respectively).

Conclusion. This study indicated that not all patients with MDD had FAA mechanisms in brain activity. The most significant finding was that MDD with FAA− had lower total theta and higher high beta compared to the healthy controls who with FAA−.

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Neurostructural Predictors of Cognitive Behavioral Therapy (CBT) for Obsessive-Compulsive Disorder: Implications for the Integration of Neurofeedback Training and CBT

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Background. Cognitive-behavioral therapy (CBT) is the most commonly used evidence-based practice in the treatment of mental disorders (Butler, Chapman, Forman, & Beck, 2006). CBT is an effective treatment for Obsessive-Compulsive Disorder (OCD) and is also applicable to patients with both OCD and Autism Spectrum Disorder (ASD). However, previous studies have reported that CBT for patients with both OCD and ASD might be less effective than for patients with OCD alone (Mito et al., 2014; Murray, Jassi, Mataix-Cols, Barrow, & Krebs, 2015). In addition, there is no evidence as to why autistic traits might be risk factors. Therefore, we investigated whether comorbidity between ASD and OCD might significantly affect treatment outcome, and discovered predictors of CBT outcomes using structural magnetic resonance imaging (MRI) data. Finally, we suggested implications for the integration of neurofeedback training (NFB) and CBT.

Methods. Fifteen patients were diagnosed with having OCD with ASD, and 22 patients were diagnosed with OCD without ASD. Both groups took CBT for 12 to 20 sessions. First, to examine the effectiveness of CBT for OCD patients with and without ASD, we compared CBT outcomes between both groups. Second, to investigate how the structural abnormalities profile of the brain at pretreatment influenced CBT outcomes, we performed a structural MRI comparison focusing on the total gray matter volume in both OCD patients with and without ASD, as well as those who reached remission and did not reach remission.

Results. OCD patients with ASD responded significantly less well to CBT than OCD patients without ASD. They had significantly smaller gray matter volumes than OCD without ASD in the bilateral occipital lobes and the right cuneus (BA 18 and 19), both of which play important roles in visuospatial processing. After controlling for autistic traits, the nonremission group displayed a smaller gray matter volume than the remission group in the left dorsolateral prefrontal cortex (DLPFC, BA 10, BA 46). The DLPFC has an important role in executive functions including spatial attention and working memory processes, and these cognitive processes at pretreatment might affect CBT outcomes. Our results support the revised model for OCD proposed by Menzies et al. (2008), which shows that the brain pathology of OCD is not only limited to the orbitofronto-striatal "affective" circuit associated with limbic structures but also involves abnormalities including the DLPFC that may represent the dorsolateral prefronto-striatal "executive" circuit.

Conclusion. In our study, after controlling for autistic traits, the smaller the pretreatment gray matter volume in the left DLPFC, the less likely the OCD patients would fully remit. The application of NFB in the treatment of OCD has not been systematically investigated; however, several studies showed that NFB in the limbic system would result in a reduction in experienced anxiety (Hammond, 2003). In addition to these studies, we suggest that NFB in the DLPFC prior to CBT could improve executive functions. As Mohlman and Gorman (2005) mentioned, the successful use of CBT is assumed to rely on cognitive skills known as executive functions (e.g., allocation of attention, self-monitoring) governed by the prefrontal cortex including the DLPFC.

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NeuroRegulation

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Re-training the Injured Brain: sLORETA Neurofeedback as an Acute Concussion Intervention

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Introduction/Support. Concussion incidence rates are at epidemiological levels and rising (Giza & Hovda, 2001). In 2011, the Center for Disease Control (CDC) estimated 1.6–3.8 million sports- or recreation-related concussions occur per year (Daneshvar, Nowinski, McKee, & Cantu, 2011), and concussion rates are increasing in adolescents (Zhang, Sling, Rugg, Feeley, & Senter, 2016). Concussion is a complex pathophysiologic process affecting the brain, induced by biomechanical forces (McCrory et al., 2013). Concussion-related symptoms interrupt the daily functioning of the concussed individual, and current concussion recovery guidelines emphasize rest and the avoidance of symptom-provoking behaviors to minimize concussion-related symptoms throughout recovery (McCrory et al., 2013). Concussion injury results in measurable EEG abnormalities detectable by electrophysiological techniques (Rapp et al., 2015). Cortical deregulation due to concussion injury as depicted by qEEG may be addressed by neurofeedback shortly after injury.

Hypothesis/Justification. Neurofeedback has been used as an intervention for traumatic brain injury, but requires further investigation as an evidence-based practice. Neurofeedback is currently ranked as "Level 3 – Probably Efficacious" by the statement of efficacy on evidence-based practice in biofeedback and neurofeedback by the Association for Applied Psychophysiology and Biofeedback (AAPB; Yucha & Gilbert, 2004). The principle investigator hypothesizes that (1) neurofeedback interventions to inhibit slow wave activity will reduce the presence of concussion related symptoms and (2) the use of the intervention will decrease recovery time compared to recommended clinical guidelines of return-to-play concussion recovery.

Methods. As soon as logistically possible, qEEG data will be collected from adolescent or young adult patients presenting autonomously to a neurology clinic for the evaluation and treatment of acute concussion related to sport or recreational activity. Cognitive measurements and concussion-related symptoms will be measured and tracked using the XLNTbrain Sport Inc. Concussion Management Program as patients recover according to current evidence-based guidelines outlined by McCrory et al. (2013) qEEG data, neurocognitive test results, concussion-related symptoms, and attending neurologist who will guide neurofeedback protocol design. Data will be recollected after patients undergo approximately 15 sessions of neurofeedback and are medically cleared of concussion injury.

Results. Surface (scalp), sLORETA, and connectivity *Z*-score qEEG metrics from multiple commercially available qEEG database suites will be assessed for change from pre-neurofeedback and post-neurofeedback qEEG assessments. Changes in deviant sLORETA *Z*-scores and affected brain volume will be emphasized. Images of sLORETA results will be displayed visually and graphed by frequency band. Cognitive scores and concussion-related symptoms following injury and after recovery will be assessed.

Conclusion. Neurofeedback may provide a novel treatment option for the pervasive neuropsychological concussion problem. Findings that yield *Z*-scored brain activity largely approaching a statistically normal range ($Z = 0$) would suggest that neurofeedback may be beneficial to concussion recovery in comparison to recovery without the use of neurofeedback, where *Z*-scores may remain statistically deviant upon recovery from concussion injury (Ims, 2016). Theoretically, interventional neurofeedback following concussion injury may enable the concussed individual to train his or her brain towards recovery and alter the long-term trajectory of the injured brain.

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ISNR FOUNDATIONS – Introduction to qEEG Concepts and Applications

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This oral presentation will provide an overview of the use of quantitative EEG (qEEG) in clinical practice. Emphasis will be placed on mental health applications. The basic functions of the human brain in relation to EEG will be described. Specific EEG components (frequency bands) will be explained, as well as the anatomical basis of EEG rhythms. Material will be drawn from published articles and books, and will emphasize current knowledge. The relationships of EEG amplitude and phase, connectivity, and brain activation will be described. From a basic knowledge of physiology and anatomy, the relevant clinical signs and symptoms can be put into context and used to create treatment planning. The use of normative reference databases will be explained, as well as relevant inclusion and exclusion criteria for creating clinically relevant databases. Signal processing concepts will also be introduced, including frequency analysis, use of summary maps and other graphical tools, and *z*-scores. The relationship between EEG, qEEG, and neurofeedback will be explained in detail and put into a clinical framework that can be applied by diverse practitioners. The historical, scientific, and medical background of these topics will also be described, and specific examples of key research and clinical activities will be presented. In order to ensure a foundational approach, the basic theory of neuronal electrophysiology, volume conduction, EEG amplification, and signal processing will be described at a level accessible to mental health and medical practitioners. Relevant specifications and performance criteria for instrumentation and software will also be described, providing a grasp of the capabilities and limits of modern technology. A variety of clinical case studies will be used to illustrate key concepts and to demonstrate the utility of these approaches in the medical and mental health practice areas. The importance of recognizing individual differences, peak performance traits, and coping and compensatory mechanisms will also be covered, including the concepts of phenotypes and individual brain optimization strategies.

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A Model for qEEG, and sLORETA Correlates to Predicting and Enhancing Human Performance: A Multivariate Approach

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The derivation of qEEG predictive functions may play a critical role in using qEEG measures that predict potential functional weaknesses or individuals "at risk" for specific academic or occupational challenges. Such measures can also hypothetically be used in a multivariate algorithm approach in neurofeedback to achieve human performance enhancement. EEG was obtained from 493 individuals ranging in age from 4 to 75 years diagnosed with a variety of disorders. All EEG data used a 19-site monopolar montage and referenced to Cz in acquisition and utilizing linked ears reference to derive digitized information in each of the following broad bands: delta (1.5–3.5 Hz), theta (4.0–7.5 Hz), alpha (8.0–12.5 Hz), beta (13.0–25.0 Hz), and beta2 (25.5–35.0 Hz) frequency bands with derived measures of absolute power, relative power, power asymmetry (inter- and intrahemispheric), coherence (inter- and intrahemispheric), and mean frequency for each broad band was attained and then converted to *z*-scores relative to a database of age-matched normal. Univariate as well as complex multivariate variables collapsed across selected regions and combination of frequencies were derived for a total of 13,712 variables. Additionally, the sLORETA voxels including weighted function voxels for subcortical structures were derived at very narrow band frequencies (.39 Hz bands) ranging from 1.5 Hz to 35.5 Hz of the EEG (87 variables). *Z*-scores of all voxels for each ROI standard in sLORETA as well as a number of weighted voxels estimating subcortical locations were derived for each very narrow band frequency for a total of 6,896 variables. Data reduction methods for this total 599,952 variable matrix were utilized by deriving the mean *Z*-score score of all voxels within each ROI and then averaging these mean *Z*-scores across the narrow band frequencies that define each of a number of broad band frequencies for each subject. Step-wise regression analyses of the resultant reduced variable sets were used to define specific weighted polynomial multivariate equations accounting for over 90% of variance that predict standard scores from neuropsychological tests and their subtests for many cognitive and behavior measures. Analyses revealed distinctive predictive equations for human performance spanning a wide range of human performance. It is proposed that these algorithms represent electrophysiological base networks (as opposed to fMRI based networks) at "resting state" that correspond to gradients of psychological performance. Pilot data from equations demonstrated predictive ability to test neuropsychological performance were tested in independent patient samples to test validity and reliability. This study demonstrates that qEEG can be used to screen for brain functional impairment with prediction of specific neuropsychological deficits that may require further assessment and intervention. A discussion will be provided regarding the use of these same algorithms for neurofeedback training optimized human performance.

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ISNR FOUNDATIONS – How Accurate Assessment Leads to Effective Intervention for ASD

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Autism Spectrum Disorder (ASD) can be described as a "group of developmental disabilities that can cause significant social, communication, and behavioral challenges." The epidemiological data presented by the CDC reported that 1 in 68 children are currently diagnosed with ASD (CDC, 2016). The CDC has noted an increase in the prevalence of ASD since the 1990s, making effective treatment an important part of the growing conversation. Providing effective treatment options is becoming more and more crucial for this population, especially when considering the cost of healthcare for these

individuals. With rates of incidence rising, this condition has become a major healthcare crisis calling for effective methods of intervention and an intimate understanding of the disorder. Neurofeedback is one promising method to treat the symptoms of ASD (Coben, 2013). This presentation will focus on providing up to date information on the clinical, neurophysiological, and neuropsychological underpinnings for individuals with Autism Spectrum Disorders (ASD) and how to use this information for better treatment plans and improved outcomes.

This presentation will discuss the importance of considering ASD in the context of underlying neurophysiological and neurocognitive correlates. When considering a treatment plan, this information can be used to rate the baseline symptoms in objective manner, as well as objectively measure change through the treatment course. This approach also allows the clinician more information to use to make adjustments during the treatment process. It is apparent that an optimal treatment course will demonstrate measurable change at the subjective, neurophysiological, and neurocognitive/ behavioral levels of analysis.

This presentation will outline assessment opportunities for various mental health professionals to consider adding to their own practice. Further discussion will relate this information to the EEG analysis. Next, steps will be provided regarding using the information for establishing the neurofeedback protocol. The presentation will provide a basic foundation for assessment opportunities for the neurofeedback clinician and strategies on how to use this information to make a more informed choice about neurofeedback treatment protocols. Using this information to measure outcome goals will also be discussed. Case presentations will also be provided to further a practical understanding.

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An Analysis of Long-Term and Secondary Outcomes of a Randomized Controlled Trial of Neurofeedback to Treat Chemotherapy-Induced Peripheral Neuropathy

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Background. CIPN is a common side effect of chemotherapy, leading to impairment in daily activities and diminished quality of life. Neurofeedback (NF) is a brain-training paradigm that induces neuroplasticity to modulate brain activity, and we have previously shown it leads to improved CIPN symptoms that were mediated by NF-induced brain changes.

Methods. Seventy-one (62 female; mean age = 63; 52 breast, 8 gynecologic, 11 other; average length of symptoms = 24 months) cancer survivors greater than three months from completing chemotherapy who reported greater than 3 on the NCI's neuropathy rating scale, were randomized to a NF group (n = 35) and underwent 20 sessions of electroencephalography (EEG) NF or a wait-list control group (WL; n = 36). We used quantitative EEG imaging to determine any EEG patterns unique to CIPN and then provided NF to change aberrant brain signatures. The primary outcome measure was the Brief Pain Inventory (BPI). Secondary outcome measures included the Pain Quality Assessment Scale (PQAS), MD Anderson Symptom Inventory (MDASI), Short Form 36 (SF-36); Brief Fatigue Inventory (BFI); and Pittsburgh Sleep Quality Index (PSQI), which were completed at baseline, at the end of treatment, 1 and 4 months later. Analyses were done using a general linear mixed model regression (GLMM), and general linear regression (GLM) determined between group differences at each time point.

Results. 89% of the participants who were randomized completed treatment and 100% of participants who started NF completed treatment. Change scores from baseline to end of treatment demonstrate NF lead to significant reduction in neuropathic symptoms such as pain and numbness (previously reported), and in cancer-related symptom interference (NF = −5.3 vs WL = −0.5, p = .000); symptom severity (NF = −5.1 vs WL = −0.8, p = .000); fatigue (NF = −3.7 vs WL = −0.8, p = .001), and sleep disturbances (NF = −2.3 vs WL = 0.8, p = .030); and improved physical functioning (NF = 3.3 vs WL = 1.4, p = .003). At 4 months, the outcomes

remained for targeted symptoms but not for secondary outcomes.

Conclusion. NF clinically and significantly improved primary outcomes at 4 months posttreatment and reduced secondary symptoms associated with CIPN.

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Depression Two Years Post Four-Channel Multivariate Coherence Neurofeedback Treatment

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Having high prevalence and a persistent nature, it becomes clear that depression can be blighting for those struggling with its symptoms (Kessler & Bromet, 2013). According to the World Health Organization, there are more than 300 million people worldwide who are suffering from depression (WHO, 2017). Many options for treatment, such as psychotherapy and medication, have been shown to be effective in reducing depression. However, a recent study by Stevens, Coben, and Middlebrooks (2015) showed that four-channel multivariate coherence neurofeedback treatment proved to be more effective in reducing depression compared to alternative methods. The current study aims to show that four-channel neurofeedback training is not only effective for the duration of treatment, but continues to maintain positive effects over time.

The original study mentioned consisted of 54 patients across three conditions: psychotherapy, neurofeedback, and a waitlist control group. The patients who did not receive neurofeedback initially were later offered neurofeedback treatment at the conclusion of the original study (crossover design). After completing the crossover study (Study 1), results showed that 15 out of the 18 patients who received NFB had significant changes over time, leading to a decrease in depression by 1 standard deviation, compared to the other conditions which did not show significance (Stevens, Coben, & Middlebrooks, 2015). Our current sample consists of 48 patients involved in the original study who were administered the Beck Depression Inventory (BDI-II). In order to show the continued effects of neurofeedback on depression, the current follow-up study will compare the differences in depressive symptoms immediately following the completion of treatment and 2 years after the treatment has concluded. SPSS software will be used in order to perform an ANOVA for analysis. Results demonstrating the changes in reported symptoms are expected to support our hypothesis that four-channel multivariate coherence training will maintain the reduction of depressive symptoms 2 years after the conclusion of treatment.

The data from the initial crossover study, as well as the current follow-up study, is expected to provide evidence that four-channel multivariate coherence neurofeedback treatment can have continuing positive effects for individuals struggling with depression. With the commonality of depression present today, it is important we continue to expand our knowledge and explore the most effective treatment options.

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The Use of Four-Channel Multivariate Training on Mild Traumatic Brain Injury: A Comparison of Newly Concussed and Remotely Concussed Individuals

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Mild traumatic brain injury (MTBI), commonly referred to as a concussion, can be described as a brain injury resulting from acute trauma to the head (Carroll, Cassidy, Holm, Kraus, & Coronado, 2004). In the United States it is reported that up to 1.7 million people sustain a traumatic brain injury (TBI) annually, which has resulted in the direct and indirect cost of $60 billion in the United Sates. However, it is estimated that the burden of TBI is dramatically underrepresented as many people who experience mild or moderate TBI do not seek medical support. With an estimated 38 million children involved in athletic activities, it is important to consider the effects that MTBI presents to the United States (Daneshvar, Nowinski, Mckee, & Cantu, 2011). MTBI is commonly associated with fatigue, headaches, memory loss, poor attention, sleep disturbances, seizures, feelings of depression, and other significant symptoms (Grady, 2010).

The scope of MTBI makes improved detection along with ease and efficacy of treatment vital. Postconcussion 86% of patients are found to have

abnormal EEG making EEG an important tool in the detection of MTBI. Additionally, the use of neuropsychological testing can help to identify the lasting effects of MTBI (Haneef, Levin, Frost, & Mizrahi, 2013). When considering the types of improvements that different therapy modalities make, time of treatment has always been a point of discussion for treatment providers. Many physicians believe that the patient should engage in a period of rest before starting therapy to improve MTBI symptomology. We intend to explore the relationship between functional outcomes of the concussed patient and the amount of time elapsed before the start of treatment.

Methods. Our study aims to compare outcomes of four-channel coherence training with recent versus remotely concussed individuals using a case series methodology. Patients diagnosed with MTBI will undergo a qEEG to develop individual protocol for four-channel multivariate coherence training. Pre- and post-qEEG will be done to appreciate global changes in coherence. Additionally, other neuropsychological testing indices will be administered to provide a functional look at changes in MTBI-related symptomology. The correlation between demographic information and outcome of treatment will be explored as well.

Assessment. Quantitative electroencephalogram studies were performed pre- and posttreatment using Brain Dx, NeuroRep, and Neuroguide. Additionally, the use of multiple neuropsychological tests was employed.

Anticipated Results/Hypothesis. We anticipate that the use of four-channel multivariate coherence neurofeedback training will improve the functional outcome of the concussed patient, regardless of time of injury.

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Enhancing Treatment Success: The Benefits of EEG Analysis

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A large number of neurofeedback candidates have tried a multitude of approaches, treatment modalities, and medications with limited success. Studies find qEEG neurofeedback successful 60 to 80 percent of the time, leaving 20 to 40 percent unsuccessful. This sizable percentage of treatment failure could be avoided by having the electroencephalogram (EEG) analyzed by a electrophysiologist or neurologist who is board certified in electroencephalography. A recent EEG/qEEG study identified four neurobiomarkers that accounted for psychotropic medication failure: focal slowing, beta spindles, encephalopathy, and transient discharges (Swatzyna et al., 2014). Although the qEEG is excellent for identifying the location and significance of focal slowing as well as excessive beta, only the EEG can identify the morphology of beta spindles. In a study by Arns, Swatzyna, Gunkelman, and Olbrich (2015), beta spindles were found to be associated with sleep issues and were best evaluated with polysomnography. In addition, Swatzyna et al. (2015) found that individuals with beta spindles were five times more likely to be diagnosed with depression and experienced treatment resistance to selective serotonin reuptake inhibitors (Arns, 2011). Many sleep issues require a medical intervention and often account for treatment failure. A low voltage slow EEG is the hallmark of encephalopathy, but only an electroencephalographer can identify the associated morphology. Unless the brain has enough oxygenation or metabolic support, all therapies and medications will have limited effectiveness. Lastly, transient discharges are often averaged out or removed in the qEEG process. However, identifying the source of these discharges is often critical to protocol design and treatment success. Although everyone who utilizes qEEG collects EEG data, few clinicians have the data read by a board certified electroencephalographer. This presentation provides case examples where data from an EEG provided critical information such as

structural, metabolic, or toxic etiology which required further testing, altered treatment, and improved the success rate of a client.

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The Effects of Misdiagnosed Attention-Deficit/Hyperactivity (ADHD) May Decrease Children's IQ, and The Efficacy of qEEG and Neurofeedback in the Assessment and Treatment of Misdiagnosed ADHD Children: A Clinical Case Series

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Background. In children with ADHD, some studies support the effect of stimulant medication on academic achievement and some do not. One problem may be the incorrect diagnosis of ADHD using subjective measures and another may be the inefficacy of treatment. If the problem is not addressed properly it may cause a decline in IQ scores as seen in our population. Neurofeedback was chosen as a treatment since there is evidence that neurofeedback in ADHD and LD has shown to be effective in this population and has also shown to be effective in improving IQ scores.

Methods. In this clinical case series, we analyzed the results of 21 medicated ADHD-diagnosed children and adolescents who did not show any substantial improvement and who had WISC-R results at least six months prior to coming to us. All the subjects were withdrawn from medication and tests were performed to determine the diagnosis and establish a baseline (qEEG Neurometric Analysis, WISC-R, TOVA, and subjective questionnaires). These children were administered a qEEG-guided Neurofeedback protocol. The rationale being that NF would be effective in this population and another consideration was the parents' wishes of having a nonmedication alternative.

Results. At the end of the treatment all the tests were readministered and compared against baseline values. The results showed an increase in IQ scores with improvement in the all tests administered.

Conclusions. In this group, incorrect diagnoses, ineffective treatment, and the side effects of medication may cause a decline in the intellectual development of the children as observed by a decline in IQ scores. This decline was reversed with Neurofeedback treatment which not only showed improvement in objective measures (IQ scores) but on subjective measures also (rating scales). The implication for a clinical practice is that the overreliance on subjective measures may lead to an incorrect diagnosis and an ineffective treatment, having untoward effects on the child's intellectual development. Another finding of this study is that Neurofeedback treatment may be an effective treatment in this group of children.

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The Effectiveness of tDCS/tACS/tRNS and pEMF Stimulation on EEG Neurotherapy Performance

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In this session, a discussion regarding neurostimulation technology will be conducted. The speaker will show how neurostimulation that is synchronized with EEG neurotherapy can enhance and facilitate regulation of the brain based on qEEG assessment and behavioral observational data. The limitations of EEG neurofeedback prevent adequate treatment outcomes on "tough cases" (such as autism) and decrease the credibility of the field in general when no treatment effects are observed. One of the main reasons for poor neurofeedback outcomes is associated with deregulation of the human connectome, or rich club. The human connectome has been strongly associated with the default mode network, and deregulation of this network can lead to poor communication between important network hubs that are responsible for regulating the brain. The speaker will discuss the current MRI BOLD research associated with physiological responses to pEMF, tDCS/tACS/tRNS stimulation. In 2016 multiple studies were published that show how stimulation technology triggers calcium ion activation in the glia which gives rise to global neuroplasticity responses. This new data supports the use of neurostimulation methods as they can help to facilitate changes in absolute power, coherence, and phase towards the norm. The speaker will show and discuss qEEG and outcome data associated with clinical cases diagnosed with Autism, ADHD, depression, anxiety and Parkinson's disease. Each of the cases discussed with include a summary of patient information, diagnosis, history, and treatment plan. Each case will be presented with pre- and posttreatment EEG data. Behavioral changes will be discussed showing the effectiveness of EEG neurofeedback.

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A Randomized Control Study of Neurofeedback Training on Children with Multiple Types of Trauma

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This research focuses on the effect of neurofeedback (NFB) on children with multiple types of childhood trauma. The Center for Disease Control (CDC) estimates that such traumas are arguably one of the most important public health challenges in the United States (van der Kolk, Roth, Pelcovitz, Sunday, & Spinazzola, 2005). They have a negative impact on the mental and neurobiological functioning (Teicher & Samson, 2016), which leads to a lower quality of life and creates a substantial financial burden for both the individuals affected and the healthcare industry (van der Kolk et al., 2005; Wang & Holton, 2007). To date, there has been little research on the impact of NFB on multiple types of childhood trauma, although two recent studies on the impact of NFB on adults have shown that it significantly improves the condition of adults with chronic PTSD (Gapen et al., 2016; van der Kolk et al., 2016).

We present a randomized control design study of NFB on 37 children ages 6 to 13 who suffered from at least two types of trauma. The participants were randomly assigned into one of the two groups: Active (n = 20) and Control/waiting list (n = 17). The Active group received 24 NF training sessions at T4-P4 twice a week and underwent four periods of assessment: at baseline, midway through NFB, immediately posttraining, at a 1-month follow-up. The control group had assessments at equivalently spaced time points. Chi-square analyses were conducted to evaluate the impact on PTSD diagnoses (present/absent) according to K-SAD

assessment. Piecewise growth curve analyses were run to explore differences in rates of change from baseline to posttreatment and from posttreatment to follow-up for both groups.

The results suggest that NFB significantly reduced the number of participants who met PTSD diagnosis criteria. Moreover, NFB significantly reduced, with effect sizes ranging from −0.49 (medium effect) to −0.96 (large effect), the symptoms for alexithymia, as measured in CAM assessment; cognitive and executive functioning, as measured in BRIEF assessment; and internalizing and externalizing behavior, as measured in CBCL assessment.

This study suggests that NFB is an effective treatment for improving the condition of children with multiple types of trauma. Moreover, most care givers reported that the children were resistant to other therapies (note that resistant to other therapies was not an inclusion criteria).

We therefore recommend further study with a larger number of participants, personalized protocol and more NFB sessions.

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Impact of Developmental Trauma on Brain Function and Connectivity

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The effect of trauma upon anyone can have a long-lasting impact on their brain. For children, trauma can have a permanent impact on their developing brain, yet they may never meet the criteria for PTSD (Teicher, Andersen, Polcari, Anderson, & Navalta, 2002). For children however, traumatic stress can come from multiple and/or chronic and prolonged, developmentally adverse traumatic events during early childhood development (van der Kolk, 2005). This has led to a new classification, Developmental Trauma (DT). Areas of the brain involved in the stress response include the amygdala, hippocampus, and prefrontal cortex, which also play a role in memory (Bremner, 2006). Research by Sapolsky found stress can alter plasticity of the limbic system, not only affecting hormone secretion, but also how the hippocampus and amygdala work together to form memories about the stressor (2003). Comparing maltreated groups to control groups, Teicher, Samson, Anderson, and Ohashi (2016) also found connectivity issues as well in the left anterior cingulate, right occipital pole, left temporal pole, and right medial frontal gyrus. Regions of decreased connectivity were found in areas important to emotional regulation, attention, and social cognition, while areas with increased connectivity seemed to occur in areas of self-regulation (Teicher, Samson, Anderson, & Ohashi, 2016).

EEG/qEEG research on developmental trauma is quite scant. One study found that abused children had higher left hemisphere coherence and a reversed asymmetry as well as a slower rate of decay of left hemisphere coherence over electrode distance suggesting deficit in left cortical differentiation (Ito, Teicher, Glod, & Ackerman, 1998). Our study aims to study the impact of repeated developmental trauma on brain function and connectivity. We hypothesize adults that experienced DT will show significantly different findings than those that did not have such a history. Further, we anticipate that susceptible regions may include those near the anterior cingulate left frontal temporal and limbic regions and right posterior regions involved in social engagement.

We are in the midst of collecting QEEG data (19 and 64 channels) on 30 survivors of DT and a comparison group. The groups will be compared for differences in EEG power, coherence, and connectivity. Using EEGLAB and MVGC (multivariate granger causality toolbox) we will measure scalp and source measures for comparison as indicated above. Source comparisons will be made insuring finer spatial localization of the network components while minimizing signal processing confounds produced by broad volume conduction from neural sources to the scalp electrodes (Coben, Mohammad-Rezazadeh, &

Cannon, 2014). Source-derived connectivity measures including Granger Causality and partial directed coherence will be applied. Group-based comparisons of these metrics will be displayed and case examples will be used as well for illustrative purposes. The implications of these findings for understanding DT and its treatment will be discussed.

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Alpha Phase Synchrony Based Neurofeedback for Chronic Back Pain

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Chronic back pain is a well spread phenomenon affecting as many as 2% of the French population with a conservative estimate of 1.5m chronic patients just in France for whom all therapeutic options have failed. The direct cost for the payer is estimated to a yearly €1.6b for France, turning a relatively small population into a public health issue. Neurofeedback (NFB) is a self-paced brain neuromodulation technique that represents one's brain activity in real-time using auditory or visual modulations, on which the subject can exerts voluntary control, or which is used to "condition" certain neural mechanisms. Brain activity is captured using an electroencephalographic (EEG) device.

The goal of this pilot study is to evaluate the efficiency of alpha synchrony based NFB, applied to chronic low back pain patients (n = 16) with whom all available therapeutic options have failed. The intervention investigated is twenty 30-min-long alpha synchrony neurofeedback session using an EEG cap of 21 electrodes. It is an open-label study with no control group. Patients were included after failing all other therapeutic options including a 2-week-long pluri-disciplinary approach dispensed at a tertiary hospital.

First, progression of clinical scores (before and after intervention) such as pain, anxiety, depression, and quality of life are shown to have been reduced by more than 25% in most of patients. Likewise, electromyographic (EMG) signals show a statistically significant increase of the median frequency, associated to a gain of motor units of bigger diameters and more dynamic, the opposite that one can observe during muscle fatigue. Finally, alpha synchrony neuromarkers extracted from EEG signals at each session show progressions along blocks and sessions. More interestingly, the slope progression over sessions is correlated with the decrease of clinical score, which indicates specificity of the trained neuromarker with respect to clinical outcomes.

Future works involves the analysis of 6- and 12-month clinical and EEG follow-up data to investigate the long-term efficacy of neurofeedback. The results of this pilot project would ultimately be the clinical and technical foundations of a high-impact RCT to limit use of analgesics and nonsteroidal anti-inflammatory drugs (NSAID) and promote quick return to work for these patients.

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The Effects of Mobile Application for Cardiorespiratory Synchronization Training on Heart Rate Variability and Electroencephalography

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Background and Description. Cardiorespiratory synchronization training (CRST) is a biofeedback intervention that uses slow and deep diaphragmatic breathing to increase autonomic activations, decrease symptoms of physical and mental disorders, and decrease negative emotions. Diaphragmatic breathing decreases central neuron system activations, increases the theta and alpha powers, and decreases the beta power of electroencephalography (EEG). High-technology mobile applications (APPs) combined with CRST brings innovation and convenience to users in the field of clinical psychological intervention. The aims of this study were to examine the effects of mobile APP for CRST on heart rate variability (HRV) and EEG.

Method. Two hundred participants were recruited from a university and communities. Ninety-two healthy participants were screened and assigned randomly to the CRST group, relaxation training group (RT group as a sham-control group), and control (C) group. The CRST group received resonance frequency and diaphragmatic breathing training with an APP, and the RT group received muscle relaxation with normal breathing rate achieved by using an APP. The training program took 1 hour and was conducted weekly for 4 weeks. The C group did not undergo any APP training. All the participants underwent pretest and posttest measurements performed using psychological questionnaires, electrocardiography, and EEG. The raw electrocardiographic signals were transformed to HRV indexes, which included standard deviations of all normal-to-normal intervals (SDNN), low frequency (LF), high frequency (HF), total power, and maximum and minimum heart rate (HRmax–min). The EEG parameters included absolute power and relative power of delta, low/high theta, low/high alpha, and low/high beta powers at Fz, Cz, Pz, F3, F4, C3, and C4.

Results. The CRST group had significantly higher HRV indexes (including SDNN, LF, total power, and HRmax–min) than the RT and C groups; decreased relative high beta power at Pz, F4, C3, and C4; and increased absolute high alpha power at Pz. The CRST group also had a significantly higher increase in the change scores of HRV indexes (△SDNN, △LF, △total power, and △HRmax–min) than the RT and C groups, increased △absolute high alpha, and decreased △relative high beta from pretest to posttest.

Conclusion. Combining CRST with mobile APPs not only increased autonomic activations but also improved cortical activations. This program allows participants to practice everywhere and all the time and will be applied to different populations to improve autonomic dysregulation and cortical hyperarousal in the future.

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Relationships Between Cortical Hyperarousal and Sleep Quality Among Patients Comorbid Major Depressive Disorder and Insomnia

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Background. Previous studies confirmed cortical hyperarousal at pre-sleep and sleep stages among patients with primary insomnia or major depressive disorder (MDD); few studies explored cortical hyperarousal at daytime. This study aims to investigate: (1) cortical hyperarousal at daytime among patient comorbid MDD and insomnia and (2) relationships between cortical hyperarousal and sleep quality.

Methods. Seventy-seven healthy participants and 111 patients with MDD were recruited in this study. Pittsburgh Sleep Quality Index (PSQI) was used to separated participants into healthy controls (PSQI ≤ 5), MDD with mild insomnia (5 < PSQI ≤ 11), and MDD with severe insomnia (PSQI > 11). Seven subscales of PSQI (subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction) were used to explore the relationships between sleep quality and cortical hyperarousal. Electroencephalography (EEG) was measured at Fz, Cz, and Pz for 5-min resting state with their eyes-closed during daytime via 19-channel BrainMaster equipment (BrainMaster Technologies, Inc., Bedford, OH). The peak-to-peak amplitude of EEG was analyzed and showed low beta (12–20 Hz) and high beta (21–32 Hz) as the indices of cortical hyperarousal.

Result. Significant greater high beta at Fz and Cz in MDD with mild/severe insomnia and at Pz in MDD with severe insomnia compared to healthy controls. Significant greater low beta at Fz in MDD with mild/severe insomnia and at Cz in MDD with mild insomnia compared to healthy controls. However, no significant difference in low/high beta between MDD with mild and severe insomnia. In addition, significant positive correlations between sleep efficiency with low/high beta at Fz, Cz, and Pz in MDD with severe insomnia group. Significant positive correlations between use sleeping medications with low/high beta at Fz, Cz, and Pz; and negative correlations between daytime dysfunction with high beta at Fz, Cz, and Pz in MDD with mild insomnia.

Conclusion. Patients comorbid MDD and insomnia had higher cortical hyperarousal at the midline area of brain compared to the healthy controls. Poor sleep efficiency was related to cortical hyperarousal in MDD with severe insomnia; frequency of using sleep medications and daytime dysfunction were related to cortical hyperarousal in MDD with mild insomnia.

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Atypical Processing of Novel Distracters in a Visual Oddball Task in Children with Autism Spectrum Disorder: An ERP Study

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Background. Several studies have shown that children with autism spectrum disorder (ASD) show abnormalities in ERPs (Baruth, Casanova, Sears, & Sokhadze, 2010; Bomba & Pang, 2004; Kemner, van der Gaag, Verbaten, & van Engeland, 1999; Sokhadze, Baruth, Tasman, & Casanova, 2013). Children with ASD have been found to differ from typical developing (TD) children mainly with respect to the parietal P3b to targets in standard oddball tasks (Cui, Wang, Liu, & Zhang, 2017). The proposed study employed a three-stimulus visual oddball task with ERP recording and focused on

analysis of responses to both target and nontarget items. In order to better understand attentive orienting to novel signals, we studied both frontal and parietal ERP indices of information processing. The oddball task was aimed to test our hypothesis that children with autism are abnormally orienting attention to novel distracters probably due to impaired habituation to novelty. We predicted a lower selectivity in early ERPs components in response to target, frequent nontarget, and rare distracters and delayed endogenous ERP components in autism group.

Methods. We enrolled 24 children with ASD (13.4 ± 1.9 years) and 19 TD children (14.1 ± 3.05 years). The ERP test used letters "X" (target 25%), "O" (standard, 50%), and novel distracters ("v," "^," ">," and "<," 6.25% each) presented for 200 ms at approximately 1 Hz rate. Reaction time (RT), accuracy, and post-error RT were analyzed as behavioral measures, while ERPs recorded with EGI EEG system at the frontal region-of-interest (ROI) and parietal ROI.

Results. One-way ANOVA showed that children with ASD compared to the TD controls yielded group differences in response error rate (17.7 in ASD vs. 4.6% in TD, p = .043) and did not show normative post-error RT slowing (−17.3 vs. 19.5 ms, p = .028). Parietal P100 was higher to novels in ASD (3.66 vs. 2.16 uV, F = 4.5, p = .041). At the frontal ROI ASD group showed higher amplitudes of exogenous components (e.g., N100, −4.05 vs. −2.69 uV, p = .044) and higher amplitude of endogenous ERP components (e.g., P3a, 4.88 vs. 2.17 uV, p = .015) to novel distracters.

Discussion and Conclusion. These results indicate a reduced capacity for the ASD group to process distracters and orient attention to novelty. The findings are in line with our prior studies using different tasks with visual and auditory stimuli (Kiser et al., 2012; Sokhadze et al., 2009, 2012). Augmented early potentials and a delayed frontal P3a to novel stimuli suggest low selectivity in preprocessing of distracters resulting in excessive processing at the later stages at frontal regions. This may indicate a reduction in the discriminative ability of the ASD group. These results may reflect a locally overconnected network where sensory inputs evoke abnormally large ERP for unattended stimuli with signs of a reduction in the selectivity. This may incur a high load at the later stages of perceptual and cognitive processing and response selection when novel distracter stimuli are differentiated from targets. Analysis of ERP in autism may provide important biomarkers for functional diagnostics and in addition these biomarkers could be used as outcomes in interventions such as rTMS or neurofeedback.

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Emotional Changes of ALAY Neurofeedback for Patients Comorbid of Anxiety Symptoms and Major Depressive Disorder

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Background. Previous studies indicated that ALAY neurofeedback (NFB) was an effective protocol for reducing depression and increasing frontal alpha asymmetry (FAA). However, most studies were preliminary case studies of major depression disorder and do not include a control group which could compare with neurofeedback group to examine the effect of ALAY NFB. The purpose of the present study was to examine the effect of ALAY

NFB for patients comorbid of anxiety symptoms and major depression disorder (MDD).

Methods. Twenty-six patients of comorbid anxiety symptoms and MDD were assigned to the ALAY NFB group and the control group. All participants received psychological questionnaires and 5-min resting electroencephalography (EEG) with eyes-closed measurement at pretest and posttest. Beck Depression Inventory II (BDI-II) and Beck Anxiety Inventory (BAI) were administered, and 19-channel EEG was measured and analyzed by BrainAvatar (BrainMaster Technologies, Inc., Bedford, OH). A1 score [log (F4 alpha) – log (F3 alpha)] were calculated as the index of FAA. Participants in the ALAY NFB group received increased A1 score training 1 hour twice weekly for 5 weeks by BioGraph Infiniti (Thought Technology Ltd., Montreal, Quebec, Canada) with bipolar–channel at F3 and F4. Participants in the control group received pretest and posttest.

Results. No significant difference between two groups on age (t = 1.89, p = .07) and sex ($\chi 2$ = .01, p = .91) at pretest. The pair t test revealed that lower scores on anxiety (t = 2.18, p = .047) and depression (t = 3.01, p = .009) in the ALAY NFB group at posttest than that at pretest. However, no emotional change on anxiety and depression in the control group.

Conclusion. This study indicated that ALAY NFB was an effective protocol for reducing negative emotion for patients of comorbid anxiety symptoms and MDD.

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The Different Levels of Golf Players on Mu Rhythm Coherence Prior to the Golf Putt

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Background and Description. The Mu rhythm (8–13 Hz), located in the sensorimotor cortex, is related to visual processing and motor control and coordination during activation. Mu rhythm coherence would further understanding of the relationship between brain regions of the functional connections in precise action during the preparation period. Past studies have shown that experts in visual processing (occipital area), motor control and coordination (parietal area), and oral analysis (left hemisphere) showed lower brain coherence, which was consistent with the neural efficiency hypothesis. However, the neural efficiency hypothesis was regulated by the task properties and experience level. Therefore, the purpose of this study was to use Mu rhythm coherence to explore the differences of functional connection from sensorimotor area to other areas with different levels of golf players by controlling putting task difficulty. The hypothesis was that experts would show lower coherence than novices.

Methods. Sixteen experts (mean handicap = 4.44 ± 2.06), 10 amateurs (mean handicap = 32.20 ± 7.61) and 17 novices were recruited. The task difficulty depended on 50% putting successful rate of the individual performance. Sixty putts were executed and divided into six blocks, where each block contained 10 putts. The positions at F3, F4, C3, C4, T3, T4, P3, P4, O1 and O2 were assessed.

Results. When putting difficulty was set at 50% for each group, putting distance performance was experts (402.50 ± 46.55 cm) > amateurs (356.00 ± 27.16 cm) > novices (248.24 ± 43.05 cm). Under the same putting difficulty, compared to novices, experts exhibited significantly higher coherence between the sensorimotor area and parietal area, and between the sensorimotor area and left hemisphere. Also, experts and amateurs demonstrated higher coherence between the sensorimotor area and occipital area.

Conclusion. Under the same effortful difficulty task, compared to novices, experts significantly involved more resources into visual-motor integration, coordinated control, and verbal analysis to come into better putting performance. The excellent cortical functional organization experts have shaped might be flexibly adjusted according to external requirements and performance needs. In terms of space experts might recruit more related cortical regions to parallel signal processing, and in regard to time experts might activate the dominant cortical region more neurons simultaneously, increasing calculation speed, rather than being confined to a "neural efficiency" strategy for the reduction of cortical activation.

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Artifact-Controlled Neurofeedback: A Pilot Study

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Neurofeedback (NF) allows individuals to train and control their own brainwaves. It has been used to assist individuals with attention-deficit/hyperactivity disorder (ADHD) since the 1970s (Lubar & Shouse, 1976). Research supports the view that NF improves attention, although there remains a dearth of research on improvements in academic achievement. Traditionally, NF research has been conducted by clinical psychologists, psychiatrists, and other medical professionals. However, technological advances now permit NF research to be conducted in schools, thereby opening a potentially useful intervention for special educators. In one study, academic achievement in a school setting found that NF may improve scores on measures of reading comprehension (La Marca & O'Connor, 2016).

This poster session will examine the initial findings of a pilot study that examined EEG "artifact"—electrical activity generated through muscle activity that is not associated with brainwaves. The presence of artifact inserts additional signals that are detected by the EEG equipment used to train brainwaves and, therefore, may impair the efficacy of NF training (Goncharova, McFarland, Vaughan, & Wolpaw, 2003). NF training is traditionally done without any control for eye movement, eye blink, or muscle tension artifacts. However, these muscle-based events generate electrical activity that interfere with the ability to accurately read brainwaves, thus potentially diminishing the effect of NF training (Montgomery, 2001).

This poster session will examine the efficacy of NF software that automatically removes artifact and report if automatic artifact removal simplifies the tasks that highly trained special educators may utilize in schools. Study data will inform future research that examines the use of NF to improve academic performance in students with ADHD. The study hypothesized that NF training without any artifact control inhibits students' abilities to learn how to self-regulate their brainwaves, while the elimination of artifact on the fly may decrease the time needed for NF. Thus, elimination of artifact may make use of the intervention more amenable to special educators.

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External and Internal Foci of Attention with Frontal Midline Theta

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Background. Frontal midline theta (Fm θ, 4–7 Hz) is related to top–down control and attentional resources engagement during activation. Lower Fm θ power in expertise of precise sport means less willing effort and automatic processing alike when in preparation period. Past studies have shown that internal focus of attention during motor preparation makes chocking, which is consistent with the constraints action hypothesis. However, the research in expertise of precise sport was not consistent with past studies. Therefore, the purpose of this study was to use Fm θ to examine the

constraints action hypothesis. The research question was that whether external focus of attention makes expertise more automatic processing than internal focus of attention? The hypothesis is that Fm θ power of external focus of attention (Fm E) is significantly lower than internal focus of attention (Fm I).

Methods. One expert (handicap = 0) was recruited. Both foci of attention were used in personal 50% hole-rate distance as the radius with 40 different positions. A total of 80 putts were executed and divided into four blocks, each block containing 20 putts. Fm θ was recorded and assessed at each putt.

Results. For behavior, both foci of attention were with 12 in-holes in 40 putts. For Fm θ power, external focus of attention (8.622) was larger than internal focus of attention (6.987).

Conclusion. The result of Fm θ was reverse to our study hypothesis; the reason might be that the expert necessarily redeployed attention resource at each putt at different positions with 50% putting task difficulty, especially external cues. Therefore, it led to more external attention than internal attention. Besides, the innovation of improving methodology of this study was measuring EEG and behavior information by each putt at different sites, and it increased ecological validity.

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Biofeedback Intervention for Anger Management: A Case Study

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Although the two are not synonymous, stress is usually tied into anger; both of which have been proven to have negative health effects. Many studies have discussed biofeedback and the effect it can have on relieving stress, as well as its effect on other health conditions (Greenspoon & Olson, 1986; Shellenberger, Turner, Green, & Cooney, 1986; Wyner, 2015). And, although the results weren't conclusive, biofeedback has been shown to be a viable method of tracking and regulating emotions such as anger (Francis, Penglis, & McDonald, 2016) and is suggested as an intervention for anger management. A United Kingdom study indicated that self-monitoring alone isn't enough to manage anger; when paired with self-intervention the results are more positive (Fernandez & Beck, 2001). One of the goals of the present case study was to attempt to target my anger so that it was at appropriate levels of frequency and intensity. The approach was to utilize biofeedback to self-monitor heart rate variability (HRV) through practicing focused breathing and using positive thoughts when I felt angry; this approach was also utilized as a maintenance strategy. This approach is based on protocols developed by HeartMath LLC. The intervention took place at home, but the measurement of frequency and intensity of the emotion took place both at home and in public. The baseline was 12 days; interventions occurred twice daily, with times of each increasing every 7 days and tracked for 4 consecutive weeks. The intervention showed a significant reduction in the number of anger events, as well as a marked decrease in the intensity of each event. The results of this case study indicate that biofeedback paired with HRV can be a successful intervention for a broad range of anger issues. The limitation is that the intervention was with a single person and self-implemented.

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Stress Recovery and Psychophysiological Self- Awareness and Mindfulness

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Cumulative stress can negatively impact emotional and psychological states. When faced with stress, one of the first line of recommendations is to take time away and withdraw from stressors…rest.

Mindfulness practice has been increasingly recommended by many healthcare professionals. The simple nature of the practice can be easily misunderstood and understated, without the backing of empirical evidence of its benefits. Mindfulness research has shown that this practice shows improvement in attention, focus, emotion regulation, and self-awareness (Keng, Smoski, & Robins, 2011; Weinstein, Brown, & Ryan, 2009).

Researchers in the field of neurology have reported that Mindfulness Meditation training can alter regions of the brain known to coordinate stress processing and physiological stress responses (Taren et al., 2015). In field research and in real life it can be difficult to maintain a practice of mindfulness. Without daily practice the benefits of Mindfulness are reduced. Neuro/biofeedback can be used as real-time feedback to teach self-regulation and potentially be used as an aid for Mindfulness Meditation (Brandmeyer & Delorme, 2013).

Purpose. To assess the effects of self-awareness (mindfulness) on stress recovery (rest/neuro-psychophysiology).

Hypothesis. Mindfulness Meditators (M) have significant difference in psychophysiological self-awareness and emotion regulation during rest and recovery than non-Mindful Meditators(nM).

Procedure. Real-time psychophysiological methods to measure two major effects of mindfulness: self-awareness and emotion (stress) regulation in those scoring high on MindfulnessScales (Mgroup) and those scoring lower on MindfulnessScales (NMgroup). Specifically, two major components of Mindfulness will be analyzed:

- Self-awareness: through neuro/biofeedback
- Emotion regulation: neuropsycho-physiological measures of rest/stress recovery from stressors

Psychophysiological Measure (GSR, EEG, EEG; EMG, HR, Temperature) used to measure Baseline, Rest (Post-stressors)/Recovery. Script on a computer screen with the following sequence of events will be presented: 1. Baseline psychophysiology (no stressor), stressor 1 (color Stroop test), rest, stressor 2 (numbers and speed), rest, stressor 3 (timed recall), and rest period.

Self-Report Methods. Mindfulness attention awareness scale (MAAS) and Short Compassion Scale N = 15, Mindful group, n = 7; nMindful group, n = 8.

Preliminary results. Normalized HR and GSR at rest for M and nonM groups, A non-parametric test (Mann-Whitney test) was used to compare two groups, as a more flexible option because the data is likely to be skewed. This is also the reason to report median values for measures of central tendency (instead of means). Results showed that mindful people have lower GSR at rest 1 (median = 1.18) compared to non-mindful participants (median = 1.60), p = .037. Median of 1.60 indicates that a "typical" non-mindful participant has GSR at rest 60% higher than baseline. Median of 1.18 indicates 18% higher for mindful participants compared to baseline. Between the two groups we can assume a difference of 60−18 = 42%.

Participants with high mindfulness score also had lower GSR scores at rest; even though scores were higher during stressors, recovery was closer to baseline than those with lower mindfulness scores. This is a pilot study. The main study has a larger population and more results will be available.

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Isochronic and Binaural Beats Affect the EEG to a Similar Degree at the Cranial Vertex

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Purpose. Brainwave entrainment (the frequency following effect) using sonic beats has long been demonstrated, but there are conflicting claims as to whether isochronic auditory beats or binaural auditory beats are more effective at entraining brainwaves. This study confirmed that brainwaves can be entrained by auditory stimuli and examined whether binaural beats or isochronic tones are more effective at entraining brainwaves at the cranial vertex.

Procedure. Sixty sessions were conducted using eight participants. An active EEG electrode was placed at the cranial vertex, with a reference electrode on the left earlobe and a ground electrode on the right earlobe. The EEG was measured for 8 min under three conditions, in random order for each subject, with a 20-min delay between conditions: (1) a control sessions of soft piano music, (2) piano music with isochronic tones at 10.88 Hz, and (3) piano music with binaural beats set for 10.88 Hz. Statistical tests were performed to assess statistical significance.

Data. Exposure to soft piano music and an auditory stimulus at 10.88 Hz increased the percentage of alpha power at the cranial vertex, compared to piano music alone ($p <= 0.05$). No differences were noted based on the order of the sound exposures. Binaural beats increased the alpha power ratio by 11.1%. Isochronic tones increased the alpha power ratio by 11.5%. Compared to control, both auditory stimuli decreased the total EEG brain power ($p <= 0.05$); the binaural beats by 20.5% and the isochronic tones by 19.3%. The auditory stimuli entrained brainwaves more effectively in subjects with lower alpha power ratios in the control session.

Conclusion. Brainwaves can be entrained to auditory stimulation. Although the absolute alpha wave power decreased with the auditory stimuli, the ratio of alpha wave to total EEG power increased. The isochronic tones were slightly more effective, but the difference was not statistically significant. More research is needed to assess how long the effect will last, and to correlate the changes to other psychological measures.

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Comparing the Effectiveness of Recall of Traumatic Memories (RTM), Eye Movement Desensitization and Reprocessing (EMDR), and Neurofeedback (NFB) on Veterans Diagnosed with PTSD Using a 19-Channel EEG

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Many veterans return from conflict zones suffering from Posttraumatic Stress Disorder (PTSD). Current treatments provide partial symptom relief that is lengthy and ineffective (Schiller & Phelps, 2011). This research seeks to address the impact of PTSD on warriors and veterans by enhancing treatment outcomes, encouraging treatment participation and completion, and decreasing treatment expense by introducing better treatments for the intrusive and hypervigilant symptoms for PTSD. Between September 2001 and August 30, 2011, more than two million (2,333,972) American military personnel were deployed to Iraq, Afghanistan, or both (Martinez & Bingham, 2011). The prevalence of PTSD among veterans of Operation Iraq Freedom (OIF) and Operation Enduring Freedom (OEF) ranges between 13% and 17% (Tanielian & Jaycox, 2008). Between 2002 and the third quarter of fiscal 2011, 711,986 veterans used Veteran Affairs health care (Martinez & Bingham, 2011). Only 23–40% of veterans diagnosed with a mental disorder sought mental health care (Hoge et al., 2004). Low motivation to seek help for mental health care has been attributed to stigma (Hoge et al., 2004), lengthy

waiting periods for obtaining treatment, inconsistent results from currently approved treatments, the length of time in treatment, and the high rate of relapse (Gray & Liotta, 2012). In light of the need for treatment, the frustration that service members and their families experience with current treatments and increasing fiscal restraints, new treatment options are needed. This research study will compare three treatment protocols: a recognized PTSD treatment, Eye Movement Desensitization and Reprocessing (EMDR) therapy, the adapted Reconsolidation of Traumatic Memories (RTM), and Neurofeedback (NFB). EMDR, RTM, and NFB therapies are noninvasive minimal exposure-based interventions that are typically completed in 3 to 20 sessions of 60 to 90 minutes each.

This study researched veterans for noninvasive shorter term, comprehensive, and efficacious interventions. Our hypothesis is that, compared to the pretest and untreated group controls, all three neurotherapy treatments will show clinically significant posttreatment decreases in PTSD symptom scores. There will be statistically significant differences in the pre- and posttest 19-channel EEG's of the RTM, EMDR, and NFB treatment groups compared to the pretreatment waitlist control group

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The Combined Effects of Neurofeedback and Intensive Behavior Intervention on Children with Autism Spectrum Disorder

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Autism spectrum disorder (ASD) is a neurological disorder that affects the wiring of the brain, given variable cognitive impairment and language. These findings have been found thanks to the empirical studies that have been performed around pervasive developmental disorders (PDD), known as qualitative alterations of the communication and the mutual interaction of the individual. Additionally, some changes in the motor area can be included, along with the aforementioned communication and social skills. Neurofeedback, also known as EEG Biofeedback, teaches self-regulation of brain activity by normalizing dysregulated brains in establishing focus and concentration. A large number of studies have applied Neurofeedback in the treatment of ASD, and the results point to a considerable usefulness of this technique, so this study was proposed to review the applicability of Neurofeedback in a group of 30 children between 2.5 and 12 years of age with ASD and/or anxiety receive either both Neurofeedback and combined treatments. The participants received either a combined treatment or isolated treatment of Intensive Behavior Intervention (IBI), Neurofeedback (NF), or Speech and Language (SLP). NF starts with the TLC assessment and Brain mapping to determine specific needs to tailor a detailed and individualized training plan. NF sessions for participants range beginning from 10 to 40; half hour in length, depending upon the type of treatment and participant. Research results show improvements in speech, language, movement, attention, and focus. A calculated increase of accumulated skills estimated of a 30% behavior change with combined Neurofeedback and Intensive behavior intervention.

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EEG Data for a Significantly Improved Alzheimer's Disease Case After Photobiomodulation Treatment

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Neurofeedback (NFB) treatments often cover 10 to 40 sessions over several months. While NFB has been effective for many psychological and psychiatric conditions, significant clinical improvements are not usually observed during the early treatment sessions, and outcomes are not always predictable. An intervention that is simple for NFB practitioners to implement, produces rapid entrainment, and drastically cut short treatment time would potentially change expectations for NFB practice. Photobiomodulation (PBM) offers an intervention with these possibilities, supported by decades of research on its effect on neurological conditions (Hamblin, 2016). Latest research and development in the PBM extend expectations further by allowing the control of key parameters such pulse frequencies and nuclei targets to be controllable, opening up new solutions in personalized intervention. In addition, PBM with selected parameters are starting to produce evidence to improve Alzheimer's disease (AD) conditions. This expands the scope of NFB practice when it is partnered with PBM.

Presentation Contents. To support this argument, the presenters have been involved in recent investigations to test the hypothesis that the brain is immediately responsive to PBM, indicating rapid brain wave training. Furthermore, new scientific theories and evidence continue to build up to support PBM's efficacy for various neuropsychiatric conditions.

In the presentation, analyses of these data from four sets of studies will be discussed. They were based on home-use intervention devices directing near infrared (NIR) light at 810-nm wavelengths pulsed at either 10 Hz or 40 Hz to the hubs of the brain's default mode network. The studies analyzed with summarized results comprise:

- A case series report of five dementia patients with mild to moderately severe impairment treated over 12 weeks. It used 10-Hz pulsing devices which helped produce significant improvements measured with widely recognized cognitive scales, with no side effects (Saltmarche, Naeser, Ho, Hamblin, & Lim, 2017).
- A case report of a moderately impaired AD patient treated with a 40-Hz device and measured with electroencephalography (EEG) over 3 weeks. It presented even more significant cognitive improvement presenting more than 100% improvements in EEG measurements (Zomorrodi, Saltmarche, Loheswaran, Ho, & Lim, 2017).
- A double-blind crossover EEG observational study on PBM of 20 healthy brains. It confirms that NIR directed to the brain produces significant neuro-stimulation effects.
- New data accumulated on brain response to changes in pulse frequencies between 0 Hz to 40 Hz driven at different power. We are also able to demonstrate that changes in pulse frequencies and power evoke changes in EEG patterns in real-time, suggesting that we can rapidly modify EEG brain maps to achieve desired clinical outcomes.

Conclusions. Evidence suggest that PBM has a good argument to be a strong partner to NFB, with the potential to allow it to raise the expectation bar and opens up new solutions for NFB. It also has the potential to personalize treatments. However, to fulfill some of its potential, more work will be required to build up reference profiles related to different pulse frequencies, as well as trigger parameters.

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