NeuroRegulation

The Official Journal of

ISNR
INTERNATIONAL SOCIETY FOR NEUROFEEDBACK & RESEARCH

Volume 7, Number 1, 2020

NeuroRegulation

NeuroRegulation (ISSN: 2373-0587) is published quarterly by the International Society for Neurofeedback and Research (ISNR), 13876 SW 56th Street, PMB 311, Miami, FL 33175-6021, USA.

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).

NeuroRegulation

Volume 7, Number 1

2020

Contents

NeuroRegulation

Postsession Dreaming in Neurofeedback as an Indication of Nondeclarative Learning

Revital Yonah

BetterFly Neurofeedback, Tel-Aviv, Israel
Private practice, Jerusalem, Israel

Abstract

Clients may report increased dreaming following neurofeedback sessions. Increased dreaming may not be strictly a side effect of training but may rather be a result of the nondeclarative learning accomplished in training. Research has demonstrated the connection between dreaming and consolidation of memory in both animals and human subjects. Rapid eye movement (REM) deprivation studies have shown the importance of REM sleep to the retention of newly learned skills. Other studies have shown that learning may increase the proportion of REM sleep on subsequent nights. More specifically, REM dreaming may be related to the consolidation of procedural, nondeclarative memory, the type of learning that occurs also during neurofeedback training. When a client reports increased nocturnal dreaming following a neurofeedback session, this may serve as a valuable early indication that their brain is responding to this type of training.

Keywords: REM sleep; dreaming; neurofeedback training; nondeclarative learning; implicit learning; procedural learning and memory

Citation: Yonah, R. (2020). Post-session dreaming in neurofeedback as an indication of nondeclarative learning. *NeuroRegulation*, *7*(1), 2–7. https://doi.org/10.15540/nr.7.1.2

***Address correspondence to**: Revital Yonah, The Jerusalem Neurofeedback Clinic, P.O.B. 18144, Jerusalem, 9118101, Israel. Email: RevitalYonah@gmail.com

Edited by:
Rex L. Cannon, PhD, SPESA Research Institute, Knoxville, Tennessee, USA

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

Background

Neurofeedback is a form of neurotherapy in which the brain learns a new mode of operation. This learning is achieved as the brain gets feedback for its electrophysiological activity: positive feedback for the desired brainwave activity and negative feedback for the nondesired brainwave activity. Using this feedback, the brain learns to modify its pattern of electrophysiological activity. Most often, the feedback is given to clients in the form of sensory alterations during the session (i.e., visual and/or auditory changes to a video that the client is watching). In order to actually learn this new mode of operation and modify its electrophysiological activity in the desired direction, the brain has to understand the "language" of feedback—that is, it has to realize that there is actually a connection between its own brainwave activity and what is happening to the video being watched or the game being played on the computer. It then has to learn that this connection is causal—that is, the sensory changes, which are perceived to be pleasant or unpleasant (positive or negative feedback, respectively), are contingent on the electrophysiological activity that it produces at any given moment during session. Finally, it has to devise a way to change its pattern of activity in accordance with this feedback.

Many clients have reported changes in cognition, mentation, and emotions following neurofeedback sessions; some of the changes are perceived as positive and desirable while others are less so. In the current paper we would like to discuss the often-reported effect of increased dreaming following neurofeedback sessions and suggest that this may not be simply a side effect of training, but rather an indication that nondeclarative learning has taken place during the training session.

Increased Dreaming Following a Neurofeedback Session

Some clients experience enhanced nocturnal dreaming following neurofeedback sessions (Gruzelier, 2009; Johnson, 2011; Larsen & Verner, 2017; Leong et al., 2018a; Leong et al., 2018b). Reports of increased dreaming tend to be more common after a client's first few neurofeedback sessions, especially if the sessions are relatively long (30–40 minutes), although some clients may experience increased dreaming also through later stages of the training series and with shorter session durations. Dreams are reported to increase in quantity (more dreams than usual) and in quality (the dreams are reported to be enhanced: more vivid, more elaborate, and richer in detail than usual). Their contents may be experienced as emotionally positive or negative by the client, but the impression that they leave is strong enough for the client to at least remember having dreamed. Some clients report that while they normally experience and remember dreaming only in the early hours of the morning—just before waking up (which is in line with the fact that the late stages of a night sleep have a much higher proportion of REM sleep)—after the first neurofeedback sessions they experience dreaming "all through the night." This increased dreaming may be perceived as an adverse side effect by some, while others experience it as a positive phenomenon which they are excited to yield to and explore.

Protocol type may not be a determining factor when it comes to increased postsession dreaming. From our clinical experience, increased vivid dreaming may occur with different kinds of protocols. It has occurred when the sensors were placed frontally, centrally, or parietally, with both unipolar or bipolar electrode placements and with various protocols inhibiting or rewarding different frequency bands. A survey of existing literature reveals that increased dreaming occurred also with the alpha/theta protocol (Gruzelier, 2009; Johnson, 2011), with infra-slow neurofeedback (Leong et al., 2018a) and more.

It seems that rather than the type of protocol, the duration of each training session may be a more crucial factor. Long (30- to 40-minute sessions) may produce increased dreaming already after the first session, whereas shorter sessions (10 or 20 minutes) may produce increased dreaming only after four or five sessions (Leong et al., 2018a). Some clients report feeling more rested after such nights, while others may experience it as troubled sleep. Either way, it seems that increased dreaming following sessions may not be simply a side effect, but rather a positive indication that learning has been attained during the training. Increased postsession nocturnal dreaming may serve as an indication that the brain has done some procedural, nondeclarative learning during the session. In other words, increased vivid dreaming following a session may serve as an early indication that the brain is responding to this type of training—that it "understands the language" of feedback, so to speak.

Why would increased dreaming following a neurofeedback session be an indication of the brain responding to the neural feedback? We will explore this question next.

Dreaming as an Indication of Learning

Dreaming is a natural part of sleep in humans, and REM sleep occurs also through large parts of the animal kingdom (Ayala-Guerrero, Mexicano, & Ramos, 2003; Dement, 1958; Peever & Fuller, 2016). Some people claim to have never dreamed, but research has shown that unless a specific brain damage is present, all of us do, in fact, dream (Herlin, Leu-Semenescu, Chaumereuil, & Arnulf, 2015). While dreaming is often associated with the REM stage of sleep (Aserinsky & Kleitman, 1953; Dement & Kleitman, 1957), it also occurs in non-REM sleep (Cavallero, Cicogna, Natale, Occhionero, & Zito, 1992; Foulkes, 1962). According to different studies, the incidence of dream reports is between 70% and 90% when subjects are woken from REM sleep, but it drops dramatically when subjects are woken from non-rapid eye movement (NREM) sleep (Stoerig, 2007). While there is still some controversy among researchers as to the connection between REM sleep and dreaming, it seems to be the case that, although REM and dreaming are not the same, REM sleep is, indeed, accompanied by the subjective experience of dreaming: not only does the rate of reports of dreaming increases during REM sleep, but the reports of REM dreams tend to be longer, richer in detail, and more elaborate than those of NREM dreams (Takeuchi, Miyasita, Inugami, & Yamamoto, 2001).

There are different competing theories concerning the function and role that dreaming serves, but among the ones that have attracted most attention are the theories postulating that dreaming is crucial for learning and memory consolidation (Poe, Walsh & Bjorness, 2010; cf. Siegel, 2001). REM sleep deprivation studies have demonstrated the connection between learning and dreaming. In one

early study, Pearlman (1969) showed that rats who were trained for an avoidance response and were subsequently REM sleep deprived did not demonstrate retention of that learning. Similarly, Fishbein (1971) found that depriving mice of REM sleep after a discrimination training in a maze prevented retention of that learning (Zhang et al., 2014). Detrimental effects of REM sleep deprivations on learning have been demonstrated in human subjects as well: Karni, Tanne, Rubenstein, Askenasy, and Sagi (1994) found that selective disruption of REM sleep resulted in no performance gain after learning a basic visual discrimination task (cf. Rasch, Pommer, Diekelmann, & Born, 2009).

Another paradigm of research has been to measure the increases in REM sleep on subsequent nights following learning. In an animal study, Fishbein, Kastaniotis, and Chattman (1974) showed that mice who were trained in a shock-avoidance task displayed subsequent augmentations in slow wave sleep (SWS) and REM sleep, whereas their yoked controls showed augmentations only in SWS. In a study with human subjects, Maquet et al. (2000) showed that brain regions which were active during a serial reaction time task were also active during subsequent REM sleep, suggesting that REM sleep is involved in the reprocessing of memory traces. The same group (Peigneux et al., 2003) showed that the reactivation of cerebral regions during posttraining REM sleep is related to an implicit acquisition of the probabilistic rules that governed the sequence of stimuli during the serial reaction-time task, and that the extent to which the learning of probabilistic rules was attained is correlated with increases in regional cerebral blood flow during subsequent REM sleep.

While conflicting opinions exist among researchers as to the role of REM sleep in memory consolidation (see Rasch & Born, 2013, for a review), it seems that there is ample evidence to suggest that REM sleep may be related to the consolidation of nondeclarative memory in particular. In one study, Mednick, Nakayama, and Stickgold (2003) had subjects learn a nondeclarative visual discrimination task. They found that those subjects who took a nap and had a bout of REM sleep after learning the task performed better in a subsequent test than those who slept only SWS, and their performance was even better than those who did not take a nap at all. This study demonstrates the importance of engaging in REM sleep to consolidate the learning of procedural, nondeclarative skills. Similarly, Tucker et al. (2006) found that a nap consisting of only SWS without bouts of REM sleep improved subjects' performance only on a declarative memory task but not on a nondeclarative task, which further strengthens the assumption that there is a dichotomy in memory processing during sleep between declarative and nondeclarative memory (i.e., the dual-process hypothesis). Furthermore, Plihal, and Born (1997) found that the first half of the night (which contains a larger proportion of SWS) is related to the processing of declarative memory, whereas the second half of the night (characterized by a larger proportion of REM sleep) is related to procedural, nondeclarative memory processing. Finally, REM sleep was found to improve performance in other types of learning as well, such as intensive language learning (De Koninck, Lorrain, Christ, Proulx, & Coulombe, 1989), but these kinds of learning may have an implicit, nondeclarative memory component (Peigneux, Laureys, Delbeuck, & Maquet, 2001).

Neurofeedback as a Nondeclarative Learning-based Neurotherapy Method

Neurofeedback is a learning-based neurotherapy method. It is considered to be a process that operates on the principles of operant conditioning (Hammond, 2011), in which the brain has to learn the connection between its electrophysiological activity and the sensory feedback it gets in return. After establishing the causality and directionality of this connection, the brain has to learn how to change its activity patterns to win more positive feedback and less negative feedback. This type of learning falls under the category of implicit, procedural, nondeclarative learning, and as such may be accompanied by more REM sleep periods on subsequent nights, which may be characterized by increased and enhanced vivid dreaming.

The first couple of neurofeedback sessions may be especially taxing for the brain in this regard, for the novelty involved: the brain first has to learn that there is a connection between what it does and the kind of experience it gets in return through the computer (a momentarily rewarding or a momentarily frustrating experience); it has to learn that the changes in sound and picture quality (or other forms of feedback) are directly related to its electrophysiological activity and that they serve, in fact, as feedback for its electrophysiological activity; and it has to learn how to change its activity in order to win more positive feedback and less negative feedback. Making these associations requires the brain to notice the subtle changes of its own brainwave activity, as well as the changes in the sensory experience during session. The brain has to try to fathom the direction in which this connection works—in other words, it has to

realize that an increase or decrease in amplitude of certain brainwave frequencies brings about a negative (frustrating) feedback or a positive (rewarding) feedback. On top of it all, in these initial couple of sessions, the brain experiences its first attempt at trying to actually change its brainwave activity in response to this type of feedback. This entails a considerable amount of learning of the implicit, nondeclarative type; and, if the first session is long enough (30 to 40 minutes each), some clients may report substantially more dreaming and an enhanced vividness to their dreams already after the first session.

Our experience shows that most reports about increased dreaming following the first few neurofeedback sessions are done by adult clients rather than by young children. The reason may be that children's ability to be aware of and verbally describe such subjective experiences is less developed than that of the average adult, and this may make it harder for them to consciously access such experiences and relate them to others. Another possible explanation is that children spend a considerably higher proportion of their sleep cycles in REM sleep anyway, so the relative increases in REM sleep in their sleep due to neurofeedback training may be smaller.

Discussion and Conclusions

The field of sleep effects on learning and memory consolidation is a fascinating one, with a substantial increase in recent years in studies and theories attempting to explain the effects of the different stages of sleep on memory processing, facilitation, and consolidation. Although REM sleep has been implicated in the processing of other kinds of memory, especially in the processing of emotional memories (Groch, Wilhelm, Diekelmann & Born, 2013; Nishida, Pearsall, Buckner, & Walker, 2009; Wiesner et al., 2015), significant attention has been given to the study of REM sleep effects on implicit, nondeclarative learning.

Some researchers (Diekelmann, Wilhelm, & Born, 2009; Marshall & Born, 2007; Mednick et al., 2003; Smith, 1995) have shown support for the dual-process hypothesis, by which declarative memory is processed mostly during SWS, whereas nondeclarative memory is processed mostly during REM sleep. Other researchers (Diekelmann & Born, 2010; Ficca & Salzarulo, 2004; Gais, Plihal, Wagner, & Born, 2000; Giuditta, 2014) support the sequential processing hypothesis, by which both SWS and REM sleep are needed sequentially for the processing and consolidation of different types of memory, including procedural, nondeclarative memory.

Still, other suggestions have been made: it has been theorized that task complexity may be a determining factor, with more complex tasks being more sensitive to REM sleep deprivation (Walker, Brakefield, Morgan, Hobson, & Stickgold, 2002). Interestingly, Ribeiro and Nicolelis (2004) postulate that the consolidation of implicit memories tends to be more complex, and therefore slower, than that of explicit memories, requiring a larger number of synaptic modifications. It could be that implicit learning of the type achieved in neurofeedback training may be such a complex, elaborate process and therefore may require REM sleep to be achieved.

Of special interest is the finding by Peigneux et al. (2003) cited above, that cerebral reactivation during posttraining REM sleep was related to the attainment of probabilistic rules that governed the sequences of stimuli in a serial reaction-time task. Implicitly extracting and learning probabilistic rules is something that the brain must perform during a neurofeedback session. That is, the client's brain must fathom the probability of getting positive feedback and negative feedback for changes in amplitude in the different frequency bands in order to modify its activity accordingly. REM sleep with its accompanying subjective experience of vivid dreaming may be involved in the processing of such higher-order information, embedded in this feedback-based learning paradigm.

Without attempting to settle the discrepancy between the competing findings and theories concerning the role that different sleep stages play in memory consolidation, it seems that there is ample evidence obtained by various experimental methods in both humans and animals suggesting that REM sleep, which is characterized by the subjective experience of vivid, story-like dreaming, may be related to the processing and consolidation of nondeclarative learning and memory. Even when considering the conflict between the dual-process hypothesis and the sequential processing hypothesis, it seems that both of these theories assign importance to REM sleep when it comes to the processing of nondeclarative memory.

Our clinical experience (as well as that of other clinicians, as cited above) has shown that some clients report increased vivid dreaming following their first few neurofeedback sessions. Since

neurofeedback is based on an implicit, nondeclarative type of learning, the ensuing increase in dreaming may serve as an indication that the client's brain is processing and consolidating the products of learning obtained during training.

Neurofeedback is an efficient neurotherapy method with high success rates; yet, as it is with any form of therapy, a certain percentage of clients (fortunately, not a big one) do not respond to it. Having some initial indication that a client is a responder may be an encouraging early sign for both clinician and client, which may boost the client's motivation to persevere in performing sessions twice or more weekly for the critical first few weeks of training. If our clients report increased and enhanced dreaming on the subsequent nights following their first neurofeedback session, we may assume that their brains "understand" the language of feedback and are responding to it. Now it is our job to fine-tune our protocol selection to make sure that they get optimal results.

It is important to note that not having any increase in dreaming or enhancement of dream vividness on subsequent nights following neurofeedback sessions does not necessarily mean that no learning has occurred or that the client's brain does not respond to the training. Dreaming following sessions is not a prerequisite for success in training. But when increased vivid dreaming does occur, then we have an initial indication that the brain "understands the language" of feedback and is responding to it. It would be a good practice to ask our clients after each session about their sleep quality and if they have noticed any changes in this regard.

Lastly, we believe that effort should be made to conduct controlled studies to investigate the effects of neurofeedback on REM sleep in sleep laboratories, as well as to find the relationship between the occurrence of increased REM sleep following sessions and the overall success in training. Such research may, in turn, shed further light upon the question of REM sleep effects on nondeclarative memory processing and consolidation.

Author Disclosure

The author has no grants, financial interests, or conflicts to disclose.

References

Aserinsky, E., & Kleitman, N. (1953). Regularly occurring periods of eye motility, and concomitant phenomena, during sleep. *Science, 118*(3062), 273–274. https://doi.org/10.1126/science.118.3062.273

Ayala-Guerrero, F., Mexicano, G., & Ramos, J. I. (2003). Sleep characteristics in the turkey *Meleagris gallopavo*. *Physiology & Behavior, 78*(3), 435–440. https://doi.org/10.1016/S0031-9384(03)00032-5

Cavallero, C., Cicogna, P., Natale, V., Occhionero, M., & Zito, A. (1992). Slow wave sleep dreaming. *Sleep, 15*(6), 562–566. https://doi.org/10.1093/sleep/15.6.562

De Koninck, J., Lorrain, D., Christ, G., Proulx, G., & Coulombe, D. (1989). Intensive language learning and increases in rapid eye movement sleep: Evidence of performance factor. *International Journal of Psychophysiology, 8*(1), 43–47. https://doi.org/10.1016/0167-8760(89)90018-4

Dement, W. C. (1958). The occurrence of low voltage, fast, electroencephalogram patterns during behavioral sleep in the cat. *Electroencephalography and Clinical Neurophysiology, 10*(2), 291–296. https://doi.org/10.1016/0013-4694(58)90037-3

Dement, W. C., & Kleitman, N. (1957). Cyclic variations in EEG during sleep and their relation to eye movements, body motility, and dreaming. *Electroencephalography and Clinical Neurophysiology, 9*(4), 673–690. https://doi.org/10.1016/0013-4694(57)90088-3

Diekelmann, S., & Born, J. (2010). The memory function of sleep. *Nature Reviews Neuroscience, 11*(2), 114–126. https://doi.org/10.1038/nrn2762

Diekelmann, S., Wilhelm, I., & Born, J. (2009). The whats and whens of sleep-dependent memory consolidation. *Sleep Medicine Reviews, 13*(5), 309–321. https://doi.org/10.1016/j.smrv.2008.08.002

Ficca, G., & Salzarulo, P. (2004). What in sleep is for memory. *Sleep Medicine, 5*(3), 225–230. https://doi.org/10.1016/j.sleep.2004.01.018

Fishbein, W. (1971). Disruptive effects of rapid eye movement sleep deprivation on long-term memory. *Physiology & Behavior, 6*(4), 279–282. https://doi.org/10.1016/0031-9384(71)90155-7

Fishbein, W., Kastaniotis, C., & Chattman, D. (1974). Paradoxical sleep: Prolonged augmentation following learning. *Brain Research, 79*(1), 61–75. https://doi.org/10.1016/0006-8993(74)90566-6

Foulkes, W. D. (1962). Dream reports from different stages of sleep. *The Journal of Abnormal and Social Psychology, 65*(1), 14–25. https://doi.org/10.1037/h0040431

Gais, S., Plihal, W., Wagner, U., & Born, J. (2000). Early sleep triggers memory for early visual discrimination skills. *Nature Neuroscience, 3*(12), 1335–1339. https://doi.org/10.1038/81881

Giuditta, A. (2014). Sleep memory processing: The sequential hypothesis. *Frontiers in Systems Neuroscience, 8*, 219. https://doi.org/10.3389/fnsys.2014.00219

Groch, S., Wilhelm, I., Diekelmann, S., & Born, J. (2013). The role of REM sleep in the processing of emotional memories: Evidence from behavior and event-related potentials. *Neurobiology of Learning and Memory, 99*, 1–9. https://doi.org/10.1016/j.nlm.2012.10.006

Gruzelier, J. (2009). A theory of alpha/theta neurofeedback, creative performance enhancement, long distance functional connectivity and psychological integration. *Cognitive Processing, 10*(1), 101–109. https://doi.org/10.1007/s10339-008-0248-5

Hammond, D. C. (2011). What is neurofeedback: An update. *Journal of Neurotherapy, 15*(4), 305–336. https://doi.org/10.1080/10874208.2011.623090

Herlin, B., Leu-Semenescu, S., Chaumereuil, C., & Arnulf, I. (2015). Evidence that non-dreamers do dream: A REM sleep behaviour disorder model. *Journal of Sleep Research, 24*(6), 602–609. https://doi.org/10.1111/jsr.12323

Johnson, M. L. (2011). *Relationship of alpha-theta amplitude crossover during neurofeedback to emergence of spontaneous imagery and biographical memory* (Doctoral dissertation). University of North Texas, Denton, TX.

Karni, A., Tanne, D., Rubenstein, B. S., Askenasy, J. J., & Sagi, D. (1994). Dependence on REM sleep of overnight improvement of a perceptual skill. *Science, 265*(5172), 679–682. https://doi.org/10.1126/science.8036518

Larsen, S., & Verner, T. (2017). *The transformational power of dreaming: Discovering the wishes of the soul.* Rochester, VA: Inner Traditions Bear and Company.

Leong, S. L., Vanneste, S., Lim, J., Smith, M., Manning, P., & De Ridder, D. (2018a). A randomised, double-blind, placebo-controlled parallel trial of closed-loop infraslow brain training in food addiction. *Scientific Reports, 8*(1), 11659. https://doi.org/10.1038/s41598-018-30181-7

Leong, S. L., Vanneste, S., Lim, J., Smith, M., Manning, P., De Ridder, D., & Stoeckl-Drax, T. (2018b). Effects and side effects of infraslow network neurofeedback (ISF-NF): A randomised double blind placebo controlled trial. *International Journal of Psychophysiology, 131*(Suppl.), S151. https://doi.org/10.1016 /j.ijpsycho.2018.07.402

Maquet, P., Laureys, S., Peigneux, P., Fuchs, S., Petiau, C., Phillips, C., … Cleeremans, A. (2000). Experience-dependent changes in cerebral activation during human REM sleep. *Nature Neuroscience, 3*(8), 831–836. https://doi.org/10.1038 /77744

Marshall, L., & Born, J. (2007). The contribution of sleep to hippocampus-dependent memory consolidation. *Trends in Cognitive Sciences, 11*(10), 442–450. https://doi.org /10.1016/j.tics.2007.09.001

Mednick, S., Nakayama, K., & Stickgold, R. (2003). Sleep-dependent learning: A nap is as good as a night. *Nature Neuroscience, 6*(7), 697–698. https://doi.org/10.1038/nn1078

Nishida, M., Pearsall, J., Buckner, R. L., & Walker, M. P. (2009). REM sleep, prefrontal theta, and the consolidation of human emotional memory. *Cerebral Cortex, 19*(5), 1158–1166. https://doi.org/10.1093/cercor/bhn155

Pearlman, C. A. (1969). Effect of rapid eye movement (dreaming) sleep deprivation on retention of avoidance learning in rats. *Report No. 563.* U.S. Naval Submarine Medical Center.

Peever, J., & Fuller, P. M. (2016). The biology of REM sleep. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles /PMC5846126/

Peigneux, P., Laureys, S., Delbeuck, X., & Maquet, P. (2001). Sleeping brain, learning brain. The role of sleep for memory systems. *NeuroReport*, *12*(18), A111–A124. https://doi.org /10.1097/00001756-200112210-00001

Peigneux, P., Laureys, S., Fuchs, S., Destrebecqz, A., Collette, F., Delbeuck, X., … Maquet, P. (2003). Learned material content and acquisition level modulate cerebral reactivation during posttraining rapid-eye-movements sleep. *NeuroImage, 20*(1)**,** 125–134. https://doi.org/10.1016 /S1053-8119(03)00278-7

Plihal, W., & Born, J. (1997). Effects of early and late nocturnal sleep on declarative and procedural memory. *Journal of Cognitive Neuroscience, 9*(4), 534–547. https://doi.org /10.1162/jocn.1997.9.4.534

Poe, G. R., Walsh, C. M., & Bjorness, T. E. (2010). Cognitive neuroscience of sleep. *Progress in Brain Research, 185*, 1–19. https://doi.org/10.1016/B978-0-444-53702-7.00001-4

Rasch, B., & Born, J. (2013). About sleep's role in memory. *Physiological Reviews, 93*(2), 681–766. https://doi.org /10.1152/physrev.00032.2012

Rasch, B., Pommer, J., Diekelmann, S., & Born, J. (2009). Pharmacological REM sleep suppression paradoxically improves rather than impairs skill memory. *Nature Neuroscience, 12*(4), 396–397. https://doi.org/10.1038 /nn.2206

Ribeiro, S., & Nicolelis, M. A. L. (2004). Reverberation, storage, and postsynaptic propagation of memories during sleep. *Learning & Memory, 11*(6), 686–696. https://doi.org/10.1101 /lm.75604

Siegel, J. M. (2001). The REM sleep-memory consolidation hypothesis. *Science, 294*(5544), 1058–1063. https://doi.org /10.1126/science.1063049

Smith, C. (1995). Sleep states and memory processes. *Behavioural Brain Research, 69(*1–2), 137–145. https://doi.org/10.1016/0166-4328(95)00024-N

Stoerig, P. (2007). Hunting the ghost: Toward a neuroscience of consciousness. In P. D. Zelazo, M. Moscovitch, & E. Thompson (Eds.), *Cambridge handbook of consciousness* (pp. 707–730). Cambridge, England: Cambridge University Press.

Takeuchi, T., Miyasita, A., Inugami, M., & Yamamoto, Y. (2001). Intrinsic dreams are not produced without REM sleep mechanisms: Evidence through elicitation of sleep onset REM periods. *Journal of Sleep Research, 10*(1), 43–52. https://doi.org/10.1046/j.1365-2869.2001.00237.x

Tucker, M. A., Hirota, Y., Wamsley, E. J., Lau, H., Chaklader, A., & Fishbein, W. (2006). A daytime nap containing solely non-REM sleep enhances declarative but not procedural memory. *Neurobiology of Learning and Memory, 86*(2), 241–247. https://doi.org/10.1016/j.nlm.2006.03.005

Walker, M. P., Brakefield, T., Morgan, A., Hobson, J. A., & Stickgold, R. (2002). Practice with sleep makes perfect: Sleep-dependent motor skill learning. *Neuron, 35*(1)**,** 205–211. https://doi.org/10.1016/s0896-6273(02)00746-8

Wiesner, C. D., Pulst, J., Krause, F., Elsner, M., Baving, L., Pedersen, A., … Göder, R. (2015). The effect of selective REM-sleep deprivation on the consolidation and affective evaluation of emotional memories. *Neurobiology of Learning and Memory, 122*, 131–141. https://doi.org/10.1016 /j.nlm.2015.02.008

Zhang, J., Zhu, Y., Zhan, G., Fenik, P., Panossian, L., Wang, M. M., … Veasey, S. (2014). Extended wakefulness: Compromised metabolics in and degeneration of locus ceruleus neurons. *The Journal of Neuroscience, 34*(12), 4418–4431. https://doi.org/10.1523/JNEUROSCI.5025-12.2014

Received: January 9, 2020
Accepted: February 6, 2020
Published: March 25, 2020

NeuroRegulation

Does Neurofeedback Training Improve Performance in Athletes?

Christophe Domingos[1,2], Cristiana P. Alves[2], Edgar Sousa[1], Agostinho Rosa[2], and José G. Pereira[1]*

[1]Laboratory of Physiology and Biochemistry of Exercise, Faculty of Human Kinetics, University of Lisbon, Cruz Quebrada, Portugal
[2]Department of Bioengineering, LaSEEB – System and Robotics Institute, Instituto Superior Técnico, University of Lisbon, Lisbon, Portugal

Abstract

Introduction: Neurofeedback training has been an increasingly used technique in sport; however, most of the protocols used in athletes are based in the results obtained in nonathletic population. **Purpose**: Understand if a specific neurofeedback training protocol implemented in a nonathletic population can improve short-term memory and reaction time in athletes. **Methods:** A total of 45 subjects participated in the experiment (mean ± *SD* for age: 23.31 ± 4.20 years). For athletes, 12 neurofeedback training sessions were performed; for the nonathletes, 15 neurofeedback training were performed. Each session had 25 min of effective neurofeedback training. **Results:** Despite the nonathletes group's increased standard alpha band (SAB) relative amplitude and individual alpha band (IAB) relative amplitude after 12 sessions of neurofeedback training ($p < .005$), only the athletes intervention group had positive results in reaction time ($p < .001$ in oddball test). Not only was the null hypothesis rejected by the differences of IAB and SAB relative amplitudes between and within protocols but also by the performance tests. **Conclusion:** Neurofeedback training increases the relative amplitude of the bands in the nonathletes group; however, only the athletes have shown to improve performances tests after 12 neurofeedback training sessions.

Keywords: neurofeedback training; athletic training; reaction time; short-term memory; performance; individual alpha band

Citation: Domingos, C., Alves, C. P., Sousa, E., Rosa, A., & Pereira, J. G. (2020). Does neurofeedback training improve performance in athletes? *NeuroRegulation*, *7*(1), 8–17. https://doi.org/10.15540/nr.7.1.8

***Address correspondence to**: Christophe Domingos, Faculdade de Motricidade Humana (FMH), Universidade de Lisboa (UL), Estrada da Costa MB, 1499–002, Cruz Quebrada – Dafundo, Portugal. Email: christophedomingos@campus.ul.pt

Edited by:
Rex L. Cannon, PhD, SPESA Research Institute, Knoxville, Tennessee, USA

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

Introduction

Neurofeedback has gained interest in professional sports and performance in order to better understand the neural influences on sporting behaviors and to improve performance (Park, Fairweather, & Donaldson, 2015). Elite athletes provide an exemplary model for understanding the effects of mastery, expertise, and execution of such skills (Park et al., 2015). In order to achieve the elite level, in almost all sports, athletes take two to two and a half decades of apprenticeship involving self-control, skill learning, long-term planning, and resilience to failure, judgment, defeat, and injury (Walsh, 2014). Neurofeedback training (NFT) has produced robust findings in health (Marzbani, Marateb, & Mansourian, 2016; Noakes, 2012), and cognition and performance (Cross, Acquah, & Ramsey, 2014; Vernon, 2005). NFT in sports typically involves application of traditional protocols used in the general population or in mental health treatment. To date, few protocols have been developed for professional athletes to improve performance or identify specific neural targets associated with enhancement of performance.

Electroencephalography (EEG) is a procedure used to record the electrical activity of the brain on the scalp. Neurofeedback provides the individual feedback about this activity to potentially enhance performance in sport by retraining this activity (Mirifar, Beckmann, & Ehrlenspiel, 2017). Data have revealed distinct cortical differences between expert athletes and nonexperts (Landers et al., 1991; Salazar et al., 1990; Vernon, 2005). These results are in line with the neural efficiency hypothesis (Babiloni et al., 2010) that is based on the specific activation brain regions for a given task while disengaging irrelevant brain regions for the same task (Haier, Siegel, Tang, Abel, & Buchsbaum, 1992). It is a phenomenon that can easily be found in sport and even more in elite athletes (Milton, Solodkin, Hluštík, & Small, 2007). Data have shown that elite karate athletes show a less pronounced alpha event-related desynchronization (ERD) than amateur karate athletes during performance, and this reinforces the widely held idea that elite athletes utilize specialized zones for a particular action (Babiloni et al., 2010). This is suggested to be related to the existence of several frequency bands and the mental state that are associated to each frequency (Thompson & Thompson, 2015); that is, the alpha band relates to a state of relaxed attention (Klimesch, 1999), processing speed (Angelakis et al., 2007), better memory function (Guez et al., 2015; Nan et al., 2012), and reaction time (Ziółkowski et al., 2012), for example. It is hypothesized that those differences are not consistent in location nor direction, which might be explained by different sport-specific requirements (Vernon, 2005) or, in the case of the alpha band, by the several intervals suggested (da Silva, 2013; Thompson & Thompson, 2015). Mirifar, Beckmann, and Ehrlenspiel (2017) rightly propose the need to understand the cortical activity (site)—personalized event-locked EEG profile—that is associated with performance (Mirifar et al., 2017), which is still unrealistic due to the impossibility to assess in sports involving head movement (creating artifacts). However, it is possible to work at the individual alpha band (IAB) to specialize NFT, reducing variability in training (Bazanova & Mernaya, 2008; Klimesch, 1999). As Mirifar et al. (2017) point out in a recent systematic review, many protocols applied in sport are based on positive results found outside the area of interest (Mirifar et al., 2017).

The primary aim of this study was to evaluate the effects of an NFT protocol on short-term memory and reaction time in high performance athletes as compared to nonathletes. To understand the effects of NFT, a group of athletes (intervention group) who performed NFT sessions was compared with another group of athletes (control group) who did not perform any NFT sessions. A nonathlete group (intervention group) was also added to the study, with a similar protocol, to comprehend if the protocols should be adapted according to the populations studied. To the best of our knowledge, no study compared the effects of NFT between two athletic populations and between a nonathletic population at the same time, with the same protocol under the same conditions. We hypothesize that (a) the standard alpha band (SAB) relative amplitude and the IAB relative amplitude in NFT sessions are similar between intervention groups (similar margin progression) and (b) the performance tests (memory and reaction time) results will be the same after all NFT sessions in both groups (intervention groups and control group).

Methods

Subjects

A total of 45 subjects aged from 18 to 44 years old participated in the experiment (mean ± *SD* for age: 23.31 ± 4.20 years). All student athletes have been involved in federated sports or practicing exercise or sport regularly for more than 5 years (Baker, Côté, & Deakin, 2005), as compared to the group of nonathlete students that do not meet the minimum five times a week of at least moderate intensity requirements to be considered active (World Health Organization, 2010). The inclusion criteria were as follows:

- no history of psychiatric or neurological disorders;
- no psychotropic medications or addiction drugs;
- normal or corrected-to-normal vision;
- minimum age of 18 years and maximum age of 45 years; and
- practice moderate-intensity exercise at least 5 times a week (sport or gym) regardless of skill level (for athlete groups).

Table 1
Age for each group, M ± SD.

	Control (*n* = 15)	Athletes (*n* = 15)	Nonathlete (*n* = 15)
Age (years)	22.53 ± 3.89	27.93 ± 6.11	21.20 ± 2.62

All students were informed about the possible risks of the investigation before providing written informed consent to participate. All procedures were approved

by the Ethics Committee of the Faculty of Human Kinetics and Instituto Superior Técnico, University of Lisbon, and conducted in accordance with the Declaration of Helsinki (World Medical Association, 2001). All data collected has been stored in a database where only researchers related to the NFT project have access. Anonymity was guaranteed.

Signal Acquisition

After being carefully informed on capping, signal collection, and inherent processes of artifact production, participants sat in a room with a controlled environment. The EEG signals were recorded according to the international 10–20 system (Fp1, Fp2, F3, F4, F7, F8, C3, C4, T3, T4, P3, P4, T5, T6, O1, O2, Fz, Cz, and Pz), with a sampling frequency of 256 Hz. Feedback was from Cz channel (it was chosen since it is at the primary motor cortex and has been associated with sensory information processing over the sensorimotor area and provide a measurement of the activity in both hemispheres and in the frontal lobe; Mann, Sterman, & Kaiser, 1996; Pfurtscheller, Neuper, Ramoser, & Müller-Gerking, 1999). The ground was located at forehead and the reference was the average of left and right mastoids. The signals were amplified by a 24-channel system (Vertex 823 from Meditron Electomedicina Ltda, SP, Brazil) and were recorded by Somnium software platform (Cognitron, SP, Brazil) and NF module by Laseeb-ISR. Circuit impedance was kept below 10 kΩ for all electrodes before the sessions. Subjects were asked to sit comfortably and then to remain as still as possible and also to avoid excessive blinking and abrupt movements.

Experimental Design

In the first session of this randomized controlled study, all intervention participants performed a 5-min NFT familiarization to understand how to achieve alpha band mental state (increase the alpha amplitude [i.e., power] and the time remaining within this range; Bazanova & Vernon, 2014) or, in other words, to understand how to remain in a concentration state by the real feedback presented on the screen (Thompson & Thompson, 2015), followed by the pretests (the performance tests are the same and will be described in the Assessments section). The pre- and posttests had the same interval of time for both the control and intervention groups. Timeline of the NFT training sessions and respective performance tests (pre- and posttests) are presented in Figure 1.

Intervention group – Athletes. The intervention group performed a familiarization session and pretest before (bS^{1}) the 12 NFT sessions. Between session 6 and session 7 ($S^{6/7}$), performance tests were applied. At the end, a posttest (aS^{12}) was performed. The NFT sessions consisted in 25 trials of 60 s each with 5 s of pause between trials. The total NFT session time for each subject was 300 min. The NFT sessions were performed two times per week. Although inhibiting self-talk seems to be one of the best strategies (Harkness, 2009; Hatfield, Haufler, & Spalding, 2006; Hosseini & Norouzi, 2017; Kamata, Tenenbaum, & Hanin, 2002; Wilson, Peper, & Moss, 2006), participants were only requested to concentrate on their sport activity as much as possible but not in a specific task.

Intervention group – Nonathletes. The intervention group performed a familiarization session and pretest before (bS^{1}) the 15 NFT sessions. Between session 5 and session 6 ($S^{5/6}$), performance tests were applied. Also, between session 10 and session 11 ($S^{10/11}$), performance tests were applied. At the end, a posttest (aS^{15}) was performed. The NFT involved five blocks of trials. Each block was constituted by five 1-min trials with 5 s between trials. In this way each session had 25 min of effective NFT, and each protocol resulted in 375 min.

Control group. The control group only performed pre- (bS^{1}) and posttests (aS^{12}) over a month and a half without the training sessions.

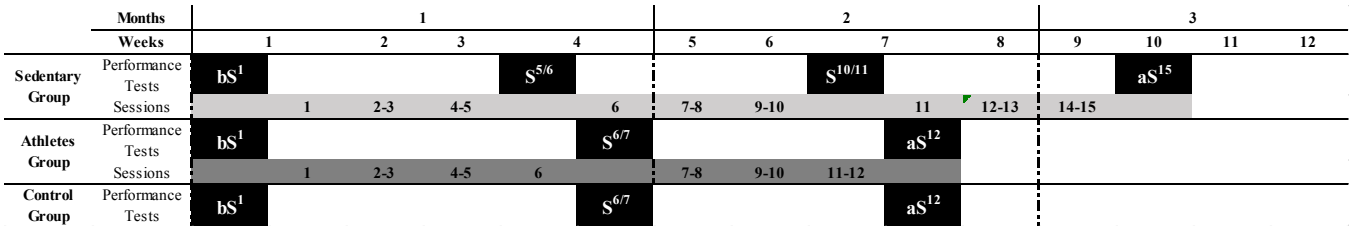

Figure 1. Timeline of the NFT training sessions and respective performance tests (bS^1, $S^{5/6}$, $S^{10/11}$, and aS^{15} for nonathletes group; and bS^1, $S^{5/6}$, and aS^{12} for athletes group and control group).

Measurements

The baseline individual alpha frequency (IAF) was determined before and after NFT. The baseline recording consisted of 2 min during the resting period, altering between eyes closed and eyes open. Recordings of eyes open and closed in baseline 1 provided data for the calculation of alpha desynchronization and synchronization respectively; this enabled determination of individual frequency bands through amplitude band crossings (Klimesch, 1999).

Feedback is a determinant step for the protocol's success. Neural activity must be fed back by some parameter(s) and presented to the participant in a simple and direct representation of their value. In this study, the feedback parameter was the relative amplitude of the IAB calculated as in Equation 1 where band amplitude was the amplitude of the IAB and EEG amplitude was the amplitude from 4 Hz to 30 Hz. Using the amplitude spectrum instead of the power spectrum prevents excessive skewing which results from squaring the amplitude, and thus increases statistical validity.

$$\textit{Relative Amplitude} = \frac{\textit{Band Amplitude}}{\textit{EEG Amplitude}} \quad (1)$$

The visual feedback display contains two tridimensional objects: a sphere and a cube. The sphere radius reflects the feedback parameter value in real time and if it reaches a threshold (Goal 1) its colour changes. The sphere has several slices (initially four, the minimum), and the more present, the smoother it looks. While Goal 1 is being achieved, slices are added; if not, the sphere loses them until it has four again. The cube height is related to the period of time that Goal 1 kept being achieved continuously. If it happens for more than a predefined period of time (2 s), Goal 2 is accomplished, and the cube rises until Goal 1 stops being achieved. Then it starts falling until it reaches the bottom or Goal 2 is achieved again. Therefore, the participant's task is to take the cube as high as possible (Rodrigues, Migotina, & da Rosa, 2010).

The feedback threshold was set to 1.0 in the first session, and it was adjusted according to the session report which showed the percentage of time for which the feedback parameter was above the threshold in each session. If this percentage exceeded 60%, the threshold would be increased by 0.1 in the next session. In contrast, if the percentage was below 20%, the threshold would be decreased by 0.1 in the next session (Nan, Wan, Lou, Vai, & Rosa, 2013).

Assessments

Digit Span (DS). Participants had to recall a random sequence of numbers in the correct order, starting with 2 digits and ending with 10 digits. Subjects were asked to introduce the digits in the order by which they appeared (YuLeung To, Abbott, Foster, & Helmer, 2016).

Oddball (OB). The oddball test is used to evaluate the attention of the subjects. In this test, different geometrical forms appear (circle, octagon, and square) and the participants were instructed to click only if the circle appeared. The test consisted of 50 trials, where the images appeared during 0.5 s with an interval of 0.5 s. It was defined by a decoy rate of 40% (Debener, Makeig, Delorme, & Engel, 2005).

Statistical Analysis

Differences in SAB and IAB bands and performance tests over time for all groups were examined using the ANOVA test and a post hoc Friedman test was performed when normality was not verified and to evaluate significant differences between groups. Comparison of performance tests means and differences between groups were performed using the ANOVA test and the post hoc Kruskal-Wallis was performed when normality was not verified and to know between which groups there were significant differences, a post hoc Tukey's test was performed. Data were analyzed with SPSS software for Windows

version 25.0 (SPSS Inc., Chicago, IL). Statistical significance was set at $p < .05$ for all tests.

Results

Although both populations increase SAB and IAB throughout the sessions, when comparing the groups there are no differences.

The SAB and IAB over the 12 sessions in both protocols during NFT sessions are presented in Figure 2. Both populations show positive slopes, but in the nonathlete population it is clearly verified that there is an effect of the sessions in the increase of SAB (R^2 = .864) and IAB (R^2 = .904). Only in the nonathlete population are there significant results in both SAB between session 1 and 12 (1.01 ± 0.13 vs. 1.15 ± 0.22; p = .018) and IAB between sessions 1 and 10 (1.04 ± 0.17 vs. 1.19 ± 0.21; p = .003) and sessions 1 and 12 (1.04 ± 0.17 vs. 1.19 ± 0.22; p = .003). In other words, SAB and IAB significantly increase from session 1 to 12 ($p < .05$).

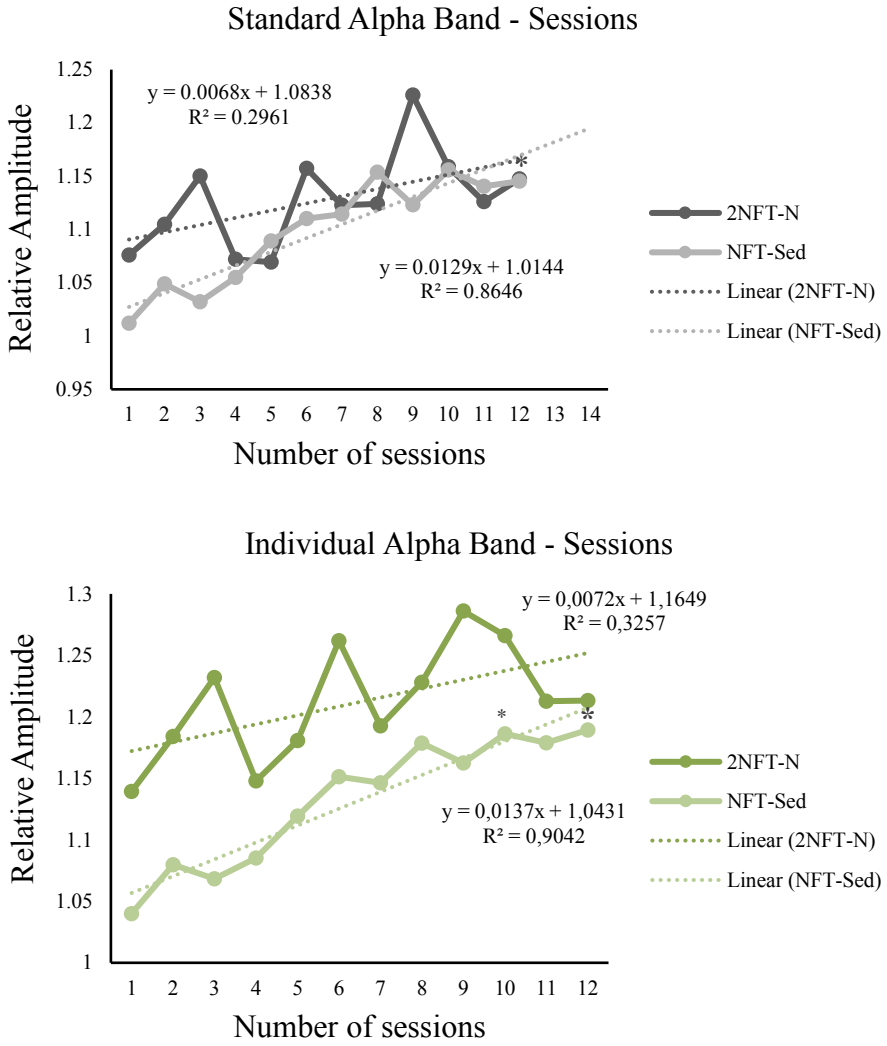

Figure 2. Differences between session 1 and 12 and in standard alpha band (SAB; top image) and individual alpha band (IAB; bottom image) for each protocol *($p < .05$).

Differences in performance tests between both populations and control group are presented in Table 2. Only differences were found between the nonathlete group and the athletes group in DS $S^{a/b}$ tests. The OB bS^{1} tests, OB $S^{a/b}$ tests, OB $S^{c/d}$ tests, and OB $S^{d/e}$ tests showed differences between the nonathlete population and the athletes population and control group.

Table 2
Differences in performance tests (bS^1, $S^{5/6}$, $S^{10/11}$, and aS^{15} for nonathlete group; and bS^1, $S^{5/6}$, and aS^{12} for athletes group and control group) between protocols, M ± SD.

	Control[b,d] (*n* = 15)	Athletes[b,d] (*n* = 15)	Nonathlete[a,c,e] (*n* = 15)	*p*
DS bS^1 tests	7.13 ± 1.36	7.20 ± 0.94	6.50 ± 1.65	.377[f]
DS $S^{a/b}$ tests	7.53 ± 1.36	7.87 ± 0.74	6.36 ± 1.45	.003[f]
DS $S^{c/d}$ tests	7.93 ± 0.96	8.13 ± 0.83	7.07 ± 1.73	.064[f]
DS $S^{d/e}$ tests	7.93 ± 0.96	8.13 ± 0.83	7.77 ± 1.92	.575[f]
Difference in DS ($S^{a/b}$ − S^1 tests)	0.40 ± 1.24	0.67 ± 0.98	-0.14 ± 1.03	.137[f]
Difference in DS ($S^{c/d}$ − $S^{a/b}$)	0.40 ± 0.91	0.27 ± 0.88	0.71 ± 1.07	.578[f]
Difference in DS ($S^{c/d}$ − S^1)	0.80 ± 1.08	0.93 ± 1.22	0.57 ± 1.55	.913[f]
Difference in DS ($S^{d/e}$ − $S^{a/b}$)	0.40 ± 0.91	0.27 ± 0.88	1.31 ± 1.38	.070[f]
Difference in DS ($S^{d/e}$ − S^1)	0.80 ± 1.08	0.93 ± 1.22	1.15 ± 1.77	.953[f]
OB S^1 tests	94.80 ± 5.28	95.20 ± 3.84	83.29 ± 8.83	< .001[f]
OB $S^{a/b}$ tests	96.27 ± 3.45	98.00 ± 2.00	88.29 ± 5.06	< .001[f]
OB $S^{c/d}$ tests	96.27 ± 3.01	98.53 ± 1.41	82.43 ± 16.04	< .001[f]
OB $S^{d/e}$ tests	96.27 ± 3.01	98.53 ± 1.41	86.00 ± 8.29	< .001[f]
Difference in OB ($S^{a/b}$ − S^1 tests)	1.47 ± 3.81	2.80 ± 3.10	5.00 ± 8.07	.175[f]
Difference in OB ($S^{c/d}$ − $S^{a/b}$)	0.00 ± 3.21	0.53 ± 1.41	−5.86 ± 14.43	.503[f]
Difference in OB ($S^{c/d}$ − S^1)	1.47 ± 2.77	3.33 ± 3.44	−0.86 ± 13.24	.421[f]
Difference in OB ($S^{d/e}$ − $S^{a/b}$)	0.00 ± 3.21	0.53 ± 1.41	−1.85 ± 6.80	.767[f]
Difference in OB ($S^{d/e}$ − S^1)	1.47 ± 2.77	3.33 ± 3.44	3.69 ± 9.34	.360[f]

M, mean; *SD*, standard deviation; DS, digit spawn test; S, session; NB, n-back test, OB, oddball test; bS^1, before session 1; $S^{5/6}$, between sessions 5 and 6; $S^{6/7}$, between sessions 6 and 7; $S^{10/11}$, between sessions 10 and 11; aS^{12}, after session 12; aS^{15}, after session 15.
[a] $S^{5/6}$; [b] $S^{6/7}$; [c] $S^{10/11}$; [d] aS^{12}; [e] aS^{15}; [f] Differences between groups tested with ANOVA – Kruskal Wallis Test

Table 3 shows the differences between performance tests for athletes, nonathletes, and control group. In the control group differences were found for the DS, where participants improved the score between bS^1 tests and $S^{c/d}$ tests. In the athlete population, results were found in both DS and OB between bS^1 tests and $S^{c/d}$ tests. In the nonathlete population differences were only found from $S^{a/b}$ tests to S^e tests.

Table 3
Differences between bS^1, $S^{5/6}$, $S^{10/11}$, and aS^{15} for nonathlete group and bS^1, $S^{5/6}$, and aS^{12} for athletes group and control group for each protocol, M ± SD.

	bS^1 tests	$S^{a/b}$ tests	$S^{c/d}$ tests	$S^{d/e}$ tests	*p*
Control					
DS	7.13 ± 1.36	7.53 ± 1.36	7.93 ± 0.96	N/A	.031[g]
OB	94.80 ± 5.28	96.27 ± 3.45	96.27 ± 3.01	N/A	.161[g]
Athletes [b, d]					
DS	7.20 ± 0.94	7.87 ± 0.74	8.13 ± 0.83	N/A	.022[g]
OB	95.20 ± 3.84	98.00 ± 2.00	98.53 ± 1.41	N/A	< .001[g]
Nonathletes [a, c, e]					
DS	6.50 ± 1.65	6.36 ± 1.45	7.07 ± 1.73	7.77 ± 1.92	.006[f]
OB	83.29 ± 8.83	88.29 ± 5.06	82.43 ± 16.04	86.00 ± 8.29	.171[g]

M, mean; *SD*, standard deviation; DS, digit spawn test; S, session; NB, n-back test, OB, oddball test; NA, Not applicable; bS^1, before session 1; $S^{5/6}$, between sessions 5 and 6; $S^{6/7}$, between sessions 6 and 7; $S^{10/11}$, between sessions 10 and 11; aS^{12}, after session 12; aS^{15}, after session 15.
[a] $S^{5/6}$; [b] $S^{6/7}$; [c] $S^{10/11}$; [d] aS^{12}; [e] aS^{15}; [f] Differences between groups tested with ANOVA; [g] Differences tested with post hoc Friedman test

The primary aim of the study was to analyze if the number of NFT sessions would be enough to increase the relative amplitude of SAB and IAB in both intervention groups. Knowing the results of relative amplitude changes, a secondary aim was to understand a possible link between NFT sessions SAB and IAB in both intervention groups and control group and the performance tests.

Our results demonstrated that only the nonathlete group increased SAB and IAB after 12 sessions of NFT. However, only the athletes intervention group had positive results in reaction time (i.e., in OB test). This finding lends preliminary support to the alternative hypothesis that the SAB and IAB will be different between groups, which means that the nonathlete population present a different progression margin from the athlete population. It is also important to note that the nonathlete group only had results in short-memory performance test after 15 sessions, while the athlete group only required 12 sessions, and the control group did not require NFT sessions to have results in this test. Not only was the null hypothesis rejected by the differences of IAB and SAB between and within protocols but also by the performance tests.

Discussion

The results that should be considered the key point of the study relate to the reaction time performance test. They suggest that the number of sessions in athletes are sufficient to have positive changes when compared to the nonathlete group that did not improve positively in OB performance test and when compared to the control group who also did not improve in this test.

SAB and IAB Over Time Results

As it can be seen in Figure 2, both intervention groups had a positive slope in SAB and IAB bands which demonstrates the effects of NFT over time. However, the SAB and IAB slopes in the nonathlete group were steeper, due to the lower initial value when compared to the athletes. Once again, it is demonstrated that athletes have a lower progression margin (R^2 = 0.32) than the nonathlete group (R^2 = 0.90) because they have higher initial values. Another curious fact that can be verified in Figure 2 is the behaviour of the bands throughout the sessions; that is, the group of athletes presents a more cyclic behaviour while the nonathlete group presents a more linear evolution. Yet, the discrete variation seen in the session intervals for SAB (Maszczyk et al., 2018; Thompson, Steffert, Ros, Leach, & Gruzelier, 2008) and for IAB (Egner & Gruzelier, 2001; Maszczyk et al., 2018) suggest different behavioral patterns as a function of number of sessions. The baseline values in SAB and IAB for both groups are slightly different but sufficient so that the interval from session 1 to session 12 demonstrates differences only in the nonathlete group. It can be concluded that to change SAB and IAB, 12 sessions of NFT performed twice a week are sufficient for nonathlete people but not for athletes.

Performance Tests Results

The results obtained in the performance tests and compared between groups (Table 2) allow to infer

that for the reaction time test there are differences; that is, both the control group (athletes) and the athletes group had initial values much higher than the nonathlete population. This first analysis makes it possible to conclude that populations are different for reaction times.

Likewise, the results for the DS performance test revealed improvements for control and athletes groups, and the OB performance test revealed improvements within the athletes group over time. There are several conclusions that can be drawn from Table 3. First of all, NFT sessions are not associated with an increase in performance tests seeing that the only group that managed to increase SAB and IAB over time was the nonathlete group but this group do not improve both performance tests after 12 NFT sessions. Secondly, the short-term memory test does not seem to be affected by the NFT sessions insomuch as both the control group and the athletes group have improved. Thirdly and most importantly, the reaction time is influenced by NFT sessions.

Literature-supported Results

These results are supported by the analyzed literature. The number of sessions shown sufficient is consistent with systematic reviews (Mirifar et al., 2017). The results found in DS to improve short-term memory in this study are also supported by the literature in nonathletic populations (Escolano, Aguilar, & Minguez, 2011; Nan et al., 2012). Escolano and colleagues (2011) showed significant results in a healthy population after five consecutive training sessions (Escolano et al., 2011). On the other hand, Nan and collaborators (2012) also obtained positive results in students but only after 20 sessions (Nan et al., 2012). Regarding reaction time, robust literature exists supporting alpha wave association with that performance indicator (Klimesch, 1999).

The higher initial values of performance tests and the results obtained in reaction time in athletes follow the same line that supports that physically active people can be more efficient in more demanding executive tasks in young adults (Kamijo & Takeda, 2010; Themanson, Pontifex, & Hillman, 2008).

Strengths, Limitations, and Considerations of the Study

The main strength of the study is that it answers one of the major limitations pointed out by the scientific community that hypothesized whether a personalized protocol should be used for athletes other than those used in nonathletes. This study, including a nonathlete group, is able to make this contribution to the scientific community (Mirifar et al., 2017). It was also adapted the Klimesch individualized NFT (Klimesch, 1999). SAB scores were also mentioned for terms of reference and comparison. A control group was used to ensure that learning depended on NFT and not on other factors. The individualized NFT and the control group are two factors of robustness (Mirifar et al., 2017; Xiang, Hou, Liao, Liao, & Hu, 2018).

There are limitations that should be considered:

- only marginal significant results were found in some parameters probably due to the sample size;
- a questionnaire or scale is needed to better understand both what strategies athletes are using during NFT and mood (Gruzelier, 2014);
- there were a large diversity of sports; and
- the athletes and nonathlete groups had not exactly the same protocol.

The present study should therefore be considered exploratory.

The NFT in athletes can be used as a complement to the training assuming that even 12 sessions improve the reaction time. In clinical settings, memory and reaction optimization could also have a positive impact in clinical neuropsychological tasks, improving global cognitive efficiency.

Conclusions and Future Research

The athletes showed greater improvement in reaction time than the nonathlete group and control group. In this study NFT increased the power of the bands in the nonathlete group; however, only the athletes improve performance tests after 12 NFT sessions.

This study has two important conclusions: (a) changes in SAB and IAB do not mean that there are automatically positive results in the performance tests applied and (b) 12 sessions of NFT are indeed important to notice positive changes in results at the reaction time in athletes. In other words, NFT produced a positive contribution in athletes for this study and produced a positive trend in both study groups.

Future research should replicate this protocol based on a pretest and posttest associated to the sport. Likewise, it would be necessary to compare with a three session per week protocol to verify if there are changes in SAB and IAB that lead to even more determining results.

Acknowledgements

This work was supported with a grant by FCT [Pest-OE/EEI/LA0009/2013].

Author Disclosures

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

Angelakis, E., Stathopoulou, S., Frymiare, J. L., Green, D. L., Lubar, J. F., & Kounios, J. (2007). EEG neurofeedback: A brief overview and an example of peak alpha frequency training for cognitive enhancement in the elderly. *The Clin Neuropsychologistigist, 21*(1), 110–129. https://doi.org /10.1080/13854040600744839

Babiloni, C., Marzano, N., Infarinato, F., Iacoboni, M., Rizza, G., Aschieri, P., ... Del Percio, C. (2010). "Neural efficiency" of experts' brain during judgment of actions: A high-resolution EEG study in elite and amateur karate athletes. *Behavioural Brain Research, 207*(2), 466–475. https://doi.org /10.1016/j.bbr.2009.10.034

Baker, J., Côté, J., & Deakin, J. (2005). Expertise in ultra-endurance triathletes early sport involvement, training structure, and the theory of deliberate practice. *Journal of Applied Sport Psychology, 17*(1), 64–78. https://doi.org /10.1080/10413200590907577

Bazanova, O., & Mernaya, E. (2008). Voluntary modification of musical performance by neurofeedback training. *Annals of General Psychiatry, 7*(1), S100. https://doi.org/10.1186/1744-859X-7-S1-S100

Bazanova, O. M., & Vernon, D. (2014). Interpreting EEG alpha activity. *Neuroscience & Biobehavioural Reviews, 44*, 94–110. https://doi.org/10.1016/j.neubiorev.2013.05.007

Cross, E. S., Acquah, D., & Ramsey, R. (2014). A review and critical analysis of how cognitive neuroscientific investigations using dance can contribute to sport psychology. *International Review of Sport and Exercise Psychology, 7*(1), 42–71. https://doi.org/10.1080/1750984X.2013.862564

Da Silva, F. L. (2013). EEG and MEG: Relevance to neuroscience. *Neuron, 80*(5), 1112–1128. https://doi.org/10.1016 /j.neuron.2013.10.017

Debener, S., Makeig, S., Delorme, A., & Engel, A. K. (2005). What is novel in the novelty oddball paradigm? Functional significance of the novelty P3 event-related potential as revealed by independent component analysis. *Cognitive Brain Research, 22*(3), 309–321. https://doi.org/10.1016 /j.cogbrainres.2004.09.006

Egner, T., & Gruzelier, J. H. (2001). Learned self-regulation of EEG frequency components affects attention and event-related brain potentials in humans. *NeuroReport, 12*(18), 4155–4159. https://doi.org/10.1097/00001756-200112210-00058

Escolano, C., Aguilar, M., & Minguez, J. (2011). *EEG-based upper alpha neurofeedback training improves working memory performance.* Paper presented at the 2011 Annual International Conference of the IEEE Engineering in Medicine and Biology Society, Boston, MA.

Gruzelier, J. H. (2014). Differential effects on mood of 12–15 (SMR) and 15–18 (beta1) Hz neurofeedback. *International Journal of Psychophysiology, 93*(1), 112–115. https://doi.org/10.1016 /j.ijpsycho.2012.11.007

Guez, J., Rogel, A., Getter, N., Keha, E., Cohen, T., Amor, T., … Gordon, S., Meiran, N., & Todder, D. (2015). Influence of electroencephalography neurofeedback training on episodic memory: A randomized, sham-controlled, double-blind study. *Memory, 23*(5), 683–694. https://doi.org/10.1080 /09658211.2014.921713

Haier, R. J., Siegel, B., Tang, C., Abel, L., & Buchsbaum, M. S. (1992). Intelligence and changes in regional cerebral glucose metabolic rate following learning. *Intelligence, 16*(3–4), 415–426. https://doi.org/10.1016/0160-2896(92)90018-M

Harkness, T. (2009). Psykinetics and biofeedback: Abhinav Bindra wins India's first-ever individual gold medal in Beijing olympics. *Biofeedback, 37*(2), 48–52. https://doi.org/10.5298 /1081-5937-37.2.48

Hatfield, B. D., Haufler, A. J., & Spalding, T. W. (2006). A cognitive neuroscience perspective on sport performance. In E. Ekkekakis, & E. Acevedo (Eds.), *Psychobiology of Phshysical Activity* (pp. 221–240). Champaign, IL: Human Kinetics.

Hosseini, F., & Norouzi, E. (2017). Effect of neurofeedback training on self-talk and performance in elite and non-elite volleyball players. *Medicina Dello Sport, 70*(3), 344–353. https://doi.org/10.23736/S0025-7826.16.03011-8

Kamata, A., Tenenbaum, G., & Hanin, Y. L. (2002). Individual zone of optimal functioning (IZOF): A probabilistic estimation. *Journal of Sport and Exercise Psychology, 24*(2), 189–208. https://doi.org/10.1123/jsep.24.2.189

Kamijo, K., & Takeda, Y. (2010). Regular physical activity improves executive function during task switching in young adults. *International Journal of Psychophysiology, 75*(3), 304–311. https://doi.org/10.1016/j.ijpsycho.2010.01.002

Klimesch, W. (1999). EEG alpha and theta oscillations reflect cognitive and memory performance: A review and analysis. *Brain Research Reviews, 29*(2–3), 169–195. https://doi.org /10.1016/S0165-0173(98)00056-3

Landers, D. M., Petruzzello, S. J., Salazar, W., Crews, D. J., Kubitz, K. A., Gannon, T. L., & Han, M. (1991). The influence of electrocortical biofeedback on performance in pre-elite archers. *Medicine & Science in Sports & Exercise, 23*(1), 123–129. https://doi.org/10.1249/00005768-199101000-00018

Mann, C. A., Sterman, M. B., & Kaiser, D. A. (1996). Suppression of EEG rhythmic frequencies during somato-motor and visuo-motor behavior. *International Journal of Psychophysiology, 23*(1–2), 1–7. https://doi.org/10.1016/0167-8760(96)00036-0

Marzbani, H., Marateb, H. R., & Mansourian, M. (2016). Neurofeedback: A comprehensive review on system design, methodology and clinical applications. *Basic and Clinical Neuroscience, 7*(2), 143–158. https://doi.org/10.15412 /J.BCN.03070208

Maszczyk, A., Gołaś, A., Pietraszewski, P., Kowalczyk, M., Cięszczyk, P., Kochanowicz, A., … Zajac, A. (2018). Neurofeedback for the enhancement of dynamic balance of judokas. *Biology of Sport, 35*(1), 99–102. https://doi.org /10.5114/biolsport.2018.71488

Milton, J., Solodkin, A., Hluštík, P., & Small, S. L. (2007). The mind of expert motor performance is cool and focused. *NeuroImage, 35*(2), 804–813. https://doi.org/10.1016 /j.neuroimage.2007.01.003

Mirifar, A., Beckmann, J., & Ehrlenspiel, F. (2017). Neurofeedback as supplementary training for optimizing athletes' performance: A systematic review with implications for future research. *Neuroscience & Biobehavioral Reviews, 75*, 419–432. https://doi.org/10.1016/j.neubiorev.2017.02.005

Nan, W., Rodrigues, J. P., Ma, J., Qu, X., Wan, F., Mak, P.-I., … Rosa, A. (2012). Individual alpha neurofeedback training effect on short term memory. *International Journal of Psychophysiology, 86*(1), 83–87. https://doi.org/10.1016 /j.ijpsycho.2012.07.182

Nan, W., Wan, F., Lou, C. I., Vai, M. I., & Rosa, A. (2013). Peripheral visual performance enhancement by neurofeedback training. *Applied Psychophysiology and Biofeedback, 38*(4), 285–291. https://doi.org/10.1007/s10484-013-9233-6

Noakes, T. D. (2012). Fatigue is a brain-derived emotion that regulates the exercise behavior to ensure the protection of

whole body homeostasis. *Frontiers in Physiology, 3*, 82. https://doi.org/10.3389/fphys.2012.00082

Park, J. L., Fairweather, M. M., & Donaldson, D. I. (2015). Making the case for mobile cognition: EEG and sports performance. *Neuroscience & Biobehavioral Reviews, 52*, 117–130. https://doi.org/10.1016/j.neubiorev.2015.02.014

Pfurtscheller, G., Neuper, C., Ramoser, H., & Müller-Gerking, J. (1999). Visually guided motor imagery activates sensorimotor areas in humans. *Neuroscience Letters, 269*(3), 153–156. https://doi.org/10.1016/S0304-3940(99)00452-8

Rodrigues, J. P., Migotina, D. G., & da Rosa, A. C. (2010). *EEG training platform: Improving brain-computer interaction and cognitive skills.* Paper presented at the 3rd International Conference on Human System Interaction, Rzeszow, Poland. https://doi.org/10.1109/HSI.2010.5514535.

Salazar, W., Landers, D. M., Petruzzello, S. J., Han, M., Crews, D. J., & Kubitz, K. A. (1990). Hemispheric asymmetry, cardiac response, and performance in elite archers. *Research Quarterly for Exercise and Sport, 61*(4), 351–359. https://doi.org/10.1080/02701367.1990.10607499

Themanson, J. R., Pontifex, M. B., & Hillman, C. H. (2008). Fitness and action monitoring: Evidence for improved cognitive flexibility in young adults. *Neuroscience, 157*(2), 319–328. https://doi.org/10.1016/j.neuroscience.2008.09.014

Thompson, M., & Thompson, L. (2015). *The neurofeedback book*: *An introduction to basic concepts in applied psychophysiology (2nd ed.)*. Wheat Ridge, CO: Association for Applied Psychophysiology and Biofeedback (AAPB).

Thompson, T., Steffert, T., Ros, T., Leach, J., & Gruzelier, J. (2008). EEG applications for sport and performance. *Methods, 45*(4), 279–288. https://doi.org/10.1016 /j.ymeth.2008.07.006

Vernon, D. J. (2005). Can neurofeedback training enhance performance? An evaluation of the evidence with implications for future research. *Applied Psychophysiology and Biofeedback, 30*(4), 347. https://doi.org/10.1007/s10484-005-8421-4

Walsh, V. (2014). Is sport the brain's biggest challenge? *Current Biology, 24*(18), R859–R860. https://doi.org/10.1016 /j.cub.2014.08.003

Wilson, V. E., Peper, E., & Moss, D. (2006). "The Mind Room" in Italian soccer training: The use of biofeedback and neurofeedback for optimum performance. *Biofeedback, 34*(3).

World Health Organization. (2010). Global recommendations on physical activity for health. Geneva, Switzerland: World Health Organization. Retrieved from http://whqlibdoc.who.int /publications/2010/9789241599979_eng.pdf

World Medical Association. (2001). World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. *Bulletin of the World Health Organization, 79*(4), 373.

Xiang, M.-Q., Hou, X.-H., Liao, B.-G., Liao, J.-W., & Hu, M. (2018). The effect of neurofeedback training for sport performance in athletes: A meta-analysis. *Psychology of Sport and Exercise, 36*, 114–122. https://doi.org/10.1016 /j.psychsport.2018.02.004

YuLeung To, E., Abbott, K., Foster, D. S., & Helmer, D. (2016). Working memory and neurofeedback. *Applied Neuropsychology: Child, 5*(3), 214–222. https://doi.org /10.1080/21622965.2016.1167500

Ziółkowski, A., Graczyk, M., Strzałkowska, A., Wilczyńska, D., Włodarczyk, P., & Zarańska, B. (2012). Neuronal, cognitive and social indicators for the control of aggressive behaviors in sport. *Acta Neuropsychologica, 10*(4), 537–546. https://doi.org /10.5604/17307503.1030215

Received: September 1, 2019
Accepted: February 11, 2020
Published: March 25, 2020

NeuroRegulation

Predictors of Neurofeedback Outcomes Following qEEG Individualized Protocols for Anxiety

J. Claire Gregory[*], *Devon E. Romero, and Mark S. Jones*

[1]Department of Counseling, University of Texas at San Antonio, San Antonio, Texas, USA

Abstract

In this retrospective study, researchers examined effects of quantitative electroencephalography (qEEG), individualized neurofeedback treatment protocols for anxiety. The present study includes 52 clients with 53.8% (*n* = 28) self-reporting as male and included two time points (pre and post). Secondary analyses utilized a subset of client data (*n* = 21) with measurements from three time points (pre, post, and follow-up). All clients completed qEEG and self-report assessments. Clients agreed to attend a minimum of 15 biweekly sessions, for one academic semester. Findings from regression analyses revealed three predictors of posttreatment outcomes. In addition, analysis of a subsample of data assessed at three time points revealed statistically significant improvement from pre to post and sustained outcomes from post to follow-up. We discuss limitations and implications for future research.

Keywords: neurofeedback; anxiety; qEEG-guided amplitude neurofeedback; predictor

Citation: Gregory, J. C., Romero, D. E., & Jones, M. S. (2020). Predictors of neurofeedback outcomes following qEEG individualized protocols for anxiety. *NeuroRegulation*, *7*(1), 18–25. https://doi.org/10.15540/nr.7.1.18

***Address correspondence to**: J. Claire Gregory, University of Texas at San Antonio, Department of Counseling, 501 W. Cesar E. Chavez, San Antonio, TX 78207, USA. Email: jessica.gregory@utsa.edu

Edited by:
Rex L. Cannon, PhD, SPESA Research Institute, Knoxville, Tennessee, USA

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

Although many Americans experience stress during their lifetime, anxiety disorders can be debilitating and disrupt daily functioning. Anxiety disorders are a pervasive and prevalent mental health concern affecting 19.1% of adults in the United States (National Institute of Mental Health [NIMH], 2017). In addition, an estimated 31.1% of adults in the United States experience an anxiety disorder at some point during their lives (NIMH, 2017). Although various anxiety disorders exist, prevalent ones are generalized anxiety disorder, panic disorder, and several phobia-related disorders (NIMH, 2018).

Frequently, the onset of anxiety disorders begins during childhood and, if an individual does not receive treatment, anxiety symptoms may persist throughout their life (American Psychiatric Association [APA], 2013). Symptoms of anxiety differ from person to person and can include a range of physiological and psychological issues. For example, people with generalized anxiety disorder can experience muscle tension, trouble concentrating, and difficulty controlling thoughts of worry; while people with panic disorder experience unexpected panic attacks, accelerated heart rate, and feeling out of control (NIMH, 2018). Although symptoms can vary from one type to another, the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; DSM-5) suggests that anxiety disorders share commonalities of "excessive fear and anxiety and related behavioral disturbances" (APA, 2013, p. 189).

Literature Review

Clinicians display use of various forms of biofeedback modalities for treating anxiety (Jones & Hitsman, 2018). Some biofeedback modalities include heart rate variability (HRV) training and electromyography (EMG). Neurofeedback is also a form of biofeedback that is showing promising effects in correcting negative symptoms including depression (Cheon et al., 2015), sleep disorders (Cheon et al., 2015), attention-deficit/hyperactivity disorder (Van Doren et al., 2019), and anxiety (Cheon et al., 2015; Kerson,

Sherman, & Kozlowski, 2009; Scheinost et al., 2013; Wang et al., 2019; Zhao et al., 2018). In addition, combinations of neurofeedback and biofeedback (e.g., HRV) have produced promising outcomes for reducing anxiety symptoms (White et al., 2017).

In 2015, Cheon et al. decided to conduct a controlled study focusing on psychiatric patients and neurofeedback. They used retrospective data, and the data collection process included the administration of the Clinical Global Impression-Severity scale (CGI-S; Busner & Targum, 2007) and the Hill-Castro Checklists (Hill & Castro, 2002) on a weekly basis. The CGI is a widely known and utilized tool for objective rating (Cheon et al., 2015) and 23.4% of their participants had an anxiety disorder recognized by the *DSM-5.* All patients participated in beta, SMR, or alpha/theta neurofeedback training at training sites: Fp1, Fp2, F3, F4, F7. F8, T3, T4, C3, C4, P1, P2, O1, O2, and Oz according to the 10–20 Electrode system. The researchers identified varying diagnoses as rationale for using unique neurofeedback protocols. In addition, the authors state that during the final neurofeedback sessions, protocol development shifted to fit individual needs (Cheon et al., 2015). Both the CGI-S and the Hill-Castro Checklist resulted in significant findings (p = .0001) for the anxiety participants.

Numerous other researchers found evidence of neurofeedback being beneficial for anxiety symptoms. Researchers Scheinost et al. (2013) sought to examine state verses trait anxiety and alpha asymmetry while using real-time functional magnetic resonance imaging (rt-fMRI). They discovered that focusing training on brain regions instead of certain brain sites was advantageous. The participants also showed lasting results for emotion regulation and decreased anxiety. In addition, proponents of a study by Zhao et al. (2019) displayed a reduction of anxiety symptoms lasting 3 days when using rt-fMRI. Drawing on work from previous studies, Zhao et al. (2019) emphasized training on connectivity of individual pathways of participants' amygdala-prefrontal area. Therefore, neurofeedback protocols based on individualized protocols and/or variations in EEG data, show promising results for improving emotion regulation and decreasing anxiety.

Each study has certain strengths and limitations and variations exist among neurofeedback training modalities and protocols. One limitation is using the same protocol for each patient, and another is utilizing only symptom-based protocols. According to Hammond (2010), it is important to assess a baseline quantitative electroencephalography (qEEG) pattern as this will help identify the heterogeneity in brain wave patterns, find comorbidities, and examine the brain for medication effects. Viewpoints for neurofeedback clinicians still vary on whether to use individualized protocols or the same protocol. Some researchers view individualized protocols as a strength. Agreeing with this viewpoint, Arns, Heinrich, and Strehl (2014) suggest that researchers may want to consider using individualized protocols. Certain researchers postulate the benefits of using individualized protocols and how they can tailor neurofeedback to every person's unique brain patterns (Arns et al., 2014; Hammond, 2010; Krigbaum & Wigton, 2014).

An individualized protocol consists of tailoring treatment to a person's specific qEEG data. This neurofeedback modality dates to the 1980s (Krigbaum & Wigton, 2014). Currently, many studies indicate the benefits of personalized protocols (Arns, Drinkenburg, & Kenemans, 2012; Ogrim & Hestad, 2013; Walker, 2012). Specifically, individualized protocols allow the clinician to determine client-based protocols which also take into consideration the diversity of qEEG patterns (Hammond, 2010).

In an additional study by Wigton and Krigbaum (2015), the researchers further assert how *z*-score protocols (e.g., individualized protocols) aid in identifying the link between specific cortical dysfunctions and connectivity concerns related to mental health symptomology. Moreover, to determine neurofeedback training sessions, the comparison of qEEG data to a normative database results in *z*-scores (Wigton & Krigbaum, 2015). This method allows for a baseline of pretreatment data for determining the progress of the client. With this knowledge, clinicians can reduce mental health issues by bringing the scores closer to the mean.

Data collection for this retrospective study consisted of methods inspired by *z*-score training. Since the current study's data was collected from a student training clinic, the neurofeedback clinic director decided on single-channel amplitude training for three reasons: (a) this training is commonly used by clinicians, (b) it is an easier starting point for students in training versus more advanced modalities, and (c) numerous one-channel amplitude training research literature is reviewed by Wigton (2014; Jones & Hitsman, 2018). Therefore, the retrospective data included in this study were examining reduction of anxiety symptoms while utilizing qEEG-guided amplitude neurofeedback training protocols.

The present study uses deidentified data collected from a graduate training counseling center with the primary aim of training master's- and doctoral-level counseling students interested in developing clinical neurofeedback competency. The purpose of this study is to examine predictors of neurofeedback outcomes following qEEG individualized protocols for treating anxiety. Specifically, the study aimed to answer the following question: "Are there differences within the individual that predict improvement in client-reported anxiety symptoms following individualized neurofeedback treatment?" Secondary research questions include:

- "Does individual neurofeedback treatment differ in participant self-report of anxiety concerns over time?"
- "Does individual neurofeedback treatment differ from participant self-report from pretest to follow-up?"
- "Does individual neurofeedback treatment differ from participant self-report from pretest to posttest?", and
- "Does individual neurofeedback treatment differ from participant self-report from posttest to follow-up?"

Method

Participants/Sample/Power

The University of Texas at San Antonio (UTSA) Institutional Review Board deemed this retrospective study exempt from review. Potential clients contacted Sarabia Family Counseling Center at the University of Texas at San Antonio (UTSA) to inquire about neurofeedback treatment for anxiety. Upon calling, a master's- or doctoral-level student in UTSA's Counseling Department screened clients to determine their eligibility for treatment. This screening process included inclusion criteria of reporting primarily anxiety symptoms, availability, and meeting the age requirements. Clients enrolled in the neurofeedback treatment program agreed to attend a minimum of 15 neurofeedback sessions biweekly, which were free of charge.

The present study consists of a sample of 52 clients aged 19 to 59 (M = 36.4, SD = 12.6). Of these clients, 53.8% (n = 28) self-reported as male. Ethnic composition of the clients included 50% (n = 26) Non-Hispanic, 44% (n = 23) Hispanic/Latino, and 6% (n = 3) did not respond. Table 1 provides a more detailed review of client demographics.

Table 1
Characteristics of the sample at time of recruitment (N = 52).

Mean age (range)	36.37 (19–59)
Gender	
Male	53.8%
Female	42.3%
Chose not to respond	3.9%
Ethnicity	
Non-Hispanic	50.0%
Hispanic/Latino	44.2%
Did not respond	5.8%
Education	
No HS diploma; no GED	1.9%
GED	1.9%
High school degree	9.6%
Some college; no degree	28.8%
Associate degree	9.6%
Bachelor's degree; RN	23.1%
Some grad school; no degree	9.6%
Master's degree	7.7%
PhD; Law degree	3.9%
Did not respond	3.9%

Secondary analyses utilized a subsample of the dataset described above. This subsample includes 21 clients with assessments completed at three time points (pre, post, and follow-up). In terms of demographic data of the subsample, clients' (n = 21) ages range from 20 to 56 (M = 38.8, SD = 12.39) with 61.9% (n = 13) of clients self-reporting as female. The self-reported ethnic composition of the subsample was 38.1% (n = 8) Non-Hispanic, 52.4% (n = 11) Hispanic/Latino, and 9.5% (n = 2) chose not to respond.

Clinicians

Clinicians for the study included student clinicians which were clinical mental health master's-level students and counselor education and supervision doctoral-level students. Before beginning their neurofeedback sessions, the students previously completed the Biofeedback Certification International Alliance requirements for didactic coursework for

neurofeedback. In addition, student clinicians are supervised by a certified and licensed supervisor. At times, trained volunteer clinicians (e.g., faculty, alumni, etc.) served as clinicians.

Measures

Demographic information and treatment record. Demographic data for this study includes age, gender, highest level of education completed, ethnicity, and previous or current experience with counseling. Additional data collected consists of number of attended sessions, session-to-session records, type of protocol, amplitude measures for each frequency band, and electrode placement.

Zung self-rating anxiety scale for adults. The Zung Self-rating Anxiety Scale (SAS) is a 20-item, Likert-type, self-report measure of state and trait anxiety based on cognitive, autonomic, motor, and central nervous system symptoms manifestations. Example items include "My face gets hot and blushes," "I have nightmares," and "I feel afraid for no reason at all." With raw scores ranging from 20 to 80, higher scores indicate greater severity of anxiety symptomatology (Zung, 1971). The SAS has demonstrated good internal consistency with a Cronbach's alpha of .82 (Tanaka-Matsumi & Kameoka, 1986).

Self-report for the Achenbach system of empirically based assessment. The Adult Self-Report (ASR) is part of the Achenbach System of Empirically Based Assessment (Achenbach & Rescorla, 2003). The ASR is a 120-item, Likert-type, self-report measure that assesses maladaptive behavioral and emotional problems. The ASR is appropriate for adults between the ages of 18 to 59 years. The ASR consists of adaptive functioning, syndrome, DSM-oriented, and substance use scales and has demonstrated good test–retest reliability (Education, r = .80; Mean Substance Use, r = .96; Achenbach & Rescorla, 2003) and internal consistency for scales utilized in the present study (Total Problems, α = .97; Achenbach & Rescorla, 2003).

Instrumentation

Quantitative electroencephalography. The research team instructed participants to limit consumption of nonessential substances 24 hours prior to the qEEG recording. However, the research team factored medically required substances into the qEEG interpretation and subsequent protocol development. The collection of qEEG data occurred with a 19-channel recording using a BrainMaster Discovery 24 (BrainMaster Technologies, Inc., Bedford, OH) high-impedance amplifier. The software utilized was NeuroGuide (Applied Neuroscience, Inc., Largo, FL) which included 5 min of eyes open (EO) and 5 min of eyes closed (EC). Clients' qEEG recordings included fittings for the correct size of Electro-Cap (Electro-Cap International, Inc., Eaton, OH) 10–20 electrode placement with impedance levels less than 5 kΩ. Preparation for the qEEG also included cleaning the ground and reference locations with abrading PCI prep pads, Nuprep skin prep gel, and rubbing alcohol (Jones & Hitsman, 2018). A member of the research team used the resulting data to develop an individualized protocol for anxiety.

Neurofeedback. For the neurofeedback sessions, clinicians used the BrainMaster Atlantis two-channel amplifiers and BioExplorer (Cyberevolution, Inc., Seattle, WA) software. When preparing the electrode sites, clinicians cleaned the skin with rubbing alcohol and used abrading PCI prep pads when needed for ground and reference locations. Clinicians used Nuprep to help impedance levels and Ten20 conductive paste to attached gold-plated electrodes to the client's scalp. During the sessions, clinicians monitored impedance measurements to ensure that interelectrode impedance was less than 5 kΩ (Jones, 2015).

Neurofeedback Protocols

The research team instructed participants to discontinue the consumption of caffeine or other nonessential substances on neurofeedback days. Range of attended sessions were 3–23 (M = 13.4, SD = 4.3) for the primary data set, and 3–20 (M = 13, SD = 4.87) for the secondary data set. Clinicians provided neurofeedback using BrainMaster Atlantis two-channel amplifiers and BioExplorer software. Training protocols included amplitude uptraining and/or downtraining of preferred frequency bands based on qEEG results. Further, protocol selections were influenced by current research and reflect markers thought to be associated with anxiety concerns (Demerdzieva & Pop-Jordanova, 2011; Gunkelman, 2006; Heller, Nitschke, Etienne, & Miller, 1997; Price & Budzynski, 2009; Stern, 2005, p. 196; Tharawadeepimuk & Wongsawat, 2014). For example, one client's protocol consisted of EO CZ downtraining 4–9 Hz, uptraining 12–15 Hz, and downtraining 17–23 Hz. Another example of a client's protocol was EC PZ downtraining 3–7 Hz, uptraining 8–10 Hz, and downtraining 25–30 Hz.

According to preferences of participants and clinicians' clinical judgment, feedback was determined using the following formats: animations, sounds, games, and analog presentations. The predetermined thresholds were set manually at the start of the session with an ideal reward rate of 50%. During the sessions, clinicians made periodic adjustments to the threshold settings as an attempt to share behavior toward the client's treatment goals. Treatment records where kept for each session and included frequency bands, threshold settings, average amplitude, type of feedback received, and any other clinician notes. Training sessions lasted approximately 20 minutes.

Statistical Analysis

Statistical analyses for this study included the Statistical Package for the Social Sciences (SPSS) software version 25 (SPSS, 2017). Missing data, examining cases for missing data, outliers, and normality were all assessed before analysis of data. Analytic computations used *p*-values set at $\alpha = 0.05$. The primary data set has 0% missing data for the SAS, and 5.8% for the ASR. For the subsample data set, there was no missing data.

The research team ran regression analyses on the primary data set to determine potential predictors of post-SAS scores. We controlled for pre-SAS scores and client-reported gender due to high correlation with the outcome variable (post-SAS scores). Education was dummy coded 0 (*no*) and 1 (*yes*) with *No high school (HS) diploma* serving as the reference group. The present study utilized control variables and predictor variables measured by the ASR at time 1. Additionally, using the subsample data set, researchers used a paired samples *t*-test to measure mean differences between pre, post, and follow-up scores of the SAS.

Results

Individuals completed the SAS and ASR at intake (time 1, pre) to assess their level of anxiety and other concerns. Upon completion of the neurofeedback treatment protocols, both assessments were readministered (time 2, post). The mean prescore results from all subjects was 45.62 (*SD* = 8.49), while the mean for the postscores was 39.50 (*SD* = 9.40).

A regression analysis displayed total problems as measured by the ASR significantly predicted post-SAS scores ($B = .26$, $SE\ B = .24$, $p = .05$). This model explained 56% of the total variance after controlling for pre-SAS scores and gender; $F(3, 48) = 21.13$, $R^2 = .56$, $p < .01$. This demonstrated a significant positive relationship between total problems and post-SAS scores, showing greater improvement in anxiety symptoms following neurofeedback treatment was associated with lower total problems scores as measured by the ASR prior to neurofeedback treatment.

An additional regression analysis revealed that a model including gender, pre-SAS scores, and mean substance use predicted post-SAS scores; $F(3, 48) = 21.74$, $R^2 = .58$, $p < .01$. Mean substance use was a significant predictor in this model and explained 58% of the total variance after controlling for pre-SAS scores and gender. This demonstrated a significant positive relationship between mean substance use and post-SAS scores, showing greater improvement in anxiety symptoms following neurofeedback treatment was associated with lower mean substance use scores as measured by the ASR prior to neurofeedback treatment.

A third regression analysis identified some college with no degree ($B = 15.84$, $SE\ B = .7.18$, $p = .03$), bachelor's degree ($B = 17.11$, $SE\ B = 7.22$, $p = .02$), and PhD or law degree ($B = 19.28$, $SE\ B = 8.69$, $p = .03$) significantly predicted post-SAS scores when controlling for pre-SAS and gender; $F(10, 39) = 6.45$, $R^2 = .62$, $p < .01$. This demonstrated a significant positive relationship between education and post-SAS scores, showing higher education was associated with greater improvement in anxiety symptoms following neurofeedback treatment. Regression results for primary analyses appear in Table 2.

Table 2
Regression analysis summary for variables found to predict post-SAS scores (N = 52).

	B	*SE B*	*t*
$F(3, 48) = 21.13$, $R^2 = .57$, $p < .01$			
Gender	1.10	1.77	0.62
Pre-SAS scores	0.70	0.15	4.856**
Total problems	0.256	0.125	2.038*
$F(3, 48) = 21.74$, $R^2 = .58$, $p < .01$			
Gender	1.83	1.72	1.06
Pre-SAS scores	0.91	0.12	7.9**
Mean substance use	−0.341	0.153	−2.237*
$F(10, 39) = 6.45$, $R^2 = .62$, $p < .01$			
Gender	4.06	2.03	1.99*
Pre-SAS scores	0.91	0.13	7.08**
GED	15.19	9.95	1.53
High school degree	12.47	7.58	1.64
Some college; no degree	15.84	7.18	2.21*
Associate degree	9.42	7.53	1.25
Bachelor's degree; RN	17.11	7.22	2.37*
Some grad school; no degree	13.72	7.62	1.8†
Master's degree	10.75	7.77	1.38
PhD; Law degree	19.28	8.69	2.22*

Note. † $p < .10$; * $p < .05$; ** $p < .01$

Secondary analyses using the subsample data included a third time point (time 3, follow-up). This time point occurred one month after posttreatment. The mean of the prescores was 45.67 (*SD* = 9.34), mean postscores was 39.14 (*SD* = 9.39), and mean follow-up scores was 41.05 (*SD* = 9.58). We ran paired sample *t*-tests to examine differences between time points of the SAS scores (time 1, time 2, and time 3). Results displayed statistically significant change from pre to post $t(20) = 4.7$, $p < .001$, $d = .68$, and from pre to follow-up $t(20) = 2.66$, $p = .015$, $d = .47$. There was no significant change from post to follow-up $t(20) = -1.67$, $p = .111$, $d = .20$. Results appear in Table 3 and Figure 1 illustrates these findings.

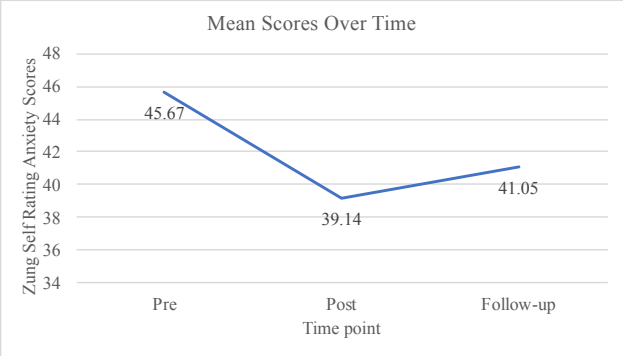

Figure 1. Zung Self-rating Anxiety Scale mean scores at pre, post, and follow-up (*n* = 21).

Table 3
Zung Self-rating Anxiety Scale (SAS) for adults.

	Time Point		Change				
	M (*SD*)	*M* (*SD*)	*M* (*SD*)	[95% CI]	*t(df)*	*p*	*d*
	Pre	Post					
Time 1 – Time 2	45.67 (9.94)	39.14 (9.38)	6.52 (6.37)	[3.63, 9.42]	4.7(20)	< .001	.68
	Post	Follow-up					
Time 2 – Time 3	39.14 (9.38)	41.05 (9.58)	−1.905 (1.14)	[−4.28, .478]	−1.67(20)	.111	.20
	Pre	Follow-up					
Time 1 – Time 3	45.67 (9.94)	41.05 (9.58)	4.62 (7.94)	[1.01, 8.23]	2.66(20)	.015	.47

Discussion

The primary aim of this retrospective study was to examine predictors of anxiety symptom outcomes following individualized neurofeedback treatment. The present study identified a large mean decrease in SAS outcomes from pretreatment to posttreatment, indicating improvement in client-reported anxiety symptoms following neurofeedback treatment. Regression analyses identified total problems, substance use, and level of education as predictors of anxiety symptoms as measured by the SAS following individualized neurofeedback treatment.

The secondary research questions posed in the present study aimed to explore whether self-reported anxiety differed over time, specifically from pre to post, pre to follow-up, and post to follow-up. Interestingly, there is no significant change from post to follow-up SAS scores. This lack of change from post to follow-up anxiety scores imply neurofeedback treatment for one university academic semester has lasting effects from post to follow-up, or around a month between time points. Our findings are comparable to results of a similar study examining post and follow-up by Van Doren et al. (2019). Their neurofeedback study for ADHD reported no significant change from post to follow-up. Additionally, the researchers stated that neurofeedback seems to be sustainable after 2 to 12 months. Our findings suggest sustainable results after 1 to 1.5 months. Similar to prior neurofeedback research, these findings indicate that neurofeedback is a sustainable and effective treatment for anxiety symptoms.

Limitations and Implications for Research

The lack of a control group is a major limitation of the study. As such, there is no way to determine what aspects of the results may be attributable to placebo effect. The individualized treatment protocols—based on qEEG results—created a variability in the treatment provided, with no analysis of whether specific protocols may have had differing effects. The smaller sample size of the primary data set and the small sample size of the secondary data set are another limiting factor for assessing statistical robustness. In addition, a number of issues are present due to the academic setting in which the research was conducted. Restricting the number of sessions to an academic semester reduced the possible number of sessions, which may have limited the effectiveness of treatment. The skill level of the student and volunteer clinicians may have varied somewhat and was not controlled for. As a result, there is no way to determine if more experienced clinicians may have had a higher level of treatment effectiveness. Finally, there was no control for the variability of other forms of treatment the subject may have received before or during the study, the result being a lack of differentiation between the effects of the study and the effects of other treatments.

The study supports the need for further research on the possible efficacy of neurofeedback for the amelioration of anxiety symptoms in a number of areas. Identifying biomarkers of anxiety in the EEG is a possible focus of future studies by comparing the qEEG and other analyses of EEG data for subjects with or without anxiety symptoms. For example, in addition to mere amplitude measures, characteristics of coherence, independent components, network hubs, event-related potentials, dynamic time–frequency analysis, and source density location may be utilized.

Conclusion

This retrospective study included data from qEEG, individualized neurofeedback treatment protocols for anxiety. After running regression analyses, the results yielded three predictors of posttreatment outcomes: total problems, substance abuse mean, and education level. Further, an analysis of a subsample of data displayed statistically significant improvement from pre to post with sustainable outcomes from post to follow-up.

Author Note

This study was financially supported by the Foundation for Neurofeedback and Neuromodulation Research.

Author Disclosure

Authors have no other grants, financial interests, or conflicts to disclose.

References

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Washington, DC: Author.

Achenbach, T. M., & Rescorla, L. A. (2003). *Manual for the ASEBA adult forms and profiles.* Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families.

Arns, M., Drinkenburg, W., & Kenemans, J. L. (2012). The effects of QEEG-informed neurofeedback in ADHD: An open-label pilot study. *Applied Psychophysiology and Biofeedback, 37*, 171–180. https://doi.org/10.1007/s10484-012-9191-4

Arns, M., Heinrich, H., & Strehl, U. (2014). Evaluation of neurofeedback in ADHD: The long and winding road. *Biological Psychology, 95,* 108–115. https://doi.org/10.1016/j.biopsycho.2013.11.013

Busner, J., & Targum, S. D. (2007). The clinical global impressions scale: Applying a research tool in clinical practice. *Psychiatry (Edgmont)*, *4*(7), 28–37. Retrieved from http://search.proquest.com/docview/733162476/

Cheon, E.-J., Koo, B.-H., Seo, W.-S., Lee, J.-Y., Choi, J.-H., & Song, S.-H. (2015). Effects of neurofeedback on adult patients with psychiatric disorders in a naturalistic setting. *Applied Psychophysiology and Biofeedback*, *40*(1), 17–24. https://doi.org/10.1007/s10484-015-9269-x

Demerdzieva, A., & Pop-Jordanova, N. (2011). Alpha asymmetry in QEEG recordings in young patients with anxiety. *Prilozi / Makedonska Akademija Na Naukite i Umetnostite, Oddelenie Za Biološki i Medicinski Nauki = Contributions / Macedonian Academy of Sciences and Arts, Section of Biological and Medical Sciences*, *32*(1), 229–244.

Gunkelman, J. (2006). Transcend the DSM using phenotypes. *Biofeedback*, *34*(3), 95–98. Retrieved from https://www.aapb.org/files/publications/biofeedback/2006/biof_34_3_DSM.pdf

Hammond, D. C. (2010). The need for individualization in neurofeedback: Heterogeneity in QEEG patterns associated with diagnoses and symptoms. *Applied Psychophysiology and Biofeedback, 35*(1), 31–36. https://doi.org/10.1007 /s10484-009-9106-1

Heller, W., Nitschke, J. B., Etienne, M. A., & Miller, G. A. (1997). Patterns of regional brain activity differentiate types of anxiety. *Journal of Abnormal Psychology*, *106*(3), 376–385. https://doi.org/10.1037/0021-843X.106.3.376

Hill, R. W. & Castro, E. (2002). *Getting rid of Ritalin: How neurofeedback can successfully treat attention deficit disorder without drugs*. Charlottesville, VA: Hampton Roads.

Jones, M. S. (2015). Comparing DC offset and impedance readings in the assessment of electrode connection quality. *NeuroRegulation, 2*(1), 29–36. https://doi.org/10.15540 /nr.2.1.29

Jones, M. S., & Hitsman, H. (2018). QEEG-guided neurofeedback treatment for anxiety symptoms. *NeuroRegulation, 5*(3), 85–92. https://doi.org/10.15540/nr.5.3.85

Kerson, C., Sherman, R. A., & Kozlowski, G. P. (2009). Alpha suppression and symmetry training for generalized anxiety symptoms. *Journal of Neurotherapy, 13*(3), 146–155. https://doi.org/10.1080/10874200903107405

Krigbaum, G. & Wigton, N. L. (2014) When discussing neurofeedback, does modality matter? *NeuroRegulation*. *1*(1), 48–60. https://doi.org/10.15540/nr.1.1.48

National Institute of Mental Health. (2017). Prevalence of any anxiety disorder among adults. Retrieved from https://www.nimh.nih.gov/health/statistics/any-anxiety-disorder.shtml#part_155094

National Institute of Mental Health. (2018). Anxiety disorders. Retrieved from http://www.nimh.nih.gov /health/topics/anxiety-disorders/index.shtm

National Institute of Mental Health. (2018). Anxiety disorders. Signs and symptoms. Retrieved from https://www.nimh.nih.gov /health/topics/anxiety-disorders /index.shtml#part_145336

Ogrim, G., & Hestad, K. A. (2013). Effects of neurofeedback versus stimulant medication in attention-deficit/hyperactivity disorder: A randomized pilot study. *Journal of Child and Adolescent Psychopharmacology, 23*(7), 448–457. https://doi.org/10.1089 /cap.2012.0090

Price, J., & Budzynski, T. (2009). Anxiety, EEG patterns, and neurofeedback. In T. H. Budzynski, H. K. Budzynski, J. R. Evans, & A. Abarbanel (Eds.), *Introduction to quantitative EEG and neurofeedback: Advanced theory and applications* (2nd ed., pp. 453–472). Burlington, MA: Elsevier Academic Press. https://doi.org/10.1016/B978-0-12-374534-7.00017-4

Stern, J. M. (2005). *Atlas of EEG patterns*. Philadelphia, PA: Lippincott Williams & Wilkins.

Scheinost, D., Stoica, T., Saksa, J., Papademetris, X., Constable, R. T., Pittenger, C., & Hampson, M. (2013). Orbitofrontal cortex neurofeedback produces lasting changes in contamination anxiety and resting-state connectivity. *Translational Psychiatry*, *3*(4), e250. https://doi.org/10.1038 /tp.2013.24

Tanaka-Matsumi, J., & Kameoka, V. A. (1986). Reliabilities and concurrent validities of popular self-report measures of depression, anxiety, and social desirability. *Journal of Consultation and Clinical Psychology*, *54*(3), 328–333. https://doi.org/10.1037/0022-006X.54.3.328

Tharawadeepimuk, K., & Wongsawat, Y. (2014, November). *QEEG evaluation for anxiety level analysis in athletes*. Paper presented at the 2014 7th Biomedical Engineering International Conference (BMEiCON 2014), Fukuoka, Japan (pp. 172–175). Piscataway, NJ: IEEE. https://doi.org/10.1109 /BMEiCON.2014.7017400

Van Doren, J., Arns, M., Heinrich, H., Vollebregt, M. A., Strehl, U., & Loo, S. K. (2019). Sustained effects of neurofeedback in ADHD: A systematic review and meta-analysis. *European Child & Adolescent Psychiatry*, *28*(3), 293–305. https://doi.org/10.1007/s00787-018-1121-4

Wang, S.-Y., Lin, I.-M., Fan, S.-Y., Tsai, Y.-C., Yen, C.-F., Yeh, Y.-C., … Lin, H.-C. (2019). The effects of alpha asymmetry and high-beta down-training neurofeedback for patients with the major depressive disorder and anxiety symptoms. *Journal of Affective Disorders*, *257*, 287–296. https://doi.org/10.1016 /j.jad.2019.07.026

Walker, J. E. (2012). Remediation of enuresis using QEEG-guided neurofeedback training. *Biofeedback, 40*(3), 109–112. https://doi.org/10.5298/1081-5937-40.3.04

White, E. K., Groeneveld, K. M., Tittle, R. K., Bolhuis, N. A., Martin, R. E., Royer, T. G., & Fotuhi, M. (2017). Combined neurofeedback and heart rate variability training for individuals with symptoms of anxiety and depression: A retrospective study. *NeuroRegulation, 4*(1), 37–55. https://doi.org/10.15540 /nr.4.1.37

Wigton, N. L. (2014). *Evaluating 19-channel z-score neurofeedback: Addressing efficacy in a clinical setting* (Doctoral dissertation). Available from ProQuest Dissertations and Theses database. (UMI No. 3625170)

Wigton, N. L., & Krigbaum, G. (2015). Attention, executive function, behavior, and electrocortical function, significantly improved with 19-channel *z*-score neurofeedback in a clinical setting: A pilot study. *Journal of Attention Disorders.* Advance online publication. https://doi.org/10.1177/1087054715577135

Zhao, Z., Yao, S., Li, K., Sindermann, C., Zhou, F., Zhao, W., … Becker, B. (2018). Real-time functional connectivity-based neurofeedback of amygdala-frontal pathways reduces anxiety. *BioRxiv*. Advance online publication (preprint). https://doi.org /10.1101/308924

Zung, W. W. K. (1971). A rating instrument for anxiety disorders. *Psychosomatics, 12*(6), 371–179. https://doi.org/10.1016 /S0033-3182(71)71479-0

Received: March 7, 2020
Accepted: March 20, 2020
Published: March 25, 2020

NeuroRegulation

Long-Term Lead Performance for Vagus Nerve Stimulation: Low Rate of Complications and Failures

Inder S. Anand[1], Imad Libbus[2], and Lorenzo A. DiCarlo[2]*

[1]Division of Cardiology, University of Minnesota, Minneapolis, Minnesota, USA
[2]LivaNova USA, Inc., Houston, Texas, USA

Abstract

Background: Vagus nerve stimulation (VNS) has been shown to improve cardiac function and heart failure symptoms. The VITARIA System provides chronic stimulation through a self-sizing, atraumatic lead placed around the cervical vagus nerve. The lead is identical to the predecessor M304 lead, which has been implanted in patients since 2009 for treatment of epilepsy and depression. Its long-term performance has not been previously reported. **Methods:** All leads implanted in the United States for any indication were included in this analysis. All available data on lead explants, replacements, and customer complaints were used to identify failures. Lead survival was defined as likelihood of the implanted lead remaining implanted and performing as intended. **Results:** The M304 lead has been part of 31,000 implantations, with 72,100 device-years of patient exposure. In 11,000 patients, 99.4% of leads remained implanted and performing as intended after 1 year. At 7 years, 95.7% of leads performed as intended. Lead failure is rare, with common causes being infection (0.87%) and vocal cord dysfunction (0.68%). **Conclusions:** The M304 VNS lead has been used for neuromodulation in over 30,000 patients for over 70,000 device-years. Cumulative lead survival has exceeded design requirements and has low rates of complications and failures.

Keywords: autonomic regulation therapy; vagus nerve stimulation; heart failure; device performance

Citation: Anand, I. S., Libbus, I., & DiCarlo, L. A. (2020). Long-term lead performance for vagus nerve stimulation: Low rate of complications and failures. *NeuroRegulation*, 7(1), 26–29. https://doi.org/10.15540/nr.7.1.26

***Address correspondence to**: Inder S. Anand, MD, VA Medical Center, Cardiology 111-C, One Veterans Drive, Minneapolis, MN 55417, USA. Email: anand001@umn.edu

Edited by:
Rex L. Cannon, PhD, SPESA Research Institute, Knoxville, Tennessee, USA

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

Introduction

Heart failure (HF) is characterized by hemodynamic abnormalities that result in an imbalance between an increase in sympathetic activity and withdrawal of parasympathetic tone. This contributes to the progression of HF and an increase in the risk of mortality and morbidity independent of ejection fraction (EF) and ventricular arrhythmias.

Autonomic regulation therapy (ART) is a novel investigational approach for the management of HF that uses cervical vagus nerve stimulation (VNS) to increase parasympathetic activity and help restore autonomic balance. ART is delivered using chronic stimulation through a self-sizing lead that is placed on the cervical vagus nerve (CVN) without requiring any mapping for placement. ART using open-loop VNS has been shown in a pilot study to be associated with long-term improvement in heart rate, heart rate variability, left ventricular function, 6-minute walk distance, NYHA class, and quality of life in patients with HF and reduced EF (HFrEF; Premchand et al., 2014, 2016, 2019) and is being evaluated further in an ongoing mortality and morbidity pivotal study in patients with HF and reduced left ventricular HF (Konstam et al., 2019).

The VNS lead that is used to deliver ART (VITARIA Model 7304; Figure 1) in the ongoing ANTHEM-HFrEF pivotal study (NCT03425422) is identical in its materials and manufacture to the Model 304 PerenniaFLEX lead, which has been implanted in more than 30,000 patients worldwide since February

2009 for the treatment of drug-refractory epilepsy (DRE) and treatment-resistant depression (TRD; Groves & Brown, 2005; Morris & Mueller, 1999). In this study, we provide findings of a survival analysis, performed to evaluate the long-term performance of the Model 304 PerenniaFLEX lead.

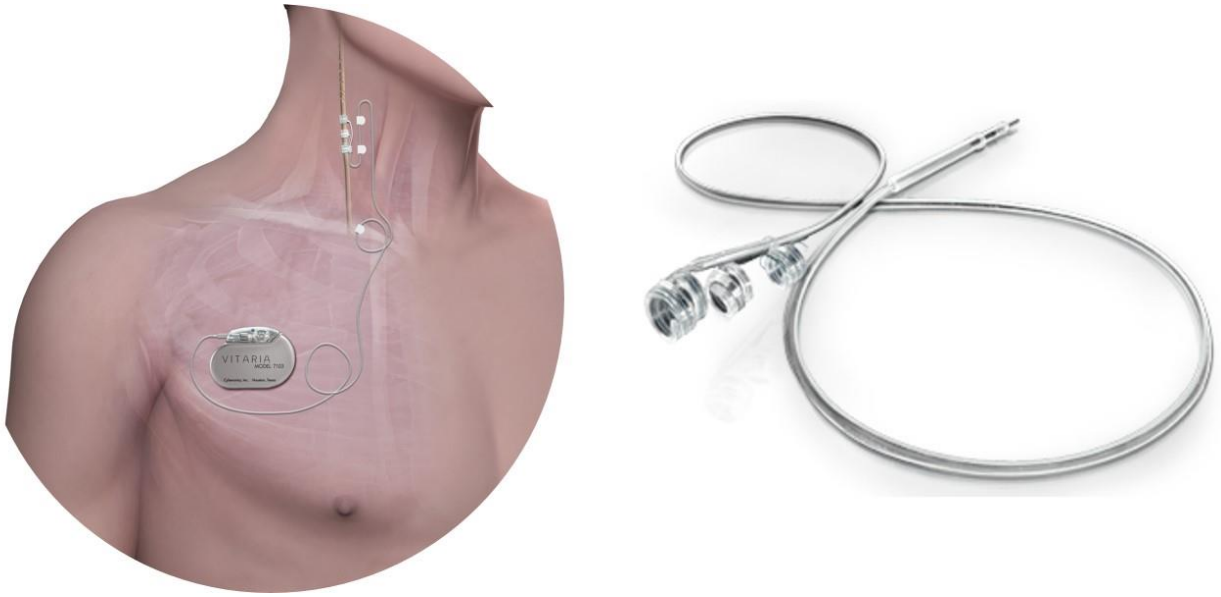

Figure 1. The VITARIA autonomic regulation therapy (ART) system implanted on the right cervical vagus nerve (left), which includes the VITARIA Model 7304 lead (right).

Methods

Data Collection

The LivaNova quality system was used to retrieve and to evaluate lead data. The system includes a device tracking system, which tracks device shipments and implant registration forms that are completed by the implanting physician or hospital staff. LivaNova collects data on device explants, device replacements, returned product analyses, and customer complaints through multiple sources, including voluntary product return, complaint reporting, and device tracking. These data are collected and used to identify failures and out-of-specification conditions. The implant registration forms allow implantable products to be tracked at the patient level from the time of device implant to the time of device explant or patient death. All leads that were registered as implanted in the United States for any indication were included in the analysis, and all data available through December 31, 2018, was analyzed. The analysis complied with the Declaration of Helsinki (World Medical Association, 1996).

To minimize the potential of underreporting of patient deaths, active surveillance was conducted of data obtained from the United States Social Security Administration Death Master File and the Center for Disease Control National Death Index. Those patients without a known Social Security Number were not included in the survival calculations.

Survival Probability Calculations

Lead survival probability was defined as the likelihood of the implanted device remaining implanted and performing as intended at a specific point in the product's service life. The actuarial method was used to estimate survival probability at any time interval (Tolley, Barnes, & Freeman, 2016). Device survival plots use the number of successfully functioning units divided by the total number of units. The cumulative survival probability at a point in time is the product of the survival probabilities for all preceding time intervals. The exponential Greenwood's formula was used to estimate the standard error of the calculated survival probabilities and 95% confidence intervals (CI; Kalbfleisch & Prentice, 1980).

Results

At the time of this analysis, there have been 31,000 registered implants of the PerenniaFLEX Model 304

VNS lead, with a cumulative implant follow-up duration of 72,100 device-years. It is estimated that 26,400 of these devices are still active. Survival status for 11,000 patients was obtainable from public records, and these implants were included in the survival calculations.

Cumulative survival of the implanted leads over time is shown in Table 1 and Figure 2. After 1 year, 99.4% of leads remained implanted and performed as intended (95% CI [99.2, 99.5]). After 5 years and 7 years, 97.1% (95% CI [96.7, 97.5%]) and 95.7% (95% CI [95.1, 96.2]) of implanted leads remained implanted and performed as intended. This survival performance exceeds the design requirement for the Model 304 lead (Figure 2).

Table 1
Cumulative survival of the Model 304 lead over various follow-up intervals, shown as a percentage with 95% confidence intervals.

	At implant	1 year	2 year	3 year	5 year	7 year
Cumulative Survival (%)	100%	99.4% [99.2, 99.5]	98.8% [98.6, 99.0]	98.4% [98.1, 98.6]	97.1% [96.7, 97.5]	95.7% [95.1, 96.2]
Number of Patients	11,000	9,700	8,500	7,200	4,600	1,800

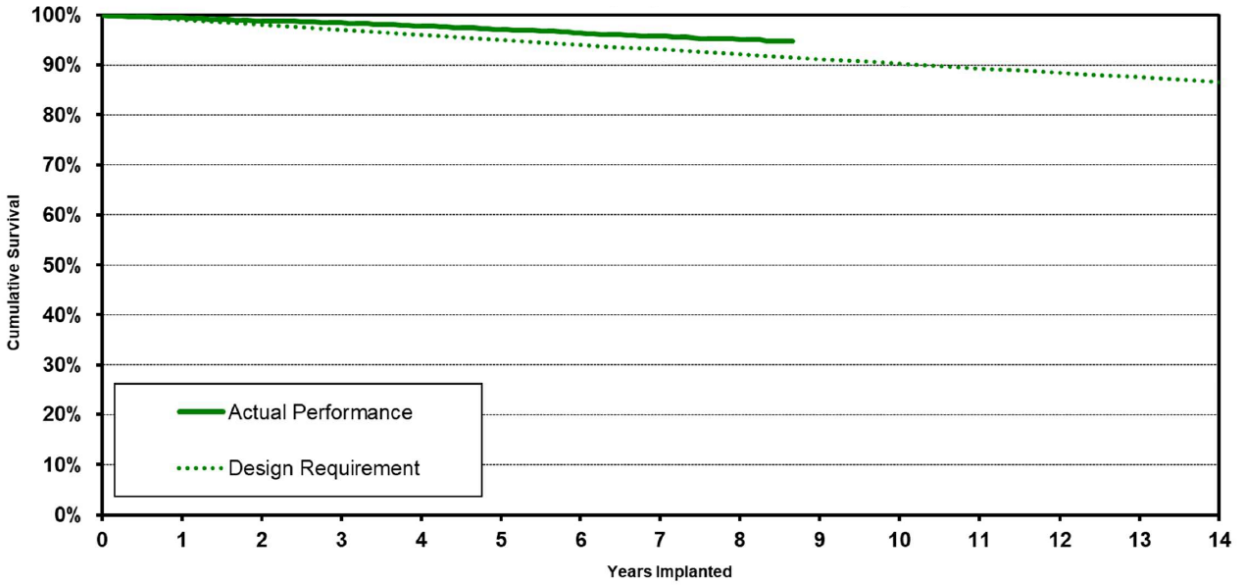

Figure 2. Cumulative survival of the Model 304 lead for US patients with known SSN (solid line) compared to design requirements (dotted line).

Lead complications and failures have been rare, with the most common complications being infection (0.87%), vocal cord dysfunction (0.68%), lead protrusion (0.36%), and lead extrusion (0.27%).

Discussion

There are several similarities in how VNS is administered for the treatment of DRE, TRD, and HF. VNS systems used in all these conditions include an implantable pulse generator, an electrode lead that surrounds the CVN. An external programming system is used to change the generator settings for stimulating the CVN. The electrode is placed around the vagus nerve without requiring intraoperative mapping. The pulse generator and lead deliver electrical stimulation to axons in the CVN. The axons are approximately 80% afferent and 20%

parasympathetic preganglionic efferents (Jänig, 2006).

VNS is administered to the left CVN using the Model 304 lead with bidirectional open-loop delivery for the management of DRE and TRD. For HF, VNS has been administered to the left or right CVN using the Model 7304 lead with bidirectional open-loop delivery that is directed preferentially toward peripheral vagal efferents that control cardiovascular function. In investigational studies in HFrEF, VNS has utilized a relatively lower amplitude (1.5 to 3 mA current) and pulse frequency (5–10 Hz) than is used for DRE. Model 304 lead for DRE and TRD and Model 7304 lead for HF are identical in materials and manufacture. The functional difference between these leads is in the polarity of the electrodes. In DRE and TRD, the cathode is positioned cranially, and in HF, the cathode is positioned caudally (Anand, Konstam, Ardell, Libbus, & DiCarlo, 2019; Ben-Menachem, 2002).

Implanted lead performance is continually tracked during clinical studies and as part of the LivaNova postmarket surveillance process to identify device failure and to determine causes and potential out-of-specification conditions. Based upon the current analysis, chronic VNS using Model 304 appears to be associated with a satisfactory long-term safety and performance profile.

Conclusions

Evaluation of the long-term performance of the Model 304 VNS lead, used in the treatment of DRE and TRD, has demonstrated excellent cumulative survival that exceeded its design requirements, and its use for neuromodulation has been associated with low rates of complications and lead failures. The VITARIA System for the treatment of HF includes the Model 7304 VNS lead, which is identical in its materials and manufacture and is being utilized in the ANTHEM-HFrEF pivotal study.

Author Note

No direct funding was provided for this study.

Author Disclosure

Dr. Anand is contracted to LivaNova as a cardiovascular consultant. Dr. Libbus and Dr. DiCarlo are employees and shareholders of LivaNova.

References

Anand, I. S., Konstam, M. A., Ardell, J. L., Libbus, I., & DiCarlo, L. (2019). Neuromodulation for drug-refractory epilepsy and chronic heart failure: Targets, delivery, composition and titration. *International Journal of Neurology and Neurotherapy, 6*(2), 091. https://doi.org/10.23937/2378-3001/1410091

Ben-Menachem, E. (2002). Vagus-nerve stimulation for the treatment of epilepsy. *The Lancet Neurology, 1*(8), 477–482. https://doi.org/10.1016/S1474-4422(02)00220-X

Groves, D. A., & Brown, V. J. (2005). Vagal nerve stimulation: A review of its applications and potential mechanisms that mediate its clinical effects. *Neuroscience & Biobehavioral Reviews, 29*(3), 493–500. https://doi.org/10.1016/j.neubiorev.2005.01.004

Jänig, W. (2006). Functional anatomy of the peripheral sympathetic and parasympathetic system. In *The integrative action of the autonomic nervous system: Neurobiology of homeostasis* (pp. 13–34). Cambridge, UK: Cambridge University Press.

Kalbfleisch, J. D., & Prentice, R. L. (1980). *The statistical analysis of failure time data*. New York, NY: John Wiley & Sons.

Konstam, M. A., Udelson, J. E., Butler, J., Klein, H. U., Parker, J. D., Teerlink, J. R., … DiCarlo, L. A. (2019). Impact of autonomic regulation therapy in patients with heart failure: ANTHEM-HFrEF pivotal study design. *Circulation: Heart Failure, 12*(11), e005879. https://doi.org/10.1161/circheartfailure.119.005879

Morris, G. L., & Mueller, W. M. (1999). Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. *Neurology, 53*(8), 1731–1735. https://doi.org/10.1212/WNL.53.8.1731

Premchand, R. K., Sharma, K., Mittal, S., Monteiro, R., Dixit, S., Libbus, I., … Anand, I. S. (2014). Autonomic regulation therapy via left or right cervical vagus nerve stimulation in patients with chronic heart failure: Results of the ANTHEM-HF trial. *Journal of Cardiac Failure, 20*(11), 808–816. https://doi.org/10.1016/j.cardfail.2014.08.009

Premchand, R. K., Sharma, K., Mittal, S., Monteiro, R., Dixit, S., Libbus, I., … Anand, I. S. (2016). Extended follow-up of patients with heart failure receiving autonomic regulation therapy in the ANTHEM-HF study. *Journal of Cardiac Failure, 22*(8), 639–642. https://doi.org/10.1016/j.cardfail.2015.11.002

Premchand, R. K., Sharma, K., Mittal, S., Monteiro, R., Libbus, I. DiCarlo, L., … Anand, I. (2019). Long-term follow-up of reduced ejection fraction heart failure patients receiving autonomic regulation therapy in the ANTHEM-HF pilot study. *Journal of the American College of Cardiology, 73*(9 Suppl. 1), 770. https://doi.org/10.1016/S0735-1097(19)31378-6

Tolley, H. D., Barnes, J. M., & Freeman, M. D. (2016). Survival analysis. In M. D. Freeman & M. P. Zeegers (Eds.), *Forensic epidemiology: Principles and practice* (pp. 261–284). London, UK: Elsevier Inc.

Received: February 24, 2020
Accepted: March 18, 2020
Published: March 25, 2020

NeuroRegulation

Protocol for a Pilot Randomized Sham-Controlled Clinical Trial Evaluating the Feasibility, Safety, and Acceptability of Infraslow Electroencephalography Neurofeedback Training on Experimental and Clinical Pain Outcomes in People with Chronic Painful Knee Osteoarthritis

Jerin Mathew[1], Divya Bharatkumar Adhia[2], Mark Llewellyn Smith[3], Dirk De Ridder[2], and Ramakrishnan Mani[1]*

[1]School of Physiotherapy, University of Otago, Dunedin, New Zealand
[2]Dunedin School of Medicine, University of Otago, Dunedin, New Zealand
[3]Neurofeedback Services of New York, New York, USA

Abstract

Introduction: Persistent pain is a significant contributor to disability in people living with knee osteoarthritis (KOA). Brain imaging, including electrophysiological studies, confirms altered cortical oscillatory and synchrony patterns in cognitive, affective, and somatosensory areas in individuals with KOA pain. Electroencephalography neurofeedback (EEG-NF) training is a form of neuromodulatory intervention that can help to reduce pain via normalizing dysrhythmic cortical oscillatory patterns that are linked to the pain experience. However, there is a dearth of evidence towards the efficacy of NF in individuals with musculoskeletal pain. **Aim:** The proposed research is intended to pilot the NF training protocol and assess the feasibility, safety, and acceptability of NF training in individuals with KOA and estimate the variability of experimental and clinical outcome measures following NF training. **Design:** A parallel, two-armed, double-blind (participant and assessor) pilot randomized sham-controlled clinical trial. **Methods:** Adults aged 44–75 years with a clinical diagnosis of KOA will be recruited and randomized to either active or sham EEG-NF training. Both groups will receive auditory feedback as a reward for achieving a predetermined activity threshold of the target areas of the brain. Outcome measures include feasibility measures (recruitment, randomization, retention, and dropout rates), acceptability, and adverse events; clinical measures (pain, interference, sleep, mood, and physical activity); and experimental pain outcomes (quantitative sensory testing procedures). **Discussion:** Outcomes from this study will inform the feasibility and methodology for a future randomized controlled clinical trial.

Keywords: EEG-neurofeedback; chronic pain; brain training; knee pain; osteoarthritis

Citation: Mathew, J., Adhia, D. B., Smith, M. L., De Ridder, D., & Mani, R. (2020). Protocol for a pilot randomized sham-controlled clinical trial evaluating the feasibility, safety, and acceptability of infraslow electroencephalography neurofeedback training on experimental and clinical pain outcomes in people with chronic painful knee osteoarthritis. *NeuroRegulation*, *7*(1), 30–44. https://doi.org/10.15540/nr.7.1.30

***Address correspondence to**: Jerin Mathew, Centre for Health, Activity, and Rehabilitation Research, School of Physiotherapy, University of Otago, 325 Great King Street, Dunedin Central, New Zealand – 9016. Email: jerin.mathew@postgrad.otago.ac.nz / jerinmathew65@gmail.com

Edited by:
Rex L. Cannon, PhD, SPESA Research Institute, Knoxville, Tennessee, USA

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

Introduction

Persistent pain is a significant contributor to disability in people living with knee osteoarthritis (KOA); a highly prevalent, chronic degenerative condition (Abbott, Usiskin, Wilson, Hansen, & Losina, 2017; Bajaj, Bajaj, Graven-Nielsen, & Arendt-Nielsen, 2001). Globally and in New Zealand, hip and knee

osteoarthritis is ranked as the 38th highest in disability-adjusted life years (DALYs) (Cross et al., 2014; Deloitte Access Economics, 2018). It is a significant burden with one in six New Zealanders affected by arthritis; 56% with the knee joint registering a higher incidence (approximately 7,000 in 2013) than the hip or any other peripheral joints.

The pathophysiology of pain due to OA changes are not fully elucidated; however, the primary triggers of nociception have been linked to synovial inflammation and bone marrow edema (Kidd, 2012). Central sensitization of pain is commonly associated with persistent musculoskeletal (MSK) pain including KOA (Woolf, 2011). Studies utilizing quantitative sensory testing observed neuropathic pain-like symptoms (pain hypersensitivity) and dysfunctional conditioned pain modulation (i.e., impaired descending nociceptive modulation) in patients with KOA (Fingleton, Smart, Moloney, Fullen, & Doody, 2015; Foucher, Chmell, & Courtney, 2019). Such symptoms suggested abnormal nociceptive processing (i.e., central sensitization) within the central nervous system (Kidd, 2012; Lee, Nassikas, & Clauw, 2011; Lluch, Torres, Nijs, & Van Oosterwijck, 2014; Martindale, Wilson, Reeve, Chessell, & Headley, 2007; Woolf, 2011). Brain imaging studies demonstrate alterations in the structural and functional organizations within the cortical and subcortical networks in various persistent pain conditions (Cottam, Iwabuchi, Drabek, Reckziegel, & Auer, 2018; Gwilym et al., 2009; Parksl et al., 2011). Such alterations have been proposed as a key factor for the maintenance of persistent pain states (Pinheiro et al., 2016; Pujol et al., 2017).

More recently, electroencephalography (EEG)-based investigations suggest that alterations in the oscillatory and synchrony of the cortical electrical activity patterns are associated with pain processing in patients with KOA (Howard et al., 2012; Ploner, Sorg, & Gross, 2017). In particular, increased amplitudes in the theta and delta frequency bands, and a corresponding decrease in the alpha and beta amplitudes, in patients with hip OA have been demonstrated (Gram et al., 2017; Pujol et al., 2017). Notably, a recent study on pain sensitization in patients with KOA demonstrates the activation of key sensory areas (primary and secondary somatosensory cortex [SSC], the posterior insula, and thalamus) and the cognitive (e.g., prefrontal lobe) and emotional areas (anterior insula [AI], anterior cingulate cortex [ACC]) of the brain (Pujol et al., 2017). Particularly, the SSC, dorsal ACC (dACC), and pregenual ACC (pgACC) are linked to the effective functioning of the descending nociceptive modulatory system via activation of brainstem centers such as periaqueductal gray (PAG), and rostral ventromedial medulla (RVM) (Brown, El-Deredy, & Jones, 2014; Osaka, Osaka, Morishita, Kondo, & Fukuyama, 2004; Tracey & Mantyh, 2007; Vanneste, Ost, Van Havenbergh, & De Ridder, 2017; Vogt, 2005).

Normalizing abnormal cortical electrical activities have been proposed as a treatment for pain (Brown et al., 2014; Ploner et al., 2017; Tracey & Mantyh, 2007; Vanneste et al., 2017). Neurofeedback (NF) is a form of noninvasive neuromodulatory technique developed for augmenting or reducing brain activity patterns that are linked to disease states (Gaume, Vialatte, Mora-Sánchez, Ramdani, & Vialatte, 2016; Hammond, 2011). NF works under the principle of operant conditioning in which a goal-directed process of modulating one's brain signals through feedback-induced learning (Collura & Thatcher, 2011). EEG-NF is a technique designed to provide feedback on the real-time brain activity to individuals for controlling the activity of critical areas of the brain involved in a disease state. NF treatment protocols can be designed either to upregulate or downregulate the oscillations at the targeted cortical networks. Several studies have investigated the clinical effectiveness of EEG-based NF in various populations include headaches, complex regional pain syndromes (CRPS-1), chemotherapy-induced peripheral neuropathy (CIPN), central neuropathic pain in paraplegia, fibromyalgia, postoperative pain, and cancer pain (Gorini, Marzorati, Casiraghi, Spaggiari, & Pravettoni, 2015; Hassan, Fraser, Conway, Allan, & Vuckovic, 2015; Jensen, Grierson, Tracy-Smith, Bacigalupi, & Othmer, 2007; Prinsloo et al., 2018; Santoro & Cronan, 2014). These studies generally used protocols to upregulate frequencies in the higher ranges (12–15 Hz) and inhibit theta (4–7 Hz) and high beta (22–30 Hz) for reducing pain severity (Santoro & Cronan, 2014). Moreover, recent studies highlight the infraslow fluctuations (ISF) which are below 0.1 Hz across brain areas and are linked with pain experience (Ploner et al., 2017). Preclinical research highlights that the infraslow fluctuations (ISF) have the ability to influence higher oscillations at alpha and gamma frequency bands associated with persistent pain conditions (Mantini, Perrucci, Del Gratta, Romani, & Corbetta, 2007; Monto, Palva, Voipio, & Palva, 2008). Infraslow fluctuation neurofeedback (ISF-NF) is a recent development in EEG-NF training, focusing on modulating slow-wave activity (0.0–0.1 Hz). Some potential therapeutic effects of ISF-NF have been established on food craving, targeting the

posterior cingulate cortex (PCC) of the brain (Leong et al., 2018).

Pain modulation involves the dynamic interaction of a complex neuronal network of multiple functional areas of the brain. This enhances a balance between the sensory discriminative, motivational affective, and descending hubs of pain neurophysiological network (Vanneste et al., 2017). Various neurofeedback protocols have been established to target individual areas of the brain instead of targeting multiple areas of the brain. We hypothesize that using a novel ISF-NF protocol that can simultaneously downregulate the electrical activities of SSC, dACC and upregulate the pgACC could reduce both experimental and clinical pain measures in people with persistent KOA pain. To date, no ISF-NF clinical trial has been performed for any MSK pain conditions. Since the proposed ISF-NF training protocol is novel, a pilot testing of the protocol including assessing the feasibility, safety, and acceptability of ISF-NF training in individuals with KOA is warranted. Therefore, the objectives of the study are:

1. To pilot a novel ISF-NF training protocol targeting three key cortical areas associated with pain modulation in individuals with KOA.
2. To assess the feasibility, safety, and acceptability of ISF-NF training in individuals with KOA.
3. To estimate the variability of experimental and clinical outcome measures following ISF-NF training to inform the sample size of the fully powered randomized controlled trial (RCT).

Methods

Study Design

This is a pilot RCT involving randomization, double-blinding (participant and assessor), two-arm, parallel, sham-controlled trial. A research administrator, not involved in any treatment or assessment procedures, will randomize eligible volunteers using an open-access randomization software program, to receive either ISF-NF or sham ISF-NF. Methodological descriptions of this study followed the CONSORT 2010 checklist for reporting feasibility trial (Eldridge et al., 2016). A well-structured description of the study intervention is summarized in Table 1 based on the TIDieR (Template for Intervention Description and Replication) guide (Hoffmann et al., 2014). Ethical approval has been obtained from the Health & Disability Ethics Committee (HDEC), New Zealand (19CEN182) and the Ngāi Tahu Research Consultation Committee was consulted. The trial has been registered with Australian New Zealand Clinical Trials Registry (ACTRN12620000273987).

Table 1
Description of ISF-NF intervention, as per the template for intervention description and replication.

Item Number	Item	Description
1	**BRIEF NAME** Provide the name or a phrase that describes the intervention.	Neurofeedback training for Osteoarthritic Knee Pain
2	**WHY** Describe any rationale, theory, or goal of the elements essential to the intervention.	Patients with persistent KOA pain have demonstrated altered cortical neuronal higher frequency oscillations in pain neuromatrix that are associated with dysfunctional pain modulation. ISF below 0.1 Hz across brain areas are capable of shaping the higher oscillations at alpha (8–12 Hz) and gamma (> 30 Hz) and expected to normalize neuronal oscillations. Therefore, ISF-NF is believed to be an effective intervention to achieve normalization of altered cortical oscillations with persistent MSK pain, thereby improving clinical/experimental pain outcomes.

Item Number	Item	Description
3	**WHAT** **Materials:** Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or training of intervention providers. Provide information on where the materials can be accessed (e.g., online appendix, URL).	An ISF-NF training program will be administered with a 21-channel DC-coupled amplifier produced by BrainMaster Technologies, Inc. An EEG cap with sensors (Ag/AgCl) will be fixed to the individual's scalp, with reference electrodes placed at the mastoids.
4	**Procedures:** Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities.	Participants will be asked to sit on a chair in an upright position with back supported and relaxed for 10 min. Both ISF-NF and sham ISF-NF will be implemented with a 21-channel DC-coupled amplifier produced by BrainMaster Technologies, Inc. The Comby EEG lead cap with sensors (Ag/AgCl) will be fixed to the individual's scalp, with reference electrodes placed at the mastoids. The impedance of the active electrodes will be monitored through the amplifier and will be kept less than 5 kΩ. Before the commencement of the training, participants will be instructed to close their eyes, relax, and listen to the sound being played. The participants will also be emphasized to minimize eyeball movement, head and neck movements, swallowing, and clenching of teeth to avoid motion artifact in EEG. A distinct tone will be played when the participant's brain activity meets infraslow magnitude at the SSC, dACC, and pgACC. Conditions for the sham ISF-NF group will be exactly the same as ISF-NF group except the participants will receive feedback according to someone else's prerecorded session.
5	**WHO PROVIDED** For each category of intervention provider (e.g., psychologist, nursing assistant), describe their expertise, background, and any specific training given.	A postgraduate student with a physiotherapy background; adequately trained to provide NF intervention.
6	**HOW** Describe the modes of delivery (e.g., face to face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group.	Each participant will receive face to face ISF-NF training.
7	**WHERE** Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features.	The intervention will be delivered in the School of Physiotherapy, University of Otago.

Item Number	Item	Description
8	**WHEN and HOW MUCH** Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity, or dose.	All participants either in ISF-NF or sham ISF-NF will be required to attend nine sessions (30-min each; three sessions per week; 3 consecutive weeks) of training. Assessment of clinical and EEG outcomes will be carried out at two separate sessions of 90-min duration; baseline (S1) and immediately following the final treatment session (S11).
9	**TAILORING** If the intervention was planned to be personalized, titrated, or adapted, then describe what, why, when, and how.	Intervention is personalized. All the participants will receive auditory feedback based on their real-time cortical activity recorded during the NF training. If required, manual NF threshold adjustments will be done based on the real-time electrical activity of each participant, for each session.
10	**MODIFICATIONS** If the intervention was modified during the course of the study, describe the changes (what, why, when, and how).	Not applicable. This is a protocol.
11	**HOW WELL** **Planned:** If intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them.	Intervention adherence will be maintained across each participant for every session; for both the groups. All the participants will undergo nine sessions of NF training for 30 min. The NF program is default set for 30 min of training.
12	**Actual:** If intervention adherence or fidelity was assessed, describe the extent to which the intervention was delivered as planned.	Not applicable. This is a protocol.

Sampling and Recruitment Strategy

Convenience sampling technique will be used to recruit participants from the Dunedin community. Periodic advertising in newspapers and social networking sites, including emails to the staff of the University of Otago, will be carried out. Patients attending primary care medical or physiotherapy practices will be invited to participate in the study. Interested volunteers will contact the primary researcher via telephone or e-mail for screening and participation. Figure 1 represents a detailed study flow chart.

Sample Size Estimation

Since this is a pilot/feasibility study, sample size was not determined.

Participants

Adults aged 44–75 years, with a clinical diagnosis of KOA; with pain (at least ≥ 4 on an 11-point numerical rating scale) for a minimum duration of 3 months will be eligible to participate in the study (Bartley et al., 2016; Fingleton et al., 2015; Goggins, Baker, & Felson, 2005).

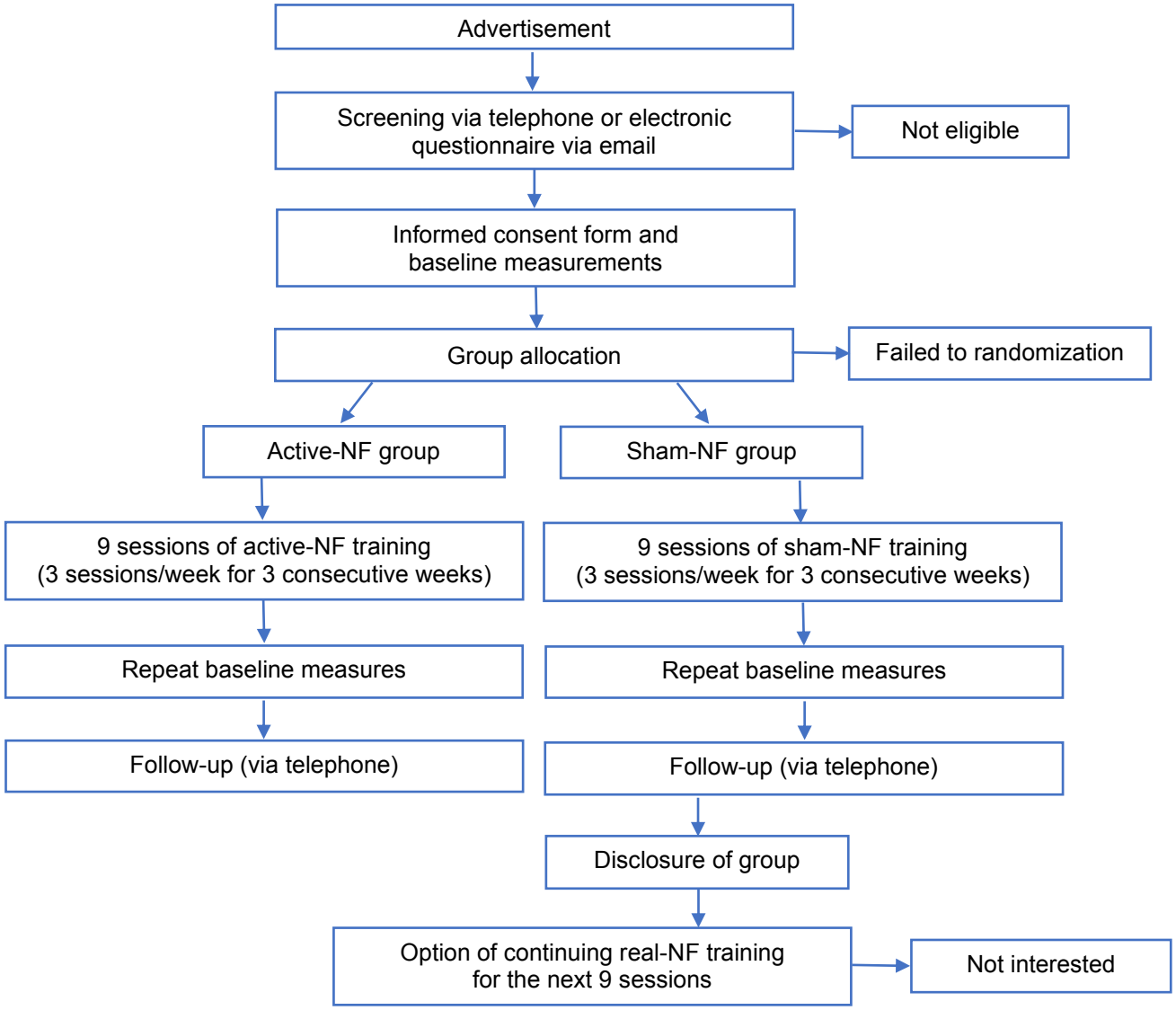

Figure 1. Diagram of participant flow for the study

The participants will be excluded if they have one of the following situations or conditions: (1) underwent surgery or other invasive procedures in the last 6 months and any surgical procedures scheduled within 8 weeks after screening; (2) undertaken any steroid injections to the knee joint in the past 3 months or on oral steroids in the previous month; (3) current intake of centrally acting medications (e.g., antidepressants, anticonvulsants, neuropathic pain drugs) or intention of taking new medications in the next 8 weeks; (4) neurological conditions or diseases (brain, spinal cord or peripheral nerve injuries, radiculopathy, and neuropathies); (5) soft tissue injuries of the knee (e.g., meniscus, muscle, tendon, or ligament injury) in the last 3 months; (6) cognitive impairments (dementia, posttraumatic stress disorders, Alzheimer's disease); (7) difficulty or inability to read or understand English, or provide informed consent: (8) hearing problems (hearing loss, tinnitus) and ear infections; (9) pregnancy or 6 months postlabor.

Confirmative Screening

A paper-based Mini-Mental State Examination (MMSE) will be carried out for screening volunteers with cognitive impairments. The maximum MMSE is scored out of 30 points, and volunteers scoring a total score of 24 or below will be excluded from the study (Mani, Adhia, Leong, Vanneste, & De Ridder, 2019;

Pottie et al., 2016). Written consent will be obtained from the eligible participants. Eligible participants will be required to attend nine sessions (30 min; three sessions/week) of NF treatment (Leong et al., 2018) at the School of Physiotherapy and two 90-min sessions for undergoing baseline (S1) and postintervention assessments (S11). Participants will require to refrain from alcohol and caffeinated drinks for 24 hours prior and from food and drinks for at least one hour respectively, prior to any assessment sessions (Jobert et al., 2012).

Baseline Assessment

Participants will complete questionnaires including demographics and general health-related information. Assessment of resting-state EEG and the clinical and experimental pain outcomes will be conducted by an independent researcher, blinded to group allocation. Resting-state EEG will be recorded using Mitsar EEG system with WinEEG software. The recording will be done for 10 min with participants' eyes closed, and the participants will be instructed to avoid any facial movements, head and neck movements, and swallowing to minimize potential artifact in the EEG recordings. At the baseline assessment, the following constructs will be measured using validated questionnaires.

Neuropathic Pain Component. The painDETECT questionnaire (PD-Q) will be used to identify the presence of a neuropathic pain component in their knee. The chosen tool was found to have the face and content validity for use in older individuals with KOA. The questionnaire consists of 12 items that measure pain quality rated on a 5-point Likert scale (1 = *never* to 5 = *very strongly*), pain radiation from the primary area of pain (*yes* or *no*), and pain course pattern (scored from −1 to 2). The total score ranges from −1 to 38 points with a score of ≥ 19 indicative of a likely neuropathic pain (≤ 12: nociceptive pain and 13–18: possible neuropathic pain component [or mixed type]; Freynhagen, Tölle, Gockel, & Baron, 2016; Mani et al., 2019).

Sleep. Sleep disturbance and quality will be measured using the Pittsburgh Sleep Quality Index (PSQI), a valid and reliable index for evaluating sleep quality in patients with arthritis. The PSQI consists of seven components: subjective sleep quality (one item), sleep latency (two items), sleep duration (one item), habitual sleep efficiency (three items), sleep disturbances (nine items), use of sleeping medications (one item), and daytime dysfunction (two items). The response options vary with different items. The overall score range is 0 to 21 points, with higher scores indicating better sleep quality (Omachi, 2011).

Coping Strategies. A brief version (14 items) of the Coping Strategies Questionnaire (CSQ) will be used to score various pain coping strategies used by the participant. A 14-item scale is scored on a 0 to 6 scale, representing the frequency of seven pain coping strategies (adaptive strategies: Diverting Attention, Reinterpreting Pain Sensations, Ignoring Sensations, Coping Self-Statements, Increased Behavioral Activities; maladaptive strategies: Catastrophizing, Praying and Hoping). CSQ is considered to be a valid and reliable toot to use in KOA (Alschuler, Molton, Jensen, & Riddle, 2013).

Fears and Beliefs. The fear and beliefs concerning knee OA will be recorded on an 11-item Knee Osteoarthritis Fears and Beliefs Questionnaire (KOFBeQ) using a 10-point Likert scale (0 = *totally agree* to 9 = *totally disagree*). Higher scores indicate substantial fears and beliefs. KOFBeQ has demonstrated good test–retest reliability with an ICC of 0.81 (Benhamou et al., 2013).

Brief Resilience Scale (BRS). BRS is a six-item reliable and valid measure of one's ability to bounce back from stress. The BRS is scored by reverse coding items 2, 4, and 6 and finding the mean of the six items. The following instructions are used to administer the scale: "Please indicate the extent to which you agree with each of the following statements by using the following scale: 1 = *strongly disagree*, 2 = *disagree*, 3 = *neutral*, 4 = *agree*, 5 = *strongly agree*" (Windle, Bennett, & Noyes, 2011).

Self-efficacy. A two-item Pain Self-Efficacy (PSE) scale will be used to rate the confidence of the participant on a 7-point scale, with 0 = *not at all confident* and 6 = *completely confident* (Nicholas, 2007).

Pain Catastrophizing Scale (PCS). The PCS will be used to measure the extent of catastrophic thoughts about the pain. The tool consists of 13 items rated on a 5-point Likert scale that measures three dimensions of catastrophizing; rumination, magnification, and helplessness. The total score ranges from 0 to 52, where higher scores indicate greater levels of catastrophic thoughts about pain (Severeijns, Vlaeyen, van den Hout, & Weber, 2001).

Depression, Stress, and Anxiety. A 21-item Depression, Anxiety, and Stress Scale (DASS-21) will be used to measure three psychological constructs:

depression, anxiety, and stress over the past week. The items will be rated on a 4-point Likert scale, with a higher score indicating higher levels of depression, anxiety, and stress (Wood, Nicholas, Blyth, Asghari, & Gibson, 2010).

Central Sensitization. Symptoms of central sensitization will be evaluated by using Central Sensitization Inventory (CSI) questionnaire. The CSI consists of two parts—part A assesses 25 health-related symptoms common to central sensitivity syndromes, with a total score ranging from 0 to 100, and part B (is not scored) asks about previous diagnoses of one or more specific disorders, including central sensitivity syndromes (Mani et al., 2019).

Level of Motivation. The level of motivation with the training will be measured using an adapted version of the Questionnaire for Current Motivation-Brain Commuter Interference (QCM-BCI) recorded on a 7-point Likert scale. Participants will rate items that assess four different components of motivation: (1) *mastery confidence*, which indicates how much confidence a participant had that the training would be successful, (2) *fear of incompetence*, which indicates how much a participant feared to fail in the training, (3) *interest*, which indicates how interested the participant was in the training, and (4) *challenge*, which indicates how challenging the participant considered the training. The tool holds acceptable psychometric characteristics and widely used in BCI-incorporated research.

The following constructs will be measured at every training session.

Mood. The mood of the participant will be measured before every NF session using a single item of Brief Mood Introspection Scale (BMIS). The overall mood of the participant will be rated on a 21-point numeric scale, with 0 being in the center. Marking of 0–10 towards right-hand side rates *very pleasant* and 0–10 towards left-hand side rates *very unpleasant*. Cronbach's alpha reliabilities of BMIS range from 0.76 to 0.83, which was deemed to be quite satisfactory. The scale was also found to have good factor validity (Kokkonen & Pulkkinen, 2001; Mayer & Gaschke, 1988).

Visual Analogue Scale (VAS) Motivation. Participants will be asked to indicate their motivation on a 10 cm long horizontal line (0 = *extremely unmotivated* and 10 = *extremely motivated*) prior to every NF session (Kleih & Kubler, 2013; Kleih et al., 2011).

Level of Engagement. The level of engagement with the NF training session will be recorded from each participant on a 10-point Likert scale after every NF session, where 1 = *least engaged* and 10 = *highly engaged*.

Randomization and Allocation Concealment

On the day of eligibility confirmation, a research administrator will randomize eligible volunteers using an open-access randomization software program, to receive either ISF-NF or sham ISF-NF. In order to ascertain an equal number of participants in both groups and decrease allocation bias, the concealed allocation will be done using block randomization. The administrator will prepare opaque sealed randomization envelopes containing the information for the participant regarding the allocation group and details. The envelope will be given to the participant by the assessor after the completion of the baseline assessment. Both the participants and the outcome assessor will be blinded to the group allocation.

Interventions

During each session, participants will be asked to sit on a chair with back supported and relaxed for 10 min, which allows the trainer to prepare the participant for NF training. Both ISF-NF and sham ISF-NF will be administered using a 21-channel DC-coupled amplifier produced by BrainMaster Technologies, Inc. The Comby EEG lead cap with sensors (Ag/AgCl) will be fixed to the individual's scalp, with reference electrodes placed at the mastoids (Leong et al., 2018; Figure 2).

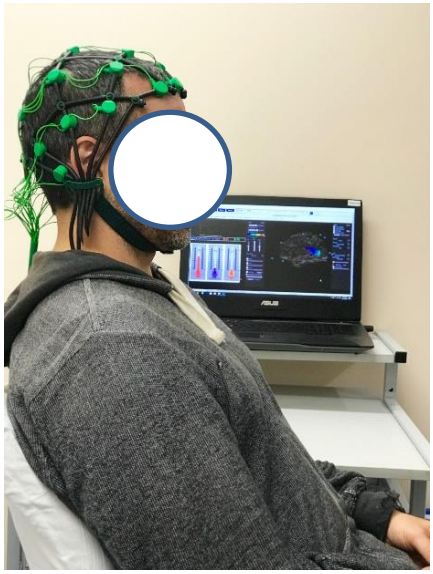

Figure 2 Intervention setup

The impedance of the active electrodes will be monitored and kept below 5 kΩ. The participants will also be emphasized to minimize eyeball movement, head and neck movements, swallowing, and clenching of teeth to minimize motion artifact in EEG.

ISNF-NF Groups

Participants will be instructed to close their eyes, relax, and listen to the sound being played. A distinct tone will be played when the participant's brain activity meets ISF (0.0–0.1 Hz) magnitude (threshold) at the following cortical areas of the brain defined as regions of interest (ROI): SSC, dACC, and pgACC. The brain regions are chosen based on brain imaging studies on KOA and previous NF studies (Gram et al., 2017; Gwilym et al., 2009; Howard et al., 2012; Ploner et al., 2017; Pujol et al., 2017; Vogt, 2005). For the purpose of this study, the authors developed an ISF-NF program to down-train SSC and dACC activity, simultaneously with the up-training of pgACC. Efforts will be made to keep the reward threshold in real-time between 60% and 80%. In other words, for 60% to 80% of the time, a sound will be played (reward) when the participant's brain activity meets the infraslow magnitude (threshold). The chosen 60% to 80% reinforcement schedule for this study was decided based on the insights from our previous study (Leong et al., 2018) and the author's clinical experience. Reaching a predetermined threshold brain activity (activities) is a response and the reinforcement to reach the threshold is the auditory stimulus. The auditory stimulus will be delivered within 30 milliseconds when the activity threshold is met (upregulation of pgACC and downregulation of SSC and dACC). However, further improvement in the response would be dependent on how the participant responds to the reinforcement.

Standardized low-resolution brain electromagnetic tomography (sLORETA) source localization permits the section of any region of the brain for feedback on the current density (Vanneste, Joos, Ost, & De Ridder, 2018). A center voxel for each ROI is given in Table 2; where dACC and pgACC are designer ROIs and SSC ROI is made up of Brodmann areas 1, 2, 3, and 5, as defined by the Montreal Neurological Institute (MNI) coordinate database (Fuchs, Kastner, Wagner, Hawes, & Ebersole, 2002; Jurcak, Tsuzuki, & Dan, 2007).

Table 2

Centre voxel coordinates for the somatosensory cortex (SSC), pregenual anterior cingulate cortex (pgACC), and dorsal anterior cingulate cortex (dACC).

		X	Y	Z
SSC				
	Right	53	−22	49
	Left	−53	−22	49
pgACC				
	Right	4	41	36
	Left	−4	41	36
dACC				
	Right	4	6	38
	Left	−4	6	38

Sham ISF-NF Group

Conditions for the sham ISF-NF group will be the same as ISF-NF group except the participants will receive feedback according to someone else's prerecorded session. To ensure this, we have trained healthy participants with an active NF program for nine sessions, and we captured the feedback sound using Audacity software, which is a free and open-source digital audio editor and recording application (Maheshkumar, Dilara, Maruthy, & Sundareswaren, 2016). Participants in the sham ISF-NF will be prepared as same as ISF-NF group, and they will receive these prerecorded feedback sounds. This process has been incorporated in order to record the real-time EEG of the participants undergoing NF training in the sham group. The Audacity software uses the computer's sound card as an audio to digital (A/D) converter and eliminates the additional requirement of an external microprocessor (Maheshkumar et al., 2016). The software has many offline editing options which could be used to draw the precise percent success of the participant during the training and average time of the feedback received by the participant during each training. The prerecorded signals will be selected randomly by the chit method form a set of nine files.

Outcome Measures

Primary Outcomes

The primary outcomes are feasibility measures and adverse events (Bowen et al., 2009; Tickle-Degnen, 2013). Feasibility outcomes from this trial include (1) recruitment rate (number of participants attending screening assessment), (2) randomization rate (a ratio of the number of participants willing to be randomized into the trial from amongst those eligible will be expressed), (3) retention rate (number of sessions attended by the participant), and (4) dropout rate (number of dropouts in each group). An adverse effect is described as any harmful sign, or symptom resulting from the trial, which could reasonably be related to the procedure. Although EEG-NF is a safe technique, participants will be asked about any adverse effects experienced from the previous session at each visit. All the participants will be instructed to complete a Discontinuation-Emergent Sign and Symptom (DESS) inventory. The DESS is a checklist of 43 symptoms, consisting of emotional, behavioral, cognitive, and physical conditions that can be considered possible side effects from NF training. The participant will report the worsening of side effects compared to the status prior to the first session. They will report "1" if the side effect worsened or a "0" if there is no change in the symptom (Rogel et al., 2015). All the participants will be asked, "Which condition do you think you received?'' at the end of the third training session every week (Leong et al., 2018). Acceptability of the NF training as an intervention will be measured in the follow-up assessment (Sekhon, Cartwright, & Francis, 2017).

Secondary Clinical Outcome Measures

The following pain, function, psychological, social, and behavioral constructs will be collected using validated questionnaires by a researcher blinded to the groups. The multidimensional constructs were chosen based on the biopsychosocial model of pain literature.

Pain Intensity and Interference. Brief Pain Inventory (BPI) is a valid and reliable questionnaire developed to measure the severity of pain and the impact (interference) of pain on daily functions. BPI includes three pain severity items (pain worst, pain average, and pain now) and the seven interference items (how pain interferes with activity, mood, relations with others, walking ability, work, enjoyment of life, and sleep) rated on an 11-point (0 to 10) numeric scale (Keller et al., 2004; Mendoza, Mayne, Rublee, & Cleeland, 2006).

Pain Unpleasantness. (Affective component) will be measured using an 11-point VAS-unpleasantness scale, with 0 = *not at all pleasant* and 10 = *most unpleasant imaginable* (Price, Bush, Long, & Harkins, 1994; Starr et al., 2011).

Pain Bothersomeness. Participants will be asked about the bothersomeness of their knee pain with a categorical question:

> "In the last one week, how bothersome has your knee pain been?''
>
> "In the last 24 hours, how bothersome has your knee pain been?''

Here will be five possible responses: *not at all*, *slightly*, *moderately*, *very much*, and *extremely*. The bothersome domain is modified and incorporated from outcome measures in low back pain (Dunn & Croft, 2005; Price, McGrath, Rafii, & Buckingham, 1983).

Physical Function, Physical Activity, and Participation. Knee injury and Osteoarthritis Outcome Score (KOOS) is a 42-item self-reported questionnaire that has five reported dimensions: pain (9 items), other symptoms (7 items), function in daily living (17 items), function in sport and recreation (5 items), and knee-related quality of life (4 items). The scoring system of the KOOS utilizes a 5-point Likert scale, with anchors of zero (*no problems*) to 4 (*extreme problems*). Scores are transformed to a 0 to 100 scale, with zero representing extreme knee problems and 100 representing no knee problems. This transformed score is calculated using the following formula: 100 − [(actual raw score × 100) / possible raw score range]. KOOS holds clinically acceptable psychometric properties (Peer & Lane, 2013). Physical activity levels, sedentary behaviour, and social participation will be captured using validated questionnaires.

Physical Performance Measure. Based on the Osteoarthritis Research Society International (OARSI) recommendations a 30-s chair stand test will be performed for every participant. The maximum number of chair stand repetitions possible in a 30-s period will be noted (Dobson et al., 2013).

Experimental Pain Outcomes Measures

The following quantitative sensory testing (QST), and activity-related pain protocols including tactile acuity and body schema assessments will be performed. All

these experimental pain and sensory outcomes will be measured in S1 and S11.

Pressure Pain Threshold (PPT). A computerized algometer (AlgoMed; Medoc Ramat Yishai, Israel) will be used for measuring PPT at the most symptomatic region over the symptomatic knee and over the dorsal distal forearm. Two familiarization trials will be performed at the mid-forearm before the formal trials. The 1-cm^2 algometer probe will be pressed over the marked test sites perpendicularly to the skin at a rate of 30 kPa/s. The participants will be instructed to press the algometer trigger button in the patient control unit when the pressure sensation changed to first sensation of pain. PPT will be measured thrice at each location and the mean of three measurements will be used for the analysis. Familiarization trial will be carried out on the forearm of the participant (Rolke et al., 2006).

Mechanical Temporal Summation (MTS). MTS will be assessed using a nylon monofilament (Semmens monofilament 6.65, 300 g) at the patella of the index knee and the back of the ipsilateral hand, in randomized order. Participants will be instructed to provide a verbal 0–100 (NRS) rating of pain following a single contact of the monofilament on the test site. Subsequently, participants will be instructed to provide another 0–100 rating of their highest pain intensity experience following a series of 10 contacts with an interstimulus interval (ISI) of 1 s (one contact per second). This procedure will be repeated thrice at each anatomical location. For each trial, MTS will be calculated as the difference between the NRS rating after the first contact and the highest pain rating after the 10th contact. An average of the three trials will be taken for pain rating, with a positive score indicating an increase in MTS (Goodin et al., 2014; Mani et al., 2019).

Conditioned Pain Modulation (CPM). Studies have demonstrated disruption of descending pain inhibition in individuals with persistent OA pain. Conditioned pain modulation (CPM) is a method of examining pain inhibitory mechanisms, by applying a noxious stimulus at a remote site, that causes inhibition of pain at the affected knee. Recent recommendations on the practice of CPM testing will be followed after 15 to 20 minutes of MTS procedure. Suprathreshold (pain40) PPT will be measured at the painful knee using a 1 cm^2 probe, applied at a rate of 30 kP/s until the participant reported a change from the pressure to a pain intensity of 40 out of 100 on the NRS. The pressure threshold at which the subject reported pain will be recorded and the average PPT from three trials will be calculated, with a 30-s time interval between trials. CPM will be established using a cold pressor test on the contralateral hand of the painful knee. The participant will be instructed to immerse their hand up to the wrist crease in a circulated cold water bath, maintained at the temperature at ~6 ± 1°C, for a maximum period of 2 minutes. The participant will report their pain intensity on NRS during immersion (every 15 s) and immediately after removing the hand from the cold bath. Total immersion time will be recorded. Three PPT (P40) trails will be measured at 30, 60, and 90 seconds after immersing the hand. A percentage score will be established for each time point of CPM measurement with a positive score indicating an increase in PPTs (pain4) after the conditioning stimulus and thus presence of CPM effect (Lewis, Luke, Rice Rome, & McNair, 2012; Mani et al., 2019; Nir & Yarnitsky, 2015; Yarnitsky et al., 2015). Participants with cardiovascular conditions, cold-sensitive conditions, and peripheral vascular diseases (PVD), involving the extremities will refrain from CPM testing.

Cold Hyperalgesia. Sensitivity to cold will be tested by massaging the knee area with an ice cube, for 30 s. Following, the participants will be asked to rate their pain on a 100 mm pain VAS, with 0 mm indicative of no pain at all and 100 mm indicative of the worst pain imaginable (Tilley & Bisset, 2017).

Vibration Detection Threshold (VDT). Ability to detect vibration will be tested using a tuning fork (64 Hz, 8/8 scale) placed on the medial tibial condyle with suprathreshold vibration intensity and kept there until the participant could no longer feel the vibration. On a 0 to 8 scale measuring the intensity of vibration, with high intensity indicating high sensitivity. The VDT will be determined as the arithmetic mean of three consecutive measurements (Jakorinne, Haanpää, & Arokoski, 2018; Panosyan, Mountain, Reilly, Shy, & Herrmann, 2016).

Tactile Acuity. Repeated light touches of a blunt tip plastic caliper tool, increasing and decreasing the distance (in mm) of two points to determine the two-point discrimination threshold (TPD). TPD is defined as the shortest distance between caliper points at which the participant could clearly detect two points instead of one. TPD will be measured 2 cm medial of the medial border of the patella (using the tibiofemoral joint line as a reference point; Stanton et al., 2013).

Body Part Recognition Task. An iPad/tablet application (Recognise) will be used to record the performance accuracy on determining the left and

right judgment of the image (a body part) appears on the screen. Participants will be required to perform the task as quickly and as accurately as possible. Accuracy of the judgment will be computed in percentage and will be generated by the software, with three trials (Stanton et al., 2013).

Sensitivity to Physical Activity (SPA). Literature has highlighted the importance of activity-related pain among individuals suffering from KOA. Commonly, the SPA is associated with weight-bearing activities like walking and stair climbing. A 6-min walk test (6MWT) will be performed to evaluate the level of knee discomfort on a 0 (no discomfort) to 100 (extreme discomfort) numeric scale. This is believed to capture a wider range of unpleasant activity related to sensation, not limited to pain sensation. Participants will be instructed to cover as many laps as they can walk in 6 min. Participants will be asked to rate their discomfort seven times in relation to each walking task, once immediately before the task and once after each minute of walking. An index of SPA will be calculated by subtracting participants' first ratings from their peak ratings for each trial (S1 and S11). SPA scores will then be averaged across both trials (Wideman et al., 2014).

Follow-up

All the participants will be contacted by phone call or email (mode preferred by the participant) after 2 weeks of the final assessment and pain intensity (BPI), pain bothersomeness, pain unpleasantness (VAS) and status with the adverse events (if any on DESS) will be recorded.

Data Analysis

Feasibility, acceptability, and adverse events over the NF will be summarized descriptively. Means and standard deviations (or medians) of the clinical (pain and function) and experimental outcome measures (PPT, MTS, CPM) for each group will be derived.

Standardized low-resolution brain electromagnetic tomography (sLORETA) software will be used to perform a voxel-by-voxel analysis (comprising 6239 voxels) for the different frequency bands of the current density distribution to identify potential differences in brain electrical activity. Nonparametric statistical analyses of functional sLORETA images (statistical nonparametric mapping: SnPM) will be performed for each contrast using sLORETA's built-in voxel-wise randomization tests (5,000 permutations) and employing a log-F-ratio statistic for independent groups with a threshold $p < .05$ to compute the cortical three-dimensional distribution of current density (Leong el al., 2018; Tanaka et al., 2019). Current density, power to power nesting, whole brain analysis, and functional connectivity will be established based on the data availability.

Discussion

This study will pilot test the novel ISF-NF training protocol and assess the feasibility of conducting a randomized sham-controlled clinical trial using the novel ISF-NF training protocol targeting multiple areas of the brain in people with chronic KOA pain. To our knowledge, for the first time, this study will use the ISF frequency range for influencing higher frequency cortical oscillations in the brain areas associated with pain modulation. The results of this pilot RCT will provide feasibility and safety data including the level of acceptability of NF intervention by study participants. Such data will be used to design a definitive randomized controlled clinical trial.

Author Note

This study will be supported and funded by the School of Physiotherapy; Department of Surgical Sciences, Dunedin School of Medicine, University of Otago; and the Neurological Foundation of New Zealand.

Author Disclosure

Authors have no grants, financial interests, or conflicts to disclose.

References

Abbott, J. H., Usiskin, I. M., Wilson, R., Hansen, P., & Losina, E. (2017). The quality-of-life burden of knee osteoarthritis in New Zealand adults: A model-based evaluation. *PLoS ONE*, *12*(10), e0185676. https://doi.org/10.1371/journal.pone.0185676

Alschuler, K. N., Molton, I. R., Jensen, M. P., & Riddle, D. L. (2013). Prognostic value of coping strategies in a community-based sample of persons with chronic symptomatic knee osteoarthritis. *Pain*, *154*(12), 2775–2781. https://doi.org/10.1016/j.pain.2013.08.012

Bajaj, P., Bajaj, P., Graven-Nielsen, T., & Arendt-Nielsen, L. (2001). Osteoarthritis and its association with muscle hyperalgesia: An experimental controlled study. *Pain*, *93*(2), 107–114. https://doi.org/10.1016/s0304-3959(01)00300-1

Bartley, E. J., King, C. D., Sibille, K. T., Cruz-Almeida, Y., Riley III, J. L., Glover, T. L., … Fillingim, R. B. (2016). Enhanced pain sensitivity among individuals with symptomatic knee osteoarthritis: Potential sex differences in central sensitization. *Arthritis Care & Research*, *68*(4), 472–480. https://doi.org/10.1002/acr.22712

Benhamou, M., Baron, G., Dalichampt, M., Boutron, I., Alami, S., Rannou, F., ... Poiraudeau, S. (2013). Development and validation of a questionnaire assessing fears and beliefs of patients with knee osteoarthritis: The Knee Osteoarthritis Fears and Beliefs Questionnaire (KOFBeQ). *PLoS ONE*, *8*(1), e53886. https://doi.org/10.1371/journal.pone.0053886

Bowen, D. J., Kreuter, M., Spring, B., Cofta-Woerpel, L., Linnan, L., Weiner, D., ... Fernandez, M. (2009). How we design feasibility studies. *American Journal of Preventive Medicine*, *36*(5), 452–457. https://doi.org/10.1016 /j.amepre.2009.02.002

Brown, C. A., El-Deredy, W., & Jones, A. K. P. (2014). When the brain expects pain: Common neural responses to pain anticipation are related to clinical pain and distress in fibromyalgia and osteoarthritis. *European Journal of Neuroscience*, *39*(4), 663–672. https://doi.org/10.1111 /ejn.12420

Collura, T. F., & Thatcher, R. W. (2011). Clinical benefit to patients suffering from recurrent migraine headaches and who opted to stop medication and take a neurofeedback treatment series. *Clinical EEG and Neuroscience*, *42*(2), VIII–IX.

Cottam, W. J., Iwabuchi, S. J., Drabek, M. M., Reckziegel, D., & Auer, D. P. (2018). Altered connectivity of the right anterior insula drives the pain connectome changes in chronic knee osteoarthritis. *Pain*, *159*(5), 929–938. https://doi.org/10.1097 /j.pain.0000000000001209

Cross, M., Smith, E., Hoy, D., Nolte, S., Ackerman, I., Fransen, M., ... March, L. (2014). The global burden of hip and knee osteoarthritis: Estimates from the Global Burden of Disease 2010 study. *Annals of the Rheumatic Diseases*, *73*(7), 1323–1330. https://doi.org/10.1136/annrheumdis-2013-204763

Deloitte Access Economics. (2018). The economic cost of arthritis in New Zealand. *Wellington, New Zealand: Deloitte Touche Tohmatsu Limited*. Retrieved from https://www.arthritis.org.nz /wp-content/uploads/Economic-Cost-of-Arthritis-in-New-Zealand-2018.pdf

Dobson, F., Hinman, R. S., Roos, E. M., Abbott, J. H., Stratford, P., Davis, A. M., ... Bennell, K. L. (2013). OARSI recommended performance-based tests to assess physical function in people diagnosed with hip or knee osteoarthritis. *Osteoarthritis and Cartilage*, *21*(8), 1042–1052. https://doi.org/10.1016 /j.joca.2013.05.002

Dunn, K. M., & Croft, P. R. (2005). Classification of low back pain in primary care: Using “bothersomeness” to identify the most severe cases. *Spine*, *30*(16), 1887–1892. https://doi.org /10.1097/01.brs.0000173900.46863.02

Eldridge, S. M., Chan, C. L., Campbell, M. J., Bond, C. M., Hopewell, S., Thabane, L., & Lancaster, G. A. (2016). CONSORT 2010 statement: Extension 42eurons4242dsed pilot and feasibility trials. BMJ, *355*, i5239. https://doi.org /10.1136 /bmj.i5239

Fingleton, C., Smart, K., Moloney, N., Fullen, B. M., & Doody, C. (2015). Pain sensitization in people with knee osteoarthritis: A systematic review and meta-analysis. *Osteoarthritis and Cartilage*, *23*(7), 1043–1056. https://doi.org/10.1016 /j.joca.2015.02.163

Foucher, K. C., Chmell, S. J., & Courtney, C. A. (2019). Duration of symptoms is associated with conditioned pain modulation and somatosensory measures in knee osteoarthritis. *Journal of Orthopaedic Research*, *37*(1), 136–142. https://doi.org /10.1002/jor.24159

Freynhagen, R., Tölle, T. R., Gockel, U., & Baron, R. (2016). The painDETECT project—far more than a screening tool on neuropathic pain. *Current Medical Research and Opinion*, *32*(6), 1033–1057. https://doi.org/10.1185 /03007995.2016.1157460

Fuchs, M., Kastner, J., Wagner, M., Hawes, S., & Ebersole, J. S. (2002). A standardized boundary element method volume conductor model. *Clinical Neurophysiology*, *113*(5), 702–712. https://doi.org/10.1016/S1388-2457(02)00030-5

Gaume, A., Vialatte, A., Mora-Sánchez, A., Ramdani, C., & Vialatte, F. B. (2016). A psychoengineering paradigm for the neurocognitive mechanisms of biofeedback and neurofeedback. *Neuroscience & Biobehavioral Reviews*, *68*, 891–910. https://doi.org/10.1016/j.neubiorev.2016.06.012

Goggins, J., Baker, K., & Felson, D. (2005). What WOMAC pain score should make a patient eligible for a trial in knee osteoarthritis? *The Journal of Rheumatology*, *32*(3), 540–542. http://www.jrheum.org/content/32/3/540

Goodin, B. R., Bulls, H. W., Herbert, M. S., Schmidt, J., King, C. D., Glover, T. L., ... Fillingim, R. (2014). Temporal summation of pain as a prospective predictor of clinical pain severity in adults aged 45 years and above with knee osteoarthritis: Ethnic differences. *Psychosomatic Medicine*, *76*(4), 302–310. https://doi.org/10.1097/PSY.0000000000000058

Gorini, A., Marzorati, C., Casiraghi, M., Spaggiari, L., & Pravettoni, G. (2015). A neurofeedback-based intervention to reduce post-operative pain in lung cancer patients: Study protocol for a randomized controlled trial. *JMIR Research Protocols*, *4*(2), e52. https://doi.org/10.2196/resprot.4251

Gram, M., Erlenwein, J., Petzke, F., Falla, D., Przemeck, M., Emons, M. I., ... Drewes, A. M. (2017). The cortical responses to evoked clinical pain in patients with hip osteoarthritis. *PLoS ONE*, *12*(10), e0186400. https://doi.org/10.1371 /journal.pone.0186400

Gwilym, S. E., Keltner, J. R., Warnaby, C. E., Carr, A. J., Chizh, B., Chessell, I., & Tracey, I. (2009). Psychophysical and functional imaging evidence supporting the presence of central sensitization in a cohort of osteoarthritis patients. *Arthritis Care & Research*, *61*(9), 1226–1234. https://doi.org/10.1002 /art.24837

Hammond, D. C. (2011). What is neurofeedback: An update. *Journal of Neurotherapy*, *15*(4), 305–336. https://doi.org/10.1080/10874208.2011.623090

Hassan, M. A., Fraser, M., Conway, B. A., Allan, D. B., & Vuckovic, A. (2015). The mechanism of neurofeedback training for treatment of central neuropathic pain in paraplegia: A pilot study. *BMC Neurology*, *15*(1), 200. https://doi.org/10.1186 /s12883-015-0445-7

Hoffmann, T. C., Glasziou, P. P., Boutron, I., Milne, R., Perera, R., Moher, D., ... Michie, S. (2014). Better reporting of interventions: Template for intervention description and replication (TIDieR) checklist and guide. *BMJ*, *348*, g1687. https://doi.org/10.1136/bmj.g1687

Howard, M. A., Sanders, D., Krause, K.’ O'Muircheartaigh, J., Fotopoulou, A., Zelaya, F., ... Williams, S. C. R. (2012). Alterations in resting-state regional cerebral blood flow demonstrate ongoing pain in osteoarthritis: An arterial spin-labeled magnetic resonance imaging study. *Arthritis & Rheumatology*, *64*(12), 3936–3946. https://doi.org/10.1002 /art.37685

Jakorinne, P., Haanpää, M., & Arokoski, J. (2018). Reliability of pressure pain, vibration detection, and tactile detection threshold measurements in lower extremities in subjects with knee osteoarthritis and healthy controls. *Scandinavian Journal of Rheumatology*, *47*(6), 491–500. https://doi.org/10.1080 /03009742.2018.1433233

Jensen, M. P., Grierson, C., Tracy-Smith, V., Bacigalupi, S. C., & Othmer, S. (2007). Neurofeedback treatment for pain associated with Complex Regional Pain Syndrome Type I. *Journal of Neurotherapy*, *11*(1), 45–53. https://doi.org /10.1300/J184v11n01_04

Jobert, M., Wilson, F. J., Ruigt, G. S., Brunovsky, M., Prichep, L. S., Drinkenburg, W. H., & IPEG Pharmaco-EEG Guideline Committee. (2012). Guidelines for the recording and evaluation of pharmaco-EEG data in man: The International Pharmaco-EEG Society (IPEG). *Neuropsychobiology*, *66*(4), 201–220. https://doi.org/10.1159/00034347

Jurcak, V., Tsuzuki, D., & Dan, I. (2007). 10/20, 10/10, and 10/5 systems revisited: Their validity as relative head-surface-based positioning systems. *NeuroImage*, *34*(4), 1600–1611. https://doi.org/10.1016/j.neuroimage.2006.09.024

Keller, S., Bann, C. M., Dodd, S. L., Schein, J., Mendoza, T. R., & Cleeland, C. S. (2004). Validity of the brief pain inventory for

use in documenting the outcomes of patients with noncancer pain. *The Clinical Journal of Pain*, *20*(5), 309–318. https://doi.org/10.1097/00002508-200409000-00005

Kidd, B. (2012). Mechanisms of pain in osteoarthritis. *HSS Journal*, *8*(1), 26–28. https://doi.org/10.1007/s11420-011-9263-7

Kleih, S. C., & Kübler, A. (2013). Empathy, motivation, and P300-BCI performance. *Frontiers in Human Neuroscience*, *7*, 642. https://doi.org/10.3389/fnhum.2013.00642

Kleih, S. C., Riccio, A., Mattia, D., Kaiser, V., Friedrich, E. V. C., Scherer, R., ... Kübler, A. (2011). Motivation influences performance in SMR-BCI. In G. Müller-Putz, R. Scherer, M. Billinger, A. Kreilinger, V. Kaiser, & C. Neuper (Eds.), *Proceedings of the Fifth International Brain-Computer Interface Conference 2011*. Graz, Austria: Verlag der Technischen Universität Graz.

Kokkonen, M., & Pulkkinen, L. (2001). Examination of the paths between personality, current mood, its evaluation, and emotion regulation. *European Journal of Personality*, *15*(2), 83–104. https://doi.org/10.1002/per.397

Lee, Y. C., Nassikas, N. J., & Clauw, D. J. (2011). The role of the central nervous system in the generation and maintenance of chronic pain in rheumatoid arthritis, osteoarthritis and fibromyalgia. *Arthritis Research & Therapy*, *13*(2), 211. https://doi.org/10.1186/ar3306

Leong, S. L., Vanneste, S., Lim, J., Smith, M., Manning, P., & De Ridder, D. (2018). A randomized, double-blind, placebo-controlled parallel trial of closed-loop infraslow brain training in food addiction. *Scientific Reports*, *8*(1), 11659. https://doi.org/10.1038/s41598-018-30181-7

Lewis, G. N., Luke, H., Rice, D. A., Rome, K., & McNair, P. J. (2012). Reliability of the conditioned pain modulation paradigm to assess endogenous inhibitory pain pathways. *Pain Research and Management*, *17*(2), 98–102. https://doi.org/10.1155/2012/610561

Lluch, E., Torres, R., Nijs, J., & Van Oosterwijck, J. (2014). Evidence for central sensitization in patients with osteoarthritis pain: A systematic literature review. *European Journal of Pain*, *18*(10), 1367–1375. https://doi.org/10.1002/j.1532-2149.2014.499.x

Maheshkumar, K., Dilara, K., Maruthy, K. N., & Sundareswaren, L. (2016). Validation of PC-based sound card with Biopac for digitalization of ECG recording in short-term HRV analysis. *North American Journal of Medical Sciences*, *8*(7), 307–311. https://doi.org/10.4103/1947-2714.187150

Mani, R., Adhia, D. B., Leong, S. L., Vanneste, S., & De Ridder, D. (2019). Sedenta43eurons43our facilitates conditioned pain modulation in middle-aged and older adults with persistent musculoskeletal pain: A cross-sectional investigation. *Pain Reports*, *4*(5), e773. https://doi.org/10.1097/PR9.0000000000000773

Mantini, D., Perrucci, M. G., Del Gratta, C., Romani, G. L., & Corbetta, M. (2007). Electrophysiological signatures of resting state networks in the human brain. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(32), 13170–13175. https://doi.org/10.1073/pnas.0700668104

Martindale, J. C., Wilson, A. W., Reeve, A. J., Chessell, I. P., & Headley, P. M. (2007). Chronic secondary hypersensitivity of dorsal ho43euronsnes following inflammation of the knee joint. *Pain*, *133*(1–3), 79–86. https://doi.org/10.1016/j.pain.2007.03.006

Mayer, J. D., & Gaschke, Y. N. (1988). The experience and meta-experience of mood. *Journal of Personality and Social Psychology*, *55*(1), 102–111. https://doi.org/10.1037/0022-3514.55.1.102

Mendoza, T., Mayne, T., Rublee, D., & Cleeland, C. (2006). Reliability and validity of a modified Brief Pain Inventory short form in patients with osteoarthritis. *European Journal of Pain*, *10*(4), 353. https://doi.org/10.1016/j.ejpain.2005.06.002

Monto, S., Palva, S., Voipio, J., & Palva, J. M. (2008). Very slow EEG fluctuations predict the dynamics of stimulus detection and oscillation amplitudes in humans. *The Journal of Neuroscience*, *28*(33), 8268–8272. https://doi.org/10.1523/JNEUROSCI.1910-08.2008

Nicholas, M. K. (2007). The pain self-efficacy questionnaire: Taking pain into account. *European Journal of Pain*, *11*(2), 153–163. https://doi.org/10.1016/j.ejpain.2005.12.008

Nir, R.-R., & Yarnitsky, D. (2015). Conditioned pain modulation. *Current Opinion in Supportive and Palliative Care*, *9*(2), 131–137. https://doi.org/10.1097/SPC.0000000000000126

Omachi, T. A. (2011). Measures of sleep in rheumatologic diseases: Epworth Sleepiness Scale (ESS), Functional Outcome of Sleep Questionnaire (FOSQ), Insomnia Severity Index (ISI), and Pittsburgh Sleep Quality Index (PSQI). *Arthritis Care & Research*, *63*(S11), S287–S296. https://doi.org/10.1002/acr.20544

Osaka, N., Osaka, M., Morishita, M., Kondo, H., & Fukuyama, H. (2004). A word expressing affective pain activates the anterior cingulate cortex in the human brain: An fMRI study. *Behavioural Brain Research*, *153*(1), 123–127. https://doi.org/10.1016/j.bbr.2003.11.013

Panosyan, F. B., Mountain, J. M., Reilly, M. M., Shy, M. E., & Herrmann, D. N. (2016). Rydel-Seiffer fork revisited: Beyond a simple case of black and white. *Neurology*, *87*(7), 738–740. https://doi.org/10.1212/WNL.0000000000002991

Parksl, E. L., Gehal, P. Y., Balikil, M. N., Katzl, J., Schnitzerl, T. J., & Apkarianl, A. V. (2011). Brain activity for chronic knee osteoarthritis: Dissociating evoked pain from spontaneous pain. *European Journal of Pain*, *15*(8), 843.e1–843.e14. https://doi.org/10.1016/j.ejpain.2010.12.007

Peer, M. A., & Lane, J. (2013). The Knee Injury and Osteoarthritis Outcome Score (KOOS): A review of its psychometric properties in people undergoing total knee arthroplasty. *Journal of Orthopaedic & Sports Physical Therapy*, *43*(1), 20–28. https://doi.org/10.2519/jospt.2013.4057

Pinheiro, E. S. d. S., de Queiróos, F. C., Montoya, P., Santos, C. L., do Nascimento, M. A., Ito, C. H., ... Baptista, A. F. (2016). Electroencephalographic patterns in chronic pain: A systematic review of the literature. *PLoS ONE, 11(2)*, e0149085. https://doi.org/10.1371/journal.pone.0149085

Ploner, M., Sorg, C., & Gross, J. (2017). Brain rhythms of pain. *Trends in Cognitive Sciences*, *21*(2), 100–110. https://doi.org/10.1016/j.tics.2016.12.001

Pottie, K., Rahal, R., Jaramillo, A., Birtwhistle, R., Thombs, B. D., Singh, H., ... Tonelli, M. (2016). Recommendations on screening for cognitive impairment in older adults. *CMAJ, 188*(1), 37–46. https://doi.org/10.150/cmaj.141165

Price, D. D., Bush, F. M., Long, S., & Harkins, S. W. (1994). A comparison of pain measurement characteristics of mechanical visual analogue and simple numerical rating scales. *Pain*, *56*(2), 217–226. https://doi.org/10.1016/0304-3959(94)90097-3

Price, D. D., McGrath, P. A., Rafii, A., & Buckingham, B. (1983). The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. *Pain*, *17*(1), 45–56. https://doi.org/10.1016/0304-3959(83)90126-4

Prinsloo, S., Novy, D., Driver, L., Lyle, R., Ramondetta, L., Eng, C., ... Cohen, L. (2018). The long-term impact of neurofeedback on symptom burden and interference in patients with chronic chemotherapy-induced neuropathy: Analysis of a randomized controlled trial. *Journal of Pain and Symptom Management*, *55*(5), 1276–1285. https://doi.org/10.1016/j.jpainsymman.2018.01.010

Pujol, J., Martínez-Vilavella, G., Llorente-Onaindia, J., Harrison, B. J., López-Solà, M., López-Ruiz, M., ... Monfort, J. (2017). Brain imaging of pain sensitization in patients with knee osteoarthritis. *Pain*, *158*(9), 1831–1838. https://doi.org /10.1097/j.pain.0000000000000985

Rogel, A., Guez, J., Getter, N., Keha, E., Cohen, T., Amor, T., & Todder, D. (2015). Transient adverse side effects during neurofeedback training: A randomized, sham-controlled, double blind study. *Applied Psychophysiology and Biofeedback*, *40*(3), 209–218. https://doi.org/10.1007/s10484-015-9289-6

Rolke, R., Baron, R., Maier, C. A., Tölle, T. R., Treede, R. D., Beyer, A., ... Wasserka, B. (2006). Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Standardized protocol and reference values. *Pain*, *123*(3), 231–243. https://doi.org/10.1016 /j.pain.2006.01.041

Santoro, M., & Cronan, T. (2014). A systematic review of neurofeedback as a treatment for fibromyalgia syndrome symptoms. *Journal of Musculoskeletal Pain*, *22*(3), 286–300. https://doi.org/10.3109/10582452.2014.883037

Sekhon, M., Cartwright, M., & Francis, J. J. (2017). Acceptability of healthcare interventions: An overview of reviews and development of a theoretical framework. *BMC Health Services Research*, *17*(1), 88. https://doi.org/10.1186/s12913-017-2031-8

Severeijns, R., Vlaeyen, J. W., van den Hout, M. A., & Weber, W. E. J. (2001). Pain catastrophizing predicts pain intensity, disability, and psychological distress independent of the level of physical impairment. *The Clinical Journal of Pain*, *17*(2), 165–172. https://doi.org/10.1097/00002508-200106000-00009

Stanton, T. R., Lin, C.-W. C., Bray, H., Smeets, R. J. E. M., Taylor, D., Law, R. Y. W., & Moseley, G. L. (2013). Tactile acuity is disrupted in osteoarthritis but is unrelated to disruptions in motor imagery performance. *Rheumatology*, *52*(8),1509–1519. https://doi.org/10.1093 /rheumatology/ket139

Starr, C. J., Sawaki, L., Wittenberg, G. F., Burdette, J. H., Oshiro, Y., Quevedo, A. S., ... & Coghill, R. C. (2011). The contribution of the putamen to sensory aspects of pain: Insights from structural connectivity and brain lesions. *Brain*, *134*(7), 1987–2004. https://doi.org/10.1093 /brain/awr117

Tanaka, K., Murata, S., Nishigami, T., Mibu, A., Manfuku, M., Shinohara, Y., ... Ono, R. (2019). The central sensitization inventory predicts pain-related disability for musculoskeletal disorders in the primary care setting. *European Journal of Pain*, *23*(9), 1640–1648. https://doi.org/10.1002/ejp.1443

Tickle-Degnen, L. (2013). Nuts and bolts of conducting feasibility studies. *The American Journal of Occupational Therapy*, *67*(2), 171–176. https://doi.org/10.5014 /ajot.2013.006270

Tilley, P., & Bisset, L. (2017). The reliability and validity of using ice to measure cold pain threshold. *BioMed Research International*, *2017*, 7640649. https://doi.org/10.1155/2017 /7640649

Tracey, I., & Mantyh, P. W. (2007). The cerebral signature for pain perception and its modulation. *Neuron*, *55*(3), 377–391. https://doi.org/10.1016/j.neuron.2007.07.012

Vanneste, S., Joos, K., Ost, J., & De Ridder, D. (2018). Influencing connectivity and cross-frequency coupling by real-time source localized neurofeedback of the posterior cingulate cortex reduces tinnitus related distress. *Neurobiology of Stress*, *8*, 211–224. https://doi.org /10.1016/j.ynstr.2016.11.003

Vanneste, S., Ost, J., Van Havenbergh, T., & De Ridder, D. (2017). Resting state electrical brain activity and connectivity in fibromyalgia. *PLoS ONE*, *12*(6), e0178516. https://doi.org /10.1371/journal.pone.0178516

Vogt, B. A. (2005). Pain and emotion interactions in subregions of the cingulate gyrus. *Nature Reviews Neuroscience*, *6*(7), 533–544. https://doi.org/10.1038/nrn1704

Wideman, T. H., Finan, P. H., Edwards, R. R., Quartana, P. J., Buenaver, L. F., Haythornthwaite, J. A., & Smith, M. T. (2014). Increased sensitivity to physical activity among individuals with knee osteoarthritis: Relation to pain outcomes, psychological factors, and responses to quantitative sensory testing. *Pain*, *155*(4), 703–711. https://doi.org/10.1016 /j.pain.2013.12.028

Windle, G., Bennett, K. M., & Noyes, J. (2011). A methodological review of resilience measurement scales. *Health and Quality of Life Outcomes*, *9*(1), 8. https://doi.org/10.1186/1477-7525-9-8

Wood, B. M., Nicholas, M. K., Blyth, F., Asghari, A., & Gibson, S. (2010). The utility of the short version of the Depression Anxiety Stress Scales (DASS-21) in elderly patients with persistent pain: Does age make a difference? *Pain Medicine*, *11*(12), 1780–1790. https://doi.org/10.1111/j.1526-4637.2010.01005.x

Woolf, C. J. (2011). Central sensitization: Implications for the diagnosis and treatment of pain. *Pain*, *152*(3), S2–S15. https://doi.org/10.1016/j.pain.2010.09.030

Yarnitsky, D., Bouhassira, D., Drewes, A. M., Fillingim, R. B., Granot, M., Hansson, P., ... Wilder-Smith, O. H. G. (2015). Recommendations on practice of conditioned pain modulation (CPM) testing. *European Journal of Pain*, *19*(6), 805–806. https://doi.org/10.1002/ejp.605

Received: February 5, 2020
Accepted: February 24, 2020
Published: March 25, 2019

NeuroRegulation

Principles and Statistics of Individualized Live and Static *Z*-Scores

Thomas F. Collura[1*] *and Jeffrey Tarrant*[2]

[1]BrainMaster Technologies, Inc., and the Brain Enrichment Center, Bedford, Ohio, USA
[2]NeuroMeditation Institute, LLC, Eugene, Oregon, USA

Abstract

This report describes and briefly characterizes a method for computing quantitative EEG (qEEG) *z*-scores based on a modification of the typical methods used for qEEG reporting. In particular, it describes using a sample of EEG from a single individual, and creating a reference database from the individual sample, in contrast to using a population of individuals as the source data. The goal of this method is to quantify and localize within-subject changes that may arise due to time or various factors. We refer to this approach as "*z*-builder," because the *z*-score reference is constructed or "built" on a per-subject basis in the office or laboratory and is not derived from a reference obtained from an outside source. It is confirmed that *z*-scores for EEG acquired during a test period can be calculated based on a single previously recorded reference sample from an individual, and that the resulting *z*-scores obey the expected statistical distribution. Reference data can be calculated using samples in the 1- to 5-minute range, and subsequent static or dynamic *z*-scores for a test sample can then be computed using this reference data in lieu of a population database. It is confirmed that, in the absence of systematic change in the EEG, *z*-scores generally fall well within the range of ±1.0, providing a sensitive indicator when changes do occur. It is shown that this method has value in assessing individual stability of EEG parameters and for quantifying changes that may occur due to time effects, aging, disorders, medications, or interventions.

Keywords: EEG; qEEG; statistics; database

Citation: Collura, T. F., & Tarrant, J. (2020). Principles and statistics of individualized live and static *z*-scores. *NeuroRegulation*, *7*(1), 45–56. https://doi.org/10.15540/nr.7.1.45

***Address correspondence to**: Thomas F. Collura, 195 Willis Street, Suite #3, Bedford, Ohio 44146, USA. Email: tomc1@brainm.com

Edited by:
Rex L. Cannon, PhD, SPESA Research Institute, Knoxville, Tennessee, USA

Reviewed by:
Jon A. Frederick, PhD, Lamar University, Beaumont, Texas, USA
Tanju Surmeli, MD, Living Health Center for Research and Education, Sisli, Istanbul, Turkey

Introduction

Z-builder is a method of producing *z*-scores based upon a reference that is computed from a single sample of EEG. The sample can be any length. The method operates in the same manner that would be used to estimate *z*-scores from a population of samples, except that it is based on a single sample of EEG from one individual, typically 1 to 3 minutes in length. The resulting norms consist of within-subject means and standard deviations for specified metrics, which are used in place of the typical "normative" samples arising from population-based databases (Collura, 2014).

In conventional normative databases, mean values for designated metrics are computed for each individual, and then the individual mean values for each subject are combined to produce a population statistic, consisting of the population mean and the population standard deviation. This includes only one source of variance, that of the difference between individual mean values. The *z*-scores resulting from such an analysis are referred to as "population-static" *z*-scores.

Alternatively, the within-subject variation can be included in the analysis, providing a wider standard deviation for the *z*-score calculations. When instantaneous variation is introduced, the result is what is referred to as "population-dynamic" *z*-scores. The resulting *z*-scores are typically smaller in absolute value, for reasons explained by Thatcher (2008) and explained further below. To date, EEG

mapping for assessment has been typically done using population-static *z*-scores, and EEG neurofeedback using live *z*-scores has used population-dynamic *z*-scores. In both cases, population means and standard deviations are being used as the references. This raises fundamental concerns when it is recognized that individuals are unique and that using a population-based statistic has the undesirable result of causing every subject to be compared to a group, raising concerns about the validity of these measurements.

When the distributions of individual and population metrics are compared, this aspect can be clarified. Figure 1 shows the relationship between static and dynamic metrics, and the resulting distributions and computed means and standard deviations.

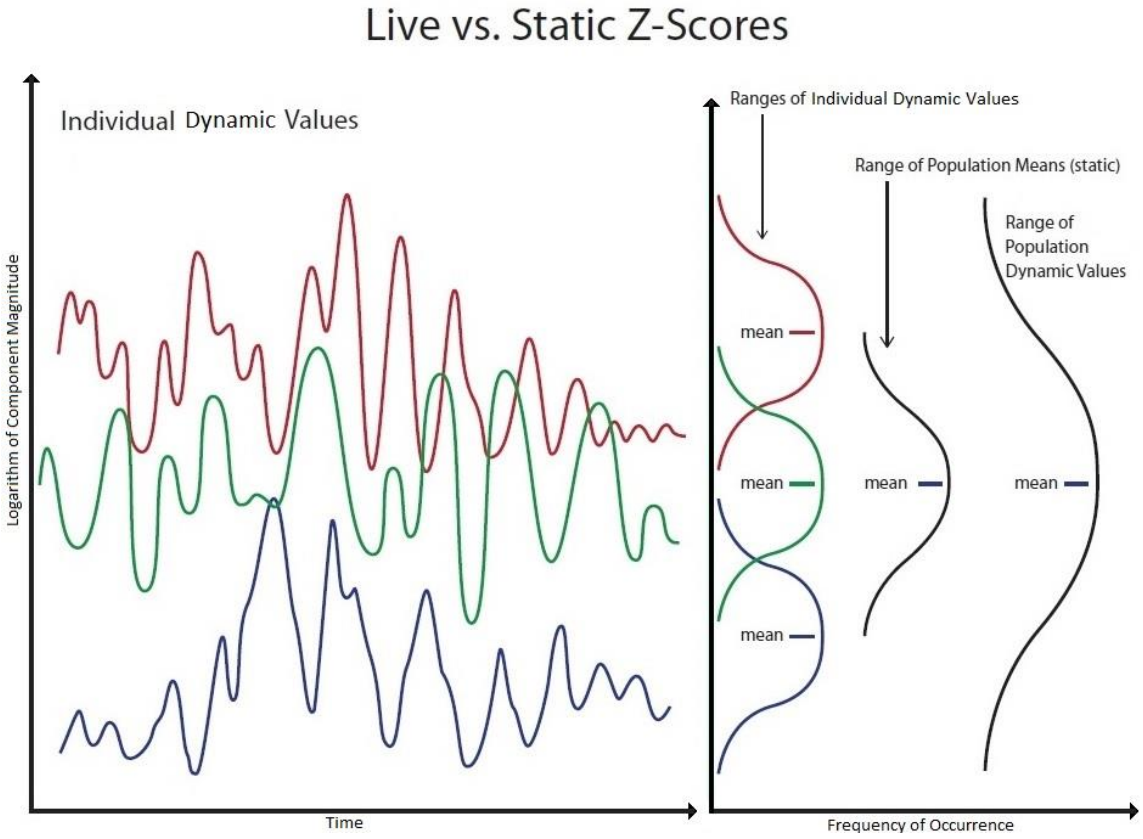

Figure 1. Live vs. Static *Z*-Scores. Example of dynamic values of a component metric (log magnitude) for three example individuals (left) and resulting statistical distribution ranges (right). Three individuals (red, green, blue) have unique means and standard deviations, which when combined, produce the population statistic. Population ranges can incorporate individual mean values (static), or individual variation as well (dynamic).

In existing live *z*-score methods, instantaneous *z*-scores are compared to a reference that is typically derived from a population. If the reference consists of static norms, then the *z*-scores will reflect how the instantaneous EEG compares to the mean value of a population, using the population variation as the standard deviation. This shows *z*-scores that, on average, will match the values shown in summary maps, also made from a static database. When a dynamic reference is used, the individual variation within sessions is added to the standard deviation using an appropriate formula. In this case the instantaneous *z*-scores reflect the deviation from the full variation within the population, so that *z*-scores are smaller in absolute value. In both cases, however, the target mean values are the same. It is only the variability that differs. This means that "*z* = 0" has the same value in both cases.

Because the averaging process is a linear operation, it follows that if you take one mean value from each individual and compute a group mean, the result will be the same as if you were to individually include all the instantaneous data into one huge sample and average it. The resulting average value is the same for both approaches. As long as the averaging occurs before conversion to a *z*-score, this equivalence will be ensured. As a result, even when it is intended to use dynamic *z*-scores for training, the target values reflect population means. Thus, each subject is being rewarded for having an EEG more similar to one's peers, which is not a truly individualized approach. This realization has likely held back acceptance of qEEG and *z*-score neurofeedback for practitioners who object to having clients assessed and/or trained against a group statistic. If target means and standard deviations can be determined that more specifically reflect the individual's characteristics, then assessment and neurofeedback can be individualized to each client.

When using the *z*-builder approach, the reference means and standard deviations are derived entirely from one individual, and the variability is strictly across time, not across individuals. In other words, the approach described here uses exclusively the EEG data from the individual subject, and no across-subject data are used in the process. While this is conceptually different from using *z*-scores for population statistics, the mathematical formalism is the same. When applied to these measurements, the intent is not to make a decision related to some population. Rather, it is to determine the typical amount of variation in the repeated measures, to estimate noise and to test the null hypothesis, which in this case is that there is no change in the readings across time. This approach has the further benefit of directly answering the question "how stable are the data?" which is fundamental to the concept of the repeatability of qEEG-based measurements. As pointed out by Messick (1998), the validity of an approach does not depend on the properties of the measurement, but rather on the inferences that are made from the measurement. In this case, the inferences are whether a process is quantifiable and stable, what is the variability, and can we test the hypothesis that "something happened."

The key assumption for a *z*-score to be valid is that the reference sample and the computation methods ensure that the reference has a Gaussian (normal) distribution. The Gaussianity of single-subject statistics is demonstrated below. This method makes use of the concept of "repeated measurements," which has been used and characterized primarily in the field of analytic chemistry (Miller & Miller, 2016). In such applications, repeated measurements are used to reveal the presence of random errors as well as to quantify changes in time. Coming from the analog world, this method produces a number of samples from a theoretically infinite number of measurements we could make, and the set of all measurements is then considered to be the "population." In the present case, we both estimate the variability of the metrics of interest and also provide a statistical means of detecting statistically significant changes in the within-subject design. We shall see that if we take measurements rapidly, the mean and standard deviations of our measurements will converge to correct values, and that the concepts of sample independence and degrees of freedom are not applied to this model.

While it may be a useful assumption that the samples are independent, it is not relevant in a repeated-measurement design. What matters is simply how fast the parameters are changing, how fast we can measure them, and what is the standard error across time. Indeed, when constructing a dynamic norm, the samples that run across the session are not necessarily independent, since they come from repeated measurements from the same system. This time-dependent source of variability is used in *z*-builder to establish reference norms, and to compute *z*-scores for both assessment and for live neurofeedback purposes. Moreover, if there is a concern with regard to independence of successive samples when using *z*-builder, then that same concern would exist for any dynamic *z*-score reference that includes within-subject variation, including those used for many years. It is true, however, that in choosing the recording length and epoch size, attention must be paid to the choice of reasonable values. For example, the use of many small epochs does not necessarily increase the degrees of freedom, so that taking, for example, estimates 10 times per second and claiming 600 degrees of freedom in a 1-min sample would not be reasonable. We therefore dispense with the concepts of sample independence and degrees of freedom in this design. In order to help ameliorate this concern, we use a consistent sampling rate and computation rate of 256 per second, using the quadrature digital filters, throughout this work.

In order to justify the use of a digital filter (a form of real-time filtering) in lieu of the more common FFT, we compared the results of the digital filter outputs with the FFT amplitude computations, on 1-s

intervals, showing a very strong correlation. The method used is “quadrature filtering” also known as “synchronous demodulation,” which was developed originally for analog computers. In the digital version, we perform computations on every sample, at a rate of 256 per second. Because the filtering method used here allows estimation of signal amplitude and phase on every data sample (Collura, 1990), the resulting metrics are heavily oversampled. This results in an accurate estimation of means and standard deviations, which are known to converge when oversampling is used (Host-Madsen & Handel, 2000). See the Appendix for the basic equations confirming this result.

Figure 2 illustrates the quality of match between the static (FFT) calculation and quadrature digital filter outputs, which provide a dynamic (JTFA) computation. The degree of fit is 97%, once a correction is applied for the difference in the windowing techniques. This result is consistent with that reported by Kerson et al. (2019), which demonstrated a similar quality of fit across two different software and two different hardware platforms. This confirms that we may use digital filter amplitudes in this work, without any systematic disagreement with the results that would result from the conventional FFT method. When applying these calculations, we will restrict our analysis to *z*-scores, avoiding the issue of *t*-tests and relative degrees of freedom.

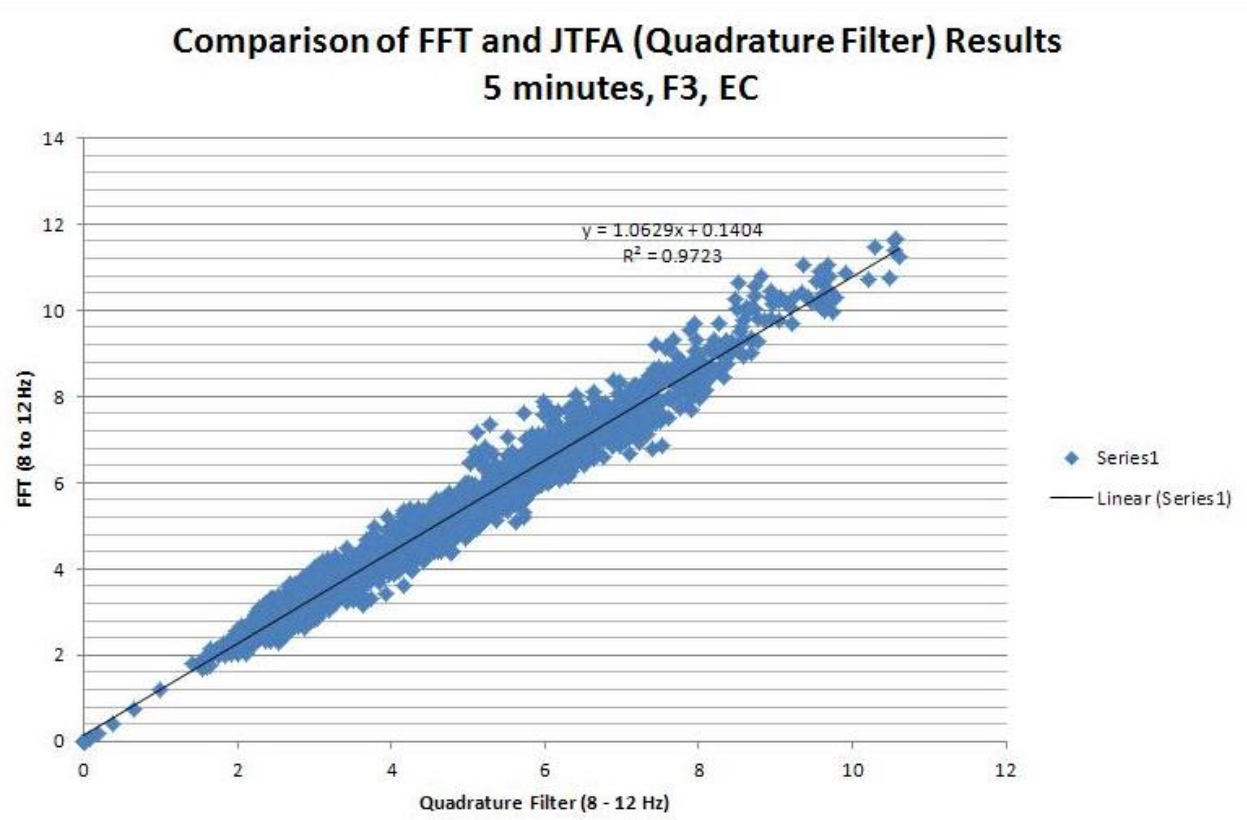

Figure 2. Illustration of the statistical agreement between FFT and JTFA computed amplitude values for the alpha band (8–12 Hz) from 5 minutes of EEG in one individual. When scatterplotted against each other, the results of an FFT analysis (y-axis) and a quadrature filter implementation of the JTFA (horizontal axis) demonstrate a statistical correlation of 97%.

Figure 3 illustrates the Gaussian distribution of the logarithm of the magnitude of one component (theta) for one individual. The goodness of fit is based upon a squared-error comparison of the actual data with an idealized Gaussian with the same mean and standard deviation.

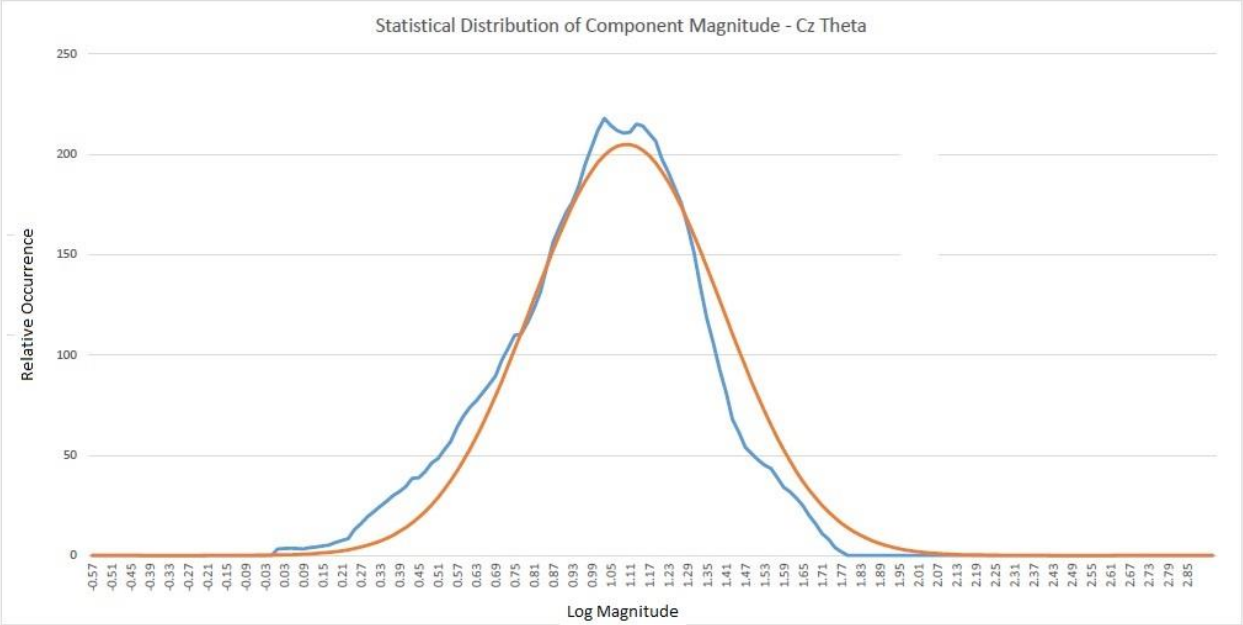

Figure 3. Demonstration of the Gaussianity of a sample of EEG processed for a single subject. Shown: log of Cz theta magnitude for a time-series of 5 minute, yielding 300 x 256 = 76,800 datapoints.

In order to determine the goodness of fit for all of the estimated magnitudes, a histogram was created with the 171 component estimates used in this study. Figure 4 illustrates the distribution of the Gaussianity estimates, confirming that Gaussianity is generally above 90%, and is centered at 94% Gaussianity. Figure 4 shows a histogram of the results of this analysis. 93% of the components (159 out of 171) have a goodness of fit of 90% or above. Two distributions are evident, one centered at 0.94 Hz and a second centered at 0.89 Hz. The lower distribution in this example was found to contain reflect activity, particularly from frontotemporal leads.

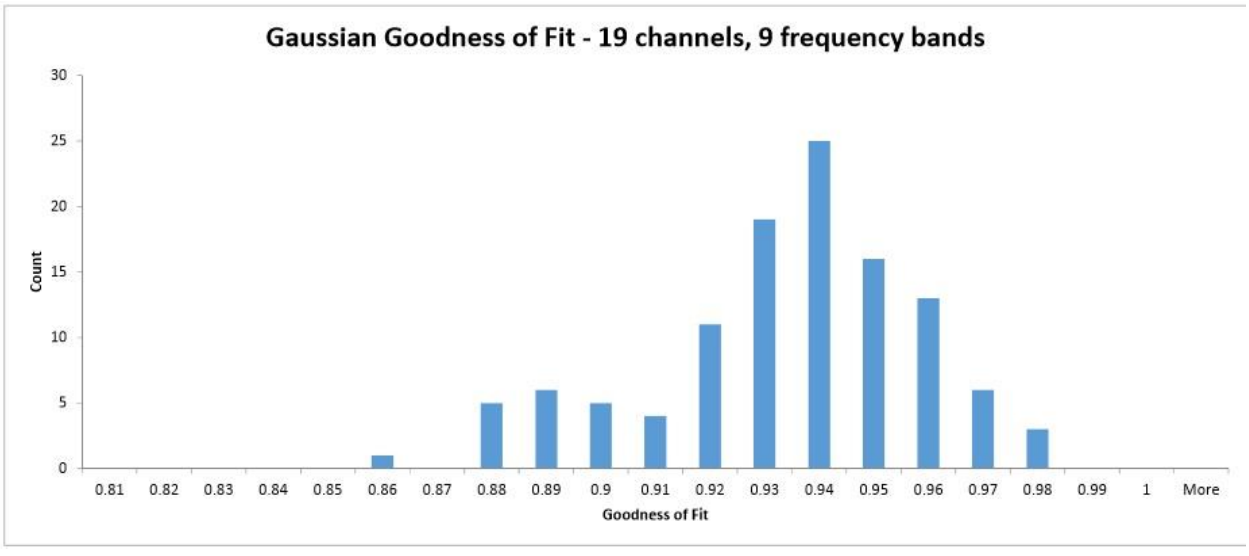

Figure 4. Histogram of the Gaussianity measurements from one individual, 19 channels and 9 frequency bands. This produces 171 component estimates. The Gaussianity of each component was computed for the same data.

Adapting Thatcher's (2008) notation, we denote the *z*-score based upon a population-static as Z_{PS}, corresponding to Thatcher's FFT, and his *z*-score based upon a population-dynamic and using the JTFA procedure as Z_{PD}. In order to compute either of these, the current sample is subtracted from the population mean, whether it is a static or an instantaneous calculation.

In both cases, the target value should be the same, after allowing for systematic differences such as windowing or other factors. This agreement in the raw values (and hence the mean) is shown in the example in Figure 2.

We use the following notation:

Z_{PS} for a population-static *z*-score

Z_{PD} for a population-dynamic *z*-score

Z_{IS} for an individual-static *z*-score

Z_{ID} for an individual-dynamic *z*-score

The sources of variation in a static *z*-score is solely *SD*s which is the variation between subjects, when each subject contributes a mean to the statistic. The sources of variation in a dynamic *z*-score are SD_t due to the time-dependent activity, and SD_s. The two sources are combined in the average, so that (per Thatcher, 2008) $SD_D = (SD_I + SD_S) / 2$. This is the method that is used when applying what we call "population-dynamic" *z*-scores, which are based on population data. Combining population variation and time-based variation in this way elevates the issue of combining two different types of variation, arising from different mechanisms, in one measurement. It also introduces the question of whether each type of variation should be weighted equally as an average, or should they be weighted in a different manner.

The approach reported here avoids this concern, because we produce *z*-scores which are based entirely on the individual's instantaneous variation and no population statistics are introduced. We refer to these as "individual" dynamic *z*-scores. Oddly, this approach may be considered database-free, as it can be applied to any individual without requiring that a "normative" or "standardized" database be introduced. In the case of the static *z*-score, the standard deviation is SD_S. In the case of an individualized instantaneous *z*-score, the standard deviation is simply that introduced by the subjects' EEG, variation across time, designated as SD_I.
When working with *z*-scores computed based on a normative sample and using a single individual as the measurements, there is a natural expectation that *z*-scores will follow the predicted distribution. That is, *z*-scores between ±1 will occur approximately 65% of the time, and scores between ±2 will occur approximately 95% of the time. This allows hypothesis testing, using these probabilities. Type 1 and type 2 error can be estimated using these distributions. The null hypothesis is that the person is entirely "average" and that no unusual *z*-scores will appear. For usual purposes, a range of ±2.0 is used, and for medical determinations, a range of ±2.5 or even ±3.0 would be more common.

As stated previously, when working within an individual, the null hypothesis is not "this is from a normal individual," but rather that "nothing happened." That is, there is no change from the sample to the current measurements. Based on this consideration and the statistical principles described below, individualized *z*-scores occupy a tighter range than those from a normative analysis. It will be seen that a *z*-score outside ±1 will be important in this case, and *z*-scores much outside of this range will be significant.

Static and Dynamic Z-Scores

We now look at the expected behavior of *z*-scores when using static or dynamic references, as well as population versus individual references. We can state in general that the expected value (mean target) for a population-dynamic *z*-scores is the same as that for a population-static *z*-scores.

$$E(X_{PD}) = E(X_{PS})$$

While this is desirable from some standpoints, such as uniformity when applying either type of analysis, the drawback is that the targets used for live *z*-score training for all individuals remain based on a population. That is, even when using current live *z*-score methods, the individual is still being compared to others, and his training targets are based on other people. Because of the additional variation included in the XJTFA calculation, we can state that, necessarily, *z*-scores from a population-dynamic process will be smaller in general than those from a population-static method:

$$|Z_{PD}| < |Z_{PS}|$$

That is, dynamically computed *z*-scores that incorporate both the across-subjects and the within-subjects variation will be smaller than conventional static *z*-scores. Moreover, we note that, generally, the expected value (mean target) of an individual-dynamic *z*-score is not the same as that of population-dynamic *z*-scores.

$$E\,(X_{ID}) \neq E(X_{PD})$$

Also, the expected value for an individual-dynamic *z*-score is not the same as that of population-static *z*-scores.

$$E\,(X_{ID}) \neq E(X_{PS})$$

In other words, when using an individual EEG as a reference, there is no reason to expect that the mean values will be the same as those from a population sample. Moreover, when an individualized approach is taken, and the included samples are from one individual only, then the sole source of variation is the time variation. Furthermore, the mean value for that individual will generally not be equal to the population average. Indeed, this may never happen. In general, the mean values for each individual will themselves follow a Gaussian distribution, which is in fact the mean data that is included in the static statistics.

Because this approach uses a different mean value (the subject's own mean value) and a different source of variation (equal to the *SD* for that individual), resulting *z*-scores will have a distribution that no longer reflects population statistics; it is solely a representation of that individual's mean values and variation across time.

It is reasonable to expect that the same transformations that produce Gaussianity in static and in dynamic *z*-scores should suffice to produce Gaussian distribution of instantaneous individual scores. This can be verified experimentally by applying a suitable test of Gaussian fit. Figure 3 demonstrates the Gaussianity of a 1-min sample of EEG transformed using the customary logarithmic equation used for static or dynamic statistics.

In order to estimate the significance of a *z*-score computed using this method, we can use basic statistical principles to determine how likely a given *z*-score would be, based on the expected results of the computations. Specifically, the references are based upon a specified sample of EEG, which includes the short-term variation, as the source of the standard deviation.

In order to compute *z*-scores, it is sufficient to demonstrate Gaussianity of the comparison data, as long as the current value is transformed in the same manner as the original samples, to follow that Gaussian distribution. The stability and usefulness of a short-term statistic is a separate issue, and must be addressed experimentally, in order to determine the realistic expected variation between samples from time to time. Indeed, repeatability studies of qEEG in general have confirmed that a single 1- to 2-min sample from an individual at rest indeed provides a useful set of estimates. The repeatability of that sample in a second recording minutes, hours, days, or even months later is a tacit assumption in the use of clinical qEEG, and one that has been evaluated. We therefore conclude that a single sample from an individual does provide a useful basis for computing expected means, as well as the expected standard deviation, which can be used for computation of *z*-scores at a future time.

In order to assign a probability, that is, a *p*-value to a given outcome, we examine the conditions used to produce the reference estimate as well as the details of how a particular *z*-score is being computed. In a case where we use, say, 1 minute to compute the mean and standard deviation of key variables, then use for example 10 seconds of live EEG to compute a semistatic *z*-score, we can estimate the likelihood of deviant *z*-scores appearing. As a simplifying assumption, we assume the subject is in stable and repeatable state; for example, eyes closed, not drowsy, etc. Additional factors such as change in conscious state or other EEG-related changes will of necessity produce more deviant *z*-scores. Therefore, this estimate provides a lower-bound to expected *z*-scores using this method.

We are now looking at the probability distributions of the *z*-scores themselves. It might seem intuitive that a *z*-score of 2, for example, indicates a deviation equal to 95% of the population, this will not always be the case. As shown by Thatcher (2008), for example, we know that dynamic *z*-scores will be smaller in value than static *z*-scores, when the same population is used for both estimates.

Whether the variation due the population is greater or less than the variation due to the intersubject variation is subject to measurement. It is clear that neither of them is insignificant; that is, neither the intersubject variation nor the intrasubject variation may be taken to be small. To calculate the significance of a particular individualized *z*-score, we make adjustments to the standard *z*-score probability

ranges, based upon the sampling details. As a first approximation, we can use the statistics of the *t*-test to provide an estimate. In a *t*-test, we compare two populations with different means and standard deviations, using the *t* value which is the difference in means divided by their joint standard deviation. This is similar to a *z*-score, which is the difference between two means, divided by the standard deviation of the reference population. When using individualized *z*-scores, if the standard deviation of a variable is assumed to remain constant as that variable varies in value, the *z*-score provides identical information as a *t*-score. When applied in this way, we are computing *t*-tests for "dependent means." This is valid as long as (1) the data are normally distributed, (2) the scale of measurement is an interval or ratio, and (3) the measurements are matched in some way. In these circumstances, a *t*-test on dependent means can test a null hypothesis that there is no difference between the two means (Social Science Statistics, 2019).

Significance of *t*-scores is based on a computation that takes into account the number of samples (degrees of freedom) in the two samples. Similarly, when computing *z*-scores, the reference as well as the current value carry with them their respective degrees of freedom. When working with a time-series, successive samples are not independent in the same manner as samples from a population. As stated by Miller and Miller (2018), when taking successive samples from a process, the assumption of statistical independence is not made, and degrees of freedom are not comparable. Rather, successive samples serve to estimate the noise in the system, as well as the repeatability of measurements over time. Despite being based on a single individual, such a time-series is nonetheless a random variable and can be studied as such. In our analysis, we observe that the bandwidth of the filters is generally 4 Hz. Based the inverse relationship of bandwidth and transient response (Collura, 2014), this corresponds to a transient rise time-constant on the order of 10 ms. Therefore, taking 256 calculations per second from each filter output should be more than adequate to capture the time behavior of the variables. Appendix I further shows that oversampling in this way does not compromise the estimate of the mean and standard deviation, as they converge when oversampled.

In general, if we compute an average and standard deviation from *n* samples of a random variable, the expected value of the mean is precisely the mean value, while the expected standard error is divided by *n*, so that the standard deviation is divided by the square root of *n*. For example, we take *n* samples of EEG and use these to compute the expected mean (average) and the standard deviation of the EEG to produce the current estimates. When we take a subsequent sample to estimate the new mean, there will be averaging over the epoch chosen. The number of samples is not important, as shown in the Appendix, but the duration of the retest calculations does matter. The relationship between filter bandwidth and rise time-constant is given by

$$t = 1 / (2 * PI * BW) = 0.35 / BW$$

So that, with a 4-Hz filter bandwidth, there is a time-constant of about 90 milliseconds.

The variation in the values will therefore occur with a maximum frequency on the order of 11 Hz, due to the filter bandwidth used. We propose that the ratio of the epoch chosen to the time-constant provides an estimate of how much damping will occur when averaging the filter outputs such as power, coherence, etc. That is,

Effective reduction in variability = (approximated by) epoch length / time-constant

With a 10-s epoch and a 90-ms time-constant, the reduction is on the order of 10 / 0.09 = 110. This is the reduction in the variance, so that this is the square of the reduction in standard deviation. Thus, using 10 s of subsequent EEG to compute a current value, the expected standard deviation becomes divided by the square root of 110, which is a scale factor of roughly 0.1. Thus, the value averaged over 10 s is expected to vary approximately one-tenth as much as an unaveraged estimate. Thus, with an optimally stable EEG, we would see 95% of *z*-scores within the range of approximately ±0.3. We conclude that, when taking a sufficient sample of reference EEG to obtain a convergence on means and standard deviations and then using a subsequent sample of EEG to calculate an updated mean value, the resulting *z*-score will have a strong tendency to be close to zero. In other words, our retest *z*-scores will typically be very low and close to zero. This is confirmed in the example data shown below.

Example Data

The data attached are *z*-builder comparisons base versus 10-min delay and base versus 30-min delay in the eyes-closed (EC) condition for three subjects. The results using 10 min of baseline EC and 10 s of test EEG, are shown in Figure 5.

Figures 5 shows three examples of a single-subject estimate of the variability in *z*-scores. Each histogram reflects the *z*-scores from 11 frequency bands and 93 sLORETA regions of interest. Each histogram therefore contains 1,023 *z*-scores. Reference sample of 10 min of EEG, test sample of 10 s of EEG.

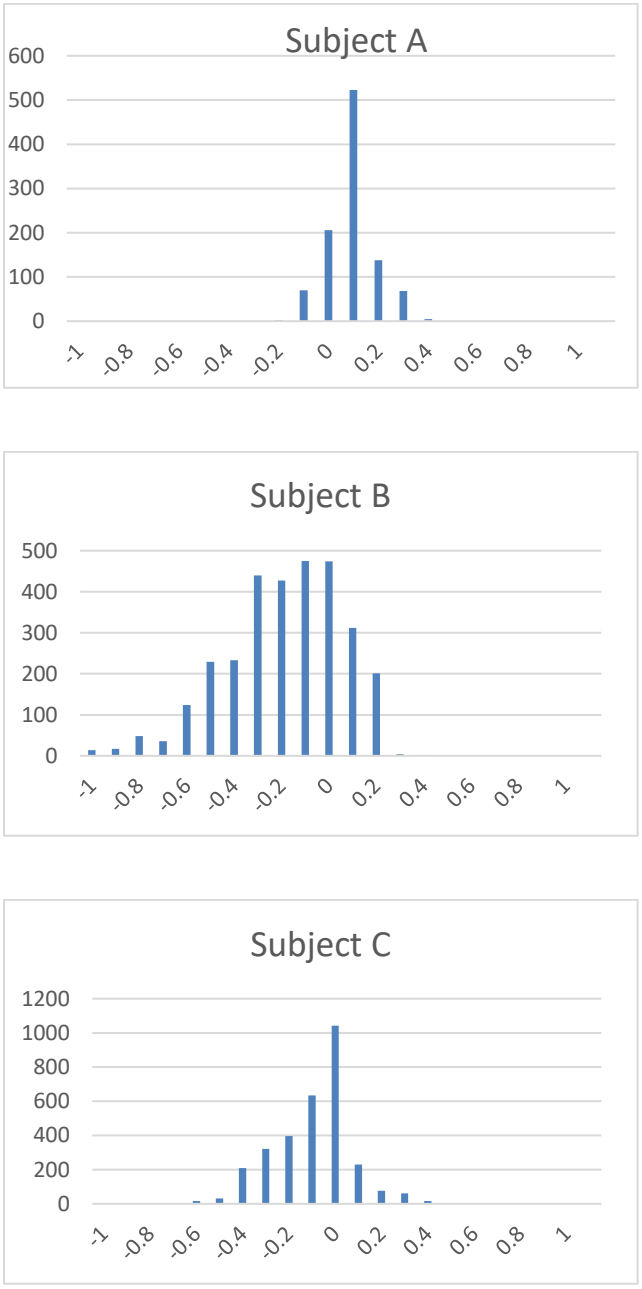

Figure 5. Three examples of a single-subject test–retest repeat measurements using 11 frequency bands and 93 sLORETA regions of interest.

A total of 12 such exercises was performed with the three subjects, with differences in the length of the reference sample (10 or 30 min) and the eyes condition (closed or open). The following table summarizes the results with these three subjects.

Table 1
Summary of z-score results for three subjects with 10-min and 30-min reference intervals.

Subject	Min	Mode	Max	Width
10 EC	−0.3	0.1	0.3	0.6
10 EO	−0.5	0.1	1.4	1.9
30 EC	−0.7	0	0.2	0.9
30 EO	−1.0	0	0.3	1.3
10 EC	−1.1	0	0.2	1.3
10 EO	−0.5	0.2	1.2	1.7
30 EC	−1.1	−0.3	0.1	1.2
30 EO	−0.5	0	0.7	1.2
10 EC	−0.7	0	0.4	1.1
10 EO	−0.6	0	−0.6	0
30 EC	−0.5	0	1.0	1.5
30 EO	−0.7	−0.2	0.3	1.0
Average	−0.6833	−0.0083	0.45833	1.14167

It is seen that, generally, such *z*-scores were within the range of ±0.6 standard deviations, reflecting the stability of the EEG during the procedure. This demonstrates that it is possible to gather some minutes of EEG, then retest at some future point, and achieve a tight distribution of repeat measurements upon retest. Subjects A and C are quite stable and fall within the predicted range of ±0.3. In contrast, subject B is skewed, and appears to exhibit a systematic drop in *z*-scores with a shift to the left of 0.3 standard deviations, from test to retest. The appearance of *z*-scores less than −0.5 in this sample represents some type of (significant) change.

Estimating Changes

One benefit of using the *z*-builder approach is that it is free of the assumptions and implications of using a reference from a population that is purportedly "typical" or "normal." Rather, this method recognizes the fact that everyone is different and has a unique set of EEG characteristics. Thus, this method can accurately determine the effects of different influences, without having to assume that the subject fits somehow into a wider population. When used for

neurofeedback (Collura, Thatcher, Smith, Lambos, & Stark, 2009), this approach would allow training to reflect any specified individual or state as the reference. This opens the possibility of individualized training that can aim to restore previous levels of brain activity or to train toward desired goals, such as reduction of specific characteristics.

A practical application of this method was reported by Siever and Collura (2017) who were able to produce sLORETA images of static *z*-scores for brain responses to repetitive photic, auditory, and magnetic stimulation. Examples are shown in Figures 6A–6C. Citing their work:

> A reference data set was first constructed by taking 1 min from a 2-min at-rest baseline, and processed using BrainAvatar *Z*-Builder signal processing (Collura, 2012, 2013, 2014a, 2014b) to produce amplitude means and standard deviations for all frequency bands, for all scalp locations, sLORETA voxels, and sLORETA Regions of Interest (ROI). ROIs were computed for 97 different homologous regions including the Brodmann areas, the named lobes and regions, and for the hubs described by Hagmann. Once this data set was computed, it was possible to compute metrics for any other selected samples and, by comparison, convert all measurements into *z*-scores.
>
> A 10-s sample was taken from the stimulus interval for each modality and analyzed using the subject's individual *z*-score database, producing *z*-score results. These *z*-scores show which qEEG components and locations have changed. These *z*-scores are not based on a normative reference database but are instead based on the subject's own initial EEG. Thus, *z*-scores reflect change from the initial state, and do not reflect "normality" or "abnormality" in any way. Because the use of *z*-scores in this manner involves multiple comparisons of many ROIs (97), Bonferroni correction was applied to the results shown here. (Siever and Collura, 2017, p. 82)

The resulting sLORETA images clearly show the sensory areas affected by the visual and auditory stimulation, as well as the fact that the pulsed EMF stimulation produced a frontal response, despite having been placed over the motor strip.

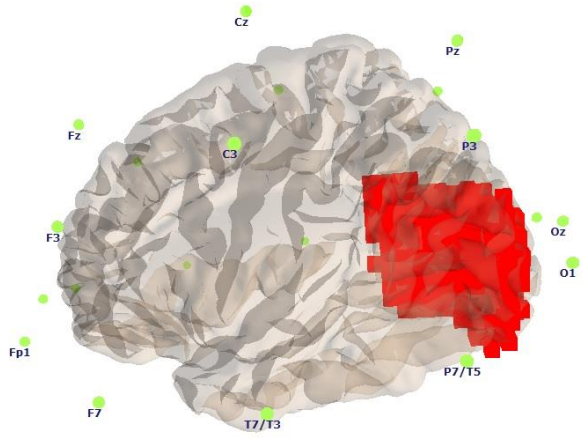

Figure 6A. Reduction in delta activity during binocular photic stimulation at 3.5 Hz. Left-side view. Affected areas include Brodmann 17 and 18 and the cuneus. These comprise the primary and secondary visual sensory areas.

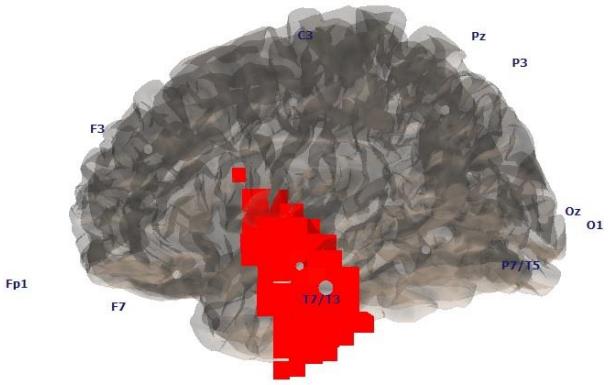

Figure 6B. Reduction in delta activity during auditory stimulation (clicks) at 3.5 Hz. Left-side view. Affected areas include Brodmann 13, 33, 24, 20, the Insula, and Sub Lobar areas. These areas are involved in auditory sensation, perception, awareness, and attentional control.

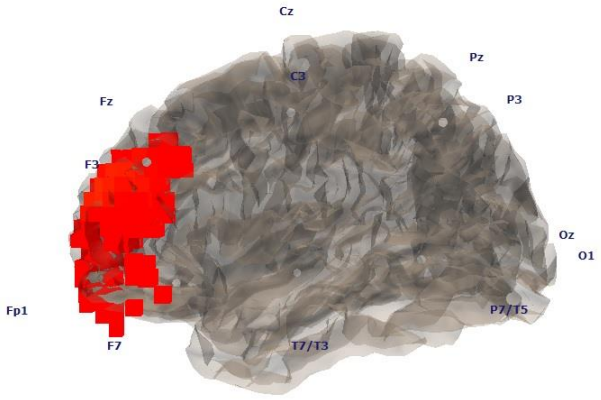

Figure 6C. Reduction in delta activity during pulsed electromagnetic stimulation at 3.5 Hz. Left-side view. Affected areas include Brodmann 45, 46, 10, and 44. These comprise the frontal lobe areas associated with executive function, attention, emotion, and decision-making.

Conclusion

These preliminary results verify that a single-subject approach to creating qEEG references and producing *z*-scores based upon time variation is feasible and statistically sound. Both surface and sLORETA *z*-scores can be computed in this manner. Individualized *z*-scores use a different theoretical foundation than population *z*-scores and are based upon time-effects, not population statistics. A continuous, repeated-measures approach that is based upon the analog world is applicable, in contrast to a sampling approach based upon population statistics. The population-based concepts of sample independence and degrees of freedom are not applicable in this situation; hence, they do not limit this approach. This method has shown the ability to quantify the stability of an individual's EEG and also to detect, quantify, and map changes that could arise due to the effects of time, state changes, disorders, or external influences.

Author Disclosure

Thomas Collura is the founder and an owner of BrainMaster Technologies, Inc. The authors have no grant support, financial interest, or conflicts of interest to report.

References

Collura, T. F. (2014). *Technical Foundations of Neurofeedback*. New York, NY: Routledge.

Collura, T. F. (2014, Spring). Specifying and developing references for live *z*-score neurofeedback. *NeuroConnections,* 26–39. Retrieved from https://docs.wixstatic.com/ugd/cba323_b824c922625941808b2d633bc63f3df7.pdf

Collura, T. F. (1990). Real-time filtering for the estimation of steady-state visual evoked potentials. *IEEE Transactions on Biomedical Engineering, 37*(6), 650–652. Accessed from https://www.ncbi.nlm.nih.gov/pubmed/2354847

Collura, T. F., Thatcher, R. W., Smith, M. L., Lambos, W. A., & C. R. Stark (2009). EEG Biofeedback training using live Z-scores and a normative database. In J. R. Evans, T. H. Budzynski, H. K. Budzynski., & A. Arbanal (Eds.), *Introduction to quantitative EEG and neurofeedback: Advanced theory and applications, Second Edition* (pp. 103–142). New York, NY: Elsevier.

Host-Mandel, A., & Handel, P. (2000). Effects of sampling and quantization on single-tone frequency estimation. *IEEE Transactions on Signal Processing, 48*(3), 650–662. Accessed from http://www-ee.eng.hawaii.edu/~madsen /papers/48sp03-hostmadsen.pdf

Kerson, C., deBeus, R., Lightstone, H., Arnold, L. E., Barterian, J., Pan, X., & Monastra, V. (2020). EEG theta/beta ratio calculations differ between various EEG neurofeedback and assessment software packages: Clinical interpretation. *Clinical EEG and Neuroscience*, *51*(2), 114–120. https://doi.org/10.1177/1550059419888320

Messick, S. (1998). Test validity: A matter of consequence. *Social Indicators Research, 45*(1–3), 35–44.

Miller, J. N., & Miller, J. C. (2018). Statistics of repeated measures. In J. N. Miller & J. C. Miller (Eds.), *Statistics and chemometrics for analytical chemistry* (6th ed., pp. 17–26). Harlow, England: Pearson. Retrieved from https://manualzz.com/doc/27792868/statistics-and-chemometrics-for-analytical-chemistry

Siever, D., & Collura, T. (2017). Chapter3 – Audio-visual entrainment: Physiological mechanisms and clinical outcomes. In J. R. Evans & R. P. Turner (Eds.), *Rhythmic stimulation in neuromodulation* (pp.51–95). New York, NY: Elsevier.

Social Science Statistics (2019). T Test Calculator for 2 Dependent Means. Retrieved from https://www.socscistatistics.com/tests/ttestdependent/default.aspx

Thatcher, R. W. (2008, April). *Z*-Score EEG biofeedback conceptual foundations. *NeuroConnections*, 9–11. Retrieved from https://docs.wixstatic.com/ugd/cba323_426c6449511f48968c49c4ee94fa0c7e.pdf

Received: September 30, 2019
Accepted: January 3, 2020
Published: March 25, 2020

Appendix

The following demonstrates that if you sample a signal to acquire real data such as amplitudes, temperatures, etc., as you sample the signal more often, the estimated mean and variability can only improve. It is shown that oversampling will not change the expected mean value, and it will only improve the estimate of the variability (variance). Given the following time series:

$$X = x_1, x_2, x_3, \ldots x_n$$

The mean is defined as:

$$\mu = \frac{1}{n}\sum_{i=0}^{n} \mathrm{x}_i$$

The variance in the data is defined as:

$$\sigma^2 = \frac{1}{n-1}\sum_{i=0}^{n} (\mathrm{x}_i - \mu)^2$$

We can represent an oversampled version of this signal by replacing each x with a copy, thus doubling the sampling rate, under the assumption that there is negligible difference between samples. That is ensured by the fact that the signal is filtered and that we are sampling at a high enough rate. The oversampled data can be written as:

$$X_o = x_1, x_1 . x_2, x_2 , x_3, x_3 \ \ldots \ x_n, x_n$$

The mean value of the oversampled signal does not change, as should be intuitively evident, as we are only adding more of the same data points. This can be shown as:

$$\mu_o = \frac{1}{2\,n}\sum_{i=0}^{n} 2\,\mathrm{x}_i$$

So that when the 2's cancel, we find that $\mu_o = \mu$.

As for the variance estimate, if we designate the variance of the oversampled signal as ${\sigma^2}_o$ we have the following:

$${\sigma^2}_o = \frac{1}{2\,n-1}\sum_{i=0}^{n} 2\,(\mathrm{x}_i - \mu_o)^2$$

Comparing this with the equation for the original variance, we find:

$${\sigma^2}_o = \frac{2\,n-2}{2\,n-1}\ \sigma^2$$

Which for large *n* is a ratio very close to 1.000. For example, if we incorporate 256 values into our estimate over 1 second, the values have converged within a factor of (512-2) / (512-1), which is a ratio of 1.002.

Therefore, as the number of samples increases, the estimated variance converges strongly to a final value, which can be considered the "true" variance which for very high values of n is essentially independent of the sampling rate. This is superior to methods that use FFTs and sliding bins, because those approaches require compromises associated with epoch selection and sliding factors. The approach of oversampling the data from continuous quadrature filter data circumvents these limitations entirely and produces results equivalent to an analog system.