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

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RESEARCH PAPERS

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Spatial Vector-based Approach to the ERP Analysis as Applied to an EEG-based Discrimination of Traffic Light Signals

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Abstract

The purpose of the study was to assess the utility of the spatial vector-based representation of multichannel electroencephalography (EEG; when each spatial vector denotes an "instantaneous" sample of cortical activation evolving over time) in the analysis of cortical responses to visual stimulation—as opposed to the traditional, temporal vector-based approach, when vectors are associated with distinct EEG channels. This representation was used in the analysis of EEG collected in the virtual traffic light environment with the attempt to determine the color of traffic light perceived by four participants. Kruskal-Wallis (K-W) analysis of variance was implemented for selected EEG electrodes. To utilize all available information, discrimination value was evaluated next for 32-dimensional EEG spatial vectors followed by modified "k nearest neighbors" (knn) classification. K-W test indicated that EEG samples at selected electrodes are different between different colors of traffic light and when observed for specific latencies. The average accuracy of a modified three-class knn classifier was approaching 60% (the random assignment would yield approximately 33%) for the specific poststimuli latencies. The proposed technique allows analyzing stimulation-synchronized cortical activity with the temporal resolution generally determined by the sampling rate of the neuroimaging modality. The discrimination value appears instrumental for predicting the clusterability of data assessed. Stimulation-evoked cortical responses are often of interest in studies of human cognition. The proposed technique may overcome the low signal-to-noise limitation of the traditional evoked response potential (ERP) analysis and possibly provide means to assess such responses under the real-time constraint.

Keywords: traffic light perception; EEG spatial vectors; VEP; discrimination value; modified knn classifier

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Introduction

Understanding cognitive processes involved in critical tasks may be essential for future scientific and technological advances. Virtual technologies and simulated environments utilized during the last decade allow studying cognitive mechanisms evoked under various perception scenarios in the controlled laboratory setting rather than in the real-life scenery. Analysis of electroencephalogram (EEG) is an established and potentially accurate technique to study human cognitive tasks. Event related potentials (ERPs)—distinctive electrophysiological responses to specific (usually external) stimuli—are, among other applications, used in some neurofeedback applications (Strehl et al., 2017) and in studying visual perception (Rutiku, Aru, & Bachmann, 2016; Yigal & Sekuler, 2007). Considering letter applications, ERPs are usually registered over visual cortices. Analyzing visual evoked potentials (VEPs)—the EEG components related to perception of visual information—permits linking brain electrical activity to visual stimulation by studying changes in EEG that occur following the stimuli (Walsh, Kane, & Butler, 2005). In particular, evidences suggest that VEPs may be related to the color that a subject perceives.

For instance, Yeh, Lee, and Ko (2013) suggest that the images with high preference color combinations (blue on white or white on blue) may produce significantly faster response in EEG (peak latency of P100 component) with significantly greater amplitude of P300 component. Wang and Zhang (2010) concluded that images of a red car result in a larger amplitude of P300 component compared to blue car images.

However, evaluating ERPs or VEPs usually requires averaging of multiple EEG epochs recorded in response to identical stimulation events and thus use of VEPs in real time may be limited. In the present report, we evaluate an alternative approach to the traditional VEP analysis that may alleviate the underlined limitation. The proposed approach will be applied to the analysis of a driver's response to images of traffic lights.

Evaluating Drivers' Response to Traffic Lights: Literature Review

Analyzing drivers' cognitive responses may help developing an in-car brain computer interface (BCI) as possible means for improving road safety. Attempts were recently made to relate the perceived color of traffic light to the subject's EEG. Bayliss and Ballard (2000) have reported VEP-based discrimination between red and yellow traffic lights. Studying the P300 component of VEPs, authors suggest that this component "occurs at red and not yellow lights" (p. 189). While reporting an average accuracy of 85%, the work leaves the perception of the third, green traffic light, unaddressed. Lin et al. (2007) have further developed the yellow or red classification, reporting similar accuracy of 85%. The authors also extended their study by including all three traffic light signals (Liang, Lin, Wu, Huang, & Chao, 2005; Lin, et al., 2008). However, since the participants were instructed to act based on the traffic light color they perceive, we may hypothesize that the cognitive response to the driving environment may be contaminated by the action-related cortical response.

More recent studies by Khaliliardali, Chavarriaga, Gheorghe, and Millán (2012) utilized the contingent negative variation (CNV) potential for detection of the anticipated visual cue, such as the instruction to either "go" or "stop." A countdown appearing on the screen was used as the contingent warning stimuli designed to involve the subjects in the anticipating state. However, watching a countdown may not be a very realistic scenario. A required action (applying either the brake or the accelerator pedal) may produce a more complex cortical response than that evoked by viewing a traffic light itself.

Considering ERPs or VEPs, reports suggest that the component P100 (occurring within approximately the first 100 milliseconds after the stimuli) varies with the amount of subject's attention (Clark & Hillyard, 1996; Heslenfeld, Kenemans, Kok, & Molenaar, 1997; Kenemans, Kok, & Smulders, 1993; Mangun, Hillyard, & Luck, 1993). P300 was previously associated with a red traffic light in a virtual driving environment, while being absent when yellow traffic lights were perceived (Bayliss & Ballard, 1998). N400, observed at poststimulus latencies between 250 and 550 ms, is usually associated with semantic integration (Kutas & Hillyard, 1980, 1984) and with pseudo-action (Holcomb & McPherson, 1994; van Elk, van Schie, & Bekkering, 2008).

In the present study, participants' perception will be limited to vision only. Multichannel EEG will represent participants' cognitive response to the virtual traffic light environment in the form of static images of traffic lights. We propose utilizing an alternative, spatial vector-based, approach in the analysis of cognitive responses in terms of VEPs, which comprises the novelty of this study. We expect that different traffic light colors may be linked to the specific VEP features and that it may be further possible to classify them. Not hypothesizing regarding the origins of perceptual changes, the primary goal of the present study is to validate the proposed technique on detecting differences between the drivers' cognitive responses (via EEG) evoked by the specific traffic light color.

Material and Methods

This study followed Lamar University Institutional Review Board guidelines and was approved by the LU IRB committee. The informed consent was obtained from all study participants prior the experimentation. No identifiable personal information was retained in the research data.

Participants, Experimental Setup, and EEG Acquisition

Continuous EEG was recorded from four subjects (three males and one female, aged from 25 to 35 years) with normal color vision, corrected to normal vision, at least one year of driving experience, no history of known neurological disorders, and without being tired or sleepy during data collection. The recordings were performed using the Advanced Neuro Technology (ANT, Netherlands) system equipped with 32 electrodes positioned according to the extended International 10/20 electrode placement map. EEG was prefiltered in the 0.3–50 Hz range, notch-filtered at 60 Hz, sampled at 256 Hz, and stored in a computer for an off-line processing. One to six EEG recordings were obtained per each participant under the identical conditions; the EEG with less visible artifacts was selected for the further analysis.

Visual stimulation consisted of images of traffic light signals presented via a multimedia projector on a screen at approximately 2 meters in front of the subject. The images were covering most of the subject's visual field and were displayed for 300 ms followed by a black screen for 1500 to 2100 ms. The images of traffic light signals of different colors were displayed in a randomized order. A sample image of the red traffic light is shown in Figure 1.

Figure 1. A sample image of the traffic light signal.

Similar images of green and yellow traffic light signals were also used for visual stimulation.

EEG Analysis

EEG can be viewed as a stochastic, nonstationary in time, multichannel process. Due to its low magnitude (generally up to 100 μV), EEG is often a subject to various artifacts that originate either from the surroundings, body functions, equipment (external artifacts), or from within the brain (internal artifacts). These artifacts are usually reduced to improve accuracy of the EEG analysis. As an example, DC offsets are normally removed from EEG before further processing. Additionally, spatial filters that reduce surface currents may improve the signal-to-noise ratio of EEG potentially improving the classification of mental tasks (Mourino et al., 2001). One of such filters, a common average reference (CAR) spatial filter, is particularly popular due to its robustness, good performance, and computational efficiency (Ludwig et al., 2009). Therefore, CAR spatial filter was implemented in this project after DC offsets were removed from EEG.

We have recently demonstrated that the discrete wavelet transform (DWT) decomposition of the VEPs can be instrumental in their classification of the perceived color of traffic light (Hoque & Tcheslavski, 2018). However, the reported approach requires the complete VEP being available for the processing and, therefore, may not be suitable for real-time applications. Selection of the most appropriate EEG channels/electrodes contributing to the more accurate classification is another challenge. Besides, the temporal dynamics of VEPs may be of interest. Therefore, we propose an alternative approach to analyze EEG data acquired while participants were performing cognitive tasks.

The VEP Analysis: Its Limitations and an Alternative Approach

Traditionally, VEPs can be viewed as the time-locked responses that are treated as stimulation-specific. VEPs can be extracted by averaging the EEG segments (epochs) synchronized with the specific repetitive stimuli—the color of traffic light images, for instance—and for the EEG electrodes associated with the visual cortex. Since differences in cognition may be of interest, the VEP components related to both cognition and memory may be assessed. One of the objectives of the present project was to determine whether the VEP components—such as P100, P300, or N400—are elicited in a virtual traffic light environment and can be used for the traffic light color classification.

From a physics standpoint, discrete-time *M*-channel EEG can be viewed as a sampled in both time and space version of a continuous spatial distribution of an electric potential that evolves over time; hence a spatiotemporal distribution. From the mathematical standpoint, a discrete EEG epoch synchronized with the external (visual, in our case) stimulation can be viewed as a collection of temporal vectors, where each vector corresponds to a specific EEG channel. It is safe to assume that only the selected channels will contribute to VEPs. Another, perhaps less traditional, approach will be to consider such an epoch as a single spatial vector evolving over time. In this case, this vector at any time instance is an instantaneous sample of continuous electric potential represented by EEG that is sampled (in space) at the individual electrodes' locations. The cartoon diagram in Figure 2 illustrates this dual representation concept.

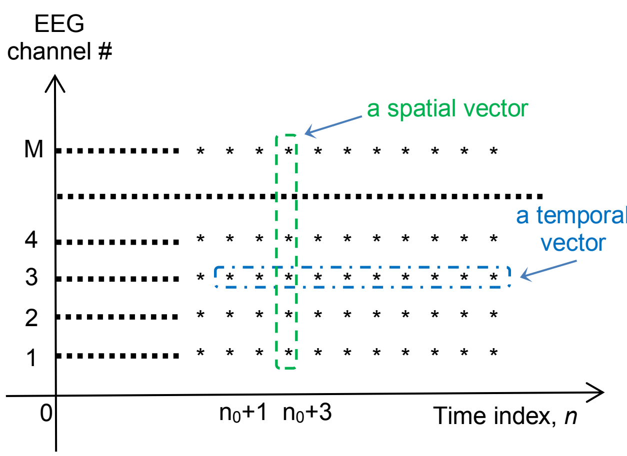

Figure 2. A schematic diagram of a dual representation of an *M*-channel discrete EEG.

The diagram in Figure 2 shows a traditional temporal EEG vector for the channel 3 that starts at the time instance n_0+1 and is 9-sample long (blue dash–dot contour) and a spatial EEG vector for all *M* EEG channels and for the time instance n_0+3 (green dash contour). We may argue that the traditional temporal vector concept can be utilized to estimate VEPs; however, the spatial vector concept may be more adequate for the analysis of the perception-related alterations in the temporal distribution of the cortical activity. We will be using the latter, spatial vector approach.

Selection of the Statistical Analysis Techniques

Problems involving assessment of statistical differences between clusters of multidimensional vectors emerge in many areas of science and engineering. Yet, no universally accepted approach seems to exist for their solution. One procedure to alleviate this problem is to reduce the assessed vectors to scalar quantities, such as vector norm or a single judiciously selected coordinate of the examined vector. Traditional statistical tools, such as ANOVA, can be applied then to scalars. Adopting the spatial vector representation of EEG, the latter would lead to evaluating statistical differences between EEG samples recorded from a specific electrode. This, however, will considerably reduce the information content available for the analysis. We will form the analysis statistics as single-channel EEG samples corresponding to the specific poststimulus latencies. Three groups of observations will be formed corresponding to red, yellow, and green colors of traffic light images; each group will consist of 140 observations (4 participants, 35 repetitions of each stimulus per participant). Kruskal-Wallis (K-W) one-way analysis of variance will be conducted to assess whether samples originate from different distributions.

On the other hand, addressing the outlined shortcoming, Krauss et al. (2018) have recently introduced the quantity referred to as *discrimination value* as means to analyze spatiotemporal cortical activations; more specifically, to assess their clusterability. In present study, EEG recordings were partitioned into epochs synchronized with stimuli presentation allowing pre- and poststimulation buffers of 100 ms and 200 ms, respectively. However, instead of the traditional temporal representation, epochs were partitioned into spatial vectors of the instantaneous EEG; that is, the vectors composed from the EEG recorded for a particular time instance and for all available 32 electrodes. Since each stimulus was repeated 35 times, three clusters of such spatial vectors were formed containing 35 vectors each. Intra- and intercluster Euclidean distances were evaluated between these vectors and the instantaneous discrimination value (IDV) was estimated for them as in (1). Please refer to the Appendix for the detailed description of the classifier design.

In the present project, the initial *k* was selected as 10 and the modified knn was implemented for three classes according to Figure A1. To evaluate the performance of the classifier, leave-one-out cross-validation was applied. Data analysis was implemented using MATLAB R2008a.

Results

After selecting the least contaminated EEG recordings, Figure 3 illustrates the VEPs obtained by averaging over 35 epochs corresponding to the red, green, and yellow images of traffic light evaluated for four subjects and for three different EEG channels.

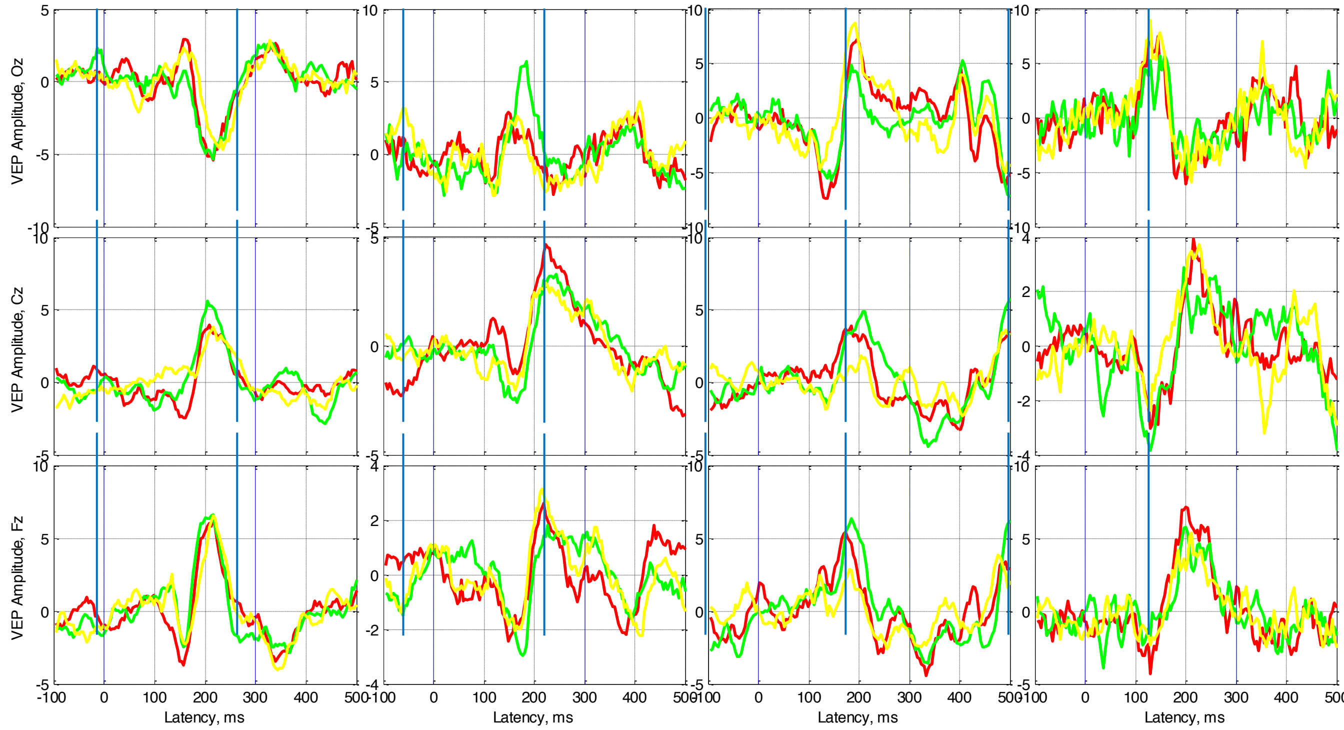

Figure 3. VEP amplitudes for four subjects, Oz, Cz, and Fz electrodes, and for three colors of traffic light images; blue vertical lines illustrate stimulation on- and offsets.

Each column in Figure 3 represents a specific participant; the graph color represents the color of the corresponding traffic light. In Figure 3, one can observe well-pronounced VEPs evaluated for different EEG electrodes. For instance, those evaluated for the first subject and for Oz channel (the upper left panel) resemble traditional flash VEPs with well-defined P200 (approximate latency of 150 ms), N300 (past 200 ms), and P300 (approximately 340 ms) components, while other participants produced somewhat less pronounced VEPs. We also observe clear responses to the stimulation at electrodes, such as Cz, not normally associated with the visual system. On the contrary, this channel, among other functions, is normally linked to the motor cortex. Similarly, the frontal channel, Fz, is usually associated with memory-related tasks and high-level information processing, rather than just vision. Perhaps, well-defined responses at these channels may indicate that the stimulation evokes a more complex response including motor- and memory-related components in addition to those from the vision-related cortical regions. Local extrema in these evoked responses evaluated for different EEG channels appear at similar latencies for each participant. Therefore, we may hypothesize that fusing information from different EEG channels could lead to more comprehensive description of perception phenomenon.

Close examination of Figure 3 shows that, although VEPs appear somewhat different for different stimuli (i.e., the color of traffic light), the observed alterations do not appear consistent between participants or even between different EEG channels recorded from the same individual. We conclude that neither the shape nor the latency of VEPs evoked by images of traffic lights of different colors appear contributing to the reliable discrimination between cognitive responses to the images. Therefore, we assess the utility of the spatial vectors approach next. EEG epochs corresponding to three images of traffic lights (i.e., red, yellow, and green) were formed for each participant. EEG was represented as collections of instantaneous spatial vectors. The dimensionality of these vectors is determined by the number of EEG channels (32 in our study). The samples corresponding to the specific channels—Oz, Cz, and Fz—were used as observations in the Kruskal-Wallis one-way analysis of variance. The resulting H-statistics is shown in Figure 4.

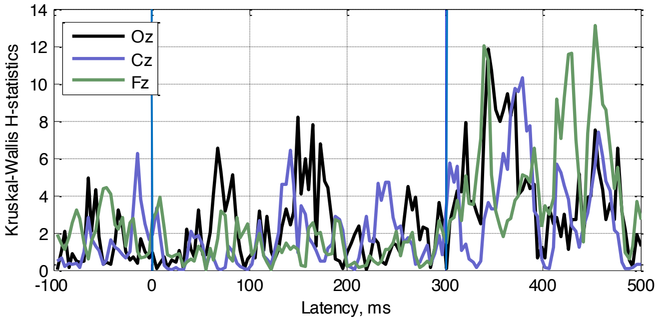

Figure 4. *H*-statistics evaluated by the Kruskal-Wallis test between instantaneous EEG samples corresponding to red, yellow, and green color of traffic light images and EEG electrodes indicated in the legend, blue vertical lines illustrate stimulation on- and offsets.

As seen in Figure 4, *H*-statistics exceeds 6 for the specific latencies and EEG electrodes. Since the distribution of *H* can usually be approximated by the chi-square distribution and assuming the significance level of 0.05, we may conclude that the null hypothesis of equal medians can be rejected for the EEG responses to different traffic light color at these latencies. On the other hand, using EEG data from a single electrode only may result in discarding important information. Additionally, spikes in *H*-statistics after the stimulation off-set (i.e., for latencies exceeding 300 ms) may be difficult to explain. Nevertheless, we may argue that local maxima in *H*-statistics may indicate significant differences in cortical activations observed in response to different stimuli. We implement the discrimination value utilizing all available EEG data followed by the classification of spatial vectors of instantaneous EEG.

Figure 5 illustrates IDVs—according to (1)—and the average instantaneous classification accuracies (ACA) for the same EEG epochs that were used for evaluating VEPs in Figure 3.

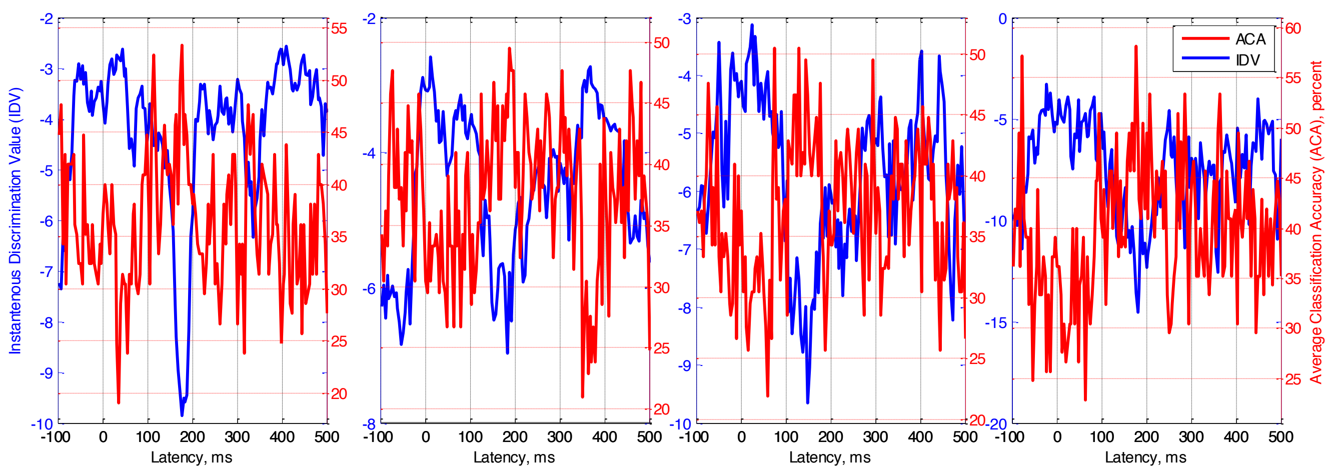

Figure 5. Instantaneous discrimination values (IDV) and average instantaneous classification accuracies (ACA) for the three-class modified knn classifier and for four participants. Blue graphs illustrate the IDV; red graphs represent ACA of a modified 3-class knn classifier.

One observation that can be made while examining Figure 5 is that the IDV and ACA graphs are generally opposite to each other; that is, local maxima in ACA are seen at approximately the same latencies as local minima in the discrimination value. The latter is consistent with the expectation that more negative IDV indicates more distinct clusters and, therefore, a better classification performance can be expected. The ACA was evaluated as the average of the percentages of correct classifications for the three classes (i.e., three traffic light colors) considered. For such problems, a random assignment to classes would lead to ACA of approximately 100/3 ≈ 33%. Therefore, ACA exceeding 50% may indicate that the underlying classification features (EEG spatial vectors) are indeed dissimilar between the different clusters.

We also observe that the classification accuracy generally reaches its local maximum at the latency between 100 and 200 ms for all participants assessed. Similar results (i.e., the opposite appearance of IDV and ACA and the highest classification accuracy within the same latency range) were also observed for other EEG sets recorded from the same participants and under the identical experimental conditions (not included in the present report).

Discussion and Conclusions

Although VEPs elicited by traffic light images of different colors appear dissimilar, such dissimilarities do not seem to be consistent between the experiment subjects. We may thus conclude that the traditional VEP-based approach may be insufficient to reliably determine EEG alterations that may be related to the specific color of traffic light that the individual perceives. On the other hand, the alternative technique handling EEG epochs as collections of instantaneous spatial vectors that are used as the classifier's feature vectors appears more promising for the EEG-based assessment of traffic light perception. Furthermore, this approach appears suitable for real-time processing (after the classifier is trained with the appropriate library of feature vectors). The well-established techniques assessing statistical differences, such as ANOVA or Kruskal-Wallis tests, can be applied to the instantaneous EEG samples evaluated for the individual electrodes prior attempting the classification of spatial vectors. Additionally, the discrimination value evaluated for the feature vectors—spatial EEG—appears instrumental for predicting the outcomes of such classification.

Positions of local ACA maxima shown in Figure 5 can be related to the results of previous studies on human cognition. For instance, we may conclude that no reliable detection of traffic light color arises at the poststimulus latencies prior 100 ms. The latter agrees with Thorpe, Fize, and Marlot (1996) who suggested that the recognition of familiar objects generally occurs within 150 ms after stimulus onset. Another local maximum in ACA that is evident for all assessed participants at the approximate latency of 300 ms, perhaps, can be attributed to the P300 component of VEP that was previously reported as contributing to the classification of traffic light color (Bayliss & Ballard, 2000; Liang et al., 2005; Lin et al., 2007).

We have observed that the classification performance was greatly affected by the implemented EEG preprocessing steps, especially by the baseline correction applied to epochs. Perhaps implementing more sophisticated baseline correction methods may lead to an improved performance. Another potential improvement could be an incorporation of EEG artifact suppression techniques. Replacing the knn classifier with more advanced methods may also contribute to a better performance.

Addressing the possible limitations of the present study, one such limitation is a relatively small participant pool, although it may be sufficient considering the pilot nature of the report. Additionally, participants with more diverse background and of broader age range could be of interest. It is unclear whether the observed discrimination between EEG vectors is due to the mere recognition of colors or to more complicated perceptual mechanisms involving the environment analysis. Perhaps using images of solid color or colored figures for visual stimulation or including participants with no driving experience could provide further insight to this question.

We hypothesize that the temporal resolution of the proposed technique is mostly determined by the sampling rate of the neuroimaging modality used (i.e., EEG in the present study). Therefore, increasing this rate may improve the temporal resolution of the stimulation-related analysis. It may also be of interest to apply the proposed technique for the interparticipants comparison of cortical activations evoked by the identical stimulation, although individual cognitive specifics may diminish the utility of such comparison.

Based on the reported results, we conclude that representing stimulation-synchronized EEG epochs as collections of spatial vectors may better reveal the temporal structure of event potentials and that the discrimination value is instrumental for the prediction of clusterability (i.e., whether the analyzed data set can be partitioned into distinct clusters) of event-related cortical activity.

Due to the very low signal-to-noise ratio in EEG, evaluating ERPs normally requires averaging over multiple EEG epochs collected in response to the same stimulus. The latter severely limits the use of evoked potentials in real-time applications including neurofeedback, in which the effectiveness of operant conditioning decreases dramatically with the number of seconds between the behavior and the reinforcer/punishment (Sherlin et al., 2011). Although the spatial vector-based analysis also assumes collection of the library of responses (EEG epochs in our study) to train the classifier, the classification stage may occur in real time. This advantage of the proposed technique may make it attractive for applications requiring instantaneous feedback. Finally, we further hypothesize that the spatial vector-based approach may also be instrumental for other multichannel neuroimaging techniques, such as magnetoencephalography (MEG).

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Author Disclosure

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References

Bayliss, J. D., & Ballard, D. H. (1998). The effects of eye tracking in a VR helmet on EEG recording. *Technical Report 685, University of Rochester National Resource Laboratory for the Study of Brain and Behavior*.

Bayliss, J. D., & Ballard, D. H. (2000). A virtual reality testbed for brain–computer interface research. *IEEE Transactions on Rehabilitation Engineering, 8*(2), 188–190. https://doi.org/10.1109/86.847811

Clark, V. P., & Hillyard, S. A. (1996). Spatial selective attention affects early extrastriate but not striate components of the visual evoked potentials. *Journal of Cognitive Neuroscience, 8*(5), 387–402. https://doi.org/10.1162/jocn.1996.8.5.387

Duda, R. O., Hart, P. E., & Stork, D. G. (2000). *Pattern Classification, 2nd edition*. New York, NY: Wiley.

Heslenfeld, D. J., Kenemans, J. L., Kok, A., & Molenaar, P. C. M. (1997). Feature processing and attention in the human visual system: An overview. *Biological Psychology, 45*(1–3), 183–215. https://doi.org/10.1016/S0301-0511(96)05228-3

Holcomb, P. J., & McPherson, W. B. (1994). Event-related brain potentials reflect semantic priming in an object decision task. *Brain and Cognition, 24*(2), 259–276. https://doi.org/10.1006/brcg.1994.1014

Hoque, M. R. U., & Tcheslavski, G. V. (2018). Can electroencephalography improve road safety? An EEG-based study of driver's perception of traffic light signals in a virtual environment. *International Journal of Vehicle Safety, 10*(1), 78–86. https://doi.org/10.1504/IJVS.2018.093062

Kenemans, J. L., Kok, A., & Smulders, F. T. Y. (1993). Event-related potentials to conjunctions of spatial frequency and orientation as a function of stimulus parameters and response requirements. *Electroencephalography and Clinical Neurophysiology, 88*(1), 51–63. https://doi.org/10.1016/0168-5597(93)90028-N

Khaliliardali, Z., Chavarriaga, R., Gheorghe, L. A., & Millán, J. d. R. (2012). Detection of anticipatory brain potentials during car driving. *2012 Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, 3829–3832. https://doi.org/10.1109/EMBC.2012.6346802

Krauss, P., Metzner, C., Schilling, A., Tziridis, K., Traxdorf, M., Wollbrink, A., … Schulze, H. (2018). A statistical method for analyzing and comparing spatiotemporal cortical activation patterns. *Scientific Reports, 8*(1), 5433. https://doi.org/10.1038/s41598-018-23765-w

Kutas, M., & Hillyard, S. A. (1980). Reading senseless sentences: Brain potentials reflect semantic incongruity. *Science, 207*(4427), 203–205. https://doi.org/10.1126/science.7350657

Kutas, M., & Hillyard, S. A. (1984). Brain potentials during reading reflect word expectancy and semantic association. *Nature, 307*, 161–163. https://doi.org/10.1038/307161a0

Liang, S.-F., Lin, C.-T., Wu, R.-C., Huang, T.-Y., & Chao, W.-H. (2005). Classification of driver's cognitive responses from EEG analysis. *2005 IEEE International Symposium on Circuits and Systems, 1,* 156–159. https://doi.org/10.1109/ISCAS.2005.1464548

Lin, C.-T., Chung, I-F., Ko, L.-W., Chen, Y.-C., Liang, S.-F., & Duann, J.-R. (2007). EEG-based assessment of driver cognitive responses in a dynamic virtual-reality driving environment. *IEEE Transactions on Biomedical Engineering, 54*(7), 1349–1352. https://doi.org/10.1109/TBME.2007.891164

Lin, C.-T., Lin, K.-L., Ko, L.-W., Liang, S.-F., Kuo, B.-C., & Chung, I.-F. (2008). Nonparametric single-trial EEG feature extraction and classification of driver's cognitive responses. *EURASIP Journal of Advances in Signal Processing, 2008*, 849040. https://doi.org/10.1155/2008/849040

Ludwig, K. A., Miriani, R. M., Langhals, N. B., Joseph, M. D., Anderson, D. J., & Kipke, D. R. (2009). Using a common average reference to improve cortical neuron recordings from microelectrode arrays. *Journal of Neurophysiology, 101*(3), 1679–1689. https://doi.org/10.1152/jn.90989.2008

Mangun, G. R., Hillyard, S. A., & Luck, S. J. (1993). Electrocortical substrates of visual selective attention. In D. Meyer & S. Kornblum (Eds.), *Attention and Performance XIV* (pp. 219–243). Cambridge, MA: MIT Press.

Mourino, J., del R. Millan, J., Cincotti, F., Chiappa, S., Jane, R., & Babiloni, F. (2001). Spatial filtering in the training process of the brain domputer interface. *2001 Conference Proceedings of the 23rd Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBS)*, 639–642. https://doi.org/10.1109 /IEMBS.2001.1019016

Phyu, T. N. (2009, March). Survey of Classification Techniques in Data Mining. *Proceedings of the International MultiConference of Engineers and Computer Scientists, Vol I.* IMECS 2009, Hong Kong.

Rutiku, R., Aru, J., & Bachmann, T. (2016). General markers of conscious visual perception and their timing. *Frontiers in Human Neuroscience, 10*, 23. https://doi.org/10.3389/fnhum.2016.00023

Sherlin, L. H., Arns, M., Lubar, J., Heinrich, H., Kerson, C., Strehl, U., & Sterman, M. B. (2011). Neurofeedback and basic learning theory: Implications for research and practice. *Journal of Neurotherapy, 15*(4), 292–304. https://doi.org/10.1080/10874208.2011.623089

Strehl, U., Aggensteiner, P., Wachtlin, D., Brandeis, D., Albrecht, B., Arana, M., ... Holtmann, M. (2017). Neurofeedback of slow cortical potentials in children with attention-deficit/hyperactivity disorder: a multicenter randomized trial controlling for unspecific effects. *Frontiers in Human Neuroscience, 11*, 135. https://doi.org/10.3389 /fnhum.2017.00135

Thorpe, S., Fize, D., & Marlot, C. (1996). Speed of processing in the human visual system. *Nature, 381*, 520–522. https://doi.org/10.1038/381520a0

Van Elk, M., van Schie, H. T., & Bekkering, H. (2010). The N400-concreteness effect reflects the retrieval of semantic information during the preparation of meaningful actions. *Biological Psychology 85*(1), 134–142. https://doi.org/10.1016/j.biopsycho.2010.06.004

Walsh, P., Kane, N., & Butler, S. (2005). The clinical role of evoked potentials. *Journal of Neurology, Neurosurgery & Psychiatry, 76*(Suppl. 2), ii16–ii22. https://doi.org/10.1136/jnnp.2005.068130

Wang, H., & Zhang, N. (2010, June). *The analysis on vehicle color evoked EEG based on ERP method*. Poster presented at the. 2010 4th International Conference on Bioinformatics and Biomedical Engineering (iCBBE), Chengdu, China.
Yeh, Y.-Y., Lee, D.-S., & Ko, Y.-H. (2013). Color combination and exposure time on legibility and EEG response of icon presented on visual display terminal. *Displays, 34*(1), 33–38. https://doi.org/10.1016/j.displa.2012.11.007
Yigal, A., & Sekuler, R. (2007). Interactions between working memory and visual perception: An ERP/EEG study. *NeuroImage, 36*(3), 933–942. https://doi.org/10.1016/j.neuroimage.2007.04.014

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Appendix
A Three-class Classifier Design

Utilizing the proposed approach and assuming that the data can be partitioned into three clusters A, B, and C (that are related to the color of traffic light perceived), the discrimination value of these data can be estimated as (Krauss et al., 2018):

$$\Delta = d(A,A) + d(B,B) + d(C,C) - \left[d(A,B) + d(A,C) + d(B,C) \right] \quad (1)$$

where *d*(*A,A*), *d*(*B,B*), and *d*(*C,C*) are the average intracluster distances, while *d*(*A,B*), *d*(*A,C*), and *d*(*B,C*) are the average intercluster distances. According to Krauss et al. (2018), the more negative IDV is, the more distinct the assessed clusters are. Perhaps, we may argue that IDV can be used to predict the classification success if the underlying vectors are used as the classification features. Next, the “k nearest neighbors” (knn) algorithm was implemented for classification. The following training matrix was used for a three-class problem:

$$X = \left\{ \left(x_A, \theta(x_A)\right), \left(x_B, \theta(x_B)\right), \left(x_C, \theta(x_C)\right) \right\} \quad (2)$$

where the training (feature) sample x_n belongs to the n^{th} out of three possible classes—A, B, or C—and $\theta(x_n)$ represent the class associations. The Euclidean distances between the test *N*-dimensional vector *z* and all training vectors constituting to each of three classes was evaluated as (Duda, Hart, & Stork, 2000):

$$d(z, x_n) = \sqrt{\sum_{i=0}^{N} \left(z(i) - x_n(i) \right)^2} \quad (3)$$

k training vectors were selected that were closest (i.e., having the shortest distances) to the test vector. Such training vectors are referred to as “nearest neighbors.” The test vector *z* is assigned to the class, to which the majority of its *k* nearest neighbors belong. Here, *k* is a scalar value selected by a user. Regrettably, the performance of knn classifiers may be affected by tied votes. While tied votes can easily be avoided for two-class discriminations by selecting odd values of *k* (Phyu, 2009), no straight-forward solutions seem to exist for multiclass problems. We propose a simple iterative technique for tied votes’ avoidance in knn classification. The implemented algorithm is summarized in Figure A1.

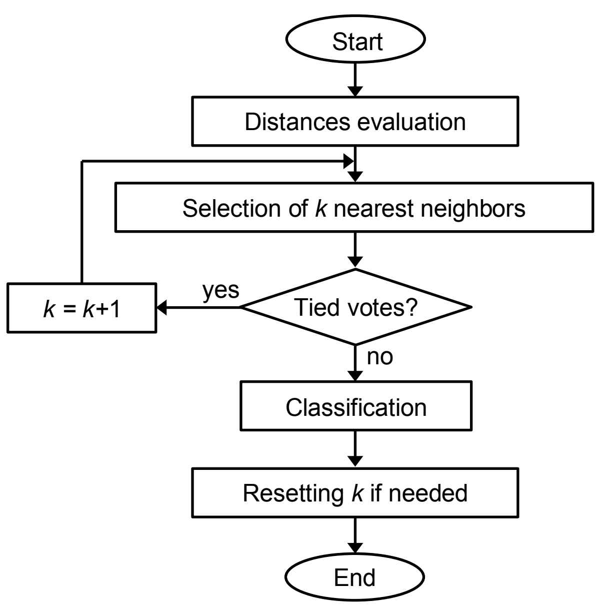

Figure A1. A schematic diagram of the modified knn

Tied votes occur if, among the *k* nearest neighbors, more than one group produces the maximum number of neighbors. Therefore, we propose monitoring group membership among the *k* neighbors to detect tied votes and, if such votes occur, incrementing *k* by one, reselecting neighbors, and reevaluating their membership until no tie votes arise.

NeuroRegulation

Slouched Posture, Sleep Deprivation, and Mood Disorders: Interconnection and Modulation by Theta Brain Waves

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Abstract

Factors such as sleep, posture, and diet can impact EEG readings and have physiological and neurological effects that, when in dysfunctional ranges, may increase susceptibility to developing affective mood disorders or other psychiatric issues. Based on an observation of a neurofeedback client generating excessive amounts of theta rhythms while in a slouched posture, we discuss the role of theta rhythms in brain function and emotional regulation. Slouched posture has been strongly correlated with depressive symptoms. Although the precise nature of the relationship between slouched posture, sleep, and depressive symptoms remains unclear, the literature suggests a cyclical, reciprocal dynamic that is modulated by the involvement of theta rhythms. We recommend that neurofeedback practitioners assess their patients' posture while training, as it could affect the training's effectiveness. Sleep patterns should be assessed prior to the initiation of neurofeedback; if sleep issues remain a consistent problem, efforts to optimize the biological matrix may be indicated. Simple changes in body posture, diet monitoring, and strategies to reduce sleep deprivation may be helpful.

Keywords: body posture; REM sleep; mood disorders; theta rhythms; emotional regulation

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A 19-year-old male diagnosed with major depressive disorder (MDD) and attention-deficit/hyperactivity disorder (ADHD), during a neurofeedback session, began to produce excessive amounts of theta brain waves in the frontal lobe, which he was having difficulty suppressing. Upon noticing that his posture was slouched, with his head tilted downwards, he was asked to correct his posture by sitting straight up, and the theta rhythms diminished once this was done.

This observation spurred our investigation into the possible relationship between body posture, theta rhythms, sleep, and emotional affect, particularly in the case of affective mood disorders.

Introduction

With the increasing incorporation of electroencephalograph (EEG) technology into psychiatric practice, more attention is being directed to the role of brain waves in the manifestation of psychiatric issues such as mood. Preliminary evidence suggests that specific EEG patterns are associated with certain affective states. Emotional affect has been described as a function of the interplay of chemical, electrophysiological, and homeostatic processes (John & Prichep, 2006), thus EEG could reasonably reflect emotional states.

An aspect of sleep that is often overlooked is its role in emotional functioning. Many conceptualize sleep as a process by which one replenishes their energy and "recharges" for the next day. This perspective may be too narrow since research indicates that the benefits of getting a good night's rest and the consequences of sleep deprivation extend far beyond that. Further, the interplay between sleep and posture may be far more cyclical than previously thought.

Research on the relationship between posture and mood suggests a strong correlation between slouched posture and depressive symptoms (Peper & Lin, 2012; Peper, Lin, Harvey, & Perez, 2017). While slouched, it is more difficult to access positive memories than in the erect posture, and the brain is more activated in the slouched position than erect position while trying to access positive memories (Peper et al., 2017; Tsai, Peper, & Lin, 2016; Wilson, & Peper, 2004). This indicates that accessing positive memories while in a slouched posture requires more areas of the brain to be active to accomplish this task than it would in an erect posture.

This paper focuses on the possible affect fmodulation of oscillatory theta rhythms, 4.0–7.5 Hz slow waves, and how this modulation is altered by the lifestyle factors of sleep and body posture.

Theta and Brain Function

Theta brain waves have been broadly categorized into two types: hippocampal theta rhythms and cortical theta rhythms (Theta Waves, n.d.). Hippocampal theta is an oscillatory slow-wave rhythm that is generated subcortically, as the name implies, in the hippocampus. The majority of research on hippocampal theta comes from studies conducted on rodents and neurosurgical/epileptic patients that have had electrodes implanted deep into the hippocampus or surrounding subcortical structures; scalp EEGs cannot detect this type of theta. While its exact functions in humans are still hotly debated and heavily associated with sleep (Buzsáki, 2002), it is important to note that the presence of theta may not be indicative of a less active or idle brain. It has been suggested that hippocampal theta is actually linked to attention and arousal (Jacobs, Lega, & Watrous, 2017). This type of theta has been linked to sensorimotor functions (Bland & Oddie, 2001; Burgess, Barry, & O'Keefe, 2007; Ekstrom et al., 2005; Hoffman et al., 2013; Jacobs et al., 2017; Lopour, Tavassoli, Fried, & Ringach, 2013; Mormann et al., 2005; Watrous, Fried, & Ekstrom, 2011), spatial navigation (Aitken, Zheng, & Smith, 2018; Ekstrom et al., 2005; Jacobs et al., 2017; Kahana, Sekuler, Caplan, Kirschen, & Madsen, 1999; Vass et al., 2016; Watrous et al., 2011), episodic memory coding (Jacobs et al., 2017), and, of particular interest, head position all through its connection to the vestibular system (Aitken et al., 2018).

Alternately, cortical theta rhythms can be detected on a scalp EEG, despite being generated subcortically. An important distinction is that this type of theta is, in actuality, alpha rhythms that have slowed into the theta band (personal communication with Jay Gunkleman, July 11, 2019). We will continue to refer to these rhythms as theta on the basis that they are functionally similar to hippocampal theta. A form of this cortical theta has been termed "frontal midline theta" (FMT) and has been the subject of research. Ishihara and Yoshii (1972) first introduced the term to describe the prominent theta oscillations found primarily at the Fz electrode site while doing arithmetic. This finding, as well as numerous subsequent studies, has led to the association of FMT with working memory (Gevins, Smith, McEvoy, & Yu, 1997; Hsieh, Ekstrom, & Ranganath, 2011; Jensen & Tesche, 2002; Raghavachari et al., 2001) and sustained attention over a long period of time (Hseih & Ranganath, 2014). Another speculation is that FMT has a function in temporal order maintenance; individual items in a sequence are associated with each successive theta phase (Hseih et al., 2011).

The commonality among these neural functions is the cooperation of disparate areas of the brain. While engaging in a task like navigation, a person uses numerous cognitive functions simultaneously: visual perception (to see their environment), motor functions (to coordinate body movement), vestibular system (to maintain balance while in motion and detect the speed of movement), sensory integration, etc. It has been posited that theta rhythms help to coordinate brain-wide network functioning (Buzsáki, 1996; Zhang & Jacobs, 2015), wherein theta rhythms act as a "carrier frequency" that allows disparate areas of the brain to interact (Goldstein & Walker, 2014).

Vestibular System, Head Position, and Theta Production

Recent research has found high comorbidity between psychiatric issues, such as depression, anxiety, and panic disorder, and vestibular system dysfunction (Mast, Preuss, Hartmann, & Grabherr, 2014). This could account for vestibular symptoms, such as dizziness, often experienced by those with anxiety disorders. Those with panic disorder and certain specific phobias (i.e., agoraphobia, acrophobia, basophobia, etc.) have been shown to have multisensory integration issues (Jacob, Furman, Durrant, & Turner, 1996; Mast et al., 2014), particularly concerning inadequate visual and proprioceptive input. The connection between the vestibular system and emotional processing is much more direct; a region of the brain stem (an area known to produce theta rhythms), the parabrachial nucleus (PBN), provides a direct link between the vestibular system and the emotional processing structures of the brain (Balaban, 2004; Mast et al., 2014) that have been implicated in affective disorders. Therefore, it may be that dysfunction in the vestibular system correlates with impaired emotional processing.

One of the functions of the vestibular system, specifically that of the vestibular organs within the inner ear, is to allow people to sense head acceleration; from this, the head position can then be calculated (Aitken et al., 2018). While there is currently very little research on how EEG brain waves change as head position shifts, Spironelli, Busenello, and Angrilli (2016) found that lying in a supine position correlated with decreased cortical activity and increased alpha and delta wave amplitude compared to seated position. Given these effects, it may be reasonable to think that tilting the head downwards, in a chin-to-chest direction, would also produce noticeable changes in brain wave activity.

REM Sleep and Emotional Reactivity

Many people report that when they have been sleep-deprived, having stayed up much too late, they woke up feeling cognitively absent, physically exhausted, and probably quite cranky. Subjective self-reports have consistently linked sleep deprivation with increased emotional volatility and impairments to attention, alertness, and memory (Horne, 1985). Although the irritability is often explained as the result of being tired, it may be that being easily agitated is not a side effect of being tired; rather, it is a direct side effect of the lack of sleep itself.

The limbic lobe has been implicated in a variety of emotional functioning processes; during REM sleep, emotion-related subcortical structures (the amygdala, striatum, and hippocampus) and cortical areas such as the medial prefrontal cortex (mPFC) and the insula (Dang-Vu et al., 2010; Goldstein & Walker, 2014; Miyauchi, Misaki, Kan, Fukunaga, & Koike, 2009; Nofzinger, 2005) show approximately similar, if not higher, levels of activity as with resting wakefulness (Dolcos, LaBar, & Cabeza, 2005). This further suggests that the emotional processing that occurs during REM sleep is equally as impactful as that which occurs during wakefulness.

One week of sleep deprivation (4 to 5 hours of sleep [Dinges et al., 1997; Motomura et al., 2013]) has been shown to amplify the sensitivity and reactivity of dopaminergic limbic structures (Gujar, Yoo, Hu, & Walker, 2011), particularly the amygdala. This is coupled with dulling of the regulatory executive functions of the prefrontal cortex, resulting in decreased alertness, attention, and memory recall. Yoo, Gujar, Hu, Jolesz, and Walker (2007) estimated that one night of sleep deprivation increases the sensitivity and reactivity of the amygdala by 60%, a condition made more severe by the decreased regulatory connectivity to the mPFC. This results in an overreactive, hypersensitive amygdala being allowed to run rampant, unchecked by the mPFC; denying oneself the proper allotment of sleep could mean not allowing certain processes to occur.

One of the often-unnoticed functions of REM sleep is a process called “next day emotional recalibration”; this process functions to recalibrate the brain’s sensitivity in response to emotional events and it primes the brain to react appropriately to emotional experiences that occur the next day (Goldstein & Walker, 2014). Not only that, but it also "strip[s] away the visceral charge (the emotion) from affective experiences of the prior day(s), depotentiating their emotional strength while still consolidating the information (the memory) contained within that experience," (Goldstein & Walker, 2014, p. 9). This is particularly relevant to emotionally challenging or distressing experiences (Phelps, Delgado, Nearing, & LeDoux, 2004; Van der Helm & Walker, 2012; Walker, 2009) since “deficits in the extinction and ability to appropriately utilize surrounding contextual information underlie fear-related disorders such as specific phobia and PTSD” (Goldstein & Walker, 2014, p. 8). In other words, REM sleep may serve as an emotional reset button that removes the emotions associated with memories from that day while also preparing for emotional experiences that one will encounter the next day. It may be that those who are deprived of this function are much more likely to develop more severe psychiatric symptoms.

Sleep abnormalities have been associated with many affective psychopathologies. The altered reactivity of the mesolimbic structures and reduced connectivity to the prefrontal cortex is a neurological pattern often seen in disorders such as depressive disorders (Siegle, Thompson, Carter, Steinhauer, & Thase, 2007), bipolar disorder (Drevets, Savitz, & Trimble, 2008), anxiety disorders (Davidson, 2002; Etkin & Wager, 2007; Nitschke et al., 2009; Paulus & Stein, 2006), substance use disorder (SUD; Arnedt, Conroy, & Brower, 2007; Brower & Perron, 2010), and PTSD (Rauch et al., 2000; Shin, Rauch, & Pitman, 2006). In these disorders, sleep abnormalities are highly comorbid and are, in some cases, part of the diagnostic criteria.

Posture and Mood

Peper and Lin (2012) demonstrated that if people tried skipping versus walking in a slouched posture, subjective energy after the exercise was significantly higher. Among the participants who had reported the highest level of depression during the last two years, there was a significant decrease of subjective energy when they walked in a slouched position as compared to those who reported a low level of depression. There was also a shift in the EEG power during recall of positive memories in the collapsed state. Tsai, Peper, and Lin (2016) showed that when participants sat in a collapsed position, evoking positive thoughts required more "brain activation" (i.e., greater mental effort) compared to that required when walking in an upright position. While in the upright position, it is easier to access positive thoughts and experience significantly improved cognitive performance. Namely, in the upright position, participants report that performing mental serial subtraction is significantly easier than in the slouched position (Peper, Harvey, Mason, & Lin, 2018). Although it was highly significant for the whole group (125 students), posture did not affect those students who reported that they did not have test anxiety, math difficulty, and "blanking out" scores.

Most likely, the collapsed posture evokes a defense reaction that occurred previously during an experience of defeat and hopelessness. Then, if one is in a slouched position, it is easier to access hopeless, helpless, powerless, and defeated memories than in an upright position (Peper et al., 2017). Thus, posture becomes the conditioned stimulus to trigger the emotions and body state associated with fear and defeat. Even physically, the person experiences reduced strength to resist the downward pressure on their arm when standing collapsed versus erect (Peper, Booiman, Lin, & Harvey, 2016). The slouched position also tends to increase shallow thoracic breathing and slightly reduce heart rate variability (Peper et al., 2017).

For some people, shallow, rapid breathing could cause overbreathing (hyperventilation) which lowers the partial pressure of carbon dioxide (pCO2) and may interact with low blood sugar to reduce EEG frequency. Namely, if blood sugar is very low and a person hyperventilates, the EEG frequency decreases into the theta range, as shown in Figure 1, which would also reduce the cerebral circulation as shown in Figure 2.

In addition, blood circulation may be affected in the slouched position when the person looks upward and scrunches their neck. Harvey, Peper, Booiman, Heredia Cedillo, and Villagomez (2018) showed that when participants scrunched their necks for 30 s, 98.4% of the participants experienced a significant increase in symptoms of pressure in the head, stiff neck, eye tension, and headaches. Although the symptoms may be caused by muscle tension, it may also be caused by vertebrobasilar insufficiency due to the scrunching of the neck, which causes transient or permanent reduction or cessation of blood supply to the hindbrain through the left and right vertebral arteries (VA) and the basilar artery (Kerry, Taylor, Mitchell, McCarthy, & Brew, 2008).

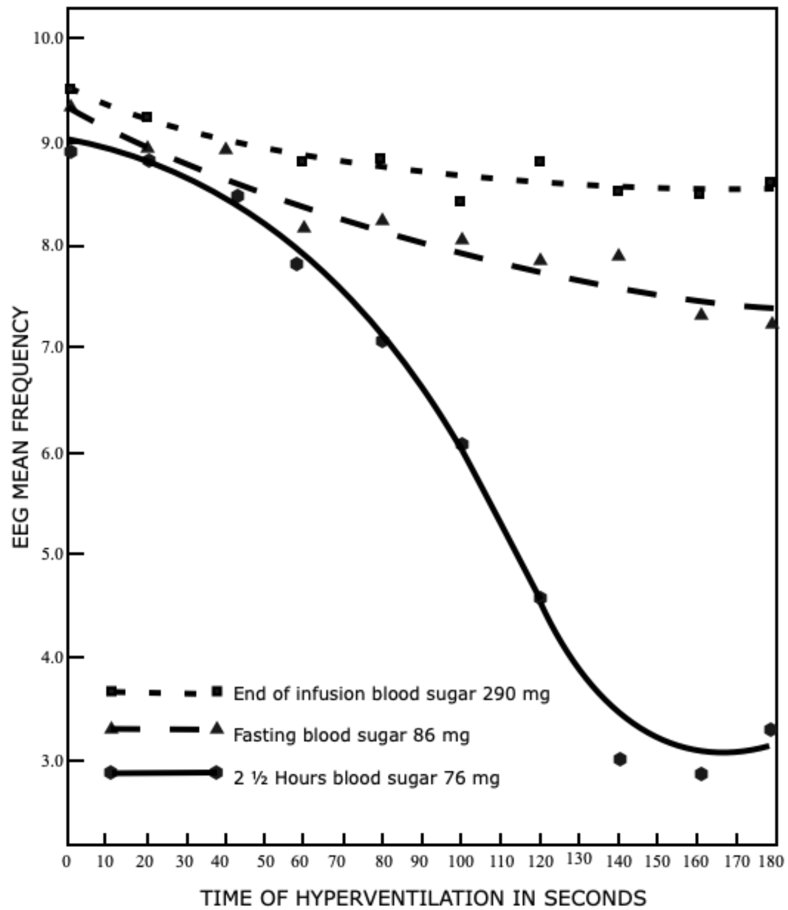

Figure 1. EEG mean frequency change at different blood sugar levels. Adaptation of graph from 'Hyperventilation: Analysis of clinical symptomatology,' by G. L. Engel, E. G. Ferris, and M. Logan, 1947, *Annals of Internal Medicine, 27*(5), p. 690.

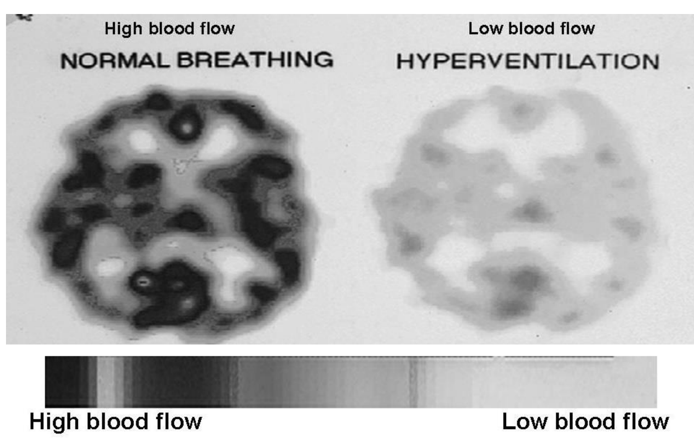

Figure 2. Blood flow through the brain in healthy subjects as measured with single photon emission computed tomography (SPECT) by looking at the brain from above during normal breathing and hyperventilation. The darker color indicates increased blood flow. During hyperventilation (PCO2 < 20 torr) there was a significant decrease in blood flow throughout the brain. Reprinted with permission from Scott Woods, M. D., Yale University, unpublished data, 1987.

Discussion

The precise nature of the relationship between slouched posture, sleep, and depressive symptoms remains unclear, although the literature suggests a cyclical, reciprocal dynamic that is modulated by the involvement of theta rhythms (see Figure 3).

Maintaining poor sleep habits, either by hypersomnia or insomnia, may contribute to disrupted emotional functioning or increase the severity of existing depressive symptoms through the heightened sensitivity of limbic structures. Additionally, poor sleep, particularly in the case of insomnia, can lead to fatigue, thus increasing the likelihood of having slouched posture. This paper focused on the consequences of insomniac sleep habits, so the effects of hypersomnia within this dynamic remains unclear. An avenue of future research could be to investigate how, or if, hypersomnia fits into this model.

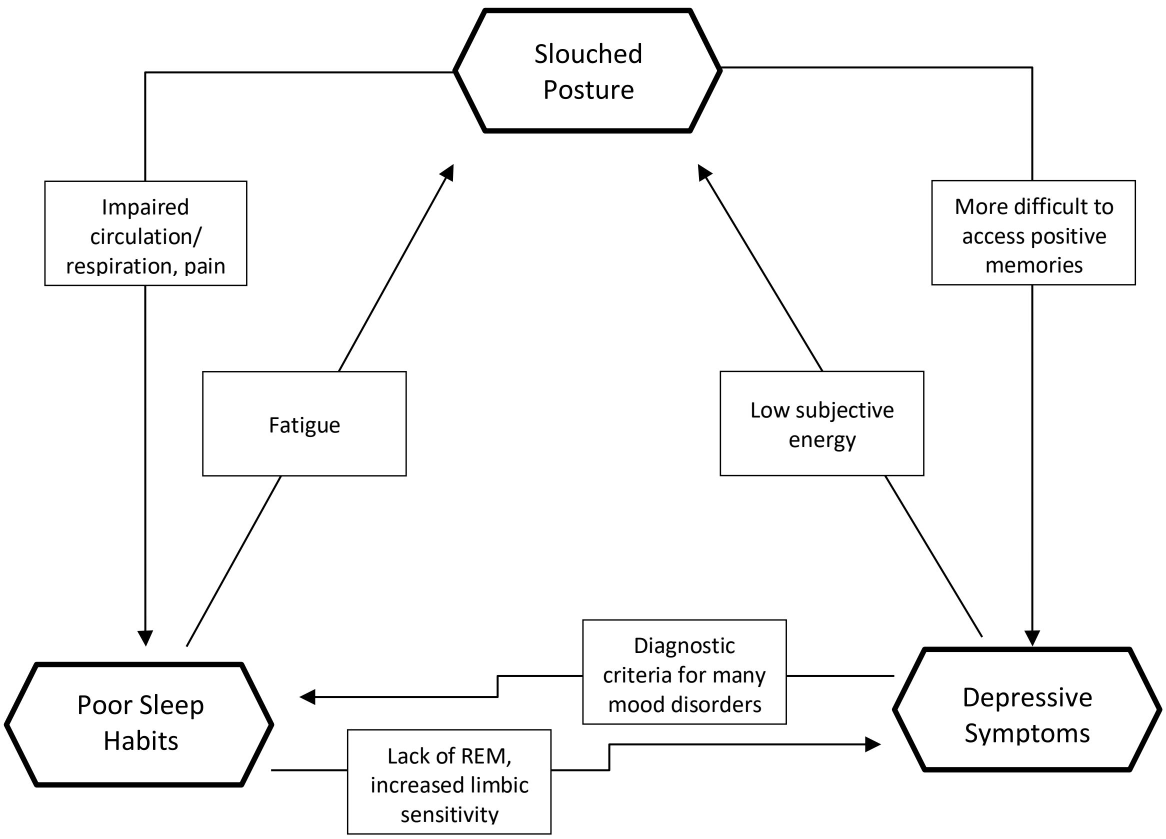

Figure 3. The relationship and feedback loops between posture, sleep and depressive symptoms.

Slouched posture has been found to have a number of physiological effects that could interfere with one's ability to get adequate sleep, increase shallow respiration, impair cerebral circulation, and increase symptoms such as headaches, back/shoulder/neck pain, etc. Although theta rhythms are heavily associated with sleep, they are not known to facilitate the descent into sleep stages. Given that theta rhythms have been found to correspond with heightened mental activity and that hyperventilation, and subsequent shallow breathing, can lead to increased theta rhythms, we can see how poor posture could cause poor sleep through the generation of excessive theta. We also see how the association of slouched posture with feelings of defeat and hopelessness can lead to a fixation on memories connected with such feelings, making it more difficult to recall more positive memories to mind.

Affective mood disorders are highly comorbid with dysfunctional sleep, both in the forms of hypersomnia and insomnia; this correlation is so robust that sleep issues are part of the diagnostic criteria. This aspect appears to resemble a negative feedback loop in which symptom severity increases as sleep decreases. The reports of low subjective energy in those with depressive symptoms can lead to slouched posture in a similar fashion to lack of sleep. While sleep deprivation seems to cause bodily fatigue, depression seems to elicit a type of mental fatigue. This could mean that slouched posture is the more likely point of access to this dynamic. Developing slouched posture, routinely poor sleep habits, or simply developing depressive symptoms through neurochemical or physiological process are all viable entry points to this vicious interrelationship.

A fairly new field of study, affective neuroscience, seeks to determine the neurological basis for mood and emotions. This area could be the catalyst for further research on the relationship between posture, sleep, and mood disorders. The effects of head tilt need to be investigated more thoroughly; perhaps habitual downward head tilt and the prolonged compression of the frontal lobes against the inside of the skull could have bruise-like effects. If this is the case, then poor posture could potentially have side effects more similar to that of concussive brain injuries.

The connection between limbic structures and the vestibular system could provide avenues for novel treatment approaches. Evidence suggests that stimulation of the vestibular system can alleviate depressive symptoms in some cases. In the instances that affective mood disorders are comorbid with vestibular dysfunction, it is possible that treating the vestibular issues could also treat the mood disorder. Further research needs to be done to determine the treatment efficacy of this approach.

Clinical Implications for Neurofeedback Training

When training clients with neurofeedback to reduce theta and increase beta or other EEG frequencies, EEG mastery and clinical efficacy may be increased if the biological matrix is optimized to inhibit theta. This includes sleep hygiene, diet to avoid hypoglycemic states, mastery of diaphragmatic breathing to avoid hyperventilation, and posture. We recommend that neurofeedback practitioners, before beginning neurofeedback, first assess sleep patterns and explore strategies to reduce sleep deprivation and to monitor diet. Then, teach the client self-care skills to optimize health. This means educating the client in 1) sleep hygiene, 2) appropriate diet choices to reduce hypoglycemic states, and 3) awareness of posture and how to achieve and maintain an erect, upright posture to enhance empowerment and increase vertebral artery circulation to inhibit theta. These self-care skills will optimize the physiology to reduce central theta.

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References

Aitken, P., Zheng, Y., & Smith, P. F. (2018). The modulation of hippocampal theta rhythm by the vestibular system. *Journal of Neurophysiology, 119*(2), 548–562. https://doi.org/10.1152/jn.00548.2017

Arnedt, J. T., Conroy, D. A., & Brower, K. J. (2007). Treatment options for sleep disturbances during alcohol recovery. *Journal of Addictive Diseases, 26*(4), 41–54. https://doi.org/10.1300/J069v26n04_06

Balaban, C. D. (2004). Projections from the parabrachial nucleus to the vestibular nuclei: Potential substrates for autonomic and limbic influences on vestibular responses. *Brain Research, 996*(1), 126–137. https://doi.org/10.1016/j.brainres.2003.10.026

Bland, B. H., & Oddie, S. D. (2001). Theta band oscillation and synchrony in the hippocampal formation and associated structures: The case for its role in sensorimotor integration. *Behavioural Brain Research, 127*(1–2), 119–136. https://doi.org/10.1016/s0166-4328(01)00358-8

Brower, K. J., & Perron, B. E. (2010). Sleep disturbance as a universal risk factor for relapse in addictions to psychoactive substances. *Medical Hypotheses, 74*(5), 928–933. https://doi.org/10.1016/j.mehy.2009.10.020

Burgess, N., Barry, C., & O'Keefe, J. (2007). An oscillatory interference model of grid cell firing. *Hippocampus, 17*(9), 801–812. https://doi.org/10.1002/hipo.20327

Buzsáki, G. (1996). The hippocampo-neocortical dialogue. *Cerebral Cortex, 6*(2), 81–92. https://doi.org/10.1093/cercor/6.2.81

Buzsáki, G. (2002). Theta oscillations in the hippocampus. *Neuron, 33*(3), 325–340. https://doi.org/10.1016/S0896-6273(02)00586-X

Dang-Vu, T. T., Schabus, M., Desseilles, M., Sterpenich, V., Bonjean, M., & Maquet, P. (2010). Functional neuroimaging insights into the physiology of human sleep. *Sleep, 33*(12), 1589–1603. https://doi.org/10.1093/sleep/33.12.1589

Davidson, R. J. (2002). Anxiety and affective style: Role of prefrontal cortex and amygdala. *Biological Psychiatry, 51*(1), 68–80. https://doi.org/10.1016/s0006-3223(01)01328-2

Dinges, D. F., Pack, F., Williams, K., Gillen, K. A., Powell, J. W., Ott, G. E., … Pack, A. I. (1997). Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4–5 hours per night. *Sleep, 20*(4), 267–277. https://doi.org/10.1093/sleep/20.4.267

Dolcos, F., LaBar, K. S., & Cabeza, R. (2005). Remembering one year later: Role of the amygdala and the medial temporal lobe memory system in retrieving emotional memories. *Proceedings of the National Academy of Sciences, 102*(7), 2626–2631. https://doi.org/10.1073/pnas.0409848102

Drevets, W. C., Savitz, J., & Trimble, M. (2008). The subgenual anterior cingulate cortex in mood disorders. *CNS Spectrums, 13*(8), 663–681. https://doi.org/10.1017/s1092852900013754

Ekstrom, A. D., Caplan, J. B., Ho, E., Shattuck, K., Fried, I., & Kahana, M. J. (2005). Human hippocampal theta activity during virtual navigation. *Hippocampus, 15*(7), 881–889. https://doi.org/10.1002/hipo.20109

Engel, G. L., Ferris., E. G., & Logan, M. (1947). Hyperventilation: Analysis of clinical symptomatology. *Annals of Internal Medicine, 27*(5), 683–704.

Etkin, A., & Wager, T. D. (2007). Functional neuroimaging of anxiety: A meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *American Journal of Psychiatry*, *164*(10), 1476–1488. https://doi.org/10.1176/appi.ajp.2007.07030504

Gevins, A., Smith, M. E., McEvoy, L., & Yu, D. (1997). High-resolution EEG mapping of cortical activation related to working memory: Effects of task difficulty, type of processing, and practice. *Cerebral Cortex, 7*(4), 374–385. https://doi.org/10.1093/cercor/7.4.374

Goldstein, A. N., & Walker, M. P. (2014). The role of sleep in emotional brain function. *Annual Review of Clinical Psychology, 10*, 679–708. https://doi.org/10.1146/annurev-clinpsy-032813-153716

Gujar, N., Yoo, S., Hu, P., & Walker, M. P. (2011). Sleep deprivation amplifies reactivity of brain reward networks, biasing the appraisal of positive emotional experiences. *The Journal of Neuroscience, 31*(12), 4466–4474. https://doi.org/10.1523/jneurosci.3220-10.2011

Gunkleman, J. (July 11, 2019). Personal communications.

Harvey, R., Peper, E., Booiman, A., Heredia Cedillo, A., & Villagomez, E. (2018). The effect of head and neck position on head rotation, cervical muscle tension and symptoms. *Biofeedback, 46*(3), 65–71. https://doi.org/10.5298/1081-5937-46.3.04

Hoffman, K. L., Dragan, M. C., Leonard, T. K., Micheli, C., Montefusco-Siegmund, R., & Valiante, T. A. (2013). Saccades during visual exploration align hippocampal 3–8 Hz rhythms in human and non-human primates. *Frontiers in Systems Neuroscience, 7(43)*. https://doi.org/10.3389/fnsys.2013.00043

Horne, J. A. (1985). Sleep function, with particular reference to sleep deprivation. *Annals of Clinical Research, 17*(5), 199–208. https://www.ncbi.nlm.nih.gov/pubmed/3909914

Hsieh, L., Ekstrom, A. D., & Ranganath, C. (2011). Neural oscillations associated with item and temporal order maintenance in working memory. *The Journal of Neuroscience, 31*(30), 10803–10810. https://doi.org/10.1523/jneurosci.0828-11.2011

Hsieh, L., & Ranganath, C. (2014). Frontal midline theta oscillations during working memory maintenance and episodic encoding and retrieval. *NeuroImage, 85*, 721–729. https://doi.org/10.1016/j.neuroimage.2013.08.003

Ishihara, T., & Yoshii, N. (1972). Multivariate analytic study of EEG and mental activity in Juvenile delinquents. *Electroencephalography and Clinical Neurophysiology, 33*(1), 71–80. https://doi.org/10.1016/0013-4694(72)90026-0

Jacob, R. G., Furman, J. M., Durrant, J. D., & Turner, S. M. (1996). Panic, agoraphobia, and vestibular dysfunction. *The American Journal of Psychiatry, 153*(4), 503–512. https://doi.org/10.1176/ajp.153.4.503

Jacobs, J., Lega, B., & Watrous, A. J. (2017). Human hippocampal theta oscillations: Distinctive features and interspecies commonalities. In D. E. Hannula & M. C. Duff (Eds.), *The Hippocampus from Cells to Systems: Structure, Connectivity, and Functional Contributions to Memory and Flexible Cognition* (pp. 37–67). New York, NY: Springer.

Jensen, O., & Tesche, C. D. (2002). Frontal theta activity in humans increases with memory load in a working memory task. *European Journal of Neuroscience, 15*(8), 1395–1399. https://doi.org/10.1046/j.1460-9568.2002.01975.x

John, E. R., & Prichep, L. S. (2006). The relevance of QEEG to the evaluation of behavioral disorders and pharmacological interventions. *Clinical EEG and Neuroscience, 37*(2), 135–143. https://doi.org/10.1177/155005940603700210

Kahana, M. J., Sekuler, R., Caplan, J. B., Kirschen, M., & Madsen, J. R. (1999). Human theta oscillations exhibit task dependence during virtual maze navigation. *Nature, 399*(6738), 781–784. https://doi.org/10.1038/21645

Kerry, R., Taylor, A. J., Mitchell, J., McCarthy, C., & Brew, J. (2008). Manual therapy and cervical arterial dysfunction, directions for the future: A clinical perspective. *Journal of Manual & Manipulative Therapy, 16*(1), 39–48. https://doi.org/10.1179/106698108790818620

Lopour, B. A., Tavassoli, A., Fried, I., & Ringach, D. L. (2013). Coding of information in the phase of local field potentials within human medial temporal lobe. *Neuron, 79*(3), 594–606. https://doi.org/10.1016/j.neuron.2013.06.001

Mast, F. W., Preuss, N., Hartmann, M., & Grabherr, L. (2014). Spatial cognition, body representation and affective processes: The role of vestibular information beyond ocular reflexes and control of posture. *Frontiers in Integrative Neuroscience, 8*, 44. https://doi.org/10.3389/fnint.2014.00044

Miyauchi, S., Misaki, M., Kan, S., Fukunaga, T., & Koike, T. (2009). Human brain activity time-locked to rapid eye movements during REM sleep. *Experimental Brain Research, 192*(4), 657–667. https://doi.org/10.1007/s00221-008-1579-2

Mormann, F., Fell, J., Axmacher, N., Weber, B., Lehnertz, K., Elger, C. E., & Fernández, G. (2005). Phase/amplitude reset and theta–gamma interaction in the human medial temporal lobe during a continuous word recognition memory task. *Hippocampus*, *15*(7), 890–900. https://doi.org/10.1002/hipo.20117

Motomura, Y., Kitamura, S., Oba, K., Terasawa, Y., Enomoto, M., Katayose, Y., ... Mishima, K. (2013). Sleep debt elicits negative emotional reaction through diminished amygdala-anterior cingulate functional connectivity. *PLoS ONE, 8*(2). https://doi.org/10.1371/journal.pone.0056578

Nitschke, J. B., Sarinopoulos, I., Oathes, D. J., Johnstone, T., Whalen, P. J., Davidson, R. J., & Kalin, N. H. (2009). Anticipatory activation in the amygdala and anterior cingulate in generalized anxiety disorder and prediction of treatment response. *The American Journal of Psychiatry, 166*(3), 302–310. https://doi.org/10.1176/appi.ajp.2008.07101682

Nofzinger, E. A. (2005). Functional neuroimaging of sleep. *Seminars in Neurology, 25*(1), 9–18. https://doi.org/10.1055/s-2005-867070

Paulus, M. P., & Stein, M. B. (2006). An insular view of anxiety. *Biological Psychiatry, 60*(4), 383–387. https://doi.org/10.1016/j.biopsych.2006.03.042

Peper, E., Booiman, A., Lin, I.-M., & Harvey, R. (2016). Increase strength and mood with posture. *Biofeedback, 44*(2), 66–72. https://doi.org/10.5298/1081-5937-44.2.04

Peper, E., Harvey, R., Mason, L., & Lin, I.-M. (2018). Do better in math: How your body posture may change stereotype threat response. *NeuroRegulation, 5*(2), 67–74. https://doi.org/10.15540/nr.5.2.67

Peper, E. & Lin, I.-M. (2012). Increase or decrease depression: How body postures influence your energy level. *Biofeedback, 40*(3), 125–130. https://doi.org/10.5298/1081-5937-40.3.01

Peper, E., Lin, I.-M., Harvey, R., & Perez, J. (2017). How posture affects memory recall and mood. *Biofeedback, 45*(2), 36–41. https://doi.org/10.5298/1081-5937-45.2.01

Phelps, E. A., Delgado, M. R., Nearing, K. I., & LeDoux, J. E. (2004). Extinction learning in humans: Role of the amygdala and vmPFC. *Neuron, 43*(6), 897–905. https://doi.org/10.1016/j.neuron.2004.08.042

Raghavachari, S., Kahana, M. J., Rizzuto, D. S., Caplan, J. B., Kirschen, M. P., Bourgeois, B., … Lisman, J. E. (2001). Gating of human theta oscillations by a working memory task. *The*

Journal of Neuroscience, 21(9), 3175–3183. https://doi.org/10.1523/JNEUROSCI.21-09-03175.2001

Rauch, S. L., Whalen, P. J., Shin, L. M., McInerney, S. C., Macklin, M. L., Lasko, N. B., ... Pitman, R. K. (2000). Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: A functional MRI study. *Biological Psychiatry, 47*(9), 769–776. https://doi.org/10.1016/s0006-3223(00)00828-3

Shin, L. M., Rauch, S. L., & Pitman, R. K. (2006). Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. *Annals of the New York Academy of Sciences, 1071*(1), 67–79. https://doi.org/10.1196/annals.1364.007

Siegle, G. J., Thompson, W., Carter, C. S., Steinhauer, S. R., & Thase, M. E. (2007). Increased amygdala and decreased dorsolateral prefrontal BOLD responses in unipolar depression: Related and independent features. *Biological Psychiatry, 61*(2), 198–209. https://doi.org/10.1016/j.biopsych.2006.05.048

Spironelli, C., Busenello, J., & Angrilli, A. (2016). Supine posture inhibits cortical activity: Evidence from delta and alpha EEG bands. *Neuropsychologia, 89*, 125–131. https://doi.org/10.1016/j.neuropsychologia.2016.06.015

Theta Waves. (n.d.). Retrieved from http://scottsdaleneurofeedback.com/services/qeeg-brain-mapping/eeg-brainwaves/theta-waves/

Tsai, H.-Y., Peper, E., & Lin, I.-M. (2016). EEG patterns under positive/negative body postures and emotion recall tasks. *NeuroRegulation, 3*(1), 23–27. https://doi.org/10.15540/nr.3.1.23

Van der Helm, E., & Walker, M. P. (2012). Sleep and affective brain regulation. *Social and Personality Psychology Compass, 6*(11), 773–791. https://doi.org/10.1111/j.1751-9004.2012.00464.x

Vass, L. K., Copara, M. S., Seyal, M., Shahlaie, K., Farias, S. T., Shen, P. Y., & Ekstrom, A. D. (2016). Oscillations go the distance: Low-frequency human hippocampal oscillations code spatial distance in the absence of sensory cues during teleportation. *Neuron, 89*(6), 1180–1186. https://doi.org/10.1016/j.neuron.2016.01.045

Walker, M. P. (2009). The role of sleep in cognition and emotion. *Annals of the New York Academy of Sciences, 1156*(1), 168–197. https://doi.org/10.1111/j.1749-6632.2009.04416.x

Watrous, A. J., Fried, I., & Ekstrom, A. D. (2011). Behavioral correlates of human hippocampal delta and theta oscillations during navigation. *Journal of Neurophysiology, 105*(4), 1747–1755. https://doi.org/10.1152/jn.00921.2010

Wilson, V. E., & Peper, E. (2004). The effects of upright and slumped postures on the generation of positive and negative thoughts. *Applied Psychophysiology and Biofeedback, 29*(3), 189–195. https://doi.org/10.1023/B:APBI.0000039057.32963.34

Woods, S. (1987). [Blood flow through the brain in healthy subjects as measured with SPECT]. Unpublished raw data. New Haven, CT: Yale University.

Yoo, S.-S., Gujar, N., Hu, P., Jolesz, F. A., & Walker, M. P. (2007). The human emotional brain without sleep—a prefrontal amygdala disconnect. *Current Biology, 17*(20), 877–878. https://doi.org/10.1016/j.cub.2007.08.007

Zhang, H., & Jacobs, J. (2015). Traveling theta waves in the human hippocampus. *The Journal of Neuroscience*, *35*(36), 12477–12487. https://doi.org/10.1523/jneurosci.5102-14.2015

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NeuroRegulation

Zebrafish: An *In Vivo* Model for the Study of Therapeutic Targets of Epilepsy

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Abstract

Epilepsy is a common neurological disorder due to excessive brain cell activity. It is characterized by unpredictable seizures resulting in cognition. The release of abnormal electric discharge in the regions of the brain causes epileptic seizures. Neurotransmitters play an important role in normal functioning of the brain and thus alteration of these neurotransmitters are associated with epilepsy. Zebrafish model have recently become a focus for various neurological disorders because of its high genetic similarity when compared with those of humans. Zebrafish can be grown in large numbers and their embryos are optically clear allowing examination of individual genes. This review will look at the utility of the zebrafish in the study of various therapeutic targets of epilepsy such as GABA (gamma-aminobutyric acid), AMPA, NMDA (N-methyl-d-aspartate), histamine H3, and phosphodiesters.

Keywords: epilepsy; seizures; neurotransmitters; zebrafish; therapeutic targets

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Introduction

Epilepsy is a common neurological disorder which causes biomedical disturbance resulting in abnormal electrical activity in certain neurons, which may further affect the entire brain. This abnormal neuronal activity has a significant influence in cognitive dysfunction and mental health condition (Kwan & Brodie, 2001; Meador, 2002; Smith, Craft, Collins, Mattson, & Cramer, 1986). An epileptic seizure is a sign of abnormal activity in neurons which is spontaneous. The effect of chemical reaction in the brain produces electrical discharges, and thus the disturbance of excitation and inhibition in a region of brain when moved too far in the direction of excitation results in seizures (Dekker, 2002).

The classification of epileptic seizures is divided into three categories (generalized, focal, and epileptic spasms) depending upon the release of abnormal electric discharge in the region of brain. Generalized seizures affect both hemispheres of the brain; focal seizures are limited to one hemisphere yet may progress to generalized seizures (Berg & Millichap, 2013). A seizure is accompanied with imbalance excitation and inhibition in the brain, resulting in alteration of brain functioning and genes. The imbalance leading to epilepsy can occur anywhere from circuit level to receptor level and, in some cases, it might be due to abnormal ionic channel function (Berkovic, 2015).

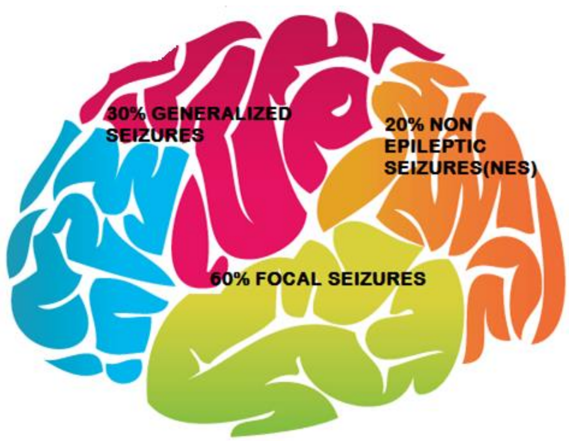

Figure 1. Classification of epileptic seizures upon abnormal electrical discharge in the human brain.

Both children and adults with epilepsy are prone to long-term forgetting in which newly acquired memories fade over days and memory impairment in which autobiographical or public facts are forgotten (Butler & Zeman, 2008). Accelerated long-term forgetting is a condition where individuals learn and initially retain information normally but forget the information at an unusually rapid rate (Blake, Wroe, Breen, & McCarthy, 2000). Accelerated forgetting has been demonstrated in both adults and children (Butler et al., 2009; Martinos et al., 2012).

Neurotransmitters (gamma-aminobutyric acid [GABA], glutamate, and acetylcholine) are associated with normal functioning of brain. The alteration of these neurotransmitters has a significant role in epilepsy (Sancheti, Shaikh, Khatwani, Kulkarni, & Sathaye, 2013). GABA is an inhibitory transmitter and helps in suppressing epilepsy, whereas glutamate causes neuronal death. Acetylcholine plays the key role in modulating glutamate release and memory formation (Ozawa, Kamiya, & Tsuzuki, 1998).

Zebrafish (Danio rerio) has become a widely used model system for the neurobehavioral system. Zebrafish are vertebrates and therefore more closely related to other model organisms and also share a high genetic similarity to humans; approximately 70% of all human disease genes have functional homologs in zebrafish (Cooper, D'Amico, & Henry, 1999).

Recent studies have proven that zebrafish possess several advantages over other animal models. Zebrafish are much easier to maintain in a laboratory and can also be grown in large numbers (Kimmel, 1989). The mode of fertilization is external, and their embryos are optically clear allowing examination of individual genes (fluorescently labeled or dyed; Bernasconi, 2004; Cendes, 2005; Kimmel & Warga 1988; Solnica-Krezel, Stemple, & Driever, 1995; Tran & Gerlai, 2015). The small size of zebrafish larvae allows easy manipulation of gene activities and screening of neuroactive compounds (Kuzniecky & Knowlton, 2002).

The aim of this systematic review summarizes the potential of zebrafish as a model organism to examine various therapeutic targets of epilepsy.

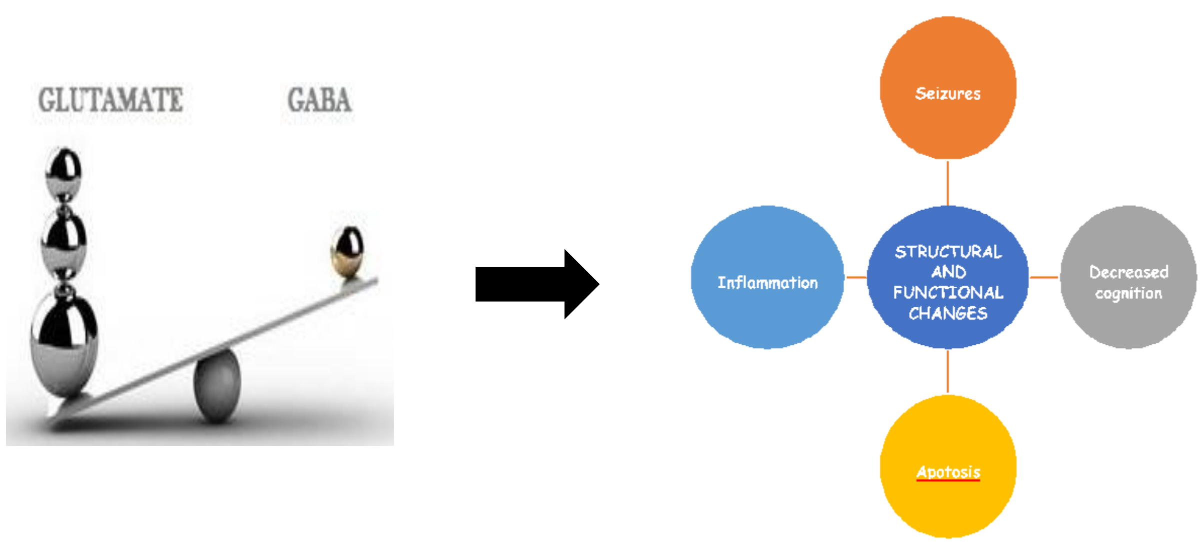

Figure 2. Schematic representation of excitatory and inhibitory neurotransmitter induced changes

Therapeutic Targets of Epilepsy

Gamma-Aminobutyric Acid

GABA is the major inhibitory neurotransmitter of the nervous system (Bowery & Smart, 2006). It acts through its receptors known as GABA receptors, which are divided into two classes, $GABA_A$ and $GABA_B$. $GABA_A$ receptors are chloride channels, while $GABA_B$ receptors belong to class of G-protein coupled receptors (GPCR). $GABA_A$ receptors are combinations of 19 different subunits (α1–6, β1–3, γ1–3, δ, ε, π, θ, and ρ1–3) and are targets for classes of clinically important drugs, such as benzodiazepines and barbiturates (Chua & Chebib, 2017; Möhler, 2006; Olsen & Sieghart, 2008).

$GABA_B$ receptors are G protein–linked receptors that decrease calcium entry and have a slow inhibitory effect. The activation of $GABA_B$ receptors is associated with a decrease in neurotransmitter release, and thus $GABA_B$ agonist drugs would have an antiepileptic effect (Swartzwelder, Bragdon, Sutch, Ault & Wilson, 1986). GABAergic neurons are ubiquitously distributed in the brain that determines the integration of all neuronal functions. Blockade of the fast inhibitory $GABA_A$ receptors might be the major cause of seizures. It has therefore been suggested that dysfunction of the GABAergic system may have an influence in the development of acute seizures and in the manifestation of epilepsy syndromes (Möhler, 2006).

Zebrafish contain at least 23 different $GABA_A$ receptor subunits. Although we observed some differences between the zebrafish and mammalian $GABA_A$ receptor subunit gene families, zebrafish contain orthologs for most of the $GABA_A$ receptor subunits found in mammals. $GABA_A$ receptors are expressed in larval zebrafish and are essential for normal brain function (Baraban, Taylor, Castro, & Baier, 2005).

Ampa Receptor Potentiators

Glutamate is the major excitatory neurotransmitter released from nerve cells of the adult mammalian brain that mediates numerous processes. Glutamates are classified into two large subclasses of receptors: the ionotropic glutamate receptors and the metabotropic glutamate receptors. The ionotropic receptors can be further subdivided into AMPA, kainate, and N-methyl-d-aspartic acid (NMDA) receptors (Featherstone, 2010; Meldrum, 2000; Seeburg, 1993). The AMPA receptor comprises four subunits, which include at least two of the following subunit types: GluA1, GluA2, GluA3, or GluA4 (Mansour, Nagarajan, Nehring, Clements, & Rosenmund, 2001). AMPA receptors are the major excitatory postsynaptic receptor which are expressed abundantly throughout the central nervous system (CNS; Rogawski, 2011).

Early studies have indicated the pathophysiologic role of AMPA receptors in epilepsy. The blockade of AMPA receptors may have a role in abnormal electrical activity in the epileptic brain (Mansour et al., 2001). The AMPA-receptor subunit expression of human epileptic brain revealed high expression of the GluA1-receptor subunit in the epileptic hippocampus (Graebenitz et al., 2011) which indeed increases the levels of homomeric GluA1 receptor, that exhibits high conductance compared with the GluA2-containing Ca2+-impermeable heteromeric receptors (Coombs, et al., 2012; Ying, Babb, Comair, Bushey, & Touhalisky, 1998). Neuronal degeneration usually occurs with increased expression of GluA2-lacking calcium permeable receptors, thus AMPA receptors might have a significant role in the pathophysiology of epilepsy: not only the expression of seizures but also the progression of epilepsy (Grossman, Wolfe, Yasuda, & Wrathall, 1999; Liu & Zukin, 2007; Swanson, Kamboj, & Cull-Candy, 1997).

The subunits of AMPA receptors have been expressed in zebrafish with a high degree of similarity when compared to those of humans, rats, and mice. AMPA receptors have been found in different regions of zebrafish (retina, hindbrain, spinal cord, and neurons; Ali, Buss, & Drapeau, 2000; Patten & Ali, 2007; Yazulla & Studholme, 2001). They are also associated with the neuromuscular junction that facilitate acetylcholine release during early development in zebrafish (Todd, Slatter, & Ali, 2004).

N-Methyl-D-Aspartate Receptors

N-methyl-d-aspartate receptors (NMDARs) are ligand-gated ionotropic glutamate receptors that are important mediators for neuronal events such as synaptic plasticity, learning and memory, neuronal development and circuit formation, and have been implicated in various neuronal disorders (Cull-Candy, Brickley & Farrant, 2001; Hua & Smith, 2004). The mammalian NMDA receptor was first cloned in 1991 (Moriyoshi et al., 1991), and its structure and function has been studied widely in mammals. These receptors are highly permeable to calcium and, thus, may play important regulatory roles in the response of neurons to signaling (Mayer & Armstrong, 2004; Riedel, Platt, & Micheau, 2003).

There are five NMDA receptor genes expressed in mammals encoding for NMDAR1 (NR1) and NMDAR2 (NR2) subunits (Cox, Kucenas, & Voigt, 2005). The NR1 subunit are widely distributed throughout the CNS, which plays an important role in voltage independent zinc inhibition, whereas the NR2 subunits exhibit cell-specific expression patterns. Pharmacological regulation of the NMDAR depends on effects on unique combinations of subunit-specific binding sites. Both the NR1 and NR2 subunits contribute to the formation of the NMDAR ion channel. The glutamate-binding site is on the NR2 subunits, and the glycine-binding site is located on the NR1 subunits. The glycine (and/or D-serine) co-agonist site must be the pathogenesis of epileptic discharges (Carter, Deshpande, Rafiq, Sombati, & DeLorenzo, 2010).

The subunits NR1 and NR2 of NMDA receptor have been expressed in zebrafish and the similarity between subunits of zebrafish when compared to those of human showed high degree of identity (NR1 subunit expressed 90% identity and NR2 receptors expressed 50–90% identity; Cox et al., 2005).

Histamine 3 Receptor Antagonists

The histamine neuroreceptor system is one of the major excitatory neurotransmitters exerting key neurological functions including alertness and sleep, seizure threshold, hormone secretion, and pain (Brown, Stevens, & Hans, 2001; Haas & Panula, 2003; Schwartz, Arrang, Garbarg, Pollard, & Ruat, 1991). Histamine belongs to a large superfamily of GPCRs that are characterized by the presence of seven transmembrane domains (Leurs, Bakker, Timmerman, & de Esch, 2005). The histamine H3 receptor (H3R), which is particularly expressed in the CNS and specifically in the brain, has led to the development of numerous antagonists/inverse agonists for the potential treatment of brain (Martinez-Mir et al., 1990). H3R is a presynaptic auto-receptor on histamine neurons and a heteroreceptor which modulates the activity of various neurotransmitters such as histamine, acetylcholine, noradrenaline, dopamine, serotonin, and GABA (Sander, Kottke, & Stark, 2008; Schlicker, Betz, & Göthert, 1988). Low levels of histamine are usually associated with convulsions (Kiviranta, Tuomisto, & Airaksinen, 1995; Tuomisto & Tacke, 1986).

The nonimidazole class has the potential to penetrate the brain more easily than those with an imidazole ring and, accordingly, H3R antagonists/inverse agonists have been targeted for a broad spectrum of brain diseases; for example, Alzheimer's disease, dementia, stroke, mood and sleep disorders, attention-deficit disorders, schizophrenia, narcolepsy, anxiety, depression, and epilepsy (Bahi, Sadek, Schwed, Walter, & Stark, 2013; Bhowmik, Khanam, & Vohora, 2012; Inocente et al., 2012; Kuhne, Wijtmans, Lim, Leurs, & de Esch, 2011; Leurs, Vischer, Wijtmans, & de Esch, 2011; Sadek et al., 2013). Furthermore, ligands for the H3R are now in clinical studies and some companies have H3R antagonists for phase 1 and phase 2 clinical trials under review that could offer potential treatment for Alzheimer's disease, schizophrenia, epilepsy, narcolepsy, obesity, neuropathic pain, and allergic rhinitis (Micallef, Stark, & Sasse, 2013; Peitsaro, Sundvik, Anichtchik, Kaslin, & Panula, 2007).

Histamine receptors have been cloned and expressed in zebrafish in which H3R is expressed throughout the zebrafish brain especially in the region of optic tectum and hypothalamus, and receptor peptide sequence showed 50% identity in comparison to human (Griffin et al., 2017; Peitsaro, Anichtchik, & Panula, 2000). A recent study has demonstrated the role of clemizole (a histamine antagonist) as a potent inhibitor of seizures activity in zebrafish (Cofiel & Mattioli, 2006).

Phosphodiesterases

Cyclic AMP (cAMP) and/or cyclic guanosine monophosphate (cGMP) are hydrolyzed by Phosphodiesterase (PDEs) that contains 11 isozymes encoded by 21 genes in mammals (Bender & Beavo, 2006; Seeger et al., 2003). PDE10A are found in multiple regions of the brain in mammalian species. The upregulation of cAMP and cGMP concentrations in different regions of brain is due to the inhibition of PDE10A (Francis, Blount, & Corbin, 2011; Grauer et al., 2009; Suzuki, Harada, Suzuki, Miyamoto, & Kimura, 2016). The presence of PDE10A in different regions of mammalian brain, suggests that it has various functions in the CNS (Leuti et al., 2013; Liddie, Anderson, Paz, & Itzhak, 2012). Several studies have clearly demonstrated the importance of PDE10A in the treatment of neurological and psychiatric disorders. The inhibition of PDE10A has proved as a promising candidate for the treatment of schizophrenia in animal or preclinical research (Siuciak et al., 2006). PDE10A may be involved in the pathophysiology of various neurological and psychiatric disorders (Giralt et al., 2013).

In zebrafish, 2',3'-cyclic-nucleotide 3'-phosphodiesterase was first reported as being induced during optic nerve regeneration study (Chang, Chandler, Williams, & Walker, 2010). Recent investigations have provided information of two enzymes of primary interest PDE4 and PDE10A which have a high percentage of identity to that of humans (Ballestero, Dybowski, Levy, Agranoff, &

Uhler, 1999). Clearly more investigations are needed to elucidate the distribution of PDEs in fish and their role epilepsy.

Conclusion

Animal models are considered as a useful tool for investigating the cause and pathology of human disease, yet to develop an animal model for brain disorder, particularly epilepsy, is very difficult because of its disease complexity. It is now recognized that zebrafish possess a great deal of similarity to mammals and are highly advantageous with their unique properties such as external fertilization, small size, as well as optical clarity of embryos. The central role of receptors in epilepsy demonstrates the potential utility of targets to control seizures. In this review we have discussed various pharmacological targets which are being investigated preclinically for epilepsy—GABA, Phosphodiesterase, Histamine 3, NMDA, and AMPA—and have illustrated the use of zebrafish in the assessment of these targets.

Author Disclosure

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

References

Ali, D. W., Buss, R. R., & Drapeau, P. (2000). Properties of miniature glutamatergic EPSCs in neurons of the locomotor regions of the developing zebrafish. *Journal of Neurophysiology*, *83*(1), 181–191. https://doi.org/10.1152/jn.2000.83.1.181

Bahi, A., Sadek, B., Schwed, S. J., Walter, M., & Stark, H. (2013). Influence of the novel histamine H3 receptor antagonist ST1283 on voluntary alcohol consumption and ethanol-induced place preference in mice. *Psychopharmacology, 228*(1), 85–95. https://doi.org/10.1007/s00213-013-3019-7

Ballestero, R. P., Dybowski, J. A., Levy, G., Agranoff, B. W., & Uhler, M. D. (1999). Cloning and characterization of zRICH, a 2',3'-cyclic-nucleotide 3'-phosphodiesterase induced during zebrafish optic nerve regeneration. *Journal of Neurochemistry,* 72(4), 1362–1371. https://doi.org/10.1046/j.1471-4159.1999.721362.x

Baraban, S. C., Taylor, M. R., Castro, P. A., & Baier, H. (2005). Pentylenetetrazole induced changes in zebrafish behavior, neural activity and c-fos expression. *Neuroscience, 131*(3), 759–768. https://doi.org/10.1016/j.neuroscience.2004.11.031

Bender, A. T., & Beavo, J. A. (2006). Cyclic nucleotide phosphodiesterases: Molecular regulation to clinical use. *Pharmacological Reviews, 58*(3), 488–520. https://doi.org/10.1124/pr.58.3.5

Berg, A. T., & Millichap, J. J. (2013). The 2010 revised classification of seizures and epilepsy. *Continuum: Lifelong Learning in Neurology, 19*(3), 571–597. https://doi.org/10.1212/01.CON.0000431377.44312.9e

Berkovic, S. F. (2015). Genetics of epilepsy in humans. *Cold Spring Harbor Laboratory Perspectives in Medicine*. https://doi.org/10.1101/cshperspect.a022400

Bernasconi, A. (2004). Quantitative MR imaging of the neocortex. *Neuroimaging Clinics of North America, 14*(3), 425–436. https://doi.org/10.1016/j.nic.2004.04.013

Bhowmik, M., Khanam, R., & Vohora, D. (2012). Histamine H3 receptor antagonists in relation to epilepsy and neurodegeneration: A systemic consideration of recent progress and perspectives. *British Journal of Pharmacology*, *167*(7), 1398–1414. https://doi.org/10.1111/j.1476-5381.2012.02093.x

Blake, R. V., Wroe, S. J., Breen, E. K., & McCarthy, R. A. (2000). Accelerated forgetting in patients with epilepsy: Evidence for an impairment in memory consolidation. *Brain, 123*(3), 472–483. https://doi.org/10.1093/brain/123.3.472

Bowery, N. G., & Smart, T. G. (2006). GABA and glycine as neurotransmitters: A brief history. *British Journal of Pharmacology, 147*(1), 109–119. https://doi.org/10.1038/sj.bjp.0706443

Brown, R. E., Stevens, D. R., & Haas, H. L. (2001). The physiology of brain histamine. *Progress in Neurobiology, 63*(6), 637–672. https://doi.org/10.1016/S0301-0082(00)00039-3

Butler, C. R., Bhaduri, A., Acosta-Cabronero, J., Nestor, P. J., Kapur, N., Graham, K. S., … Zeman, A. Z. (2009). Transient epileptic amnesia: Regional brain atrophy and its relationship to memory deficits. *Brain*, *132*(2), 357–368. https://doi.org/10.1093/brain/awn336

Butler, C. R., & Zeman, A. Z. (2008). Recent insights into the impairment of memory in epilepsy: Transient epileptic amnesia, accelerated long-term forgetting and remote memory impairment. *Brain, 131*(9), 2243–2263. https://doi.org/10.1093/brain/awn127

Carter, D. S., Deshpande, L. S., Rafiq, A., Sombati, S., & DeLorenzo, R. J. (2010). Characterization of spontaneous recurrent epileptiform discharges in hippocampal-entorhinal cortical slices prepared from chronic epileptic animals. *Seizure, 20*(3), 218–224. https://doi.org /10.1016/j.seizure.2010.11.022

Cendes, F. (2005). Progressive hippocampal and extrahippocampal atrophy in drug resistant epilepsy. *Current Opinion in Neurology, 18*(2), 173–177. https://doi.org/10.1097/01.wco.0000162860.49842.90

Chang, P., Chandler, K. E., Williams, R. S., & Walker, M. C. (2010). Inhibition of long-term potentiation by valproic acid through modulation of cyclic AMP. *Epilepsia, 51*(8) 1533–1542. https://doi.org/10.1111/j.1528-1167.2009.02412.x

Chua, H. C., & Chebib, M. (2017). GABAA receptors and the diversity in their structure and pharmacology. *Advances in Pharmacology, 79*, 1–34. https://doi.org/10.1016/bs.apha.2017.03.003

Cofiel, L. P., & Mattioli, R. (2006). Involvement of histamine receptors in the acquisition of inhibitory avoidance in Carassius auratus. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 30*(7), 1246–1250. https://doi.org/10.1016/j.pnpbp.2006.03.017

Coombs, I. D., Soto, D., Zonouzi, M., Renzi, M., Shelley, C., Farrant, M., & Cull-Candy, S.G. (2012). Cornichons modify channel properties of recombinant and glial AMPA receptors. *The Journal of Neuroscience, 32*(29), 9796–9804. https://doi.org/10.1523/JNEUROSCI.0345-12.2012

Cooper, M. S., D'Amico, L. A., & Henry, C. A. (1999). Confocal microscopic analysis of morphogenetic movements. *Methods in Cell Biology, 59*, 179–204. https://doi.org/10.1016/S0091-679X(08)61826-9

Cox, J. A., Kucenas, S., & Voigt, M. M. (2005). Molecular characterization and embryonic expression of the family of N-Methyl-D Aspartate receptor subunit genes in the zebrafish. *Developmental Dynamics, 234*(3), 756–766. https://doi.org/10.1002/dvdy.20532

Cull-Candy, S., Brickley, S., & Farrant, M. (2001). NMDA receptor subunits: Diversity, development and disease. *Current Opinion in Neurobiology, 11*(3), 327–335. https://doi.org/10.1016/S0959-4388(00)00215-4

Dekker, P. A. (2002). *Epilepsy: A manual to medical & clinical officers in Africa* (Rev. 2nd ed.). Geneva: World Health Organization.

Featherstone, D. E. (2010). Intercellular glutamate signaling in the nervous system and beyond. *ACS Chemistry Neuroscience, 1*(1), 4–12. https://doi.org/10.1021/cn900006n

Francis, S. H., Blount, M. A., & Corbin, J. D. (2011). Mammalian cyclic nucleotide phosphodiesterases: Molecular mechanisms and physiological functions. *Physiological Reviews, 91*(2), 651–690. https://doi.org/10.1152/physrev.00030.2010

Giralt, A., Saavedra, A., Carretón, O., Arumí, H., Tyebji, S., Alberch, J., & Pérez-Navarro, E. (2013). PDE10 inhibition increases GluA1 and CREB phosphorylation and improves spatial and recognition memories in a Huntington's disease mouse model. *Hippocampus, 23*(8), 684–695. https://doi.org/10.1002/hipo.22128

Graebenitz, S., Kedo, O., & Speckmann, E.-J., Gorji, A., Panneck, H., Hans, V., … Pape, H.-C. (2011). Interictal-like network activity and receptor expression in the epileptic human lateral amygdala. *Brain, 134*(10), 2929–2947. https://doi.org/10.1093/brain/awr202

Grauer, S. M., Pulito, V. L., Navarra, R. L., Kelly, M. P., Kelley, C., Graf, R., … Brandon, N. J. (2009). Phosphodiesterase 10A inhibitor activity in preclinical models of the positive, cognitive, and negative symptoms of schizophrenia. *Journal of Pharmacology and Experimental Therapeutics, 331*(2)*,* 574–590. https://doi.org/10.1124/jpet.109.155994

Griffin, A., Hamling, K. R., Knupp, K., Hong, S., Lee, L. P., & Baraban, S. C. (2017). Clemizole and modulators of serotonin signalling suppress seizures in Dravet syndrome. *Brain, 140*(3), 669–683. https://doi.org/10.1093/brain/aww342

Grossman, S. D., Wolfe, B. B., Yasuda, R. P., & Wrathall, J. R. (1999). Alterations in AMPA receptor subunit expression after experimental spinal cord contusion injury. *Journal of Neuroscience, 19*(14), 5711–5720. https://doi.org/10.1523/JNEUROSCI.19-14-05711.1999

Haas, H., & Panula, P. (2003). The role of histamine and the tuberomamillary nucleus in the nervous system. *Nature Reviews Neuroscience, 4,* 121–130. https://doi.org/10.1038/nrn1034

Hua, J. Y., & Smith, S. J. (2004). Neural activity and the dynamics of central nervous system development. *Nature Neuroscience, 7*, 327–332. https://doi.org/10.1038/nn1218

Inocente, C., Arnulf, I., Bastuji, H., Thibault-Stoll, A., Raoux, A., Reimão, R., … Franco, P. (2012). Pitolisant, an inverse agonist of the histamine H3 receptor: An alternative stimulant for narcolepsy-cataplexy in teenagers with refractory sleepiness. *Clinical Neuropharmacology, 35*(2), 55–60. https://doi.org/10.1097/WNF.0b013e318246879d

Kimmel, C. B. (1989). Genetics and early development of zebrafish. *Trends in Genetics, 5*, 283–288. https://doi.org/10.1016/0168-9525(89)90103-0

Kimmel, C. B. & Warga, R. M. (1988). Cell lineage and developmental potential of cells in the zebrafish embryo. *Trends in Genetics, 4*(3), 68–74. https://doi.org/10.1016/0168-9525(88)90043-1

Kiviranta, T., Tuomisto, L., & Airaksinen, E. M. (1995). Histamine in cerebrospinal fluid of children with febrile convulsions. *Epilepsia, 36*(3), 276–280. https://doi.org/10.1111/j.1528-1157.1995.tb00996.x

Kuhne, S., Wijtmans, M., Lim, H. D., Leurs, R., & de Esch, I. J. (2011). Several down, a few to go: Histamine H3 receptor ligands making the final push towards the market? *Expert Opinion on Investigational Drugs, 20*(12), 1629–1648. https://doi.org/10.1517/13543784.2011.625010

Kuzniecky, R. I., & Knowlton, R. C. (2002). Neuroimaging of epilepsy. *Seminars in Neurology, 22*(3), 279–288. https://doi.org/10.1055/s-2002-36647

Kwan, P., & Brodie, M. J. (2001). Neuropsychological effects of epilepsy and antiepileptic drugs. *The Lancet*, *357*(9251), 216–222. https://doi.org/10.1016/S0140-6736(00)03600-X

Leurs, R., Bakker, R. A., Timmerman, H., & de Esch, I. J. (2005). The histamine H3 receptor: From gene cloning to H3 receptor drugs. *Nature Reviews Drug Discovery, 4*, 107–120. https://doi.org/10.1038/nrd1631

Leurs, R., Vischer, H. F., Wijtmans, M., & de Esch, I. J. (2011). En route to new blockbuster anti-histamines: Surveying the offspring of the expanding histamine receptor family. *Trends in Pharmacological Sciences, 32*(4), 250–257. https://doi.org/10.1016/j.tips.2011.02.004

Leuti, A., Laurenti, D., Giampà, C., Montagna, E., Dato, C., Anzilotti S., … Fusco, F. R. (2013). Phosphodiesterase 10A (PDE10A) localization in the R6/2 mouse model of Huntington's disease. *Neurobiology of Disease, 52*, 104–116. https://doi.org/10.1016/j.nbd.2012.11.016

Liddie, S., Anderson, K. L., Paz, A., & Itzhak, Y. (2012). The effect of phosphodiesterase inhibitors on the extinction of cocaine-induced conditioned place preference in mice. *Journal of Psychopharmacology, 26*(10), 1375–1382. https://doi.org/10.1177/0269881112447991

Liu, S. J., & Zukin, R. S. (2007). Ca^{2+}-permeable AMPA receptors in synaptic plasticity and neuronal death. *Trends in Neurosciences, 30*(3), 126–134. https://doi.org/10.1016/j.tins.2007.01.006

Mansour, M., Nagarajan, N., Nehring, R. B., Clements, J. D., & Rosenmund, C. (2001). Heteromeric AMPA receptors assemble with a preferred subunit stoichiometry and spatial arrangement. *Neuron, 32*(5)*,* 841–853. https://doi.org/10.1016/S0896-6273(01)00520-7

Martinez-Mir, M. I., Pollard, H., Moreau, J., Arrang, J. M., Ruat, M., Traiffort, E., … Palacios, J. M. (1990). Three histamine receptors (H1, H2 and H3) visualized in the brain of human and non-human primates. *Brain Research, 526*(2), 322–327. https://doi.org/10.1016/0006-8993(90)91240-h

Martinos, M. M., Yoong, M., Patil, S., Chin, R. F., Neville, B. G., Scott, R. C., & de Haan, M. (2012). Recognition memory is impaired in children after prolonged febrile seizures. *Brain, 135*(10)*,* 3153–3164. https://doi.org/10.1093/brain/aws213

Mayer, M. L., & Armstrong, N. (2004). Structure and function of glutamate receptor ion channels. *Annual Review of Physiology, 66,* 161–181. https://doi.org/10.1146/annurev.physiol.66.050802.084104

Meador, K. J. (2002). Cognitive outcomes and predictive factors in epilepsy. *Neurology, 58*(8, Suppl. 5), S21–S26. https://doi.org/10.1212/wnl.58.8_suppl_5.s21

Meldrum, B. S. (2000). Glutamate as a neurotransmitter in the brain: Review of physiology and pathology. *The Journal of Nutrition, 130*(Suppl. 4S), 1007S–1015S. https://doi.org/10.1093/jn/130.4.1007S

Micallef, S., Stark, H., & Sasse, A. (2013). Polymorphisms and genetic linkage of histamine receptors. *Life Sciences, 93*(15), 487–494. https://doi.org/10.1016/j.lfs.2013.08.012

Möhler, H. (2006). $GABA_{(A)}$ receptor diversity and pharmacology. *Cell and Tissue Research, 326*(2), 505–516. https://doi.org/10.1007/s00441-006-0284-3

Moriyoshi, K., Masu, M., Ishii, T., Shigemoto, R., Mizuno, N., & Nakanishi, S. (1991). Molecular cloning and characterization of the rat NMDA receptor. *Nature, 354*, 31–37. https://doi.org/10.1038/354031a0

Olsen, R. W., & Sieghart, W. (2008). International Union of Pharmacology. LXX. Subtypes of gamma-aminobutyric acid(A) receptors: Classification on the basis of subunit composition, pharmacology and function. *Pharmacolological Reviews, 60*(3), 243–260. https://doi.org/10.1124 /pr.108.00505

Ozawa, S., Kamiya, H., & Tsuzuki, K. (1998). Glutamate receptors in the mammalian central nervous system. *Progress in Neurobiology, 54*(5), 581–618. https://doi.org /10.1016/S0301-0082(97)00085-3

Patten, S. A., & Ali, D. W. (2007). AMPA receptors associated with zebrafish Mauthner cells switch subunits during development. *Journal of Physiology*, *581*(3), 1043–1056. https://doi.org/10.1113/jphysiol.2007.129999

Peitsaro, N., Anichtchik, O. V., & Panula, P. (2000). Identification of a histamine H(3)-like receptor in the zebrafish (Danio rerio) brain. *Journal of Neurochemistry, 75*(2)*,* 718–724. https://doi.org/10.1046/j.1471-4159.2000.0750718.x

Peitsaro, N., Sundvik, M., Anichtchik, O. V., Kaslin, J., & Panula, P. (2007). Identification of zebrafish histamine H1, H2 and H3 receptors and effects of histaminergic ligands on behavior. *Biochemical Pharmacology, 73*(8), 1205–1214. https://doi.org/10.1016/j.bcp.2007.01.014

Riedel, G., Platt, B., & Micheau, J. (2003). Glutamate receptor function in learning and memory. *Behavioural Brain Research, 140*(1–2), 1–47. https://doi.org/10.1016/S0166-4328(02)00272-3

Rogawski, M. A. (2011). Revisiting AMPA receptors as an antiepileptic drug target. *Epilepsy Currents, 11*(2), 56–63. https://doi.org/10.5698/1535-7511-11.2.56

Sadek, B., Shehab, S., Więcek, M., Subramanian, D., Shafiullah, M., Kieć-Kononowicz, K., & Adem, A. (2013). Anticonvulsant properties of histamine H3 receptor ligands belonging to N-substituted carbamates of imidazopropanol. *Bioorganic & Medicinal Chemistry Letters, 23*(17), 4886–4891. https://doi.org/10.1016/j.bmcl.2013.06.075

Sancheti, J. S., Shaikh, M. F., Khatwani, P. F., Kulkarni, S. R., & Sathaye, S. (2013). Development and validation of a HPTLC method for simultaneous estimation of L-glutamic acid and γ-aminobutyric acid in mice brain. *Indian Journal of Pharmaceutical Sciences, 75*(6), 716–721. https://doi.org/10.4103/0250-474X.124797

Sander, K., Kottke, T., & Stark H. (2008). Histamine H3 receptor antagonists go to clinics. *Biological and Pharmaceutical Bulletin, 31*(12), 2163–2181. https://doi.org/10.1248/bpb.31.2163

Schlicker, E., Betz, R., & Göthert, M. (1988). Histamine H3 receptor-mediated inhibition of serotonin release in the rat brain cortex. *Naunyn-Schmiedebergs Archives of Pharmacology, 337*(5)*,* 588–590. https://doi.org/10.1007/bf00182737

Schwartz, J. C., Arrang, J. M., Garbarg, M., Pollard, H., & Ruat, M. (1991). Histaminergic transmission in the mammalian brain. *Physiological Reviews, 71*(1), 1–51. https://doi.org/10.1152/physrev.1991.71.1.1

Seeburg, P. H. (1993). The TINS/TiPS lecture the molecular biology of mammalian glutamate receptor channels. *Trends in Neurosciences, 16*(9), 359–365. https://doi.org/10.1016/0166-2236(93)90093-2

Seeger, T. F., Bartlett, B., Coskran, T. M., Culp, J. S., James, L. C., Krull, D. L., … Menniti, F. S. (2003). Immunohistochemical localization of PDE10A in the rat brain. *Brain Research, 985*(2), 113–126. https://doi.org/10.1016/s0006-8993(03)02754-9

Siuciak, J. A., McCarthy, S. A., Chapin, D. S., Fujiwara, R. A., James, L. C., Williams, R. D., … Schmidt, C. J. (2006). Genetic deletion of the striatum-enriched phosphodiesterase PDE10A: Evidence for altered striatal function. *Neuropharmacology, 51*(2), 374–385. https://doi.org/10.1016/j.neuropharm.2006.01.012

Smith, D. B., Craft, B. R., Collins, J., Mattson, R. H., & Cramer, J. A. (1986). Behavioral characteristics of epilepsy patients compared with normal controls. *Epilepsia, 27*(6), 760–768. https://doi.org/10.1111/j.1528-1157.1986.tb03607.x

Solnica-Krezel, L., Stemple, D. L., & Driever, W. (1995). Transparent things: Cell fates and cell movements during early embryogenesis of zebrafish. *Bioessays, 17*(11), 931–939. https://doi.org/10.1002/bies.950171106

Suzuki, K., Harada, A., Suzuki, H., Miyamoto, M., & Kimura, H. (2016). TAK-063, a PDE10A inhibitor with balanced activation of direct and indirect pathways, provides potent antipsychotic-like effects in multiple paradigms. *Neuropsychopharmacology, 41*, 2252–2262. https://doi.org /10.1038/npp.2016.20

Swanson, G. T., Kamboj, S. K., & Cull-Candy, S. G. (1997). Single-channel properties of recombinant AMPA receptors depend on RNA editing, splice variation, and subunit composition. *Journal of Neuroscience, 17*(1), 58–69. https://doi.org/10.1523/JNEUROSCI.17-01-00058.1997

Swartzwelder, H. S., Bragdon, A. C., Sutch, C. P., Ault, B., & Wilson, W. A. (1986). Baclofen suppresses hippocampal epileptiform activity at low concentrations without suppressing synaptic transmission. *Journal of Pharmacology and Experimental Therapeutics, 237*(3), 881–887.

Todd, K. J., Slatter, C. A., & Ali, D. W. (2004). Activation of ionotropic glutamate receptors on peripheral axons of primary motoneurons mediates transmitter release at the zebrafish NMJ. *Journal of Neurophysiology, 91*(2), 828–840. https://doi.org/10.1152/jn.00599.2003

Tran, S. & Gerlai, R. (2015). Thirty-second net stressor task in adult zebrafish. *Bio-Protocol, 5*(5), e1413. https://doi.org/10.21769/bioprotoc.1413

Tuomisto, L., & Tacke, U. (1986). Is histamine an anticonvulsive inhibitory transmitter? *Neuropharmacology, 25*(8), 955–958. https://doi.org/10.1016/0028-3908(86)90029-8

Yazulla, S., & Studholme, K. M. (2001). Neurochemical anatomy of the zebrafish retina as determined by immunocytochemistry. *Journal of Neurocytology, 30*, 551–592. https://doi.org/10.1007/978-1-4615-1089-5_2

Ying, Z., Babb, T. L., Comair, Y. G., Bushey, M., & Touhalisky, K. (1998). Increased densities of AMPA GluR1 subunit proteins and presynaptic mossy fiber sprouting in the fascia dentata of human hippocampal epilepsy. *Brain Research, 798*(1–2), 239–246. https://doi.org/10.1016/s0006-8993(98)00421-1

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KEYNOTE PRESENTATIONS

Towards Enhancing Neurofeedback Research with Advances in Real-time Monitoring of the Central, Autonomic, and Enteric Nervous Systems

Todd Coleman
University of California, San Diego, California, USA

In this talk, we will highlight recent technological and methodological advances in developing unobtrusive wearable technologies that can monitor many aspects of the central, autonomic, and enteric nervous systems. As an example, we will discuss our research group's development of stretchable electronic biosensors that can be embedded within routinely used medical adhesives and applied to any part of the body for wireless monitoring. We will also discuss methodological developments to robustly track the dynamic interplay between the central, autonomic, and enteric nervous systems with statistical signal processing of electroencephalography (EEG), electrocardiography (ECG), and electrogastrography (EGG) signals, respectively. We will further highlight recent findings in the research literature that showcase their interrelationship in health and disease and how their readouts have created new opportunities to advance neurofeedback therapies. With an interest in exploring beyond what is currently deployed or known in the neurorehabilitation field, we will highlight recent advances with the high-resolution EGG, which involves placing an array of electrical sensors on the abdomen to produce an "EKG of the digestive system." To elucidate what may be actionable, we will discuss an ongoing clinical study involving neurofeedback that exploits the dynamics of the gut–brain axis. We will conclude with a vision of how the rapid advances in multiorgan physiology research, technology miniaturization, data science, and design principles create a bright future for the field of neurofeedback.

Understanding (and Improving) Neurofeedback Efficacy: A Multidisciplinary Endeavor

Eddy Davelaar
Birkbeck, University of London, Bloomsbury, London, England

In this talk, I will present our theoretical (and empirical) work aimed at answering the question "How does neurofeedback work?". The research is guided by the recently formulated multistage theory of neurofeedback learning (Davelaar, 2018). The following examples will be explored. First, giving instructions to trainees has typically been discouraged in the literature on grounds that trainees are inconsistent in their strategy use, they have no knowledge about their strategies, and strategies do not work for everyone. Yet we find that in the case of frontal alpha upregulation, converging verbal reports emerged that are amenable for guided neurofeedback (Davelaar, Barnby, Almasi, & Eatough, 2018). These results require using the explicitation interview as a research methodology followed by a cognitive classification of the reports. Second, the typical study has a pre- and posttraining session of cognitive tests (and perhaps even a qEEG). I will demonstrate that analyzing the cognitive data beyond the superficial averaged response time and accuracy uncovers cognitive changes that are specific to certain theoretically motivated EEG frequencies (Davelaar, 2017). Thus, sensorimotor rhythm (SMR) training and midfrontal theta upregulation show differential influences on first- and second-order attention. In addition, upregulating frontal alpha or midfrontal theta have opposite effects on information processing that are referred to as nondecision processes, such as feature extraction. Finally, I will present a roadmap for how pre- and posttraining qEEG (and intratraining EEG recordings) can be analyzed to investigate the effects on brain circuitry, which after all is the main aim of neurofeedback training. In sum, the development of an explicit theoretical model opens the door for the field of neurofeedback to adopt formal qualitative and quantitative methodologies from cognitive science and tackle research questions that were hitherto beyond the field's reach.

References

Davelaar, E. J. (2017). Testing the specificity of EEG neurofeedback training on first- and second-order measures of attention. In D. Schmorrow & C. Fidopiastis (Eds.), *AC 2017: Augmented Cognition. Neurocognition and Machine Learning. Lecture Notes in Computer Science* (Vol. 10284, pp. 19–27). Switzerland: Springer. https://doi.org/10.1007 /978-3-319-58628-1_2

Davelaar, E. J. (2018). Mechanisms of neurofeedback: A computation-theoretic approach. *Neuroscience, 378*, 175–188. https://doi.org/10.1016/j.neuroscience.2017.05.052

Davelaar, E. J., Barnby, J. M., Almasi, S., & Eatough, V. (2018). Differential subjective experiences in learners and non-learners in frontal alpha neurofeedback: piloting a mixed-method approach. *Frontiers in Human Neuroscience, 12*, 402. https://doi.org/10.3389/fnhum.2018.00402

Outcomes of Double-Blind Randomized Clinical Trial of Neurofeedback for Attention-Deficit/Hyperactivity Disorder

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For the Neurofeedback Collaborative Group

Objective. To determine whether neurofeedback (NF) has a lasting and specific benefit on inattention in attention-deficit/hyperactivity disorder (ADHD) beyond artifact inhibition and other nonspecific effects such as advice on sleep hygiene, nutrition, coaching, etc. Unblinded randomized clinical trials (RCTs) have shown encouraging results, but small blinded, flawed RCTs have not.

Method. Children age 7–10 (*age* 8.4±1.14 years; 78% male, 76% Caucasian, 13% Latino, 8% African American, 4% Asian) at two sites were randomly assigned in a 3:2 ratio to 38 sessions of active neurofeedback (three times per week) using the Lubar-Monastra method to downtrain theta–beta ratio (TBR) vs. sham neurofeedback of equal duration, frequency, and intensity. Primary outcome (parent- and teacher-rated inattentive symptoms) was analyzed by a linear mixed model with time, treatment, time X treatment interaction, site, and site X treatment interaction entered.

Results. 329 children were screened, resulting in 144 randomized, with 142 in the intent-to-treat analysis. Children were diagnosed as inattentive (36%) or combined type (64%) ADHD; 69% had comorbid diagnoses (50% oppositional defiant disorder, 21% internalizing disorders). There were 10 (7%) dropouts from treatment. Treatment fidelity was good (98% by trainer report, 84% by independent fidelity rater). Across treatment arms, there were 94 adverse events possibly related to treatment (e.g., eye pain, irritability, oppositionality, crying, self-injury, headache, depression, skin irritation). Blinded guesses as to sham treatment assignment were correct 7% of the time by children, 24% by trainers, and 25% by parents. Substantial improvements on the primary outcome measure, parent- and teacher-rated inattention, were found, with a large pre- and posttreatment effect size (d = 1.1); 60% of the children responded to treatment, and, most importantly, clinical benefit appears to be maintained at 13-month follow-up. However, these benefits were seen in both groups and not significantly different between the neurofeedback and control group at treatment end. Nonetheless, preliminary results at 13-month follow-up demonstrate the neurofeedback group showed further improvements on inattention, whereas the control group remained stable with a medium effect size between-group difference. Complete statistical results on the full sample at 13-month follow-up will be presented.

Conclusion. The multimodal nature of the treatment—including supportive coaching, advice on sleep hygiene and nutrition, and practice focusing on a nonentertaining screen—likely contributed to the control group's large improvement, resulting in the lack of short-term difference. In fact, some evidence was found that the control condition might not have been fully inert, since some above-chance-level learning was observed in the control group, although that could not explain all the observed benefit for controls. Further analyses and study will have to focus on explaining the good response in the control group; however, preliminary results suggest a medium specific delayed "sleeper" effect of NF at 13-month follow-up.

Epilepsy and the Foundation of NF

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In the beginning there were those doing "state-based" EEG training like Joe Kamiya and Elmer Green, and those doing "clinical" work with epilepsy associated largely with Barry Sterman or Nils Birbaumer. ADHD and other applications came later…but the scientific proof-level work in epilepsy was quite impressive even in the mid-1970s. Despite the efficacy proofs, most NF practitioners today do not work with epilepsy as a primary indication for clinical work…. *At least not knowingly*.

However, approximately 20% of those with ADHD and from 40 to 60% of those with ASD have “unexpected” epileptiform discharges or paroxysms. These clients still need our help. There are also many thousands with intractable epilepsy.

A series of severe intractable epileptic cases illustrates the life-changing nature of applying NF clinically. Very current publications on the efficacy of treating psychiatric clients who have epileptiform activity but no seizure history will be shared, as will publications challenging the standard of practice in psychiatry in treating these clients without reviewing the EEG.

References

Boutros, N. (2009). Epileptiform discharges in psychiatric patients: A controversy in need of resurrection. *Clinical EEG and Neuroscience, 40*(4), 239–244. https://doi.org/10.1177/155005940904000406

Boutros, N. N., Kirollos, S. B., Pogarell, O., & Gallinat, J. (2014). Predictive value of isolated epileptiform discharges for a favorable therapeutic response to antiepileptic drugs in nonepileptic psychiatric patients. *Journal of Clinical Neurophysiology, 31*(1), 21–30. https://doi.org/10.1097/WNP.0000000000000023

Millichap, J. G., Millichap, J. J., & Stack, C. V. (2011). Utility of the electroencephalogram in attention deficit hyperactivity disorder. *Clinical EEG and Neuroscience, 42*(3), 180–184. https://doi.org/10.1177/155005941104200307

Swatzyna, R. J., Tarnow, J. D., Proler, M. L., Roark, A. J., MacInerney, E. K., & Kozlowski, G. P. (2017). Retrospective analysis of nonepileptic patients with isolated epileptiform discharges treated with anticonvulsants. *Clinical EEG and Neuroscience, 48*(5), 322–326. https://doi.org/10.1177/1550059417695896

Swatzyna, R. J., Tarnow, J. D., Turner, R. P., Roark, A. J., MacInerney, E. K., & Kozlowski, G. P. (2017). Integration of EEG into psychiatric practice: A step toward precision medicine for autism spectrum disorder. *Journal of Clinical Neurophysiology, 34*(3), 230–235. https://doi.org/10.1097/WNP.0000000000000365

Critical Brain Dynamics: A Novel Framework for Assessing and Regulating Brain Dynamics

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The critical brain hypothesis proposes that our brain is poised close to the border between two qualitatively different dynamical states. Whereas subcritical dynamics are characterized by premature termination of activity propagation, supercritical dynamics are associated with runaway excitation. The talk will review evidence from recent years that supports this hypothesis and will introduce the concept of neuronal avalanches, spatiotemporal cascades of activity whose sizes obey a power-law distribution. They are observed in a wide range of experiments from small-scale cortical networks to large-scale human EEG and are considered as evidence for critical brain dynamics. The avalanche analysis provides novel qEEG measures which reflect the neural gain and are sensitive to changes in the balance of excitatory and inhibitory processes. Consequently, deviations from critical dynamics could serve as biomarkers for disorders associated with altered balance. For example, in sleep deprivation and in epilepsy the system tends towards supercritical dynamics, whereas in disorders of consciousness the system displays subcritical dynamics. EEG-based measures of criticality can also be used as parameters for neurofeedback. In particular, our lab developed an EEG-based neurofeedback system that evaluates subjects' neural gain using online avalanche analysis and reflects it by means of a video game. Our preliminary results indicate that subjects can regulate their neural gain.

References

Arviv, O., Medvedovsky, M., Sheintuch, L., Goldstein, A., & Shriki, O. (2016). Deviations from critical dynamics in interictal epileptiform activity. *The Journal of Neuroscience, 36*(48), 12276–12292. https://doi.org/10.1523/JNEUROSCI.0809-16.2016

Fekete, T., Omer, D. B., O'Hashi, K., Grinvald, A., van Leeuwen, C., & Shriki O. (2018). Critical dynamics, anesthesia and information integration: Lessons from multi-scale criticality analysis of voltage imaging data. *NeuroImage, 183*, 919–933. https://doi.org/10.1016/j.neuroimage.2018.08.026

Shriki, O., Alstott, J., Carver, F., Holroyd, T., Henson, R. N. A., Smith, M. L., … Plenz D. (2013). Neuronal avalanches in the resting MEG of the human brain, *The Journal of Neuroscience, 33*(16), 7079–7090. https://doi.org/10.1523/JNEUROSCI.4286-12.2013

PLENARY SESSION PRESENTATIONS

Preventing Murder: Treating Violent Behavior with NFB + BFB

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Violent offenders often present with attention-deficit/hyperactivity disorder (ADHD). Additionally, violent behavior is associated with frontal lobe damage and, in some cases, with undiagnosed seizure disorders. Neurofeedback has established efficacy for treating both ADHD and epilepsy, so logic supports using neurofeedback in a population prone to committing violent acts. Following that logic, Douglas Quirk treated violent offenders at the Ontario Correctional Institute, eventually publishing some initial findings in 1995. He documented a dose-response curve: the greater the number of neurofeedback plus biofeedback training sessions, the less likely the individual was to reoffend. Documenting that recidivism dropped from 65% to 20%, he estimated that neurofeedback training prevented more than 100 murders. Quirk died shortly after publication of those findings. This presentation seeks to renew interest in working with this population by reviewing both his work and other research findings that support applying neurofeedback and biofeedback to treat people who display violent behavior. This presentation will review the rationale for applying neurofeedback; namely, that there is frontal lobe dysfunction, including high rates of ADHD, in the population of incarcerated people. This will be followed by a description of the intervention method of neurofeedback combined with appropriate biofeedback. The neurofeedback can be single- or two-channel, but how to assess using 19 channels and treat with LORETA NFB will also be described. The biofeedback modalities are chosen following a stress test that identifies how a client responds to and recovers from mild stressors. The BFB modalities include peripheral skin temperature, skin conduction (electrodermal [EDR]), electromyogram, heart rate, and respiration. There will be an overview of relevant research papers that support major sections of material. The talk will finish with recommendations regarding not only how further applied research might be done in correctional facilities but also with how the neurofeedback practitioner can identify and treat potentially aggressive patients.

References

Beauregard, M. & Lévesque, J. (2006). Functional magnetic resonance imaging investigation of the effects of neurofeedback training on the neural bases of selective attention and response inhibition in children with attention-deficit/hyperactivity disorder. *Applied Psychophysiology and Biofeedback, 31*(1), 3–20. https://doi.org/10.1007/s10484-006-9001-y

Ghaziri, J., Tucholka, A., Larue, V., Blanchette-Sylvestre, M., Reyburn, G., Gilbert, G., Lévesque, J. & M. Beauregard. (2013). Neurofeedback training induces changes in white and gray matter. *Clinical EEG and Neuroscience, 44*(4), 265–272. https://doi.org/10.1177/1550059413476031

Nelson, R. J. & Trainor, B. C. (2007). Neural mechanisms of aggression. *Nature Reviews Neuroscience, 8*, 536–546. https://doi.org/10.1038/nrn2174

Oded, Y. (2018). Integrating mindfulness and biofeedback in the treatment of posttraumatic stress disorder. *Biofeedback, 46*(2), 37–47.

Quirk, D. A. (1995). Composite biofeedback donditioning and dangerous offenders: III. *Journal of Neurotherapy, 1*(2), 44–54. https://doi.org/10.1080/10874208.2012.10491665

Repple, J., Pawliczek, C. M., Voss, B., Siegel, S., Schneider, F. Kohn, N., & Habel, U. (2017). From provocation to aggression: The neural network. *BMC Neuroscience, 18*(1), 73. https://doi.org/10.1186/s12868-017-0390-z

Reynolds, R. & Quirk, D. (2018). *A simple and effective cure for criminality*. Toronto, Canada: Ex Libris.

Sterman, M. B. (2000). Basic concepts and clinical findings in the treatment of seizure disorders with EEG operant conditioning. *Clinical EEG and Neuroscience, 31*(1), 45–55. https://doi.org/10.1177/155005940003100111

Takeuchi, H., Taki, Y., Sassa, Y., Hashizume, H., Sekiguchi, A., Fukushima, A., & Kawashima, R. (2013). Brain structures associated with executive functions during everyday events in a non-clinical sample. *Brain Structure and Function, 218*(4), 1017–1032. https://doi.org/10.1007/s00429-012-0444-z

Thompson, M., & Thompson, L. (2015). Functional neuroanatomy: Organized with reference to networks, lobes of the brain, 10-20 sites, and Brodmann areas. Wheat Ridge, CO: Association for Applied Psychophysiology.

Infraslow Neurofeedback for Military Trauma

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This workshop will describe infraslow neurofeedback training with soldiers whose symptoms include expressions of posttraumatic stress disorder (PTSD), anxiety, and depression. This didactic presentation will categorize symptoms and identify biological, medical, social, and emotional obstacles. The presenter will review the use of neurofeedback to improve physiological “calming,” to follow through with strategy use, and to enhance the effectiveness of interventions.

Infraslow neurofeedback offers a unique opportunity to intervene at the core source of traumatic stress. ISF has been shown to regulate the autonomic nervous system and facilitate behavioral stabilization of related functions (Lecci et al., 2017; Smith, 2013; Smith, Collura, Ferrara, & de Vries, 2014). ISF neurofeedback’s centrality in regulating the excitability cycle of interoceptive networks positively impacts treatment outcomes.

Research suggests that PTSD reflects an abnormal adaptation of neurobiological systems to traumatic stress (DiCara, 1974). This response involves systems that control endocrine pathways and brain networks that regulate, among other functions, the fear response. A primary feature of the PTSD client is persistent hyperactivity of the sympathetic branch of the autonomic nervous system. This system is impacted by the hypothalamic-pituitary-adrenal (HPA) axis: the central coordinator of neuroendocrine stress response (Daniels, Frewen, McKinnon, & Lanius, 2011; Sherin & Nemeroff, 2011). Ledoux (LeDoux & Pine, 2017) has proposed a “two-system” view of fear and anxiety. One system produces behavioral and physiological responses to threat. The other brain circuit produces the conscious feeling-states of fear and anxiety.

The physiological response to trauma activation is present despite higher level cognitive reasoning. Muscular and physiological reactions are automatic, leaving the conscious capacity to “catch up later” (Van der Kolk, 2014). Activation leads to avoidance, thus increasing the client’s disability and negatively impacting quality of life. Although psychotherapy is essential in the recovery process, without the ability to regulate the autonomic nervous system and related limbic networks sufficiently to tolerate the process, participation is often limited or unsuccessful.

By virtue of its ability to support the regulation of the autonomic nervous system/HPA axis (and subsequently the automatic physiological response to trauma), ISF neurofeedback is believed to be a foundational approach to promoting recovery.

References

Aladjalova, N. A. (1957). Infra-slow rhythmic oscillations of the steady potential of the cerebral cortex. *Nature, 179*(4567), 957–959. https://doi.org/10.1038/179957a0

Aladjalova, N. A. (1964). *Slow electrical processes in the brain* (Vol. 7, 1st ed.). Amsterdam: Elsevier Science.

Daniels, J. K., Frewen, P., McKinnon, M. C., & Lanius, R. A. (2011). Default mode alterations in posttraumatic stress disorder related to early-life trauma: A developmental perspective. *Journal of Psychiatry & Neuroscience, 36*(1), 56–59. https://doi.org/10.1503/jpn.100050

DiCara, L. (Ed.). (1974). *Limbic and autonomic nervous systems research*. New York, NY: Plenum Press.

Lecci, S., Fernandez, L. M. J., Weber, F. D., Cardis, R., Chatton, J.-Y., Born, J., & Lüthi, A. (2017). Coordinated infraslow neural and cardiac oscillations mark fragility and offline periods in mammalian sleep. *Science Advances, 3*(2), e1602026. https://doi.org/10.1126/sciadv.1602026

LeDoux, J. E., & Pine, D. S. (2017). Using neuroscience to help understand fear and anxiety: A two-system framework. The *American Journal of Psychiatry, 173*(11), 1083–1093. https://doi.org/10.1176/appi.ajp.2016.16030353

Palva, J. M., & Palva, S. (2012). Infra-slow fluctuations in electrophysiological recordings, bloodoxygenation-level-dependent signals, and psychophysical time series. *NeuroImage, 62*(4), 2201–2211. https://doi.org/10.1016/j.neuroimage.2012.02.060

Sherin, J. E., & Nemeroff, C. B. (2011). Post-traumatic stress disorder: The neurobiological impact of psychological trauma. *Dialogues in Clinical Neuroscience, 13*(3), 263–278.

Sinha, R. (2008). Chronic stress, drug use, and vulnerability to addiction. *Annals of the New York Academy of Sciences, 1141*(1), 105–130. https://doi.org/10.1196/annals.1441.030

Smith, M. L. (2013). Infra-slow fluctuation training; On the down-low in neuromodulation. *NeuroConnections,* Fall 2013, 38–46.

Smith, M. L., Collura, T. F., Ferrara, J., & de Vries, J. (2014). Infra-slow fluctuation training in clinical practice: A technical history. *NeuroRegulation, 1*(2), 187–207. https://doi.org/10.15540/nr.1.2.187

Van der Kolk, B. A. (2006). Clinical implications of neuroscience research in PTSD. *Annals of the New York Academy of Sciences, 1071*(1), 277–293. https://doi.org/10.1196/annals.1364.022

Van der Kolk, B. A. (2014). *The body keeps the score: Brain, mind, and body in the health of trauma*. New York, NY: Penguin Books.

Vanhatalo, S., Palva, J. M., Holmes, M. D., Miller, J. W., Voipio, J., & Kaila, K. (2004). Infraslow oscillations modulate excitability and interictal epileptic activity in the human cortex during sleep. *Proceedings of the National Academy of Sciences of the United States of America, 101*(14), 5053–5057. https://doi.org/10.1073/pnas.0305375101

Neural Oscillations Induced with Photobiomodulation Could Improve Neurofeedback Outcomes

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Hypothesis. Evidence supports the efficacy of transcranial photobiomodulation (PBM) to affect a wide variety of brain conditions (Hamblin, 2016; Salehpour et al., 2018). It is therefore reasonable to expect that underlying the clinical outcomes, are changes in neural oscillations. Such changes would be measurable with EEG. We could potentially use such data to adjust PBM parameters to modulate the brain to address various brain conditions or even elevate normal brain performance. This would be a novel and useful brain stimulation method for neurofeedback (NFB) practitioners.

Supporting Evidence to Date. In PBM, near infrared (NIR) light directed to the default mode network (DMN) at selected pulses could produce large brain responses. This has been suggested in studies involving dementia (Lim, 2018; Saltmarche, Naeser, Ho, Hamblin, & Lim, 2017; Zomorrodi, Saltmarche, Loheswaran, Ho, & Lim, 2017) and acute cognitive processing (Heinrich et al., 2019). In a controlled study that specifically explored neural response to 40 Hz directed to the DMN of healthy subjects (the Gamma EEG study), it was found that the power spectrum and connectivity of alpha, beta, and gamma increased significantly. Surprisingly, the opposite was found for the slower delta and theta bands where the power spectrum decreased with no significant change in connectivity. In the meantime, there was a global increase in inhibition which is often desirable (Zomorrodi, Loheswaran, Pushparaj, & Lim, 2019). The changes are observable in qEEG maps, producible with commonly used 19-channel practitioner systems. These information gives a good basis to explore another popular pulse frequency with PBM to determine how much of the effect of the previous study with 40 Hz can be replicated, and what else can be learned with pulsed PBM.

Methods. In a new study, we induce a different pulse frequency of 10 Hz. The protocol of this new study is similar to the above study except that a frequency of 10 Hz is used instead of 40 Hz. It will also be a randomized double-blind study involving 20 healthy participants. In addition, a task stimulus is added to study event-related potential (ERP). Participants cross over to a different device (either from active to sham or vice versa) after a washout period of 2 weeks.

Results. At the time of writing, the study has started but not completed. The results and analysis will focus on the similarity and differences with the Gamma EEG study so that we have new data on the effect of a different set of parameters, plus ERP. It leads to further investigations for personalized treatments.

Conclusions. Although this new study is yet to complete, the data from the Gamma EEG study has already given us considerable bases to make the following conclusions from pulsed PBM: (a) we can produce significant brain modulation that is frequency dependent, (b) it shows the potential for PBM to be an important partner to NFB practice, and (c) it will create clearer opportunities for personalized treatments. Findings in this new study inducing the alpha frequency of 10 Hz and a task could give us new data to help improve future transcranial PBM treatments.

References

Hamblin, M. R. (2016). Shining light on the head: Photobiomodulation for brain disorders. *BBA Clinical, 6*, 113–124. https://doi.org/10.1016/j.bbacli.2016.09.002

Heinrich, M. D., Sanguinetti, J. L., Hicks, G., Gibsona, B. C., Mullins, T. S., Aragon, D. F., … Clark, V. P. (2019, February). Photobiomodulation for cognitive enhancement in healthy adults. Poster presented at the Brain Stimulation Conference 2019, Vancouver, BC, Canada.

Lim, L. (2018). The growing evidence for photobiomodulation as a promising treatment for Alzheimer's disease. *Journal of Biosciences and Medicine, 6*(12), 100–110. https://doi.org/10.4236/jbm.2018.612010

Salehpour, F., Mahmoudi, J., Kamari, F., Sadigh-Eteghad, S., Rasta, S. H., & Hamblin, M. R. (2018). Brain photobiomodulation Therapy: A narrative review. *Molecular Neurobiology, 55*(8), 6601–6636. https://doi.org/10.1007/s12035-017-0852-4

Saltmarche, A. E., Naeser, M. A., Ho, K. F., Hamblin, M. R., & Lim, L. (2017). Significant Improvement in Cognition in Mild to Moderately Severe Dementia Cases Treated with Transcranial Plus Intranasal Photobiomodulation: Case Series Report. Photomed Laser Surg. 35(8): 432–441. https://doi.org/10.1089/pho.2016.4227

Zomorrodi, R., Saltmarche, A. E., Loheswaran, G., Ho, K. F., & Lim, L. (2017, July). Complementary EEG evidence for a significantly improved Alzheimer's disease case after photobiomodulation treatment. Poster presented at the Alzheimer's Association International Conference 2017, London, England.

Zomorrodi, R., Loheswaran, G., Pushparaj, A., & Lim L. (2019). Pulsed near infrared transcranial and intranasal photobiomodulation significantly modulates neural oscillations: A pilot exploratory study. *Scientific Reports, 9*, 6309. https://doi.org/10.1038/s41598-019-42693-x

The Feasibility and Validity of Cerebellar EEG Biofeedback

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Objectives and Hypotheses. The purpose of this study was to explore the feasibility and validity of cerebellar EEG biofeedback. Cerebellar EEG sources have been published using swLORETA with 128-channel EEG recordings. The questions at hand: Can cerebellar sources also be recorded using only 19 channels, can changes in limb position result in changes in cerebellar sources, and can cerebellar sources be modified using standard EEG biofeedback methods? The null-hypotheses were (a) it is not possible to measure cerebellar current sources using 19-channel EEG, (b) it is not possible to measure cerebellar functional connectivity to other brain regions, (c) it is not possible to change cerebellar EEG sources and/or connectivity by experimental manipulation, and (d) it is not possible to change cerebellar current sources using EEG biofeedback.

Methods. The electroencephalogram (EEG) was recorded from 19 scalp locations referenced to linked ears from 10 normal controls and 10 TBI patients (age 18 to 23 years). The standard MNI-Colin27 MRI with 12,056 voxels was used to compute the inverse solution using swLORETA. The Hilbert transform was used to compute the real-time auto and the cross-spectrum. Current sources from the 10 major cerebellum regions were computed off-line and in real-time (Vermis, lobules IV-VI, VIIB–VIIIB, and flocculus). The measures of functional connectivity were coherence and phase differences between the 10 left hemisphere and the 10 right hemisphere cerebellar center voxels and the center voxels of 44 left hemisphere and 44 right hemisphere Brodmann areas.

Results. All 20 subjects demonstrated cerebellar current sources in all 10 cerebellar regions in both off-line analyses and in real-time via playback of the recorded EEG. Similarly, functional and effective connectivity were successfully computed between the cerebellar center voxels and various neocortical center voxels, including Brodmann areas 3, 4, 5, and 7, which are known cerebellar projection areas.

Conclusions. The results of the analyses rejected hypotheses #1 and #2 and successfully established the feasibility of measuring cerebellar current sources and functional and effective cerebellar connectivity using 19 EEG channels. Testing of the validity of hypotheses #3 and #4 are awaiting the development of the necessary software for left versus right finger-to-nose and point-to-point cerebellar testing and neurofeedback software. We expect to complete the software development and the testing of these two hypotheses around July 2019, in advance of the ISNR conference.

References

Cebolla, A. M., Petieau, M., Dan, B., Balazs, L., McIntyre, J., & Cheron, G. (2016). Cerebellar contribution to visuo-attentional alpha rhythm: Insights from weightlessness. *Scientific Reports, 6*, 37824. https://doi.org/10.1038/srep37824

Cebolla, A.-M., Palmero-Soler, E., Leroy, A. & Cheron, G. (2017). EEG spectral generators involved in motor imagery: A swLORETA study. *Frontiers in Psychology, 8*, 2133. https://doi.org/10.3389/fpsyg.2017.02133

Collins, D. L., Neelin, P., Peters, T. M., & Evans, A. C. (1994). Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. *Journal of Computer Assisted Tomography, 18*(2), 192–205. https://doi.org/10.1097/00004728-199403000-00005

Mazziotta, J. C., Toga, A. W., Evans, A., Fox, P., & Lancaster, J. (1995). A probabilistic atlas of the human brain: Theory and rationale for its development. The International Consortium for Brain Mapping (ICBM). *NeuroImage, 2*(2, Part A), 89–101. https://doi.org/10.1006/nimg.1995.1012

Palmero Soler, E., Dolan, K., Hadamschek, V., & Tass, P.A. (2007). swLORETA: A novel approach to robust source localization and synchronization tomography. Physics in Medicine & Biology, 52(7), 1783–1800. https://doi.org/10.1088/0031-9155/52/7/002

Schmahmann, J. D., Doyon, J., McDonald, D., Holmes, C., Lavoie, K., Hurwitz, A. S., … Petrides, M. (1999). Three-dimensional MRI atlas of the human cerebellum in proportional stereotaxic space. *NeuroImage, 10*(3), 233–260. https://doi.org/10.1006/nimg.1999.0459

Peak Performance in Sports: Factors that Impair Performance and Means of Improving It

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Since the development of the Yerkes-Dodson curve of 1908, much has been learned about arousal and its relation to peak performance. Different activities require different levels of arousal for top-notch performance. For instance, the arousal necessary to play a good game of golf is very different than that required for a good game of hockey. Fear from self-criticism, stereotype threat, fear of losing a competition, excitement over the cameras, media, and new adventures often adversely affect performance. Those with the calmest level of disposition often win the competition, even if rated as the underdog prior to competition. However, some athletes start a competition with too low an arousal and do poorly in the beginnings of a competition. Also, many athletes struggle with sleep and often have their worst sleep the night prior to competition.

Audio-visual entrainment (AVE) is a technique employing light and sound stimulation at various frequencies, which in turn can dramatically affect arousal. A peak-performance AVE protocol in combination with the X-ray visualization along with heart rate variability, enhances peak performance and improves sleep, resulting in first-place finishes. Many Olympic and professional athletes have used AVE over the years to gain the mental edge over their opponents. The concepts and techniques surrounding peak performance will be reviewed and demonstrated. Jeff Simonson, a competitive and winning racquetball player will explain how AVE has helped him achieve his first place finishes.

Jeff has been playing tournament racquetball for the past 7 years. Until last year he never finished higher than third place. In 2018 he started using the AVE on a regular basis and specifically a couple hours before a tournament. Last year he started winning tournaments. He's been named to the Oregon All State Racquetball team in 2018 and 2019. Earlier this year he won the Oregon Championships for his division. He is also an avid golfer and has seen his game improve through use of the AVE.

References

Broadhurst, P. L. (1959). The interaction of task difficulty and motivation: The Yerkes-Dodson law revived. *Acta Psychologica, 16*, 321–338. https://doi.org/10.1016/0001-6918(59)90105-2

Hutchison, M. (1993, July). Mind Over Matter = Muscle. *Muscle & Fitness*, July, 1–5.

Siever, D., & Collura, T. (2017). Chapter 3 – Audio–visual entrainment: Physiological mechanisms and clinical outcomes. *Rhythmic Stimulation Procedures in Neuromodulation*, 51–95. https://doi.org/10.1016/B978-0-12-803726-3.00003-1

Optical Model of Transcranial Infrared Light and the Penetration Rate to Prefrontal Lobe

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Brain functions have been proven to be affected by external stimuli. Photobiomodulation (PBM) using near-infrared is one of the effective ways to modulate the hemodynamic activities in the brain and to activate the key enzyme cytochrome c oxidase (CCO) in electron transport chain (ETC; Anders, Lanzafame, & Arany, 2015; Anders et al., 2014; Barrett & Gonzalez-Lima, 2013; Blanco, Saucedo, & Gonzalez-Lima, 2017; Rojas & Gonzalez-Lima, 2017; Tian, Hase, Gonzalez-Lima, & Liu, 2016; Vargas et al., 2017; Wang, Tian, Soni, Gonzalez-Lima, & Liu, 2016). However, the effective dosage, or the right recipe for the power density as well as treatment time, is still not clear. To answer these questions, it is necessary to have a detailed optical model to describe the penetration rate and how photons propagate transcranially, particularly to reach the prefrontal lobe that dominates the cognitive functions. In this research, we used five layers of tissues including skin, skull, cerebrospinal fluid (CSF), gray matter, and white matter, each of which is represented by a set of wavelength-dependent Scattering coefficients μs (λ) and Absorption coefficients μa (λ). The anisotropy factor g is needed to run Monte Carlo simulations and predict the reflectance (fraction of light returning to tissue surface; Sung, Kao, Zhan, & Lin, 2019). A broadband near-infrared light source emits photons through the prefrontal area, and a linear array with 10 sensors spacing 10 mm from each other collects the photons scattering back from the superficial and deep tissues. Based on these collected data, the Monte Carlo model is built, and simulations are executed in high-speed parallel computers. The thickness of each layer of the model is from the MRI result of participants. Through the Monte Carlo simulation results, we identified that penetration rate for the skull is about 3.5% and the photons could reach as deep as 4 cm to the grey matter, with about 2% of photons. In addition, we also noticed that photons have the longest path distance horizontally in the skull layer. This indicates that photons travel longer than expected as in previous studies. Therefore, the short-channel effect completely cannot be ignored when using near-infrared spectroscopy (NIRS) techniques (Wang et al., 2016) to measure the activities of the CCO at the prefrontal lobe after the PBM treatment.

References

Anders, J. J., Lanzafame, R. J., & Arany, P. R. (2015). Low-level light/laser therapy versus photobiomodulation therapy. *Photomedicine and Laser Surgery, 33*(4), 183–184. https://doi.org/10.1089/pho.2015.9848

Anders, J. J., Moges, H., Wu, X., Erbele, I. D., Alberico, S. L., Saidu, E. K., … Pryor, B. A. (2014). In vitro and in vivo optimization of infrared laser treatment for injured peripheral nerves. *Lasers in Surgery and Medicine, 46*(1), 34–45. https://doi.org /10.1002/lsm.22212

Barrett, D. W., & Gonzalez-Lima, F. (2013). Transcranial infrared laser stimulation produces beneficial cognitive and emotional effects in humans. *Neuroscience, 230*, 13–23. https://doi.org /10.1016/j.neuroscience.2012.11.016

Blanco, N. J., Saucedo, C. L., & Gonzalez-Lima, F. (2017). Transcranial infrared laser stimulation improves rule-based, but not information-integration, category learning in humans. *Neurobiology of Learning and Memory, 139*, 69–75. https://doi.org/10.1016/j.nlm.2016.12.016

Rojas, J. C., & Gonzalez-Lima, F. (2017). Transcranial low-level laser (light) therapy for neurocognitive enhancement. In M. R. Hamblin, M. V. P. de Sousa, & T. Agrawal (Eds.), *Handbook of low-level laser therapy* (1st ed., pp. 1057–1076). Singapore: Pan Stanford Publishing.

Sung, K.-B., Kao, T.-C., Zhan, C.-S., & Lin, T.-X. (2019, April). Comparison of photon energy distributions in the prefrontal cortex between 810 nm and 1064 nm for optimizing photobiomodulation effects. Paper presented at the Biophotonics Congress: Optics in the Life Sciences Congress 2019 (BODA, BRAIN, NTM, OMA, OMP), The Optical Society (Optical Society of America, 2019), Tucson, AZ. https://doi.org/10.1364/BRAIN.2019.BW4A.5

Tian, F., Hase, S. N., Gonzalez-Lima, F., & Liu, H. (2016). Transcranial laser stimulation improves human cerebral oxygenation. *Lasers in Surgery and Medicine, 48*(4), 343–349. https://doi.org/10.1002/lsm.22471

Vargas, E., Barrett, D. W., Saucedo, C. L., Huang, L.-D., Abraham, J. A., Tanaka, H., ... Gonzalez-Lima, F. (2017). Beneficial neurocognitive effects of transcranial laser in older adults. *Lasers in Medical Science, 32*(5), 1153–1162. https://doi.org /10.1007/s10103-017-2221-y

Wang, X., Tian, F., Soni, S. S., Gonzalez-Lima, F., & Liu, H. (2016). Interplay between up-regulation of cytochrome-c-oxidase and hemoglobin oxygenation induced by near-infrared laser. *Scientific Reports, 6*, 30540. https://doi.org/10.1038 /srep30540

All Artifacts

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This course is for anyone who has wondered: “Is that real or fake?” Artifacts in EEG can seriously hinder an accurate interpretation of the qEEG, altering neurotherapeutic protocol choices and potentially threatening the patient’s clinical outcome. Muscle tension can look like anxiety, lateral eye movements and pulse artifacts can create delta and the misinterpretation of head injury, or a contaminated ear electrode can create hypercoherence! This presentation will demonstrate how artifacts appear not only in the raw EEG data, but also in the qEEG data. Tiff hopes to spare you and your patients this dilemma in the future, as well as provide tips on how to avoid any misread of quantitative and raw EEG data.

While some artifact can be prevented or omitted, other artifact must be read around. The skilled clinician needs the ability to explain these findings to their patients when asked, “what’s that?” Through exploring the more and less insidious forms of artifact, this lecture will guide the clinician through some of the more advanced ways of interpreting EEG so that the qEEG does not mislead one into misdiagnosis.

Some of the artifacts covered will include channel noise, 60 Hz/50 Hz, blinks, chewing, EKG (various presentations), electrode pops, eye rolling, sweat, lateral eye movements, medication, mixed metals, muscle tension, shared variance, as well as easily confused real conditions.

This presentation will be simple enough for the novice neurotherapist but rich enough that even the most seasoned clinician should be able to glean something new.

References

Johnstone, J. (2005, September). QEEG patterns: Subgroups, profiles, phenotypes. Paper presented at the 13th Annual Conference of the International Society for Neuronal Regulation (ISNR), Denver, CO.

La Vaque, T. J., Hammond, D. C., Trudeau, D., Monastra, V., Perry, J., Lehrer, P., … Sherman, R. (2002). Template for developing guidelines for the evaluation of the clinical efficacy of psychophysiological interventions. *Applied Psychophysiology and Biofeedback, 27*(4), 273–281. https://doi.org/10.1023/A:1021061318355

Niedermeyer, E., & Lopes da Silva, F. (1993). EEG patterns and genetics. In E. Niedermeyer & F. Lopes da Silva, *Electroencephalography: Basic principles, clinical applications and related fields* (3rd ed., pp. 192–195). Baltimore, MD: Lippincott, Williams & Wilkins.

Prichep, L. S., & John, E. R. (1992). QEEG profiles of psychiatric disorders. *Brain Topography, 4*(4), 249–257. https://doi.org/10.1007/BF01135562

Correlations Between Quantitative EEG Volumetric Analysis and Computerized Cognitive Testing Shortly After Sport Concussion Injury in High School Athletes

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The objective of this investigation is to explore the relationship between symptoms and cognitive performance and volumetric qEEG analysis after sport concussion injury in high school athletes.

Methods. Standard electroencephalograms (EEGs) were recorded in 70 high school athletes (31 males) shortly after concussion injury using sLORETA imaging compared to a normative database (NYU/BrainDx). Peak *Z*-score variation (PZV), and percentage volume of grey matter activity that fell outside $Z = -2.5$ to 2.5 (PIGMV for increased activity, PRGMV for reduced) were calculated for each of five EEG frequency bands. These data were compared for correlations to computerized neurocognitive and symptom assessment (XLNTbrain) also performed shortly after concussion injury.

Results. Statistically significant Pearson r correlations were found with XLNTbrain composite scores. For PZV: Negative correlations between delta band PZV min values and nonverbal processing and memory scores ($r = -.334$, $p = .005$; $r = -.339$, $p = .004$; respectively). Positive correlations were found with alpha band PZV max value and verbal memory score ($r = .319$, $p = .007$). For PIGMV: Positive correlations were found between alpha band PIGMV and verbal processing, verbal memory, attention, and emotional reactivity ($r = .341$, $p = .004$; $r = .351$, $p = .003$; $r = .244$, $p = .042$; $r = .254$, $p = .034$; respectively).

Taking reaction time into account with throughput measures, for PZV: Negative correlation was found between delta band PZV min and nonverbal memory. Positive correlations were found between alpha band PZV max and verbal memory. For PIGMV: Positive correlations were found between alpha band PIGMV and verbal processing and verbal memory (r = .28, = .019; r = .314, p = .008; respectively) and the beta-gamma band and nonverbal processing and nonverbal memory (r = .28, p = .019; r = .3, p = .012; respectively).

Conclusions. This study demonstrates correlations between performance on computerized neurocognitive tasks and changes in quantitative

sLORETA EEG analysis shortly after concussion injury in high school athletes. The data suggest that different cognitive processes may be supported by different frequency band activity. Further research including region specific EEG analysis and gender differences is needed.

References

Barr, W. B., Prichep, L. S., Chabot, R., Powell, M. R., & McCrea, M., (2012). Measuring brain electrical activity to track recovery from sport-related concussion. *Brain Injury, 26*(1), 58–66. https://doi.org/10.3109/02699052.2011.608216

Bricolo, A., Turazzi, S., Faccioli, F., Odorizzi, F., Sciaretta, G., & Erculiani, P. (1978). Clinical application of compressed spectral array in long-term EEG monitoring of comatose patients. *Electroencephalography and Clinical Neurophysiology, 45*(2), 211–225. https://doi.org/10.1016/0013-4694(78)90005-6

Cannon, R., Baldwin, D. R., Shaw, T. L., Diloreto, D. J., Phillips, S. M., Scruggs, A. M., & Riehl, T. C. (2012) Reliability of quantitative EEG (qEEG) measures and LORETA current source density at 30 days. *Neuroscience Letters, 518*(1), 27–31. https://doi.org/10.1016/j.neulet.2012.04.035

Cannon, R., Kerson, C., & Hampshire, A. (2011). sLORETA and fMRI detection of medial prefrontal default network anomalies in adult ADHD. *Journal of Neurotherapy, 15*(4), 358–373, https://doi.org/10.1080/10874208.2011.623093

Duffy, F. H., Bartels, P. H., & Burchfiel, J. L. (1981). Significance probability mapping: An aid in the topographic analysis of brain electrical activity. *Electroencephalography and Clinical Neurophysiology, 51*(5), 455–462. https://doi.org/10.1016/0013-4694(81)90221-2

Duncan, C. C., Kosmidis, M. H., & Mirsky, A. F. (2003). Event–related potential assessment of information processing after closed head injury. *Psychophysiology, 40*(1), 45–59. https://doi.org/10.1111/1469-8986.00006

Duncan, C. C., Kosmidis, M. H., & Mirsky, A. F. (2005). Closed head injury-related information processing deficits: An event-related potential analysis. *International Journal of Psychophysiology, 58*(2–3), 133–157. https://doi.org/10.1016/j.ijpsycho.2005.05.011

Giza, C. C., & Hovda, D. A. (2014). The new neurometabolic cascade of concussion. *Neurosurgery, 75*(Suppl. 4), S24–S33. https://doi.org/10.1227/NEU.0000000000000505

Gosselin, N., Bottari, C., Chen, J.-K., Huntgeburth, S. C., De Beaumont, L., Petrides, M., ... Ptito, A. (2012). Evaluating the cognitive consequences of mild traumatic brain injury and concussion by using electrophysiology. *Neurosurgical Focus, 33*(6), E7. https://doi.org/10.3171/2012.10.FOCUS12253

Gosselin, N., Lassonde, M., Petit, D., Leclerc, S., Mongrain, V., Collie, A., & Montplaisir, J. (2009). Sleep following sport-related concussions. *Sleep Medicine, 10*(1), 35–46. https://doi.org/10.1016/j.sleep.2007.11.023

Haglund, Y., & Persson, H. E. (1990). Does Swedish amateur boxing lead to chronic brain damage. 3.A retrospective clinical neurophysiological study. *Acta Neurologica Scandinavica, 82*(6), 353–360. https://doi.org/10.1111/j.1600-0404.1990.tb03316.x

Hanley, D., Prichep, L. S., Bazarian, J., Huff, J. S., Naunheim, R., Garrett, J., … Hack, D. C. (2017) Emergency department triage of traumatic head injury using a brain electrical activity biomarker: A multisite prospective observational validation trial. *Academic Emergency Medicine, 24*(5), 617–627. https://doi.org/10.1111/acem.13175

Jasper, H. H. (1958). The ten-twenty electrode system of the International Federation. *Electroencephalography and Clinical Neurophysiology, 10*, 371–375.

John, E. R. (1977). Neurometrics: Clinical applications of quantitative electrophysiology. Hillsdale, NJ: L. Erlbaum Associates.

Koberda, L. (2015). Z-Score LORETA neurofeedback as a potential therapy in cognitive dysfunction and dementia. Journal of Psychology & Clinical Psychiatry, 1(6), 00037. https://doi.org/10.15406/jpcpy.2014.01.00037

Kutas, M., & Hillyard, S. A. (1980). Reading senseless sentences: Brain potentials reflect semantic incongruity. Science, 207(4427), 203–205. https://doi.org/10.1126/science.7350657

Ledwidge, P. S., & Molfese, D. L. (2016). Long-term effects of concussion on electrophysiological indices of attention in varsity college athletes: An event-related potential and standardized low-resolution brain electromagnetic tomography approach. *Journal of Neurotrauma, 33*(23), 2081–2090. https://doi.org/10.1089/neu.2015.4251

McCrea, M., Prichep, L., Powell, M., Chabot, R., & Barr, W. (2010). Acute effects and recovery after sport-related concussion: A neurocognitive and quantitative brain electrical activity study. *Journal of Head Trauma Rehabilitation, 25*(4), 283–292. https://doi.org/10.1097/HTR.0b013e3181e67923

NIH SBIR Contract # NS72370-000, Rest Technologies, Chris Mann, Jerald Simmons, Continuous EEG Monitoring Methodologies, Awarded 1997.

Pascual-Marqui, R. D. (1999). Review of methods for solving the EEG inverse problem. *International Journal of Bioelectromagnetism, 1*(1), 75–86.

Pascual-Marqui, R. D. (2002). Standardized low-resolution brain electromagnetic tomography (sLORETA): Technical details. (2002) *Methods & Findings in Experimental & Clinical Pharmacology, 24*(Suppl. D), 5–12.

Schoenhuber, R., Gentilini, M., & Orlando, A. (1988). Prognostic value of auditory brain-stem responses for late postconcussion symptoms following minor head injury. *Journal of Neurosurgery, 68*(5), 742–744. https://doi.org/10.3171/jns.1988.68.5.0742

Thatcher, R. W., Walker, R. A., Biver, C. J., North, D. N., & Curtin, R. (2003). Quantitative EEG normative databases: Validation and clinical correlation. Journal of Neurotherapy, 7(3–4), 87–121. https://doi.org/10.1300/J184v07n03_05

Thatcher, R. W., Walker, R. A., Gerson, I., Geisler, F. H. (1989). EEG discriminant analyses of mild head trauma, *Electroencephalography and Clinical Neurophysiology, 73*(2), 94–106. https://doi.org/10.1016/0013-4694(89)90188-0

Thompson, M., Thompson, L., & Reid-Chung, A. (2015). Treating postconcussion syndrome with LORETA Z-Score neurofeedback and heart rate variability biofeedback: Neuroanatomical/neurophysiological rationale, methods, and case examples. *Biofeedback, 43*(1), 15–26. https://doi.org/10.5298/1081-5937-43.1.07

Vespa, P. M., Nuwer, M. R., Juhász, C., Alexander, M., Nenov, V., Martin, N., & Becker, D. P. (1997). Early detection of vasospasm after acute subarachnoid hemorrhage using continuous EEG ICU monitoring. *Electroencephalography and Clinical Neurophysiology, 103*(6), 607–615. https://doi.org/10.1016/s0013-4694(97)00071-0

Vitacco, D., Brandeis, D., Pascual-Marqui, R., & Martin, E. (2002). Correspondence of event-related potential tomography and functional magnetic resonance imaging during language processing. *Human Brain Mapping, 17*(1), 4–12. https://doi.org/10.1002/hbm.10038

Integration of Neurofeedback in the Drug Court Treatment Model: A Pilot Study

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Introduction. In their landmark 1989 paper, Peniston and Kulkosky used alpha-theta neurofeedback to promote alpha and theta wave production in alcoholics and improve treatment results. The EEG profiles of alcoholics often demonstrated reductions in alpha activity and alpha reactively increased in these individuals when alcohol was consumed (Pollack et al., 1983). Results from Peniston and Kulkosky's original methodology indicated increased alpha and theta brainwave production, normalized personality measures, and prolonged prevention of relapse for the neurofeedback group (Peniston, 1998). Research has suggested that the application of alpha-theta neurofeedback is beneficial in promoting long-term abstinence (Fisher, 2009). Independent studies with minor variations to the neurofeedback protocol have achieved similar success (Scott, Kaiser, Othmer, & Sideroff, 2005). Since 1989, drug court programs have integrated the leverage of the criminal justice system to addiction treatment services (Ritvo, Martin, & Fehling, 2015). The current study sought to apply neurofeedback within the context of a drug court program. The study participants were female members of an internal family systems (IFS) therapy group which had met for 16 weeks as required by drug court.

Methods. Pretreatment baseline and posttreatment qEEG data, cognitive testing data, and subjective symptom scores were acquired before and after treatment. Twice weekly, single-channel electrode neurofeedback training was performed on a BrainMaster Atlantis amplifier in BrainMaster 3.7i software. Twenty sessions were planned but 19 were performed due to inclement weather. Each client first completed five sessions of beta-type training. Alpha-theta training was applied during the remaining sessions.

Results. The subjective experiences of all three study participants improved with the neurofeedback sessions. QEEG analysis used ANI and BrainDx databases. Each participant in the study demonstrated changes in qEEG profiles over the course treatment. Alpha and beta bands demonstrated the most remarkable changes. Symptom scores reduced and trended towards improvement in two of three cases, while the last case remained elevated at a near constant level. Cognitive testing measures were varied and unreliable due to testing error.

Discussion. While changes in the objective measures was mixed, making it difficult to draw concrete conclusions from this case series, dramatic changes were noted on some qEEG maps. No subjects relapsed during the neurofeedback program. In follow-up discussions all subjects reported improved self-regulation, emotional regulation, and executive functioning. Group therapy facilitators and drug court council personnel noted changes in the participants' demeanor, mood, and personality. Follow-up with the drug court council 2 months later revealed all three study participants were doing well and were on track to graduate from the drug court program within 3 months.

Conclusion. Study limitations and variance of objective results in the present study prevent clear conclusions about the efficacy of neurofeedback in this model, but interviews with the study participants, group therapy facilitators, and drug court council suggest neurofeedback had a positive effect. Future research is needed and currently a second study to use neurofeedback with individuals recovering in the drug court program is in development.

References

Fisher, C. (2009). An overview of alpha-theta neurofeedback and its treatment effectiveness for substance abuse. Retrieved from http://www.bmedreport.com/archives/6071

Peniston, E. G. (1998). The Peniston-Kulkosky brainwave neurofeedback therapeutic protocol: The future of psychotherapy for alcoholism/PTSD/behavioral medicine. Retrieved from http://www.aaets.org/article47.htm

Peniston, E. G. & Kulkosky, P. J. (1989). Alpha-theta brainwave training and beta-endorphin levels in alcoholics. *Alcoholism: Clinical and Experimental Research, 13*(2), 271–279. https://doi.org/10.1111/j.1530-0277.1989.tb00325.x

Pollack, V. E., Volavka, J., Goodwin, D. W., Medrick, S. A., Gabrielli, W. F., Knop, J., & Schulsinger, F. (1983). The EEG after alcohol in men at risk for alcoholism. *Archives of General Psychiatry, 40*(8), 857–864.

Ritvo, J. I., Martin, L. F., & Fehling, P. D. (2015). Community-based treatment. In M. Galanter, H. D. Kleber, & K. Brady (Eds.), *The American Psychiatric Publishing Textbook of Substance Abuse Treatment* (5th ed., pp. 531–543). Washington, DC: American Psychiatric Publishing.

Scott, W. C., Kaiser, D., Othmer, S., & Sideroff, S. I. (2005). Effects of an EEG biofeedback protocol on a mixed substance abusing population. *The American Journal of Drug and Alcohol Abuse, 31*(3), 455–469. https://doi.org/10.1081/ada-200056807

Heart Rate Variability: Psychological Factors and a Novel Technique for Dramatically Enhanced Results

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Heart rate variability (HRV) is often referred to as a "window to the soul," a reflection of thoughts and emotions within the individual in which the heart is contained. And yet, for most heart rate variability biofeedback, a simplistic approach has been developed, practiced, and—unfortunately—accepted as status quo for the treatment of HRV issues.

HRV issues are prevalent in relation to traumatic brain injury and mental health conditions in which anxiety is a major presenting symptom. Also, it appears that the more anxious or afraid of failing that one is, the more likely that person will fail when attempting to breathe to a regimented fashion. So, a regimented and paced biofeedback system is particularly distressing to these sufferers. Suppose there was a technique that simultaneously calmed the mind while also providing gentle breathing cues?

The essence of this workshop will be to bring light the way in which the heart's rhythm is of absolute importance as a guide for counselling and cognitive behavioral techniques, which in themselves can completely resolve an HRV issue. That being said, the more extreme a mental health condition is, especially that of PTSD, trauma, TBI and the resultant anxiety, the tougher it is to employ traditional HRV biofeedback techniques and the greater the failure rate.

Audio-visual entrainment (AVE) is a technique employing flashing lights within a pair of sunglasses and pulsing tones within a pair of headphones at various brain wave frequencies. AVE has the exceptional ability to induce deep meditative and parasympathetic states of mind within the user. This workshop will demonstrate a novel and highly effective method involving an AVE-based technique involving a Windows-based Breathe app alongside a unique AVE protocol for advanced HRV therapy for the toughest of patients struggling with anxiety. This protocol utilizes the changing of color cues for inspiration and expiration, simultaneously with mind-calming AVE, typically in the alpha brain wave band (although any brain wave band may be chosen).

References

Moss, D. (2004). Heart rate variability and biofeedback. *Psychophysiology Today: The Magazine for Mind-Body Medicine, 1*, 4–11.

Siever, D. (2012). Heart rate variability and Audio-visual entrainment. Retrieved from http://mindalive.com/index.cfm/research/hrv-ave/

Winkelmann, T., Thayer, J. F., Pohlack, S., Nees, F., Grimm, O., & Flor, H. (2017). Structural brain correlates of heart rate variability in a healthy young adult population. *Brain Structure and Function, 222*(2), 1061–1068. https://doi.org/10.1007/s00429-016-1185-1

Understanding the Neurophysiology of PTSD, Moral Injury, and Posttraumatic Growth: How It Can Guide Training Protocols

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Posttraumatic stress is distinct from moral injury. The former is a natural, automatic response to defend against danger, whereas the latter is the interpretation of such an event, in light of an individual's values, beliefs, and world view. Moral injury, unlike posttraumatic stress, occurs when a person is able to reflect upon a traumatic experience after the immediate danger has passed (i.e., interpretation; Ames et al., 2019). PTSD is a fear reaction to danger and has identifiable trauma symptoms such as flashbacks, nightmares, hypervigilance, and dissociation. On the other hand, moral injury is an inner conflict based on a moral evaluation of having inflicted harm, a judgment grounded in a sense of personal agency. Moral injury is strongly related to negative consequences associated with war-zone stressors that transgress military veterans' deeply held values and beliefs (Currier, Drescher, Holland, Lisman, & Foy, 2016). Currier, Holland, and Malott (2015) hypothesized that lack of meaning increases the risk for adjustment problems after war-zone service. Moral injury describes the effects of acts of commission or omission in war that result in mental, emotional, and spiritual struggle (Currier et al., 2016). In the past 15 years, the literature on disasters and mental health has shifted from a focus on psychopathology, to an interest in documenting manifestations of resilience in the face of mass trauma (Cerdá, 2014). Positive psychology has provided a new forum for discussion about how we construe mental health issues. Each generation and each culture face basic questions about the meaning of birth, suffering, and dying. Each has its own social constructions and ways of managing these very basic human experiences (Joseph, 2009). Posttraumatic growth is the positive psychological change experienced as a result of a struggle with challenging life circumstances that represent significant challenges to the adaptive resources of the individual and an individual's way of understanding the world and his place in it. This positive change depends on an individual's perceived control that he has over a stressor, which in turn determines the stressor's impact. From a neurophysiological perspective, and individual's perceived control over a stressful situation suggests that the dorsal raphe nucleus (DRN) in the brainstem and the ventral medial prefrontal cortex (mPFCv; i.e., Brodmann areas 24, 25, and 32) are key in this process. Indeed, the prelimbic and infralimbic areas of the mPFCv ascertain whether a stress inducing stimulus is under an individual's control. Therefore, when an individual perceives that such a stimulus is under his control, the stress-induced activation of the DRN is mediated or inhibited by the mPFCv, and the effects of the "uncontrollable" stressor are thereby blocked. This process implies that the perceived manifestation of control mediates the stress response that is triggered in the brainstem. Thus, as a practical matter the negative impact of stressors that cause dysregulation of the autonomic nervous system can be mitigated via entraining the functional neural networks that involve the mPFCv and DRN via biofeedback and neurofeedback protocols.

References

Ames, D., Erickson, Z., Youssef, N. A., Arnold, I., Adamson, C. S., Sones, A. C., … Koenig, H. G. (2019). Moral injury, religiosity, and suicide risk in U.S. veterans and active duty military with PTSD symptoms. *Military Medicine, 184*(3–4), e271–e278. https://doi.org/10.1093/milmed/usy148

Cerdá, M. (2014). Posttraumatic growth in the aftermath of a disaster: Looking for the role of gender. *Social Psychiatry and Psychiatric Epidemiology, 49*(12), 1859–1860. https://doi.org/10.1007/s00127-014-0949-2

Currier, J. M., Drescher, K. D., Holland, J. M., Lisman, R., & Foy, D. W. (2016). Spirituality, forgiveness, and quality of life: Testing a mediational model with military veterans with PTSD. *The International Journal for the Psychology of Religion, 26*(2), 167–179. https://doi.org/10.1080/10508619.2015.1019793

Currier, J. M., Holland, J. M., & Malott, J. (2015). Moral injury, meaning making, and mental health in returning veterans. *Journal of Clinical Psychology, 71*(3), 229–240. https://doi.org/10.1002/jclp.22134

Joseph, S. (2009). Growth following adversity: Positive psychological perspectives on posttraumatic stress. *Psihologijske Teme* [Psychological Topics]*, 18*(2), 335–343.

Emotions: Exposing the Neurological Pathways that Far Too Often Control Our Behaviors

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Social science literature offers many models of human emotions. Each model provides descriptive terminology but for the most part fails to identify the neuronetworks that are activated when elicited by external emotionally laden stimuli. Historically, science has viewed emotions as primitive and instinctive responses that were not associated with complex intellectual or cognitive functions. However, cognitive-emotional interactions are extremely important in everyday decision-making and represent a significant area of study at present. In addition, the brain has a striking capacity to learn and remember the emotional significance of diverse stimuli and memorial events. Furthermore, the thought process allows humans to assign emotional valence to stimuli, and as a result can change the value that was previously assigned to a stimulus. Studies of brain functions reveal that neural pathways exist for these important cognitive-emotional interactions, but crosswalking these cognitive-emotional interactions to widely used behavioral assessments is missing from the literature. Electroencephalographic (EEG) electromagnetic tomographic analysis (ETA) imaging techniques provide a mechanism for exposing neurological pathways of the emotional spectrum, while an individual is reliving emotional loaded past experiences. This presentation will focus on frontal EEG gamma band asymmetry, at the precognitive level and then will expand this examination to include other frequencies as well as other key subcortical structures.

During the presentation, a number of experimental findings will be shared, including brain imaging of emotional triggers using the categories of fear, joy, anger, and love. Experimental protocols require that each participant complete a behavioral insights assessment survey prior to coming to the lab for an EEG session. Participants are asked to write down three to five stimuli (single words or short phrases) for each of the four categories. The stimuli represent events that they believe will invoke feelings that fall into one of these categories. Next, they are asked to rate how strong they believe the emotion response will be on a Likert scale. While connected for EEG data collection, each stimulus is presented on screen for a period of 2 s and spaced with a blank screen with a randomized time between 3 to 5 seconds before a new stimulus is presented. The EEG process is followed by a postprocess interview. Participants are asked to review each of the stimuli they provided and reflect on their experience. The debrief includes asking if any particular stimuli stood out to them as being stronger or weaker than they originally thought, as well as exploring if any stimuli seemed to provoke additional thought or reflection when presented. All feedback is recorded and cross-referenced to EEG output as well as a comparison to their behavioral style as identified in their behavioral assessment profile.

Documenting the pathways exposed for each of these four emotional categories and then cross-referencing findings to a populate behavioral assessment is intended to provide new insights into the emotional tendencies of various behavioral styles and expose how different behavioral styles may process emotional stimuli differently.

References

Bonnstetter, B. J., Bonnstetter, R. J., Hebets, D., & Collura, T. F. (2015). *U.S. Patent No. 9,060,702*. Washington, DC: U.S. Patent and Trademark Office.

Bonnstetter, B. J., Bonnstetter, R. J., Hebets, D., & Collura, T. F. (2016). *Canadian Patent No. 2,808,691*. Gatineau, Québec: Canadian Intellectual Property Office.

Bonnstetter, R. J., Gehrig, E., & Hebets, D. (2018). Response process validation protocol using neurophenomenological gamma asymmetry. *NeuroRegulation, 5*(3), 93–102. https://doi.org/10.15540/nr.5.3.93

Bonnstetter, R. J., Hebets, D. & Wigton, N. L. (2015). Frontal gamma asymmetry in response to soft skills stimuli: A pilot study. *NeuroRegulation, 2*(2), 70–85. https://doi.org/10.15540/nr.2.2.70

Collura, T. F., Wigton, N. L., Zalaquett, C., Chatters-Smith, S. S., & Bonnstetter, R. J. (2016). The value of EEG-based electromagnetic tomographic analysis in human performance and mental health. *Biofeedback, 44*(2), 58–65. https://doi.org/10.5298/1081-5937-44.2.03

Collura, T. F., Zalaquett, C. P., Bonnstetter, R. J., & Chatters, S. J. (2014). Toward an operational model of decision making, emotional regulation, and mental health impact. *Advances in Mind-Body Medicine, 28*(4), 18–33.

Damasio, A. R., Tranel, D. & Damasio, H. (1991). Somatic markers and the guidance of behaviour: Theory and preliminary testing. In H. S. Levin, H. M. Eisenberg & A. L. Benton (Eds.), *Frontal lobe function and dysfunction* (pp. 217–229). New York, NY: Oxford University Press.

Davidson, R. J. (1992). Emotion and affective style: Hemispheric substrates. *Psychological Science, 3*(1), 39–43. https://doi.org/10.1111/j.1467-9280.1992.tb00254.x

Davidson, R. J. (2000). Affective style, psychopathology, and resilience: Brain mechanisms and plasticity. *American Psychologist, 55*(11), 1196–1214. https://doi.org/10.1037/0003-066X.55.11.1196

Davidson, R. J. (2002). Anxiety and affective style: Role of prefrontal cortex and amygdala. *Biological Psychiatry, 51*(1), 68–80. https://doi.org/10.1016/S0006-3223(01)01328-2

Davidson, R. J. (2004). What does the prefrontal cortex "do" in affect: Perspectives on frontal EEG asymmetry research. *Biological Psychology, 67*(1–2), 219–234. https://doi.org/10.1016/j.biopsycho.2004.03.008

Davidson, R. J., Ekman, P., Saron, C. D., Senulis, J. A., & Friesen, W. V. (1990). Approach-withdrawal and cerebral asymmetry: Emotional expression and brain physiology: I. *Journal of Personality and Social Psychology, 58*(2), 330–341. https://doi.org/10.1037/0022-3514.58.2.330

Davidson, R. J., Pizzagalli, D., Nitschke, J. B., & Kalin, N. H. (2003). Parsing the subcomponents of emotion and disorders of emotion: Perspectives from affective neuroscience. In R. J. Davidson, K. R. Scherer, & H. H. Goldsmith (Eds.), *Series in affective science. Handbook of affective sciences* (pp. 8–24). New York, NY: Oxford University Press.

Davidson, R. J., Schwartz, G. E., Saron, C., Bennett, J., & Goleman, D. J. (1979). Frontal versus parietal EEG asymmetry during positive and negative affect. *Psychophysiology, 16*, 202–203.

Gordon, E., Barnett, K. J., Cooper, N. J., Tran, N., & Williams, L. M. (2008). An "integrative neuroscience" platform: Application to profiles of negativity and positivity bias. *Journal of Integrative Neuroscience, 7*(3), 345–366. https://doi.org/10.1142/S0219635208001927

Haidt, J. (2001). The emotional dog and its rational tail: A social intuitionist approach to moral judgment. *Psychological Review. 108*(4), 814–834. https://doi.org/10.1037/0033-295x.108.4.814

Harmon-Jones, E. (2004). Contributions from research on anger and cognitive dissonance to understanding the motivational functions of asymmetrical frontal brain activity. *Biological Psychology, 67*(1–2), 51–76. https://doi.org/10.1016/j.biopsycho.2004.03.003

Kim, J. (1993). *Supervenience and mind: Selected philosophical essays*. Cambridge, UK: Cambridge University Press.

Kim, J. (1999). Making sense of emergence. *Philosophical Studies, 95*(1-2), 3–36. https://doi.org/10.1023/A:1004563122154

Nitschke, J. B., Heller, W., Etienne, M. A., & Miller, G. A. (2004). Prefrontal cortex activity differentiates processes affecting memory in depression. *Biological Psychology, 67*(1–2), 125–143. https://doi.org/10.1016/j.biopsycho.2004.03.004

Naccache, L., Gaillard, R., Adam, C., Hasboun, D., Clémenceau, S., Baulac, M., … Cohen, L. (2005). A direct intracranial record of emotions evoked by subliminal words. *Proceedings of the National Academy of Sciences of the United States of America, 102*(21), 7713–7717. https://doi.org/10.1073/pnas.0500542102

Oakes, T. R., Pizzagalli, D. A., Hendrick, A. M., Horras, K. A., Larson, C. L., Abercrombie, H. C., … Davidson, R. J. (2004). Functional coupling of simultaneous electrical and metabolic activity in the human brain. *Human Brain Mapping, 21*(4), 257–270. https://doi.org/10.1002/hbm.20004

Pascual-Marqui, R. D. (2002). Standardized low-resolution brain electromagnetic tomography (sLORETA): Technical details. *Methods and Findings in Experimental and Clinical Pharmacology, 24*(Suppl. D), 5–12.

Pizzagalli, D. A., Greischar, L. L., & Davidson, R. J. (2003). Spatio-temporal dynamics of brain mechanisms in aversive classical conditioning: High-density event-related potential and brain electrical tomography analyses. *Neuropsychologia, 41*(2), 184–194. https://doi.org/10.1016/S0028-3932(02)00148-3

Pizzagalli, D. A., Nitschke, J. B., Oakes, T. R., Hendrick, A. M., Horras, K. A., Larson, C. L., … Davidson, R. J. (2002). Brain electrical tomography in depression: the importance of symptom severity, anxiety, and melancholic features. Biological Psychiatry, 52(2), 73–85. https://doi.org/10.1016/S0006-3223(02)01313-6

Pizzagalli, D., Pascual-Marqui, R. D., Nitschke, J. B., Oakes, T. R., Larson, C. L., Abercrombie, H. C., … Davidson, R. J. (2001). Anterior cingulate activity as a predictor of degree of treatment response in major depression: Evidence from brain electrical tomography analysis. *The American Journal of Psychiatry 158*(3), 405–415. https://doi.org/10.1176/appi.ajp.158.3.405

Rock, D. (2008). SCARF: A brain-based model for collaborating with and influencing others. *NeuroLeadership Journal, 1*, 1–9.
Rolls, E. T. (1999). *The brain and emotion*. New York, NY: Oxford University Press.
Thatcher, R. W. (2013). Latest developments in live *z*-score training: Symptom check list, phase reset, and LORETA *z*-score biofeedback. *Journal of Neurotherapy, 17*(1), 69–87. https://doi.org/10.1080/10874208.2013.759032
The KEY Institute for Brain-Mind Research. (2014). Zürich, Switzerland: University of Zurich. Retrieved from http://www.uzh.ch/keyinst/
Sireci, S. G., & Sukin, T. (2013). Test validity. In K. F. Geisinger, B. A. Bracken, J. F. Carlson, J.-I. C. Hansen, N. R. Kuncel, S. P. Reise, & M. C. Rodriguez (Eds.), *APA handbooks in psychology*. *APA handbook of testing and assessment in psychology, Vol. 1. Test theory and testing and assessment in industrial and organizational psychology* (Ch. 4, pp. 61–84). Washington, DC: American Psychological Association. https://doi.org/10.1037/14047-004

To Neuromarkers And Beyond: Importance of Identifying Neuromarkers and Biomarkers to Predict and Improve Treatment Outcome for People with Developmental Trauma

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Developmental trauma (DT) or complex childhood trauma is arguably one of the most important public health challenges in the United States. It has a negative impact on the mental, physiological, and neurobiological functioning; leads to a lower quality of life or early death; and creates a substantial financial burden for the individuals affected, their families, and the healthcare system as a whole. Moreover, people with DT are often more resistant to traditional therapy. Research have shown that neurofeedback and biofeedback effectively treat people with DT. While most of the outcome of the research and of clinical treatment is based on subjective measurements, such as questionnaires, less is known about objective measurements, such as neuromarkers and biomarkers in predicting and quantitatively measuring outcome improvement due to the treatment. The goal of this presentation is to deepen the participants' understanding of DT and to address the ways to effectively collect and identify neuromarkers and biomarkers.

This presentation will highlight the importance of conducting neurological and physiological assessments (i.e., neuromarkers and physiomarkers), in addition to using traditional subjective assessments (e.g., questionnaires). At the individual level, we will explore ways of assessing clients' baseline functioning, providing guidance for treatment, and tracking progress. To further the use and improve the outcome of these techniques, we will discuss the benefits and challenges of identifying patterns of brain and physiological activities.

This presentation will begin by discussing ways to detect DT and how it differs from PTSD. After providing an overview of the impact of DT on health and well-being, it will focus on the brain development and functioning. Next, the presentation will identify several markers such as quantitative EEG (qEEG), event-related potential (ERP), and heart rate variability (HRV). We will continue by using these markers to track progress and measure the impact of the treatment at the individual level. Case presentations and clinical examples will be used to demonstrate these points. We will talk about implementation of the individual data to identify patterns of activities. These patterns can be used to predict the effectiveness of the treatment and to improve the outcome.

Overall, this workshop will provide participants with a more complete understanding of DT and ways to use neuromarkers and biomarkers to predict effectiveness of treatment and to improve treatment outcomes. We will finish with future directions and challenges to collect and identify these markers and what we can do as a community to collect and analyze this valuable data in order to understand DT and improve outcome of treatment.

References

Cook, A., Spinazzola, J., Ford, J., Lanktree, C., Blaustein, M., Cloitre, M., ... & van der Kolk, B. (2005). Complex trauma in children and adolescents. *Psychiatric Annals, 35*(5), 390–398.
Huang-Storms, L., Bodenhamer-Davis, E., Davis, R., & Dunn, J. (2006). QEEG-guided neurofeedback for children with histories of abuse and neglect: Neurodevelopmental rationale and pilot study. *Journal of Neurotherapy, 10*(4), 3–16. https://doi.org/10.1300/J184v10n04_02
Tan, G., Dao, T. K., Farmer, L., Sutherland, R. J., & Gevirtz, R. (2011). Heart rate variability (HRV) and posttraumatic stress disorder (PTSD): A pilot study. *Applied Psychophysiology and Biofeedback, 36*(1), 27–35. https://doi.org/10.1007/s10484-010-9141-y
Teicher, M. H., Andersen, S. L., Polcari, A., Anderson, C. M., Navalta, C. P., & Kim, D. M. (2003). The neurobiological consequences of early stress and childhood maltreatment. *Neuroscience & Biobehavioral Reviews, 27*(1–2), 33–44. https://doi.org/10.1016/s0149-7634(03)00007-1

The Effect of NeuroField Neurostimulation and Neuromdulation on Acute Opiate Detoxification

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Opiate addiction has been defined as a national epidemic in the United States according to a 2017 report from the Centers of Disease Control and Prevention (CDCP). The rise of opioid deaths can be traced to three waves, with the first occurring in the 1990s when there was a significant increase in opioid prescriptions. The second wave occurred in 2010 when there was a spike in heroin deaths. The third wave occurred in 2013 when there was a significant increase in synthetic opioid deaths. According to the CDCP over 350,000 people have died from opioid overdoses from 1999 to 2017. The common method for medical detoxification from opioids is a 6-day taper in which the patient is given suboxone to reduce pain and cravings. During the 6-day taper, tDCS, tACS, and tRNS cranial stimulation were used and hypothesized to reduce cravings, anxiety, and depression and to improve sleep. The opioid group consisted of 53 patients. Pre- and post-EEGs were taken and analyzed showing significant changes in absolute power, coherence, and phase as compared to controls and neurofeedback only conditions. Furthermore, patient symptom ratings and PHQ9 and GAD7 surveys showed significant reduction in cravings, depression, and anxiety symptoms. No serious adverse side effects were reported in the stim-only condition. In this session, data will be presented showing the outcomes of this study.

References

Antonenko, D., Faxel, M., Grittner, U., Lavidor, M., & Flöel, A. (2016). Effects of transcranial alternating current stimulation on Cognitive Functions in healthy young and older adults. *Neural Plasticity, 2016*, 4274127. https://doi.org/10.1155/2016/4274127

Bikson, M., Grossman, P., Thomas, C., Zannou, A. L., Jiang, J., Adnan, T., … Woods, A. J. (2016). Safety of transcranial direct current stimulation: Evidenced based update 2016. *Brain Stimulation, 9*(5), 641–661. https://doi.org/10.1016/j.brs.2016.06.004

Brunoni, A. R., Moffa, A. H., Fregni, F., Palm, U., Padberg, F., Blumberger, D., … Loo, C. K. (2016) Transcranial direct current stimulation for acute major depressive episodes: Meta-analysis of individual patient data. *The British Journal of Psychiatry, 208*(6), 522–531. https://doi.org/10.1192 /bjp.bp.115.164715

Palm, U., Chalah, M. A., Padberg, F., Al-Ani, T., Abdellaoui, M., Sorel, M., … Ayache, S. S. (2016). Effects of transcranial random noise stimulation (tRNS) on affect, pain and attention in multiple sclerosis. *Restorative Neurology and Neuroscience, 34*(2), 189–199. https://doi.org/10.3233/RNN-150557

Van den Heuvel, M. P., & Sporns, O. (2011). Rich-club organization of the human connectome. *The Journal of Neuroscience, 31*(44), 15775–15786. https://doi.org/10.1523/JNEUROSCI.3539-11.2011

The Psychology of Adopting Medical Device Innovations in Mental Healthcare: The Case of Neurofeedback in the United States and the Netherlands

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Barriers to the acceptance of a medical device innovation, electroencephalogram neurofeedback (EEG-NFB) for the treatment of ADHD in children, were investigated with a mixed-method embedded design utilizing the theoretical frameworks of Latour and Rogers. Within Latour's framework EEG-NFB is a technological innovation that is part of a larger paradigm shift going on in medical healthcare treatment. Healthcare professionals act as "gatekeepers" to medical innovation within Roger's framework. Eighteen U.S. and Dutch healthcare professionals, who commonly diagnose and treat children with ADHD, participated in the study. The mixed-method design involved a semistructured interview embedded with quantitative assessments. The assessments included a self-monitoring questionnaire, selection and ranking of recommended treatments for a child with ADHD from a vignette, and identification and ranking of factors that influence the healthcare professional's decision-making process. Quantitative analyses were conducted with Tukey-Duckworth tests and a Spearman correlation. Qualitative analysis was conducted by word analysis with Leximancer. No significant differences were present between the U.S. and Dutch healthcare professionals. The sample were all highly aware of EEG-NFB with half being EEG-NFB practitioners, some who refer for EEG-NFB and some who were aware of EEG-NFB but did not refer patients for treatment or practice it themselves. EEG-NFB was one of the most commonly recommended treatments, and the highest ranked treatment, for the child with ADHD from the vignette. The main barrier identified was awareness about EEG-NFB as a treatment for ADHD in children. Technical knowledge about how to actually conduct, refer for, and evaluate progress in EEG-NFB was another major barrier. One of the recommendations to increase adoption is to initiate marketing campaigns focused on increasing awareness among healthcare professionals. Another recommendation is affordable or free continuing education courses for healthcare professionals targeted toward how to speak to a patient about the proposed mechanism of action for EEG-NFB, find a provider to refer to, and evaluate a patient's progress during a course of EEG-NFB treatments.

References

Denis, J.-L., Hébert, Y., Langley, A., Lozeau, D., & Trottier, L.-H. (2002). Explaining diffusion patterns for complex health care innovations. *Health Care Management Review, 27*(3), 60–73. https://doi.org/10.1097/00004010-200207000-00007

Epocrates. (2016). Attention deficit hyperactivity disorder in children: Common Vignette 1. Retrieved from https://online.epocrates.com/diseases/14222/Attention-deficithyperactivity-disorder-in-children/Common-Vignette

Epstein, R. M., Siegel, D. J., & Silberman, J. (2008). Self-monitoring in clinical practice: A challenge for medical educators. *Journal of Continuing Education in the Health Professions, 28*(1), 5–13. https://doi.org/10.1002/chp.149

European Commission. (2016). Joint-Statement on Mental Health for the EU Health Policy Platform on Mental Health and Policy. Retrieved from https://ec.europa.eu/health/sites/health/files/interest _groups/docs/ev_20161205_co02_en.pdf

HollandZorg. (2016). Alternative therapies and medicines. Ministry of Health, Government of the Netherlands. Retrieved from https://www.hollandzorg.com/dutch-healthcare-insurance/reimbursements/alternative-therapies-and-medicines

Latour, B. (1990). Technology is society made durable. *The Sociological Review, 38*(S1), 103–131. https://doi.org/10.1111/j.1467-954X.1990.tb03350.x

Pigott, H. E., Cannon, R., & Trullinger, M. (2018). The fallacy of sham-controlled neurofeedback trials: A reply to Thibault and Colleagues (2018). *Journal of Attention Disorders*. https://doi.org/10.1177 /1087054718790802

Rogers, E. M. (2010). *Diffusion of innovations* (5th ed.). New York, NY: Free Press.

Smith, A. E., & Humphreys, M. S. (2006). Evaluation of unsupervised semantic mapping of natural language with Leximancer concept mapping. *Behavior Research Methods, 38*(2), 262–279. https://doi.org/10.3758/BF03192778

Snyder, M. (1974). Self-monitoring of expressive behavior. *Journal of Personality and Social Psychology, 30*(4), 526–537. https://doi.org/10.1037/h0037039

Thibault, R. T., & Raz, A. (2017). The psychology of neurofeedback: Clinical intervention even if applied placebo. *American Psychologist, 72*(7), 679–688. https://doi.org/10.1037/amp0000118

Thibault, R. T., Veissière, S., Olson, J. A., & Raz, A. (2018). Treating ADHD with suggestion: Neurofeedback and placebo therapeutics. *Journal of Attention Disorders, 22*(8), 707–711. https://doi.org/10.1177/1087054718770012

Tukey, J. W. (1959). A quick compact two sample test to Duckworth's specifications. *Technometrics, 1*(1), 31–48. https://doi.org/10.1080/00401706.1959.10489847

Van Doren, J., Arns, M., Heinrich, H., Vollebregt, M. A., Strehl, U., & Loo, S. K. (2018). 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

Walshe, K., & Rundall, T. G. (2001). Evidence-based management: From theory to practice in health care. *The Milbank Quarterly, 79*(3), 429–457. https://doi.org/10.1111/1468-0009.00214

An Integrative Neurotherapy Approach to Balancing the Gut-Brain Axis

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Recent research within the fields of medicine, neuroscience, psychiatry, and microbiology has revealed a complex, remarkably interconnected relationship between the brain and gastrointestinal system. The gut-brain axis involves a number of complex feedback loops between the microbiome, intestinal barrier, mucosal immune system, neuroendocrine system, and hypothalamic-pituitary-adrenal (HPA) axis, as well as the enteric, autonomic, and central nervous systems (De Palma, Collins, Bercik, & Verdu, 2014; Mayer, 2011). Through these communication channels, signals from the brain can modulate motor, sensory, and secretory functions of the gut, and signals from the gut can influence various aspects of psychological and cognitive function (De Palma, Vida, et al., 2014; Grenham, Clarke, Cryan, & Dinan, 2011; Mayer, Knight, Mazmanian, Cryan, & Tillisch, 2014). As such, alterations in one component can trigger a cascade of effects throughout the axis.

Exposure to prolonged or excessive stress—whether emotional trauma or pathogenic invasion—can produce especially detrimental effects on this axis, leading to chronic physical and psychological disorders (Bell & Ross, 2014; Mayer et al., 2014). In fact, gut-brain imbalances have been implicated in a myriad of ailments, including anxiety, depression, PTSD, autism, attention deficits, eating disorders, irritable bowel syndrome, inflammatory bowel disease, Chron's disease, and ulcerative colitis, among others (Bischoff et al., 2014; Cryan & Dinan, 2012; Mayer, 2011). Consequently, a failure to adequately address imbalances throughout this axis might inhibit clients' progress in neurotherapy.

This presentation will provide an overview of research on the gut-brain axis as it relates to the fields of neurofeedback and mental health. We will especially examine the impact of stress on the gut-brain axis, as well as the role of this axis in stress-related disorders. We will then discuss practical recommendations for an integrative neurotherapy approach to help clients effectively balance this axis, thus maximizing their physical, cognitive, and emotional well-being. This will include methods for reducing the brain's stress reactivity, balancing the neuroendocrine system, optimizing microbiota compositions, repairing the gut lining, restoring tight junctions in the blood-brain barrier, ensuring adequate nourishment, and reducing inflammation.

References

Bell, A., & Ross, K. M. (2014). The neuro psycho physiological effects of chronic and excessive stress. *American International Journal of Social Science, 3*(1), 159–173.

Bischoff, S. C., Barbara, G., Buurman, W., Ockhuizen, T., Schulzke, J.-D., Serino, M., … Wells, J. M. (2014). Intestinal permeability—A new target for disease prevention and therapy. *BMC Gastroenterology, 14*, 189. https://doi.org/10.1186/s12876-014-0189-7

Cryan, J. F., & Dinan, T. G. (2012). Mind-altering microorganisms: The impact of the gut microbiota on brain and behaviour. *Nature Reviews Neuroscience, 13*(10), 701–712. https://doi.org/10.1038/nrn3346

De Palman, G., Collins, S. M., Bercik, P., & Verdu, E. F. (2014). The microbiota-gut-brain axis in gastrointestinal disorders: Stressed bugs, stressed brain or both? *The Journal of Physiology, 592*(14), 2989–2997. https://doi.org/10.1113/jphysiol.2014.273995

De Palma, G., Vida, C., Santacruz, A., De Castro, N. M., De la Fuente, M., & Sanz, Y. (2014). Impaired responses to gliadin and gut microbes of immune cells from mice with altered stress-related behavior and premature immune senescence. *Journal of Neuroimmunology, 276*(1), 47–57. https://doi.org/10.1016/j.jneuroim.2014.08.007

Grenham, S., Clarke, G., Cryan, J. F., & Dinan, T. G. (2011). Brain-gut-microbe communication in health and disease. *Frontiers in Physiology, 2*, 94. https://doi.org/10.3389/fphys.2011.00094

Mayer, E. A. (2011). Gut feelings: The emerging biology of gut–brain communication. *Nature Reviews Neuroscience, 12*(8), 453–466. https://doi.org/10.1038/nrn3071

Mayer, E. A., Knight, R., Mazmanian, S. K., Cryan, J. F., & Tillisch, K. (2014). Gut microbes and the brain: Paradigm shift in neuroscience. *The Journal of Neuroscience, 34*(46), 15490–15496. https://doi.org/10.1523/JNEUROSCI.3299-14.2014

Meta-Analysis of Mulitvariate Coherence Neurofeedback research

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As the field of neurofeedback grows, a few novel neurofeedback approaches have emerged. While the use of functional magnetic resonance imaging (fMRI)-based neuromodulation has shown efficacy as a form of treatment, fMRI is not cost effective or practical and yields low temporal resolution (Frey, Mühl, Lotte, & Hachet, 2013). However, electroencephalography (EEG) is relatively inexpensive, practical, and yields high temporal resolution (Frey et al., 2013). Successful EEG-based neurofeedback therapy has been demonstrated in the treatment of clinical conditions and symptoms including decreasing symptoms related to seizure disorders (Sterman & Egner, 2006) and learning disabilities (Coben, Wright, Decker, & Morgan, 2015; Fernández et al., 2003). Additional findings have shown that EEG-based neurofeedback can reduce symptoms associated with autism spectrum disorder (Coben, 2013; Kouijzer, de Moor, Gerrits, Buitelaar, & van Schie, 2009). Furthermore, a study by Wang et al. (2016) found that EEG characteristics associated with autism were reduced using prefrontal neurofeedback treatment. There is also evidence that the effects of these interventions last beyond the initial training period (Coben, 2013; Gevensleben et al., 2009).

Some researchers have found success using two-channel coherence training. However, the growing body of research concerning coherence assessment suggests that using a greater number of electrodes relative to the standard two-channel approach increases spatial acuity (Blinowska, 2011). Research has shown the use of four-channel multivariate coherence training is associated with significantly greater changes in power and coherence as compared to two-channel coherence training (Coben, Middlebrooks, Lightstone, & Corbell, 2018). Advancing to four channels and calculating coherence metrics in a multivariate fashion led to greater changes in power by more than 50% and coherence by more than 400% (Coben et al., 2018).

This presentation will focus on the results of a meta-analysis on previous research conducted on several disorders whose subjects have received four-channel multivariate coherence training and were compared to an alternate treatment or comparison group. These include a mixed diagnosis study (n = 174), symptoms of autism (n = 110), mu suppression in autism (n = 78), depression (n = 54), developmental trauma (n = 40), learning disabilities (n = 63), epilepsy (n = 52), and traumatic brain injuries (n = 20) with a total sample size of N = 591.

We plan to conduct this meta-analysis to help us understand the general impact of this form of neurofeedback which then may be compared to other types. Such a statistical approach will also help us understand if this form of neurofeedback has greater efficacy for certain conditions over others. We will also seek to understand if there are any mitigating factors such as medications, age, gender, or others. These findings will be presented and their implications discussed.

References

Blinowska, K. J. (2011). Review of the methods of determination of directed connectivity from multichannel data. *Medical & Biological Engineering & Computing, 49*(5), 521–529. https://doi.org/10.1007/s11517-011-0739-x

Coben, R. (2013). Neurofeedback for autistic disorders: Emerging empirical evidence. In M. F. Casanova, A. S. El-Baz, & J. S. Suri (Eds.), *Imaging the Brain in Autism* (pp. 107–134). New York, NY: Springer. https://doi.org/10.1007/978-1-4614-6843-1_6

Coben, R., Middlebrooks, M., Lightstone, H., & Corbell, M. (2018). Four channel multivariate coherence training: Development and evidence in support of a new form of neurofeedback. *Frontiers in Neuroscience, 12*, 729. https://doi.org/10.3389/fnins.2018.00729

Coben, R., Wright, E. K., Decker, S. L., & Morgan, T. (2015). The impact of coherence neurofeedback on reading delays in learning disabled children: A randomized controlled study. *NeuroRegulation, 2*(4), 168–178. https://doi.org/10.15540/nr.2.4.168
Fernández, T., Herrera, W., Harmony, T., Díaz-Comas, L., Santiago, E., Sánchez, L., ... Valdés, G. P. (2003). EEG and behavioral changes following neurofeedback treatment in learning disabled children. *Clinical Electroencephalography, 34*(3), 145–152. https://doi.org/10.1177/155005940303400308
Frey, J., Mühl, C., Lotte, F., & Hachet, M. (2013). Review of the use of electroencephalography as an evaluation method for human-computer interaction. *Proceedings from the International Conference on Physiological Computing Interface Workshop and Training Course* (pp. 214–223), Lisbon, Portugal.
Gevensleben, H., Holl, B., Albrecht, B., Schlamp, D., Kratz, O., Studer, P., … Heinrich, H. (2010). *European Child & Adolescent Psychiatry, 19*(9), 715–724. https://doi.org/10.1007/s00787-010-0109-5
Kouijzer, M. E. J., de Moor, J. M. H., Gerrits, B. J. L., Buitelaar, J. K., & van Schie, H. T. (2009). Long-term effects of neurofeedback treatment in autism. *Research in Autism Spectrum Disorders, 3*(2), 496–501. https://doi.org/10.1016/j.rasd.2008.10.003
Sterman, M. B., & Egner, T. (2006). Foundation and practice of neurofeedback for the treatment of epilepsy. *Applied Psychophysiology and Biofeedback, 31*(1), 21. https://doi.org/10.1007/s10484-006-9002-x
Wang, Y., Sokhadze, E. M., El-Baz, A. S., Li, X., Sears, L., Casanova, M. F., & Tasman, A. (2016). Relative power of specific EEG bands and their ratios during neurofeedback training in children with autism spectrum disorder. *Frontiers in Human Neuroscience, 9*, 723. https://doi.org/10.3389/fnhum.2015.00723

The Wisdom of Morphology

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Reading the raw EEG is an artform that is an essential knowledge base of any practitioner using EEG to assess and diagnose their patients' conditions. Spindles, triangular shapes, sinusoidal, monomorphic, and archiform waveforms are just a few telling morphological signs that are imperative in understanding what is really going on. Does the waveform wax and wane? Does it travel in spindles or bursts? Does it appear only a few times in the record? What if it is rhythmic? These temporal dynamics are also imperative in a proper assessment of the person. When looking at the raw waveform, you will learn more than what any qEEG alone can tell you.

Through exploring the more insidious forms of artifact (i.e., electricity, channel noise, mixed metals, etc.) to detecting less commonly seen morphological forms in the EEG (i.e., lambda, mu, OIRDA, beta spindles, etc.), this lecture will guide the clinician through some of the more advanced ways of interpreting EEG so that the qEEG does not mislead one into misdiagnosis.

We are privileged to have many analysis and diagnostic tools to help us dissect, spatially and temporally analyze, condense, and summate the EEG into neat and tidy diagrams, but we fail our patients and our profession if we miss the devils in the details.

Finally, montages are necessary to understand the many ways in which we can assess and view the EEG. There is no best montage for all purposes. While linked ears can provide a global view, it is prone to contamination if there is a strong temporal finding or if there is contamination otherwise in the ear electrodes. Average and weighted average montages (such as the Laplacian and Hjorth montages), will highlight any local phenomena, and will uncover any significant temporal component, but will fail us to see global information. Bipolar montages are excellent for displaying phase reversals, which are indispensable in issues of head injury and seizure focus.

References

Chatrian, G. E., Bergamini, L., Dondey, M., Klass, D. W., Lennox, M., Buchthal, I., & Petersen, I. (1974). A glossary of terms most commonly used by clinical electroencephalographers, *Electroencephalography and Clinical Neurophysiology, 37*, 538–548.
Nunez, P. L. (1995). *Neocortical dynamics and human EEG rhythms*. New York, NY: Oxford University Press.
Sanei, S., & Chambers, J. A. (2007). *EEG signal processing*. Hoboken, NJ: John Wiley & Sons, Inc.

Cognitive Function Enhancement Through Photobiomodulation on Prefrontal Lobe and the EEG measurements

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Brain functions have been proven to be affected by external stimuli. Photobiomodulation (PBM) using near-infrared is one of the effective ways to modulate the hemodynamic activities in the brain and to activate the key enzyme cytochrome c oxidase (CCO) in electron transport chain (ETC; Anders, Lanzafame, & Arany, 2015; Anders et al., 2014; Barrett & Gonzalez-Lima, 2013; Blanco, Saucedo, & Gonzalez-Lima, 2017; Rojas & Gonzalez-Lima, 2017; Tian, Hase, Gonzalez-Lima, & Liu, 2016; Vargas et al., 2017; Wang, Tian, Soni, Gonzalez-Lima, & Liu, 2016). An 808-nm LED system with 250 mW/cm2 power density, 10 min treatment on prefrontal area is adopted in this research. We investigated the cognitive effects of PBM using prefrontal cortex measures of attention, Psychomotor Vigilance Task (PVT), and memory, Delayed Match to Sample (DMS), to show the cognitive function enhancement. In addition, the primary brain activities as electroencephalography (EEG) is investigated to establish the link between the PBM and the EEG. In our preliminary results (n=12), the EEG related to the PBM on the subjects of various ages shows different responses in spectral and time domains, especially during the resting states. After PBM treatment, the peak-valley ratio of the waves in EEG has stronger contrast, and the effect lasts even the PBM has been stopped. This shows the PBM is not a short-term effect and could be observed in EEG. Our research indicates that the aging process and the brain function deterioration could be observed through the peak-valley ratio of the spectral-time measurements. Baseline vs. chronic (10 daily sessions, 10 min each) comparisons of mean cognitive scores all showed improvements, significant for PVT reaction time ($p < 0.001$), PVT lapses ($p < 0.001$), and DMS correct responses ($p < 0.05$). The peak-valley ratio is enhanced about 3 dB. This finding opens a window to investigate how the brain function enhancement is achieved at the system level and how the signaling enhancement are propagated.

References

Anders, J. J., Lanzafame, R. J., & Arany, P. R. (2015). Low-level light/laser therapy versus photobiomodulation therapy. *Photomedicine and Laser Surgery, 33*(4), 183–184. https://doi.org/10.1089/pho.2015.9848

Anders, J. J., Moges, H., Wu, X., Erbele, I. D., Alberico, S. L., Saidu, E. K., ... Pryor, B. A. (2014). In vitro and in vivo optimization of infrared laser treatment for injured peripheral nerves. *Lasers in Surgery and Medicine, 46*(1), 34–45. https://doi.org /10.1002/lsm.22212

Barrett, D. W., & Gonzalez-Lima, F. (2013). Transcranial infrared laser stimulation produces beneficial cognitive and emotional effects in humans. *Neuroscience, 230*, 13–23. https://doi.org /10.1016/j.neuroscience.2012.11.016

Blanco, N. J., Saucedo, C. L., & Gonzalez-Lima, F. (2017). Transcranial infrared laser stimulation improves rule-based, but not information- integration, category learning in humans. *Neurobiology of Learning and Memory, 139*, 69–75. https://doi.org/10.1016/j.nlm.2016.12.016

Rojas, J. C., & Gonzalez-Lima, F. (2017). Transcranial low-level laser (light) therapy for neurocognitive enhancement. In M. R. Hamblin, M. V. P. de Sousa, & T. Agrawal (Eds.), *Handbook of low-level laser therapy* (1st ed., pp. 1057–1076). Singapore: Pan Stanford Publishing.

Tian, F., Hase, S. N., Gonzalez-Lima, F., & Liu, H. (2016). Transcranial laser stimulation improves human cerebral oxygenation. *Lasers in Surgery and Medicine, 48*(4), 343–349. https://doi.org/10.1002/lsm.22471

Vargas, E., Barrett, D. W., Saucedo, C. L., Huang, L.-D., Abraham, J. A., Tanaka, H., ... Gonzalez-Lima, F. (2017). Beneficial neurocognitive effects of transcranial laser in older adults. *Lasers in Medical Science, 32*(5), 1153–1162. https://doi.org/10.1007/s10103-017-2221-y

Wang, X., Tian, F., Soni, S. S., Gonzalez-Lima, F., & Liu, H. (2016). Interplay between up-regulation of cytochrome-c-oxidase and hemoglobin oxygenation induced by near-infrared laser. *Scientific Reports, 6,* 30540. https://doi.org/10.1038 /srep30540

POSTER PRESENTATIONS

Dosage of Low Frequency rTMS Affects Event-Related Potentials and Evoked and Induced 40 Hz Gamma Oscillations in Autism Spectrum Disorder

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Background. Autism is defined as a spectrum of behavioral disorders that have in-common impairments in social interaction and communication skills, language deficits, and a restricted repertoire of interests and stereotyped activities. There are several theoretical models of the neuropathology of autism spectrum disorders (ASD), and one of them suggests the presence of an excessive cortical excitation/inhibition (E/I) ratio (Casanova, Buxhoeveden, & Gomez, 2003; Rubenstein & Merzenich, 2003) that affects functional connectivity. This model explains atypical event-related potential (ERP) and gamma oscillations observed in ASD during task performance (Sokhadze et al., 2009; Uzunova, Pallanti, & Hollander, 2016).

Objectives. In our prior exploratory studies, we used different schedules of rTMS to investigate outcomes of rTMS in ASD. In this study, 124 high-functioning ASD children (IQ > 80, < 18 years of age) were recruited and assigned to either a waitlist group or one of three different number of weekly rTMS sessions (i.e., 6, 12, 18) to investigate effects of dosage on functional and behavioral outcomes. The project was aimed at selection of more effective length of rTMS course.

Methods. TMS consisted of trains of 1.0-Hz pulses applied over dorsolateral prefrontal cortex. The experimental task was a three-stimulus visual oddball with illusory Kanizsa figures. Behavioral response variables included reaction time and error rate along with EEG indices such as ERP and evoked and induced gamma oscillations. One hundred and twelve patients completed the assigned number of rTMS sessions.

Results. We found significant positive changes post-TMS treatment in motor responses accuracy (percentage of committed errors, normative posterror slowing), in ERP indices and in evoked and induced gamma responses. Parental reports showed significant reductions in aberrant behavior scores as well as decreased scores of repetitive and stereotypic behaviors. The gains of outcomes increased with the total number of treatment sessions. Behavioral questionnaires (ABC, Aman & Singh, 1994; RBS-R, Bodfish, Symons, & Lewis, 1999; SRS-2, Constantino & Gruber, 2005) showed significant improvements in ratings of autism symptoms both post-12- and 18-session rTMS course. Results of our clinical research study showed most significant changes from baseline in functional measures of performance in oddball task and in behavioral symptom ratings following 18 sessions of rTMS treatment. Several measures showed a difference from baseline and waitlist in reaction time and ERP/EEG variables after 12 sessions of rTMS, but only a few of them reached statistical significance post-6-session rTMS course.

Conclusions. Our results suggest that rTMS, particularly after 18 sessions, facilitates cognitive control, attention, and target stimuli recognition by improving discrimination between task-relevant and task-irrelevant illusory figures in an oddball test. Improvement in executive functions and behavioral symptoms of autism further suggests that TMS has the potential to target core features of ASD. The results of this dosage-response study could serve as important prerequisites that could inform the planning of a blinded randomized clinical trial. Among potential implications should be considered combining rTMS with neurofeedback training aimed at reinforcement of neuromodulation effects using operant conditioning in similar manner as it was reported by our group earlier (Sokhadze et al., 2014).

References

Achenbach, T. M., & Rescorla, L. A. (2012). *Multicultural guide for the ASEBA forms and profiles for ages 1½–18* (2nd ed.). Burlington, VT: University of Vermont.

Aman, M. G., & Singh, N. N. (1994). *Aberrant behavior checklist – community. Supplementary manual*. East Aurora, NY: Slosson Educational Publications.

Bodfish, J. W., Symons, F. J., & Lewis, M. H. (1999). *Repetitive behavior scale.* Morganton, NC: Western Carolina Center Research Reports.

Casanova, M. F., Buxhoeveden, D., & Gomez, J. (2003). Disruption in the inhibitory architecture of the cell minicolumn: Implications for autism. *The Neuroscientist, 9*(6), 496–507. https://doi.org/10.1177/1073858403253552

Casanova, M. F., Sokhadze, E., Opris, I., Wang, Y., & Li, X. (2015). Autism spectrum disorders: Linking neuropathological findings to treatment with transcranial magnetic stimulation. *Acta Paediatrica, 104*(4), 346–355. https://doi.org/10.1111/apa.12943

Constantino, J. N., & Gruber, C. P. (2005). The social responsiveness scale (SRS): manual. Los Angeles CA: Western Psychological Services.

Rubenstein, J. L. R., & Merzenich, M. M. (2003). Model of autism: Increased ratio of excitation/inhibition in key neural systems. *Genes, Brain, and Behavior, 2*(5), 255–267. https://doi.org/10.1034/j.1601-183X.2003.00037.x

Sokhadze, E. M., El-Baz, A., Baruth, J., Mathai, G., Sears, L., & Casanova, M. F. (2009). Effects of low frequency repetitive transcranial magnetic stimulation (rTMS) on gamma frequency oscillations and event-related potentials during processing of illusory figures in autism. *Journal of Autism and Developmental Disorders, 39*(4), 619–634. https://doi.org/10.1007/s10803-008-0662-7

Sokhadze, E. M., El-Baz, A. S., Tasman, A., Sears, L. L., Wang, Y., Lamina, E. V., & Casanova, M. F. (2014). Neuromodulation integrating rTMS and neurofeedback for the treatment of autism spectrum disorder: An exploratory study. *Applied Psychophysiology and Biofeedback, 39*(3–4), 237–257. https://doi.org/10.1007/s10484-014-9264-7

Uzunova, G., Pallanti, S., & Hollander, E. (2016). Excitatory/inhibitory imbalance in autism spectrum disorders: Implications for interventions and therapeutics. *The World Journal of Biological Psychiatry, 17*(3), 174–186. https://doi.org/10.3109/15622975.2015.1085597

Incorporation of Neurofeedback to Improve Sustained Attention During Learning Tasks

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This project aimed to improve learning outcomes for students using an intelligent tutoring system (ITS) by employing electroencephalography (EEG)-based neurofeedback (NF). Our two-part hypothesis was 1) upregulating sensorimotor rhythm (SMR) increases a subject's ability to sustain attention for longer periods compared to a sham group and 2) the increase in sustained attention translates to improvements on cognitive tasks. Twenty-three adult subjects were recruited from the community to participate in six sessions, two or three times per week over a 3-week period. All subjects gave informed consent. Three subjects were unable to complete all six sessions and were removed from the study. Subjects were evenly divided between males and females. Subjects were randomly assigned to a NF protocol, either sham or active, and were evenly split between groups with 10 active and 10 sham. The study was double-blinded so that neither investigators nor subjects knew which protocol they received. Each session consisted of the NF protocol in addition to a battery of cognitive tasks, which were counterbalanced in order across sessions. The tasks consisted of single-digit column add (CA-1), triple-digit column add (CA-3), rotation tasks, and the Conners' Continuous Performance Test (CPT), intermixed with math tutorials presented by an ITS. The selected SMR-upregulation NF protocol (Vernon et al., 2003) has been reported to affect the SMR band, which is believed to contribute to sustained attention ability. The NF protocol was implemented using Mensia's Modulo software and Wearable Sensing's DSI-24 dry electrode EEG system. In this protocol, subjects were trained to fill in a jigsaw puzzle by raising the total power in their SMR band. Each training block lasted 3 min, across five blocks with a 10-s break between each block. Subjects were presented two indicators: a power bar on one side of the screen that fluctuated with the total SMR power and a jigsaw puzzle that filled in when the power met threshold requirements. Subjects were randomly assigned to one of two protocols. Group 1 was the active protocol, which used subjects' real-time EEG measurements; Group 2 was the sham condition, which used a random generator coupled with the subject's real-time noise metrics to keep the simulated training as realistic as possible. Results indicated that NF was effective at producing the targeted change in brain activity (upregulating SMR). Subjects in the active NF group also had significant increases in their sustained attention on the CPT task. Specifically, compared to the active group, the sham group had a slower reaction time by 9–70 ms (4–35% change; $p < .009$) and a greater change in omissions ($p < .01$) on the learning task. Although we did not find any significant improvements in accuracy across the other cognitive tasks, we found that the active group missed between 6–26% fewer questions than the sham group ($p < .006$) and responded faster ($p < .006$) on the CA-3 task. In summary, while NF increased SMR activity and significantly improved sustained attention, performance on to learning and cognitive tasks were encouraging but not significant over this limited number of NF sessions.

References

Vernon, D., Egner, T., Cooper, N., Compton, T., Neilands, C., Sheri, A., & Gruzelier, J. (2003). The effect of training distinct neurofeedback protocols on aspects of cognitive performance. *International Journal of Psychophysiology, 47*(1), 75–85. https://dx.doi.org/10.1016/S0167-8760(02)00091-0

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Neurofeedback: Behavioral and Neural Changes in College Students with ADHD

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Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by a consistent presentation of inattentive, hyperactive, and/or impulsive behavior (American Psychiatric Association [APA], 2013). The subgroup of young adults with ADHD who pursue postsecondary education is of particular interest due to their enduring deficits in spite of relative academic achievement when compared to peers with the disorder who do not attend college (DuPaul, Weyandt, O'Dell, & Varejao, 2009). Pharmaceutical treatments are among the most common strategies for mitigating symptoms of ADHD; however, due to trends in the sharing and illicit use of stimulant medication across universities, alternative treatment strategies that target the underlying neural mechanisms of the disorder are warranted. A meta-analysis concluded that neurofeedback (NF) treatment yields strong effect sizes, particularly for behavioral symptoms of ADHD (inattentiveness and impulsiveness; Arns, Conners, & Kraemer, 2013). Moreover, the American Academy of Pediatrics (2011) listed NF as a promising treatment but highlighted the need for additional research.

The present proposal is part of one of the first investigations of NF that utilizes a randomized control design with a placebo condition in the treatment of college students with attention deficits. Moreover, the overarching aim of this study is to provide a better understanding of the utility of NF in the treatment of ADHD in college students, with the specific intention of exploring behavioral changes in the primary symptom domains of ADHD pre- and posttreatment. Additionally, exploratory analyses will be conducted to examine the relationship between behavioral presentations of the disorder and neural profiles. We hypothesize that students in the NF condition will demonstrate greater improvement on behavioral-based measures (according to symptoms outlined in the DSM-5; APA, 2013), as compared to students in the placebo condition. Additionally, we hypothesize that neural profiles, as measured by qEEG, will be associated with behavioral changes. Participants for the current study included undergraduate college students with a documented diagnosis of ADHD. Diagnostic status was confirmed by a trained doctoral-level graduate student using multimodal assessment procedures. Each student who met inclusion criteria completed a baseline qEEG.

Students who did not display qEEG abnormalities consistent with ADHD (as measured by the Neuroguide symptom checklist) were excluded from the study, resulting in 16 participants who continued to the treatment phase. Participants were randomly assigned to the NF treatment condition (n = 8) and the placebo condition (n = 8). Treatment effects will be assessed by examining the changes in behavioral profiles using measures focused on primary symptom domains (i.e., inattentiveness and hyperactivity/impulsivity) between the baseline and posttreatment assessments. Additionally, the relationship between behavioral changes and neural profiles (as measured by pre- and posttreatment qEEG metrics) will be examined. Should significant differences be observed after participating in the NF treatment condition, it will be concluded that NF is a potentially viable tool for mitigating behavioral symptoms in university students with ADHD.

References

American Academy of Pediatrics. (2011). Neurofeedback, Hypnotherapy, and Guided Imagery. Retrieved from http://www.healthychildren.org/English/health-issues/conditions/adhd/Pages/Hypnotherapy-Guided-Imagery-and-Biofeedback.aspx

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

Arns, M., Conners, C. K., & Kraemer, H. C. (2013). A decade of EEG theta/beta ratio research in ADHD: A meta-analysis. Journal of Attention Disorders, 17(5), 374–383. https://doi.org/10.1177/1087054712460087

DuPaul, G. J., Weyandt, L. L., O'Dell, S. M., & Varejao, M. (2009). College students with ADHD: Current status and future directions. *Journal of Attention Disorders, 13*(3), 234–250. https://doi.org/10.1177/1087054709340650

Neurofeedback: Performance-Based Profile Changes in the ADHD-Afflicted Brain

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While current prevalence rates for ADHD vary, it is estimated to affect five to eight percent of the general population across the lifespan (Goldstein, 2011). Though the characteristics of the disorder may change across development, symptoms of ADHD often continue to impair multiple functional domains of daily living.

Individuals with behavioral symptoms of ADHD often show deficits on performance-based measures (for a review see Woods, Lovejoy, & Ball, 2002). Implementing compensatory strategies is the primary practice to improve overall prognosis. Since there is no cure for ADHD, interventions that target neural mechanisms of ADHD, other than psychiatric drugs, are in desperate need.

Research has clearly demonstrated the utility of EEG in diagnostic clinical evaluations for many neurological dysfunctions (Croona, Kihlgren, Lundberg, Eeg-Olofsson, & Eeg-Olofsson, 1999; Leach, Stephen, Salveta, & Brodie, 2006; McGonigal, Oto, Russell, Greene, & Duncan, 2002; Mormann, Lehnertz, David, & Elger, 2000; Thatcher, Walker, Gerson, & Geisler, 1989). A new area of research, neurofeedback (NF), extends the functionality of EEG into a method of treatment. NF is one method that shows promise in treating neurodevelopmental conditions because it purportedly directly impacts brain functioning. Many research studies have generally supported the efficacy of NF for the treatment of neurodevelopmental disabilities in learning or attention (i.e., Breteler, Arns, Peters, Giepmans, & Verhoeven, 2010; Gevensleben et al., 2009; Walker, 2010).

Although research studies support the use of neurofeedback, most published studies have methodological limitations. Namely, the American Academy of Pediatrics (2011) listed NF as promising but in need of more research. The current study uses a randomized control research design with a placebo (or sham) condition for the treatment of children with learning and attention problems. By overcoming the methodological limitations of past research, this study will provide a better understanding of the effectiveness of NF. The goal of this study is to test the effects of NF in college students who experience functional impairment as a result of ADHD, with the underlying hypothesis that students in the NF condition will demonstrate greater improvement on performance-based measures (i.e., CPT, BG-II, and WJ III subtests) than students in the sham condition.

Participants included 16 college undergraduates who were documented as having a diagnosis of ADHD. Each potential participant completed a baseline qEEG; using the Neuroguide symptoms checklist, only those students who exhibited qEEG abnormalities consistent with ADHD were permitted to continue in the study (N = 16).

Treatment effects will be assessed by examining the changes in performance on the neurocognitive measures (i.e., CPT, BG-II, and WJ III subtests) between the baseline and posttreatment assessments. We expect to see significant improvements between pre- and post-NF cognitive measures in the treatment group, but stable performance in the sham group. Should significant changes be observed after receiving NF training, we will conclude that NF has the potential to improve cognitive functioning in college students with ADHD, and thus postulate that NF may be a viable treatment option to improve the prognosis for individuals afflicted with ADHD.

References

American Academy of Pediatrics. (2011). Neurofeedback, Hypnotherapy, and Guided Imagery. Retrieved from http://www.healthychildren.org/English/health-issues/conditions/adhd/Pages/Hypnotherapy-Guided-Imagery-and-Biofeedback.aspx

Breteler, M. H. M., Arns, M., Peters, S., Giepmans, I., & Verhoeven, L. (2010). Improvements in spelling after QEEG-based neurofeedback in dyslexia: A randomized controlled treatment study. *Applied Psychophysiology and Biofeedback, 35*(1), 5–11. https://doi.org/10.1007/s10484-009-9105-2

Croona, C., Kihlgren, M., Lundberg, S., Eeg-Olofsson, O., & Eeg-Olofsson, K. E. (1999). Neuropsychological findings in children with childhood epilepsy with centrotemporal spikes. *Developmental Medicine & Child Neurology, 41*(12), 813–818. https://doi.org/10.1111/j.1469-8749.1999.tb00547.x

Gevensleben, H., Holl, B., Albrecht, B., Vogel, C., Schlamp, D., Kratz, O., … Heinrich, H. (2009), Is neurofeedback an efficacious treatment for ADHD? A randomized controlled clinical trial. *Journal of Child Psychology and Psychiatry, 50*(7), 780–789. https://doi.org/10.1111/j.1469-7610.2008.02033.x

Goldstein, S. (2011). Attention-deficit/ hyperactivity disorder. In S. Goldstein & C. R. Reynolds (Eds.), *Handbook of Neurodevelopmental and Genetic Disorders in Children* (2nd ed.). New York, NY: The Guilford Press.

Leach, J. P., Stephen, L. J., Salveta, C., & Brodie, M. J. (2006). Which electroencephalography (EEG) for epilepsy? The relative usefulness of different EEG protocols in patients with possible epilepsy. *Journal of Neurology, Neurosurgery & Psychiatry, 77*(9), 1040–1042. https://doi.org/10.1136/jnnp.2005.084871

McGonigal, A., Oto, M., Russell, A. J. C., Greene, J., & Duncan, R. (2002). Outpatient video EEG recording in the diagnosis of non-epileptic seizures: A randomised controlled trial of simple suggestion techniques. *Journal of Neurology, Neurosurgery & Psychiatry, 72*(4), 549–551. https://doi.org/10.1136/jnnp.72.4.549

Mormann, F., Lehnertz, K., David, P., & Elger, C. E. (2000). Mean phase coherence as a measure for phase synchronization and its application to the EEG of epilepsy patients. *Physica D: Nonlinear Phenomenon, 144*(3–4), 358–369. https://doi.org/10.1016/S0167-2789(00)00087-7

Thatcher, R. W., Walker, R. A., Gerson, I., & Geisler, F. H. (1989). EEG discriminant analyses of mild head trauma. *Electroencephalography and clinical neurophysiology, 73*(2), 94–106. https://doi.org/10.1016/0013-4694(89)90188-0

Walker, J. E. (2010). Recent advances in quantitative EEG as an aid to diagnosis and as a guide to neurofeedback training for cortical hypofunctions, hyperfunctions, disconnections, and hyperconnections: Improving efficacy in complicated neurological and psychological disorders. *Applied Psychophysiology and Biofeedback, 35*, 25–27. https://doi.org/10.1007/s10484-009-9107-0

Woods, S. P., Lovejoy, D. W., & Ball, J. D. (2002). Neuropsychological characteristics of adults with ADHD: a comprehensive review of initial studies. *The Clinical Neuropsychologist, 16*(1), 12–34. https://doi.org/10.1076/clin.16.1.12.8336

Pilot Study of the Efficacy of Mobile Neurofeedback for Attention-Deficit/Hyperactivity Disorder (ADHD)

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Background. Neurofeedback is commonly regarded as an adjunctive treatment for ADHD, and randomized controlled trials have shown significant benefit attributable to this intervention (Arns, Ridder, Strehl, Breteler, & Coenen, 2009; Lofthouse, Arnold, Hersch, Hurt, & DeBeus, 2012; Micoulaud-Franchi et al., 2014). The present study is a controlled trial to evaluate the specific benefit of neurofeedback training using Myndlift, a clinician-guided wearable, mobile neurofeedback system.

Methods. Nineteen participants (all male, ages 8–15) diagnosed with ADHD were recruited. The intervention group (n = 12) engaged in theta/beta neurofeedback training three to four times per week for 9 weeks, totaling an average of 21 sessions per participant. The control group (n = 7) did not receive any treatment during the 9-week period. Participants in both groups were assessed with a computerized continuous performance test (CPT; MOXO, Neuro Tech Solutions Ltd.) before and after the 9-week period. During the CPT, participants were to respond to target stimuli and ignore nontarget stimuli in the presence of visual and auditory distracters. Outcomes were age- and gender-adjusted z-scores for overall (total) performance, attention, timeliness, impulsivity, and hyperactivity. The CPT assessment report indicated a performance level for each obtained score as follows: *good* (1), *standard* (2), *weak* (3), or *difficulty in performance* (4). The report further classified performance levels 1–3 as “within the norm” and performance level 4 as “outside the norm.”

Results. Sixteen participants completed the study (n = 10 in the intervention group; n = 6 in the control group). The intervention group showed significant improvement in overall performance, attention, inhibition, and hyperactivity ($p < .008$). In contrast, the control group did not show significant improvement. Change from 0 to 9 weeks was significantly greater in the intervention group for overall performance and attention ($p = .030$). Overall performance level was improved for 90% of neurofeedback participants as compared with 34% of controls. Knowledge of whether the participant was assigned to the intervention or control group improved prediction of change in overall CPT performance level by 70% ($p < .001$). For all

outcomes, a greater percentage of participants in the intervention group improved in performance level compared with controls. Change in performance level was significantly greater for the intervention group compared with controls for overall performance (*p* = .018) and attention (*p* = .048). For all outcomes, median change in performance level for the passive control group was 0, reflecting no change. Finally, compared with controls, more participants were reclassified as "within the norm" following neurofeedback. The difference was most salient for overall performance—8 of the 10 neurofeedback participants were reclassified as normal compared with one of the six control participants.

Conclusions. This controlled study provides encouraging evidence for the efficacy of the Myndlift home-based clinician-guided neurofeedback system. In a small cohort of children with ADHD, a 9-week neurofeedback training protocol consistently improved performance on objective measures of ADHD symptomatology. Follow-up randomized controlled trials including active control conditions in larger cohorts are needed to further establish the efficacy of the tool.

References

Arns, M., deRidder, S., Strehl, U., Breteler, M., & Coenen, A. (2009). Efficacy of neurofeedback treatment in ADHD: The effects on inattention, impulsivity and hyperactivity: A meta-analysis. *Clinical EEG and Neuroscience, 40*(3), 180–189. https://doi.org/10.1177/155005940904000311

Lofthouse, N., Arnold, L. E., Hersch, S., Hurt, E., & DeBeus, R. (2012). A review of neurofeedback treatment for pediatric ADHD. *Journal of Attention Disorders, 16*(5), 351–372. https://doi.org/10.1177/1087054711427530

Micoulaud-Franchi, J.-A., Geoffroy, P. A., Fond, G., Lopez, R., Bioulac, S., & Philip, P. (2014). EEG neurofeedback treatments in children with ADHD: An updated meta-analysis of randomized controlled trials. *Frontiers in Human Neuroscience, 8*, 906. https://doi.org/10.3389/fnhum.2014.00906

Predictors of Neurofeedback Outcomes Following qEEG Individualized Protocols for Anxiety

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According to the National Institute of Mental Health (NIHM), anxiety disorders are a prevalent mental health concern affecting 19.1% of adults in the United States (NIMH, 2017). A majority of Americans experience stress during their lifetime; however, anxiety disorders are pervasive and disrupt daily functioning. Neurofeedback, a form of biofeedback, has displayed positive outcomes for reducing anxiety symptoms (Dreis et al., 2015).

The current study uses a within-subjects research design which included qEEG-individualized neurofeedback protocols for anxiety. Protocols were determined by comparing a client's pretest qEEG data to a normative database, and the resulting data was used to develop an individualized protocol. Feedback consisted of games, sounds, animations, and analogical presentations. In addition, the Zung Self-Rating Anxiety Scale for adults, Screen for Anxiety-Related Disorders (SCARED) for children, and Achenbach System of Empirically Based Assessment (ASEBA) were used as self-report assessments for anxiety during pre, post, and follow-up qEEG sessions. Clients were recruited from San Antonio and the surrounding area to receive counseling and neurofeedback treatment free of charge. Clients were asked to attend biweekly neurofeedback sessions for which they agreed to attend a minimum total of 15 training sessions. The neurofeedback training sessions were administered by clinical mental health counseling students and counselor education doctoral students.

The purpose of the current study is to use multilevel modeling to determine predictors of neurofeedback outcomes following individualized neurofeedback anxiety protocols. For this study, a two-level growth model was constructed to identify predictors of outcomes. The times of measurement were level-1 and individual client characteristics were level-2. The individual growth trajectories were fitted in the level-1 model. Outcome scores from the qEEG and other identified instruments were modeled as a function of time. Data will be presented from research findings and implications for neurofeedback will be discussed. In addition, implications for future research and counseling will be discussed.

References

Dreis, S. M., Gouger, A. M., Perez, E. G., Russo, G. M., Fitzsimmons, M. A., & Jones, M. S. (2015). Using neurofeedback to lower anxiety symptoms using individualized qEEG protocols: A pilot study. *NeuroRegulation, 2*(3), 137–148. https://doi.org/10.15540 /nr.2.3.137

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

Psychophysiological Correlates of Prefrontal Neurofeedback in Children with Autism Spectrum Disorder: Pilot Study

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Background. Neurofeedback is one of the most promising methods for training EEG self-regulation in children with autism spectrum disorder (ASD). There are several neurofeedback protocols proposed for ASD with most differences being in the type of training (e.g., theta/beta ratio, coherence), topography (Cz or Pz), guidance by quantitative EEG (qEEG) and number of sessions (e.g., 20 vs. 30). Most studies of neurofeedback in ASD focus on behavioral and EEG outcomes and do not analyze associated psychophysiological processes taking place during successful training. In particular, some cardiorespiratory and electrodermal effects of training are important for the understanding of neurofeedback training effects and defining their role as potential moderators.

Objectives. We proposed that 24 sessions of prefrontal neurofeedback training will be accompanied by changes in power of targeted EEG bands (e.g., 40 Hz-centered gamma band) and ratios of individuals bands (e.g., theta/beta ratio), as well as by changes in electrodermal and cardiorespiratory indices. Autonomic activity patterns were hypothesized to reflect specifics of psychophysiological processes occurring during neurofeedback training in children with autism (Sokhadze, Casanova, Casanova, Klusek, & Roberts, 2019).

Methods. Outcomes measures along with EEG, ECG, pneumogram, and skin conductance measures included behavioral ratings by parents. The protocol used a training for wide-band EEG amplitude suppression (“InhibitAll”) with simultaneous upregulation of the relative power of 40 Hz-centered gamma subband activity. In a pilot study on six children diagnosed with ASD (13.6 years, *SD* = 1.3, two girls) in a 24-session course aimed at prefrontal 40 Hz-centered EEG gamma upregulation and theta-to-beta ratio downregulation we recorded ECG, pneumogram, and electodermal activity. For each session of neurofeedback, qEEG analysis at the training site was completed to determine the relative power of the individual bands (theta, beta, and gamma) and their ratios (theta/beta) within and between sessions. We analyzed Aberrant Behavior Checklist (ABC; Aman & Singh, 1994) and ASEBA (Achenbach & Rescorla, 2012) ratings by parents (pre- and posttreatment).

Results. Dynamics of psychophysiological measures were analyzed during each neurofeedback session and across the whole course. Regression analysis revealed significant linear increase of skin conductance level (SCL, p = 0.002) along with decrease of respiration rate (RSR, $p < .001$) during each neurofeedback session without any statistical changes of SCL of RSR across the course of training. Heart rate variability (HRV) measures (e.g., HF of HRV) showed significant increase during each individual session. According to parental reports hyperactivity subscale scores of ABC (p = .024) and ASEBA DSM-oriented scores of attention-related problems (p = .014) decreased by the end of neurofeedback course.

Conclusions. Psychophysiological measures represent useful markers of attention and emotional engagement of children with ASD during neurofeedback and can be used as predictors of successful performance during training sessions and general behavioral outcome of the intervention. In particular, trend towards increase of electrodermal activity along with RSR deceleration and increased indices of respiratory sinus arrhythmia in HRV may reflect more active attention to training targets and/or experience of emotion states reflected in the observed pattern of psychophysiological indices.

References

Achenbach, T. M., & Rescorla, L. A. (2012). *Multicultural guide for the ASEBA forms and profiles for ages 1½–18* (2nd ed.). Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families.

Aman, M. G., & Singh, N. N. (1994). *Aberrant behavior checklist – community. Supplementary manual*. East Aurora, NY: Slosson Educational Publications.

Sokhadze, E. M., Casanova, M. F., Casanova, E. L., Klusek, J., & Roberts, J. (2019). Autonomic nervous system dysfunctions in children with autism spectrum disorder. In E. M. Sokhadze & M. F. Casanova (Eds.), *Autism Spectrum Disorder: Neuromodulation, Neurofeedback and Sensory Integration Approaches to Research and Treatment* (pp. 169–206). Murfreesboro, TN, FNNR.

Stuttering Throughout Development: A Case Series of Neuromodulation Patients

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Stuttering has been found to affect approximately 5% of preschool-aged children and an overall 1% of the

general population (Chang, Garnett, Etchell, & Chow, 2018; Kent, 2000). Known by several names (e.g., childhood-onset fluency disorder, developmental stuttering), the cause of stuttering has been, and still is, the subject of a lively debate among researchers. While the primary theory of etiology is that stuttering is the result of dysregulation between auditory processing and motor areas of the brain (Kent, 2000; Postma, Kolk, & Povel, 1990), there are still others who view stuttering as a disorder of speech motor control specifically (Einarsdóttir & Ingham, 2008), and yet further research has indicated that the basal ganglia also play a significant role in the disorder (Craig-McQuaide, Akram, Zrinzo, & Tripoliti, 2014). Many different therapeutic interventions have been researched for stuttering, including behavioral therapy (Ingham, Ingham, Euler, & Neumann, 2018) and deep brain stimulation (Craig-McQuaide et al., 2014), and there is even a growing literature on neurofeedback (Bingham, 2013). In 2004, Özge and colleagues found increased delta activity in stutterers vs. age-sex matched controls (especially in right-frontal brain regions; Özge, Toros, & Çömelekoğlu, 2004). Similarly, a 2008 paper by Dr. Ratcliff-Baird showed an increase in frontal theta in stutterers compared to a group of controls. The same study also found a deficit in alpha (Ratcliff-Baird, 2008) and suggested that since similar EEG phenotypes of ADHD had been shown to respond well to neurofeedback (Monastra, 2005) that using neurofeedback as an intervention for stuttering would be worth pursuing. In this study, we present a case series of four neurofeedback patients who were seen for developmental stuttering ranging in age from 8 to 20 years old. All four of the patients had positive outcomes from neurofeedback paired with a whole-person approach (including nutrition, sleep-habits, and interaction with digital technology). For each patient qEEG analysis was performed on eyes-open and eyes-closed baseline data both before and after neurofeedback therapy, and all patients reported a positive improvement in symptoms.

References

Bingham, B. (2013). Multi-modal treatment of stuttering: A case study showing neurofeedback coupled with traditional speech therapy. ISNR 20th Annual Conference. International Society for Neurofeedback and Research, Orlando, FL.

Chang, S.-E., Garnett, E. O., Etchell, A., & Chow, H. M. (2018). Functional and neuroanatomical bases of developmental stuttering: Current insights. *The Neuroscientist*, 107385841880359. https://doi.org/10.1177/1073858418803594

Craig-McQuaide, A., Akram, H., Zrinzo, L., & Tripoliti, E. (2014). A review of brain circuitries involved in stuttering. *Frontiers in Human Neuroscience, 8*, 884. https://doi.org/10.3389/fnhum.2014.00884

Einarsdóttir, J., & Ingham, R. J. (2008). The effect of stuttering measurement training on judging stuttering occurrence in preschool children who stutter. *Journal of Fluency Disorders, 33*(3), 167–179. https://doi.org/10.1016/j.jfludis.2008.05.004

Ingham, R. J., Ingham, J. C., Euler, H. A., & Neumann, K. (2018). Stuttering treatment and brain research in adults: A still unfolding relationship. *Journal of Fluency Disorders, 55*, 106–119. https://doi.org/10.1016/j.jfludis.2017.02.003

Kent, R. D. (2000). Research on speech motor control and its disorders: A review and prospective. *Journal of Communication Disorders, 33*(5), 391–428. https://doi.org/10.1016/S0021-9924(00)00023-X

Monastra, V. J. (2005). Electroencephalographic biofeedback (neurotherapy) as a treatment for attention deficit hyperactivity disorder: Rationale and empirical foundation. *Child and Adolescent Psychiatric Clinics of North America, 14*(1), 55–82. https://doi.org/10.1016/j.chc.2004.07.004

Özge, A., Toros, F., & Çömelekoğlu, Ü. (2004). The role of hemispheral asymmetry and regional activity of quantitative EEG in children with stuttering. *Child Psychiatry and Human Development, 34*(4), 269–280. https://doi.org/10.1023/B:CHUD.0000020679.15106.a4

Postma, A., Kolk, H., & Povel, D.-J. (1990). On the relation among speech errors, disfluencies, and self-repairs. *Language and Speech, 33*(1), 19–29. https://doi.org/10.1177/002383099003300102

Ratcliff-Baird, B. (2008). ADHD and stuttering: Similar EEG profiles suggest neurotherapy as an adjunct to traditional speech therapies. *Journal of Neurotherapy, 5*(4), 5–22. https://doi.org/10.1300/J184v05n04_02

The Effect of Thermal Biofeedback on Migraine, Disability, and Quality of Life in an Underserved Pediatric Neurology Population

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Headache is the most common disabling neurological disorder, with migraine affecting an estimated 1 in 10 school-age children and directly costing around $1 billion per year (Bellini et al., 2013; DeMaagd, 2008; Hu, Markson, Lipton, Stewart, & Berger, 1999). Pediatric migraine affects quality of life resulting in greater risk of impaired physical health, school absenteeism, decreased involvement in peer activities, and altered relationships with family and friends (Stubberud, Varkey, McCrory, Pedersen, & Linde, 2016). Depression and anxiety are prevalent comorbid conditions in migraineurs, and symptoms are positively correlated with headache frequency (Chu et al., 2018). The need for a nonpharmacologic approach to headache treatment in children stems from concerns about prevention headache medication and reluctance to take them, side effects, and poor efficacy (Powers et al., 2017). Biofeedback therapy, an effective treatment for headaches, teaches a patient how to control their body responses to pain and stress, the most frequently reported migraine trigger (Stubberud et al., 2016). Our prospective, randomized, wait-listed controlled study population is comprised of children and adolescents (ages 8–21) recruited from general pediatric and neurology clinics. To qualify, participants must experience at least four migraine headaches a month using the International Headache Society (IHS) criteria and be Medicaid/Medicaid managed care plan insured. The purpose of this trial is to determine if thermal biofeedback therapy is more effective than the standard headache treatment in improving headache frequency, duration, intensity, disability, and quality of life. The waitlist control group will be given the standard of care headache treatment, lifestyle modification education, acute and preventative medication treatments, and routine follow-up. In addition, the treatment group will undergo eight weekly 20-min biofeedback sessions. Data will be compared between the biofeedback and control groups, obtained using a paired *t*-test of headache diary, the Pediatric Migraine Disability Assessment (PedMIDAS), and the Pediatric Quality of Life Index (PedsQL) questionnaire. Subjects who receive thermal biofeedback therapy are hypothesized to demonstrate short- and long-term improvements in headache characteristics, quality of life, and migraine disability. We will discuss the preliminary results comparing data in both groups from baseline appointment, final session, 1-month follow-up, and 3-month follow-up.

References

Bellini, B., Arruda, M., Cescut, A., Saulle, C., Persico, A., Carotenuto, M., ... Guidetti, V. (2013). Headache and comorbidity in children and adolescents. *The Journal of Headache and Pain, 14*, 79. https://doi.org/10.1186/1129-2377-14-79

Chu, H.-T., Liang, C.-S., Lee, J.-T., Yeh, T.-C., Lee, M.-S., Sung, Y.-F., & Yang, F.-C. (2018). Associations between depression/anxiety and headache frequency in migraineurs: A cross-sectional study. *Headache, 58*(3), 407–415. https://doi.org/10.1111/head.13215

DeMaagd, G. (2008). The pharmacological management of migraine, part 1: Overview and abortive therapy. *P & T, 33*(7), 404–416.

Hu, X. H., Markson, L. E., Lipton, R. B., Stewart, W. F., & Berger, M. L. (1999). Burden of migraine in the United States: Disability and economic costs. *Archives of Internal Medicine, 159*(8), 813–818. https://doi.org/10.1001/archinte.159.8.813

Powers, S. W., Coffey, C. S., Chamberlin, L. A., Ecklund, D. J., Klingner, E. A., Yankey, J. W., … Hershey, A. D. (2017). Trial of amitriptyline, topiramate, and placebo for pediatric migraine. *The New England Journal of Medicine, 376*(2), 115–124. https://doi.org/10.1056/NEJMoa1610384

Stubberud, A., Varkey, E., McCrory, D. C., Pedersen, S. A., & Linde, M. (2016). Biofeedback as prophylaxis for pediatric migraine: A meta-analysis. *Pediatrics, 138*(2), e20160675. https://.doi.org/10.1542/peds.2016-0675

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