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NeuroRegulation

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Aim and Scope

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

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***Address correspondence to**: Rex L. Cannon, PhD, BCN, Knoxville Neurofeedback Group, 7147 Kingston Pike, Ste 103, Knoxville, TN 37919, USA. Email: rcannonphd@gmail.com

Welcome to *NeuroRegulation* Volume 6, Issue 1. Thank you for joining us as we open the first issue of this year with a truly international offering; we are pleased to have articles from Russia, Turkey, and China, in addition to the United States. In the Research section of this issue, Olga R. Dobrushina, Zukhra Sh. Gadzhieva, Sofya N. Morozova, Elena I. Kremneva, Marina V. Krotenkova, and Larisa A. Dobrynina examine the role of the prefrontal cortex and compensatory mechanisms in mild cognitive impairment that may be a target for neuromodulation techniques. Then, Barış Gökşin, Bülent Yılmaz, and Kutay İçöz present data on the effects of neurofeedback of the alpha band on working memory performance in a normative sample of students. Finally, Lauren Kelley, Whitney Strunk, Rex Cannon, and Jeffrey Leighton present pilot data examining differences between groups of children with intrauterine drug exposure (IUDE) and attention deficit/hyperactivity disorder (ADHD). In the Perspectives section, Mark Trullinger, Allen Novian, Lori Russell-Chapin, and Deepti Pradhan present a perspective on recent publications exaggerating the effects of placebo in neurofeedback with specific focus on how non-inert shams, the false no-effect, ad hoc explanations, and confirmation bias lead to Type III statistical errors. In the Technical Notes section, Stewart P.W. Lam, Henry S.R. Kao, Xiaoyang Kao, Miranda M. Y. Fung, and Tin Tin Kao present technical and pilot data of an app that utilizes Chinese calligraphic finger-writing and Guqin music to produce changes in heart rate variability (HRV).

NeuroRegulation thanks these authors for their valuable contributions to the scientific literature for neurofeedback, neuroscience, and learning. We strive for high quality and interesting empirical topics. We encourage the members of ISNR and other biofeedback and neuroscience disciplines to consider publishing with us. It is important to stress that publication of case reports is always useful in furthering the advancement of an intervention for both clinical and normative functioning. We encourage researchers, clinicians, and students practicing neurofeedback to submit case studies, or groups of case studies!

In our sixth year, *NeuroRegulation* has made great strides for increasing the scientific integrity of neurofeedback, biofeedback, and applied neuroscience. We would like to thank our associate editors, reviewers, and contributors for this success. Moreover, we extend an invitation to all researchers and clinicians interested in human performance, the human brain, and methods to improve its functionality to submit reviews, theoretical articles, and research data. If we are rigorous in our efforts and clear with our data presentation, learning methods and confounds that exist in the polemic discourse between disciplines might be reduced, making way for a united, unambiguous pursuit to ensue. Our primary purpose is to aid individuals in improving functionality, no matter the obstacles one may struggle with. If we are clear in purpose, we are capable of much. I look forward to more discoveries and processes uncovered to aid in improving human performance across all functional domains.

We thank you for reading *NeuroRegulation*!

Rex L. Cannon, PhD, BCN
Editor-in-Chief
Email: rcannonphd@gmail.com

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NeuroRegulation

The Compensatory Role of the Frontal Cortex in Mild Cognitive Impairment: Identifying the Target for Neuromodulation

Olga R. Dobrushina, Zukhra Sh. Gadzhieva, Sofya N. Morozova, Elena I. Kremneva, Marina V. Krotenkova, and Larisa A. Dobrynina*

Research Center of Neurology, Moscow, Russia

Abstract

Introduction: Development of individualized neuromodulation techniques for mild cognitive impairment (MCI) is a feasible practical goal. Preliminary research exploring the brain-level compensatory reserves on the base of neuroimaging is necessary. **Methods:** Twenty-one older adults, representing a continuum from healthy norm to MCI, underwent functional MRI while performing two executive tasks—a modified Stroop task and selective counting. A functional activation and connectivity analysis were conducted with the inclusion of a BRIEF–MoCA covariate. This variable represented the difference between the real-life performance measured by Behavior Rating Inventory of Executive Function (BRIEF) and the level of cognitive deficit measured by Montreal Cognitive Assessment (MoCA) Scale, an ability to compensate for impairment. **Results:** Both tasks were associated with activation of areas within the frontoparietal control network, along with the supplementary motor area (SMA) and the pre-SMA, the lateral premotor cortex, and the cerebellum. A widespread increase in the connectivity of the pre-SMA was observed during the tasks. The BRIEF–MoCA value correlated, first, with connectivity of the left dorsolateral prefrontal cortex (LDLPFC) and, second, with enrollment of the occipital cortex during the counting task. **Conclusion:** The developed neuroimaging technique allows identification of the functionally salient target within the LDLPFC in patients with MCI.

Keywords: mild cognitive impairment; executive functions; fMRI; functional connectivity

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***Address correspondence to**: Olga R. Dobrushina, PhD, Research Fellow, Third Neurological Department, Research Center of Neurology, 125367 Volokolamskoe shosse, 80, Moscow, Russia. Email: dobrushina@mipz.ru

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

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

Introduction

Neurocognitive disorders are a major burden of the aging population (Hugo & Ganguli, 2014). While dementia is a frequent cause of death, even mild cognitive impairment (MCI) is associated with increased mortality (Bae et al., 2018). The incidence of MCI is high: 6.7% for ages 60–64, 8.4% for 65–69, with a subsequent increase up to 25.2% for ages 80–84. Neurocognitive disorders dramatically affect quality of life (Hugo & Ganguli, 2014), and a key contributor to maladaptation is executive dysfunction (Marshall et al., 2011).

Treatment options for MCI are limited. Cholinesterase inhibitors, commonly used to treat dementia, along with other drugs showed no benefit in MCI (Petersen et al., 2018). Thus, the development of nonpharmacological approaches for the improvement of cognitive functioning in MCI is feasible. The clinical application of neurophysiological research has resulted in an increased use of neuromodulation techniques, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). While there is currently insufficient evidence to evaluate the efficacy of these methods in MCI, some trials show promising results (Drumond Marra et al., 2015).

In a study by Drumond Marra et al. (2015), 34 patients with MCI were randomized for 10 sessions of high-frequency rTMS over the left dorsolateral prefrontal cortex (LDLPFC) or sham TMS. The intervention resulted in enhanced everyday performance according to the Rivermead Behavioural Memory Test, with the effect lasting at least one month (Drumond Marra et al., 2015). According to another study, rTMS of the LDLPFC in MCI leads to compensatory recruitment of the frontoparietal control network (FPCN), which may explain its beneficial effects (Solé-Padullés et al., 2006). Artificial stimulation during neuromodulation has similarities with the natural functional adaptation of the brain observed in cognitive decline—increased recruitment of the cortex during challenging tasks, especially in the frontal areas (Clément, Gauthier, & Belleville, 2013; Naumczyk et al., 2017). This mechanism is also in line with the gold standard of neuropsychological rehabilitation: since memory training is proven to be ineffective, promoting compensations that improve everyday life is the main aim of rehabilitation (Wilson, Gracey, Evans & Bateman, 2009). At the same time, the importance of adjustment of the neuromodulation protocol on the base of neuroimaging is discussed, since MCI is a heterogenous phenomenon (Anderkova, Eliasova, Marecek, Janousova, & Rektorova, 2015). Along with evaluation of the clinical efficacy of neuromodulation, it is important to continue improving these techniques.

In the current study, we evaluate the organization of executive functions in MCI in conjunction with everyday functioning. As an a priori hypothesis, we assume that the top-down regulatory influences of the frontal cortex during an artificial task reflect the same brain-level mechanisms that allow compensation for cognitive decline in real life. We aim to reveal these mechanisms using functional connectivity analysis. This study is forming a basis for the development of individualized neurostimulation approaches.

Methods

Participants

Participants were selected among older adults (45 years and older) who volunteered to participate in the project. First, a structured interview and a neurological examination were performed to exclude participants with neurological and psychiatric diseases other than MCI. Second, a neuroimaging inclusion criterion was applied; that is, a structural brain MRI scan graded as 0 or 1 on the Fazekas scale (absent or minor white matter lesions; Fazekas, Chawluk, Alavi, Hurtig, & Zimmerman, 1987). Any other brain damage, including any findings with a Fasekas rating of 2 or higher, served as an exclusion criterion, in order to avoid excessive heterogeneity of the sample. The study included 21 adults aged 45–71 years (median 57; 1st quartile 52; 3rd quartile 59.5), representing a continuum from healthy norm to MCI. Subjects with lower cognitive levels did not enter the study, because of their failure to fit into the Fasekas 0–1 range. We did not aim to define a clear margin between normal aging and MCI within the scope of the study, as this is problematic in this borderline group.

All participants underwent a cognitive assessment, performed by the same trained examiner, that included the Montreal Cognitive Assessment Scale (MoCA; Nasreddine et al., 2005), the Frontal Assessment Battery (FAB; Dubois, Slachevsky, Litvan, & Pillon, 2000), the Luria Memory Words Test (Luria, 1980), and the Trail Making Test (Delis, Kaplan, & Kramer, 2001). Executive functioning in daily life was self-rated using the Behavior Rating Inventory of Executive Function (BRIEF; Gioia, Isquith, Guy, & Kenworthy, 2000). To account for emotional factors, the Hospital Anxiety and Depression Scale (HADS) was also included into the assessment (Zigmond & Snaith, 1983).

The protocol and informed consent form were approved by the Ethics Committee and the Institutional Review Board of the Research Center of Neurology, and all participants signed the informed consent form before entering the study.

fMRI acquisition and preprocessing. MRI was performed with a Siemens MAGNETOM Verio 3T scanner (Erlangen, Germany) located at the Research Center of Neurology. Functional images were acquired using T2*-gradient echo imaging sequences (TR 3000 ms, TE 30 ms, FA 90, voxel size 3x3x3 mm^3, FOV 192 mm). Four extra functional volumes were acquired at the start of the session and discarded by the scanner software in order to prevent the usage of artifactual data obtained before the magnetic equilibrium is reached. A three-dimensional structural image consisted of a sagittal T1-weighted 3D-MPRAGE sequence (TR 1900 ms, TE 2.5 ms, FA 9, voxel size 1x1x1 mm^3, FOV 250 mm).

All participants underwent two fMRI sessions with a block design with an interval of no less than 48 hours:

a simplified version of a classical Stroop task (Stroop; Stroop, 1935) and an original selective counting paradigm developed at our center (Count). Each task consisted of four active and four rest blocks with a duration of 30 s (4 min total). During the Stroop session, the rest periods (fixation cross) alternated with a slideshow consisting of 20 stimuli (1.5 s each): a word indicating a color (red, blue, green, or yellow) was presented on the display, written in either congruent or conflicting font color. The participants were required to inwardly answer “yes” if the color of the word corresponded to the text. During the Count task, eyes-open rest periods alternated with the selective counting task: the participants were instructed to inwardly count up from one, omitting the numbers divisible by three (one, two, four, five, seven, etc.). Before both sessions, a 5- to 10-min training was performed outside the scanner. Such simplified variants of executive tasks specifically address the population of cognitively impaired patients and allow further transfer of the technology to patients with dementia.

Data were analyzed in MATLAB 2017b (http://www.mathworks.com), with the use of the statistical parametric mapping software SPM12 (http://www.fil.ion.ucl.ac.uk/spm) and CONN17f (http://www.nitrc.org/projects/conn). A standard preprocessing protocol was utilized and included motion correction, slice-timing correction, realignment, co-registration of functional and anatomical data, normalization into the Montreal Neurological Institute (MNI) stereotactic space, segmentation of the average structural image into tissue images (grey matter, white matter, and CSF volumes) and smoothing with an 8-mm Gaussian kernel. All coordinates are presented in MNI space (x, y, z).

To evaluate block consistency, the raw activation data were extracted with the use of the MarsBaR toolbox (http://marsbar.sourceforge.net), and a comparison between blocks was performed with the SPSS v22 (http://www.ibm.com/products/spss-statistics) package using a general linear model.

The functional neuroimaging results were rendered and visualized with the use of the MRIcroGL program (http://www.cabiatl.com/mricrogl).

Functional activation and connectivity analysis. Statistical parametric maps for each participant were calculated using a general linear model. To compute group activation maps, a second-level analysis was performed using one-sample T-tests with $p < .001$ uncorrected at the voxel level.

The task-related functional connectivity analysis aimed to evaluate the regulatory influences of the areas within the frontal lobes during the executive tasks. On the basis of the activation analysis for both the Stroop and Count conditions, we identified the key areas within the frontal cortex, and the regions of interest (ROIs) for the connectivity analysis were constructed as spheres of 10-mm radius around the centers of these clusters (see Results section, Table 2).

Based on the assumption that the task-based connectivity of the frontal areas might correlate with the ability to compensate for cognitive decline in real life, we included the second-level covariates BRIEF and BRIEF–MoCA into the analysis. To compute the BRIEF–MoCA value, we transformed absolute BRIEF and MoCA scores into scales from 0 to 10 (MoCA: 0 for the lower and 10 for the higher value in the sample, BRIEF: 0 for the higher and 10 for the lower value in the sample) and then calculated the difference between these ratings. A higher BRIEF–MoCA value represents better executive functioning in everyday life, despite a cognitive deficit.

Denoising of the functional data included linear regression of the confounding effects of the white matter, CSF, correction for realignment and scrubbing, and the application of a band-pass filter of 0.008–0.09 Hz. Functional connectivity evaluation was performed using Pearson’s correlation analysis with a subsequent Fischer transformation during the first-level analysis. Multiple-comparison adjustments were implemented with a false discovery error rate (FDR) of $q < .05$ at the cluster-level, given a voxel-wise statistical threshold of $p < .001$ uncorrected. A Bonferroni correction was applied for the number of ROIs entered into the ROI-to-voxel connectivity analysis.

Results

Cognitive assessment data. The results of the cognitive assessment are summarized in Table 1. According to the MoCA scale (Nasreddine et al., 2005), the study sample included a continuum from healthy norm to MCI, with a range of 25–30. The evaluation of executive functions with the FAB revealed no significant impairment (score 17–18 of 18), while the results of the more sensitive TMT indicated some decline in performance. According to the BRIEF, the participants experienced variable difficulties with self-regulation in daily life. While these tests gave us only a general impression regarding the level of executive functioning, this battery, in combination with the neuroimaging procedure, was already very demanding for our sample of older adults.

HADS ratings indicated that the majority of the subjects did not have clinically significant anxiety or depression, and it is thus unlikely that emotional factors had any valuable influence on cognitive performance.

Table 1
The results of the cognitive assessment.

	Median	Min	First Quartile	Third Quartile	Max
Montreal Cognitive Assessment Scale (MoCA)	28	25	25	29	30
Frontal Assessment Battery (FAB)	18	17	17	18	18
Behavior Rating Inventory of Executive Function (BRIEF)	123	88	107	139	156
Luria Memory Words Test (quantity of words memorized after 5 trials, of 10)	9	7	9	10	10
Luria Memory Words Test (quantity of words recalled after 30-min interference, of 10)	8	2	7	9	10
Trail Making Test, part A (time in seconds)	34	21	28.5	42.5	65
Trail Making Test, part A (normalized percentile)	30	10	10	60	80
Trail Making Test, part B (time in seconds)	89	54	59.5	103.5	154
Trail Making Test, part B (normalized percentile)	20	10	10	60	70
HADS Anxiety	5	0	2	7.5	11
HADS Depression	4	2	3	5.5	11

Functional activation analysis. Both the Stroop and Count task resulted in activation of areas within the frontoparietal control network, along with the SMA and pre-SMA, the lateral premotor cortex, and the cerebellum (see Figures 1, 2). In addition, there was a predictable activation of the occipital cortex during the Stroop task. Outside of the visual cortex, we found no significant differences between activation patterns during the two tasks.

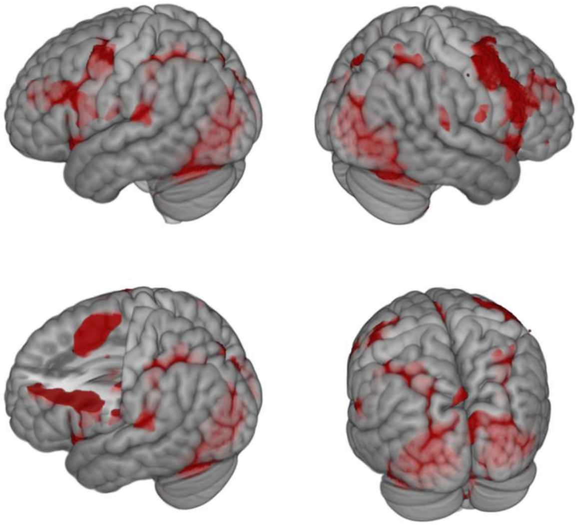

Figure 1. Activation map for the Stroop task (*p* < .001 uncorrected).

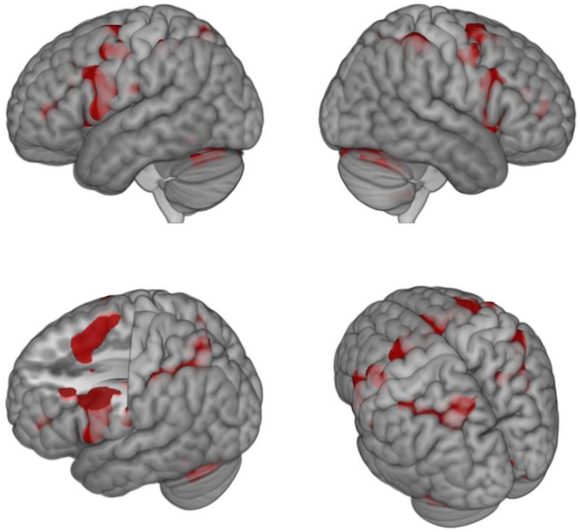

Figure 2. Activation map for the Count task (*p* < .001 uncorrected).

Table 2
Regions of interest within the frontal cortex (MNI coordinates of the center of the cluster).

	Stroop Task			Count Task		
	x	y	z	x	y	z
LDLPFC	−37	44	21	−41	42	9
RDLPFC	33	57	18	38	47	0
SMA	2	−1	61	0	−3	65
Pre-SMA	−8	16	48	−2	10	54
L lateral premotor cortex superior	−43	−3	58	−40	2	36
L lateral premotor cortex inferior	−56	9	12	−59	7	9
R lateral premotor cortex superior	51	4	50	34	4	61
R lateral premotor cortex inferior	51	27	26	55	4	41

On the basis of the activation analysis for both the Stroop and Count condition, we identified the following areas within the frontal cortex that were used as ROIs for the connectivity analysis: LDLPFC, RDLPFC, SMA, pre-SMA, and left and right lateral premotor cortex (divided into superior and inferior parts due to elongated form of the clusters; Table 2).

To evaluate block consistency, a post hoc analysis was performed for the pre-SMA ROI (the selection of this area was influenced by the results of the connectivity analysis, as outlined below). No significant differences were observed between the four task blocks (see Figures 3, 4).

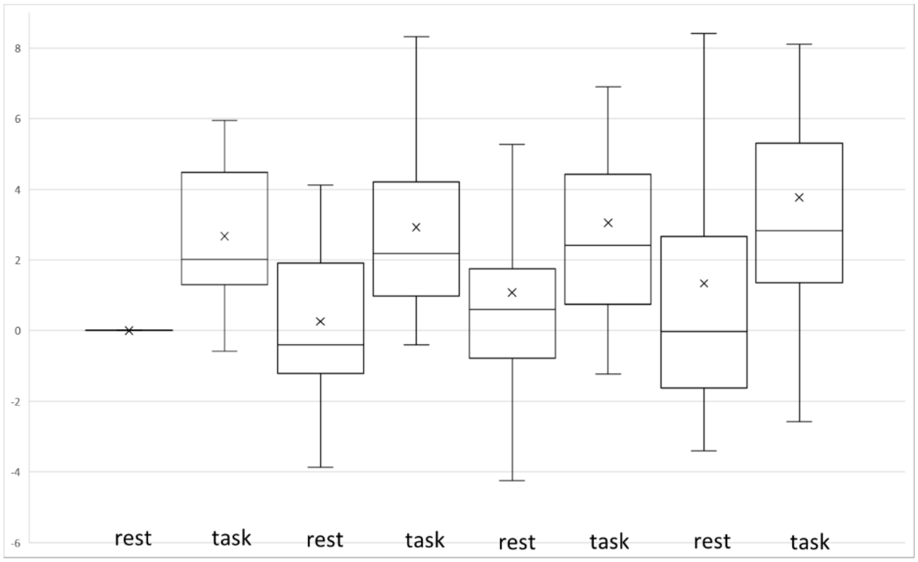

Figure 3. Time course of the activation of the pre-SMA during the Stroop task. Rest and task blocks are shown on the diagram; activation is expressed as the difference from baseline; boxes represent first to third quartile; whiskers represent minimal to maximal values; middle line represents the median; "x" sign represents the mean.

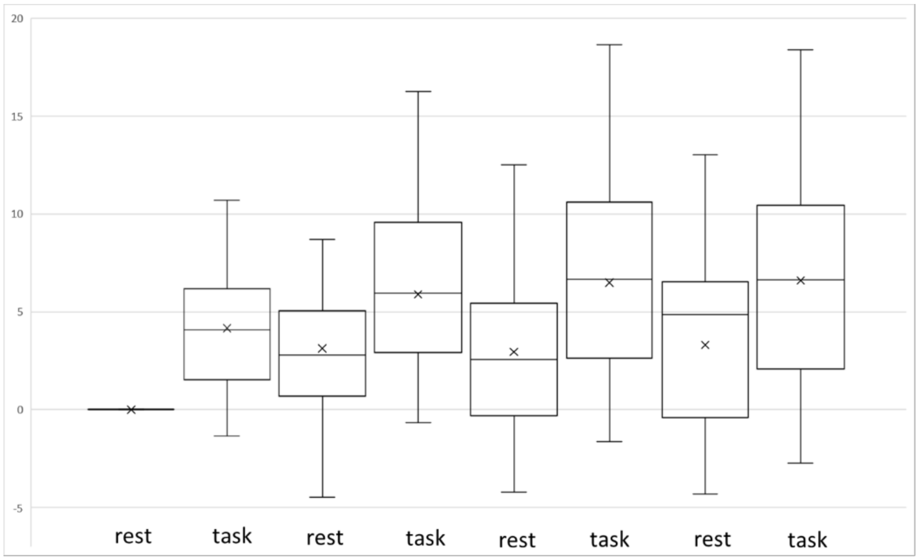

Figure 4. Time course of the activation of the pre-SMA during the Count task. Rest and task blocks are shown on the diagram; activation is expressed as the difference from baseline; boxes represent first to third quartile; whiskers represent minimal to maximal values; middle line represents the median; "x" sign represents the mean.

Functional connectivity analysis. Both the Stroop and Count task were associated with a widespread increase in connectivity in the pre-SMA, suggesting a major regulatory role of this area (Tables 3 and 4; Figures 5 and 6).

To a lesser extent, there was an increase in connectivity of other premotor areas: the left lateral premotor cortex during the Count task and the right lateral premotor cortex during the Stroop task. The counting task was also associated with functional coupling of the RDLPFC and the posterior cingular cortex.

Table 3
Connectivity of the frontal cortex during the Stroop task.

Seed ROI	Clusters showing an increase in connectivity with the seed ROI	Activation peak			Cluster size	*p* (cluster, FDR-corrected)	*p* (peak, uncorrected)
		x	y	z			
Pre-SMA	L lateral occipital cortex	−32	−90	8	463	< .001	< .001
	R lateral occipital cortex	26	−88	8	213	.004	< .001
	R paracingulate gyrus, superior frontal gyrus	8	36	38	167	.016	< .001
R lateral premotor cortex superior	L postcentral gyrus	−42	−32	44	86	.02	< .001

Table 4
Connectivity of the frontal cortex during the Count task.

Seed ROI	Clusters showing an increase in connectivity with the seed ROI	Activation peak			Cluster size	*p* (cluster, FDR-corrected)	*p* (peak, uncorrected)
		x	y	z			
Pre-SMA	R angular gyrus, superior parietal lobule, lateral occipital cortex	40	−56	46	267	.005	< .001
	L superior temporal gyrus, planum temporale, middle temporal gyrus	−66	−26	2	190	.02	< .001
	R planum temporale, superior temporal gyrus	62	−12	4	164	.04	< .001
RDLPFC	R posterior cingulate cortex	14	−50	24	90	.03	< .001
L lateral premotor cortex superior	R insular cortex and putamen	30	14	−4	171	.04	< .001
L lateral premotor cortex inferior	R superior frontal gyrus	8	52	34	346	< .001	< .001

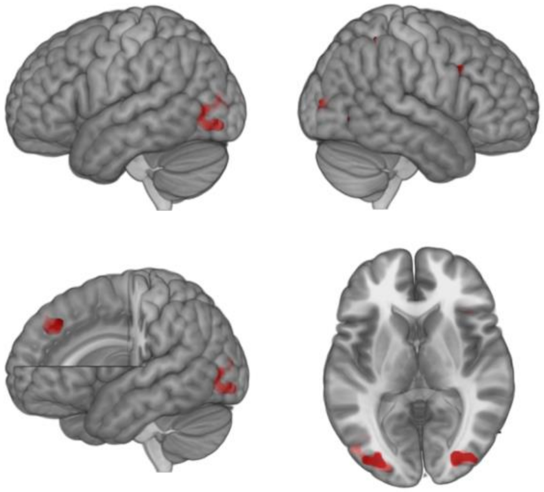

Figure 5. Connectivity map of the pre-SMA during the Stroop task (Stroop vs. rest, $p < .001$ uncorrected at voxel level).

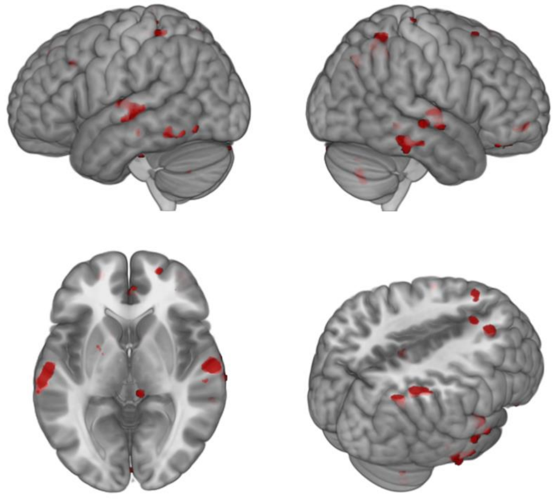

Figure 6. Connectivity map of the pre-SMA during the Count task (Count vs. rest, $p < .001$ uncorrected at voxel level).

Table 5
Connectivity of the frontal cortex during the Count task: Effects of BRIEF–MoCA value.

Seed ROI	Clusters showing an increase in connectivity with the seed ROI	Activation peak			Cluster size	*p* (cluster, FDR-corrected)	*p* (peak, uncorrected)
		x	y	z			
LDLPFC	R and L cuneal cortex	20	–72	20	712	< .001	< .001
	L superior frontal gyrus	–16	–2	68	148	.05	< .001
	L inferior frontal gyrus	–60	16	4	141	.05	.001
Pre-SMA	R cuneal cortex	14	–74	22	370	< .001	< .001
SMA	L intracalcarine cortex, lingual gyrus	14	–68	8	176	.02	< .001

Next, we evaluated the correlations between the BRIEF–MoCA value and task-based connectivity in the frontal areas. This analysis enabled us to reveal two main effects, both stemming from the counting task (Table 5). The ability to compensate for cognitive decline, measured by the BRIEF–MoCA value, correlated, first, with connectivity in the LDLPFC, and, second, with enrollment of the occipital cortex (Table 5; Figure 7). To exclude a possible effect of outliers, the main correlation effects were also explored visually (Figures 8A–8D).

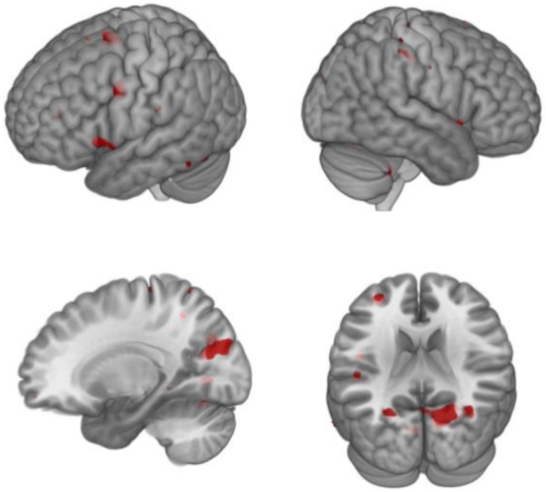

Figure 7. Connectivity map of the LDLPFC during the Count task: correlation with BRIEF–MoCA value (count vs. rest, effect of BRIEF–MoCA covariate, $p < .001$ uncorrected at voxel level).

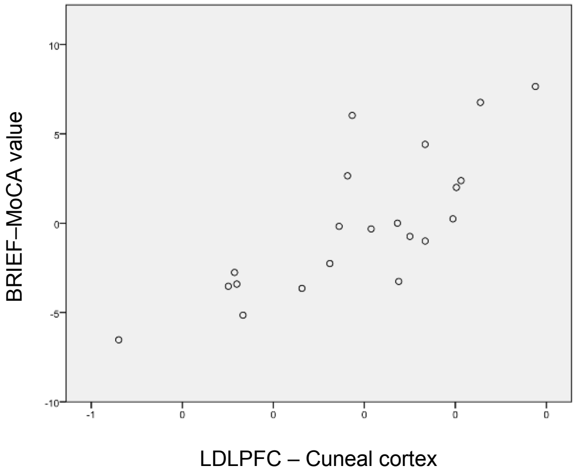

Figure 8A. Correlation of the BRIEF–MoCA value with connectivity in the frontal cortex during the Count task: between the LDLPFC and the cuneal cortex.

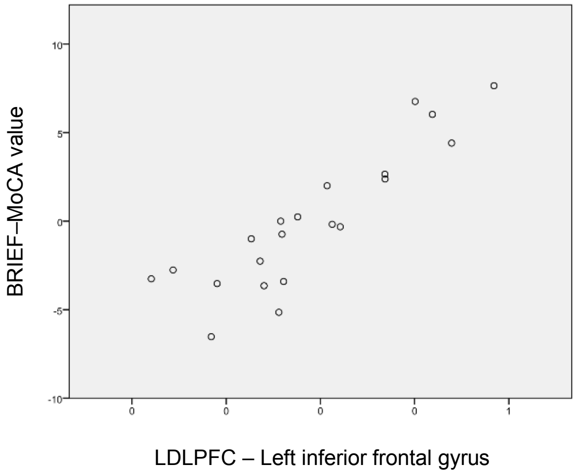

Figure 8B. Correlation of the BRIEF–MoCA value with connectivity in the frontal cortex during the Count task: between the LDLPFC and the left inferior frontal gyrus (IFG).

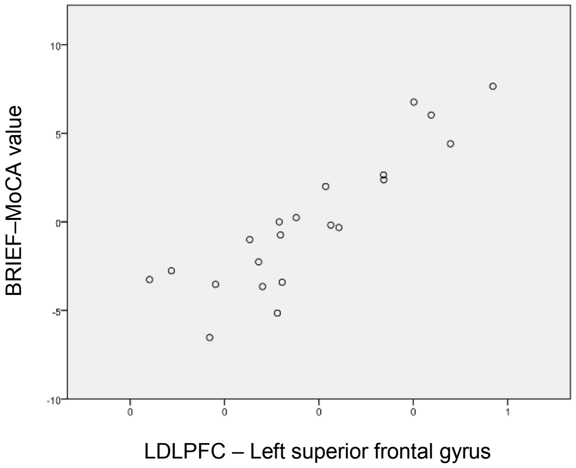

Figure 8C. Correlation of the BRIEF–MoCA value with connectivity in the frontal cortex during the Count task: between the LDLPFC and the left superior frontal gyrus (SFG).

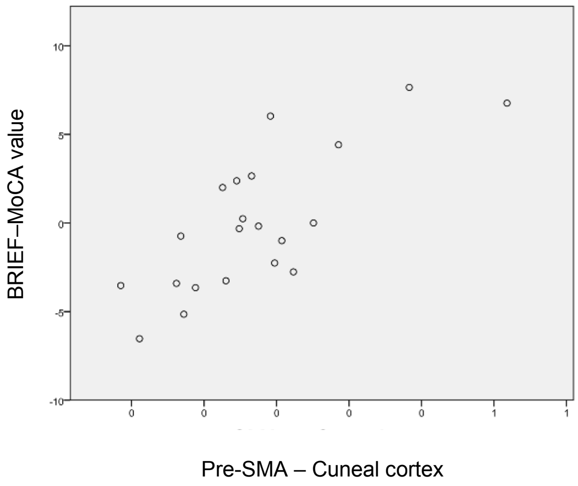

Figure 8D. Correlation of the BRIEF–MoCA value with connectivity in the frontal cortex during the Count task: between the pre-SMA and the cuneal cortex.

Discussion

While designing the study, we kept in mind a very practical goal—the possible application of fMRI maps for individualized neuromodulation. Despite the increasing clinical use of rTMS and tDCS, the complex problem of target individualization remains to be solved (Fitzgerald et al., 2009; Luber et al., 2017). First, the preference of the LDLPFC over other functionally salient brain areas is not based on systematic investigation; the correctness of this empirical choice is unknown. Second, the standard method of DLPFC identification—positioning the coil 5 cm anterior to the motor “hotspot”—is very inaccurate; it allows correct positioning of the coil over the DLPFC in only 36% of cases (Ahdab, Ayache, Brugières, Goujon, & Lefaucheur, 2010). Third, the prefrontal cortex is known to be functionally heterogenous; in fact, there are multiple areas within the DLPFC with different functional profiles (Cieslik et al., 2013; Fox, Liu, & Pascual-Leone, 2013). Mispositioning of the stimulation coil or electrode may interfere with the efficacy of neurostimulation.

To overcome the limitations related to individual variance in structural and functional brain anatomy, navigated TMS can be used. Neuronavigation allows a precise delivery of the stimulus based on neuroimaging, which results in an enhanced efficacy of rTMS, at least in motor applications (Bashir, Edwards, & Pascual-Leone, 2011). Functional neuroimaging can be used for identification of the salient areas. Both paradigms, Stroop and Count, being easy in comprehension and technically simple, may be implemented in clinical practice for the goal of pretreatment executive function mapping in cognitively impaired patients.

The pattern of activation elicited by both paradigms is typical for brain-level organization of task management (Figures 1, 2). The revealed areas within the frontoparietal control network—the DLPFC and the posterior parietal cortex—participated in high-order regulation. However, the main control region was the secondary motor cortex (lateral premotor, SMA, pre-SMA)—the stereotypical character of the paradigms allowed the delegation of control towards lower-order frontal areas (automatization). The secondary motor cortex is known to participate in various tasks including, but not limited to, motor paradigms (Lima, Krishnan, & Scott, 2016). While the SMA is responsible for movement generation and control, the pre-SMA supports more complex aspects of action, including action preparation and sequencing (Rizzolatti, Cattaneo, Fabbri-Destro, & Rozzi, 2014; Sakai et al., 1999). In general, the revealed patterns of activation were close to the findings of earlier studies (Kaufmann et al., 2008; Naumczyk et al., 2017).

The results of the connectivity analysis support a major regulatory role of the pre-SMA. During the Stroop condition (Figure 5), increased connectivity was seen between the pre-SMA and the lateral occipital cortex, responsible for the synthesis of visual information, and between the pre-SMA and the anterior cingulate cortex, which has been linked to error detection (Bush, Luu, & Posner, 2000). A different pattern was observed during the Count task (Figure 6). Functional connectivity of the pre-SMA indicated that the task was accomplished with the use of verbal working memory: the superior temporal gyrus is involved in sound processing, and the angular gyrus is responsible for manipulations involving numbers in their verbal form, such as “one”, “two”, and “three” (Dehaene, Piazza, Pinel, & Cohen, 2003). As predicted, recruitment of the temporal cortex was seen predominantly on the left side. More surprising, the connectivity between the pre-SMA and the parietal cortex was lateralized towards the right angular gyrus. The right parietal cortex is known to be responsible for number processing that is spatially organized by numerical proximity (Zago et al., 2008). In the current task, the right angular gyrus might be involved in manipulation of the number line that represents a spatial structure.

From a practical point of view, executive tasks used in the fMRI settings are of questionable ecological value: it is unclear to what extent the observed brain functioning reflects its performance in real life. To address this limitation, we included a measure of everyday functioning—the BRIEF questionnaire—into our analysis. We propose that this score is a composite of cognitive capacities per se and of the ability to compensate for existing weaknesses. To clearly separate the second factor, which represents the main target of rehabilitation, we calculated the BRIEF–MoCA value and explored the correlation of this covariate with task-related connectivity in the frontal areas.

The covariate functional connectivity analysis (Table 5) revealed two main findings. First, the ability to compensate for cognitive decline, measured by the BRIEF–MoCA value, correlated with connectivity between the LDLPFC and premotor areas, including the Broca area (Figure 7). The Broca area is involved in the transformation of the sensory representations of words forwarded from the temporal cortex into articulatory code (Flinker et al., 2015). It also resolves the conflict between alternative representations in verbal and other domains (Hsu, Jaeggi, & Novick, 2017). In the Count task, this area might be responsible for the selection and encoding of the correct number in a situation of conflict (e.g., “four” vs. “three”) and, thus, has a major regulatory role. The LDLPFC exerts higher-order supervision over the secondary frontal areas, and identical top-down control might serve to compensate for cognitive decline in everyday life. Second, the BRIEF–MoCA value correlated with the enrollment of the medial occipital cortex: cuneal, intracalcarine, and lingual gyrus (Table 5; Figure 7). This phenomenon may reflect compensatory strategies based on the recruitment of an additional modality—visual Arabic representations of numbers (i.e., “1”, “2”, “3”).

The results of our study may be implemented in clinical practice. In order to increase the efficacy of neuromodulation, the target area within the LDLPFC may be identified during pretreatment executive function mapping with the developed modified counting task. The utility of this individualized approach remains to be evaluated in further studies.

Author Disclosure

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

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NeuroRegulation

Improving Short-Term Memory Performance of Healthy Young Males Using Alpha Band Neurofeedback

Barış Gökşin, Bülent Yılmaz, and Kutay İçöz*

School of Engineering, Abdullah Gül University, Kayseri, Turkey

Abstract

To examine whether it was possible to improve short-term memory performance of healthy participants by increasing relative alpha band power (7–11.5 Hz) using neurofeedback, we first converted a commercial EEG device (EmotivEpoc) to a neurofeedback tool and collected data from 11 healthy Turkish male graduate students in five neurofeedback sessions. Before and after neurofeedback training, a memorization task using 10 English words and their Turkish meanings was applied to all participants. The results indicated that 6 out of 11 participants were able to enhance their relative alpha band power with respect to other bands in the frequency spectrum during neurofeedback sessions. Although there was no obvious improvement in their short-term memory performance, we may conclude that neurofeedback training was beneficial for the participants to focus their minds consciously. However, it is not easy to mention that neurofeedback training certainly improved or was irrelevant with short-term memory performance. This study is important in the sense that for such a focused group the use of a commercial, customized low-cost EEG device was shown to be feasible for neurofeedback training sessions.

Keywords: short-term memory; neurofeedback; alpha band

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***Address correspondence to**: Bülent Yılmaz, Department of Electrical & Electronics Engineering, School of Engineering, Abdullah Gül University, Sümer Campus – 38080 Kayseri, Turkey. Email: bulent.yilmaz@agu.edu.tr

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

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

Introduction

It is a fact that human physical and psychological functions start to degrade with aging, which causes a significant decrease in life quality (Wang & Hsieh, 2013). Considering all the cognitive functions of the brain, memory is likely to be one of the most important cognitive abilities for individuals to sustain their life quality and productivity.

Klimesch, Doppelmayr, Pachinger & Ripper (1997) reported that there was a relationship between memory performance and the alpha band activity. When an individual's resting-state alpha activity was high, long-term memory performance was also high (Klimesch, 1999). Besides that, it was reported that not only alpha activity is related with memory but also some other bands' activities are related to memory performance (Reis et al., 2016). Wang and Hsieh (2013) reported that frontal-midline theta band enhancement improves working memory and attention. Vernon et al. (2003) reported that enhancement of sensorimotor rhythm (SMR; 12–15 Hz) activity improves working memory performance. Although there are many reports that memory performance is associated with alpha activity, Bauer (1976) studied whether increasing (8.5–12.5 Hz) alpha activity improves recall performance, but he could not observe such a relationship for short-term memory.

Neurofeedback training (NFT) method gives subjects audio/visual feedback of their brain wave activity so that they can learn to control their own brain rhythm. In addition, it has been studied for several decades as an alternative to traditional medication for some psychological disorders such as attention-deficit/hyperactivity disorder (ADHD; Friel, 2007), substance addiction (Sokhadze, Cannon, & Trudeau, 2008), epilepsy (Sterman & Egner, 2006), and autism (Coben, Linden, & Myers, 2010). NFT has also been used to enhance the cognitive performance of healthy participants. Besides its function in psychological disorders, NFT has been shown to have some positive effects on cognitive performance of healthy individuals having different occupations, for example, musicians and surgeons (Gruzelier, Egner & Vernon, 2006; Ros et al., 2009). Although there are many studies which support that NFT has positive effects on some areas including cognitive performance improvement using alpha band power (Marzbani, Marateb, & Mansourian, 2016), there are limited studies which show the effects of NFT on short-term memory in the literature (Conway, Cowan, Bunting, Therriault & Minkoff, 2002).

Lecomte and Juhel (2011) investigated whether increasing upper alpha band (10–12 Hz) power over theta band (4–7 Hz) power could improve short-term memory performance or not. In their electroencephalography (EEG) experiments, C3, C4, and Cz (ref) electrodes were used, and an audio-visual feedback was employed. After four neurofeedback training sessions, they showed that subjects could increase alpha band power and alpha/theta band power, however, there was no memory performance improvement in elderly participants. Kober et al. (2015) examined whether increasing the SMR (12–15 Hz) band power or upper alpha (10–12 Hz) band power could improve short-term memory performance in post-stroke patients. In EEG experiments, Cz electrode was used for SMR, Pz electrode was used for upper-alpha training, and a visual feedback was employed. After 10 neurofeedback training sessions, they showed that participants who took the SMR training were able to improve their visuospatial short-term memory performance. Moreover, participants who took the upper-alpha training could improve their working memory performance. Nan et al. (2012) investigated the potential of increase in the individual alpha band power to improve the short-term memory performance. In the experiments, only Cz electrode was used, and a visual feedback was employed. After 20 neurofeedback training sessions, they showed that participants could increase their individual alpha band power and improve the short-term memory performance. Finally, Wang (2017) examined whether increasing the alpha band power could improve the working memory performance in the students with ADHD. In EEG experiments, only FCz electrode was used. After 10 neurofeedback training sessions, he showed that the participants could increase alpha band power and improve working memory performance.

In this study, we first converted a wireless EEG device (Emotiv EPOC) to a neurofeedback tool. Later, we examined whether it was possible to improve short-term memory performance of 11 healthy participants by increasing relative alpha band power using neurofeedback training. Before and after 5 days of neurofeedback training sessions, we measured the improvement on participants' short-term memory by performing a test that consisted of memorizing and recalling the Turkish meanings of some English words which were not previously known by the participants.

Materials and Methods

Participants

The 11 subjects who participated in the experiments were chosen among male graduate students, with an average age of 29 and with standard deviation of ±3.04. One participant was left-handed and five of them wore glasses. For the experiment, there was no payment to the participants except for a chocolate bar for every session. Before experiments, written approval from Abdullah Gül University Internal Review Board and oral consent from participants were received.

EEG Recordings

During the experiments the setup shown in Figure 1 of the Emotiv EPOC system, a 14-channel wireless EEG device with 128-Hz sampling frequency, was used. According to Emotiv manufacturer, the "measurement accuracy of the device is technically: minimum voltage resolution 0.51 μV, 14-bit accuracy, 0.2–43 Hz bandwidth" ("How Accurate Is Your Detection", 2019). The voltage resolution was suitable to measure EEG signals, because the EEG signal varied around a voltage level that was above ±10μV. The reference electrodes were placed on the left and right mastoids. Another important component of the EEG recoding was the real-time signal acquisition and processing of the brain waves. For this purpose we first installed MATLAB 2012b (32-bit version) to our computer and Visual C++ 2010 to compile MATLAB. Later, we used the modified version of a MATLAB file called "eeglogger.m" that was developed and shared by the manufacturer of the wireless headset. By means of the modifications we were able to convert the system into a neurofeedback tool (necessary files can be found as supplementary materials). In this work we used only P8 electrode (according to the international 10–20 system), because it was one of the suitable places to record the signals without getting affected from the eyeblinks.

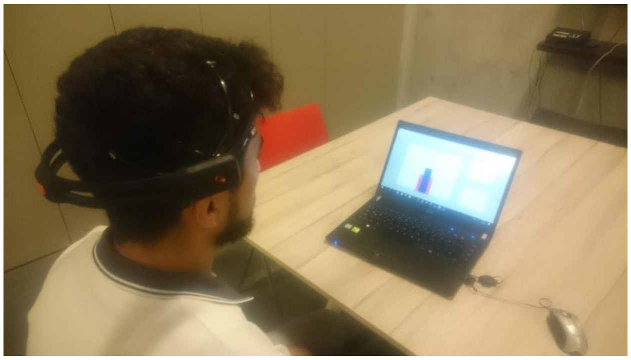

Figure 1. Experimental setup.

Study Design

Before the neurofeedback training sessions were started, a baseline EEG measurement obtained with eyes open and a pretraining test was given to the participants to be able to measure short-term memory performance of the participants. The pretraining test included 10 words such as exigency, innocuous, and desultory, which were not known by the participants beforehand. Firstly, the participants were let memorize the words by looking at the selected words shown one by one on the screen followed by its meaning. There was no time limit in this part. Once the memorization part was over, it was requested from each participant to remember the meanings when each English word was shown on the screen. No multiple-choice type approach was followed. Memorization time, recall time, and the number of accurately recalled words were recorded manually. After the pretraining test, five sessions of neurofeedback training were applied (Figure 2). Each day only one session was applied, and the training sessions lasted at most for 10 days according to the availability of the participants. One session included three subsessions and five trials constituted one subsession, and thus one training session included 15 trials. Each trial lasted for 45 s, and 10 s were placed between two subsequent trials. After five trials (one subsession) the participants had enough time to rest, approximately one to two minutes. After the neurofeedback training sessions, a posttraining test was given to the participants. This test also included 10 different English words with similar memorization difficulty. The recall performances of the participants were manually recorded.

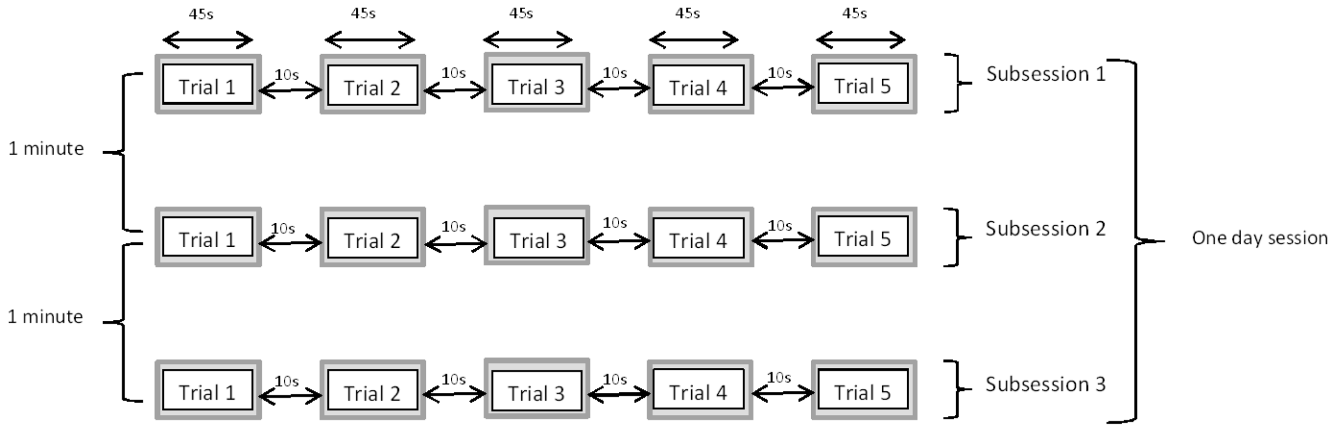

Figure 2. Neurofeedback training paradigm.

Neurofeedback Training

During the design stage, we recorded EEG signals from an individual with closed and open eyes for a few times, and then found the intersection of these two cases. The data collected with open and closed eye method made it possible to observe alpha band synchronization and desynchronization, which can be used to figure out alpha frequency band by using band crossings (Nan et al., 2012). We found that open and closed eyes spectra intersect at approximately 7 Hz and 11.5 Hz, and we decided to use this band for all participants in our experiments. Relative band power (RBP) was used as the neurofeedback parameter. RBP represents the ratio between the absolute band power in 7–11.5 Hz range and the absolute band power in 3.5–35 Hz range.

During the training, the participants were able to see the panels shown in Figure 3. We oriented the participants about the system and the feedback panel before the sessions had started. The blue bar on the left panel indicated the dynamically changing relative alpha band power, and the red bars depicted the mean value of the relative alpha band power measured during the baseline recordings. The mean power values were updated after each training subsession.

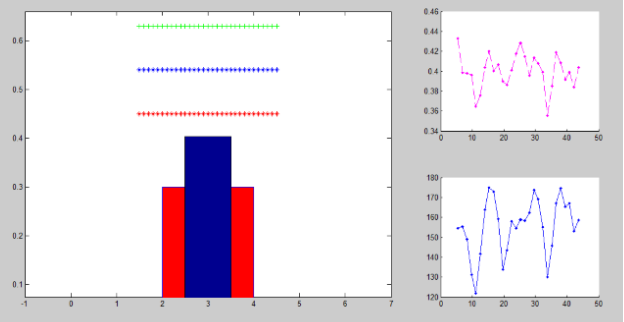

Figure 3. User interface of neurofeedback training sessions.

The participants tried to increase the blue bar's level to pass the red bars (baseline level), which worked as a visual feedback. We also used an audio feedback as a beep sound when the level was surpassed. Some participants asked us to turn the sound off, because they thought that it was distracting their concentration. On that panel the red, blue, and green lines showed some levels that the participant would aim to pass as a challenge. They were utilized to motivate the participants. On the right panel, the dashed pink line showed relative alpha band power, and the blue line indicated the absolute alpha band power. We asked them to focus on the left panel only.

Before the training session started, several thinking strategies were advised to the participants. For example, the alpha power generally is related to the relaxation process, and positive thinking such as thinking about the family, friends and natural scenes increase the alpha power (Nan et al., 2012). On the first, second, and third sessions it was requested from the participants to determine the best thinking strategy that helped them to increase their alpha power. However, on the fourth and fifth sessions, it was requested not to find any new thinking strategies but to focus on what they had figured out before to increase the relative alpha band power as much as they could. At the end of the subsessions, the participants were able to see their performances as shown in Figure 4.

Real-time EEG Processing

Before performing the real-time spectrum analysis of the EEG signals obtained, several preprocessing steps were applied. When we acquired the EEG signals, we observed that there was a positive offset around 4150 μV, and we removed that offset by subtracting 4150 from each value in the dataset. After offset removal, the signal was fed into a fifth-degree Butterworth high-pass filter whose cut-off frequency was 3 Hz. Because we were only interested in the alpha band power, we selected this cut-off in order not to affect any spectral coefficients in that band. When we did not perform the filtering excessive low-frequency power dominated the spectral coefficients.

In the power spectrum computations Welch's method was used. This method first divides data into windows (200 samples per iteration). Adjacent windows have some overlap (50%) between each other, and the method calculates the spectrum of these windows. Finally, averaging is applied to compute the spectrum of the data. The spectrum coefficients were computed for every 0.25 Hz (frequency resolution). During the training sessions, before computing alpha band power values in real-time, sufficient number of samples had to be collected. The first computed power spectrum was seen on the screen once we acquired 700 samples. During the spectrum computations, the last 512 samples were used (last 4 s). In addition, in real-time computations, there was no artifact removal.

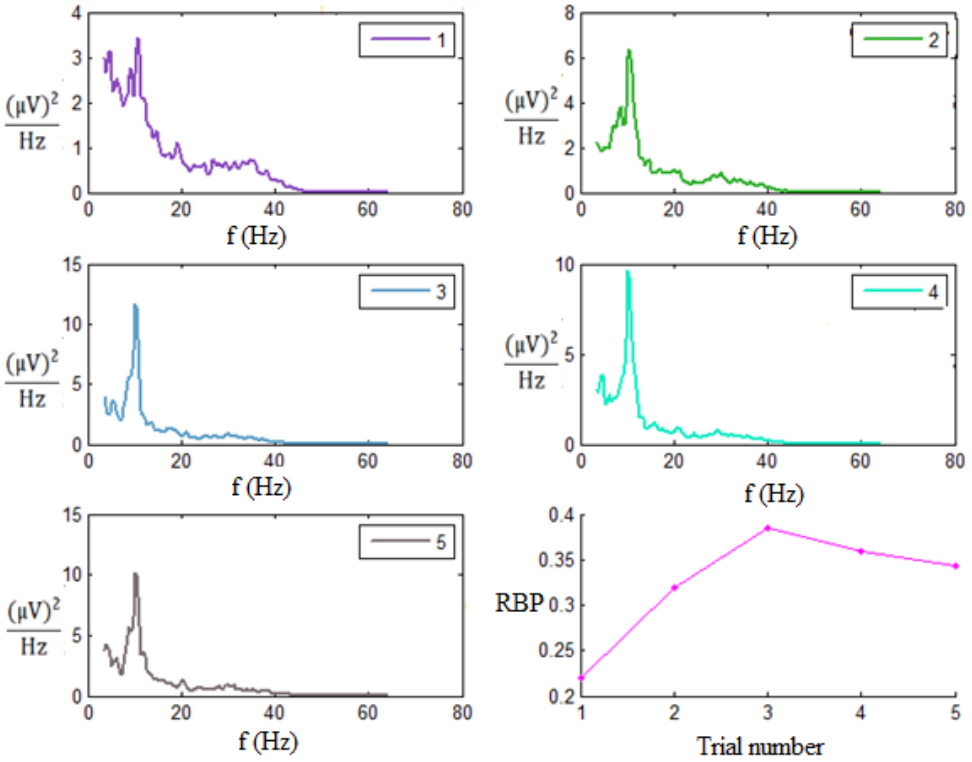

Figure 4. EEG spectra of the participant #10 from the first day, third subsession. Relative band power (RBP) is also shown on the bottom-right panel.

Results

Table 1 summarizes the results obtained during this study indicating the average alpha band power (ARABP) values during the baseline recordings and each training session, pretraining and posttraining memorization and recall durations and the number of correct answers.

It is important to note that 6 out of 11 participants were able to increase their ARABP values between 2.7% and 11.75%, 3 participants slightly increased their ARABP ~1%, and 2 of them slightly decreased their ARABP values below approximately 1%. Taking all participants into consideration, it was observed that the ARABP increase was on average 4.4% as depicted in Figure 5. Including only the successful participants, who increased alpha band power over 1%, they were able to increase the ARABP 7.73% as depicted in Figure 5.

Four participants who increased ARABP were also able to increase the number of the correct recalls, which they increased recall performances between 2 and 4 folds. One of the successful participants could not increase or decrease the number of correct recalls. One participant increased the ARABP (> 1%) but decreased the number of correct recalls. Two participants who were able to slightly increase ARABP could increase the number of correct recalls (5 to 7 folds). One participant who was able to slightly increase alpha band power decreased the number of correct recalls. Two participants decreased their alpha band power but increased the number of correct recalls (2 to 2.25 folds). When all participants were considered, they were able to increase the number of correct recalls 2.63 fold on average. All subjects increased posttraining memorization duration compared to the pretraining memorization duration of 4.76 s per word.

Table 1
Results obtained during neurofeedback experiments combined in one table.

Participant	Baseline	Day 1	Day 2	Day 3	Day 4	Day 5	Pretest Memorization Duration (s)	Posttest Memorization Duration (s)	Pretest Recall Duration (s)	Posttest Recall Duration (s)	Pretest # of Correct Answers	Posttest # of Correct Answers
#1	0.1601	0.1978	0.1999	0.1841	0.2515	0.2284	95	123	N/A	59	3	9
#2	0.1071	0.1491	0.1646	0.1937	0.1726	0.1885	86	91	120	136	3	2
#3	0.2128	0.2055	0.2143	0.2241	0.1945	0.2382	46	75	69	61	1	7
#4	0.1759	0.2116	0.1892	0.2000	0.1950	0.2185	117	182	103	105	2	8
#5	0.2158	0.2458	0.2201	0.2057	0.2486	0.1897	42	45	45	85	4	1
#6	0.1567	0.1513	0.1622	0.1498	0.1641	0.1505	82	116	113	105	2	4
#7	0.1429	0.2110	0.1854	0.1909	0.2024	0.204	139	241	N/A	78	4	8
#8	0.2797	0.3090	0.3965	0.4211	0.423	0.4363	90	159	62	51	8	8
#9	0.1789	0.1887	0.1848	0.1833	0.1817	0.1860	64	101	N/A	86	1	5
#10	0.3039	0.2301	0.313	0.3071	0.3163	0.3233	88	153	N/A	62	4	9
#11	0.1073	0.1529	0.1394	0.1792	0.1926	0.1612	94	162	103	94	4	7
Mean	0.1856	0.2048	0.2154	0.2217	0.2311	0.2295	82	129	-	-	3.27	6.18

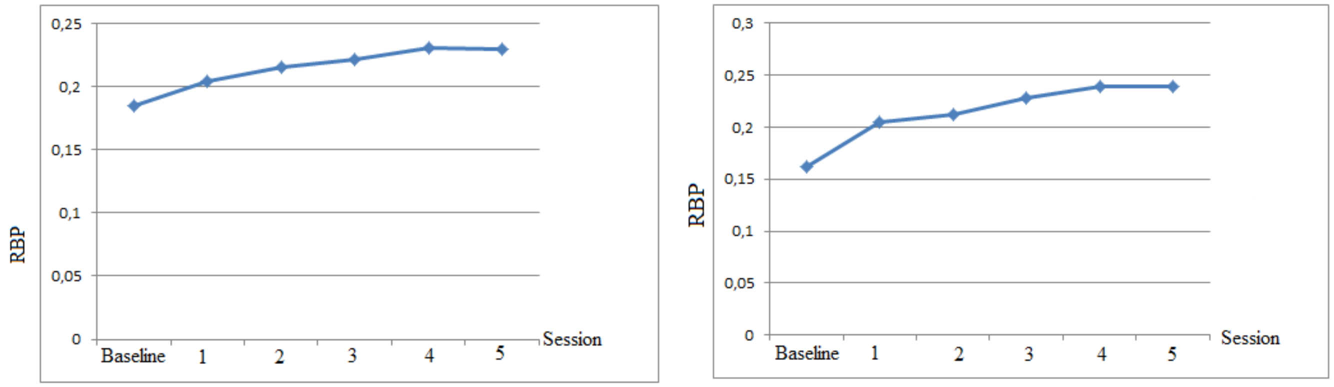

Figure 5. All (left) and successful (right) participants' average relative alpha band power enhancement day by day.

Discussion

In this study we asked two related questions about the relative alpha band power during the neurofeedback training sessions and short-term memory improvement. The first question was the following: "Is it possible to increase the alpha band power intentionally when compared to respect to other bands (theta, beta, and gamma bands) of the EEG spectrum?" According to our results, the answer to this question may be positive. More than half of the participants were able to increase their alpha band power when compared to the other bands.

The second question we investigated was the following: "Were participants, who increased relative alpha band power, also able to improve short-term memory performance?" In this study 8 out of 11 participants were able to increase the number of words correctly remembered (correct recalls). However, for the successful participants, only four of them were able to increase the number of correct recalls. Therefore, we were not able to give a positive answer to this question. This did not mean that neurofeedback training was not related to short-term memory performance. These findings comply with the results of the study undertaken by Lecomte and Juhel (2011). In that study, a group of elderly participants experienced four neurofeedback training sessions, and the participants were requested to memorize a list of words. They found that the participants were able to increase alpha band power; however, there were not any improvements in the memory performance.

Feedback from the participants revealed that positive thinking such as thinking of the family, friends, beautiful scenes and so forth was effective in increasing the alpha band power. However, not only positive thinking increases alpha band power but also some participants used negative motives such as getting angry with someone or something in order to improve the desired band power. This finding complies with the study of Nan et al. (2012).

Another finding was that when some subjects focused on one type of thinking style, this increased their alpha band power first, but decreased later. In one participant, the relative alpha band power firstly increased, and then decreased after the third trial of a subsession. This observation was generally true especially after the third and fourth trials. This finding might have arisen due to the exhaustion of the brain while thinking about the same feeling or object for a long time. Therefore, it may be useful for someone to have a rest during the neurofeedback sessions by changing the thinking style or the work, which they did from one session to another. One neurological explanation of this suggestion might be that the activation of another neural network might help the exhausted one rest.

A limitation of this study was the number of subjects who participated in the neurofeedback sessions. Inclusion of only 11 graduate students in the study might have biased the interpretation of the results; however, we think that this study is important in the sense that for such a focused group the use of a commercial, customized low-cost EEG device was shown to be feasible. Another limitation was the number of sessions and their durations. Although there are studies reported in the literature which included experiments with five sessions such as Escolano, Aguilar, and Minguez (2011) and Zoefel, Huster, and Herrmann (2011), the number of training sessions and session durations might not be sufficient for some participants to adapt with the environment, and determine strategies to control their brains in parallel with the aim of the study, which was increasing the alpha band power. However, we thought that if we increased the number of sessions or durations the participants would get bored, and this might affect the results negatively. In addition, several subjects mentioned that they got bored of viewing bar graphs in all training sessions. If we were to use a game in the neurofeedback sessions, it would have been more interesting and motivating for the participants, and they might have been more enthusiastic about the sessions. In our future endeavor we will increase the number of participants, the neurofeedback training sessions and their durations to investigate the phenomenon on the children with learning difficulties.

In the neurofeedback literature, during the experiments participants were requested to find their way to synchronize with the feedback signals (visual or auditory) by themselves. There was an “aha” point which participants could understand and synchronize with the screen or the sound (Collura, 2000). However, in our study, due to the limited number of sessions we advised some thinking strategies to the participants before the neurofeedback training. Participants indicated that they could not fully synchronize with the blue bar during training, which means they were not sure whether one type of thinking style increased or decreased the alpha power. However, at the end of the trial, they mentioned that a particular thinking style was generally useful in increasing the alpha power.

In the literature, this is the first study in which Turkish students were trained via neurofeedback sessions in order to improve their short-term memory performances by using English words.

According to the findings reported by Klimesch in 1997, memory retrieval performance of subjects who had high resting state peak of alpha frequency, which is the frequency of maximum amplitude in alpha band, was better than others. In a future study, memory performance improvement may be examined by increasing the peak alpha frequency with increased number of participants and number of sessions using motivating games.

Conclusion

In conclusion, the findings of this study are neither sufficient to prove that neurofeedback training improves the short-term memory performance, nor it is irrelevant with the short-term memory performance. However, we may mention that the neurofeedback training is beneficial for the subjects to orient their conscious minds to their goals.

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Author Disclosure

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NeuroRegulation

EEG Source Localization and Attention Differences Between Children Exposed to Drugs in Utero and Those with Attention-Deficit/Hyperactivity Disorder: A Pilot Study

Lauren Kelley[1,4], Whitney Strunk[1,3], Rex L. Cannon[1,2], and Jeffrey Leighton[2,3]*

[1]Knoxville Neurofeedback Group; Knoxville, Tennessee, USA
[2]SPESA Research Institute, Bloomfield Hills, Michigan, USA
[3]Grand Canyon University, Phoenix, Arizona, USA
[4]Maryville College, Maryville, Tennessee, USA

Abstract

Introduction: Intrauterine drug exposure (IUDE) including neonatal abstinence syndrome (NAS) is a group of problems that occur in a newborn exposed to drugs in the womb. Currently, there is no consensus on diagnostic criteria for addressing the cluster of problems present in children suffering from IUDE. The current data sought to examine differences between IUDE and attention-deficit/hyperactivity disorder (ADHD) clients to elucidate specific differences between these groups in the Conners Continuous Performance Test (CPT-3/K-CPT) and EEG source localization data using standardized low-resolution electromagnetic brain tomography (sLORETA). **Methods**: This study utilizes archived data from two groups 14 IUDE and 9 clients with standing diagnosis of ADHD between the ages of 4 and 13 without the presence of fetal alcohol syndrome (FAS). All clients completed a standard protocol to assess functional domains, including diagnostic interview, review of records, and tests of attention, executive functions, and psychological status. IUDE clients at time of initial assessment were taking one or more medications. ADHD clients consisted of medicated and unmedicated individuals. **Results**: Significant differences were found between resting-state baseline sLORETA parameters in temporal, limbic, and precuneus regions. **Conclusions**: IUDE presents a growing problem in the United States due to current opioid problems, and it is imperative to accurately classify these children according to this specific set of problems. sLORETA assessment may be useful as one marker of IUDE. Directions for future treatment paradigms are discussed as well as potential applications of neurofeedback and learning.

Keywords: intrauterine drug exposure; EEG; LORETA; sLORETA; attention deficits; neurophysiology

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***Address correspondence to**: Rex Cannon, PhD, 214 S. Peters Rd., Ste 102, Knoxville, TN 37923, including USA or country. Email: rcannonphd@gmail.com

Edited by:
Nancy L. Wigton, PhD, Grand Canyon University, Phoenix, Arizona, USA

Reviewed by:
John Davis, PhD, McMaster University, Hamilton, Ontario, Canada
Randall Lyle, PhD, Mount Mercy University, Cedar Rapids, Iowa, USA

Introduction

Prenatal exposure to drugs of abuse (illicit, legal, or prescribed) has been a major public health concern for decades and is subsumed by the term *intrauterine drug exposure* (IUDE). In recent years the opioid epidemic and its effects have increased attention to this crisis. It is estimated that 5.9% of pregnant women engage in illicit drug use; thus, it is difficult to convey the very high need for specific diagnostic and treatment paradigms to aid these children across the developmental continuum until one has encountered them in the clinical setting. The smallest victims of the opioid and polydrug exposure epidemic are underserved and present great challenges to socioeconomic, healthcare, and education systems. An extensive review of prenatal drug exposure and descriptive patterns of effects of substances on the developing brain provides a well-done knowledge base (Ross, Graham, Money, & Stanwood, 2015), with projected rates of exposure and substance specific characteristics. Numerous studies have described behavior and attentional problems in children exposed to drugs in utero as well as associated patterns in overall cognitive functioning (Butz, Pulsifer, Leppert, Rimrodt, & Belcher, 2003; Franck, 1996; Freeman, 2000; Kelley, 1992; Kne, Shaw, Garfield, & Hicks, 1994; Mayes, Cicchetti, Acharyya, & Zhang, 2003; McNichol, 1999). The sequelae of IUDE include deficits of sustained attention, language, social and emotional comprehension and affect regulation, social executive, and adaptive functions. IUDE includes neonatal abstinence syndrome (NAS) and fetal alcohol spectrum disorder (FASD). Notably, FASD has surpassed genetic anomalies as the leading contributor to mental retardation in North America (Nash, Sheard, Rovet, & Koren, 2008; Ross et al., 2015). Disruptions to numerous systems of the body may accompany IUDE including motor slowing, gastrointestinal difficulties, cardiovascular issues, and other disrupted homeostatic and regulatory functions (Eiden et al., 2009; Kleiber et al., 2014; Li et al., 2009; Wu, Yan, Qu, Feng, & Jiang, 2012; Zhao et al., 2015).

IUDE may produce negative effects on neural proliferation, migration, dendrite growth, and axonal elongation (Geng, Salmeron, Ross, Black, & Riggins, 2018; Riley, Kopotiyenko, & Zhdanova, 2015; Roitbak, Thomas, Martin, Allan, & Cunningham, 2011; Yip et al., 2014), as well as the disruption of the functional integrity of neural networks (Chater-Diehl, Laufer, Castellani, Alberry, & Singh, 2016; Posner & Rothbart, 2007; Schweitzer et al., 2015; Willford, Singhabahu, Herat, & Richardson, 2018). Studies of neonatal electroencephalogram (EEG) have shown delayed maturation and reduced hemispheric functional connectivity in IUDE children at 1 month of age (Akyuz et al., 2014; Conradt et al., 2014; Fisher et al., 2011; LaGasse et al., 2011; Lester, 2000; Lester et al., 2012). IUDE children also show characteristics of attention-deficit/hyperactivity disorder (ADHD), tend to have poorer performance in an attention test battery and show EEG alterations in P300 and N200 event-related potential (ERP) measures. These findings suggest that there may be deleterious long-term effects of prenatal drug exposure on executive function domains of attention, classification, and decision-making (Jaeger, Suchan, Schölmerich, Schneider, & Gawehn, 2015).

Studies of prenatal development have shown important interdependencies between the insula and amygdala in affective and social adaptivity (Bellucci, Feng, Camilleri, Eickhoff, & Krueger, 2018; Di Cesare, Marchi, Errante, Fasano, & Rizzolatti, 2018; Grecucci, Giorgetta, Bonini, & Sanfey, 2013; Klumpp, Post, Angstadt, Fitzgerald, & Phan, 2013). The interactions between these regions and the noted deficits suggest important to potential treatment paradigms for IUDE given the rate of growth in the prenatal period and disruptions in connectivity amongst these regions in adolescents and adults with IUDE or cocaine dependence (K. Li et al., 2013; Li et al., 2009; Z. Li et al., 2013; McHugh et al., 2013; McHugh et al., 2014; McHugh, Gu, Yang, Adinoff, & Stein, 2017). Differences in functional connectivity between insula, amygdala, orbitofrontal, anterior cingulate, and sensorimotor cortices have been implicated in behavioral issues including attention and arousal deficits found in IUDE children (Grewen, Salzwedel, & Gao, 2015; Salzwedel et al., 2015). Connectivity issues associated with the consequences of IUDE involve numerous regions and functions. Of these, the orbitofrontal, amygdala, insula, sensorimotor, anterior cingulate, cuneus, precuneus, inferior parietal, subcortical, and limbic regions are also found disrupted in adolescent and adult populations with substance use disorders (SUD). IUDE children have shown reduced global brain volume as well as regional differences in the cortex, amygdala, nucleus accumbens, cerebellum, brainstem, and basal ganglia. White matter volume and disruptions in functional connectivity at rest have been noted in IUDE, as well as associations with cognitive deficits related to processing speed, mathematics ability, executive functions, and eye-blink conditioning (Adinoff et al., 2015; Grewen et al., 2015; Lotfipour et al., 2010; McHugh et al., 2017; Rando, Chaplin, Potenza, Mayes, & Sinha, 2013; Riggins et al., 2012; Roussotte et al., 2012; Salzwedel, Grewen, Goldman, & Gao, 2016; Salzwedel et al., 2015; Tamnes et al., 2010).

The effects of IUDE opioid and polydrug exposure on the brain continue into childhood, and data have shown reduced cortical volume and thinner layer surface than normative controls (Nygaard et al., 2018). It has also been proposed that many of the regulatory difficulties found in these children may not be fully actualized until they begin the education process. These problems are proposed to increase after the age of 4 and progress over the course of further development. The reasons for this increase are suggested to include the increasing complexity of social, educational, and adaptive demands and the lack of functional integration of multiple concepts by these children. It has been reported that 36% of individuals exposed to substances prenatally are likely to receive a diagnosis of ADHD as contrasted to

2% of nonexposed controls (Nygaard, Slinning, Moe, & Walhovd, 2016). In the current data set, 99% of the IUDE population had received a diagnosis of ADHD—primarily combined type prior to admission—and 96% of these children were being treated with traditional and nontraditional pharmacological agents.

Low-resolution electromagnetic brain tomography (LORETA) is a method of probabilistic source estimation of EEG signals in a standardized brain atlas space utilizing a restricted inverse solution (Pascual-Marqui, Esslen, Kochi, & Lehmann, 2002; Pascual-Marqui et al., 1999). LORETA and standardized LORETA (sLORETA) have been used to examine EEG sources in depression (Pizzagalli, Oakes, & Davidson, 2003), in epilepsy (Zumsteg, Wennberg, Treyer, Buck, & Wieser, 2005) and to evaluate temporal changes associated with differential task-specific default network activity (Cannon & Baldwin, 2012). LORETA has been adapted to provide real-time feedback to participants in order to facilitate operant conditioning. For example, LORETA investigation has documented learning of improved regulation of the current source density in a specific frequency range at a specific region of training within Talairach space. The effects of LORETA neurofeedback have also been replicated (Cannon, Congedo, Lubar, & Hutchens, 2009; Cannon et al., 2007; Cannon, Lubar, Sokhadze, & Baldwin, 2008), and seen increasing use clinically (Cannon, 2014; Cannon, Strunk, Carroll, & Carroll, 2018). In recent years LORETA and the standardized version have been shown to localize medial default network regions with complementary accuracy, as well as detecting anomalies in network connectivity (Cannon, Kerson, Hampshire & Coleman, 2012).

It is important to consider the greatest common factors (e.g., sustained attention, mood regulation, social and emotional delays, and specific cognitive issues) found in IUDE populations across specific substances and then progress on a course to influence the brain in such a way as to facilitate learning and self-regulation of one or more of the identified regional connective hubs to adjust the brain's performance (e.g., neural efficiency) and facilitate data acquisition, encoding, and learning. The most salient symptoms found in IUDE across the developmental continuum include emotional dysregulation and reactivity, developmental delays, motor slowing, impulsivity and hyperactivity, difficulties with sustained attention, impaired executive functions and self-regulation, deficient social comprehension and interactions, social development delays, learning impairment, and processing speed difficulties.

This study sought to examine differences between groups of children with IUDE and a contrast group of children with ADHD. We hypothesized that there would be significant differences on the functional measure of attention and notable group differences between EEG sources in an eyes-opened baseline sample using sLORETA.

Participants

This study examined archived data from 23 (10 female) children and early adolescent clients with mean age 8.38, *SD* = 2.80, (ages 4–13 years) seen at an outpatient mental health clinical in Knoxville, TN. Fourteen of the clients were exposed to drugs of abuse in utero without the presence of fetal alcohol syndrome (FAS) with mean age 7.86, *SD* = 2.79, (ages 4–13). All IUDE clients (7 female) would be classified as polydrug exposed. All IUDE clients had been removed from biological parents and had been adopted by family members or foster parents. 99% of the IUDE group had received a prior diagnosis of ADHD. The second group (3 female) were clients admitted for ADHD with three having comorbid generalized anxiety disorder (GAD) with mean age 10, *SD* = 2.29 (ages 6–13). There were no reports or records to indicate the ADHD children had been exposed to drugs or alcohol during the prenatal period. The IUDE group on average was younger than the ADHD group. The differences did not reach significance in this study population with $t(21) = -1.91$, $p = .067$. There was no difference for gender between groups, $t(21) = -0.438$, $p = .66$, and medications showed no differences, $t(21) = 0.249$, $p = .806$. The IUDE group was taking medications for ADHD symptoms, which included Clonidine, Adderall, Concerta, Tenex, Straterra, and combinations thereof. The ADHD group was taking Ritalin or Adderall. All assessment data were reviewed with parents and informed consent was reviewed and signed.

Methods

This study was conducted with approval from an institutional review board (IRB) at Maryville College, Maryville, TN, to examine attention and drugs of abuse in utero. All clients completed a standard protocol for admission to the program, including a diagnostic interview, prior record review, and psychological and neurophysiological measures. This manuscript examines select components of this protocol for contrasting the two clinical groups. The clients completed the Conners Kiddie Continuous Performance Test, 2nd Edition, (K-CPT 2); or the Conners Continuous Performance Test 3rd Edition (CPT 3). Both are computerized performance tests. The K-CPT 2 is a 7.5-min performance-based assessment that uses pictures of objects familiar to young children, whereas the CPT 3 is a 14-min, 360-trial administration in which respondents are required to respond when any letter appears, except the nontarget letter "X" (MHS Assessments, Tonawanda, NY).

The clients were prepared for EEG recording using a measure of the distance between the nasion and inion to determine the appropriate international 10–20 system cap size for recording (Blom & Anneveldt, 1982). The head was measured and marked prior to capping for placement of frontal electrodes. The ears and forehead were cleaned for recording with a mild abrasive gel to remove any oil and dirt from the skin. After fitting the caps, each electrode site was injected with an electrode gel and prepared so that impedances between individual electrodes and each ear were less than 10 KΩ. The data were collected and stored utilizing the Deymed TruScan amplifier and acquisition software (Deymed Diagnostics, Payette, ID) with a band-pass set at 0.5–64 Hz, and a sampling rate of 256 samples per second. Standard 6-mm tin cup ear electrodes were used. All recordings were carried out in a quiet, comfortably lit, clinical neurofeedback room at the clinic. Lighting and temperature were held constant for the duration of the data collection. We elected to use eyes-opened baseline recordings, as many of the IUDE population struggled to keep the eyes closed during this condition, while others could not maintain the condition of keeping their eyes closed for more than a few seconds at a time.

Data Processing

The EEG stream was edited using Eureka 3 software (NovaTech EEG, Mesa, AZ). EEG editing and resampling was obtained by means of natural cubic spline interpolation (Congedo, Özen, & Sherlin, 2002). All active task conditions and baseline data were processed with particular attention given to eye movement and jaw tension in frontal and temporal leads. All episodic eye blinks, eye movements, teeth clenching, jaw tension, body or neck movements, and possible electrocardiogram (EKG) artifacts were removed from the EEG record. Fourier cross-spectral matrices were then computed and averaged over 75% overlapping 4-s artifact-free epochs, which resulted in one cross-spectral matrix for each subject for each discrete frequency. The EEG data were analyzed utilizing the following frequency domains: delta (1.0–4.0 Hz); theta (4.0–8.0 Hz); alpha 1 (8.0–10.0 Hz), alpha 2 (10.0–13.0 Hz) and beta (13.0–32.0 Hz).

Data Analyses

In order to assess the electrophysiological differences between groups, sLORETA was employed to localize the sources of scalp EEG power spectra. The sLORETA solution space is restricted to the cortical gray matter in the digitized Montreal Neurological Institute (MNI) atlas with a total of 6,329 pixels with 5mm^3 spatial resolution (Pascual-Marqui et al., 2002; Pascual-Marqui et al., 1999). To test the specific hypotheses of the differences in cortical activity between groups, independent *t*-tests were used. The average common reference was computed prior to the sLORETA estimations. The calculated tomographic sLORETA images correspond to the estimated neuronal generators of brain activity within each frequency domain (Frei, Gamma, Pascual-Marqui, Lehmann, Hell, & Vollenweider, 2001). This procedure results in one 3D LORETA image for each subject for each frequency range. The significance threshold is based on a randomization test utilizing 5,000 data randomizations.

The Conners CPT assessment includes nine scales to measure distractibility, omissions, commissions, perseverations, reaction time, reaction time standard deviation, variability, reaction time block change, and reaction time for interstimulus intervals. The scores are expressed in *T*-scores with higher scores indicating greater severity. We utilized independent *t*-tests to contrast the nine scales of the CPT between groups.

Results

Figure 1 shows the mean *T*-scores and standard deviation for each CPT scale, side by side for each group. The test results show elevations on nearly all scales for the IUDE group as contrasted with the ADHD group except for perseverations. The only scale that showed significance between IUDE and ADHD groups was omissions, yet results of all scale differences are important to the overall description. The results show distractibility (D), $t(21) = 1.65$, $p = .113$; omissions (O), $t(21) = 2.62$, $p = .016$; commissions (C), $t(21) = 0.917$, $p = .370$; perseverations (P), $t(21) = -0.195$, $p = .847$; reaction time (HRT), $t(21) = 1.66$, $p = .111$; reaction time standard deviation (HRTS), *t*(21) = 1.57, *p* = .130; variability (V), *t*(21) = 0.361, *p* = .722; reaction time block change (HRTB), *t*(21) = 0.220, *p* = .828; and reaction time for interstimulus intervals (HRTISI), *t*(21) = 0.570, *p* = .575. The results show clear differences between the two groups with IUDE performing with less accuracy and speed than the ADHD group on most measures except for perseverations.

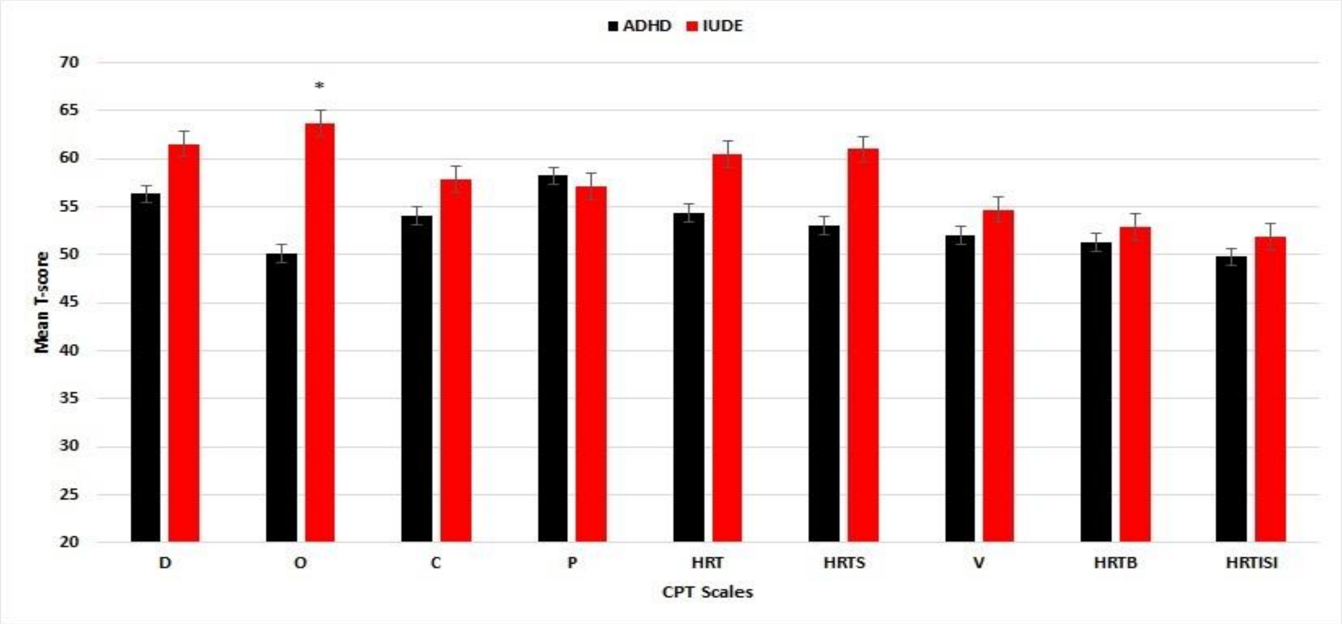


Figure 1: Contrast results between groups for scales on the Conners CPT. Red is the IUDE group and black the ADHD group. From left to right the measures are distractibility (D), omissions (O), commissions (C), perseverations (P), reaction time (HRT), reaction time standard deviation (HRTS), variability (V), reaction time block change (HRTB) and reaction time for interstimulus intervals (HRTISI). *Only the omission scale was statistically significant at *p* = .016.

Table 1 shows the sLORETA statistical contrasts between groups (IUDE > ADHD). In the table from left to right are the frequency range, sLORETA x, y, and z coordinates, hemisphere, anatomical label/Brodmann area (BA), *t* value for the IUDE versus ADHD contrasts, and its probability. From top to bottom are the frequency domains and coordinates for both the maximum and minimum levels of current source density (CSD) at specific regions of interest for sLORETA findings.

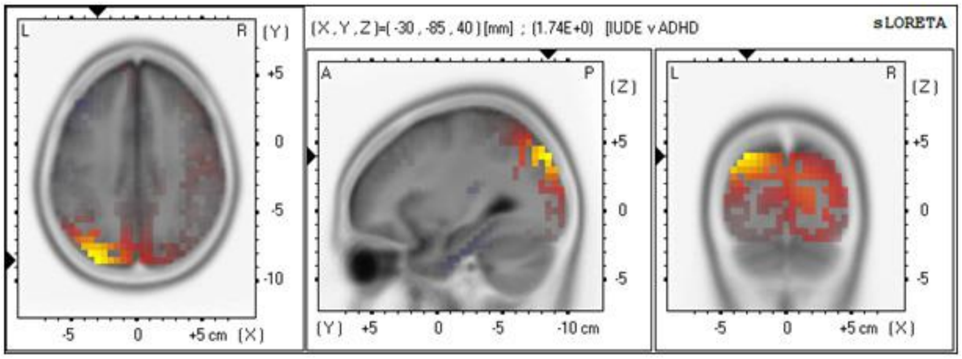
Table 1
sLORETA Results for Contrasts IUDE > ADHD

Frequency Range		x, y, z Coordinates	Hemisphere	Anatomical Label	*t* Value	*p*
Delta		–		–	–	ns
Theta						
	Max	−30, −85, 40	L	BA 19, precuneus, parietal	1.74	.096
	Min	−35, −15, −35	L	BA 20, uncus, limbic	−0.74	ns
Alpha 1						
	Max	−30, −85, 40	L	BA 19, precuneus	2.11	.047*
	Min	−40, 35, 35	L	BA 9, superior frontal gyrus	−1.65	.113
Alpha 2						
	Max	70, −35, −5	R	BA 21, middle temporal gyrus	0.048	ns
	Min	−50, −70, 35	L	BA 39, angular gyrus	−2.37	.027*
Beta						
	Max	−40, 35, 35	L	BA 9, superior frontal gyrus	2.16	.042*
	Min	15, −100, 15	R	BA 18, cuneus	2.32	.030*

Note: **p* values are statistically significant.

In Figure 2 the images shown are horizontal, sagittal, and coronal slices of the brain in MNI space. There were no significant effects for gender in any of the measures. CSD differences were not significant for the delta frequency bin. Theta CSD was elevated in the IUDE group in posterior parieto-occipital regions but did not reach statistical significance. The lower range of alpha 1 CSD did show significant elevations in IUDE compared to ADHD in BA 19, posterior parietal regions, notably the same region of interest as theta power. Alpha 2 CSD showed significantly less CSD in IUDE as compared to ADHD at BA 39, angular gyrus. Beta CSD showed significant elevations in IUDE as compared to ADHD in left BA 9, superior frontal gyrus, and less CSD in right BA 18, cuneus.

sLORETA Regions of Interest Contrasts IUDE > ADHD



Theta

sLORETA Regions of Interest Contrasts IUDE > ADHD

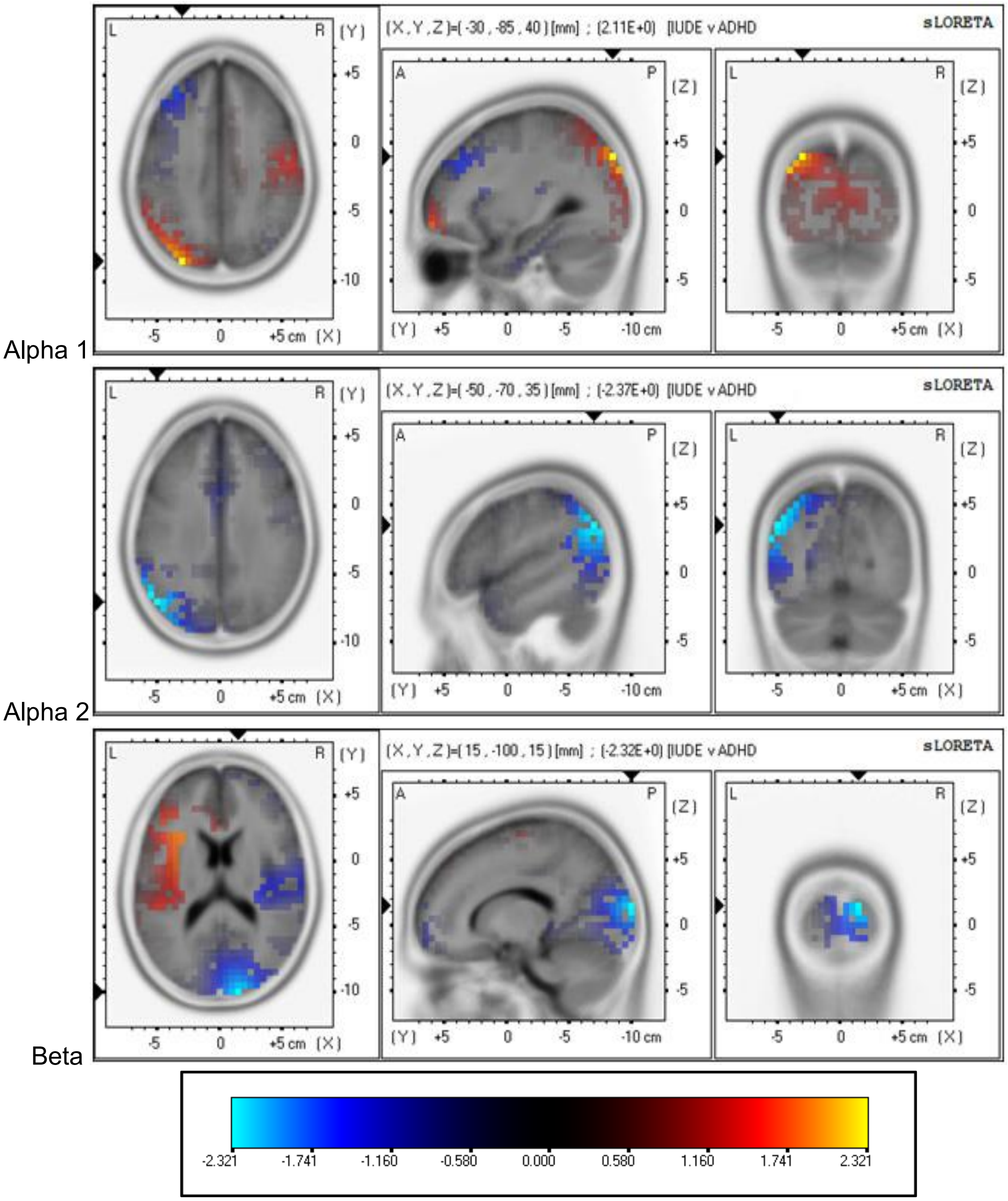


Figure 2. sLORETA contrast images for IUDE group compared to ADHD group. From left to right are horizontal, sagittal, and coronal slices from the MNI atlas. The brighter the colors the greater the CSD amplitude difference between groups (red, yellow, orange) whereas the darker the colors indicate less CSD amplitude between groups (light blue, blue). Delta showed no differences between groups. Theta CSD levels between groups neared significance with *p* = .096. The lower end of alpha power showed significantly elevated CSD in IUDE as compared to ADHD with *p* = .047. Alpha 2 showed significantly less CSD in IUDE as compared to ADHD with *p* = .027. Beta CSD showed differences between groups with elevated CSD in left BA 9 superior frontal gyrus (SFG) with *p* = .042, and less CSD in right cuneus, BA 18 with *p* = .030. The last row in the figure shows the scale for the contrast results for IUDE compared to ADHD.

Discussion

The present findings are the first of their kind showing differences between children with IUDE compared to children with ADHD using sLORETA. The current data show children with IUDE perform less well than children with ADHD on the Conners CPT. Specifically, IUDE children showed more omissions, to a statistically significant degree. Given the CPT and classification procedures *T*-scores of 60 or above would produce atypical results for the test and increase the likelihood of positive classification in the ADHD index. With the pattern of results, it is not surprising that 99% of the IUDE population had received a prior diagnosis of ADHD at or before the age of 5, even though 96% of the IUDE population was taking medications for ADHD at the time of admission to the program. These medications included Clonidine, Adderall, Concerta, Tenex, Straterra, and combinations thereof. Prior research has shown that IUDE children exhibit extreme difficulties with self-regulation across numerous domains associated with attention including arousal, emotional reactivity, sustained attention (Accornero et al., 2007; Gabriel & Taylor, 1998; Garavan et al., 2000; Gendle et al., 2003; Jaeger et al., 2015; Noland et al., 2005; Slinning, 2004; Willford et al., 2018), and in some cases at our clinic a lack of understanding about the importance and significance of giving an appropriate effort on these types of tests. Close monitoring during test administration in these children and clear instructions are good clinical practice to increase the accuracy of the results. It is also important to consider that the IUDE children will not meet all criteria for ADHD, and in many cases the more pronounced issues are impulsivity and emotional reactivity, motor slowing (reaction time), and difficulties with sustained attention (Nygaard et al., 2016).

The sLORETA contrasts show significant CSD differences between IUDE and ADHD groups in the alpha and beta bands. Theta (4.0–8.0 Hz) showed a nonsignificant trend toward elevated CSD in IUDE as contrasted with the ADHD group at BA 19 and associated posterior regions. This is an important finding given the indications that excess theta power has been associated with a higher likelihood of having ADHD and the potential comodulated slowing between theta and alpha power (Bink et al., 2015; Gloss, Varma, Pringsheim, & Nuwer, 2016; Koehler et al., 2009; Tye, Rijsdijk, & McLoughlin, 2014). Mazaheri and colleagues (2010) found a functional disconnection between frontal and occipital regions in children with ADHD as contrasted with normal controls and suggested a deficit in top-down regulated attentional processes. Cannon (2014) showed specific inverse correlations between posterior alpha and frontal theta in children with ADHD.

Maturation of the alpha rhythms is associated with an increase in frequency and reduction in amplitude between ages of 3 and 10. The significant difference between IUDE and ADHD groups in lower alpha CSD is found at BA 19 (precuneus and associated posterior areas). Interestingly, alpha and theta power showed elevations in the same area with differing effects in a hypothesized self-regulation network (SRN) ipsilateral and contralaterally (Cannon, 2014; Cannon, Strunk, Carroll, & Carroll, 2018), although not reaching significance. Alpha rhythms are suggested to perform as other EEG phenomena and exhibit an opposite relationship between amplitude and frequency. For example, the higher the amplitude the slower the signal becomes. One can think of this in terms of information being carried along a signal. The greater the peaks and valleys, the slower the information travels. This carrier signal and these patterns are important to numerous processing speed and learning processes (Cannon, 2015). Certain drugs of abuse and conditions may cause reductions of alpha frequencies together with increased amplitudes, while others may be more associated with increased amplitude of low-frequency beta activity superimposed on scalp alpha rhythms (Nunez, 2006; Sokhadze, Cannon, & Trudeau, 2008). Although it is difficult to ascertain specific EEG patterns related to exposure to drugs of abuse in children, adolescent and adult populations provide replicable information concerning these patterns. Alpha 2 (10–13 Hz) shows a significant deficit in IUDE children as contrasted with the ADHD group in BA 39 and associated cortex. The angular gyrus (BA 39) has broad implications associated with receptive language, perceptual, memory, and sensory processes as well as learning (Bonnici, Cheke, Green, FitzGerald, & Simons, 2018; Boylan, Trueswell, & Thompson-Schill, 2017; Bravo et al., 2017; Matchin, Liao, Gaston, & Lau, 2019; Thakral, Madore, & Schacter, 2017; van der Linden, Berkers, Morris, & Fernández, 2017; van Kemenade, Arikan, Kircher, & Straube, 2017). Studies have examined alpha EEG power in attentional, saccadic, and cognitive processes, although the higher band of alpha power is often described as having no association with the maintenance of attention (Babiloni et al., 2004; Dockree, Kelly, Foxe, Reilly, & Robertson, 2007; Jaime et al., 2016; Klimesch, Doppelmayr, Russegger, Pachinger, & Schwaiger, 1998; Kornrumpf, Dimigen, & Sommer, 2017; Sauseng et al., 2005) and therefore may play are more important role in encoding the stream of information being attended to (e.g., related to learning; Fell et al., 2011; Lenartowicz et al., 2016; Molle, Marshall, Fehm, & Born, 2002; Wang, Kamezawa, Watanabe, & Iramina, 2017), and associated language and working memory indices.

Beta CSD shows elevations in IUDE as compared to ADHD in left superior frontal gyrus (SFG) and insular cortex, and in the right cuneus (BA 18). The SFG and associated cortex has been implicated in motor, language integration, impulse control, and speech production, as well as executive and social functions (Fujii et al., 2015; Hu, Ide, Zhang, & Li, 2016; W. Li et al., 2013; Ookawa et al., 2017; Tsujii, Sakatani, Masuda, Akiyama, & Watanabe, 2011; Vogel et al., 2016). BA 18 and associated regions are implicated in visual and perceptual processes, as well as symptoms of anxiety, panic, posttraumatic stress, and other psychiatric issues (Heesink et al., 2017; Lai & Wu, 2013; Parise et al., 2014; Whitford et al., 2012; Yu et al., 2018).

The insular cortex is typically divided into three subsections—the anterior, middle, and posterior. The anterior insula is proposed to be associated with subjective intensity and self-awareness concerning experience and perception. The middle insula is suggested to be associated with polymodal integration and may also play an important role in motor processes and regulation. The posterior insula is proposed to be associated with interoceptive processes and awareness of the bodily state, as well as potential in attention, sensory, and social processes (Di Cesare, Pinardi, et al., 2018; Duval, Joshi, Russman Block, Abelson, & Liberzon, 2018; Schiff et al., 2018; Wang et al., 2018; Zhang et al., 2019). It is of note that most differences, even those not reaching significance, were found in the left hemisphere. In prior research it has been shown that important interactions exist between frontal theta and posterior alpha power distributions in ADHD (Cannon, 2014). It appears that IUDE children show an inverse pattern of EEG CSD levels as contrasted with ADHD samples, distinct parietal and associated network and parieto-frontal interactions, and associated social and emotional issues found in ADHD samples (Castellanos, 2015; Castellanos & Elmaghrabi, 2017; Castellanos & Hyde, 2010; Castellanos & Proal, 2012; Cortese et al., 2012; Petrovic & Castellanos, 2016).

Further, data have shown that prenatal exposure can alter development of opioid and dopaminergic systems in striatal and mesocorticolimbic areas given there is a rapid and massive growth and organization process during prenatal development (Wang, Dow-Edwards, Anderson, Minkoff, & Hurd, 2006). Data have reported reductions in bilateral caudate and left anterior insula connections with the cerebellum, as well as right caudate connectivity disruptions with occipital and fusiform regions in IUDE as contrasted with nonexposed infants (Grewen et al., 2015; Salzwedel et al., 2016). Additional data have shown disruptions in connectivity amongst frontal, amygdala, insula, thalamus, and anterior cingulate regions. These functional associations involving the thalamus are important to arousal regulation, sustained attention, detection of salient qualities of stimuli, and working memory (Salzwedel et al., 2016).

The current data are in line with other neuroimaging data concerning IUDE and its effects on the brain and attentional processes. There have been numerous studies indicating substance exposure in utero impacts the developing brain in significant fashion. The orbitofrontal region has been implicated in learning, sensory processing, reward prediction, and behavioral responses (McDannald, Jones, Takahashi, & Schoenbaum, 2014; Sadacca et al., 2018; Wikenheiser, Marrero-Garcia, & Schoenbaum, 2017). Social cognition and the perception of social interactions and behavioral and emotional responses are also reported to involve orbitofrontal, insula, and default network engagement and potential integrity anomalies (Li et al., 2011; Weng et al., 2010) that persist into adolescent years. Social and emotional processes involve a complex interaction between brain regions and networks, and substance exposure creates a complex disruption in these processes that delays the maturation and adaptive development of these vital functions (Estelles, Rodríguez-Arias, Maldonado, Aguilar, & Miñarro, 2005; Fernandes, Rampersad, & Gerlai, 2015; Greenwald et al., 2011; Kabir, Kennedy, Katzman, Lahvis, & Kosofsky, 2014; Kully-Martens, Denys, Treit, Tamana, & Rasmussen, 2012; Sobrian & Holson, 2011). There are data suggesting IUDE impacts the maturation of the brain and its contributions to behavior and attentional processes (Chiriboga, Starr, Kuhn, & Wasserman, 2009; Church, Overbeck, & Andrzejczak, 1990; Hammer & Scheibel, 1981; Tamnes et al., 2010; Walhovd, Tamnes, & Fjell, 2014); however, there are few data providing behavioral and standardized assessment examples of what these deficits may resemble in the clinical setting.

In the clinical environment, one of the most prevalent issues reported by parents and teachers is the discrepancy between age-expectation of behavior and actual social/emotional regulation maturation which can differ by years in context. For example, a 10-year-old throwing tantrums, hitting, or breaking things in response to environmental demands and not getting what he/she wants is age inappropriate. Likewise, there may be behaviors present such as taking others' property, or performing acts that are dangerous with an impairment in understanding the inherent danger (e.g., why is it dangerous to play with fire in your bedroom? "It is against the rules and I am not 18 yet"). In future research paradigms it would be useful to attempt to determine the greatest common factors impacted by IUDE including regional brain differences, cognitive or attentional processes, and social and emotional delays. These issues are present in most studies examining the effects of IUDE. However, in order to begin the first step in planning interventions these commonalities across substances must be uncovered and targeted (McDannald et al., 2014; Morrow et al., 2006). In this study's sample, the first intervention in 99% of the IUDE children was for ADHD. This is an important finding due to the lack of specific criteria for diagnosis and treatment for this growing population with IUDE. It is also important to consider the increased risk in IUDE of cognitive deficits, antisocial behaviors, substance abuse, academic and educational failure, and emotional/mood disorders (Li et al., 2011), not to mention the side effects of medications on these children.

The current study has several limitations, which suggest steps for subsequent research. First, a larger sample size for both IUDE and ADHD groups will provide statistical tests with greater power to detect real differences between groups. Second, a healthy normal control group will also provide a contrast that shows the clinical significance of the IUDE group. Third, a contrast between subgroups of IUDE children with and without exposure to adverse childhood experiences (ACE) would be of interest. Last, eyes-closed resting states are relevant to evaluate.

Prenatal drug exposure is not a new problem; however, over the past few decades more attention has been directed to it. The numbers of children exposed to drugs prenatally is growing, not all of whom are born addicted. IUDE children do exhibit attentional difficulties that strongly increase the likelihood of an ADHD diagnosis. Sensory and auditory processing issues may also be present. There are also major delays in social cognition and emotional regulation associated with a frontal, insula, and amygdala dysregulation that have been noted in numerous studies including this study data. The sLORETA findings in this study provide some insight into regions of the brain and frequency distributions that may serve as markers to monitor treatment methods or develop novel approaches to help this population including neurofeedback-based models (Cannon, Strunk, Carroll, & Carroll, 2018).

Author Disclosure

Dr. Cannon directs a neurofeedback-based outpatient program for mental health and IUDE children. No other financial interests or financial support for this research exists.

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NeuroRegulation

Perspectives on Type III Statistical Errors: Exaggerating the Effects of Placebo in Neurofeedback

Mark Trullinger[1,2], Allen Novian[3,4], Lori Russell-Chapin[5,6], and Deepti Pradhan[1,2]*

[1]The Chicago School of Professional Psychology, Washington, District of Columbia, USA
[2]NeuroThrive, LLC, Lutherville, Maryland, USA
[3]St. Mary's University, San Antonio, Texas, USA
[4]integrative Counseling & Neurofeedback Solutions (iCNS), San Antonio, Texas, USA
[5]Bradley University, Peoria, Illinois, USA
[6]Neurotherapy Institute of Central Illinois, Peoria, Illinois, USA

Abstract

Evaluating the efficacy of electroencephalography neurofeedback (EEG-nf) for the treatment of attention-deficit/hyperactivity disorder (ADHD) has been a topic of vigorous debate over the past few years. However, many of the articles state a lack of efficacy and insist on placebo as the explanation for any positive effects found in the EEG-nf treatment group. Several critical flaws in this analysis are discussed including the existence of non-inert shams, the false no-effect, and placebo as an ad hoc explanation. These flaws lead to Type III statistical errors, which are often repeated in other articles. It is recommended that journals, books, and media articles publishing new research and reviews on the efficacy of EEG-nf be vigilant for these errors in order to improve the quality of the EEG-nf body of research. Requiring researchers and authors reviewing the literature to verify assumptions of non-inert shams, ensure the use of best practices in the EEG-nf treatment groups, and clearly identify ad hoc conclusions can avoid these Type III errors.

Keywords: EEG-nf; sham; false no-effect; placebo; ADHD; Type III errors; non-inert shams

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***Address correspondence to**: Mark Trullinger, 1205 York Rd, Suite 11, Lutherville, MD 21093, USA. Email: neurothrive@gmail.com

Edited by:
Nancy L. Wigton, PhD, Grand Canyon University, Phoenix, Arizona, USA

Reviewed by:
John Davis, PhD, McMaster University, Hamilton, Ontario, Canada
Randall Lyle, PhD, Mount Mercy University, Cedar Rapids, Iowa, USA

Reviews of electroencephalography neurofeedback (EEG-nf) have led to an often published, yet flawed, conclusion that EEG-nf research does not support efficacy for the treatment of attention-deficit/hyperactivity disorder (ADHD) and that effects of EEG-nf arise primarily from placebo (Ghaziri & Thibault, 2019; Thibault, Lifshitz, Birbaumer, & Raz, 2015; Thibault, Lifshitz, & Raz, 2016, 2017a, 2017b; Thibault & Raz, 2017; Thibault, Veissière, Olson, & Raz, 2018). This analytical approach is commonly based on a literature review, specifically examining randomized placebo-controlled trials of EEG-nf with a preference towards higher amounts of blinding. However, these literature reviews commit at least two Type III statistical errors, as we illustrate below. We therefore suggest that the conclusions of inefficacy of EEG-nf in the treatment of ADHD and the placebo explanation are misguided and invalid.

The argument against the efficacy of EEG-nf is based on the assumption that sham EEG-nf is inert, thus rendering it an effective sham. Sham control study designs require an inert sham, which is a fake treatment that does not have a significant specific (i.e., non-placebo) effect on the condition being studied, such as the effect of a sugar pill in medication studies (Thornton, 2018). Most EEG-nf studies lack inert shams, and instead use another active treatment as a sham. An active sham, or non-inert sham, is when the treatment in the sham condition has a significant positive effect on ADHD that is comparable to other known treatments or beyond what could be due to placebo. This means that these studies are actually comparing two active conditions, both of which are found to have a positive treatment effect on ADHD symptoms. Since such study questions hypothesize a result based on comparing EEG-nf to an inert sham, which would have no effect beyond placebo, it often appears as if EEG-nf is not creating a significant change in comparison to the sham control. This study design only works if the sham control does not create a statistically significant effect itself. Moreover, if learning occurs on the target EEG variables within the sham group, which is the active ingredient of EEG-nf, then the sham is rendered ineffective because it is actually a valid form of EEG-nf.

The recent reviews of EEG-nf claiming a lack of efficacy in the treatment of ADHD, positing placebo as the explanation for any positive effect, base their argument on studies that contain a non-inert EEG-nf sham condition (Ghaziri & Thibault, 2019; Thibault et al., 2015; Thibault et al., 2016, 2017a, 2017b; Thibault & Raz, 2017; Thibault et al., 2018). The EEG-nf shams used in many of these cited studies are not inert because they have a significant and positive effect on ADHD symptoms, with effect sizes comparable to known effective treatments for ADHD (Shönenberg et al., 2017; Van Doren et al., 2018). When a study, or group of studies, does not find separation between an active (non-inert) sham and true EEG-nf, it is an illusion called a false no-effect.

In instances of a false no-effect, no conclusions are to be drawn from these studies on efficacy or the presence of placebo because they are entirely subjective and absent of objectivity (Horn, Balk, & Gold, 2011). This flaw is well understood in complementary and alternative medicine (Horn et al., 2011), and the issue of active shams are specifically identified as being present in studies of EEG-nf in the treatment of ADHD by both supporters and detractors of EEG-nf (Loo & Makeig, 2012; Van Doren et al., 2018). Thibault and Raz (2018) even pointed out that the sham in all but two of the studies they cite have a positive effect on ADHD symptoms (Logemann, Lansbergen, Van Os, Böcker, & Kenemans, 2010; Vollebregt, van Dongen-Boomsma, Buitelaar, & Slaats-Willemse, 2014). The two studies excluded from that statement did not follow best practices in the actual EEG-nf condition, which likely explains the lack of difference between the sham and attempted EEG-nf (Pigott, Cannon, & Trullinger, 2018). This creates an easy-to-make Type III statistical error, or an error in which the data is collected and analyzed correctly but while it rejects the null hypothesis, it does not confirm the hypothesis that the researchers originally proposed (Tate, 2015).

Due to the misinterpretation of the false no-effect in these trials as an actual lack of effect, researchers often provide an ad hoc explanation, or a specific reason given to explain why a significant difference is or is not shown in the data. However, presenting ad hoc explanations is not advisable because they are not the specific, or only, difference between conditions being studied (Tate, 2015). There are possible reasons, other than placebo, that could contribute the lack of difference between EEG-nf and sham. Yet, the placebo is often presented definitively as the source of positive effects from EEG-nf in reviews of the literature (Ghaziri & Thibault, 2019; Thibault et al., 2015; Thibault et al., 2016, 2017a, 2017b; Thibault & Raz, 2017; Thibault et al., 2018). The continual repetition of this ad hoc placebo explanation in publications damages the overall quality and reliability of the published research, especially in the evaluation of efficacy, because it is a Type III statistical error and an unsubstantiated conclusion.

The sham EEG-nf designs of studies cited by several recent publications (Ghaziri & Thibault, 2019; Thibault et al., 2015; Thibault et al., 2016, 2017a, 2017b; Thibault & Raz, 2017; Thibault et al., 2018) use sham conditions that have not been validated as effective. One example is van Dongen-Boomsma, Vollebregt, Slaats-Willemse, and Buitelaar (2013), in which the sham condition trained a simulated signal of the EEG not coming from the participant with an 80% positive reinforcement rate that was adjusted to maintain that reward level identical to the reward ratio and adjustments in the actual EEG-nf condition. The participants receiving this sham treatment would be told that they are attempting to change their brainwaves through doing better at the assigned task, or similar instructions, which were identical to those given to the participants in the actual EEG-nf group.

The sham used by van Dongen-Boomsma et al. (2013) may actually achieve a significant amount of contingent reinforcement on the target EEG variable. Therefore, the sham may not actually represent a different treatment from what was administered in the actual EEG-nf condition (Thatcher & Lubar, 2014). Moreover, the only way to know for sure would be to analyze whether or not learning occurred on the target EEG variable in the sham condition. Yet, the authors of this study did not do that. Neither did the recent reviews that cited these articles when claiming a lack of efficacy for EEG-nf in the treatment of ADHD and explanatory placebo effects (Ghaziri & Thibault, 2019; Thibault et al., 2015; Thibault et al., 2016, 2017a, 2017b; Thibault & Raz, 2017; Thibault et al., 2018).

Another example is Shönenberg et al. (2017), in which the sham condition received the sham during only 50% of the sessions. The EEG-nf treatment used in the actual EEG-nf group made up the last 50% of the sessions in the sham condition. Clearly, this sham condition cannot be assumed to be effective, or very different from the actual EEG-nf condition, because half of the treatments were identical to those administered to the actual EEG-nf group. Therefore, the risk of a false no-effect error is even higher in Shönenberg et al. (2017) because of the similarity between the sham and actual EEG-nf conditions. These are just two examples, but an analysis of all of the citations provided by these recent reviews of the literature (Ghaziri & Thibault, 2019; Thibault et al., 2015; Thibault et al., 2016, 2017a, 2017b; Thibault & Raz, 2017; Thibault et al., 2018) reveals that the sham conditions may have had some level of contingent reinforcement on the targeted EEG signal and did not provide evidence to prove otherwise.

Since the EEG-nf sham likely achieved some level of contingent reinforcement in the studies cited in recent reviews due to poor behavior modification designs (Ghaziri & Thibault, 2019; Thibault et al., 2015; Thibault et al., 2016, 2017a, 2017b; Thibault & Raz, 2017; Thibault et al., 2018;), these sham conditions are actually another form of EEG-nf with a theoretically less optimal behavioral modification paradigm. Therefore, they are not an effective sham and certainly cannot be assumed to be inert. In an even more recent publication, Ghaziri and Thibault (2019) state that that EEG-nf is not efficacious and the majority of the effect is placebo. They go on to state that EEG-nf needs to be compared to a specific sham condition, training a recorded signal that is not coming from the actual participants' real-time EEG, to prove EEG-nf is efficacious and not due to placebo. However, they do not cite any new research since Thibault et al. (2018) that has tested this sham to prove it is effectively not reinforcing the target EEG-nf variable. Nor do they provide any evidence that it is inert and does not significantly improve ADHD symptomology.

Just as those who support the efficacy of EEG-nf have to prove it works beyond placebo and generalized treatment effects, when researchers argue that placebo explains all of the effects of EEG-nf, they too must provide convincing proof that all other explanations for the effect are incorrect and cite research that shows placebo accounts for all of the positive clinical effect. As has been pointed out in this article, those claiming that placebo explains all of the effects of EEG-nf (Ghaziri & Thibault, 2019; Thibault et al., 2015; Thibault et al., 2016, 2017a, 2017b; Thibault & Raz, 2017; Thibault et al., 2018) have only succeeded in committing two distinct Type III statistical errors. There simply is not sufficient research to support the idea that placebo can make significant and sustainable changes that can explain the entirety of the effect of EEG-nf in the treatment of ADHD.

In fact, there is direct evidence that EEG-nf cannot be fully explained by placebo. A recent meta-analysis proves that the effects of appropriately administered EEG-nf last over time, even after the effects of placebo would wear off (Van Doren et al., 2018). Moreover, a second recent reanalysis of Cortese et al. (2016) statistically calculated results in a subgroup of the data that used the best practices in EEG-nf for their true EEG-nf condition. The studies that used the best practices in the EEG-nf field yielded significant evidence that EEG-nf effects in the treatment of ADHD cannot be fully explained by placebo in short-term studies (Bussalb et al., 2019) despite the presence of a non-inert sham. Therefore, professing that placebo can explain all of the effect of EEG-nf in the treatment of ADHD is unsupported by the literature and exaggerates the effects of placebo interventions.

In the future, it is recommended that journal reviewers, editors, book publishers, and the general media should require authors to prove assumptions that the shams used in cited studies are both inert and effective. Additionally, the publishers should require proof that the EEG-nf condition being evaluated is a form of EEG-nf that is in alignment with the best practices of the field in all of the studies being cited. Finally, ad hoc explanatory explanations, such as placebo, are a Type III statistical error and should be excluded from the publication or appropriately and clearly identified as an ad hoc explanation and a Type III statistical error. Future research should assess the efficacy of EEG-nf as a treatment for ADHD within a more objective framework designed for dealing with non-inert shams, complex behavioral modification principles that need to be effectively administered, and a multifactorial effect of the treatment. The American Psychological Association has criteria for evaluating psychotherapy that meet these requirements (Chambless & Hollon, 1998).

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Mark Trullinger receives grant funding as a primary investigator from BrainFutures, is a board member of the Foundation for Neurofeedback and Neuromodulation Research, and is the managing director of NeuroThrive, LLC.

Allen Novian is the owner of integrative Counseling & Neurofeedback Solutions (iCNS), practices EEG-nf, and is an adjunct professor at St. Mary's University.

Lori Russell-Chapin is a Professor at Bradley University and also practices EEG-nf.

Deepti Pradhan is the chief operating officer of NeuroThrive, LLC.

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HRV Regulation by Calligraphic Finger Writing and Guqin Music: A Pilot Case Study

Stewart P. W. Lam[1], Henry S. R. Kao[1], Xiaoyang Kao[2], Miranda M. Y. Fung[3], and Tin Tin Kao[1]*

[1]University of Hong Kong, Hong Kong, China
[2]University of Illinois at Urbana–Champaign, Champaign, Illinois, USA
[3]China Academy of Chinese Medical Sciences, Beijing, China

Abstract

Introduction. Previous research shows that brush Chinese calligraphy handwriting (CCH) improves one's cognitive functions as well as emotional and mental health. Similarly, Guqin, the popular Chinese musical instrument, induces positive emotions and emotional stability. The present study tested the efficacy of using the index finger to achieve similar mind–body changes. **Methods**. We employed a heart rate variability (HRV) Calligraphy–Guqin biofeedback intervention that was implemented with a Zephyr HxM Bluetooth chest heart rate monitoring device and an Android smartphone. A web-based HRV big database app stored the data from three consecutive sessions: (1) 5 min of Guqin music listening; (2) 5 min of CCH finger writing of calligraphy; and (3) again 5 min of Guqin music listening. The second session was designed to explore additive effects of the finger-writing task. One subject participated with the index finger employed for the writing task. **Results**. The results showed that the first and third Guqin sessions elicited 55% and 68% HRV coherences, respectively, while the CCH finger writing in the second session elicited 31% of high HRV coherence. The increase in HRV coherence between the two Guqin sessions was attributed to the calligraphy finger writing training effect. The practice of finger writing contributed to increased HRV regulation through heightened attention and concentration.

Keywords: calligraphy; finger writing; Guqin music; emotion; HRV biofeedback; rehabilitation

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***Address correspondence to**: Henry S. R. Kao, No. 45, 4th Floor, 5th Street, Zhongyang Road, Xindian District, New Taipei City, Taiwan 23150. Email: henrysrkao@gmail.com

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

Reviewed by:
Rex L. Cannon, PhD, Knoxville Neurofeedback Group, Knoxville, Tennessee, USA
Genomary Krigbaum, PsyD, Grand Canyon University, Phoenix, Arizona, USA

Introduction

Background

Research in Chinese calligraphy handwriting (CCH) has produced interesting and highly significant findings in the nature, processing, and outcomes of the practice of Chinese script. It is established that the processing of Chinese characters exerts positive and beneficial effects on one's perceptual, cognitive, and brain activities during handwriting. The contributing factors relate to the interactions between the character's visual-spatial properties and its associated cognitive and neural activities of the practitioner (Kao, Lam, & Kao, 2018). Sustained practice of Chinese character writing has the function of perceptual and cognitive activation and has been shown to contribute to functional plasticity in the human cerebral cortex.

Previous studies have also discovered that the cingulate cortex is involved in the process of visual stimulus, premotor planning, and memory operations, which are vital in CCH training. The finding of a smaller cingulate gyrus volume (CGV) in the CCH groups suggested that long-term CCH practice may reshape the brain structure by increasing the efficiency of neural activity (Chen, Chen, He, Wang, & Wang, 2016). Recent neuroimaging research also finds that CCH practitioners show better neural functions of updating and inhibition. The CCH group also shows stronger resting-state functional connectivity than the control group in the brain areas also shows stronger resting-state functional connectivity than the control group in the brain areas involved in updating and inhibition. These outcomes suggest that long-term CCH training may be associated with improvements in specific aspects of the executive functions and the strengthened neural networks in related brain regions (Chen et al., 2017). At a deeper level of analysis, when processing the visual-spatial configurations of Chinese characters at the cortical level, the act of writing can initiate and facilitate cognitive activities and functions of related cortical substrates (Kao et al., 2018; Xu, Kao, Zhang, Lam, & Wang, 2013).

The Theory

A conceptual framework has been advanced to account for the character's roles and practical impact on handwriting within a dynamic behavioral cybernetic system (Kao, 2006, 2010). Handwriting consists of three main components in the writing of script: the hand, the writing instrument, and the paper or surface of writing material. The theory of handwriting operation and skills training has its conceptual origin in the context of a cybernetic system of perception and motor performance (Kao & Smith, 1969; Smith & Smith, 1962, p. 341). The writing of script and the tool used during handwriting result in different forms of feedback: reactive feedback from the hand itself, instrumental feedback from the action of the writing instrument, and operational feedback from the resulting handwriting traces on the paper or writing surface (Smith, 1961; Smith & Smith, 1962; Smith & Smith, 1988). Moreover, skill learning such as handwriting occurs as a result of motor control mechanisms interfacing the motor displacements relative to the spatiotemporal coherence between mind–body movements and its instrumental sensory feedbacks during the task. This displacement control process is mediated by neuronal detector mechanisms (Smith & Smith, 1988) as well as a full spectrum of behavioral feedback mechanisms (Kao, 2000) underlying the writing motions with the characters.

The theoretical bases for calligraphy writing by brush are threefold (Kao, 2000; Zhu et al., 2014). First is the sensory feedback: the individual receives sensory feedback from the graphic record while practicing calligraphy. Second is the bioemotional feedback: the calligraphy involves the movement of the arms and the body as the guide to regulate their movements. Finally, the cognitive feedback: the subjective experiences of heightened attention, alertness, and quickened responses during the writing acts (Xu et al., 2013; Zhu et al, 2014). Our past research has been guided by these measures of brush handwriting.

As for the crucial role of the Chinese characters as the materials in brush handwriting, we have followed a set of psychogeometric which states that characters with Gestalt and topological properties such as balance, closure, orientation, connectivity, etc. are space-structured, easily recognized, and speedily processed. The visual facilitating effect of each single property on processing the characters is formed upon the practitioner's response to the visual-spatial structure of Chinese characters or English letters that are relative to the practitioner's body and hand movements, taking place in the course of the writing tasks (Kao, 1999).

The Applications

The positive effects of CCH practice at the fundamental behavioral level have included identified enhancements in one's attention and concentration, physical relaxation, and emotional stabilization, among others. Specifically, effective outcomes with CCH intervention have been obtained in a variety of disease and clinical applications as well as behavioral changes. These include significant results of (1) patients of strokes in palm strength of the affected hand and increased response facilitation in fine motor coordination (Chiu, Kao, & Ho, 2002); (2) the awakening of a coma patient after stroke with significantly enhanced focusing, alertness, visual scan and span, and quickened visual and motor responses (Kao, Lam, & Kao, 2018); and (3) Alzheimer's disease patients showing significant improvement in short-term memory tasks and verbal ability (Kao, 2010).

In addition, other clinical areas of CCH treatment include (1) Chinese cancer (nasopharyngeal carcinoma) patients with CCH training who demonstrated gradually lowered systolic blood pressure and respiration rate at pre- and posttreatment measures as the intervention proceeded, as well as elevated level of concentration and reduced mood disturbance (Yang, Li, Hong, & Kao, 2010); (2) our CCH training of post-earthquake PTSD children, which led to significant decrease in hyperarousal symptoms and salivary cortisol levels among the child survivors (Zhu et al., 2014); and (3) that CCH training plus Wenlafaxine drugs, which yielded better effects in treating patients of anxiety disorder that were measured by the Hamilton Anxiety Scale (HAMA), Self-Rating Anxiety Scale (SAS), and Clinical Global Impression (CGI) Scale (Dong, Jia, Wang, Cui, & Zhang, 2006). These results provide encouraging evidence on the strength of CCH intervention toward reducing certain neuropsychiatric symptoms and conditions (Chu, Huang, & Ouyang, 2018; Wagner, 2018).

The above studies and findings have all been conducted using the traditional Chinese brush as the exclusive writing instrument. It is interesting to explore whether a shift to a newer and different writing instrument would yield the same or similar research outcomes. The purpose of the present study was to test this notion by resorting to the use of a finger for writing. This idea is significant in view of the current surge of interest and development of touch-screen writing technologies in the cyber age of innovation.

We designed this pilot study (1) to analyze finger writing as an efficacious writing tool, (2) to test its contributions to health enhancement, and (3) to examine its writing effectiveness on a new surface platform of a smartphone.

Finger Writing: The New Instrument

Research results have suggested that repetitive movements on a smooth touchscreen reshape sensory processing from the hand and the thumb. It is proposed that cortical sensory processing in the brain is continuously shaped by the use of personal digital technology (Gindrat, Chytiris, Balerna, Rouiller, & Ghosh, 2015). Recent results indicate that a combination of motor training with mirrored visual feedback (MVF) therapy can induce significant neuroplasticity changes through multisensory integration. The findings of this finger movement therapy lend support to the application of finger calligraphy writing for inducing cortex plasticity in the course of treatment (Kumru et al., 2016). We have made initial attempts to develop finger writing as a new mode for calligraphy therapy. Pilot studies have included using finger writing with a tablet computer for calligraphy writing in treating an Alzheimer's patient as well as a coma patient (Kao, Lam, & Kao, 2018).

This initial experience prompted our interest in exploring finger writing in connection with a new smartphone platform with a touch-screen surface for handwriting. The present study is the first test of the efficacy of handwriting in a handheld mobile smartphone and represents a new tactile-motor feedback-based finger writing system.

The Gugin Music

The Guqin (Chinese zither), also known as a seven-stringed Qin, is the most ancient plucked instrument of China with a history of over 3,000 years. It was a prerequisite subject for the ancient scholar, as well as an art for personal development and cultural cultivation in ancient China (Fung & Wang, 2011; Wang, 2006, p. 60).

Along with calligraphy training as a therapeutic system, Guqin has also been promoted recently as a method of relaxation therapy (Lam, Kao, & Fung, 2012; Yeh, 1991) and shown to be capable of inducing a state of psychological quiescence that improves symptoms of insomnia (Fung & Wang, 2011). Guqin music was adopted in this study as a complementary intervention along with the act of finger writing characters.

The HRV Coherence

The rhythm of a healthy heart—even under resting conditions—is actually irregular, with the time interval between consecutive heartbeats constantly changing, which is known as Inter-Bit-Interval (IBI) changes. The naturally occurring beat-to-beat variation in heart rate is called heart rate variability (HRV). Any generation of sustained positive emotions facilitates a body-wide shift to a specific, scientifically measurable state, which is termed psychophysiological coherence because it is characterized by increased order and harmony in both our psychological (mental and emotional) and physiological (bodily) processes. Psychophysiological coherence is a state of optimal function, which generates increased mental clarity and improved cognitive function. Simply stated, as our body and brain work better, we feel better, and we perform better herein (McCraty, Atkinson, Tomasino, & Bradley, 2009).

HRV and Behavior

A review of literature suggests that heart rate oscillations can enhance emotion by entraining brain rhythms in ways that enhance regulatory brain networks. Because blood flow timing helps determine brain network structure and function, slow oscillations in heart rate have the potential to strengthen brain network dynamics, especially in medial prefrontal regulatory regions that are particularly sensitive to physiological oscillations. It supports that individuals with high HRV tend to have better emotional well-being than those with low HRV (Mather & Thayer, 2018). In addition, HRV is impacted by stress (Kim, Cheon, Bai, Lee, & Koo, 2018) and associated with level of anxiety (Chalmers, Quintana, Abbott, & Kemp, 2014). These studies provide a glimpse of the applications of HRV relative to emotion, stress and anxiety, and other disorders.

Inter-Bit-Interval (IBI) and CCH

We have investigated some psychophysiological changes on the part of the CCH practitioner. Results showed a consecutive reduction in heart rate for the first 10 s during brush handwriting. This indicates that a significant increase in IBI means that the HRV is measured in the time domain (Kao, Lam, Guo, & Shek, 1984; Kao, Lam, Robinson, & Yen, 1989). Based on these findings we believe that the state of

HRV coherence could be regulated as an index (Appelhans & Luecken, 2006) of the effects that are induced by the Guqin listening as well as by finger-writing intervention in this study.

We introduce the smartphone in this study as an advanced alternative practice with calligraphy finger writing and Guqin music listening, forming a new system of HRV regulation for cognitive neural interventions.

Aims of the Study

1. To investigate the complementary roles and effects of calligraphy training and Guqin listening in HRV regulation through using a smartphone as an active HRV biofeedback platform.

2. To develop the HRV regulation function of finger writing using a smartphone. It is expected that calligraphic finger writing can promote the effects of Guqin music listening with meditation toward a deeper and positive level of mind–body harmony (HRV coherence).

Materials and Methods

Participant

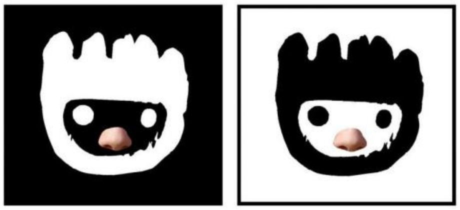
The case study subject was a 56-year-old male with treated hypertension and no history of psychiatric disorders or decline in cognitive functions. The trials were conducted in the home environment.

Selection of Gugin Music and Writing Protocols

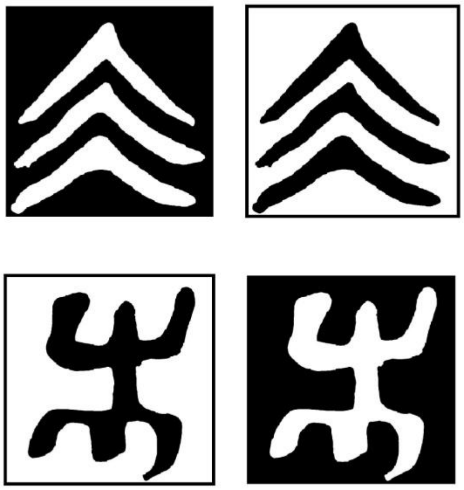
In the first and third sessions, 5 min of Guqin music are selected from Li Xiangting's Guqin album "Heart".

In the second session of 5 min of calligraphic finger writing, calligraphy graphic characters are selected from a newly developed "iPad calligraphy: fingering writing psychotherapy" design (Kao & Lam, 2011).

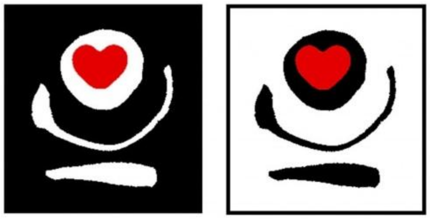
Finger Writing Materials: The Graphic Characters



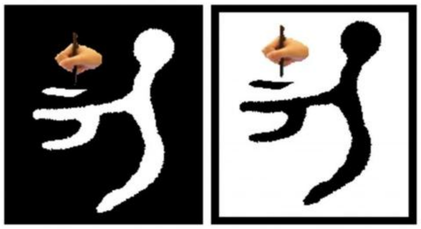
Patterning the Breath
XY Kao and Henry Kao 2009



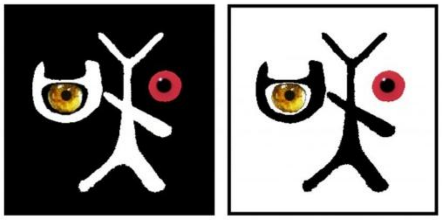
The Healing Characters



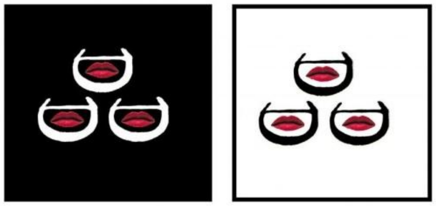
Resting Emotions
Henry Kao and XY Kao 2009



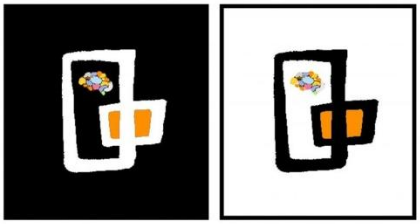
Steady Hand
Henry Kao 2009



Perceptive Eyes
Henry Kao 2009



A Taste of Art
Henry Kao and Tintin Kao 2009



Active Mind
Henry Kao and XY Kao 2009

"Calligraphy–Guqin" HRV Biofeedback Design

"Calligraphy–Guqin" HRV is a system is based on the "Biofeedback-based System of Calligraphy Therapy" (Lam & Kao, 2007) which was invented by our team and shown at the Innovation Expo 07 in Hong Kong in 2007; the Zephyr HxM Bluetooth chest heart rate monitoring device; the HTC EVO 3D Android smartphone; and the Heart-Love HRV Android app, an HRV Internet big database that is used to analyze and store the data collected from three 5-min sessions for HRV regulation.

An HTC EVO 3D Android smartphone in Figure 1 is used for Guqin music playback and the ongoing finger writing of the participant.

The Zephyr HxM Bluetooth chest heart rate monitoring device is set up for the participant, as illustrated in Figure 2.

1. First session: 5 min of meditation with Guqin music listening. See Figure 3.
2. Second session: 5 min of calligraphic finger writing intervention. See Figure 4.
3. Third session: 5 min of meditation with Guqin music listening. See Figure 5.

Instant analysis of recorded HRV through Internet cloud big databases as a remote and mobile healthcare platform is shown in Figure 6.

Improved process outcomes that regulate HRV coherence after intervention and the HRV are graphically displayed in Figure 7, while the HRV coherence for the control trial is graphically displayed in Figure 8.

The Procedure

The design of this 15-min protocol of meditation with Guqin music listening and calligraphic finger writing intervention for HRV regulation is tested with a single trial case study to evaluate the efficacy of both the new protocol and the finger writing as an instrument for CCH therapy.

The HRV coherence app is installed, the Guqin music is recorded, and the graphic characters are all stored in the smartphone in advance of the display of Guqin music and the graphic characters in a predefined sequence. The conventional equipment setup and procedures are followed. Refer to separate descriptions under the respective figures.

Figure 1. The HTC EVO 3D Android smartphone.

Before wearing the Zephyr HxM Bluetooth chest heart rate monitoring device: (1) clip the Zephyr monitor to the chest strap, (2) put on the chest strap around the chest as shown in Figures 1 and 2, and (3) the Zephyr monitoring device will be turned on automatically. Note: In order to ensure a good connection, it might be necessary to sprinkle a small amount of water on the fabric sensors before wearing. The monitoring device is then paired with the HTC EVO 3D Android smartphone. The audio output of the smartphone is connected to a surround sound receiver for playback of the Guqin music and also for the tone for biofeedback of the Heart-Love's HRV coherence Android app.

Figure 2. The Zephyr Bluetooth chest heart rate monitoring device and setup illustration.

The subject sits comfortably in an armchair, turns on the smartphone, the monitoring device, and the surround sound receiver. For the first session (see Figure 3), initiate playback of the Guqin music and the HRV coherence app, pay attention, and enjoy the Guqin music; the higher tone for biofeedback will change as a higher HRV coherence is reached.

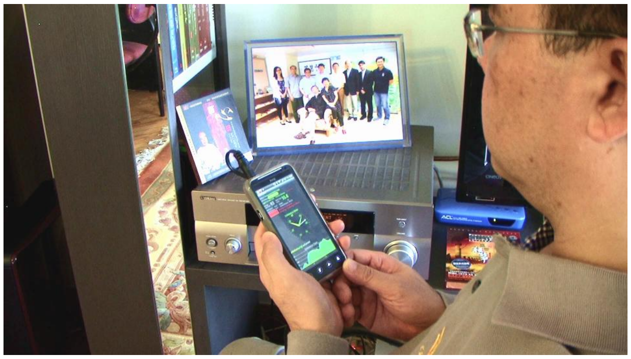


Figure 3. The first session: 5 min of meditation with Guqin music listening.

Save the HRV coherence result after 5 min of the first session of Guqin music listening. Then, proceed to the second session (see Figure 4), display the first graphic character, initiate the HRV coherence app, and then start tracing the graphic character with the index finger on the touch screen; the higher tone for biofeedback will change as a higher HRV coherence is reached.

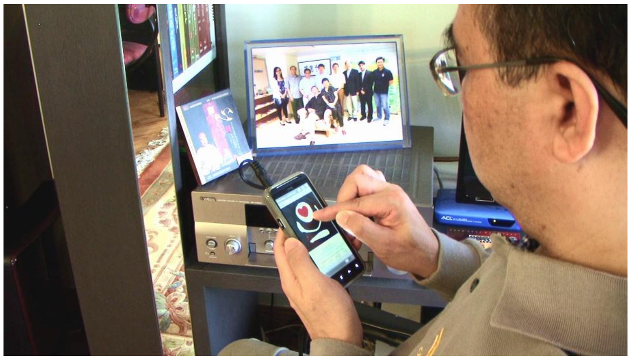


Figure 4. The second session: 5 min of calligraphic finger writing on the touch screen of an HTC smartphone.

After completing the first graphic character, display the second graphic character for tracing and so on for 5 min of the second session. Save the HRV coherence result after 5 min of the second session of CCH finger writing. Then, proceed to the third session as the procedure of the first session (see Figure 5). Save the HRV coherence result after 5 min of the third session of Guqin music listening. The three sessions of intervention are then completed.

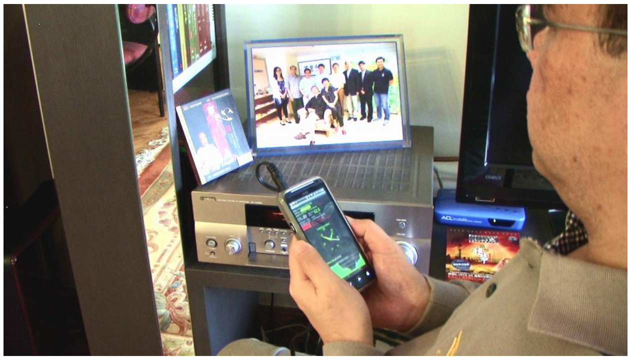


Figure 5. The third session: 5 min of meditation with Guqin music listening.

4:51 PM

Heart Love

Status:Connected:HXM007379

HxM Battery Charge Logged In

Average Heart Rate 61 Heart Love Score 55.6

HxM Speed 0 m/s Strides 2

HxM Distance 2 m Stride Distance 10.0 m

4:52 PM

Heart Love

Status:Connected:HXM007379

HxM Battery Charge Logged In

Average Heart Rate 65 Heart Zone Alert IN

HxM Speed 0 m/s Strides 2

HxM Distance 2 m Stride Distance 10.0 m

4:53 PM

Heart Love

Heart-Love.com Login

Login to Heart-Love.com (Required for personal session tracking)

General Settings

Monitor Mode

What would you like to monitor?

General Settings

Age, stride calibration, wake lock settings and more.

Sound Settings

Mute

Mute all sounds

Volume

Set volume for alerts

Chart Visibility

Chart Visibility Settings

HR, HR Variation and PSD chart visibility

Figure 6. HRV graphic data icons on smartphone showing instant analysis of Internet big databases as remote and mobile healthcare platform.

Results & Discussion

The results of the percentage of HRV coherence of the three sessions of the saved test trial and control trial in the cloud database are plotted with Microsoft Excel in Figures 7 and 8, respectively.

The video version of the biofeedback trial of application of the calligraphic finger writing and Guqin music listening process can be viewed online from YouTube (https://youtu.be/eyr6ziNHHyw).

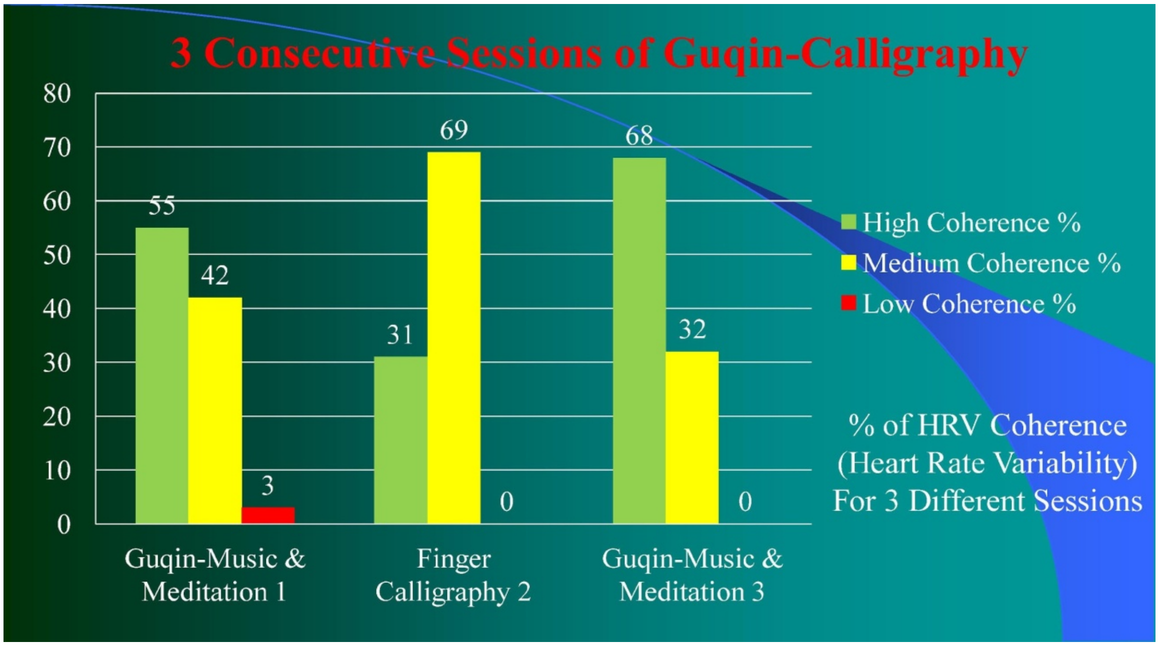


Figure 7. HRV results plotted for three different sessions of Guqin music listening and finger writing.

Results in Figure 7 demonstrated that after the calligraphic finger writing intervention, the first and third sessions of meditation with Guqin music listening elicited 55% and 68% of high HRV coherence respectively, while the second session of calligraphic finger writing elicited 31% of high HRV coherence. This indicated a preliminary observation that calligraphic finger writing and Guqin music listening both improved one's HRV regulation, and that this effect could mean a shortening of intervention duration as well as a potential application of both for treatment and rehabilitation with the use of a smartphone or a handheld tablet computer. It is noted that previous research on Guqin music listening for insomnia treatment elicited also a marginal significance (*p* = .055) of HRV coherence after intervention (Fung, Han, & Lee, 2014; Fung, Kao, Lam, & Kao, 2019).

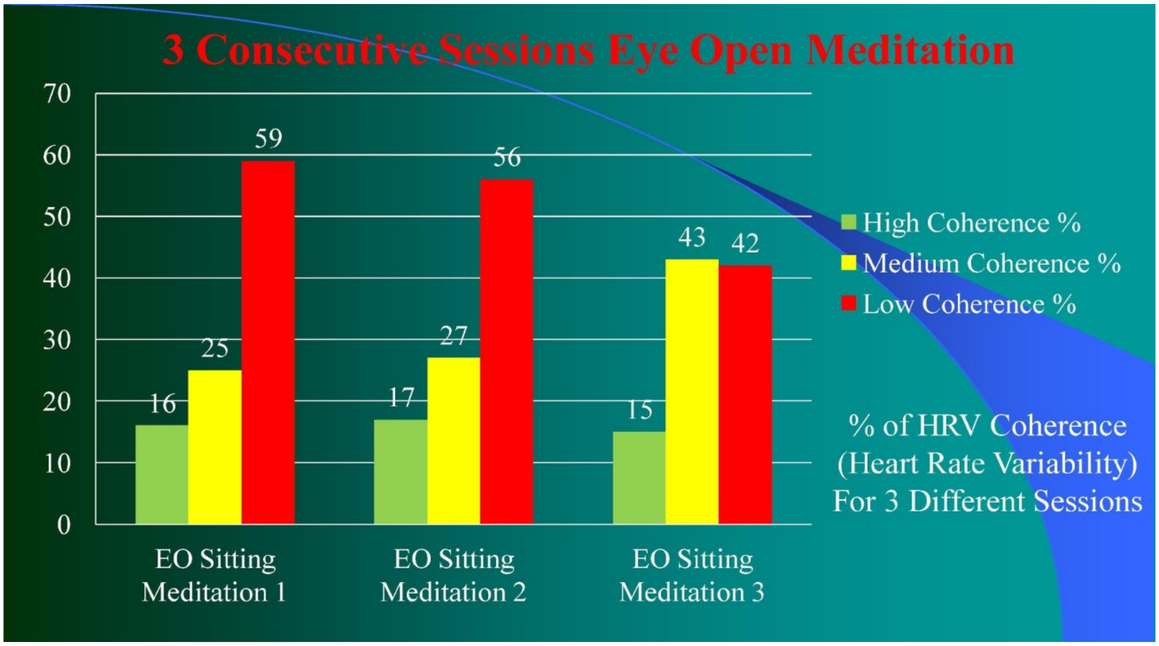


Figure 8. HRV results plotted for three consecutive sessions of eyes-open sitting meditation.

Results in Figure 8 showed that, as a control trial with three consecutive sessions of eyes-open sitting meditation, the first, second, and third eyes-open meditation sessions only elicited 16%, 17%, and 15% of high HRV coherence respectively with little differentiation. This demonstrated that, in Figure 7, the high HRV coherence result in the third session of Guqin music listening is solely due to the intervention effect of calligraphic finger writing. We believe that this practice contributed to increased HRV regulation from 55% to 68% of high HRV coherence through an increase in attention and concentration that are associated with the practice of calligraphic finger writing.

The third session of meditation with Guqin music listening has confirmatory data not only on the positive effect of Guqin music listening in the literature alone but also suggestive of an additive value of accompanying calligraphic finger writing during the process of dual factor intervention. This would suggest the likely value of combined treatment system for behavioral intervention. A first implementation in this direction has seen a recent investigation of applying combined Gugin music and calligraphy in the successful treatment of symptoms of primary insomnia. The results have shown this joint intervention being effective in promoting heart rate coherence as well as optimum brain functions (Fung, Kao, et al., 2019).

In line with previous studies in which HRV is positively associated with stress decrease (Chalmers et al., 2014; Kim et al., 2018), anxiety reduction (Dong et al., 2006) as well as PTSD hyperarousal decrease (Zhu et al., 2014) reviewed in previous sections, we believe that the significant increase in high HRV coherence induced by calligraphic finger writing on the touch screen of the smartphone plus Guqin music listening can exert a curative and effective treatment for the emotional conditions of stress and anxiety.

The HRV and Emotion theory and research support the utility of HRV as a noninvasive, objective index of the brain's ability to organize regulated emotional responses through the autonomic nervous system (ANS) and as a marker of individual differences in emotion regulatory capacity (Appelhans & Luecken, 2006) and the reviewed findings suggest that heart rate oscillations can regulate emotion by entraining brain rhythms in medial prefrontal regulatory regions. It supports that individuals with high HRV tend to have better emotional well-being than those with low HRV (Mather & Thayer, 2018). On the basis of such observations, we speculate that high HRV coherence induced by calligraphic finger writing on the touch screen of a smartphone plus Guqin music listening may also be able to regulate emotions.

This preliminary case study has provided valuable findings toward further development of systematic application of finger writing together with the smartphone toward a curative and effective platform of behavioral treatment. We conclude that Guqin music and calligraphic finger writing contributes to inducing the harmonious effect of "mind and body" coherence and emotional relaxation. Further testing and validation of the present system are warranted for broader clinical applications in the areas of brain health and treatment of neuropsychiatric diseases.

Conclusion

This new, shortened 15-min protocol is designed in order to adapt to the busy style of modern life by using a smartphone to store and playback the graphic characters and Guqin music which can be completed either at home, school, or at work. The whole treatment protocol is automated using the smartphone in guiding the practitioner to work through the intervention processes with a light handheld indoor or outdoor calligraphy and Guqin finger writing intervention platform which may be limited to effective treatment for the emotional conditions of stress and anxiety.

Calligraphy treatment usually completes a psychotherapy intervention process with a 3-min sitting meditation—30 to 45 minutes of calligraphy handwriting intervention followed by 3 min of sitting meditation. Because calligraphy is written with a brush as the main tool, it requires a place and a relatively quiet environment, together with a longer intervention program that takes about 45 to 60 minutes including preparation work (Kao et al., 1984). To apply as a clinical trial in the future, a design of different graphic characters to target specific neuropsychiatric diseases (Chu, Huang, & Ouyang, 2018) with 30 to 45 minutes intensive treatment is required for calligraphy and Guqin finger writing.

For future development, cloud database is to connect to upload trials, and view Sessions, Goals and Achievement scores. Daily Coherence Ratio, Achievement Totals and Community Achievement Scores may be all visible to the clients and may also be visible to an assigned and authorized clinical therapist for coaching.

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Author Disclosure

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

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