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Original article

A randomized controlled trial (RCT) to explore the effect of audio-visual entrainment among psychological disorders

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Abstract. *Background and aim:* Although many mental disorders have relevant proud in neurobiological dysfunctions, most intervention approaches neglect neurophysiological features or use pharmacological intervention alone. Non-invasive Brain-Computer Interfaces (BCIs), providing natural ways of modulating mood states, can be promoted as an alternative intervention to cope with neurobiological dysfunction. *Methods:* A BCI prototype was proposed to feedback a person's affective state such that a closed-loop interaction between the participant's brain responses and the musical stimuli is established. It returns flickering lights in real-time matching with the individual's brain rhythms subjected to auditory stimuli. A RCT was carried out on 15 individuals of both genders (mean age = 49.27 years) with anxiety and depressive spectrum disorders randomly assigned to 2 groups (experimental *vs.* active control). *Results:* Outcome measures revealed either a significant decrease in Hamilton Rating Scale for Depression (HAM-D) scores and gains in cognitive functions only for participants who undergone to the experimental treatment. Variability in HAM-D scores seems explained by the changes in Beta 1, Beta 2, and Delta bands. Conversely, the rise in cognitive function scores appear associated with Theta variations. *Conclusions*: Future work needs to validate the relationship proposed here between music and brain responses. Findings of the present study provided support to a range of research examining brain modulation with BCIs and contribute to the understanding of this technique as instruments to alternative therapies. We believe that Neuro-Upper can be used as an effective new tool for investigating affective responses, and emotion regulation (www.actabiomedica.it).

Key words: Entrainment, Brain-Computer-Interface, Psychological disorders, Intervention

Introduction

Many psychiatric disorders, such as anxiety and depression, have their source in emotional dysfunctions (1). Brain Computer Interfaces (BCI) has been advocated as a powerful tool for scientific inquiry of the brain in vivo, most especially for investigating the nervous system's adaptive capacities during interaction with external stimuli. BCI has the clear methodological benefit of offering interactive approaches to catching neural responses that may be applied to improve self-regulation of affective states (2-3). BCIs recorded electrical potentials through non-invasive techniques. Electroencephalogram (EEG) is the preferred method for its non-invasiveness, time resolution, ease of acquisition, and cost effectiveness. Intermittent Photic Stimulation (IPS) associated with binaural beats has showed as effective (4-5). Attending brain activity by mean of non-invasive stimulation can highlight on causal relations between Alpha rhythms (~8-12 Hz) and behavioural changes (6-8). The Alpha frequency is decomposed into sub-bands with differential role -

lower Alpha 1 (6-8 Hz), medium Alpha 2 (8-10 Hz), and upper Alpha (10-12 Hz) - with the first associated with attentional loads and the upper with semantic memory and cognitive control (9). It was also suggested that Alpha training led to plastic modulation of both the DMN (Default Mode Network) and SN (Salience Network) inducing brain alterations that survive the entrainment. Alpha oscillations appear explain about the 64% of the variability in perceptual learning (10) that is regarded as a proof of brain plasticity induced by external stimuli and related to long-term potentiation (LTP) and long-term depression (LTD) (e.g., Sale et al., 2011).

BCI methodologies to affective states are of unique value, not only to advance our understanding of emotion induction processes by examining the neural signatures of emotions, but also for numerous possible medical applications, such in mood disorders and depression that have their origin in emotional dysfunctions. Unveil the relationship between ongoing brain activity and learning could yield new approaches to neuromodulation in clinical settings (4, 12). Several investigations have confirmed that individuals with anxiety and depression showed a typical EEG pattern characterized by a higher Beta rhythm (13-14). Theta-Alpha range (4-12 Hz) is relevant for perceptual learning produced by repetitive sensory stimulation (RSS) (15). Delta oscillations are increased in some disorders, like anxiety, depression, or obsessive compulsive. The relationship between Delta and reward circuits suggested that in individuals suffering from depression the reward system is dysfunctional (16-17). Similarly, augmented Theta and Delta have been related with a low antidepressant efficacy and it was showed (18) that Delta increased in the frontal medial areas mostly for individuals with high state anxiety who receive less dopaminergic firing from the nucleus accumbens.

The presence of several conditions sharing patterns of neural oscillatory disturbance suggests a possible value for technologies that may regulate neural pathways. In psychological disorders also networks' involvement was deemed relevant, as in Default Mode Network (DMN) and Salience Network (SN) (1). The DMN is a pillar of cortical integration as the SN has a crucial function in relevance detection and in integration/regulation of somatic, autonomic, and emotional information. Both networks are recognized relevant for anxiety, depression, and impulse control (19). Anxiety disorder is a generalized concept for a variety of abnormal and pathological fear states, including Generalized Anxiety Disorder (GAD), agoraphobia, Obsessive-Compulsive Disorder (OCD), phobic disorders, or Post-Traumatic Stress Disorder (PTSD). Depressive and anxiety disorders are highly prevalent and associated with large use of services, disease burden, and loss of quality of life. Technology based intervention might provide a valuable treatment approach (20). To assist potential BCI methods for emotion regulation, music is a valuable medium, as it is widely acknowledged to be very effective in eliciting affective responses. Hence, incorporating musical feedback into BCI offers excellent possibility for emotion-regulation systems. Several studies have suggested functional relationships between specific structural parameters of music and emotional responses (21). Diverse music arrangements can trigger specific brain waves and several studies have employed music to trigger specific patterns of brain activity in treating mental disorders, and other clinical conditions (22-24).

The present study explored the efficacy of Neuro-Upper (NU), a BCI prototype aimed at calibration of neural oscillations (2, 25). NU combines repetitive visual and auditory stimulation feed backing individual's EEG signals as flicker light so that a continuous closed loop can be obtained (13, 21, 26). Previous research (27) has offered preliminary evidence that NU may have a potential application for clinical use. However, this technique is still at the prototypical stage, consequently demanding more experimentation able to suggest if it can be an effective method. The main purpose of the current work is to investigate the modulatory effect of NU through a RCT providing an active control group (CG) comparison for the experimental group (EG).

Method

Design

The research protocol followed the CONSORT checklist. This was a randomized controlled trial (RCT) conducted in line with the Code of Ethics of

the World Medical Association (Declaration of Helsinki). A 2 (Groups) x 2 (Times) repeated measures design was used. The trial included screening, intervention, and post-intervention phases. The EG participants received NU stimulation. CG involved several meetings talking in an unstructured way about participants' problems to balance the treatment sessions for the EG. The EG participants received NU stimulation 5 times a week for eleven consecutive weeks (55 total sessions). All participants were assessed for the outcome measure at week 16. Considering that the study did not encompass clinical tests, use of pharmaceutic or medical equipment, discomfort in any participant's other way, approval of Ethics Committee for Clinical Research of the University of Parma (AVEN) was deemed unnecessary.

Participants' recruitment

The study flow-chart is depicted in Figure 1. Eligible individuals were invited in the laboratory and were enrolled based on the inclusion criteria: i) Age between 18-60 years; ii) Depression score between eight and more at the HAM-D at the Hamilton Rating Scale for Depression (HAM-D, 28); iii) Trait anxiety score above the 95th percentile at the State Trait Anxiety Inventory Form Y (STAI-Y, 29); iv) Voluntary participation and written informed consent. Any individual showing one or more of the following criteria was excluded: i) Symptoms of dementia (scoring < 23) at the Mini Mental State Examination (MMSE, 30), other severe medical conditions; ii) Photosensitive epilepsy; iii) History of alcohol abuse or dependency, or suicide risk; iv) Current participation in other clini-

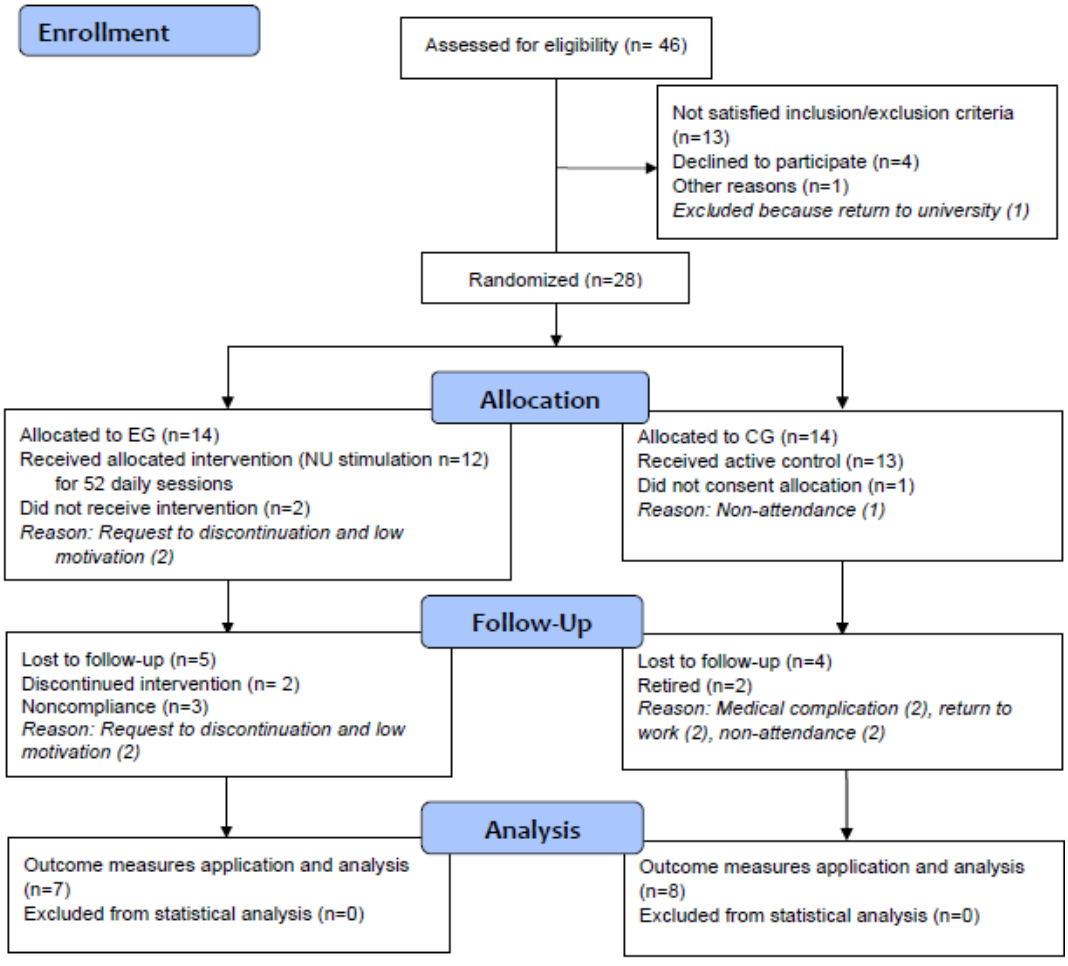

Figure 1. Flow-chart of the study

cal research. Forty-six individuals were assessed for eligibility. At screening 18 of the 46 individuals did not meet inclusion criteria. Of the 33 eligible subjects, 4 did not consent to participate and 1 was excluded. The remaining 45 individuals were randomly allocated at a 1:1 ratio to the EG or the CG.

Instruments and outcome measures

Participants were assessed at pre- and post-intervention assessments by one psychologist blind to group allocation through a combination of psychometric: i) Structured Clinical Interview for DSM-IV-R Axis II Disorders (SCID-4-RV, APA, 2013), ii) Spielberg State Trait Anxiety Inventory (STAI), iii) Hamilton Rating Scale for Depression (HAM-D), iv) Wechsler Adult Intelligence Scale Revised (WAIS-R, 31), v) Raven's Progressive Matrices (SPM, 32), and vi) MMSE. For HAM-D scoring, the severity ranges: no depression (≤7), mild (8-17), moderate (18-24), and severe depression (≥25) indicated that the cut-off to suggest remission should be equal or lower than 7. The STAI-Y is composed by two forms of twenty-four-point Likert statements: STAI-Y1 assessing state anxiety and STAI-Y2 for trait anxiety. The WAIS-R contained 11 subtests employed to derive Full Scale, Verbal (Information, Digit Span, Vocabulary, Arithmetic, Comprehension, and Similarities), and Performance (Pictures Completion, Pictures Arrangement, Block Design, Object Assembly, and Digit Symbol) IQs. These measures were administered at baseline (T1) and post-intervention (T2). The primary outcome is the differences in HAM-D and STAI-Y scores between the two times. These scores were compared between groups on week 16. The WAIS-R scores and the relationship between brainwaves changes and psychometric measures were assessed as secondary outcomes only for the EG participants.

Device and equipment

NU is described in Figure 2. EEG-patterns were acquired through NeuroSky MindWave EEG® headset. This is a low-cost, single-channel, dry EEG headset, but research examining the use of low-cost EEG devices indicated that even with a single electrode it can achieve high accuracy (32-33). Signal processing, feature extraction, and classifier calibration are performed. A time-frequency analysis of the electric signals is used that decomposed the original EEG signal in the frequency bands: Delta (0.5 - 2.75 Hz), Theta (3.5 - 6.75 Hz), Alpha 1 (7.5 - 9.25 Hz), Alpha 2 (10 - 11.75 Hz), Beta 1 (13 - 16.75 Hz), Beta 2 (18 - 29.75 Hz), Gamma 1 (31 - 39.75 Hz), and Gamma 2 (41 - 49.75 Hz). Extracted signals were continuously transferred, by a proprietary hardware-software system, as flicker stimulation through eight coloured lamps (34). Due to rhythms acquisition and processing, a delay between brain activation and the consequent corresponding flash in the range of 0.2-0.4 ms is inevitable. Nu is a passive BCI where its output is derived from automatic, spontaneous brain activity, interpreted in the given context. This activity is then used as implicit input to support an ongoing task. The user exerts no effort to explicitly or voluntarily elicit or modulate own activity. Instead, the user concentrates on the task at hand while a passive BCI system monitors her/his brain activity for informative correlates of relevant cognitive or affective states. The closed-loop system concerns the output is feedback to the system as new input. Thus, the produced output affects the later cycle. In NU, the ultimate source of input is the human user's mental state. The procedure to fulfil a closed feedback loop is to have the generated feedback cause a transformation in the user state. By influencing the mental state that is measured, the system influences its own next input. The motivation for such an implementation is to encourage and maintain a desirable psychological state induced by the play-lists.

Procedure

Intervention phase involved 55 attendances (five times a week) of 45 min. Subjects of EG seated in a comfortable chair wearing the Mindwave® headset receiving the instruction of direct their gaze towards the visual effector with eyes open. Musical excerpts are binaurally presented through Sennheiser HD 215 headphones at a comfortable hearing level. Developer and researchers are not aware of any heavy adverse consequence. The stimulation was well tolerated. To provide a stringent active control for the experimen-

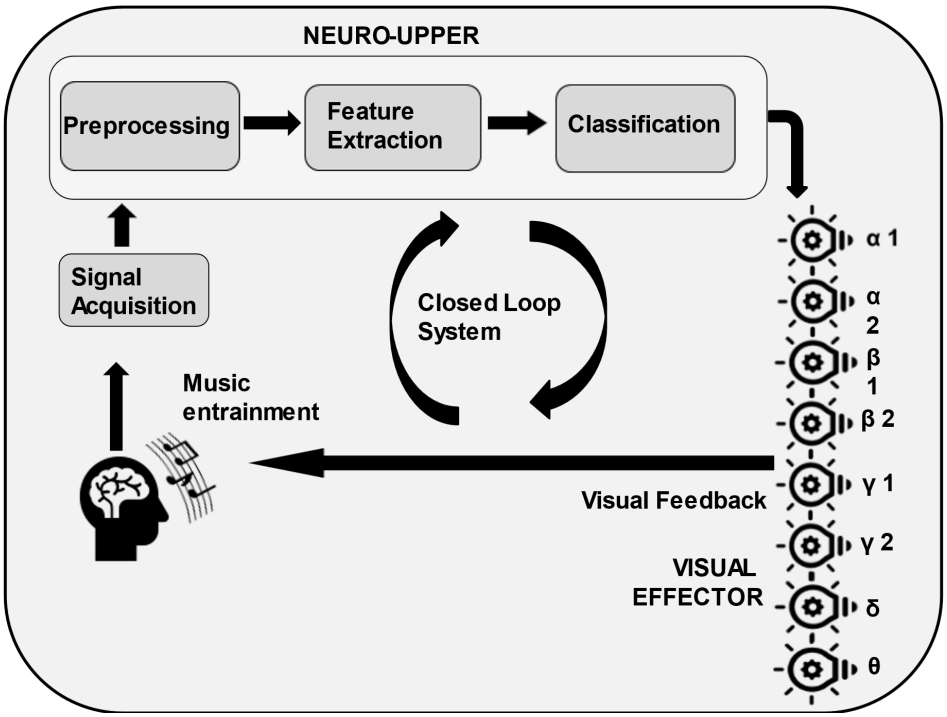

Figure 2. Principal components of NU as a close-loop BCI system

tal stimulation, CG participants were invited for individual face-to-face sessions in which they obtained psychoeducation and simple tips on how to handle their condition and watched non-interactive videos. All participants were assessed for the outcome measure at week 16.

Statistical analysis

Each EG participant ran an average of 52 sessions. For each signal, a mean value from all sessions was obtained. Then, descriptive statistic for each band was computed. It was initially conducted analysis for the first outcome comparing baseline and post-intervention scores. The Wilcoxon rank-sum test was employed to define differences between T1 and T2 ($p < .05$). According to the outcome of the normality test, Wilcoxon - Mann - Whitney (WMW) test for independent samples was calculated. Once verified the assumptions of the normal distributions and the homoscedasticity of their variances (with Shapiro-Wilks and Levine test), U tests were first applied to the mean scores of the two groups at T1 and, if no significant difference emerged, were applied to T2 scores. Due to the small sample size, these analyses were preferred rather than mixed ANOVAs. For the analysis of brainwaves, the power spectra of M seconds of data were estimated.

Results

In Table 1 all mean scores and standard deviations for groups and times are reported. All subjects did not differ for age and educational level. Wilcoxon-Mann Whitney's U tests revealed significant baseline differences for STAI Y-2 scores of EG and CG ($U=49.5$, $p=.014$). The average scores at baseline for the other assessment tools did not differ STAI Y-1 allowing the applicability of the analyses at the T2. The statistical analyses comparing EG data yielded significant differences between T1 and T2 for depressive symptoms and cognitive function (IQ). A significant decrease in the HAM-D from T1 to T2 indicated a remission of depressive symptoms ($p=.022$), and the significant comparison ($W=0$, $p=.016$) of the IQ measured with

WAIS-R showed a growth along times. The mean Verbal IQ (VIQ) significantly (W=0, p=.016) increases, as the Performance IQ (W=0, p=.016). STAI Y-1 and Y-2 scores revealed a significant increase in anxiety (W=3, p=.14 for State and W=5, p=.15 for Trait). Data analysis by Wilcoxon for the CG indicated a significant difference between T1 and T2 for STAI Y-1 score (W=36, p=.014). Moreover, STAI Y-2 scores revealed a noteworthy decrease (W=29, p=.141). At T2 between group comparisons indicated that EG exhibited a PIQ average score significantly higher (U = 3, p =0.004) than the CG.

Time-series analysis carried out on median values of spectral power for each band indicated some of them stationary, as Delta (R2=0.007) and Theta (R2=0.005), and other rhythms declining. To explore the relationships between brainwave and assessment scores, either the median differences for each band and tests differences between T1 and T2 for the EG were calculated and included in multiple regression models using a stepwise back procedure.

For each model, the independent variables were represented by the differences in those signals that, basing on the anticipated hypothesis, should affect the dependent variable: Alpha 1, Alpha 2, Beta 1, Beta 2 and Delta for clinical measures, and Gamma 1, Gamma 2 and Theta medians for psychological tests. Variability in the HAM-D scores seems to be explained by the differences in Beta 1, Beta 2 and Delta, with a model in which the probability value associated with F [3, 3] = 8.268 is at the threshold of significance (p=.058). Variations in STAI Y-1 (State Anxiety) scores revealed a correlation with the predictors "Alpha 2" and "Beta 2" (F [2, 4] = 10.07, p=.027). Finally, increases in PIQ scores appear influenced by variations of Theta (F [1, 5] = 11.76, p=.018).

Table 1. Average data and standard deviation from groups and comparisons between times

	Measures	Pre-test	Post-test	*p* value *
Experimental Group	HAM-D	19.71 (6.37)	7.71 (3.81)	.022 *
	STAY Y1	42.14 (9.85)	53 (8.74)	.14 *
	STAY Y2	40.71 (5.93)	48.14 (8.74)	.15
	RPM	45.57 (5.76)	48.14 (3.97)	.209
	IQ Total	117.85 (14.35)	143.86 (7.87)	.016 *
	IQ Verbal	104.14 (22.84)	130.57 (14.84)	.016 *
	IQ Performance	104.14 (35.68)	145.57 (7.87)	.016 *
Control group	HAM-D	14 (5.52)	11.62 (6.47)	.270
	STAY Y1	53.25 (10.92)	41.37 (13.29)	.014 *
	STAY Y2	55.12 (10.23)	51.50 (13.29)	.141
	RPM	42 (11.23)	45.25 (10.05)	.126
	IQ Total	116.12 (11.78)	120.12 (12.07)	.161
	IQ Verbal	114.37 (9.82)	118 (10.69)	.195
	IQ Performance	115.75 (15.86)	121.75 (14.02)	.079

*Wilcoxon - Mann Whitney test

Discussion

Findings of the current study indicated that the audio-visual stimulation could entrain the EEG frequencies with an impact on depressive symptoms and cognitive function. The remission of depressive symptoms evaluated with HAM-D revealed an association with the variations in Beta 1 and Beta 2, confirming the decreased high-Beta power among individuals with depression and anxiety symptoms. The rise in the state anxiety symptoms (STAI Y-1), which seems predicted by both Alpha 2 and Beta 2 variations, can be partially explained through the reduction of Alpha 2, as the prevalence of Alpha is often related with relaxation. A further finding about the relationship between brain activity and test changes was the correlation between the increase in PIQ and the variations of Theta at T2. Theta activity reflects cognitive control mechanisms for processing performance information.

Important caveats temper our conclusions. The main limitation concerned the small sample size. A second limitation is the absence of a follow-up. Other research needs to explore in what extent brain self-regulation persists along time. A third limitation concern the EEG recording collected with the Mindwave® headset that is not perfectly comparable to that of other systems. Thus, future study will be needed to expand our findings. Subsequent investigations should consider methods that allow a higher spatial resolution and reconstruction, such as high-resolution EEG with a more appropriate headset. An increase of the interactivity of the closed-loop system will be useful in the sense that it should be able to respond purposefully monitoring the effect of each response on the ongoing interaction. Therefore, an adaptive system should apply mental status assessment to obtain a measure on-

line and respond to certain states - or changes in states - with actions that influence that same mental state. Finally, future research should probe the relationship between musical structure and musical engagement to effectively observe neural entrainment.

Conclusions

The construct of entrainment as a mechanism to extract important temporal regularities from the environment has gained admiration in recent years. Despite the above-mentioned limitations, findings support the idea that a dysregulation of brainwaves may account for symptoms and affective disorders, and that they can be partially relieved by audio-visual entrainment. While some findings are inconsistent with the expected increase in Alpha band, others confirmed that Beta decreases are associated with reductions in anxiety feelings, ruminative thoughts, and obsessive/compulsive-like behaviours. Many psychological symptoms are strengthened by excess cortical activation, and after stimulation several participants reported to feel more relaxed, alert, with a greater sense of well-being. BCI have gained much interest over the last years. We believe this is because, at core, they are leaving the labs, and taking steps into the "real" world. The present study highlights the potential of NU as support for psychophysiological intervention, but further research is necessary to deeply elucidate its efficacy. This paper suggests a new methodology for brainwaves entrainment via EEG. It also presents neuroscientific evidence to bolster theories about how music captivates the mind.

Conflict of Interest: Each author declares that she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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