

Effects of Prefrontal 40 Hz-Centered EEG Band Neurofeedback on Emotional State and Cognitive Functions in Adolescents



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Abstract: *Background*: In addition to well-known cognitive impairments, there are disruptions in processing emotions in individuals with substance dependence and in those predisposed to drug abuse. Neurofeedback training-based intervention is one of the potentially efficacious non-pharmacological treatment options for substance use disorders. Several neurofeedback protocols which reported success in treating addictive behaviors have been employed. However, there are no studies on the use of neurofeedback in occasional drug users who have a drug use history have not yet developed substance use disorder or substance dependence.

ARTICLEHISTORY

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DOI: 10.2174/22106766066661610251156 16 *Method*: We tested a protocol that may be useful to prevent drug abuse through self-regulation training aimed at enhancing EEG measures of positive emotional states. One of the aims of this pilot case series study was to determine the dynamics of self-reported perceived positive emotional state rating before, during and after twelve 25-minute long neurofeedback training course in two groups of subjects. One group of subjects (N=6) had a documented drug use history, most of them referred from the local metro operated mental health community center for adolescents; and the other group were drug-naïve subjects (N=5), recruited mostly from undergraduate students. Our hypothesis was that learning to increase the prefrontal 40 Hz-centered EEG band (a gamma frequency) power over 12 training sessions is possible and will be accompanied by increased ratings of positive affect. We trained subjects to increase a 40 Hz gamma measure (*i.e.*, a "clarified 40 Hz-centered gamma" index termed "Neureka!") at a prefrontal site above FPz, in the middle of the forehead, referenced to the left ear.

Results and Discussion: Neurofeedback training was accompanied by a highly significant linear increase of the "40 Hz gamma" measure and a less significant change in the relative power of the gamma activity in 35-45 Hz range. Individual reports of self-recorded happiness scores assessed during each neurofeedback session using the Continuous Response Digital Interface (CRDI) showed a linear increase both during and across training sessions. Both post-training evaluations and 3.9 months follow-ups showed increased happiness ratings in both groups of subjects in this study. Neurofeedback training also resulted in better performance on the MicroCog and IVA+Plus neurocognitive tests.

Conclusion: This proposed neurofeedback training method is promising for increasing both present happiness and future health. It needs further research and clinical trials to be validated as a method of positive emotion self-regulation in adolescents, particularly those predisposed towards drug abuse.

Keywords: Adolescents, drug abuse, EEG, emotion, neurofeedback.

INTRODUCTION

The high prevalence of illicit drug, prescription medication and alcohol use, and the incidence of

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substance use disorder (SUD) in adolescence has become a major public health concern in the US (SAMHSA, 2014). It is clear that we need new approaches in order to understand, prevent and treat this serious problem. Research reviews from the National Institute on Drug Abuse (Volkow, Fowler, & Wang, 2003, 2004; Volkow & Koob, 2015; Volkow & Morales, 2015) have pointed out

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the importance of emotional disturbances in drug abuse, and actually come full circle back to their earlier idea of "hypophoria" (see Psychopathic State Inventory (PSI) by Haertzen, Martin, Ross, & Neidert, 1980) In the interim, dysfunctions of dopamine system, related to the hedonic misadjustment and globally lower sensitivity to positive affect were hypothesized to be an inherited trait predisposing afflicted individuals to drugseeking and drug-taking behaviors that may result ultimately in drug dependence (Blum et al., 2000). These ideas were incorporated by Volkow et al. (2004) into their view that the etiology of substance abuse problems is related to lower dopamine levels in certain brain networks at critical points in the drug seeking cycle.

Stating this in a clear but oversimplified fashion, drug abusers who have an insufficient blood drug level become unhappy and experience other negative feelings, in association with lower dopamine levels in particular brain centers, and crave their drug of choice to relieve these imbalances. If they can be taught to increase happiness and enhance their positive feelings by other means, and thereby modify the functional level of their dopaminergic centers and change the "setpoint" (ongoing average level) of their happiness system to a higher level, they may be able to resist the desire to use the drug for the same purpose. This will improve the probabilities of preventing both initial drug use and relapse.

Neurofeedback is a type of operant conditioning in which an individual modifies the frequency, amplitude, or other characteristic of his or her own EEG. It is especially effective in ADHD treatment (Arns, Heinrich, & Strehl, 2014; Gevensleben et al., 2009; Sherlin, Arns, Lubar, & Sokhadze, 2010), where significant positive changes in clinical symptoms and EEG profiles have been frequently reported. Neurofeedback training-based neurotherapy is one of the potentially efficacious non-pharmacological treatment options for substance use disorders (Sokhadze, Cannon, & Trudeau, 2008; Sokhadze, Trudeau, & Cannon, 2013; Sokhadze, Trudeau, Cannon, Bodenhamer-Davis, & Davis, 2016; Trudeau, Sokhadze, & Cannon, 2008).

Neurofeedback is promising as a treatment modality for adolescents, especially those with substance abuse co-occurring with attention deficit, disruptive behaviors or emotional problems (Trudeau, 2005). There is no literature on the use of neurofeedback in adolescent drug abusing population. There are no studies on the use of neurofeedback in adolescents and young adults with occasional drug use when individuals have drug use history but have not yet developed substance use disorder or substance dependence. A number of neurofeedback protocols have been reported to be successful in treating a variety of addictive behaviors (Peniston & Kulkosky, 1989,1991; Scott, Kaiser, Othmer, & Sideroff, 2005). Neurofeedback techniques for SUD may be of special interest for adolescent medicine because of the high comorbidity of SUD and attention problems and emotional disturbances in adolescents (Trudeau, 2005). By providing low-risk and medication-free therapy for SUD, neurofeedback becomes another treatment to complement options of interventions open to practitioners reluctant to prescribe controlled substances (e.g., stimulants, pain relievers or benzodiazepines) to adolescents at risk for or with SUD (Sokhadze, Stewart, Tasman, Daniels, & Trudeau, 2011).

One of the most promising directions of neurofeedback research is development of protocols that might be used to prevent drug abuse or relapse through training aimed at the enhancement of EEG measures of positive emotional states. Previous studies showed an association of clarified prefrontal gamma (~40 Hz) oscillations with positive emotional states (Cowan & Rubik, 2009; Cowan & Sokhadze, 2011ab; Rubik, 2011), particularly happiness. There was another pilot study (Clemans, El-Baz, Cowan, & Sokhadze, 2013) which showed that EEG segments as short as six seconds can significantly discriminate various positive feelings from baseline, using the clarified 40 Hz rhythm analysis employed in this study.

Furthermore, emotional states such as happiness may have important effect on general measures of present and future well-being and health (Diener & Chan, 2011). Based on surveys performed by the Australian government on 9,981 participants, those who rated themselves as happier in 2001 were 50% more likely to report themselves as healthier in 2004. They were also 53% less likely to have long-term, limiting health conditions in 2004. They showed significantly better ratings on the Physical Health Summary Scale (Siahpush, Spittal, & Singh, 2008). To create a potential relationship, we employed the same happiness measure in this study.

The rationale of this suggested approach of neurofeedback intervention in adolescents fits with the model of addiction and strategies of intervention proposed by Volkow and colleagues (2003, 2004, 2014, 2015). The authors suggested that the treatment of drug dependence should focus on decreasing the reward value of drugs while increasing saliency and motivational values for natural rewards. The approach considers strategies designed to increase frontal executive functions as a potential moderators of self-regulation skills and ability to over-ride habitual drug seeking and drug-taking behaviors.

It has been shown that emotional abnormalities are typical for addicts at any age (Fukunishi, 1996). Alexithymia, (i.e., a state of deficiency in understanding, processing, or describing emotions), as well as dysphoria, (i.e., a state of inability to experience positive emotions), mood lability, dysthymia, hypophoria, and anhedonia (i.e., decreased emotional reactivity to natural positive reinforcers) (Gerra et al., 2003) are highly prevalent among substance abusers. On the other hand, the same emotional deficits are reported also in those at risk for development of substance use disorders (Hestler, Dixon, & Garavan, 2006; Ouimette, Finney, & Moos, 1999). There is emerging evidence that abnormalities in emotional processes may have an important role in the predisposition to drug abuse and in the development of addiction. Emotional alterations, both premorbid and those resulting from acute or chronic drug use, may compromise the effectiveness of treatment approaches in addiction. This supports the idea that efforts aimed to prevent or treat the compulsive drug-taking behavior should be more focused on regulation of addicts' emotions and provide ways of learning to adapt during negative emotional states. Training emotional self-regulation at the early stages of drug abuse seems very promising. Teaching youth how they can train emotional selfregulation seems to be a logical approach. According to the "allostasis" theory (Koob & Le Moal, 2001; Koob, 1999) sensitization to drugs and counter-adaptation are hypothesized to contribute to dysregulation of hedonic homeostasis and to observed brain reward system abnormalities in already addicted individuals. However, in some cases hedonic dysfunctions and globally lower sensitivity to positive affect are considered as premorbid traits predisposing individuals to experimentation with drugs that may end up as drug dependence (Blum et al., 2000). Our study targets a population that might fit in this category, in particular, occasional drug users (i.e., adolescents with a documented record of drug use). This review leads to the suggestion that the strategy of intervention in the field of addiction, and specifically in adolescent addiction, should incorporate techniques aimed to re-educate patients to control and self-regulate their emotional and motivational states, and train to re-learn induction of positive affect in an attempt to try to re-establish the normal biological, cognitive, behavioral and hedonic homeostasis distorted by drug abuse.

One of the aims of this pilot study was to determine the dynamics of self-reported perceived positive emotional state ratings before, during and after twelve weekly 25-minute long neurofeedback training course. Another aim was to investigate ability of trainees to learn self-regulation of 40 Hz centered gamma band power in 12 sessions of neurofeedback (NFB). A further aim was to evaluate the effects of prefrontal gamma band neurofeedback on cognitive functions, attention and emotional state using cognitive tests and evaluations. Our hypothesis was that a prefrontal high frequency power increase over 12 neurofeedback training sessions can be learned and will be accompanied by increased subjective rating scores of positive emotional states. Our prediction was that successful completers of the neurofeedback training in the groups of adolescents and young adults both with and without drug/alcohol abuse history will improve subsequent performance on cognitive tests and will increase positive affect.

METHOD

Subjects

One group of subjects had documented drug use history (ADU group, N=6), most of them referred from Louisville Adolescent Network for Substance Abuse Treatment (LANSAT) now renamed to Adolescent Intensive Outpatient Program (IOP) a community mental health system of care for adolescents with substance use/abuse issues); and one subject was referred from university-based Psychiatry Physician group by an addiction specialist serving students. Other participants were a group of drug-naïve subjects (CNT group, N=6, recruited mostly from local undergraduate students and out-of-city undergraduate summer research students). Data from one subject from the CNT group was excluded from the analysis because participant was diagnosed with ADHD and started taking prescribed stimulant medication. Mean age across all subjects was 17.2 ± 2.49 years, while in ADU group it was 15.5 ± 1.87 years. All participants were screened for history of mental and physical disorders to rule out those with history of neurological of psychiatric disorders using the Global Appraisal of Individual Needs (GAIN) (Dennis, White, Titus, & Unsicker, 2006), a screening technique adopted at LANSAT (IOP). The GAIN is a semi-structured bio-psychosocial interview comprising more than 100 scales and indices in 11 domains, and is normed and validated on adults and adolescents. The protocol was approved by the Institutional Review Board (IRB) at the University of Louisville. All required IRB-approved consent and assent forms were signed by the participants and when appropriate by their parents/guardians.

Neurofeedback Training Protocol

The neurofeedback procedure was based on a Peak customized BrainHappiness Training [PBHT] design of the Peak Achievement Trainer (PAT; Cowan, 2015). During neurofeedback training, patients were instructed to try to increase the clarified gamma activity centered around 40 Hz ("clarified 40 Hz-centered gamma" index; or "Neureka!" in the PBHT's terminology, hereafter also referred to as "40 Hz-centered gamma index" or "40 Hz gamma"). In our prior studies on different patient populations (ADHD, autism) and controls, this "40 Hz-centered gamma" index showed a positive correlation with the relative power of 40 Hz gamma (in 35-45 Hz range). The size of a pleasant video was controlled by the 40 Hz centered gamma index-it increased as the index did. Additional audio feedback was provided when the "40 Hz-centered gamma" index was out of threshold ranges, too high or low. At the same time they were instructed to try to keep over the threshold level the so called "Focus" index in PBHT's terminology, although this index was not designated as a target neurofeedback measure. The latter is also referred to as " Inhibit All" protocol and targets decrease of high amplitude slow waves (delta, theta, etc.) and encourages increase of desynchronized low amplitude high frequency bands (*e.g.*, beta). To keep the subjects from being distracted from the task, they were instructed to try to keep the "Focus" index over its threshold, although this index was not used as a neurofeedback goal. The "Focus" index threshold was deliberately set low to avoid training this measure, but when the subject's "Focus" level approached the threshold, the picture became progressively dimmer, and the video stopped when the Focus level went below the threshold. The screen also provided the subject with analog representations of indices and showed the raw EEG signal from the recording site, along with the percentage over threshold and other training success information.

Twelve sessions of NFB training according to this Peak BrainHappiness PAT protocol were conducted during the training course on weekly basis. If a subject missed a session, she/he had to have extra session the following week to make up. The active NFB training session was 25 min. long and used auditory and video feedback (DVD feedback with an emotionally positive documentary film, e.g., BBC's "Planet Earth", "Life", and National Geographic DVD series, etc.). All EEG signals and training parameters were measured using three electrodes, one active electrode at the prefrontal EEG (FPz) site, the second being a reference on the left ear, and a third sensor serving as ground and located between the other two electrodes. All of the subjects in the study were requested to complete a 25 min recording per session and a total of 12 weekly neurofeedback sessions, in order to train to increase the " clarified 40 Hz-centered gamma" index using the "Peak BrainHappiness" PBHT protocol. More than 90% of the sessions met the requirement of a 20-minute minimum usable EEG data recording. Eye blink and EMG artifacts removal was implemented using the specific BioExplorer application that is described in the operating manual of the NFB device.

The EEG Signal Processing

The EEG signal collected and recorded by Bio-Explorer applications during NFB treatments were exported and further analyzed by a series of customized codes using Matlab software (MathWorks Inc, Massachusetts). A BioReview report was used to export the raw EEG and the desired frequency band (*i.e.*, gamma in 35–45 Hz window) and the clarified 40 Hz gamma index. For the relative power calculation, it was necessary first to get the total power of the band from 2 to 45 Hz using a band-pass filter application integration of wavelet transformation and a Harris window configuration (Hillard, El-Baz, Sears, Tasman, & Sokhadze, 2013; Wang, Li, Sears, Casanova, Tasman, & Sokhadze, 2016).

Perceived Subjective Happiness Rating

Individual reports of self-perceived happiness scores were assessed during each session using the Continuous Response Digital Interface (CRDI) dial. During "clarified 40 Hz-centered gamma" indices neurofeedback training procedure, the CRDI-based perceived happiness ratings were recorded using a 0-256 scale. The CRDI device was developed to measure subjects' continuous or discrete nonverbal responses. It consists of a dial that can be controlled by an individual and may be turned as the individual's perception of something is assessed. The dial can be moved to any point and has been used to assess a range of responses, including emotional responses to music (Geringer, Madsen, & Gregory, 2004; Gregory, 1995; Madsen, 1997a, 1997b). In our modification, the CRDI had a scale showing visual representations of the happiness signs using a 0 to 128 range rating. Instructions to subjects did not include any information about an expectation of increased happiness or linking their happiness rating with neurofeedback training targets.

Statistical Analysis

The primary statistical analyses in the study mainly were linear regression estimation and paired sample t-test methods. Group differences we assessed using Group (ADU, CNT) factor. Each EEG, neurofeedback (NFB) and CRDI dependent variable over 12 sessions of neurofeedback course was analyzed using linear regression analyses and the mean values of dependent (EEG, NFB and CRDI) variables at the first and last session of the NFB course. The pre- and post-NFB subjective measures using the Happiness and Life Satisfaction questionnaires (Siahpush et al., 2008) were compared with the paired sample t-test method. The MicroCog (PsychCorp, Harcourt Assessment Inc., TX, reviewed in Elwood, 2001) neurocognitive tests and the Iva+Plus (BrainTrain Inc., VA; reviewed in Arble, Kuentzel, & Barnett, 2014) selective attention outcomes were analyzed statistically in a similar manner using paired sample t-tests. EEG and CRDI variables and the "clarified 40 Hz-centered gamma" NFB training index were calculated as well on per minute basis during each training session. Each dependent EEG variable went through the normality distribution analysis using *t*-test to ensure appropriateness for the test, and 95% confidence intervals (95% CI) were included in outcomes when appropriate. Pearson correlation analysis was used for individual EEG measures, neurofeedback training indices, and emotional measures (*e.g.*, CRDI-based happiness rating).

RESULTS

CRDI-based Self-reported Happiness Measure

Analysis of minute-by-minute changes during individual sessions of NFB across the course of training showed highly significant linear increase $(R=0.79, R^2=0.64, t=65.17, df=24, p<0.001, Fig.$ 1a) without notable group differences, indicating a improvement during the session. powerful Changes of happiness rating from the first 2 minutes to the last 2 minutes of the sessions in all subjects were also very significant (19.4 \pm 40.5, t=4.30, p<0.001), but without showing any group differences. Regression analysis showed statistically significant linear increase of CRDI-based perceived happiness rating across 12 NFB sessions (R=0.60, R²=0.36, t=2.37, df=11, p=0.039, Fig. **1b**). Changes of self-reported happiness ratings from the first to the last session of NFB were also significant (mean 23.6 ± 25.5 [SD –standard deviation] units on 0-256 scale, t=3.06, df=10, p=0.012, 95%CI from 6.4 to 40.8). Between group differences were not significant $(1.9 \pm 16.3 \text{ in})$ CNT vs. 36.6 ± 30.2 in ADU, t=1.67 p=0.13 n.s.), although adolescents with drug abuse history tended to show a more pronounced increase.

Neurofeedback Measures

During neurofeedback sessions "clarified 40 Hz-centered gamma" linear changes on minute-byminute basis were not significant (p=0.15), but across 12 sessions this NFB index showed a highly significant linear increase (R=0.89, R²=0.82, p<0.001, Fig. 2). Changes of the index from the first to last session were significant (t=3.06, p=0.012). The measure of "40 Hz gamma" showed positive correlation with the perceived happiness



Fig. (1). (a) Continuous Response Digital Interface (CRDI) based subjective ratings of perceived happiness during 25 min of neurofeedback training across 12 sessions in 11 subjects. Regression analysis shows statistically significant linear increase of subjective happiness rating scores (R^2 =0.64, t=65.17, p<0.001). (b) Regression analysis showed statistically significant linear increase of CRDI-based perceived happiness rating across 12 neurofeedback sessions (R^2 =0.36, t=2.37, p=0.039). The Y-axis shows values of CRDI divided by 2 for better visibility.



Neuroreedback session

Fig. (2). Linear regression of the "clarified 40 Hz gamma" index across 12 sessions of weekly neurofeedback training in 11 adolescents. Increase of this measure was highly significant ($R^2=0.82$, p<0.001). Y-axis shows conventional units (c.u.) of the Peak BrainHappiness Trainer PAT device for the "Neureka!" index (*i.e.*, 40 Hz-centered gamma measure).

rating scores across 12 sessions of NFB training (r=0.64, p=0.024, Fig. 3). In all the above changes no group differences were detected.

Gamma Band Changes During Training

The relative power of gamma band (35-45 Hz) showed a statistically significant linear increase

over 12 sessions of training course (R=0.60, R^2 =0.36, t=2.37, p=0.039, Fig. 4), not nearly as strong as the clarified 40 Hz gamma measure. However, changes from the first to the last session did not reach significance (p=0.19), and minute to minute changes were unclear (p =0.15). The relative power of gamma band did not show any group differences across NFB sessions.



Fig. (3). Covariation of the "clarified 40 Hz gamma" index of neurofeedback protocol and CRDI-based subjective reports of perceived happiness ratings (means divided by 2) in 12 sessions of neurofeedback training course. Correlation between the variables was statistically significant (r=0.64, p=0.024).



Fig. (4). Regression analysis shows statistically significant linear increase of relative power of gamma band in 35-45 Hz range in 12 sessions of neurofeedback training in 11 subjects ($R^2=0.36$, p=0.039). The Y-axis depicts relative power of gamma (35-45 Hz within 2-45 Hz spectrum, units are in 0 to 1 range, *e.g.*, 0.025 corresponds to 2.5%).

MicroCog Measures

The most significant MicroCog outcomes are also depicted in (Fig. 5). In particular, General Cognitive Functioning, combining processing speed and accuracy measurements for all the tests it offers showed a very significant (p <0.001) 7% increase. General Cognitive Processing was increased by 6% (p<0.05). The improvements were all due to better Information Processing Accuracy (13% increase, p<0.05) rather than Information Processing Speed (1.5% change). More specifically, the largest increase was in Memory (13%), significant at the p < 0.05 level. More specifically, changes in the ADU group were significant for General Cognitive Functioning (8.46%, t=4.40, p=0.007), General Cognitive Processing (8.52%, t=5.21, p=0.003) and reaction time (-6.37 %, t=6.19, p=0.002). No group differences were significant.

Iva+ Plus Outcomes

There were significant improvements of IVA+ Plus (Arble, Kuentzel, & Barnett, 2014) selective audio-visual attention scores for all 11 subjects.



Fig. (5). The most significant MicroCog outcomes: General Cognitive Functioning (GSF) showed a very significant (p < 0.01) increase. General Cognitive Processing (GCP) also increased (p < 0.05). The improvements were due to better Information Processing Accuracy (IPS, p < 0.05). The largest increase was in Memory (p < 0.05) and Attention (p < 0.05) scores.

Most notable were improvements in Attention Quotient (t=3.46, p=0.006), Sustained Auditory Attention Quotient (t=3.19, p=0.01), Sustained Visual Attention Quotient (t=3.13, p=0.011) and Auditory Reaction Time (t=-2.41, p=0.041). The group of adolescents with drug abuse history did better on visual tasks, in particular, increasing Visual Attention Quotient (t=2.56, p=0.05), Sustained Visual Attention Quotient (t=3.14, p=0.026) and decreased Visual Reaction Time (t=-2.85, p=0.036).

Happiness Scores

This question from the Australian study of Siahpush *et al.* 2008 (on 1 to 6 scale) did show a significant increase post-neurofeedback (t=2.39, p=0.038), and remained different from initial level at the follow up stage (t=2.67, p=0.024, Fig. 6). The mean happiness rating for the total group increased by 32% (p<0.05), which was somewhat limited by ceiling effects for some subjects. Group differences were not statistically significant. Of particular interest, the post-treatment and follow



Fig. (6). This question from the Australian (Siahpush *et al.*, 2008) study (on 1 to 6 scale) did show a significant increase post-neurofeedback (t=2.39, p=0.038), and remained different from initial level at the approximately 4 month follow up stage (t=2.67, p=0.024).

up assessment happiness evaluation on 0-100% scale both showed a significant increase in the ADU group (t=2.82, p=0.030). Life Satisfaction rating scores did not show any post-neurofeedback improvements.

DISCUSSION

One of the most important findings of this study is the demonstration that adolescents are able to increase the "clarified 40 Hz gamma" index during 12 session-long prefrontal neurofeedback course and that this increase was accompanied by a gradual increase of their perceived happiness rating, and increased relative power of the 40 Hz-centered gamma band. The study showed an increase of the reported happiness rating using the Australian Department of Labour questionnaire (Siahpush *et al.*, 2008). The training also resulted in improved performance on the MicroCog test battery and on IVA+Plus audio-visual selective attention tests.

Cowan and Albers (2009) reported finding that a single channel prefrontal EEG measurement responds to a variety of positive feelings such as happiness, love, joy, and satisfaction. The finding was later supported by a study by Rubik (Cowan & Rubik, 2009; Rubik, 2011) and our studies. In prior studies we have shown that this method of quantitative processing of the 40 Hz rhythm from a mid-forehead site (between FPz and AFz) provides significantly increased amplitude output when the subject is asked to feel a number of positive emotions (Cowan & Sokhadze, 2010, 2011a,b; Clemans et al., 2013). As little as six seconds of the EEG during and after the spoken stimulus emotion produced significantly higher output of this 40 Hz index.

It is possible to propose that it is a measure which captures some of the 40 Hz "event binding rhythm" discovered by Llinas, Ribary, Contreras, & Pedroarena (1998). This specific rhythm originates in the central nuclei of the thalamus and scans the cortex from front to back 40 times per second, returning modified information to the center of the thalamus, where it is integrated into an interpretation of the events that are taking place. It plays an important role in awareness, new learning, and memory. We have repeatedly observed during pilot tests that efforts to store information in memory or recall it from either short-term or remote memory increase the output of this index. The results of this study suggest that the clarified 40 Hz-centered EEG activity is a measurement of processes that enhance learning, cognition and provide positive feelings as a reward for learning. These were all improved by neurofeedback training used in the study.

The finding that attention measures of the IVA+Plus test were so strongly improved in this study is surprising but consistent with our other study where prefrontal neurofeedback protocol was used in the ADHD population (Hillard et al., 2013). Prior studies showed that the EEG gamma band (40 Hz) is enhanced in a whole range of cognitive processes, according to studies which used simple bandpass measurements. Application of the 40 Hz EEG band for neurofeedback has a long history, however, early studies were targeting only training of focused attention (Bird, Newton, Sheer, &Ford, 1978ab; Ford, Bird, Newton, & Sheer, 1980). These measurements probably confounded at least two different sources of the 35-45 Hz rhythms, one of which comes from the relay nuclei in the peripheral thalamus and may be similar to beta rhythms, reflecting arousal and attention.

The "clarified 40 Hz gamma" index used in the study was designed to eliminate most of the peripheral rhythms and contamination by EMG. It is interesting to note that this index (*i.e.*, "Neureka!" measure in the PBHT terminology) showed more significant improvement than the measure of the relative power of 35-45 Hz range gamma band. This may be due to the fact that it was the target of training here. However, it is possible to suggest that it is a measure that better reflects positive feelings and memory than the relative power of the 35-45 Hz band as the higher relationship with CRDI changes indicates.

The results of this study suggest that the clarified 40 Hz-centered EEG activity is also a measurement of processes that provide positive feelings as a reward for learning. Measures of memory and learning as well as happiness were all improved by neurofeedback training used in the study. fMRI studies have shown that midline prefrontal cortex activity, under the prefrontal site used in our study, is enhanced by positive feelings (Knutson, Fong, Bennett, Adams & Hommer, 2003; Knutson, Taylor, Kaufman, Peterson, & Glover, 2005; Knutson *et al.*, 2003) and that this area has the highest density of dopaminergic innervation of any cortical area (Gaspar, Berger, Febvret, Vigny, & Henry, 1989) and is directly connected to the midbrain ventral tegmental area, a well known dopaminergic reward center. Knutson et al. (2003) proposed that the medial prefrontal cortex is activated by positive rewards. The ability to enhance positive feelings at this prefrontal site with "clarified 40 Hz gamma" neurofeedback suggests that 40 Hz activation may enhance dopaminergic activity there, and that this may increase the rewarding positive feelings in that location as well as modulate the activity of the dopaminergic reward system at other sites. The 40 Hz-centered gamma rhythm, which characteristically occurs in short spindles, and produces short bursts of positive feelings as a reward. We, along with Cowan and Albers (2009), hypothesize that the 40 Hz-centered gamma rhythm, which characteristically occurs in short spindles, interacts with this dopaminergic activity, and produces short bursts of positive feelings as a reward. Even more intriguing is the well established finding that dopamine release enhances memory consolidation (Arias-Carrion & Poppel, 2007), the conversion of short-term memories to long-term ones. This may form the basis of an explanation of the memory improvements we observed in this study, some of which were very significant for just twelve sessions of training. Although the improvements in attention on the IVA+ may be influenced by improved memory of how to perform the task from pre- to post training, we hesitate to attribute all of this improvement to memory and dopamine. There may be other improvements in the functioning of the 40 Hz " Event Binding Rhythm" (Llinas Ribary, Contreras, & Pedroarena, 1998) system due to this neurofeedback which should be investigated.

The finding that a happiness measure was enhanced for at least 3.9 months without decreasing may be quite important. There are 157 studies (out of 160), cited in a meta-analysis by Diener and Chan (2011) which indicate that enhanced happiness leads to improved future health. One of the most thorough studies was done by the Department of Labour in Australia, (Siahpush *et al.*, 2008). They looked at two representative population-based samples of 9981 people surveyed in 2001 and 2004. They examined the relationship between happiness in 2001 and their health in 2004. Their survey data from 2004 found that the odds of reporting good health were 50% better for those who were happy most or all of the time in

2001. Similarly, the odds of having no limiting, long term health conditions were 53% better. We used their happiness questionnaire in an attempt to support the implication that "40 Hz gamma" index training may also enhance future health. The possibility that this neurofeedback training could actually decrease the incidence of future illness and health care costs makes this approach well worth exploring further.

Self-regulation of brain activity has more potential in adolescence due to the higher level of neuroplasticity of neural systems at this age as compared to adult population. Although operant conditioning theory posits that changes in EEG patterns can be learned using instrumental conditioning paradigm, how changes in specific EEG frequencies mediate the effects of neurofeedback on patient outcomes in substance abuse is not sufficiently well explored. Pre- to post-treatment changes in theta (4-7 Hz), and high frequency EEG (beta, 13-30 Hz, gamma, 30-45 Hz) are considered to positively affect cortical inhibition function, general arousal and alertness level. This mediates the positive effects of proposed neurofeedback protocol not only on emotional states but probably also on attention deficit and impulsivity symptoms, including drug-seeking behaviors.

The results of our study suggest clinical research directions for the development and implementation of substance use treatment and prevention approaches in adolescence that specifically target the development and strengthening of executive functions and improvements in positive emotional states using operant conditioning of specific EEG frequencies at the prefrontal site. Furthermore, pre-, post-treatment and follow-up assessments using clinical, behavioral, and specific executive and emotional functioning tests provide insight on possible mediators and moderators of the intervention outcome. Our study outcomes suggest the usefulness of providing adolescents with the opportunity to practice skills related to emotional state self-control through EEG training. These skills may help prevent drug seeking and other aberrant behaviors. Few, if any, substance abuse interventions explicitly intend to promote the development of emotional self-regulation abilities using specific training based on real-time EEG analysis. The neurofeedback based intervention used in our study promotes skills such as conscious strategies for emotional self-control, attention and concentration ability, that may ultimately aid in the development of adolescents' neurocognitive and neuroemotional capabilities.

Current theoretical models suggest that a core deficit typical for drug abuse in youth might be sought in the disruption of executive functions, and in particular a behavioral inhibition deficit. Converging evidence supports the view that specifically the vulnerability to impulsive behavior is related to atypical development of cognitive control along fronto-striatal networks. The resulting deficit is presented by a combination of hypofunctional "top-down" executive processes (e.g., inhibition) regulated by the frontal lobe, and hypofunctional "bottom-up" regulation (e.g., activation) regulated by the brainstem and thalamo-cortical pathways (Barkley, 1997; Miller & Cohen, 2001). These self-regulation deficits occur in adolescent individuals predisposed to SUD. In addition to attentional and cognitive impairment, there are disruptions in processing emotion and mood abnormalities in individuals with substance abuse history, but little is known about the neural basis of these affective impairments. The ability to selfregulate specific EEG patterns and the underlying brain systems that produce them by using neurofeedback training could be considered as a promising strategy to overcome these cognitive and emotional impairments in adolescents with drug abuse history.

Neurofeedback for high drug abuse risk adolescent individuals with behavioral and emotional problems holds promise as an intervention modality for adolescents, and is attractive as a medication-free neurophysiological treatment that is a potentially powerful prevention technique for substance use disorders in youth.

Several limitations of the study should be mentioned. Even though there were two groups of adolescents and it was initially planned as an exploratory controlled study, the subjects were not matched by gender, socio-economic status and other parameters that could affect outcome. The sample size was small for between group differences detection. The study should be considered as a case series pilot research focusing on feasibility, tolerability of procedure of simultaneous training and subjective state reporting with the CRDI and other aspects important as preliminary steps for a larger scale controlled trial. Our analysis did not

pha/gamma ratios), though this might contribute to better understanding of functional significance of 40 Hz-centered gamma activity. Our future methodology developments will include adding EMG for more accurate identification of potential muscle activity that may contaminate gamma recording.

Nevertheless, the pilot study is an important step in combining neurofeedback training with concurrent subjective reports of perceived emotional state in adolescents. This proposed neurofeedback training method is promising for increasing both present happiness and future health. It needs further research and clinical trials to be validated as a method of positive emotion selfregulation in adolescents, particularly those predisposed towards drug abuse. The potential for improving all of these abilities with one low-cost intervention makes further research and clinical use particularly worthwhile.

LIST OF ABBREVIATIONS

ADU	=	Group of adolescents with drug use history
ADHD	=	Attention deficit hyperactivity disorder
BBC	=	BRITISH Broadcasting Company
BDI	=	Beck Depression Inventory
CNT	=	Group of drug-naïve participants
CRDI	=	Continuous Response Digital In- terface
EEG	=	Electroencephalogram
EMG	=	Electromyogram
GCF	=	General Cognitive Functioning
GCP	=	General Cognitive Processing
GAIN	=	Global Appraisal of Individual Needs
IOP	=	Adolescent Intensive Outpatient Program
IPA	=	Information Processing Accuracy
IPS	=	Information Processing Speed

LANSAT	=	Louisville Adolescent Network for Substance Abuse Treatment
NFB	=	Neurofeedback
PAT	=	Peak Achievement Training
PBHT	=	Peak Brain Happiness Training
PSI	=	Psychopathic State Inventory
SAMHSA	=	Substance Abuse and Mental Health Services Administration
SD	=	Standard deviation
SUD	=	Substance use disorder

CONTRIBUTION OF AUTHORS

Estate Sokhadze was responsible for study design, developments of neurofeedback and CRDI applications, physiological data analysis, statistical analysis and interpretation of data. Robert Daniels was responsible to participants recruitment, their evaluation using GAIN and participants records, interpretation of neurocognitive outcomes and he contributed to writing manuscript, specifically parts related to adolescents drug abuse.

CONFLICT OF INTEREST

The authors declare that this article content has no conflict of interest of any kind.

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