Journal of Health Sciences. 2013; 3 (10): 325-336
The journal has had 4 points in Ministry of Science and Higher Education of Poland parametric evaluation. Part B item 683.



Conflict of interest: None declared. Received: 15.07.2013. Revised: 12.11.2013. Accepted: 25.11.2013.

# COMBINED PSYCHO-PHYSICAL NEUROFEEDBACK THERAPY IN THE STIMULANT ADDICTION TREATMENT: CLINICAL-PSYCHOLOGICAL AND EEG/FMRI STUDY

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## Abstract

Stimulant usage progressively replaces opiate and cannabis addiction and become substance dependence problem of today. Treatment of stimulant users is traditionally the same as for the opiate addiction. Asthenia, dysphoria and negativism are common causes for psychological dependence. Tranquilizers, antipsychotics, sedatives can quickly help to cope with the negative behavioral disorders that accompany drug usage, but reduced psycho-physical and bio-social activity are common side effects of their use. Thus development of the new replacement therapy methods for stimulant addiction is urgent task for today's medicine. We propose neurofeedback audiovisual stimulation (AVS) in combination with hypnotic suggestion as a new approach for stimulant addiction treatment. The group of patients was treated with AVS therapy in combination with hypnotic suggestion, which was used as the replacement therapy at the abstinence period. Psychological testing, EEG and fMRI were used for the evaluation of the AVS effects. Psychological tests showed that AVS combined with hypno-suggestive therapy helped to reduce negative psychotic symptoms of the drug withdrawal syndrome. EEG effect of the AVS appeared in predominant delta rhythm displacement by the alpha rhythm after the treatment. fMRI exams showed considerable increase of the volumes of activation after the AVS and almost complete

extinction of the deactivation, which is normally present at the time of task execution. The last could be also considered as a marker for prolonged effect of brain stimulation by the AVS therapy. Thus AVS combined with hypno-suggestive therapy is a promising method for the rehabilitation of patients, which are addicted to stimulants.

**Keywords**: drug addiction, stimulants, neurofeedback therapy, audio-visual stimulation, psychotherapy.

**Introduction**

Nowadays stimulant usage progressively replaces opiate and cannabis addiction and become substance dependence problem of today. Psychiatric and physical disorders which are typical for stimulant addicts (SA) include violent behavior, psychosis, risk-taking, unprotected sex, multiple sex partners, and consequently HIV transmission [Ersche, 2013; Rastegar, 2013]. Usually SA patients have no appropriate medical care, because of police control of the outpatient department for drug addicts, and subsequent driving restriction etc. SA patients' treatment today traditionally is the same as for the opiate addiction. In Ukraine typical scheme for drug addiction (DA) treatment include 12-steps program, also religious centers visits for psychological support, but they are designed for opiate addicts. Psychological addiction to stimulants arises much earlier than physical. Asthenia, dysphoria and negativism are common causes for psychological dependence. Patients' understanding of the addiction occurs very late, usually after the physical addiction stage has come. Treatment of anxiety, dysphoria, agitation, depression is the main target for DA therapy. But usually it can't replace specificity of emotions which could be obtained under the drug consumption [Kirkpatrick, 2013; Shuto, 2012]. Pharmacotherapy efficiency could rescue from suicide, aggression and self-injury. Tranquilizers, antipsychotics, sedatives can quickly help to cope with the negative behavioral disorders that accompany drug usage, but reduced psycho-physical and bio-social activity are common side effects of their use. Timoleptics and antidepressants, soft psychostimulants start to have an impact over a longer period [Malat, 2013]. Thus development of the new replacement therapy methods for stimulant addiction is urgent task for today's medicine. We propose neurofeedback audiovisual stimulation (AVS) in combination with hypnotic suggestion as a new approach for SA treatment.

**Materials and Methods**

The group of 8 patients was studies. The group consisted of cocaine addicts (2 persons), methamphetamine users (5 persons), 1 patient which was using ecstasy. The average duration of addiction was 3,56±1,23 years. All the patients independently have requested for medical care and psychological support. All of them have signed an informed consent form for participation in research and treatment, including the methods of hypno-suggestive impacts.

We used audio-visual player NovaPro-100 (Photosonixinc., USA) with LED glasses «ColorTrack» for AVS stimulation (Fig.1). Special «ColorTrack» characteristic is that it changes color according to the frequency of stimulation. NovaPro-100, referred to the mind-machines (devices for correction of psycho-emotional state), is hygienically certified by GOST standards and ISO-9000.

The protocol of AVS treatment consisted of AVS stimulation sessions twice a day (morning session – from 9.00 a.m. to 11.00 a.m.; afternoon session – from 3.00 p.m. to 5.00 p.m.), each lasting for 45 minutes. Summarily 20 days of treatment for each patient was done. Morning AVS session consisted of the following patterns of frequencies: 12 Hz - 10 minutes, 24 Hz - 15 min , 40 Hz - 10 Hz and 10Hz min - 10 min (preprogrammed under the name “Start-up energy cocktail”). Afternoon session was done using such stimulation protocol: 12 Hz - 5 min, 8Hz - 10 min, 6Hz - 10 min, 3Hz - 10min, 8Hz - 10 min (preprogrammed under the name "Stress - killer"). Such combination of frequency pattern provided psycho-mimetic effect in the morning to increase the patient's vitality, as the replacement therapy (AVS increases the level of endorphins, serotonin, dopamine, norepinephrine by 20% - each in different way) [Kang JM, 2011; Pollock S, 2013]. The combination of stimulation with rhythmic music enhances the effect, by creating some “psychedelic” atmosphere. The afternoon stimulation session was aimed to produce anti-stress effect, sedation, anxiety reduction, and lead the patient to the alpha-theta frequencies range allows hypnotic suggestive therapy with the formation of self-recovery and negativization to drugs. Such combination of two sessions of stimulation allows us to cure the drug cessation effect by replacement the drug effect onto the brain. It makes psychotherapy and rehabilitation effective.

Electroencephalographic studies were performed using 16-channel EEG device (NPO DX-Systems, Kharkiv, Ukraine). EEG data analysis was performed using software package BRAINTEST SPECTR 16, supplied with EEG recorder.

The level of anxiety (Spielberger Ch.D. and Hanin Y. L., 1986) and psychological distress scale PSM-25 (Lemyr-Tessier-Fillion) were measured as recommended by WHO (1995), the American Psychiatric Association (1994) and the International Society of psychopathologist (1998).

fMRI data were acquired on 1.5T Signa ExciteHD (General Electric, USA) scanner. Multislice T2*-weighted gradient echo EPI images were obtained with such parameters: TR/TE=3000/71 ms, FA=90, NEX=1, FoV=25.6 cm, matrix 64x64, slice thickness 6 mm, voxel dimensions 4x4x6 mm. 25 slices covering full brain were acquired for each volunteer. Resting state and motor task model based fMRI data were acquired before and after the application of AVS neurofeedback therapy. Duration of resting state scan was 7 min, 140 timepoint images were acquired. The duration of motor task execution scan was 5 min, 100 timepoint images were received. Task execution was formed into 5 blocks of rest and activation, each lasting for 30 s. During the scan volunteers were asked to lay motionless, except executing right hand index to the thumb finger tapping task, with closed eyes and supine palms, thinking of nothing in particular. High resolution T1-weighted anatomical scans were obtained using pulse sequence FSPGR, with such parameters TR/TE=11.6/5.2 ms, TI=450 ms, FoV=25x20 cm, matrix=256x192, slice thickness=1,5 mm, voxel dimensions=0,98x1x1,5 mm.

Model based fMRI data processing was carried out using general linear modeling as implemented in FEAT application, part of FSL (FMRIB's Software Library). The following pre-statistics processing was applied: motion correction using MCFLIRT [Jenkinson, 2002]; slice-timing correction using Fourier-space time-series phase-shifting; non-brain removal using BET [Smith, 2002]; spatial smoothing using a Gaussian kernel of FWHM 8.0mm; grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor; highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma=20.0s). Z (Gaussianised T/F) statistic images were thresholded using clusters determined by Z>3.09 and a (corrected) cluster significance threshold of P=0.05 [Worsley, 2001]. Activation and deactivation was modeled with GLM as an opposite contrasts. Resting state data were analyzed using Probabilistic Independent Component Analysis [Beckman, 2004] as implemented in MELODIC, part of FSL. Resting state SMN and DMN networks were delineated by visual analysis of its correspondence to earlier mentioned brain structures. The average power value was calculated at each frequency.

**Figure 1**. NovaPro-100 (Photosonix Inc., USA), with LEDs glasses «ColorTrack».

**Results and Discussion**

The study has begun with the patients' agreement of voluntarily terminated drug use, thus the abstinence was caused. As the patient couldn't cope with the withdrawal symptoms on his own he had to ask for the medical care and for psychological support. The course of treatment started at the third-fifth day after the drugs cessation, when the symptoms of withdrawal began to arise and patients began to feel increasing anxiety, agitation, and dysphoria. Six patients have undergone the full course of treatment. Two patients (amphetamine addicted) were excluded from the study because of the uncontrolled use of the drugs, and the lack of cooperation with the doctor. At the time the study was finished, all six patients, that have undergone the full course of treatment, had steady remission, lasted for 105±12,8 days. Patients had not symptoms of physical or psychological discomfort, have returned back to the active personal, professional and social life. Monitoring visits to the doctor are held once a week with the obligatory urine test for the drugs. Using the psychological testing, electrophysiological measurements and functional MRI modalities we received such results.

**Assessment of the psycho-emotional state.**

At the time of withdrawal symptoms manifest patients experienced a high level of reactive and personal anxiety 66,28±10,53 points and 58,32±5,29 points respectively, as measured by mentioned psychological testing. The level of reference allowable value is 45 points. Stress measurement revealed it's considerably increased levels up to 163,87±9,73 (reference adaptation rate is 100 points).

After the implementation of AVS and hypno-suggestive therapy patients demonstrated decreased levels of stress and stress-induced anxiety. After the 20 days treatment patients still demonstrated increased level of personal anxiety. We can hypothesize that this sort of anxiety has already become a personal feature of the individual patient and it's reduction needs a longer period of time (Table 1).

**Table 1**. Dynamics of psycho-emotional sphere indicators for observed patients (points).

| **Tests** | **Before the treatment** | **After the treatment** |
|---|---|---|
| The level of anxiety (reactive) | 66,28±10,53* | 32,86±7,21 |
| The level of anxiety (personal) | 58,32±5,29 | 43,26±3,52 |

| | | |
|---|---|---|
| Scale of psychological distress | 163,87±9,73* | 122,65±7,33 |

*The differences were significant at the p<0,05.

**Electro-physiological effects of AVS.**

Electro-physiological changes of the brain bioelectric activity during AVS were manifest by appearance of evoked potentials, "delight" pacemaker, synchronization of α-waves in the first phase of stimulation and generalization, which was 73,54±12,76% of frequency spectrum. During the AVS stimulation intra the β–range, EEG recorded part of delta rhythm was increased to 25,78±10,07%. When the stimulation return to the alpha range of stimulation marked decrease in the proportion of delta rhythm at an average of 68,32±15,65% in comparison with that in the previous step is reduced to 10,23 ± 4,78% of the total frequency spectrum.

In general, the primary performance of neurofeedback AVS in addictive patients due to an increase in power of alpha waves and prevalence of alpha waves to 67,35 ± 13,32% and a decrease in the spectrum of particles delta waves on average 14,32 ± 4,67% (Fig.2).

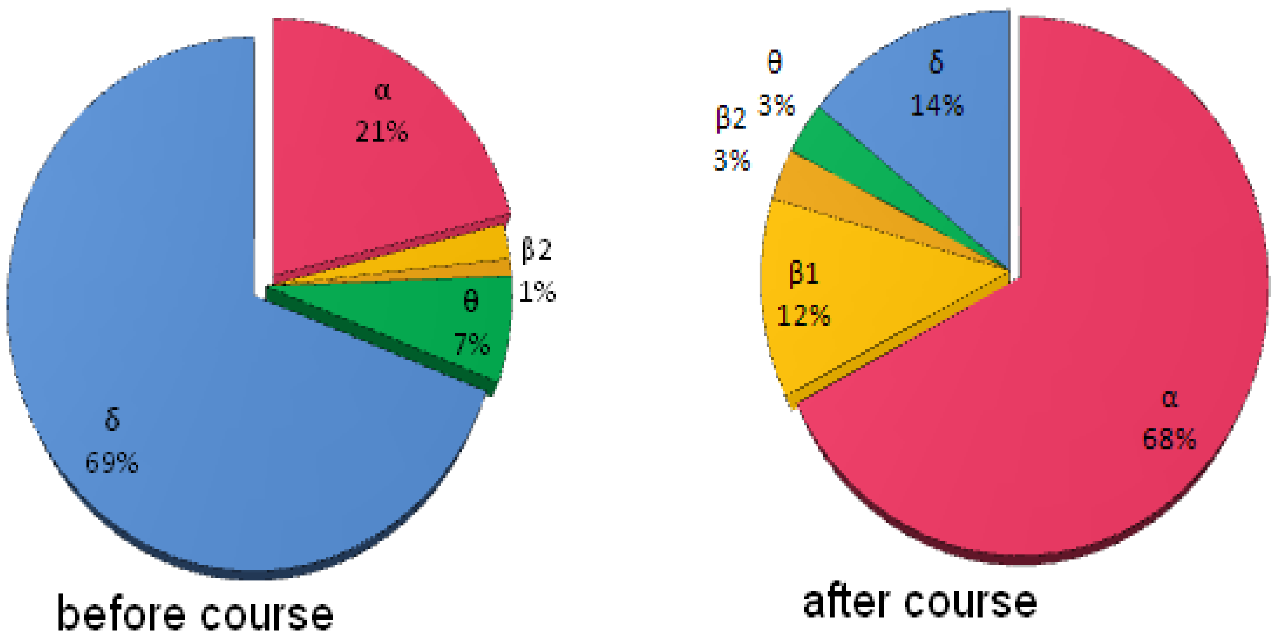


**Figure 2**. Frequency spectrum of EEG before and after the treatment.

**AVS-effects on brain excitability measured with fMRI.**

The most interesting results were obtained with the fMRI.

From the GLM analysis of task-based fMRI data, received before the application of neurofeedback audiovisual stimulation, we have found out that during simple unilateral finger tapping task expected activation occurred in such regions: contralateral, to the hand movement, primary sensory-motor area (M1, S1), supplementary motor area (SMA), ipsilateral hemisphere of cerebellum. Unexpected activation occurred in the region of inferior part of precentral gyrus, bordering upon the pars opercularis of the inferior frontal gyrus (Broca’s area, BA44), and near posterior section of the superior temporal gyrus (Wernicke's area, BA22), also activation occurred at the ipsilateral inferior part of precentral gyrus, ipsilateral angular gyrus and contralateral hemisphere of cerebellum. The activation was accompanied by the deactivation of the region ipsilateral primary sensory-motor area (ipsiM1, ipsiS1) and the regions of precuneus, posterior cingulated cortex, inferior medial prefrontal cortex, parts of so-called default-mode network (DMN). fMRI data, received after the application of neurofeedback audiovisual stimulation, showed that during simple unilateral finger tapping task activation occurred at the previously described regions but also at the bilateral striatum, lateral prefrontal cortex and left parietal cortex (Table 2) (Fig. 4).

**Table 2**. Regions of activation and deactivation before and after the neurofeedback AVS, as measured by fMRI, threshold Z≥3.09.

| Region of activation | BA | Volume, $cm^3$ | Cluster Z-score maximum | Centre of mass | | |
|---|---|---|---|---|---|---|
| | | | | *x* | *y* | *z* |
| Before the neurofeedback AVS stimulation | | | | | | |
| Activation | | | | | | |
| Contralateral pre-, postcentral gyri, midline surface of the posterior frontal gyrus M1/S1/SMA | 4/3/6 | 35.8 | 8.07 | -38.4 | -16 | 50.2 |
| Contralateral supramarginal gyrus (near angular gyrus, posterior section of the superior temporal gyrus - Wernicke's area) | 22 | | | | | |
| Contralateral inferior part of precentral gyrus bordering upon the pars opercularis of inferior frontal gyrus, Broca’s area | 44 | 7.5 | 6.22 | -52.2 | 10.5 | 11.6 |
| Ipsilateral inferior part of precentral gyrus bordering upon the pars opercularis of inferior frontal gyrus | 44 | 1.8 | 4.25 | 57.1 | 11.6 | 14.3 |
| Ipsilateral angular gyrus, posterior section of the superior temporal gyrus | 39 | 3.3 | 4.5 | 55.9 | -32.7 | 35 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Ipsilateral hemisphere of cerebellum | - | 20.7 | 8.27 | 21.5 | -55.5 | -26.3 |
| Contralateral hemisphere of cerebellum | - | 2.9 | 4.44 | -25.7 | -64.4 | -33 |
| Total volume of activation | | **72** | | | | |
| Deactivation | | | | | | |
| Ipsilateral pre-, postcentral gyri, M1/S1, precuneus | 4/3/7 | 53.7 | 7.39 | 14.5 | -49.5 | 34.4 |
| Posterior cingulated cortex | 31 | 2.3 | 4.82 | 1.98 | -17.4 | 48.6 |
| Inferior medial prefrontal cortex | 11 | 21.3 | 5.92 | 0.9 | 59.6 | 2.43 |
| Total volume of deactivation | | **77.3** | | | | |
| After the neurofeedback AVS stimulation | | | | | | |
| Activation | | | | | | |
| Contralateral pre-, postcentral gyri, midline surface of the posterior frontal gyrus M1/S1/SMA | 4/3/6 | 72.1 | 10.9 | -34.7 | -14.1 | 52.3 |
| Contralateral supramarginal gyrus (near angular gyrus, posterior section of the superior temporal gyrus - Wernicke's area) | 22 | | | | | |
| Contralateral inferior part of precentral gyrus bordering upon the pars opercularis of inferior frontal gyrus, Broca’s area | 44 | 21.6 | 7.6 | -45 | 11.1 | 2.05 |
| Ipsilateral inferior part of precentral gyrus bordering upon the pars opercularis of inferior frontal gyrus | 44 | 15.3 | 5.9 | 55.8 | 28.2 | 35.1 |
| Ipsilateral angular gyrus, posterior section of the superior temporal gyrus | 39 | 3.3 | 4.5 | 55.9 | -32.7 | 35 |
| Ipsilateral hemisphere of cerebellum | - | 15.1 | 10.1 | 18.4 | -55.1 | -18.5 |
| Contralateral hemisphere of cerebellum | - | 4 | 5.07 | -34.2 | -61.9 | -23 |
| Other regions of activation (bilateral striatum, lateral prefrontal cortex, left parietal) | - | 30.6 | aver. 6.82 | - | - | - |
| Total volume of activation | | **162** | | | | |
| Deactivation | | | | | | |
| Ipsilateral pre-, postcentral gyri, M1/S1 | 4/3 | 2.3 | 4.65 | 39.9 | -21.3 | 67.3 |
| Ipsilateral occipital cortex, V2 | 18 | 2.2 | 4.4 | 40.9 | -21.3 | 67.3 |
| Total volume of deactivation | | **4.5** | | | | |

Analysis of the volume of activation/deactivation showed the before the application of the audiovisual stimulation its ratio was close to the 0.93 (72/77.3 cm3), but after the stimulation ratio value changed to 36 (162/4.5 cm3) (Fig.3).

In our study ICA analysis of the resting state fMRI data defined 15 ICA components (as revealed by maps thresholded at Z=2.3), which reflected real functional connectivity (DMN, visual, fronto-temporal), and artificial components (breathing, heart rate). Anatomical revision of independent component map constituents revealed functional connectivity of the regions of inferior medial pre-frontal cortex, posterior cingulate cortex, precuneus and lateral parietal cortex which are widely accepted to form DMN. Also we have found functional connectivity in the region of occipital lobe, which is widely accepted to form resting state visual network. We selected defined IC components for future analysis of its normalized signal timecourse and frequency spectrum. Analysis of the BOLD signal oscillations spectrum from the DMN regions revealed low frequency amplitude prevalence in the range of 0.0067-0.03 Hz with primary peaks at f=0.0167Hz (Power=1392) and f=0.0262 (Power=1435). Visual network timecourse analysis revealed prevalence frequency of f=0.0167Hz (Power=2076) and oscillation became most periodical after the 2 minutes of rest. ICA analysis of the resting state fMRI data recorded after the neurofeedback therapy failed to reveal functional connectivity in the region of visual cortex. Spectrum analysis of the BOLD timecourse in the region of DMN revealed primary frequency of f=0.0357Hz (Power=1051) with much more subpeaks presence. Analysis of the frequencies which were prevailing before the neurofeedback therapy revealed considerable power reduction: f=0.0167Hz (Power=1.2), f=0.0262 (Power=380).

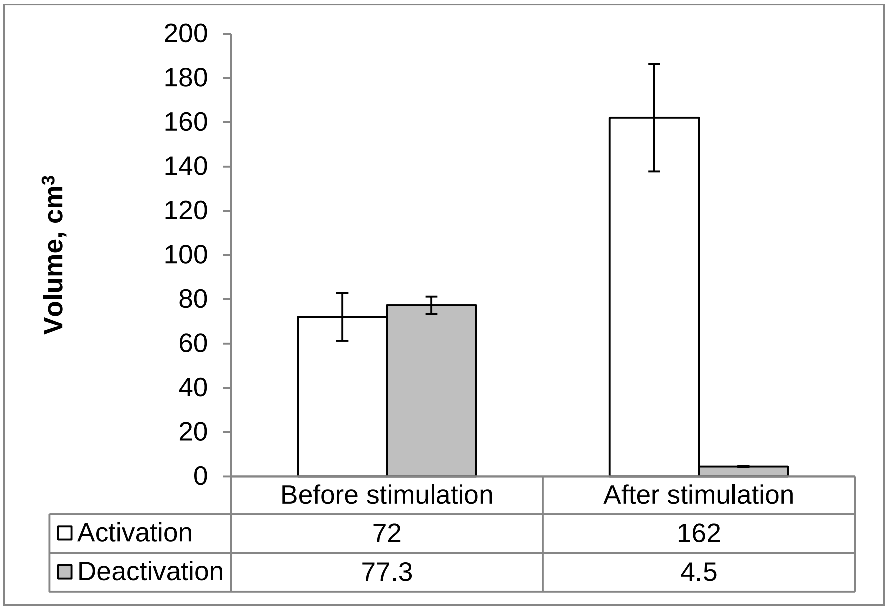


**Figure 3**. Total activation and deactivation volumes before and after the neurofeedback audiovisual stimulation, as measured by fMRI, threshold Z≥3.09.

fMRI data acquired at the resting state with closed eyes clearly shows functioning of the DMN and visual networks. But measurement made after the stimulation failed to shows functioning of the resting state visual network which may be possible evidence of partly prolonged effect (which lasted after the cessation of stimulation) of neurofeedback audiovisual stimulation onto the visual cortex. Spectral analysis of the BOLD oscillation at the regions of DMN showed that after the stimulation prevailing frequency changed to the higher values (0.0167Hz and 0.0262Hz to 0.0357Hz) which could be the biomarker for internal brain processes stimulation effect.

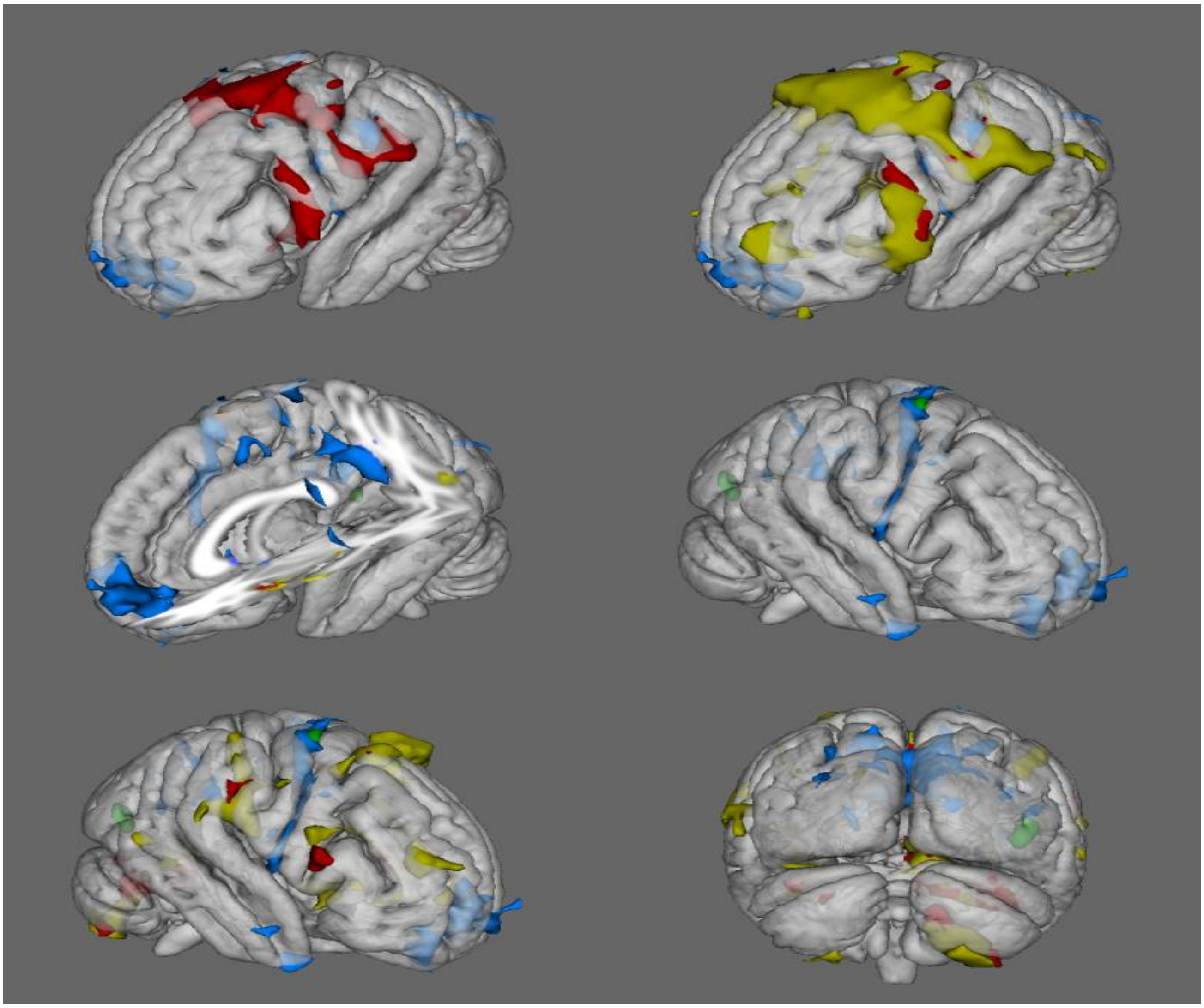

**Figure 4**.Anatomical representation of the activation and deactivation, measured by fMRI, $Z \geq 3.09$. Red – regions of activation before the stimulation. Blue – regions of deactivation before the stimulation. Yellow – regions of activation after the stimulation. Green – regions of deactivation after the stimulation.

**Conclusions**

1. The use of audio-visual stimulation combined with hypno-suggestive therapy can helps to reduce the negative psychotic symptoms of the drug withdrawal syndrome. The most important is to reduce

the level of anxiety and the stress reduction.

2. Electro-physiological effects of the influence of AVS is to synchronize the alpha rhythm displacement predominant delta rhythm. This effect brings the performance of electrical activity of the brain in health waking indicators.

3. Analysis of the task-based fMRI test showed considerable increase of the activation after the audiovisual stimulation and almost complete extinction of deactivation which is normally present at the time of task execution. The last could be also considered as a marker for prolonged effect of brain stimulation by the AVS- therapy.

4. Audio-visual stimulation combined with hypno-suggestive therapy is a promising method for the rehabilitation of patients, which are addicted to stimulants.

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