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Effects of Semax on the Default Mode Network of the Brain

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The effects of nootropic drug Semax on the neuronal network of the brain were studied by the resting state functional magnetic-resonance imaging (resting state fMRI). The study was carried out on two groups of healthy volunteers (11 men and 13 women aged 43.9±9.5 years). Resting state fMRI was carried out 3 times: directly before and 5 and 20 min after intranasal 1% Semax (14 subjects) or placebo (10 subjects). The topography of the resting state default mode network was studied. A greater volume of the default mode network rostral (medial frontal cortex) subcomponent was detected in the Semax group in comparison with controls. Resting state fMRI confirmed Semax effects on the neuronal network of the brain and demonstrated topography of these effects.

Key Words: *Semax; default mode network; resting state functional magnetic-resonance imaging; brain*

Numerous clinical and experimental studies have confirmed high efficiency of peptide nootrop Semax in neurology and psychiatry [2,12]. The neurophysiological mechanisms of these effects, however, remain nor quite clear.

The method of functional magnetic-resonance imaging (fMRI) is based on registration of shifts in the blood oxygenation level-dependent parameters (BOLD signal), which are assumed to reflect the dynamics of relevant neuronal activity. One of highly prevalent approaches to these studies is analysis of the relationships between the studied parameters in various topographic loci and detection of the functionally specific neuronal networks associated with certain brain structures [6-9].

The default mode network (DNM) of the brain represents a group of structures (as a rule, the medial frontal cortex, medial parietal cortex, and lateral parietal cortex) with the maximum functional relations at rest, in the absence of any kind of explicit (external) task. The network is associated with processes of common evaluation of information about the inner status and the environment [8], processing of information about the status of the organism and free flow of thoughts (about past, future, *etc.*), with emotions experienced by the host [6], episodic memory [4], capacity of the host to social interactions [5].

We study the type and degree of Semax effects on DMN.

MATERIALS AND METHODS

The study was carried out on healthy volunteers. The study group consisted of 14 subjects, 7 men and 7 women aged 27-59 (42.6±9.5) years. Control group consisted of 10 subjects: 4 men and 6 women aged 27-61 (45.8±9.8) years. The groups did not differ by age (t=-0.8, p=0.4) and sex (precise Fisher test, p=0.69).

The study was carried out with due consideration for the ethic philosophy presented in the Helsinki Declaration of the World Medical Association. All volunteers signed informed voluntary consent to participation in experiment.

The study was carried out on a 3T Philips Ingenia tomograph. First, anatomical T1 images were recorded: 170 sections, 1×1×1 mm voxel size, MPR (TR/TE/FA 8 msec/4msec/8°). Resting state fMRI T2* images were recorded using EPI sequence (TR/TE/FA

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3s/35msec/90°), 35 sections, 128×128 voxel matrix, voxel size 1.8×1.8×4 mm. After structural images were recorded, fMRI was carried out three times: directly before injection (zero point) and 5 and 20 min after a single instillation of Semax (60 μl into each nostril, total dose of 1.2 mg) in the main group or placebo (3% nipagin, 60 μl into each nostril) in the control group. The drugs were a kind gift from Peptogen Company.

The volunteers were randomly distributed into the main and control groups. During fMRI recording, the volunteers lay still with open eyes, the gaze fixed on the white cross in the middle of the gray field of the monitor over 5 min. The volunteers were instructed to evade any kind of systematic thinking.

The images were preprocessed using SPM12 software (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Processing of resting state fMRI images consisted in detection of correlations of spontaneous low frequency (<0.1 Hz) fluctuations of BOLD signal in various zones of the brain and in the in-depth structures. The data of resting state fMRI were processed by GIFT 3.0a software (http://icatb.sourceforge.net) by detecting the independent components (n=20; threshold z>1) at the group level (6 groups were distinguished, 3 studies for the main and control groups). The individual components were then extracted, from which, by means of spatial sorting on the base of data on DMN [11] and expert evaluations, the components that could be referred to the DMN were detected. The spatial topography of the network elements was analyzed using SPM12 software only for regions corresponding to this network [11], the data in the main group and controls before drug administration were compared, after which paired values were compared separately in each group for each study. The statistical significance threshold value of p<0.001 at the voxel level with the cluster correction for FDR multiple comparisons (q(FDRc)<0.05) was chosen, clusters of more than 20 voxels were taken into consideration.

RESULTS

The groups in fact did not differ by the DMN topography in the zero point. No appreciable changes in the DMN topography were detected in the main group 5 min after Semax instillation (in comparison with the zero point). By min 20 the volume of the DMN network, frontal subcomponent increased significantly in comparison with min 5 (the cluster reflecting the topography of significant changes had a volume of 9693 mm^3 and was located in the frontal compartments of the brain; Fig. 1). No appreciable changes in the parietal subcomponents were detected.

In the placebo group, the subcomponent volume in the frontal compartments increased by min 5 in comparison with the zero point: the volumes of clusters reflecting the topography of significant changes were 2187 and 702 mm^3 (Fig. 2).

By min 20, the volumes of the frontal and parietal subcomponents decreased in comparison with min 5 (the volumes of clusters reflecting the topography of significant changes were 729 and 621 mm^3).

The increase in spatial volumes of DMN subcomponents under the effect of Semax can reflect the effects of two types. It can be a result of involvement of a greater number of neuronal populations in the network (as a result of synchronization of activity). Local changes in the hemodynamic parameters, essential for the level of BOLD signal, are also possible. It is difficult to interpret the data on the increase of the frontal subcomponent 5 min after nipagin dose. Presumably, this was the placebo effect (subsequent reduction of the component seems to support this hypothesis).

The noncoinciding loci of the detected effects are worthy of note. The increase in the DMN frontal subcomponent in the main group was presented by a large cluster including the paracingular gyrus, frontal cingular cortex, and frontal pole, while in the placebo group two clusters were detected: one partially overlapped the above cluster and included the paracingular

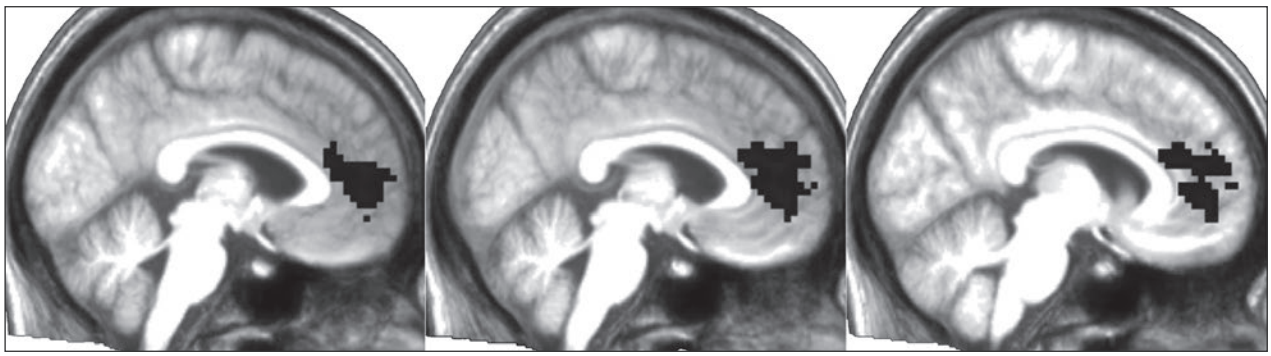

Fig. 1. Images recorded 20 and 5 min after Semax instillation in the main group. The topographic cluster of significant differences is shown with black color. Cluster volume is 9693 mm^3, peak coordinates (3;47;14); (6;53;-10); (3; 32;17). Components are shown in a brain image averaged for group. Location of the cluster in several sections of the brain is shown.

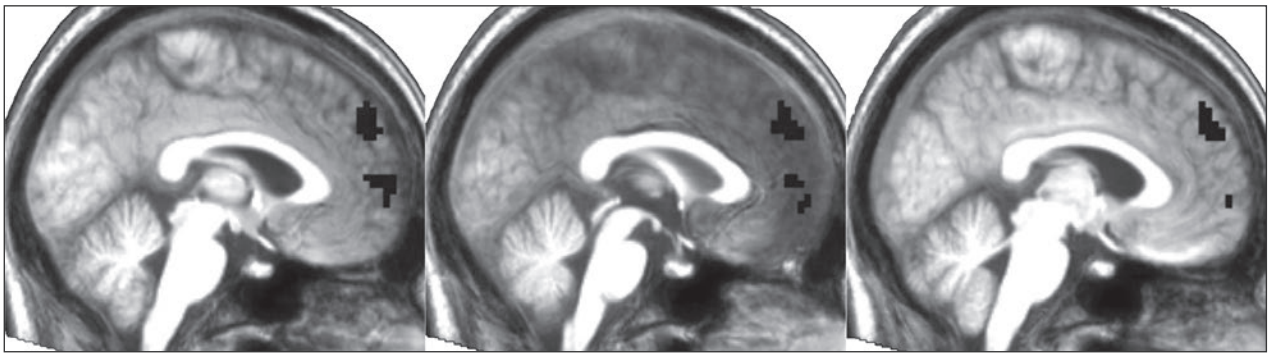

Fig. 2. Images recorded before and 5 min after placebo instillation in control group. The topographic cluster of significant differences is shown with black color. Cluster volumes are 2187 mm^3, with peak coordinates (-3;47;38), (-3;50;29), and (6;50;32); 702 mm^3, peak coordinates (-3;59;5) and (0;59;-4). Components are shown in a brain image averaged for group. Location of clusters in several sections of the brain is shown.

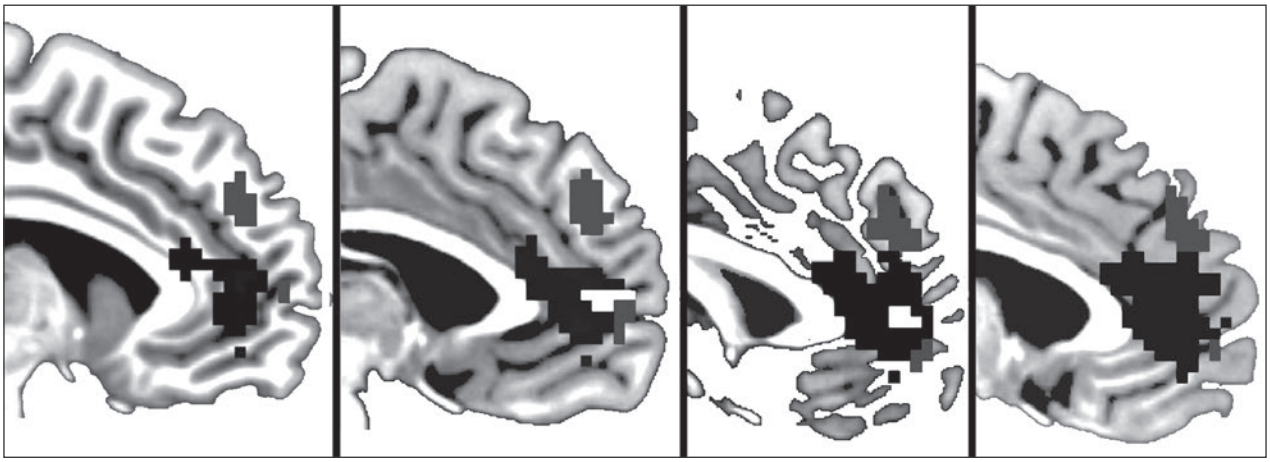

Fig. 3. Zone of spatial overlapping (shown with white color) of the results in the main group (black) and control (gray). Clusters are superimposed with individual brain pattern in MNI space; images of several brain sections are used.

gyrus, frontal pole, and frontal medial cortex, while the other included the superior frontal gyrus (Fig. 3).

Importantly, no special evaluation of the brain status was carried out; however, some data indicate functional significance of a greater functional connectivity to the DMN frontal subcomponent. A phenomenon of this kind is observed as a result of improvement of the cognitive functions due to appropriate training in elderly people [3]. Meta-analysis of the data recorded in young volunteers has shown that effective cognitive training increases activation of the medial prefrontal cortex, the region located in the DMN frontal subcomponent [7]. The main function of the medial cortex, closely connected to the limbic system and reticular formation, consists in "regulation of brain states, modification of cortical tone, cravings, and affective life" [1].

The detected topographic locus of the effect of a single Semax dose in the frontal compartments of the brain correlates with its tropic effects in the frontal cortex of animals under conditions of chronic treatment [10] and with the data on its high efficiency in the carotid form of ischemic stroke [3].

Hence, the study by the resting state fMRI confirmed the effect of Semax on the neuronal networks of the brain and detected the topography of these effects. The data indicate good prospects and high informative value of resting state fMRI in studies of the mechanisms of activity of the peptide neurotropic drugs.

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