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CHEREDNICHENKO

DENIS VLADIMIROVICH

# MODERN TECHNOLOGIES OF MEDICAL AND BIOLOGICAL CONTROL OF THE PSYCHOPHYSIOLOGICAL STATE OF ATHLETES

3.1.33 – rehabilitation medicine, sports medicine, therapeutic exercise, resortology and physiotherapy, medical and social rehabilitation

DISSERTATION

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Scientific consultants:
Doctor of medical sciences, Professor
Didur Mikhail Dmitrievich

Doctor of biological sciences
Kireev Maksim Vladimirovich

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# INTRODUCTION

## Rationale of the study topic

“The Procedure for Healthcare Delivery to Persons Doing Gymnastics and Going in for Sports” (Procedure) is the base for organization and delivery of healthcare to sportsmen in the recent years and especially after adoption of the Federal Law No. 323-FZ dated 21.11.2011 “On Fundamental Healthcare Principles in the Russian Federation”. [3, 10]. Many researchers and specialists in practice sports medicine note that in the current Procedure the interrelation between evidence-based methods for assessment of the somatic health (sportsman’s physical condition) has absolute imbalance in favor of parameters of sportsman’s physical working capacity and somatic health (physical qualities) as compared to evaluation of psychic functions and psychological condition. [407, 464, 488]. At the same time, the Procedure accumulates modern expert concepts of priority importance and validity of certain technologies for monitoring of the sportsman’s physical condition and his somatic health but the content of the psychological control (psychological condition monitoring) and the necessity to perform it are mentioned only in the group of highly qualified sportsmen and are not described at all both regarding to monitoring procedures and applicably to other sportsmen groups with other qualification level. Urgency of the legal and methodical harmonization of procedures for diagnostics and correction of changed functions, when organizing the medical and biological follow-up of sportsmen, is emphasized by many researchers [455, 459].

The modern development strategy of sports medicine (SM) determines multidisciplinary nature and scientific validity of basic measures for medico-sanitary, medico-biological and medical provision of the sports activity. Such approach includes obtaining and introduction of urgent scientific achievements in the field of medicine and related sciences (psychology of sports activities, neurophysiology and psychophysiology) [443, 504]. But most specialists acknowledge the fact of significant deficit of evidence-based procedures for psychophysiological investigation of sportsmen. [396, 439].

Urgency of studies in this area is confirmed by recent state decisions concerning introduction of new scientific specialties (5.12.2 – Interdisciplinary studies of brain) which should provide for accumulation of the scientific data on "study, diagnostics and correction of cerebral cognitive function disorders in acute and chronic stress", what is especially urgent for sports medicine. The development of electrophysiological methods for studying the brain and cognitive functions is stated as one of priority fields for the new group of scientific specialties [1].

Thus, there exists a state requirement to solve an important scientific and practical problem of performing fundamental studies in the field of the sportsman's psychophysiological and cognitive activities [2].

**The degree of scientific development of the research topic**

It is a generally recognized opinion that there exists the influence of the sportsman's psychological condition and specific features of the cognitive functions on implementation of the sports activities. The known results of psychological studies show that relatively more high-level sportsmen leave behind less accomplished sportsmen regarding the results of sports-specific psychological test tasks requiring the use of sports skills, [199] e.g., tests associated with episodic time or spatial elimination of a video clip presented visually with a task to prognosticate further movement of a rival or a gymnastic apparatus. [123]. The similar comparative studies of basic cognitive functions show that while the higher class of a sportsman is characterized by better levels of inhibitory control processes and cognitive flexibility parameters, other processes associated with the working memory, attention and metacognitive assessment, as a rule, do not exhibit such difference between sportsmen of different level [77, 121]. The results of recent meta-analytical research of respective psychological studies [257, 314], are evidence of the fact that the test tasks aimed at assessment of decision-making processes allow to differentiate better the highly and relatively less accomplished sportsmen than the parameters of psychological tests for general cognitive functions (including those associated with executive control processes). But it is stated that insufficient number of such psychological studies does not allow to establish reliably the cause-effect relationship

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[1] https://vak.minobrnauki.gov.ru/searching#tab=_tab:materials~

[2] Decree of the Government of the Russian Federation No. 3081-r dated November 24, 2020 "Strategy for Development of Physical Culture and Sports in the Russian Federation for the Period till 2030"

between such behavioral parameters of psychological tests and the efficiency of implementation of the sports activities [314]. Taking this into account and also considering the variability of psychological data observed in different studies, at present an opinion dominates in many reports that it is early to introduce the existing psychological testing approaches into the monitoring practice of sportsmen’s cognitive functions which could be used as reliable efficiency and productivity predictors of the sports activities.

Neurophysiological studies, which use the levels of total electrical activity of the brain as objective parameters in the comparative analysis of sportsmen having different levels of mastery, report also the high variability of experimental data and its insufficient volume for establishing the cause-effect relationships with sports productivity. It is considered that the higher the sportsman’s professional level is, the more effective the brain functioning is in the process of activities provision what is reflected in lowered latency and increased amplitude of components of event-related potential (ERP), e.g. recorded when performing the Go/NoGo task [200, 205, 486]. A similar effect of training level also is often observed in the frequency EEG analysis, in which sportsmen, who are more effective from viewpoint of sports actions, are characterized by high values of theta and alpha rhythm power with lowered values of EEG beta rhythm. However in the literature there are not rare reports also about opposite directions of these effects [239]. The contradictory nature of change direction in the total electrical activity of the brain is observed also when analyzing EEG coherence: some studies demonstrate increased coherence values in highly accomplished sportsmen and other studies vice versa reveal its lowering [336].

So, similar to results of psychological studies, the pattern of experimental effects of the EEG activity looks contradictory what prevents the establishment of a specific relationship between certain EEG activity parameters and productivity of the sports activities.

The comparable nature of experimental data is observed also in the studies using the tomographic neurovisualization methods which are applied mainly for: 1) structural MR neurovisualization of the training level effect of characteristics of the cerebral gray matter,

2) for comparative fMRI investigations of sportsmen having different level of sports mastery and productivity. The studies within the first area report gray matter restructuring in the human brain associated both with long trainings [230, 283], and short-term effects of the training process [153]. And the higher individual learnability parameter values are during such trainings in sportsmen, the more pronounced cerebral structure changes are, which are associated with provision of the respective motor activity [106]. Researchers report, as a rule, direct relationship between the gray matter volume in the human cerebral structures, which are important for provision of the motor activity types which are associated specifically with the sport under study. They include: cerebellum [35, 133], somatosensory cortex and supplementary motor area [284], hippocampus [269] etc. At the same time, the functional activity level recorded in fMRI investigations demonstrates vice versa the opposite relationship: its high values are observed in sport beginners as compared to more experienced sportsmen [158]. But such type of the relationship is seen not in all fMRI investigations. Some links in the neuronal fronto-parietal action perception system (so-called action observation network [302]), e.g. the posterior insula region, are more active in sportsmen of the higher level as compared with less experienced sportsmen [30]. The structures of the ventral and dorsal information processing paths manifest themselves differently. So, the highly accomplished elite sportsmen are characterized by the increased activity level in the brain regions involved in the dorsal path, including the structures of the occipital cortex, temporoparietal junction [19]. But the effect of increased activity in relatively less accomplished sportsmen is reported for the brain structures included in the ventral information processing path in the inferior frontal gyrus, ventral prefrontal cortex, primary motor cortex, etc.

In accordance with the above data, other fMRI investigations found that the higher the expertness level in the motor activity was, the higher activity level was in the structures of the motor and premotor cortex in the human brain [63, 339]. According to fMRI findings, functional interactions of the brain structures in the condition of operational rest demonstrate a similar nature of the dependence on productivity level of highly qualified sportsmen: the swimmers being at the top rating positions have the higher level of thalamocortical functional connectivity with the somatosensory cortex [266, 297]. The similar dependence on the professional level of sport fitness and productivity is demonstrated by the functional connectivity between the links of the neuronal system providing for the central autonomic regulation.

Notwithstanding the certain efficiency of tomographic neurovisualization methods, when they are used to determine the structural and functional characteristics of some brain structures, which are important for productivity of the sports activities, small number of such studies does not allow to state possible prognostic signs of the registered brain activity, which could evidence the potential risk of lowered efficiency of the sports activities.

One of the most important defects in the above psychological and neurophysiological studies consists in uncertainty of the cause-effect relationships between the revealed changes in the course of psychological processes and functional brain activity when comparing sportsmen having different professional level and sports productivity. The effects observed in such studies may be associated both with sportsmen's innate individual peculiarities (e.g., level of aptitude or ability to somatic recovery after intense loads, psychological personal peculiarities) and with some factors related, e.g., to difference in the total duration of completed training preparatory cycles or competition experience, their success, etc. Besides that, the issue on, whether the observed effects of changes in the brain activity can be used for individual monitoring during the complicated training process, remains not studied. In other words, the issue on which of the neurophysiological effects discussed in literature and in which brain structures/systems can be markers of lowering of the sports activities productivity both for highly qualified sportsmen of international class and for those who only begin the professional sports career, remains unsolved.

Thus, at present it is not evident, to which degree the results obtained in such comparative psychophysiological studies can be used for introduction into the practice of medico-biological support of sportsmen's training. Just this is one of the causes preventing the introduction of the objective monitoring of the cognitive functions condition [261] as an integral part of the medico-biological support regarding the objective monitoring of the sportsman's condition during the training process [228]. This is caused to a great extent by the fact that the knowledge degree of brain provision patterns of implementation of the sportsman's activity under conditions of the training process and competitions is insufficient for the full scale and effective use of neurophysiologic methods for assessment of the brain activity in diagnostics of its condition associated with the productivity.

The professional sportsman functions under conditions of constant competitive stress (pressure of the necessity to achieve sports results), high of extreme physical loads, what poses high requirements to the optimum psychophysiological condition both during the preparatory training cycles and in the period of competitions. Deviation from the optimum condition can negatively tell upon not only sports results but also the skills formation process, which are critical for the professional sports activities. Such deviations can be associated with changes of normal cognitive functions, related to activities monitoring (e.g., executive control), which manifest not always evidently at the behavioral level or in psychological diagnostics. E.g., lowered efficiency of activities implementation or even destroying of a sensorimotor skill can be observed under conditions of the competitive pressure (competitive stress), which can be associated with the activities monitoring disturbance. In particular, the involvement of implementation monitoring processes of skills with the high automation degree can result in disturbance of their implementation [54]. One of the hypothetic mechanisms for implementation of such influence consists in an excessive control hypothesis leading to choking under pressure [364, 409] what results in increase of the response rate and mistakes, which are the behavioral signs of lowered activity efficiency and productivity. But comparative studies of professional sportsmen do not allow to determine possible parameters of the functional brain activity, which could be considered as signs of such or comparable change in the control functions associated with the involvement of control influences leading to lowering of the sports activity productivity. It is evident that the principal possibility of adequate diagnostic monitoring of conditions characterized by such changes in the control functions, in which it is possible to correct the sports productivity, is extraordinarily demanded in the medico-biological sports control.

Thus, modern psychophysiological studies aimed at investigations of the neuronal base of the efficiency of sports activities are focused mainly to search for differences between the various level of sports mastery associated with the sports productivity, what is insufficient for development and introduction of neurodiagnostic methods into the practice of medico- biological monitoring of signs evidencing the lowered efficiency of implementation, which critical for realization of sports skills. In the literature some authors report that the development of methodical approaches allowing to perform individual diagnostics is a necessary but still not elaborated area. The PCA-based scaled subprofiled model (SSM-PCA [222, 273, 274, 275]) can be one of such methodical approaches. It allows to translate the results obtained in group studies of the functional brain condition to the individual diagnostics level.

**Objective of the study**

Increasing the efficiency of technologies for medical and medico-biological monitoring of sportsmen's psychofunctional condition by the development of new methodical and diagnostic approaches using different models of somatic and psychological status in the norm and pathology.

**Tasks of the study**

1. To analyze the structure and scientific validity of the medico-biological monitoring of sportsmen from viewpoint of clinical medicine and rapidness of modern technologies transfer associated with diagnostics of the psychophysiological status and neurovisualization of psychic functions basing on the data of fundamental scientific studies.

2. To perform psychological investigation of highly qualified sportsmen in order to determine factors influencing the efficiency and productivity of implementation of the sports activities and, taking into account the obtained results, to determine the target function, psychophysiological monitoring of which will have diagnostic value regarding the assessment of the sportsman's functional state associated with the productivity of the sports activities. To suggest a clinical model of change in brain provision of the target function associated with the activities productivity basing on the obtained results.

3. To substantiate selection of the test task and neurovisualization method allowing to assess objectively the selected target function and its brain provision under conditions of change in it activity which are associated with the disease under study within the limits of the suggested clinical model.

4. To determine the human brain structures, the activity of which is associated with change in the work of the selected target function in setting of a test task creating conditions for its involvement in provision of the behavior of a sick and healthy human. To establish patterns of changes in the activity of the human brain structures providing for changes in the work of the studied target function which are associated with the disease under study.

5. To suggest and test a neurovisualization method the use of which allows to take into account the revealed patterns in changes of the brain provision of the target function under study and provides for their effective transfer to the practice of the thorough medical examination of a sportsman for monitoring of his psychophysiologic condition associated with diagnostics of the target function condition.

6. To test the suggested neurovisualization method in the working clinical model using the comparative analysis parameters values of healthy normotypical subjects and patients with disturbed activity of the selected target function.

7. To determine a set of human brain structures and diagnostically significant parameters of their functional activity the use of which in the psychophysiologic monitoring of the target function is promising for revealing the signs of lowered productivity of the sports activities.

**Scientific novelty of the study**

The study suggested for the first time a clinical model of brain mechanism restructurings of action executive control in case of anxiety change allowing to assess at the individual level changes of the sportsman’s functional condition linked with lowering of the activities implementation efficiency and productivity.

Within the limits of studying the peculiarities in the structural and functional organization of the brain nonselective inhibitory control (NSIC) system, for the first time in investigation of pathophysiology of generalized anxiety disorder (GAD), we revealed GAD-associated extension of the element composition of this brain system when implementing the activity for inhibition and performing actions prepared in advance under conditions of the Go/NoGo test task. Such extension was realized due to additional (relative to the norm) inclusion of elements localized in the anterior insula and inferior frontal gyrus of the right hemisphere of the human brain.

It was possible to establish this fact thanks to a new statistical approach to functional mapping of the human brain developed by us and allowing to reveal statistically significant absence of brain activity changes (so-called ROPE-mapping) on the base of interval statistics.

We showed for the first time that the above GAD-associated NSIC elements demonstrated differently directed changes in functional connectivity in GAD as compared to the norm when recording the brain activity with the help of fMRI in the operational rest condition.  The obtained new data suggests the compensatory nature of the revealed element composition reorganization of the neuronal system of nonselective inhibitory control in the human brain in case of generalized anxiety disorder which can be associated with non-optimum regimen of the brain provision of the control functions which is linked with lowered activities productivity.

As a result of the study series performed by us we suggested for the first time a set of the human brain structures, fMRI monitoring of the functional connectivity of which can be valuable for diagnostics of the change in the sportsman’s functional condition linked with lowering of activities efficiency and implementation productivity.

For the first time we suggested a diagnostic approach, which combines recording the brain activity in the operational rest condition using fMRI, calculation of amplitude of low-frequency fluctuation of BOLD signal in the set of human brain structures suggested by us and a diagnostic criterion/parameter based on the combined use of the PCA-based scaled subprofiled model (SSM-PCA) which allows to detect at the individual level possible signs of change in the control functions associated with lowered productivity.

**Methodology and methods of the study**

The thesis study was performed in accordance with the topic plan of research works, within the limits of the state task of the Ministry of Science and Higher Education of the Russian Federation (“Brain provision of nonselective inhibitory control in the norm and pathology” (topic of fundamental scientific studies FMMW-2022-0002 (2022–2024)) and within the limits of the research work “The development of new methods and technologies for diagnostics and treatment of brain diseases basing on multi-method investigation of change patterns of functional brain activity reorganization and brain system connectomics (FMMW-2022-0003) (state registration number of the topic: 122041500044-1).

The study was planned and performed according to the principle of successive actualization of a three-level pyramid of the data bank and diagnostic methods, which are prioritized in the field of sports medicine.

The pyramid base included the methods (technologies) of medico-biological monitoring (MBM) having the long history of scientific studies, many-year practice of use and presented in different versions of “Procedures of Healthcare Delivery to Sportsmen”; the middle part of the pyramid included technologies having modern interpretation and adapted to sports medicine basing on the experience of clinical medicine and neurophysiology and modern technology transfer through the example of neurovisualization of psychic functions based on fundamental studies was positioned at the pyramid apex.  It is to be noted that the work included all modern types of scientific medical studies: fundamental, observational, experimental studies, systematic reviews.

The study presents successively the results of many-year observations for the period from 2011 to 2023 describing the areas for increasing the efficiency of medico-biological monitoring from metabolism disorders at the level of the organism main systems to assessment of anxiety parameters using the modern procedures for neurovisualization of the higher control psychic and behavioral functions which are critical in the sports activities and the least scientifically developed and methodically substantiated.

The study was performed taking into account the accepted and regulated ethical norms, with participation of patients and healthy subjects with different level of sports qualification. We studied the possibility to use the developed neurophysiologic approach for solving the problems within the limits of the through medical examination of sportsmen. The retrospective data analysis obtained during the experimental studies was performed. The diagnostic and testing methods were used, which are allowed for application and used in scientific and clinical studies. In order to confirm confidence of the results the mathematical and statistical data processing methods, recommended for medical and psychophysiological studies, were used. The modified assessment method based on Bayesian interval statistics was used for some studies. The brain activity was recorded using the method of functional magnetic resonance imaging (fMRI). In order to confirm confidence of the results we used the mathematical and statistical data processing methods of psychological and fMRI investigations. In order to solve the tasks of our thesis study we suggested a new approach to mapping of the human brain functions basing on the interval statistics using fMRI data (ROPE-mapping [244]) which was methodically tested within the limits of study of the brain nonselective inhibitory control system in patients with obsessive compulsory disorder (OCD) [156]. In order to go over from group studies of fMRI data to individual diagnostics we suggested a diagnostic approach for introduction into the technology for medico-biological monitoring of the sportsman's functional condition with the help of PCA-based scaled subprofiled model (SSM-PCA [259]), which was methodically tested by us on the material of PET data [222]. To analyze psychological data of healthy subjects the k-means++ clustering algorithm was used, which was methodically tested by us within the limits of psychophysiological studies of the relationship between the individual psychologic features and brain gray matter structure [91].

**Applicant's personal contribution.** The author himself organized and performed a cycle of studies for determination of diagnostically significant parameters of the sportsmen's somatic and psychophysiological condition for 15 years. The dissertator substantiated and determined the main areas of studies in different periods of legal regulation of procedures for healthcare delivery to sportsmen. The author of the thesis study performed analysis of the statutory documents regulating the medico-biological support of sportsmen and of the scientific literature basing on the results of which the objectives and tasks of the study were stated. The methods for analysis of the brain functional activity were selected and their methodical testing was performed. The studies were performed, the experimental data was processed and generalized. A new method for mapping of human brain functions using the so-called interval statistics was suggested. The dissertator made a crucial contribution to each of the thesis study stages, made conclusions and stated the main provisions to be defended and also practical recommendations. The author suggested a methodical approach for determining the functional state of the human brain structures which can be linked with change in the control functions.

**The confidence degree and results testing**

The confidence degree of the study results is ensured by the correct design of the work, proper use of approved technologies, the use of metrologically certified equipment, a significant number of many-year observations, substantiated methods for data processing and statistical analysis in accordance with the accepted principles. This allowed to obtain confident results, suggest a diagnostic approach based on the combined special organized analysis of fMRI data, which will make it possible to improve the efficiency of existing medical technologies aimed at increase of the functional readiness of highly qualified sportsmen engaged in different sports.

The performance of the study was approved by the Ethics Committee of Bekhtereva Institute of Human Brain of the Russian Academy of Sciences.

The results obtained during the implementation of the thesis study were reported and discussed at the following conferences and scientific and practical events:

– II All-Russian Congress (with international participation) “Medicine for Sports”, May 31 – June 01, 2012;

– IV International Scientific and Practical Conference “Modern Approaches of Rehabilitation, Adaptive Physical Culture in the Work with Persons Having Health Limitations”, Nizhny Novgorod, 2013;

– International Scientific and Practical Conference “Safe Sports – 2014”, St. Petersburg;

– First National Congress on Cognitive Studies, Artificial Intelligence and Neuroinformatics. Ninth International Conference on Cognitive Science: Moscow, October 10–16, 2020;

– International Scientific Conference “34th European College of Neuropsychopharmacology”, October 2–5, 2021;

– XVII International Scientific Conference on the State-of-Art and Perspectives for Development of Medicine in the High Performance Sports “SportMed-2022”, December 8–9, 2022, Moscow;

– X International Congress “Safe Sports-2023. Overtraining in Sports. Interdisciplinary Approach”, St. Petersburg, 2023;

– XIV All-Russian Scientific and Practical Conference “Olympic Readings: from Sports Results to Pedagogical Achievements”, St. Petersburg, February 29, 2024;

– III International Congress “Medical Rehabilitation: Scientific Studies and Clinical Practice”, St. Petersburg, March 21–22, 2024.

**Introduction of the results into practice.** The materials of the thesis study during its performing were introduced in:

– Order of the MoH of Russia No. 1144n dated 23.10.2020 “On approval of the procedure for healthcare delivery to persons doing gymnastics and going in for sports (including during training and conducting athletic events and sports events) including the procedure for medical examination of persons wishing to have sports training, do gymnastics and go in for sports at organizations and/or reach the norms of trials (tests) of the All-Russian Sports Complex “Ready for Labor and Defense (RLD)” and forms of medical conclusions on admission to participation in athletic and sports events”;

– methodical recommendations: A.V. Kalinin, M.Yu. Lobanov, E.V. Lomazova, V.I. Danilova-Perley, E.V. Bryntseva, D.V. Cherednichenko. Methodical recommendations for conducting the stage and current medical investigations, medical and pedagogical observations in persons doing gymnastics and going in for sports at the initial training level // Health Committee of St. Petersburg Government, Physical Culture and Sports Committee of St. Petersburg Government, St. Petersburg State Budget-funded Health Institution “City Exercise Therapy Centre”. – 2022. – 37 p. UDK 61:796/799;

– methodical recommendations: E.V. Lomazova, A.V. Kalinin, N.V. Melnichuk, E.V. Bryntseva, O.N. Sokolova, M.Yu. Lobanov, D.V. Cherednichenko. Methodical recommendations for revealing sportsman’s fatigue (medical service B03.020.007 – Revealing sportsman’s fatigue) // Health Committee of St. Petersburg Government, Physical Culture and Sports Committee of St. Petersburg Government, St. Petersburg State Budget-funded Health Institution “City Exercise Therapy Centre”. – 2022. – 15 p. UDK 61:796/799;

– methodical recommendations: A.V. Kalinin, M.Yu. Lobanov, E.V. Lomazova, V.I. Danilova-Perley, E.V. Bryntseva, D.V. Cherednichenko. Methodical recommendations for conducting the stage and current medical investigations, medical and pedagogical observations in sportsmen of sports representative teams of St. Petersburg // Health Committee of St. Petersburg Government, Physical Culture and Sports Committee of St. Petersburg Government, St. Petersburg State Budget-funded Health Institution City Exercise Therapy Centre. – 2022. – 60 p. UDK 61:796/799;

– St. Petersburg State Budget-funded Health Institution “City Exercise Therapy Centre”;

– St. Petersburg State Budget-funded Health Institution “Interdistrict City Exercise Therapy Centre No. 1”;

– Department of Physical Methods of Treatment and Sports Medicine of the Faculty of Post-graduate Education, Federal State Budget-funded Educational Institution of Higher Education “First Pavlov St. Petersburg State Medical University” of the Ministry of Health of the Russian Federation;

– St. Petersburg State Budget-funded Vocational Educational Institution “School of Olympic Reserve No. 1”;

– Department of Medical Rehabilitation of the Federal State Budget-funded Institution of Science “Bekhtereva Institute of Human Brain” of the Russian Academy of Sciences (IHB RAS).

Registration certificate of the BAYINF TOOLBOX program for electronic computing machine was received; this program implemented a new method for functional mapping of the human brain on the base of Bayesian interval statistics: Registration certificate of the program for electronic computing machine RU 2023665868, 20.07.2023. Application No. 2023663641 dated 29.06.2023.

**Association with the scientific topic of the organization where the work was performed.** The study was performed in accordance with the topic plan of research works approved by the Institute of Human Brain of the Russian Academy of Sciences as per the state task of the Ministry of Science and Higher Education of the Russian Federation and supported by scientific foundations of the Russian Federation, including the following topics: 1) Systemic organization patterns of brain provision mechanisms of human higher psychic functions using the data of quantitative EEG and functional MRI (FMMW-2022-0001); 2) Brain mechanisms of the cognitive control, inhibitory control and predictive coding for construction of new artificial intelligence architectures and diagnostics of psychic and neurological diseases (FMMW-2022-0002); 3) Functional organization of brain provision systems of interpersonal interactions under conditions of the virtual environment: effect of anonymity and deficit of socially significant information (No. 19-18-00436, Russian scientific foundation); 4) Inapparent elements of the human brain systems: fMRI investigation of specific features of interregional interactions under conditions of complicated verbal and non-verbal information processing (No. 19-18-00454, Russian scientific foundation) .

**Compliance of the thesis with the certificate of scientific specialty 3.1.33. Rehabilitation medicine, sports medicine, therapeutic physical training, spa medicine and physiotherapy, medico-social rehabilitation.** The thesis study is complex and includes analysis of specific features in the use of modern methods for diagnostics of the sportsmen’s somatic and psychophysiological condition during through medical examinations what is in accordance with items 5—7 (“The development of methods for rational use of physical exercises, other means of physical culture and sports for health strengthening, prevention and treatment of diseases, improvement of physical working capacity. Determination of effective measures for prevention of diseases and injuries in sportsmen, the most expedient hygienic conditions for physical education. The development of means and methods for medical control of the functional condition of persons going in for sports and also sportsmen's disturbed functions recovery and rehabilitation programs". "The development of new and improved medical technologies for medico-biological support of sportsmen in all age categories and in the wide range of sports. Study of the influence exerted by external and internal factors on the structural peculiarities, functioning and pathologic signs of the sportsman's organism". "The development of evidence-based problems of medico-biological sportsmen support including problems of organization and optimization of medico-biological support when conducting mass athletic and sports events").

**Volume and structure of the study**

The thesis consists of introduction, 4 chapters, summary, conclusions, references. The main content of the study is presented in 270 pages of typed text; the thesis is illustrated with 26 tables, 46 figures. The bibliographical index contains 541 references including 217 Russian and 324 foreign ones.

**Publications.** The results, methodical approaches and basic provisions of the thesis study were published in 35 printing works including 1 monograph, 3 methodical recommendations, 14 articles in the scientific journals recommended by the Higher Attestation Commission under the Ministry of Science and Higher Education (9 of them were published in the scientific journals indexed in the WOS/Scopus) of the Russian Federation for publishing the basic scientific results of doctoral theses, and one result of intellectual activity (certificate for tollbox Bayinf):

1. Autoimmune reactions in athletes with inflammatory periodontal diseases / P.G. Nazarov, M.Y. Levin, D.V. Cherednichenko, I.A. Afanasyeva // Teoriya i praktika fizicheskoy kultury. - 2012. - № 9. - P. 58-61.

2. Autoimmune processes in athletes of the highest qualification in different periods of the training cycle / M.Y. Levin, P.G. Nazarov, D.V. Cherednichenko, I.A. Afanasyeva // Teoriya i praktika fizicheskoy kultury. - 2012. - № 9. - P. 54-57.

3. Cherednichenko, D.V. Endothelial dysfunction - is it the result of damage in physical exercise? / D.V. Cherednichenko, M.D. Didur, V.N. Lebedev // Sportivnaya meditsina: nauka I praktika. - 2013. - № 1. - P. 301.

4. On the legal harmonisation of medical massage activity in structural units of manual therapy and osteopathy / Didur, M.D., Kurnikova, M.V., Cherednichenko, D.V., Kravchenko, A.S. // Manualnaya terapiya. - 2020. - № 3-4. - P. 65-70.

5. Providing Evidence for the Null Hypothesis in Functional Magnetic Resonance Imaging Using Group-Level Bayesian Inference / R. Masharipov, I. Knyazeva, Y. Nikolaev [et al.] // Frontiers in Neuroinformatics. – 2021. – Vol. 15. – P. 738342. – DOI. 10.3389/fninf.2021.738342.

6. Chutko, L.S. Neurological aspects of anxiety disorders / L.S. Chutko, S.Y. Surushkina, E.A. Yakovenko, Cherednichenko D.V. // Meditsinskiy alfavit. - 2022. - № 10. - P. -11.

7. Features of emotional regulation in children with anxiety disorders / S.Y. Surushkina, L.S. Chutko, E.A. Yakovenko, [ et al.] // Zhurnal nevrologii i psikhiatrii im. S.S. Korsakova - 2021. - Vol. 121. - № 11-2. - P. 95-102.

8. The Interaction Between Caudate Nucleus and Regions Within the Theory of Mind Network as a Neural Basis for Social Intelligence / M. Votinov, A. Myznikov, M. Zheltyakova [et al.] // Frontiers in Neural Circuits. – 2021. – Vol. 15. – P. 727–960. – DOI: 10.3389/fncir.2021.727960.

9. Suppression of non-selected solutions as a possible brain mechanism for ambiguity resolution in the word fragment task completion task / M. Kireev, V. Gershkovich, N. Moroshkina [et al.] // Scientific Reports. – 2022. – Vol. 12, № 1. – DOI: 10.1038/s41598-022-05646-5.

10. Social Interaction With an Anonymous Opponent Requires Increased Involvement of the Theory of Mind Neural System: An fMRI Study / M. Zheltyakova, A. Korotkov, R.

Masharipov [et al.] // Frontiers in Behavioral Neuroscience. – 2022. – Vol. 16. – P. 807599. – DOI: 10.3389/fnbeh.2022.807599.

11. Features of the choice of functional criteria evaluating the direct effect of manual influence / M.D. Didur, M.V. Kurnikova, D.V. Cherednichenko, A.S. Kravchenko // Manualnaya terapia. - 2022. - Vol. 86. № 2. - P. 10-14.

12. Impaired Non-Selective Response Inhibition in Obsessive-Compulsive Disorder / R.S. Masharipov, A. Korotkov, I. Knyazeva [et al.] // International Journal of Environmental Research and Public Health. – 2023. – Vol. 20, № 2. – P. 1171. – DOI: 10.3390/ijerph20021171.

13. Parkinson’s Disease-Related Brain Metabolic Pattern Is Expressed in Schizophrenia Patients during Neuroleptic Drug-Induced Parkinsonism / Kotomin I., Korotkov A., Solnyshkina I., Didur M., Cherednichenko D., Kireev M // Diagnostics. – 2023. – Vol. 13. – P. 74. – DOI:10.3390/diagnostics13010074.

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**Main scientific results**

1. A systematical analysis of the structure and content of modern approaches to medical care for athletes, using the results of our own studies on the peculiarities of lipid metabolism, endothelial dysfunction, autoimmune processes and the state of cardiovascular systems of athletes (see publications No. 2-4 from the list of published papers - references [351, 352, 530] on pp. 39, 40, 195, 196), revealed not only a significant delay in the transfer of new scientific data on key physical functions of the organism into the system of medical and biological control, which was traced back to three revisions of

the Procedures of Medical Care for Athletes, but also a complete focusing on somatic indicators to the detriment of psychophysiological ones. We found that sports activity leads to unfavourable immunological shifts, for example, year-round presence of the athlete's heart under constant autoimmune attack, due to high physical and psychoemotional loads. Diagnosis of endothelial dysfunction has not received adequate attention in the orders governing advanced medical examination. Our comprehensive studies reflect a general picture of the problem of limited transfer and regulatory consolidation of basic research results into medical technologies. This trend is most pronounced in the area of athlete psychophysiological monitoring (see section 1.3. on pp. 38-47, the author's personal contribution – 70%).

2. Methods of legal and terminological regulation, are discussed at all stages of work, and are universal normative transfer of scientific data into the practice of sports medicine and rehabilitation. Successfully implemented approaches are not only reflected in publications (see publication No. 5 and 12 from the list of published works - references [455] and [459] on pp. 6, 31, 195, 198), but also reflected in normative and methodological documents (order of the Ministry of Health, the author's personal contribution – 50%).).

3. The results of our research on gymnasts of the St. Petersburg and national teams have shown that one of the key factors affecting the performance of highly skilled athletes is personality anxiety (see sections 3.1.2.-3.1.3 on pp. 102-108, the author's personal contribution - 60%). It has been found (see publication No 7 from the list of publications – reference [535] on pp. 60, 62) that anxiety-related disorders are characterised by impairments in executive functions and inhibitory control (manifested as emotional dysregulation, reduced memory function and perceptual processes, and increased impulsivity), accompanied by certain rearrangements of rhythmic brain activity (e.g., reduced spectral power of the theta and alpha ranges of the EEG (see publication No 8 from the list of publications - reference [461] on pp. 68, 61)), which allows GTR to be considered as a clinical model for alterations in executive functions.

4. Using a new method for functional brain mapping using functional MRI data which was developed and tested in the present research (see publications No. 6 and No.

13 from the list of publications - references [244] and [156]) on pp. 16, 56, 74, 76, 80, 111, 118, 176, 179 and 16, 56, 76, 80, 117, 118, 122, 176, 177 respectively), which is implemented on the principles of interval statistics, we, for the first time, revealed not only the fact of involvement of the brain system of non-selective inhibitory control (NSIC) in the pathogenesis of generalised anxiety disorder (GAD), but also the fact of GAD-induced expansion of this neuronal system. Relative to the healthy control, the GD patients in the settings of uncertainty associated with the need to inhibit a prepared action performing Go/NoGo task, were characterized by the involvement of additional nodes of the NSIC network. Those nodes were localised in the anterior insular cortex and orbital part of the inferior frontal gyrus of the right hemisphere of the human brain (see Section 4.1.3 on pages 128-130, the author's personal contribution - 80%).

5. Our analysis of functional connectivity (FC) performed on fMRI data in resting state allowed us to establish that the node of NSIC network located in the right anterior insula is the only one of all other nodes of this neural brain system that demonstrates an increase in functional connectivity of FC in GAD patients (as compaed with healthy subjects), which could be considered as an evidence of the compensatory nature of involvement of this node in the action control at GAD (see Section 4.3.1 on pp. 159-164, the author's personal contribution - 95%).

6. In a series of studies we established the locations of a nodes of the neuronal systems of the human which undery the processing of: 1) socially significant information (see publications No. 9 and No. 11 from the list of publications - references [303] and [270] on pp. 66, 82, 86, 138, 150, 164, 175, 179, 181 and 66, 82, 140, 145, 148, 166 respectively), 2) executive control of cognitive activity (see publication No. 10 from the list of publications - reference [285] on pp. 66, 82, 93, 95, 151, 153, 167, 179). The analysis of resting state functional connectivity of these nodes allowed us to establish a GAD-related decrease in their functional connectivity relative to the healthy contol (Sections 4.3.2 and 4.3.3 on pp. 164-173, the author's personal contribution - 80%).

7. Using resting state fMRI the analysis of functional state of human brain allowed us to reveal brain stuctutres as candidates for objective monitoring of changes in control

functions, associated with a possible decrease in the efficiency of activity and performance (section 4.3.4 on pp. 173-185, the author's personal contribution - 95%).

8. Based on the obtained results of resting state fMRI data, a separate study was conducted to develop a diagnostic approach using multivariate factor analysis, which consisted of: 1) preliminary testing of the k-means++ machine clustering method on the material of psychodiagnostic data used in neuroimaging research (see publications No. 15 of the list of publications - reference [91] on pages 16, 189, 190), and its application for selection of subjects with low values of trait anxiety as a control group, 2) preliminary testing of the SSM-PCA method on the experimental material of PET study of drug-induced parkinsonism (see publication No. 14 of the list of publications - reference [222] on pp. 12, 16, 186, 188), and its application to the resting state data of amplitude of low-frequency oscillations of BOLD signal (ALFF) healthy subjects with low values of personality anxiety and GAD patients. As a result we developed a diagnostic approach based on GAD related SSM-PCA pattern for ALFF data, which can be used as an objective marker of an athlete's functional state related to the control functions of the human brain (Section 4.4 on pages 183-192, author's personal contribution - 90%).

**Main theses to be defended:**

1. The content and structure of the medico-biological monitoring of sportsmen do not meet the modern needs and trends in the development of sports medicine, especially due to pronounced disbalance of diagnostic approaches and procedures between somatic and psychophysiological parameters what requires formation of new methodical approaches regarding procedure unification, accumulation of data and method bank, development of clinical recommendations and expert opinions applicably to operational and successive accumulation and transfer of new scientific data into the practice of sports medicine and regulatory documents.

2. The personal anxiety level, which is closely associated with the control functions, whose parameters of brain provision mechanisms are a promising diagnostic criterion, is an important psychological factor influencing the

efficiency and success of implementation of the highly qualified sportsmen’s competitive activities.

3. The high anxiety level in patients with generalized anxiety disorder is characterized by restructuring of functioning of the brain nonselective inhibitory control system, which results in extension of its element composition and such extension has a partially compensatory nature associated with the intensified control of the current activities what can be an objective indicator of lowered efficiency of its implementation and productivity.

4. The change in the functional activity level and functional connectivity of the anterior insula/frontal opercular cortex revealed using fMRI at rest is a sign showing activation of compensatory mechanisms of nonselective inhibitory control. The characteristic of the functional activity level and functional connectivity of this brain region was used in the practice of thorough medical examination of a sportsman for monitoring of his psychophysiological condition associated with the target function at rest.

5. The investigated set of the brain structures providing for both control functions through the brain processes of inhibitory and executive control of the activities and processing of socially significant information demonstrates the unidirectional nature of changes in the functional connectivity when the personal anxiety level is increased. The combined/cumulative lowering of the functional connectivity between these brain structures in subjects with increased personal anxiety levels revealed in the operational rest condition suggests the diagnostic significance of established parameters of functional interactions between these structures in psychophysiological monitoring of the sportsman’s control functions.

# CHAPTER 1 LITERATURE REVIEW

## 1.1. Main trends in the development of scientific studies in the field of sports medicine

At the modern stage sports medicine (hereinafter referred to as SM) is one of the most actively developing interdisciplinary fields of science and professional medicine, whose all types of activities are aimed at health preservation and strengthening, prevention and treatment of diseases and simultaneous improvement of control efficiency of sports events and training measures in persons doing gymnastics and going in for sports [1] [406, 407, 433, 457].

Professor S.M. Razinkin, Head of the Laboratory of Experimental Sports Medicine at the Federal State Budget-funded Institution "State Scientific Center – Federal Medical Biophysical Center n/a A.I. Burnazyan" of the Federal Medical and Biological Agency of Russia [407] offers to distinguish the following modern conceptual areas for development of SM: occupational health of the professional sportsman; health strengthening of the healthy human doing gymnastics and going in for sports; sportsman's physical and medical rehabilitation.

In the Russian Federation the strategy for development of the medical and medico-biological support of high performance sports in accordance with modern trends in SM development in the world is formed by the Federal Medical and Biological Agency (FMBA of Russia). FMBA of Russia, within its authorities and together with other departments [4], implements different programs within the limits of the scientific and medical activities, in which case the following areas are emphasized:

1. Multidisciplinary approach to medico-sanitary, medico-biological and medical support of professional sports and high performance sports including obtaining and introduction of urgent scientific achievements in the field of medicine and related sciences (biomechanics and biomechanical analysis of movements using the latest movement video analysis systems, functional diagnostics and its modern equipment,

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[1] As applicable to the sports and training activity, characteristics of the examined contingent, the thesis text will use concepts and terms established in the Federal Law No. 329-FZ dated 04.12.2007 "On Physical Culture and Sports in the Russian Federation" [2].

pharmacology in the field of sports medicine, psychology of sports activities, neurophysiology and psychophysiology, high technology treatment and rehabilitation methods, measures for prevention of sports injuries and diseases).

2. Wide introduction of molecular genetics methods in the high performance sports.

3. Individualization of the medico-biological sportsman support including that basing on medical and genetic data.

It should be noted that the explosive growth of scientific studies in SM fell on the period of development of a principally new “three P” strategy, i.e. predictive, preventive and personalized medicine (PM) [379, 510], which evolved rapidly from 3P medicine to 4P (participatory) medicine and then to translation, integrative medicine ending with precision medicine [537]. Individualization of approaches and principles of predictive medicine are of special importance for SM.

The prominent scientists in the field of investigation of the human genome [79, 80, 88, 226, 537] consider that the glory days of predictive medicine will come in 5–10 years and 4P medicine will evolve gradually into 10P medicine and involve actively patients themselves [511]. 10P medicine will include such sections as [467]: predictive; preventive; personalized; participatory (with participation of the patient); practical; permanent; proactive; positive; precision; promotional medicine [88, 253]. The studies in this area at the population level are very promising in solving many applied aspects in the practice activity of SM: selection in sports, specialization criteria and determination of prospectivity, key health parameter monitoring, prevention of genetic and sports-associated diseases, withdrawal from the professional sports activity etc.

4. The active development of the information and technological support of sports medicine (generation of electronic sportsmen’s health certificates, providing for the development of information technologies in accordance with the requirements of the federal legislation [3], generation of data bases on the grounds of “special standards” conception as applicable to sports developing different physical qualities and requiring different somatometric characteristics). But the preparatory work for generation of electronic sportsmen’s certificates has been lasting already for more than 20 years, it was suspended many times and did not lead yet to planned results. The “special standards”

conception has been discussed also for several decades but out analysis of the practice of home SM did not reveal any examples of development of such standards [491].

It is evident that the planned programs cannot be implemented without systemic introduction of the modern evidence-based methods and technologies for control of the sportsman's physical and functional condition. The present study is just devoted to solution of this scientific and medical problem; the literature review for the present study was formed taking into account modern recommendations [434], and, considering the many-year performance of the work, it contains references to the authors studies performed earlier within the limits of implementation of the study working hypothesis regarding the development of diagnostic algorithms.

### 1.2. General issues of terminology and structuring of the technologies for medical and medico-biological monitoring of the functional condition as applicable to scientific medical studies in the field of sports medicine

The term "technology" is widely used in medico-biological studies, in which case it is applied in very different contexts and not always for a good reason. Inclusion of this term into the title of our study is not the mechanical following the formed trend in the working practice and study areas in the healthcare and sports activities systems but an emphasis to the conceptual essence of the term as applicable to medico-biological studies basing on understanding of the main physiologic mechanisms just in the field of sports medicine.

One should discuss briefly the issues of legal and conceptual regulation of this term because inconsistent attempts to regulate this term were made in the healthcare system over the last 20 years, therefore, when analyzing information sources in the regulatory documents and scientific studies, one can find word combinations "new technology" [16], "new medical technology" [7], "medical technology", "psychological technology" [5] and other variations with the term "technology" which are not statutory or conceptually established [455, 459].

At the legislative regulation level, the Federal Law No. 127-FZ dated 23.08.1996 (version dated 17.02.2023), [1] Article 2, includes the technological activities in the scientific and technical and innovation activities: “The scientific and technical activities are the activities aimed at obtaining and use of new knowledge for solving technological, engineering, economic, social, humanitarian and other problems, for providing for functioning of science, engineering and production as a single system”. The term “technologies” is also presented in different articles of direct and indirect operation of this federal legislation.

The Federal Law No. 323-FZ dated 21.11.2011 (version dated 28.12.2022) “On Fundamental Healthcare Principles in the Russian Federation” [3] describes in detail different aspects of technologies used in the medical activities. E.g., “The high technology medical aid being a part of specialized medical aid includes the use of new complex and/or unique treatment methods and also resource-demanding treatment methods with scientific-based efficiency including cell technologies, robot-assisted equipment, information technologies and genetic engineering methods developed on the base of advances of medical science and related fields of science and technology” (Article 34, version dated 25.11.2013). Telemedical technologies and artificial intelligence technologies are regulated in Articles 36.1–36.2. The assisted reproductive technologies (Article 55), complex medical technologies (Article 34) and information technologies (Article 91) are also regulated by this law.

According to studies found in the literature and dedicated to the development of new medical technologies, when developing them, special attention is paid to terminology, according to which, any technology and, especially a new technology, should be just a technology and it should be “described in terms known in science and medicine, without using references to transcendent factors, mysticism and chance events”, to studies with low evidentiality level [381,420]: broadly speaking, “the generally accepted definition of the term “Technology” (from Ancient Greek τέχνη – art, mastery, skill; λόγος – thought, cause; procedure, method of production) is a totality of methods, processes and materials used in any branch of activities and also the scientific description methods for technical production or achievement of the preset result; in the strict sense it is a complex of organizational measures, operations, techniques, interventions aimed at production, servicing, repair and/or operation of an article with the rated quality and optimum expenses and determined by the current level of science, technics and society on the whole".

The conceptual limits of the technology in its initial meaning within the limits of medico-biological and especially psychological studies can be defined as "a science on the mastery to carry out transformations in the preset space of problems, objects, knowledge or information" [429].

The detailed statutory regulation for the specific technology form, i.e. medical technologies, is contained in GOST R 56044-2014. National Standard of the Russian Federation. Assessment of medical technologies. General provisions [15]. This GOST defines medical technologies as methods for diagnostics, medicinal and non-medicinal treatment, prevention and rehabilitation, health protection and strengthening systems used in the healthcare service. One of the key tasks for introduction of GOST R 56044-2014 consists in "planning scientific studies in healthcare service".

According to this GOST, a quite wide range of substantiated regulated medical and organizational interventions are referred to medical technologies. These interventions include "– the use of devices (computer tomograph, ..., technical devices ad applications for mobile telephones and mini-computers; – therapeutic and surgical procedures (acupuncture, plasmapheresis, endoscopic cystectomy, methods for psychological action)".

According to our opinion, inclusion of methods for psychologic action in the section of therapeutic and surgical procedures is not completely substantiated because, e.g., the list of methods for psychologic diagnostics and action for sports medicine is not established yet and its formation has been lasting already for several decades [412].

The document defines also that the potential of a medical technology represents effects caused by the use of the medical technology under conditions of controlled clinical trials [12] and efficiency of a medical technology means effects caused by the use of the medical technology under conditions of typical clinical practice (real world).

It is obvious that all listed items are referred to the activities of specialists in the field of sports medicine.

Basing on the above, a medical technology (MT) should contain the description of its applicability conditions including determination of the disease and condition range at diagnostics and treatment of which it is aimed, i.e. it should meet the criteria set for prevention, diagnostics, treatment and rehabilitation technologies. In particular, positive effects caused by the use of a medical technology should be reproducible irrespective of the place of their practical application (healthcare facility). And the obtained effects should be associated with improved accuracy of diagnostics or treatment and prevention efficiency. As MT are introduced into practice, the accumulated data on the results of its use should be generalized; this data should enrich the respective clinical experience and optimize the conditions and parameters of using MT. In accordance with the above, today the "Procedure for Healthcare Delivery to Sportsmen" [10] accumulates, in the essence, the whole list of MT generally accepted by the professional community and having a certain scientific evidence base.

In psychological practice, the "technology" means generation of "well operationalized concepts about target direction of influences, methods and procedures for their implementation including organizational aspects of use and ways for obtaining the adequate feedback, whose integrated application provides for successful solution of some or other human problems" [429]. In case of the directed action of the psychological sphere, this is a problem region of human condition control in which the most effective method consists in teaching of skills of own condition self-regulation [429].

The term "medical-biological support" (MBS) has a complex history of legislative establishment in the healthcare service and sports [3, Art. 39]. MBS is defined as "a complex of measures aimed at sportsmen's working capacity and health recovery, including medical interventions, measures of psychologic nature, systematic sportsmen's health condition control, provision of sportsmen with drugs, medical products and specialized foodstuffs, performing scientific studies in the field of sports medicine, and implemented in accordance with requirements concerning prevention of use of performance-enhancing drugs in sports and fight against them established by the legislation on physical culture and sports..." [3, Art. 42.1]. Medical interventions have distinct statutory regulation in the healthcare system [] but the list of measures of psychologic nature is not scientifically substantiated yet either regarding diagnostics or regarding correction and remains unformed [413].

MBS and MBM (medico-biological monitoring) are an integral part of the more general concept of “control”. Any monitoring is carried out with the purpose to achieve the targeted changes in the organism condition or a functional system [462]. The term “control” in medical studies is defined as “a process of change in the biological object or individual system condition resulting in achievement of a certain purpose” [477, 500].].

The basic term “control" has been in the professional use and nomenclature of scientific specialties in the field of medico-biological scientific studies for more than 25 years. E.g., theses were actively defended in the specialty 05.13.09 – Control in biological and medical systems and at the junction of scientific specialties from late 90s of the past century [371, 387, 403, 413, 426, 440, 450, 456, 379, 490, 517]. Forty eight theses on these topic were defended in the period from 1998 to 2000 [1].

The control theory is being actively introduced into the medical practice and used in medico-biological scientific studies what is a typical example of interdisciplinary interaction [477]. In this situation, the leading role of control consists in thinking optimization and making the most reasonable decisions [444].

General principles of control of biological systems, to which the human also belongs, assume: availability of the data on “assessment of the initial, intermediate and final conditions (what is, in essence, MBM); development of a general control algorithm; carrying out the operational and integrative monitoring (MBM components) during prevention, treatment and optimization of the training or rehabilitation programs” [477, 526].

As applicable to control in sports medicine, the main task of MBM consists in achievement of the desired or preset effect in the controlled biological object or system [451, 477] and the achieved effect can be training, preventive, therapeutic or rehabilitation one [457, 462].

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[1] https://freereferats.ru/index.php?cat=270&cPath=1_155_263_270&sort=year&direction=desc

The great majority of applied control tasks in the modern medical practice is solved by a doctor in sport medicine and members of the interdisciplinary team basing on the personal experience and knowledge and extremely rarely relying on evidence-based algorithms. In this situation, a doctor acts as a specific (intellectual) and at the same time subjective control factor in the control system [348]. Sports medicine needs the development and testing of a wide range of methodical and organizational models allowing to assess the condition and dynamics of changes in the most important functional systems using mathematical methods. This is an urgent problem solution of which will make is possible to objectivize and enhance the efficiency of control process of the sportsman's organism functional systems.

Solving the problem of achieving a preset result with preservation of certain psychic and somatic health parameters is associated very closely with diagnostics and prognostication tasks [173]. Diagnostics of conditions (initial, intermediate, final ones) is a key aspect of prognostication at different stages of the training process and formation of the optimum control algorithm, which is important for its planning. If necessary, this allows to return to the tasks solved earlier at different rehabilitation stages (diagnostics and prognostication of control efficiency) [169]. In this situation diagnostics should reveal the reserve and adaptation possibilities of the sportsman's organism on the whole and/or its basic systems.

The use of control theory assumes the "optimum combination of training or rehabilitation actions in order to bring the organism into a preset condition change the structural and functional optimum of its systems" [413, 450, 472, 477]. The theory of functional modelling and its methods allow to overcome a contradiction between complexity (and, consequently, insufficient knowledge of biological objects and their behavior) and the need to control these objects in the best way already today, not making this dependent on the time when an adequate analytical theory of their functioning is created [466].

The functional modelling is based on a wide range of experimental studies and procedures tested using the maximally approximated models. The mathematical description of such studies has only information similarity with a biological object or system. Such models allow to assess qualitatively and quantitatively dynamics of selected parameters irrespective of the object complexity and influence of the main acting factors.

Specificity of human organism condition control using MBM is determined by the structural and functional complexity, multidimensionality, multi-parameter nature and multiple connectivity [516]. Many parameters and variables of the controlled functional systems change over time with different speed and dynamism. Functional changes in the cardiorespiratory system during physical activities are an example of operative dynamism but changes associated with the training or physical rehabilitation process reflect long dynamism. The necessity to maintain homeostatics of other parameters comes into dialectic conflict with dynamism of change in the parameters of different functional systems under the influence of sports training means. The analysis should take into account the nature of adaptation changes which affect both constantly changing and homeostatic parameters [456, 477].

The various different-level systems are functioning simultaneously in the human organism. Both substantial (hormone and biologically active substance concentration in different organism media) and energy (mechanical vibration, physical load, sound, electric current, light, etc.) and information factors (words, sentences, commands) can act as control signals for these systems [350].

The human is an hierarchical complex of media of various complexity and with different nonlinearity and basing on synergetics concepts – self-organization theory, the path to a complex system is a path to media with large nonlinearities and, consequently, new properties [341, 421, 423]. The human organism functions in a model of "ordered chaos" and consists of certain functional units, which are the structures being simultaneously dynamic variables. Attractors are distinguished among such structures; they are peculiar points of attraction which cause specific metabolic and functional responses at the given moment. Complex nonlinear systems have multistability, what is in compliance with existence of many attractors each of which has its own region of attraction. Thanks to this, chaotic systems can function in a wide range of different conditions and, therefore, they are able to adapt to changing conditions of the external environment and internal medium. Any disturbance of the functional system adaptation means loss of multistability and development of greater orderliness and in this situation some attractors assume unduly great significance (from viewpoint of the health state and adaptation mechanisms). Therefore, these synergetics patterns cause the influence of physical loads aimed at trainings or recovery of the organism adaptation reserves, i.e., finally, at multistability restoration. Basing on the literature data, one can suppose that final action mechanisms of such externally different factors as physical loads, psychologic stress, physical rehabilitation means are characterized by principal similarity. All these methods influence the stress-limiting systems; at the same time there is no direct dependence on the "dose" and the effect is not rarely achieved by just small influencing factors materializing thanks to phenomenon of "growth of a little" which is typical of nonlinear systems [435, 509]. In this situation, dosed physical loads are in the essence a trigger for sanogenesis and multistability recovery process taking into account the "vegetative memory" of neurons and autoregulation principles.

In the recent years researches focus more and more often on SM problems from biocybernetical and neurophysiologic viewpoints and distinguish a common mechanism for many physiological and pathophysiological conditions, namely, the system's ability to learning and control. In this case, learning is understood as a system's ability for form different physiological and pathophysiological stereotypes from the whole arsenal of determined biological reactions. Therefore, e.g., the overtraining condition is considered as a polytrigger multi-level pathologic system which is capable of both negative learning, i.e. chronification, and positive learning, i.e. recovery [469, 479, 498

### 1.3. Analyzing the efficiency and scientific validity of medical monitoring technologies of the sportsmen's functional condition

The normative documents regulating the content of medical examinations of sportsmen accumulate the basic achievements of medical and physiologic science and also opinions of leading experts and professional communities, therefore, we analyzed three versions of "Procedures" [6, 9, 10] which were in force in the period from 2010 to 2023; this analysis showed that the list of diagnostic methods and parameters was increased gradually as the scientific data was accumulated. But parallelism between the results of scientific studies accumulated in clinical medicine and sports medicine is not observed. E.g., the scientific data on functioning of the immune and metabolic system in the sportsman's organism remain beyond normative consolidation for a long time though genetic analysis of hereditary risk factors (as medically required) is included in the last version of the "Procedure".

Such situation is illustrated by the example of introduction of the results obtained by studies of the immune system functioning into the development of new diagnostic methods within the limits of MBM of highly qualified sportsmen. So, in the period from 2010 to 2015 we studied actively peculiarities of lipid metabolism, endothelial dysfunction, autoimmune processes, immune system functioning in highly qualified sportsmen at different stages of the training cycle in order to broaden the diagnostic algorithms [398, 399, 527, 528, 529, 530, 531]. Our previous studies [351] have shown that high physical and psycho-emotional loads influencing the organism of highly qualified sportsmen cause considerable immunological readjustment which is manifested: firstly, by intensified tissue destroying what is confirmed by appearance of autoantigens of different tissue origin in the sportsmen's blood, and, secondly, by the autoimmune response involving both T-lymphocytes (what is evidenced by presence of T-cell sensitization to tissue antigens in leukocyte migration inhibition test (LMIT)) and B-lymphocytes, the number and activity of which in sportsmen increases what is accompanied by total production intensification of immunoglobulins of different classes and autoantibody production against tissue autoantigens. Accordingly, it is important to specify that T-cell sensitization of the myocardium tissue is characterized by greater duration as compared to sensitization to other tissue antigens. At the same time T-cell sensitization to the cardiac tissue is not reduced but even increases during the transitional period of the training cycle. So, it was found that the sportsman's heart was under constant T-cell autoimmune shock all the year round [351].

We also have shown in another series of studies that parodontium diseases are accompanied by the development of autoimmune processes which can be a leading factor for chronification of inflammatory diseases of the parodontium and a significant component in its pathogenesis and also exert a pathologic effect on the cardiovascular system [352].

We also found that hyperhomocysteinemia being one of the typical signs of early atherosclerosis and thrombus formation due to unfavorable damaging effect on the vascular endothelium and blood coagulation factors, intensified thrombocyte adhesion, is revealed in 60.6% of sportsmen. Our results were confirmed in more recent studies [454]. In this regard it is important to note that increased blood level of D-dimers, the fibrin cleavage products being a typical sign of venous hemostasis activation (thrombus formation) is revealed in every forth sportsman (27.3%) [530].

The totality of the above facts suggests the need to include these parameters in the thorough medical examination (TME) but this did not receive due attention and none of the “Procedure” versions issued from 2010 mention any endothelial dysfunction and coagulogram parameters. Such situation is an example of certain disagreement between the level and results of modern scientific studies and the content of documents regulating medical examinations of sportsmen. It is evident that there is a certain delay between the achieved level of professional knowledge and diagnostic algorithms included in TME programs and the regulatory documents.

The current “Procedure for Healthcare Delivery to Persons Doing Gymnastics and Going in for Sports” [10] is in compliance with the above conceptual scheme of human functional state control (diagnostics, control action, change monitoring) and provision of high quality and evidence-based MBM by the performance regulation, grouping of the subjects ad observed contingents. These approaches have been used in the practice of sports medicine in our country already for more than 30 years. In this situation, an emphasis in diagnostics and control of the functional condition is made on somatometry parameters, assessment of clinical-and-laboratory and functional-and-diagnostic parameters providing for sports implementation of the sportsman’s main physical qualities (endurance, strength, coordination, flexibility, speed) and basic functional systems (Table 1.1).

But a paradox situation is formed when one of the most important principles of Olympic sports stated by Pierre de Coubertin already in 1886: “Psychology wins in the struggle of equal rivals" [cited according to 491] gains new urgent significance and requires evidence-based methodical, neurophysiological and diagnostic sense.

Many researchers note [407, 415, 493] that inclusion of the instructions concerning participation of a medical psychologist/psychotherapist in TME in the Procedure and inclusion of a diagnostic method "Investigation of the psycho-emotional status" in TME of Russian representative teams without describing its content are evidently insufficient for high quality assessment of the sportsman's psychologic condition and for performing his functional state monitoring aimed at health preservation and achievement of the preset sports result.

**Table 1.1.** Analysis of the Procedure requirements to TME at different training stages

| **Procedure requirements** | **Training stages** | | | | |
|---|---|---|---|---|---|
| | **I** | **II** | **III** | **IV** | **V** |
| Frequency of medical examinations (TME) | annually | annually | every 6 months | every 6 months | every 6 months |
| Number of specialist doctors | 2 | 8 (+4)[1] | 11 (+3)[2] | ≥ 14 | ≥ 14 |
| Number of diagnostic methods (parameters) | 10 | 13<br>Complete blood count<br>Blood biochemistry (22)<br>U/S (three organs) | 14<br>Blood biochemistry (28) | 17<br>Blood biochemistry (28) | 24[3]<br>Complete blood count (max)<br>Blood biochemistry (60)<br>U/S<br>(nine organs) |
| Psychological monitoring | - | - | Medical psychologist/psychotherapist | Medical psychologist/psychotherapist | Medical psychologist/psychotherapist<br>Investigation of the psycho-emotional status |

[1] Henceforth the number of specialist doctors participating in TME as medically required

[2] Medical psychologist/psychotherapist are included in the medical team and at stages III–V and the content of their work and diagnostic methods used by them are not established by the Procedure.

[3] The "Investigation of the psycho-emotional status" is included in a group of diagnostic methods and concerns only members of the Russian representative teams (stage V), and the content of this diagnostic investigation is not described in the Procedure.

In 2015 a group of leading specialists prepared clinical recommendations which specified maximally the content of psychological monitoring in sportsmen taking into account the regulatory documents in the field of medical service nomenclature which were valid at that time [415].

But, taking into account the actual financing of healthcare to the sportsman, only Procedure provisions, which are obligatory for fulfilment, are used in practice till now while the clinical recommendations are advisory and do not have the financial provision mechanism what prevents often their actual introduction into practice.

By the regulated extent of diagnostic investigations, the assessment of the sportsman's physical (somatic) condition, when implementing the "Procedure for Healthcare Delivery", takes more than 99%, and psychological investigations take only 1%. While it is evident that achievement of the sports result, provided that the somatic and psychic health parameters are preserved, is possible only in case of the sportsman's certain psychophysiological condition in most sports. This is associated to the large extent with the fact that the search for and development of objective biomarkers of psychophysiological condition are considerably difficult notwithstanding the recent significant advances in the technology for collection and analysis of neurophysiologic data including that with the use of methods for functional mapping of the human brain functions. This is also associated with the fact that, on the one hand, the tools for assessment of the psychophysiological condition used in SM are transferred mechanically from clinical medicine or general psychology and do not consider many aspects of sports selection and peculiarities of the sports activities [162, 173, 205, 233, 236], and, on the other hand, the so-called psychophysiological problem of the relationship between the psychic activity patterns and their neurophysiological, brain provision is far from resolution. At the same time it is considered that resources of such functional neurovisualization methods as functional magnetic resonance imaging (fMRI), quantitative electroencephalography (qEEG), magnetic encephalography and functional near infrared spectroscopy (fNIRS) have a great potential for solving the problem concerning the development of the sportsman's psychophysiological condition biomarkers. The use of such methods allows to study in detail brain functioning at the systemic level of its organization under conditions of materialization of the higher psychic activity types which are critical for the sports activities.

The consideration of brain mechanisms from viewpoints of the modern ideas about organization of the brain functional systems providing for the higher nervous activity makes the base for the detailed characteristics of the brain control systems and study of peculiarities of their functioning in association with human individual peculiarities and their restructurings in the behavior dynamics [365, 366, 414, 438]. All these factors determine a potential, but yet not fully known, efficiency of use of just functional neurovisualization methods for creation of specific neurotechnologies for SM.

Investigating the association between characteristics of the psychic activity course and efficiency of the sports activities implementation is a focus for a large number of psychological and neurophysiological studies what allows in principle to outline several investigational directions having the potential for inclusion in TME. Nevertheless, the selection of a target function, the objective psychophysiological assessment of which would allow to suggest possible candidates for the role of diagnostic criteria (whether an individual parameter of the brain total electric activity or characteristic of the neurophysiologic activity in a specific brain region) is difficult to a certain degree due to absence of a consensus regarding the nature of some or other psychic processes or mechanisms associated with such function.

Within the limits of this thesis study we suggested a function of behavior control or action control processes as such target function. As we shall show below, the study included the analysis of informal description of the control processes (and also psychologic operations associated with them), their neurobiological support and also factors influencing their functioning.

Changes in functioning of action control processes play an important role in lowered productivity of the sports activities. The failure of automatic skills materialization, when destroying of a sensorimotor skill occurs under conditions of the competitive stress, is an example of such situation. Several quite widespread viewpoints on the problem of lowered efficiency of the sports activities implementation under conditions of competitions can be for clarity called the “resource” ones. E.g., in accordance with such viewpoints, the lowered efficiency of the current activities implementation or even destroying of a highly professional sensorimotor skill under conditions of the competitive pressure can be associated with disturbance of the activities control. First of all, the matter concerns the distraction theory within the limits of attentional control, when resources (e.g., of the working memory) are spent to anxiety associated with possible defeat and, among other issues, emphasize the role of anxiety condition in lowered efficiency of the activities (see, e.g., [38]). These mechanisms are associated with so-called bottom-up or ascending neurophysiological information processing processes. The conditions of ignoring the influence or processes distracting from fulfillment of a test task, the so-called tasks for ignoring as, e.g., in situation of dichotic listening to verbal stimuli of different loudness, are an example of such situation [318]. A stimulus not favoring the achievement of the purpose of the current cognitive activity or the anxiety condition can take away the resources required for implementation of the purposeful activity and result in lowering of its efficiency and productivity (see also [125]).

In accordance with other concepts, the lowered productivity of the current activities implementation is associated with the arousal caused, e.g., by the financial reward (e.g., the situation of high rates) (see, e.g., [176]). In other words, one can find study results in the literature, which are interpreted both from viewpoints of excessive influence of the affective-motivation component associated with avoidance of loss (penalty – [206]) and with viewpoints of the resource approach, i.e. the results are interpreted as control process disorder [178].

Lately an approach is developed from viewpoint of peculiarities of activities control which is closely associated with the concept of cognitive control (see, e.g., [236]), which means the individual's ability to carry out the operative control of own cognitive activity in order to achieve the set tasks [405]. There exists many synonyms for the concept of cognitive control. It is limited in some cases only by peculiarities of attention processes and specifics of information processing associated with them, etc. But there exists also the broader understanding of cognitive control when an emphasis is made on flexible distribution of mental resources for control of thoughts and actions for achieving the set purposes [73], and also control and information retrieval from the long-term memory and its correlation with the current purposes [329]. So, e.g., Baumeister's theory [54] states that destroying of a skill under stress conditions is associated with an attempt of conscious control of the processes, which develop automatically. But the causes for activation of such control are not described.

At the same time, psychological studies of repeating mistakes in somatosensory learning suggest explanations for the phenomenon of lowered efficiency and productivity of formed skills implementation [374]. Greshkovich et al. suggest to consider the sportsman's condition basing on two concepts concerning his possible psychophysiological condition. The sports activities under conditions of competitions differ greatly from similar activities under conditions of the training process, because, in accordance with one of viewpoints (distraction theory, processing efficiency theory [123]), the sportsman is distracted by many distracting factors which are absent during trainings, when a skill is being formed. As a result, materialization of the purposeful task suffers because of attention distraction, what, as a consequence, leads to lowered efficiency of the activities implementation and increased number of mistakes. In accordance with the considered alternative viewpoint (explicit monitoring theory, reinvestment theory [187]), such lowered efficiency of the activities implementation is associated with choking due to enhanced control. As it is known, control enhancement is accompanied by the extension of reaction or response time and also, under certain conditions, by increased number of mistakes (e.g., during implementation of complicated sensorimotor skills in musicians or sportsmen). Such opinion about the problem is in compliance with provisions developed in the works of N.A. Bernstein who noted that "directing the conscious attention to baseline movement levels almost always exert the distorting action" [364]. This conforms to opinion of E.P. Ilyin [409] who emphasized in his report that excessive control associated with high significance of the skill implementation (during competitions) was observed the most often in sportsmen going in for technically difficult sports such as jumps, gymnastics, shooting, etc. This agrees to a significant degree with purposeful studies of lowering of sports activities efficiency through the example of shooting, which showed that a threat of penalty resulted in lowered accuracy due to provocation of increased number of checking operations [374].

In other words, the excess of checking operations modelled by the instructions before the study can evidence in favor of existence of ineffective strategies for activities control. In some cases, choking can occur under external (e.g., muscle condition) or internal conditions [409] such as the emotional condition (e.g., anxiety) what can also result in enhanced control of the current activities implementation.

Another aspect of the problem of control functions is closely connected with the issue of the relationship between conscious and non-conscious cognitive control which is not always distinguished in the scientific literature. E.g., cognitive control is understood as a broad totality of interconnected processes which are responsible for planning, cognitive flexibility, abstract thinking, selection of relevant sensory information, etc. [243]. But the available data shows also that cognitive control can function also with non-conscious information. The influence of subthreshold primes and implicit regularities on the behavior is explained by this [112, 142, 157, etc.]. No consensus exists also relative the fact what specifically is done by non-conscious cognitive control. Some authors acknowledge that the nature of cognitive control in unclear (e.g., [335]). Other authors speak of a serious theoretical crisis in concepts of cognitive control [405]. The third authors consider cognitive control even as a theoretical construct, which is inaccessible for scientific knowledge [49, 217 etc.].

The concept of cognitive control and its brain provision as applicable to the tasks of the present thesis study will be considered in more detail in the sections below. It should be mentioned here that absence of generally accepted understanding of psychologic patterns in the activity of the control function mechanisms and their brain provision is a very urgent problem in psychophysiology, what cannot fail to tell upon introduction of methods for objective assessment of the sportsman's psychophysiological condition into the regulated TME practice.

Considering the above, the present study is aimed at the development of potential candidates for the role of diagnostically significant parameters of the brain functional activity reflecting such condition of the structures regulating its behavior, which can be evidence of a possible change in the sportsman's psychophysiological condition associated with worsened implementation of the sports activities.

Within the limits of this study it is suggested to solve the above problem in several stages associated with determination of the factors which are crucial for implementation of the control functions, changes in the activity of which can be potentially related to lowered efficiency of sports activities, on the one hand, and selection of an adequate clinical model and test conditions allowing to assess efficiently and/or visualize the brain provision condition of mechanisms for such functions implementation at the accessible level of neurophysiological objectification, on the other hand. Basing on the above, the next section is dedicated to more detailed consideration of neurobiology of human brain control functions.

### 1.4. Human brain control functions in context of medico-biologic monitoring of the sports activities

The idea of the brain control function is one of the central concepts in the modern understanding of the human higher nervous activity. The concepts and definitions of the behavior control function gained different terminological designation depending on traditions formed in one or another field of sciences about the brain and psychic. A conception of executive functions came into being thanks to appearance of the discipline "neuropsychology" the founder of which is A.R. Luria [48, 164, 437]. As a rule, executive functions are understood as a wide range of processes and operations which allow to regulate proactively and reactively the current behavior through planning and programming the actions, monitoring of their implementation, their inhibition and selection. This totality of processes is designated often by terms used interchangeably: cognitive control/functions [437], executive control/functions [344, 436, 487], control functions [354, 380, 436]. The relatively recent analysis of the Pubmed base has shown [437] that the term "cognitive" and "executive" control is often used for designation of these functions depending on the field of studies. E.g., the term "cognitive control" is more often used in the field of psychology, neurovisualization and so-called computational neurosciences, and the term "executive control" got more widespread use in neuropsychology. Notwithstanding the certain terminological ambiguity, in accordance with common concepts, the "cognitive"/"executive functions" are provided for in general by the structures of the prefrontal, frontal cortex and basal ganglia of the human brain (see, e.g., [140, 436]). It is difficult to overestimate the role of executive functions in behavior regulation and just their major disorders are observed in many psychic and neurologic diseases. Therefore, it is important to specify exactly what kind of processes and psychological operations is associated with executive functions.

As a rule, in order to study the executive functions, different researchers specify processes or operations which are related to implementation of the target-oriented behavior through selection, coordination and monitoring of actions [111]. These operations can be involved in two functioning regimens, one of which precedes a target-oriented action/act (proactive regimen) and the second one reactively follows its implementation (reactive regimen) [64, 137, 172, 213]. The proactive cognitive control assumes formation or retention of the purpose of activity (including planning) in the memory, formation of waiting for forthcoming stimuli and preparation of responses to them [21, 330], ignoring the distracting stimuli and focusing the attention on the relevant current task in the environmental region, making decisions, etc. The reactive cognitive control is associated with such operations as action monitoring and conflict monitoring (interferences between relevant and irrelevant information or between several variants of actions) and detection of mistakes [55, 116, 321], selection of one of variants among available variants of action (including that through overcoming the interference), suppression of the prepared (prepotent) response or suppression of irrelevant actions not selected for implementation [43, 48, 51, 52, 323] and also switching over between the tasks. The so-called cold and hot executive functions are distinguished additionally. The latter are understood as the affective aspect the above processes associated with the emotional reaction and the motivation component. It is evident that involvement of the listed processes in the flexible regulation of target-oriented behavior is impossible without such psychological mechanisms as attention, memory and control. In accordance with this, at the modern stage it is considered however that inhibitory control, working memory and cognitive flexibility are the key components of executive functions [94, 95, 160, 312]. A special role in implementation of cognitive control processes or executive functions is assigned just to inhibitory control. Several authors distinguish inhibitory control as a central mechanism for implementation of cognitive control and cognitive activity on the whole providing for focusing and concentration on the current task, the ability to suppress irrelevant actions (including those which are prompted by distracting stimuli) or actions which lost their urgency in connection with the current purposes [95, 108]. Just disorders in the function of inhibitory control are one of frequent manifestations in the diseases associated with impulsivity (e.g., attention deficit and hyperactivity disorder [119]), obsessions [57, 76, 104, 218, 249, 301] or pathologic gambling addictions [104]. The function of inhibitory control during provision of executive functions consists in suppression of motor or cognitive variants of actions (e.g., mental operations when selecting one of potential variants of the task being solved) which are not appropriate to the current situation. Taking into account the fact that involvement of inhibitory control processes can be realized in the proactive and/or reactive regimens and just inhibitory control is a key process providing for flexible behavior regulation basing on the purposes of the activity. This explains also the great interest to studying the relationship patterns between characteristics of inhibitory control and efficiency of the activities implementation in sportsmen including sportsmen of high class. Taking into account the known data on disorders in the function of inhibitory control it is reasonable to suppose that “high” characteristics of its functioning are associated with the optimum nature of the activities implementation in professional sportsmen.

Lately the association between characteristics of functioning of inhibitory control and quality of activities implementation was actually studied quite actively. The efficiency of self-regulation processes under conditions requiring endurance when the sportsman is in condition of fatigue (as, e.g., in case of long distance running) is associated with the efficiency of voluntary target-oriented attention and also suppression of distracting environmental stimuli and also ignoring the predominant desire to lower running intensity in case of limiting levels of long-term physical load. The enhanced efficiency of self-regulatory processes in professional sportsmen is considered as reflection of the interrelationship between the efficiency of inhibitory control functioning and success of self-control during long running requiring endurance [315]. A similar correlation between inhibitory control and the quality of activities implementation is observed also when analyzing the self-control quality during autonomous trainings [65, 221]. The above statement is true also for games-based ports, e.g., football. So, the study performed by Albuquerque et al. [46] showed that those sportsmen, who demonstrated better parameter values of tactic actions during the play, were characterized by enhanced individual parameter values of inhibitory control.

It follows quite reasonably from the above that individual parameters characterizing the ability to inhibitory control can serve as predictors of success in activities implementation under conditions of sports competitions. This can be evidenced by the results of certain studies which demonstrated such relationship for different sports: accuracy of shooting [313], number of effective balls or number of goals in football [86, 120, 181] and also sports rating [166, 167]. The experimental results obtained in the above studies allow to speak of the fact that inhibitory control has an optimizing and modulating effect on tactic decision-making processes associated with perception processes and cognitive functions [325]. The professional sportsmen is often under conditions of high physical loads (and, consequently, fatigue), competitive stress pressure, rapidly changing environment and time deficit for making a decision (especially in games-based sports at high professional level), what determines the high requirements to optimality of such decisions. This requires also the optimum and stable activity of executive functions on the whole and, in particular inhibitory control, because the latter is important for regulation of not only the motor activity but also the mental activity. Therefore, it is not surprising that in the literature one can find the data evidencing the availability of a positive statistical relationship between the expertness level (sportsman's professional level) and inhibitory control characteristics [120, 168, 237]. It follows from this that more cognitively "loaded" activities, such as in game-based sports (hockey, basketball, football, etc.) in the permanently dynamically changing environment will depend on individual characteristics of inhibitory control to a greater degree as compared to other individual sports. Such requirements to executive functions will be relatively lowered , e.g., in case of running, swimming, etc. under conditions of relatively stable environment not assuming constant assessing and reacting to context changes (including that to behavior dynamics of the team partners). In fact, the studies comparing two sportsmen groups showed that these assumptions were true. The study [161], which used the findings of stop-test (assessing the ability to interrupt implementation of a prepared action), demonstrated positive statistical relationship between the sportsman's professional level self-assessment rating and his evaluation by coachers in game-based sports (football, rugby, basketball). The recent meta-analytical study of literature data, which evaluated the behavior parameters (response time, number of mistakes) reflecting the efficiency level of inhibitory control processes also confirmed this assumption: the higher parameter values of inhibitory control were typical of more high-level sportsmen [110, 333]. The totality of the above data complies with the concepts according to which the sportsmen with relatively better parameter values of inhibitory control in game-based sports are characterized by superiorities in perception and decision-making processes under conditions of dynamically changing environment [46, 315]. The latter include also the actions of other opponent players which should be adequately taken into account to optimize the behavior strategy.

There exist also opposite observations. E.g., in several studies the patterns discussed above were manifested only in the group of young developing sportsmen [206, 227], and such changes were not revealed in relatively older, formed sportsmen. In addition to importance of considering the dynamics of individual psychophysiological development, this data suggests that behavioral parameters not always are a reliable indicator of the condition/working capacity or efficiency of executive functions evidencing directly the sports productivity. E.g., the study of sportsmen from such individual sports as badminton and fencing, did not reveal significant group parameters of inhibitory control (response time in the stop-signal test task) between sportsmen groups of different professional level [45, 249]. And the study [111], which involved sportsmen-badminton players, revealed a difference only between professional sportsmen and amateurs. Thus, taking into account the available contradictions, one can conclude that only behavioral data (response time, number of mistakes) obtained within the limits of common test tasks, in principle is not a reliable indicator of the executive functions condition. One should mention here that the following behavioral tests are used to assess inhibitory control characteristics: Stroop test task [280], Simon test task [268], Eriksen flanker test [115], Go/NoGo test tasks [324] and stop-signal test task [182]. But, as it is noted in several studies, the results obtained when fulfilling these test tasks not always agree with each other what is manifested by weak statistical correlation between them [197, 216]. Thus, the behavioral parameters of executive functions are characterized by such level of inter-subject variability that this does not allow to consider them as a highly reliable indicator or predictor of the optimum condition of the brain control functions. At the same time, at the modern level of psychophysiological studies, the approaches are available, which use methods of tomographic functional neurovisualization and allow not only to determine a set of the brain structures being the key elements in the inhibitory control system but also to obtain the characteristic of their functional condition. At the same time, this aspect associated with the use of these parameters for assessing the executive function condition remains beyond the attention of researchers. One of significant limitations in the use of the data on brain provision of inhibitory control in the assessment of the executive function condition consists in absence of non-contradictory concepts concerning the element composition of the brain inhibitory control system and characteristics of its functioning when the brain control functions are changed. This issue will be considered in the next section of the literature review.

### 1.5. Inhibitory control mechansms in the healthy human brain

When speaking about the brain provision of inhibitory control processes, it is necessary to consider a problem of selective and nonselective inhibition. It is considered, as a rule, that nonselective inhibition is involved in those situations when it is necessary to suppress all components of the probable behavior (action, response). E.g., when a potential threat is detected, it is necessary to stop all current activities for selecting the further nature of behavior implementation (e.g., selecting the strategy “to run away” or “to struggle”, etc.). The selective inhibition is involved in relatively more complicated situation, under conditions, when action suppression assumes suppression of only a part of response components (see [58]), e.g., for complicated coordination of actions when selecting one of several variants of actions with different effectors (extremities). A situation of driving a motorcar is often presented as a variant of such situation, when control of a steering wheel, handle of gear change and brake and accelerator pedals is distributed in a certain way between the arms and legs. The selective inhibition can be used to coordinate effectively the activities for driving a motor car (e.g., to suppress selectively the process of steering wheel control).

Thus, selective inhibition is realized as a cognitive control mechanism at the stage of perception or at the motor stage of behavior regulation. The selectivity can be associated with a certain set of behaviorally significant stimuli at the perceptive control level [58] or during suppression of one of preliminarily prepared action variant at the motor control level [89]. The combination of these inhibition processes allows to regulate almost the whole range of behavioral reactions and acts but the experimental data is known which suggests that such selective inhibition can result in a nonselective effect, namely suppression interference to other behavior components what leads to their slowed down implementation [82, 229]. This emphasizes a complex nature of the interrelationship between selective and nonselective inhibition which depends on the context of the current behavior and which can differently tell upon the balance between selective and nonselective inhibition [118, 327, 328, 338]. E.g., in the context of stimulus-selective interruption of the activities, the inhibition processes are investigated using special test tasks for inhibitory control, in which implementation of a preliminarily prepared action is controlled by specialized stimuli of the "to ignore" or "to continue" type [103, 118, 172]. In other words, in order to fulfill a test task correctly, it is necessary to carry out discrimination (categorization) of such control stimuli and only after than to implement or stop implementation of such action prepared for implementation. From viewpoints of concepts of selective inhibition, such strategy is called sometimes "discriminate-then-stop" [58]. From viewpoints of concepts concerning nonselective inhibition such situation is considered somewhat differently, and, namely, as a strategy of "stop-then-discriminate" type [300], in accordance with which the occurrence of a control stimulus at first initiates automatically activity inhibition and only after that there takes place (or does not take place) restart of the motor program if the stimulus is not identified as a "stop-signal". Under conditions of the test task with Go/NoGo stimuli, such situation is manifested a extension of the response time to Go stimuli. The extension of the response time to Go stimuli is observed at the level of motor inhibition similarly as a result of selective inhibition interference. The matter concerns just involvement of nonselective inhibition in both listed cases.

Thus, an issue on the relationship between selective and nonselective inhibition is one of the central problems for studying the inhibitory control. And, what is more important, if conditions for involvement of nonselective inhibition occur, it influences the efficiency of planned actions implementation. In a wider context, nonselective inhibition is one of key factors for effective activities regulation and it occurs both at the moment of action implementation and in case of their suppression.

It is considered that action inhibition due to involvement of selective inhibition is provided for by the neuronal network consisting of the so-called hyperdirect and indirect pathway which includes the human brain cortical structures and basal ganglia (see e.g., [131]). The hyperdirect pathway, which is believed to provide for reactive inhibition, includes such brain regions as the right inferior frontal cortex, pre-supplementary motor cortex and subthalamic nuclei. Functional specialization of these brain regions connected with white matter fibers is associated with provision of rapid and global inhibition of the motor activity (see, e.g. [196]). While the proactive, relatively slow and purposeful inhibition of the motor activity is associated with functioning of the indirect inhibitory pathway, which is provided for by the activity of subthalamic nuclei and striatum (see, e.g., [179]). The selective inhibition processes are provided for by the brain structures included in both the direct and hyperdirect pathways [134, 319]. At the same time, individual behavioral manifestations of inhibition interference correlate negatively with the tract thickness of the brain white matter connecting the structures of the hyperdirect pathway [33, 134]. This suggests the potential association between the hyperdirect pathway and nonselective inhibition [148]. As concerns selective inhibition, a relationship with similar pattern is demonstrated for the indirect inhibitory pathway for values of response time under conditions of the stop-signal test task [33, 134]. The latter is in compliance with the data on functioning of the inhibitory control in the proactive context, when preparation for selective inhibition of one of action variants was characterized by greater levels of the striatum functional activity [319].

Thus, it is considered that interaction between the hyperdirect and indirect pathways of inhibitory control provides for the dynamic balance between selective and nonselective inhibition processes. E.g., according to the theoretical action inhibition model, which was called “pause-then-cancellation” [258], cancellation of a planned action consists of two complementary stages of involvement of nonselective and selective inhibition (see, e.g. [96]). The stage “pause” is characterized by involvement of the hyperdirect inhibitory pathway structures [127, 144] providing for rapid global inhibition, e.g., in response to actuation of a distracting but valuable for the current behavior stimulus according to orientation response type. At the same time, relatively slower processes provided for by the indirect inhibitory pathway are associated with selective inhibition with involvement of the brain structures included in the cortico-basal neuronal system [41].

But under conditions of uncertainty of whether it is necessary to inhibit or implement the forthcoming action, nonselective inhibition processes begin to play the leading role in the inhibition processes. As recent fMRI investigation under conditions of the Go/NoGo test task [118] using the so-called mapping based on the region of practical equivalence or null hypothesis (ROPE mapping) showed, the human brain structures associated with provision of inhibitory control demonstrated practically equivalent activity level both in Go and NoGo tests. These were the brain structures which were associated with provision of inhibitory processes in several previous fMRI studies using the Go/NoGo test: right dorsolateral prefrontal cortex, inferior frontal lobe, temporoparietal junction and also left inferior frontal gyrus (including frontal operculum) and frontal eye field. In the essence, this is the first tomographic study, which demonstrated the direct evidence in favor of involvement of these brain structures in provision of nonselective inhibition and confirmed the assumptions suggested earlier by other researchers [177, 262, 271, 295]. One should pay attention to the fact that just the right inferior prefrontal cortex is considered a key element in the brain action inhibitory control system among the above listed regions. Though the role of this brain structure was demonstrated both in the studies involving healthy volunteers using the stop-test [42, 280] and in patients with brain damages, the issue on the nature of its functional specialization regarding inhibition processes remains the subject for active discussion

[194, 287, 288, 144, 145]. In this context, the data evidencing the role of the contralateral inferior frontal gyrus in provision of nonselective control broadens the concepts concerning the element composition of the brain inhibitory control system on the whole.

Thus, the selective inhibitory control processes have been studied by now relatively more comprehensively as compared to nonselective inhibition (and also interactions between them). This is associated to a significant extent with the fact that, as a rule, the tests, in which it is necessary to suppress the response, are relatively rare in the test tasks for inhibitory control. At the same time, the tests with equally probable presentation of Go and NoGo tasks are relatively not numerous (see, e.g., [118]). And only the use of just this modification of the GoNoGo test task and a specially developed statistical method for assessment of the so-called null effects [118] allowed for the first time to prove experimentally the association between the brain structure activity and functioning of nonselective inhibition which is involved in processing of not only NoGo stimuli but also Go stimuli. This demonstrates clearly functioning of the neuronal inhibitory control system in the nonselective regimen, i.e., global inhibition regimen.

At the same time, there are few studies in this area and the issue on the nature of interrelationship between functional characteristics of the brain system providing for nonselective inhibition and the efficiency of the implemented activity is to be investigated in future. E.g., it was shown that the neuronal inhibitory control system in the nonselective regimen could be reorganized in obsessions [156]. We tested a developed new approach to the so-called ROPE mapping within the limits of this study for the first time for the clinically-oriented studies [244]. We found for the first time that extension of the element composition of the brain inhibitory control providing for nonselective inhibition was observed under conditions of the equally probable Go/NoGo test task in patients with obsessive compulsory disorder (OCD), one of the important signs of which is inhibitory control process disturbance and uncertainty intolerance [156]. The neuronal system providing for nonselective inhibition in patients with OCD includes the regions of the anterior cingulate cortex and inferior frontal gyrus (tectum zone) of the right hemisphere as compared to healthy subjects. And the more pronounced disorders in functioning of inhibitory control are (in terms of response time), the lower the activities of the element in the region of the right anterior cingulate cortex are. The obtained data not only suggests involvement of restructuring of the brain nonselective inhibitory control system in pathogenesis of obsessions but also demonstrates a possible potential of using the functional parameters of this system as an objective indicator showing the efficiency of the executive control functioning. In this connection it should be specified that OCD is a quite severe psychic disorder with highly pronounced disturbances in the behavior control processes, inhibitory control, action monitoring, etc. At the same time the task to reveal signs of lowered activities implementation efficiency and productivity in sportsmen does not imply gross disturbances in the inhibitory control functioning, in addition to specifics of the sports activities. Basing on the above, the further development of studies in this area and achievement of the objectives of our thesis study require to use a clinical model which allows to generate the conditions for studying changes in the brain provision of the control functions on the whole and, in particular inhibitory control, which are associated with lowered efficiency and productivity of the implemented activities. Such clinical model should demonstrate reliably the parameters and indicators of the brain activity (markers) reflecting changes in the functioning of the elements of the brain inhibitory or executive control system or possible reorganization of this system which could be used in future as a "diagnostic" sign showing lowered efficiency of the executive/inhibitory control. The present thesis study selected generalized anxiety disorder as such clinical model of restructurings in the brain mechanisms of action executive control. The association of this disorder with changes in the activity of executive functions will be considered in detail in the following section.

### 1.6. Changes in the human brain control functions in generalized anxiety disorder

Anxiety disorders, which are one of the most frequent diseases, are characterized by disturbances of control functions. So, every third resident of well-developed countries (33.7%) has anxiety disorders during the life, and this pathology is observed 1.5 times more often in women than in men [129]. E. Ramon-Arbues et al. report revealing of moderate anxiety in 18% of students [310], and different anxiety disorders are diagnosed in 7–15% of children [461]. Our analysis of literature dedicated to studying anxiety disorders [534] shows that, according to generally accepted viewpoint, anxiety is defined as a subjectively unpleasant emotional condition: feeling of uncertainty, waiting for bad events, difficult to define apprehensions. It is considered that pathologic anxiety is the leading symptom of anxiety disorders; according to R. Lieb and G.-U. Wittchen, its basic signs are: "1) an anxiety response and avoidance behavior are experienced by the people suffering from this disease as unjustified, inadequately intense reactions occurring too often, 2) they begin to avoid situations causing anxiety and lose control of anxiety, 3) anxiety responses develop successively and last longer that usually and 4) results in lowered life quality" [430, 534]. According to S. Kierkegaard, anxiety is generated by freedom of selection, is a result of human's encounter with diversity of possibilities [427], what, in its turn, in the essence, is an example of uncertainty situation. This is associated to a great extent with the fact that selection of one out of possible action variants is linked, as a rule, with result uncertainty what favors the development of anxiety. It is noted also that during the COVID-19 pandemic the incidence of anxiety disorders increased considerably [239, 242].

Generalized anxiety disorder (GAD) is one of the most frequent variants of clinical anxiety manifestation [304]. The prevalence of GAD over the life varies from 0.1 to 8.5% and is on average approximately 5% of cases in the adult population. GAD takes a considerable percentage (from 12 to 25%) among other anxiety disorders. This pathology is characterized by anxiety which has generalized and stable nature while not being restricted to any certain situations. That is, anxiety has "free floating" character [50]. It was shown that GAD is observed more often at the age from 20 to 40 years. In this situation, the average age of disorder onset is 15.6 years and onset of GAD was observed before the age of 20 years in 75% of cases [32]. GAD incidence increases with age reaching maximum at the middle age. The leading symptoms of GAD include internal strain, high concerns, different apprehensions and unjustified worry because of different causes which are experienced for not less than 6 months. Patients with GAD complain the most often of constant nervousness feeling linked with muscle strain and shiver, palpitation, dizziness and sweating. GAD begins often at the young age and develops as a chronic disease. Patients with GAD tolerate uncertainty very difficultly [141]. Patients with GAD represent in advance the most unfavorable variant out of all in principle possible variants of the course of events [507]. A.B. Kholmogorova reports that pronounced chronic uncontrollable worry poorly responding to the therapy has become a special feature of this type of anxiety disorders [524]. The external signs in a patient with GAD include usually uneasy movements, restlessness, habit to fumble something, finger tremor, knitted brows, stiff face, deep sighs, or hurried breathing, pale face, frequent swallowing movements.

The main distinguishing feature of GAD is the fact that vegetative symptoms in patients with GAD are observed only permanently but not as paroxysms [373]. Different headaches are frequent comorbid disorders in GAD. Our earlier studies showed that headaches were observed in 87% of patients. In this situation, tension headaches (THA) were observed the most often (63% of cases) [418]. Migrainous pains were noted in 34% of patients with GAD. Twenty nine percent of patients with GAD had cervicocranialgia (pains localized in the cervical and occipital regions with irradiation to the parietal region which develop in forced static head and neck positions and become more intense during movements). It should be mentioned that 24% of patients with GAD had several headache types simultaneously [512]. The HADAS multi-center study involving patient with tension headaches revealed signs of GAD in 19% of cases [150]. The significant increase of anxiety level in patients with chronic THA as compared to patients with episodic THA is reported also by other researchers [39]. Sleep disorders are also a frequent cause for visits of patients with GAD to a neurologist. Sleep disorders were reported by 60–70% of patients with GAD, and insomnia appears with simultaneous development of GAD in most cases [81, 162]. The studies reveal often awakenings, extended time of falling asleep and keeping wake in the sleep period, reduced representation of deep (delta) sleep. These are so-called adaptation changes associated with the high level of cerebral activation observed both in case of anxiety and in proper insomnia [473].

An important aspect in investigation of GAD consists in description of accompanying changes in both cognitive functions (including executive control) and emotional hypersensitivity [331], disposition toward focusing on potential hard or danger of stimuli, especially under conditions of result uncertainty [141]. According to B.A. Volel, cognitive disorders are a quite often and stable symptom in patients with anxiety disorders which has a negative effect on the patients' everyday life [419]. Anxiety disorders were shown to be linked with attention disorders [369], according to type of hyperfocus to stimuli characterized by a potential threat [71]. Moreover, it is considered that such patients have transition from automatic (or not evident) to controlled (or evident) regimen of cognitive processing of the coming information. But the more processes need voluntary control, the greater the cognitive load degree and energy consumption are and the lower the possible information processing rate is [264]. Researchers report [135] the significant role of control function disorders ("executive dysfunction"), the complex of capabilities required for control and self-regulation of behavior and emotions.

According to the model of K. Cicerone et al., four aspects are distinguished in the composition of control functions: 1) control cognitive functions associated with control and planning, purposefulness of the activities; 2) behavior self-regulation functions associated with emotional reinforcement; 3) functions regulating activation i.e. providing for the initiative and behavior activation; 4) metacognitive processes [78].

Our analysis of the literary data [535] shows that observed emotional dysregulation of the activities in affective disorders is linked often with such cognitive disorders as impaired working memory, disturbed perception processes of spatial relations and behavior control processes. As a rule, such changes are accompanied by prevalence of negative emotions and anxiety-depressive conditions [470]. Generalized anxiety disorder is manifested by change in the human brain total electrical activity in the form of increased EEG (electoencephalogram) power spectrum practically in all frequency ranges. E.g., prevalence of slow-wave activity predominantly in the region of central frontal and parietal leads is often observed in GAD in the condition of operational rest. Some authors report possible involvement of the human brain hypothalamic-septo-hippocampal system structures in GAD pathogenesis what is reflected by increased power spectrum in EEG theta range [538]. Moreover, the EEG functional connectivity in the theta range in the operational rest in GAD is lowered relative to standard values [408].

But when patients with GAD are involved in the activity implying emotional reacting the increase of EEG power spectrum in theta range is observed, on the contrary, what is considered as GAD – associated hyperactivity of the human brain cortical-hippocampal-limbic system [538]. Such picture of changes in the brain rhythmical activity in the operational rest is observed not only in adults but also in children with GAD [461]; it is accompanied by impulsivity at the behavior level what can suggest GAD-associated lowering of functional efficiency of inhibitory control processes. Moreover, as the results of our studies show the effective pharmacological correction of anxiety disorders in children is accompanied by lowering of impulsivity and EEG power spectrum in alpha and theta ranges what, can reflect, probably, the normalized control function activity [461]. Thus, under conditions of the high individual level of nonspecific activation, patients with anxiety disorders are characterized by low energy reserves and disposition to formation of protective inhibition what is manifested by increased slow-wave activity index in EEG.

The analysis of studies using functional tomography and aimed at revealing functional pattern of certain brain structures in GAD and also their interactions can be divided for clarity into studies evaluating the effect on the functional activity level of certain structures in case of involvement in the activities or the force of functional connectivity between the elements of the functional brain systems in the operational rest. E.g., under experimental conditions requiring emotion regulation, researchers report disturbances in the process of involvement into these processes of the dorsal part on the anterior cingulate cortex (ACC), lateral frontal cortex and inferior parietal cortex in GAD [170, 207]. The above brain structures are the part of the so-called fronto-parietal system, which is considered to be involved in provision of cognitive control processes (processes of inhibitory control, working memory, action monitoring and their selection). In this context it is not surprising that local activity in these brain structures is lowered in GAD. Convergent findings obtained by EEG and fNIRS methods also suggest inhibitory control disorders in GAD [207].

Thus, the currently available experimental clinical and psychophysiological data not only suggest the presence of correlation between GAD symptoms and inhibitory control processes [535] but demonstrate also adequacy of our selected clinical model of GAD-associated changes in the brain provision of the human inhibitory control. Taking this into account, GAD is suggested within the limits of our thesis study as the key aspect in the clinical model of inhibitory control process disturbance. It is supposed within the limits of the present study that neurovisualization signs of the disturbed brain provision of inhibitory control, which are planned to be established when studying patients with generalized anxiety disorder, can be used as potential indicators showing changes in control functions associated with changes in the inhibitory control activity and lowered efficiency of the current activity implementation. Basing on the fact that the issue on functional patterns of the brain inhibitory control system in the nonselective regimen (global inhibition regimen) in GAD conditions remains insufficiently investigated, the experimental work within the limits of this thesis study relies on the study results of nonselective inhibition under conditions of the Go/NoGo test task in healthy subjects. The previous fMRI studies, involving healthy subjects and using the modified two-stimulus Go/NoGo test [172] and a new method for brain mapping based on Bayesian statistics developed by us earlier [118], established for the first time a set of elements of the brain inhibitory control system which are involved in provision of the nonselective regimen of this mechanism functioning under uncertainty conditions which are modelled by equally probable presentation of Go and NoGo stimuli. The issue of how functioning of the neuronal system changes in GAD under conditions of nonselective regimen of inhibitory control functioning remains uninvestigated. Moreover, it should be mentioned that the Go/NoGo test is the most promising for assessing the efficiency of inhibitory control processes in professional sportsmen what should be considered in more detail.

### 1.7. The Go/NoGo functional test in the studies of inhibitory control in sportsmen

In addition to studying the relationship between sports activities efficiency parameters and functioning of the inhibitory control mechanism, which was considered above, the nature of association between them is studied from viewpoints of the influence exerted by the complicated activities (including sports activities) on the inhibitory control parameters. One of the approaches to studying this issue consists in assessment on the influence exerted by training, aimed at improving the efficiency of fulfillment of the Go/NoGo behavioral tests and stop-test, on the functional efficiency of inhibitory control under other conditions [215]. The matter concerns the so-called “transfer” effect, when training using test tasks for inhibitory control exerts a general optimizing effect on the activities in general what can be manifested, e.g., as response time decrease what is linked with plastic changes in functioning of the respective brain structures providing for inhibitory control [148]. The Go/NoGo test task is one of the tests frequently used in the studies in this area [56]. It was shown in a group of elite fencers that trainings, aimed at optimization of inhibitory control, could be accompanied by changes in the activity of the frontal cortex and basal ganglia [286] and anterior cingulate cortex [205]. So, it was found that, as compared to the control group, elite fencers were characterized by larger N2-P3 component amplitude of event-related potentials (ERP) in NoGo tests, in which a prepared action was inhibited under conditions of Go/NoGo test task. In spite of the fact that the similar increase of these components amplitude is quite reproducible when studying just elite fencers, the study of, e.g. boxers, did not reveal such amplitude changes [98]. This is in compliance the findings of the studies which did not reveal the effect of training using the Go/NoGo test task on the inhibitory control characteristics [215]. One of the possible causes of such results consists in the fact that not the amplitude of respective ERP components but their latency is a relatively more reliable indicator of inhibitory control efficiency [332]. A series of studies concerning the influence of the professional sports activities on characteristics of the functional activity of the brain structures compared the highly qualified sportsmen with a healthy subject group [201, 205, 286]. The analysis of two sportsmen groups (basketball and table tennis) used the Go/NoGo test to compare with sportsmen from the endurance group (running, swimming, etc.) [301]. It was found that the best parameter values in terms of the response time were demonstrated for tennis players. Moreover, this sportsmen group showed less latency of ERP components associated with decision making in the time window, in which ERP components associated with inhibitory control are usually recorded.

It should be mentioned also that parameters of inhibitory control functioning can vary significantly depending on the sports. So, e.g., the comparative study of fencers and boxers using the Go/NoGo test task showed that the latter demonstrated worse parameter values [93]. In particular, boxers (as compared to fencers), whose sports activities are linked with permanent head traumatization, showed increased latency of P300 component for NoGo stimuli, which was comparable by its amplitude with the results of control subject group not being sportsmen. The obtained data was considered by the authors as reflection of the negative influence exerted by repeating brain concussions on the inhibitory control processes. Also in this context, the Go/NoGo test is an adequate way for revealing changes in the control functions associated with brain traumatization due to professional sports activities. One should mention the good perspectives of the Go/NoGo test for studying the traumatization consequences in sports and this can be one of the study areas where this test task is effective for assessing the functioning of inhibitory control mechanisms. At the same time, it is worth mentioning that we did not find similar works in this area using functional tomography methods, which would allow to reveal the brain structures associated with provision of the effects discussed above.

Thus, the above allows to conclude that the neuronal activity recorded under conditions of fulfillment of the Go/NoGo test task can be a reliable indicator of the brain inhibitory control system condition. The considered studies show either the effect of exerted by inhibitory control optimization on characteristics of the sportsman's professional activities or productivity lowering associated with negative consequences of the sports activities. Moreover, studies aimed to revealing characteristics of the element composition of the brain systems providing for inhibitory control in case of lowered productivity of the sport activities implementation and also characteristics of the functional activity of such elements were not performed (including studies using the Go/NoGo test tasks which demonstrated their adequacy in assessment of inhibitory control mechanism functioning).

The state-of-art in this study area is such that the necessity to establish typical neurobiological signs of changes in the brain provision of inhibitory control associated with potentially suboptimal regimen of the current activities implementation becomes evident. The present study is dedicated to solving this scientific problem.

# CHAPTER 2. METHODS OF THE STUDY

## 2.1. General characteristics of the study

To solve the tasks set in this thesis two series of studies were performed: 1) Psychodiagnostic investigations of highly qualified representatives of precise sports (rhythmic-sportive gymnastics); 2) psychophysiological investigations using fMRI data obtained within the limits of the clinical model of GAD-associated changes in the brain provision of executive control, using intergroup data comparison of healthy subjects and patients with GAD in two experimental conditions, i.e. when performing the test task for inhibitory control (two-stimulus Go/NoGo test) and in the operational rest condition. The psychophysiological investigation was performed in several stages which are presented in Fig. 2.1. The first stage implied performing the comparative study of patients with generalized anxiety disorder (24 study participants) and healthy subjects (35 study participants). At the second study stage the fMRI data, obtained in independent samples of healthy subjects, was used for searching for the brain structures the activity of which makes a key contribution to provision of the higher activity types, changes in which can be caused by GAD: 1) socially significant information processing processes, which are important, first of all, for game-based sports [270, 303], 2) executive control processes under conditions of the cognitive activity on the material of multiple-meaning verbal information processing [285]. The brain structures revealed in these studies and also in investigations of the first stage of our thesis study were used at the third stage, i.e. intergroup comparative study of fMRI data of patients with GAD and healthy volunteers recorded in the operational rest condition. It was planned to use the fMRI data obtained in the operational rest condition for assessment of the influence exerted by GAD on characteristics of functional connectivity of the elements of the brain systems for nonselective inhibitory control, socially significant information processing and also executive control. We planned to use the results of the studies, performed in our clinical model of GAD-associated changes in the brain provision of the control functions, for assessing the possible diagnostic value of analyzing the functional connectivity of the above elements when solving the task on assessment of the sportsman's psychophysiological condition regarding possible disorders in parameters of the integrative activities of the brain systems associated with behavior control (including general cognitive and social aspects (which are important, in particular for game-based sports)).

1. fMRI-study under two-stimulus Go/NoGo test conditions. Number of participants: 34 - healthy subjects, 25 - patients with generalized anxiety disorder (GAD):

1.1. Identification of nodes in the brain system of non-selective inhibitory control (NSIC) in patients with GAD and their comparison with data obtained from healthy subjects.

1.2. Intergroup comparison of fMRI-data from GAD patients and healthy subjects: local activity levels and functional connectivity (FC) comparison.

1.3. Correlation analysis between local activity levels in structures identified at stages 1.1.-1.2. and psychological data - intragroup analysis of data from patients with GAD:

1.3.1. Correlation analysis with average BOLD-signal values in the brain structures identified during the analysis of data from patients with GAD.

1.3.2. Voxelwise correlation analysis of local activity levels from patients with GAD.

↓

2. A series of studies in order to select regions of interest for the resting state FC analysis based on fMRI-data in healthy subjects and patients with GAD:

2.1. A study of resting state FC changes associated with the level of social intelligence. Number of participants: 42 - healthy subjects

2.2. fMRI-study of local brain activity and modulated FC during social interactions under conditions of anonymous opponent. Number of participants: 42 - healthy subjects

2.3. fMRI-study aimed at identifying nodes in brain systems underlying executive processes involved in resolving lexical ambiguity. Number of participants: 48 - healthy control subjects.

↓

3. Intergroup analysis of resting state FC in patients with GAD using areas of interest identified in stages 1-2. Number of participants: 100 - healthy subjects, 25 - patients with GAD.

3.1. FC analysis between areas of interest – nodes of the NSIC and its correlation with psychological data.

3.2. FC analysis between areas of interest – brain structures and all other voxels in the brain for the following areas of interest:

3.2.1. Brain structures involved in NSIC (under Go/NoGo test conditions).

3.2.2. Brain structures involved in the processing of social information during social interactions.

3.2.3. Brain structures involved in executive control of cognitive activity during ambiguity resolution.

**Figure 2.1.** Study design. Designations: GAD – generalized anxiety disorder, FC – functional connectivity.

## 2.2. Psychodiagnostic investigation of highly qualified sportsmen

the first series investigations of the thesis study performed in 2010–2012 [425] involved 31 women-gymnasts from representative teams of Russia (n = 18, age: 16.2 ± 0.3 years (henceforth, mean ± standard deviation)) and St. Petersburg (n = 13, age: 18.1 ± 0.4 years). To solve the tasks of the present thesis study we performed the comparison of psychometrical data reflecting anxiety level in highly qualified representatives of precise sports of different qualification representative team of Russia – representative team of St. Petersburg [425, 532].

The precise sports as, e.g., rhythmic-sportive gymnastics, were selected as a model for this psychological investigations because these sports make high requirements both to motor (physical) qualities and to controlled characteristics of the psychologic condition in the process of training and competitive activities. Female sportsmen – members of the representative team of the Russian Federation (RF) in rhythmic-sportive gymnastics (RSG) were selected for the comparative study of psychological characteristics of the highly qualified representatives of precise sports; their parameter values were compared to those of women-gymnasts from the representative team of St. Petersburg (SPb). The period in sports of all female sportsmen included in the study was more than 10 years, the level of sport qualification: Candidate Master of Sports (CMS), Master of Sports (MS), Master of Sports of International Class (MSIC). Psychological diagnostic investigations were performed in the beginning of the second preparation stage of the annual training cycle using the Spielberger-Khanin Personal and Situational Anxiety Scale and Martens Competitive Personal Anxiety (CPA) Scale adapted by Yu.L. Khanin [523].

It should be mentioned that, as it is known, the Spielberger-Khanin Personal and Situational Anxiety Scale is intended to assess the anxiety condition taking into account its deepness, what is made in order to reveal the necessity to provide psychological aid. The use of these psychometrical parameters allows to reveal the conditions and factors under the influence of which there occurs the high anxiety condition, and also the degree of possible personal deadaptation in case of a psycho-traumatic situation. Additionally, the personal and situational anxiety scale makes it possible to reveal personal characterological peculiarities, which can be useful for the sportsman's psychological condition monitoring: lack of confidence, susceptibility to suggestion, dependency in making decisions and actions, etc. This procedure consists of two questionnaires, which allow to determine the personality's situational anxiety level under conditions of a difficult psychological situation, personal anxiety level as an individual feature which does not depend on a specific situation [359].

The Eysenck Personality Inventory (EPI [505]) was used to assess the possible influence of the individual's characterological features on the signs of the anxiety condition (which is manifested in certain situations and defined as anxiety) [431]. This questionnaire was used to assess such characterological features of the female sportsmen involved in the study as extraversion-introversion and neuroticism-stability. Taking into account the main principles of the so-called resource approaches, which emphasize the role of anxiety condition, the relative intensification of which is associated with lowered activities productivity (see, e.g. [38]), the increased levels of personal anxiety could be an indicator of lowered efficiency of activities implementation within the limits of this study. Moreover, the sportsman's professional level (the representative team at the level of the country and city) can be an indirect efficiency indicator.

The individual characteristics of psychological defense were assessed additionally on the base of coping-strategies. It is known that the so-called Stress Coping Strategies Indicator is one of the procedures for diagnostics of stress-coping behavior. This procedure based on studying the basic variants of coping-strategies was developed by James Amirkhan in 1990 [36] and later it was adapted by N.A. Sirota [499] and V.M. Yaltonsky [540] for use in Russian. The procedure is a brief self-assessment questionnaire consisting of 33 statements determining characteristics of basic coping-strategies, their degree in the structure of the stress-coping behavior. The three-staged factor analysis of various situation-specific responses to stress allowed J. Amirkhan to determine three basic coping-strategies: solving problems, search for social support and avoidance (evasion). It is known that this questionnaire can be used effectively both for investigation of adolescents and young adults and adults [541], what determines adequacy of its use in sports medicine and makes it appropriate for the objectives of the the present study.

The Plutchik-Kellerman-Conte (the so-called Life Style Index, (LSI)) developed in 1979 is another one of the methods for assessment of coping-strategies which are widely used and which showed their efficiency. This tool can be used to diagnose the wide range of manifestations of the psychological defense mechanisms: to determine the strain level of eight basic psychological defenses, investigate the hierarchy of the psychological defense system and assess the total strain of all measured defenses (TSD), i.e. arithmetic mean of all measurements of eight protective mechanisms. According to Chudnovsky and Sutomina, “several scientists state that compensation and rationalization are the most constructive psychological defenses and projection and repression are the most destructive ones” [533].

Taking into account that several previous studies [362, 385, 422, 503] have found that most professional and highly qualified sportsmen leave sports quite early from the viewpoint of age periodization, this is associated to a great extent with psychological fatigue, i.e. emotional burnout [363]. The high emotional and psychological loads of highly qualified sportsmen require large physical and psychic energy consumption. The long-term emotional strain without due psychological support or in case of incorrectly developed recovery program can promote formation of emotional burnout syndrome.

Emotional burnout is a psychological defense mechanism generated by a personality in the form of complete or partial exclusion of emotions in response to selected psycho-traumatic factors [372]. This mechanism allows the human to dose and use sparingly the energy resources. But at the same time, its dysfunctional consequences can occur when burnout tells negatively upon implementation of the professional activities and in relations with the sports team members.

A series of studies performed by E.I. Grin [389, 390, 392] analyzed the personal resources for coping with psychic burnout in sportsmen. While investigating the influence of gender, age and qualification on emotional burnout in sportsmen, the author considered specific features of psychic burnout in representatives of the team and individual sports. It was shown, in particular, that representatives of individual sports had emotional burnout relatively more often as compared to group sports. A similar effect was demonstrated for sportsmen of mass athletic titles as compared to highly qualified sportsmen. Moreover, men are susceptible to emotional burnout to a greater degree than women.

In accordance with the above A.G. Barabanov and N.YU. Veprintseva [358] “revealed negative correlations between the levels of adaptation potential and symptoms of emotional burnout: sensation of being entrapped in a cage, anxiety and depression, emotional deadaptation, extended sphere of emotion sparing, emotional deficit” when investigating female sportsmen of the “Smena" team of Top League in women’s hockey. The results obtained by the authors substantiated the need to use Boiko questionnaire in the psychological monitoring system [370]; it allows to determine the leading symptoms of emotional burnout and the burnout level on the whole.

At the same time, one cannot say that diagnostic significance of emotional burnout in highly qualified representatives of precise sports is studied comprehensively. Therefore, it seemed urgent to study the parameters of emotional burnout syndrome and the possibility to use them within the limits of psychological monitoring in the complex monitoring in rhythmic-sportive gymnastics basing on the experimental psychodiagnostic data obtained in the above sportsmen contingent.

Taking into account that the procedures based on assessment of the life quality are quite widely used for the complex evaluation of diverse aspects of the lifestyle and risk factors for health worsening [345, 360, 367, 402], we analyzed the life quality parameters what included assessment criteria of individual psychic and social wellbeing, functional adequacy of the specific organism systems and also subjective assessment reflecting all mentioned concepts. It should be mentioned that two aspects can be distinguished in understanding of life quality problems: objective and subjective (psychological). Therefore, the life quality is studied basing on two conceptual models: objectivistic model (official statistical data block) and subjectivistic (psychological) model using sociological survey, i.e. people's opinions about their life. Accordingly, the life quality is assessed by two methods, i.e. with the help of objective indicators and subjective estimates.

The assessment of the life quality associated with the health in different population groups is one of the used approaches [384, 452, 474]. The medical concept of the life quality includes parameters determined by the health condition (health related quality of life) and reflects the level of physical and social activities, emotional wellbeing and also subjective perception of own health.

The Russian version of SF-36 questionnaire was used to assess subjective parameters of the life quality.

Considering the above, we investigated self-assessment of the health related quality of life depending on the professional success of highly qualified representatives of precise sports . For this purpose, we performed questioning of the cohort including the women gymnasts from the representative team of RF (18 female sportsmen) and representative team of SPb (13 female sportsmen) investigated in this thesis study.

The correlation analysis was performed to assess a possible relationship between the analyzed psychodiagnostic parameters. Differences/correlation coefficients at $p < 0.05$ were considered significant both when analyzing each test and when assessing the correlations.

## 2.3. Psychophysiological investigations of human using the method of functional magnetic resonance tomography

### 2.3.1. The study of functional patterns of the human brain nonselective inhibiting control system associated with generalized anxiety disorder when controlling actions under conditions of the two-stimulus Go/NoGo test

The investigations at this stage of the thesis study were aimed at revealing the elements of the brain nonselective inhibitory control (NSIC) system in patients with generalized anxiety disorder (GAD) and comparison with the data obtained in health subjects (see items 1.1–1.3 in Fig. 2.1).

#### *2.3.1.1. Healthy subjects and patients with generalized anxiety disorder*

The study used the data collected at the Institute of Human Brain of the Russian Academy of Sciences earlier from healthy right hand subjects and we also performed a study involving patients with generalized anxiety (hereinafter referred to as patients with anxiety). The health subject group included 34 subjects (10 males, 24 females, average age: 25.9 ± 5.2 years) and the patient group with generalized anxiety involved 25 persons (9 males and 16 females, average age: 37.2 ± 11.9 years). All study participants were right-handed. Manual dextrality was assessed using the Oldfield inventory [219]. The performance of the study was approved by the Ethics Committee of Bekhtereva Institute of Human Brain of the Russian Academy of Sciences. All study participants signed the informed consent form for participation in the study.

#### *2.3.1.2. The fMRI test task under conditions of two-stimulus Go/NoGo test*

The test task represented two-stimulus modification of the Go/NoGo test (see Fig. 2.2) [171]. The first, preparatory stimulus warned the subjects about appearance of the second, imperative stimulus or indicated absence of the necessity of any response to the second stimulus. The investigation included two variants of the test task fulfilled by the subject during two different sessions. At session No. 1 (see Fig. 2.2. A), the subject performed action after appearance of the image pair “animal-animal” (A-A Go tests) and suppressed the desire to perform action after appearance of the pair “animal-plant” (A-P NoGo tests). At session No. 2 (see Fig. 2.2. B) the subject performed action when the pair “animal-plant” was presented (A-P Go tests) and suppressed action when the pair “animal-animal” was presented (A-A NoGo tests). At both sessions, presentation of the first stimulus in the form of “plant” image meant that the subject should not perform any actions after presentation of the second stimulus, i.e. the subject ignored the second stimulus waiting for the nest stimulus pair (P-A Ignore and P-P Ignore tests).

Fifty stimulus pairs of each type were presented at random at each session. The order of fulfilling the instructions was alternated among different subjects. A cross for glance fixation appeared in the center of the screen when there was no stimulation. Images were presented for 100 ms, the inter-stimulus interval was 1,000 ms; the interval between presentation of stimulus pairs varied from 2,800 to 3,200 ms with increment of 100 ms. Besides that, in order to improve the efficiency of the study design, 50 blank tests (cross for glance fixation) with duration ranging from 3,000 to 5,000 ms with increment of 500 ms were presented at random between stimulus pairs. Performing action meant pressing a button by the thumb of the right hand. The scheme of the task is presented in Figure 2.2.

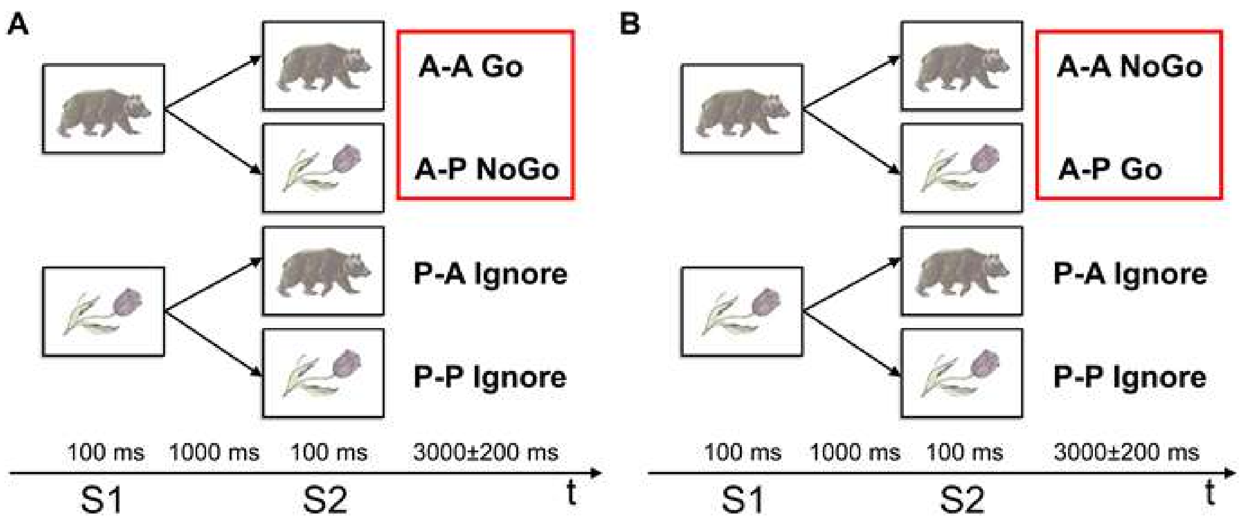


**Figure 2.2.** Study design Go/NoGo.

***2.3.1.3. Specifications of data recording using functional magnetic resonance tomography***

Recording and preliminary processing of fMRI images. The investigation was performed using the Philips Achieva 3.0 Tesla tomograph. Structural T1-images were recorded with parameters: field of view (FOV) – 240×240 mm; repetition time (TR) – 25 ms; echo time (TE) – 2.2 ms; 130 axial slices 1 mm thick with pixel size of 1×1 mm; flip angle – 30°. Echo planar single-pulse sequence was used to record functional T2*-images. The data recording time from 32 axial slices was 2 s (TR = 2 s, TE = 35 ms). FOV – 200×186 мм, flip angle – 90°. Voxel size – 3×3×3 mm.

The specifications of fMRI data collection presented in this section were used in all fMRI investigations of activation type (implying recording fMRI data when the activity of the test task is implemented) in this thesis study. Their methodical aspects will be provided below.

***2.3.1.4. Preliminary preparation and statistical analysis of fMRI data recorded under conditions of the activation investigation using the two-stimulus Go/NoGo test.***

The preliminary processing of fMRI images obtained when involving the study participants in performing the activities control (performing and suppression of actions under conditions of the Go/NoGo test task [156]), included: realignment of images, correction for the recording time of one image slices, co-recording of structural and functional images, segmentation of structural images into different tissue types, normalization relative to standard coordinate space of the Monreal Neurological Institute (MNI) and spatial smoothing (Gaussian filter with width of 8 mm). The image processing and statistical analysis were performed using SPM12 (Statistical parametric mapping) package (http://www.fil.ion.ucl.ac.uk/spm) [279].

The intra-subject or the first analysis level of the BOLD-signal changes using fMRI data was carried out with the help of classical frequency statistics. The inter-subject or the second analysis level was done using Bayesian statistics [244]. At the first stage the brain activity associated with performing the test tasks was determined for each volunteer. The general linear model (GLM) included regressors for analyzed experimental test conditions. The regressors convoluted with the canonical hemodynamic function. To take into account the influence of movement artifacts 24 regressors were used according to Friston et al. [198]. The GLM regressor parameters were converted in percentage of BOLD-signal (blood-oxygen-level-dependent signal) change relative to mean signal values in the whole brain volume at the baseline [233].

As it was already said above, the first analysis level was carried out using frequency statistics and the second analysis level was performed with the help of Bayesian statistics [72, 203, 279]. At the first stage the brain activity associated with performing the test tasks was determined individually for each volunteer. The general linear model (GLM) [195] included several regressors for different experimental conditions: "A-A Go", "A-P NoGo", "A-A NoGo", "A-P Go" and also "P-A Ignore", "P-P Ignore" separately for sessions No. 1 and No. 2 (see items describing the Go/NoGo test task). Mistakes in performing the test task were indicates in a special regressor. The regressors convoluted with the canonical hemodynamic function. Six regressors of the head position shifts calculated at the stage of realignment, were introduced to GLM additionally to consider the influence of movement artifacts [72]. Basing on determined parameter values of GLM regressors, linear contrasts of the following type: [0.5*"A-P NoGo" + 0.5*"A-A NoGo" – 0.5*"A-A Go" – 0.5* "A-P Go"] were calculated for each subject. These contrasts were used as a variable for testing hypotheses on selective and nonselective inhibitory control.

When performing group comparison, we analyzed only those voxels which were referred to the brain gray matter, for which purpose a mask was generated basing on the structural T1-images segmentation data of each subject. If posterior probability map (PPM) for the contrast larger than a certain value $\gamma$ exceeds the probability threshold $\alpha = 95\%$ set by us, the hypothesis on presence of the "NoGo > Go" effect is accepted. If the contrast value falls within the interval $[-\gamma; \gamma]$ with probability of more than 95%, the null hypothesis on absence of the "NoGo = Go" is accepted and we can speak of practical equivalence of two tests. The use of such threshold is in compliance with False Discovery Rate (FDR) approach with correction of multiple comparisons [139]. The present study used the threshold of γ = 0.1% of the BOLD-signal change [72]. The obtained statistical images for two different sessions (1 and 2) were binarized and multiplied together (logic “I”) for obtaining conjunction static maps of “NoGo > Go” type and “NoGo = Go” type [Nichols, 2005]. Selectivity implies selective intensification of neuronal activity in response to presentation of NoGo-stimuli as compared to Go-stimuli (“NoGo > Go”, PPM(contrast>0.1) > 0.95). Nonselectivity implies practically equivalent neuronal activity level in Go and NoGo tests (“NoGo = Go”, PPM(-0.1<contrast<0.1) > 0.95).

In order to perform group analysis, we used linear contrasts of compared experimental test conditions converted to percentage of the mean general brain activity at the baseline. Conversion of the linear contrasts in percent signal change (PSC) was performed using the following equation [186, 233]:

$$PSC_{ki} = SF * \frac{b_{ki}}{\sum_{k=1}^{m} b_{kconst}} * 100\%$$

where bki – parameter assessment for $k^{th}$ voxel in the $i^{th}$ experimental condition; SF – scaling factor (SF = 0.21), denominator – baseline activity value averaged by all m voxels of the brain image.

When using classical statistics for tomographic data, the least square method (LSM) is applied for each voxel of the analyzed 3D image to assess parameters βi, at which sum of squares of random errors Ei reaches minimum. It is supposed that error has normal distribution (while LSM corresponds to the method of maximum likelihood): p(E)~N(0,σ_e^2).

The classical approach does not any additional assumptions on parameter β distribution or one can say that the assumption of continuous equally probable distribution of parameters (“Flat Prior”) is used. Bayesian approach makes a posterior assumption on nonuniform distribution of parameters. The posterior assumption can be made basing on the data itself if the data is arranged hierarchically. The parametric empirical Bayesian estimation (PEB) is used in this case. Parameters are updated basing on hyperparameters corresponding to them and obtained at the higher level of hierarchy (parameter variability). When performing intra-subject analysis, the parameter assessment for $i^{th}$ voxel can be updated basing on their variability among adjacent voxels. When performing inter-subject analysis, the parameter assessment can be updated basing on parameter variability among all subjects in the whole brain volume. The parameters are updated using Bayes formula: $p(\beta|Y) \sim p(y|\beta)p(\beta)$, where $p(\beta|Y)$ – posterior probability, $p(\beta)$ – prior probability, $p(Y|\beta)$ – probability to obtain data Y with parameters β.

In frequency statistics the effect is fixed and equal to zero. A conclusion is made basing on the probability to obtain data with the preset effect: $p(Y\ |\mu\ [PSC]=0) \leq \alpha$ . If $\alpha = 0.05$ it is expected that the effect is not equal to zero in 95 measurements out of 100. Besides that, is should be considered that the conclusion is made for many voxels, therefore, one should use correction for multiple comparisons (reduce α for each of comparisons), i.e. the classical conclusion depends on the volume of the investigated brain region. In Bayesian statistics, on the contrary, data Y is fixed (specific data is considered but not multiplicity of repeated measurements) with the effect taking random values. These values – the probability to obtain an effect of a certain size for recorded data – is characterized by posterior probability distribution. We are interested in changes in the neuronal activity [post PSC] exceeding a certain threshold γ. If posterior probability for the effect with a size of higher that a certain value γ exceeds the probability threshold (1 – α) preset by us we accept a working hypothesis on presence of the effect (so-called activation): $p\_act=p([post\ PSC]>\gamma \mid Y)\geq(1-\alpha)$.

The hypothesis on presence of a negative effect (so-called deactivation) is accepted provided that: $p\_deact=p(\ [post\ PSC]<-\gamma|Y)\geq(1-\alpha)$.

The use of such threshold corresponds to correction for multiple comparisons using the method for control of false discovery rate (FDR) of the null hypothesis used in classical statistics [139]. Thus, Bayesian conclusion does not depend on the volume of the investigated brain region because it allows to go around the problem of multiple comparisons [72]. Besides that, acceptance of the null hypothesis becomes possible. For this, the condition shall be met: p_null =p( -γ<[post PSC]<γ | Y)≥(1-α).

This condition means that the effect size falls in the interval [-γ: +γ], which is called the region of practical equivalence (ROPE), hereinafter referred to as practical equivalence), with probability of more than (1 – α) (e.g., > 95%). Increase of the threshold γ and, consequently, extension of ROPE results in a stricter criterion of activation selection and more liberal threshold for accepting the null hypothesis. The opposite picture is observed in case of decrease of the threshold γ and narrowing of ROPE. In this situation there occurs a problem of selecting such threshold γ, at which the balance between sensitivity to detection of activation and null effect would be observed. Standard thresholds used in the SPM12 software are calculated basing on the information on effect distribution in the whole brain volume. At the group analysis level, the standard threshold corresponds to one posterior standard deviation prior σβcon [72].

Thus, a new method for brain function mapping – ROPE mapping developed by us was used in order to reveal brain structures associated with nonselective inhibitory control [244]. This mapping method was methodically tested in independent studies of healthy subjects and patients suffering from obsessions [156] who fulfilled the Go/NoGo test task used in the present thesis study. This work resulted in obtaining a certificate of state registration of the BayInf toolbox program allowing to carry out this type of mapping basing on fMRI findings [496]. The results obtained at this study stage are presented in section 4.1.2, chapter 4.

The next stage of the thesis study associated with the comparative analysis of BOLD-signal level recorded under conditions of the Go/NoGo test task (see item 1.2 in Fig. 2.1) was performed by the method of direct intergroup comparison: the classical frequency conclusion was used (two-sample t-test). Thus, this analysis was used with the help of frequency parametric statistics. We compared linear contrasts “Go+NoGo > baseline” and also contrasts “Go > baseline” and “NoGo > baseline” calculated for the groups of healthy volunteers and patients with anxiety disorder. The intergroup comparison was performed with correction for multiple comparisons using the method of Family-Wise error correction with significance level of 0.05 at the cluster level. Besides the comparative intergroup analysis of the brain local activity in patients with GAD and healthy subjects, we assessed functional connectivity at the moment of fulfillment of the Go/NoGo test task for two different experimental sessions differing in the cognitive load level (pressing the button to identical successively presented stimuli (session AAGO) or when stimuli of two categories APGO were presented). The parameters of preliminary data processing and its statistic analysis are presented below in section 2.4; they were similar to those, which are used in the operational rest condition.

The analysis of correlations between local BOLD-signal values of the brain structures revealed at the above study stages (see item 1.3.1 in Fig. 2.1) was performed with the help of multiple regression using frequency parametric statistics. In order to determine the relationships between fMRI signal level in the Go and NoGo tests we used a linear regression model with behavioral data (mean response rate and number of mistakes when performing the Go/NoGo test) and also with the data on the age and gender as non-interesting variables (covariates). The relationship was considered between the contrasts “Go+NoGo > baseline”, “Go > baseline”, “NoGo > baseline” and the following psychometric and physiologic parameters: personal and situational anxiety according the Integrative Test for Anxiety, vigilance according to Melbourne Decision Making Questionnaire anxiety assessed by Hamilton Anxiety Scale, general wall internality assessed by Level of Subjective Control Questionnaire and Kerdo index. This analysis type was carried out so that the mean BOLD-signal value in the statistical cluster revealed at the previous stage was used as one of variables (in addition to parameter of psychodiagnostic testing). The results of this study stage are presented in section 4.1.3, chapter 4.

Additionally, voxel-based correlation analysis was used with the help of the multiple regression model which, besides to above regressors, included the ones associated with covariates of interest (see item 1.3.2 in Fig. 2.1): data of psychodiagnostic investigation and physiologic monitoring as variables of interest.

For this analysis, correction for multiple comparisons was applied using the method of Family-Wise error correction with significance level of p-FWE < 0.05 at the cluster level. The results of this study stage are presented in section 4.1.4, chapter 4.

### 2.4. A series of studies for selecting regions of interest in order to analyze functional connectivity of the human brain in the rest condition basing on fMRI data in healthy subjects and patients with GAD

At this stage of the thesis study we performed a series of independent studies of the brain provision for those variants of the cognitive activity, which, to our opinion: 1) are associated with implementation of sports activities (socially significant information processing under conditions of social interactions [270, 303] and executive control processes under conditions of the cognitive activity [285]), 2) and their brain provision, according to the selected clinical model, can be restructured in case of changes in control functions caused by generalized anxiety disorder. The performed independent studies were aimed at revealing the brain structures – regions of interest which were used at the third stage of the psychophysiological investigation, which consisted in intergroup comparison of fMRI data of healthy subjects and patients with GAD recorded in the operational rest condition.

#### 2.4.1. Study of changes in the human brain functional connectivity in the rest condition associated with social intelligence level

The study involved 42 healthy subjects at the of 24.6 ± 3 years (henceforth mean ± standard deviation), 27 of whom were women [303]. Manual dextrality was assessed using the Oldfield inventory [219]. The performance of the study was approved by the Ethics Committee of Bekhtereva Institute of Human Brain of the Russian Academy of Sciences. All study participants signed the informed consent form for participation in the study.

During the fMRI in the operational rest condition, patients were asked to lie maximally still with opened eyes fixing their glance to the white cross located on a black background of the monitor screen. The scanning duration was 5 minutes.

#### *2.4.1.1. Recording fMRI data in the operational rest condition when analyzing the association between the social intelligence level and human brain functional connectivity*

For all subjects functional T2*-images were collected under conditions of operational rest (with opened eyes and glance fixation) using echo planar imaging (EPI) of pulse sequence (repetition time [TR] = 2,500 ms; echo time [TE] = 35 ms; flip angle = 90°; 32 slices, field of view [FOV] = 208 × 208 mm; matrix = 128 × 128, slice thickness = 3 mm, distance between slices = 4 mm). For all subjects, 120 dynamic volumes of human brain images were collected, which covered the hemispheres and superior cerebellum regions.

The specifications presented in this section were used to obtain fMRI data in all cases when the operational rest conditions were analyzed (provided in the section describing the third stage of the psychophysiological investigation).

This study used the standardized Guilford-Sullivan Four Factor Test of Social Intelligence [220], which allows to assess in a complex the human social intelligence level separately from his general intelligence. This test is based on the D. Guilford's social intelligence model. According to this model, the social intelligence includes 30 capabilities four of which can be assessed quantitatively using 4 subtests. These subtests assess the 1) capability to classify different manifestations of mental conditions (Expression Groups test); 2) capability to understand logics of development of social interactions (Histories with Addition subtest); 3) capability to forecast consequences of social behavior (Histories with Completion subtest); 4) capability to understand similar verbal responses depending on the situation context (Verbal Expression subtest). The subtests include 14, 15, 12 and 14 tasks, respectively: the sum of raw scores for all subtests is transformed into a composite assessment of the social intelligence from 1 (minimum) to 5 (maximum). The above subtests are characterized by different modality of stimulus material (verbal and visual) and types of tasks (grouping, forecasting, interpretation). They are closely connected with tasks aimed at measurement of capabilities [220] associated with formation processes of conceptions on the content of opponents' intentions and thoughts (the totality of such processes is designated in the English literature by a term "Theory of Mind"). E.g., the Expression Groups subtest is similar to the Reading Mind in the Eyes (RMET) test while the Histories with Addition and Histories with Completion subtests are used separately from each other to assess the development of capabilities associated with TOM [66, 211, 247]. The subtest variants are presented in Fig. 2.3.

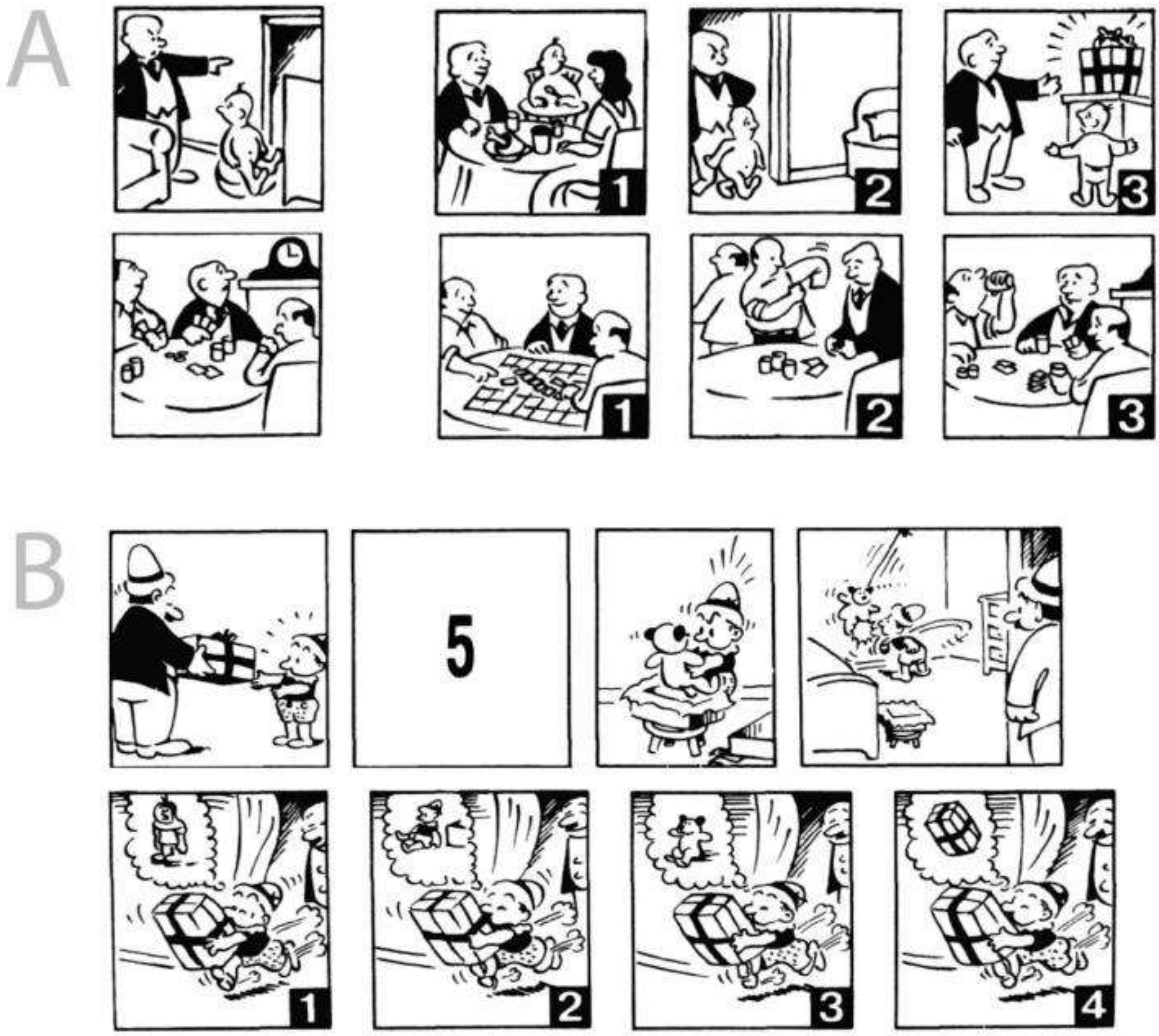


**Figure 2.3.** Examples of measurements in the Guilford-Sullivan test. Task A represents the Cartoon Predictions subtest, where participants must select one of three cartoons that most appropriately describes the outcome of the suggested situation. Task B represents the Missing Cartoons subtest, where participants are

required to choose one of four cartoons, which correctly fills the suggested sequence of cartoons

It should be mentioned here that this test was successfully used earlier when studying the relationship between the social intelligence and morphological peculiarities of the human brain gray matter [208]; the results of this study were used for selecting regions of interest for analysis of the functional connectivity at this stage of the thesis.

***2.4.1.2. Preliminary fMRI data processing and statistical analysis in the operational rest condition when analyzing the association between the social intelligence level and human brain functional connectivity***

The preliminary rest fMRT date processing was performed in the CONN Functional Connectivity Toolbox package [334]. Realignment and slice-timing correction were performed for all functional images. The parameters of spatial normalization to the standard anatomic space were calculated for all anatomic images, after that these parameters were applied to functional images. Then a smoothing Gaussian filter with point size of 8 mm was applied to all functional images. After preprocessing all images were subject to the denoising procedure. In order to remove signals not associated with neuronal activity, the CompCor strategy was used [17], which allows to extract the signal part from the white matter ad cerebrospinal fluid. Six movement parameters and their first-order derivatives were used as regressors of the general linear model. The last stage consisted in the use of a frequency filter with frequency range of 0.008–0.09 Hz.

The analysis between the regions of interest and other voxels of functional images (ROI-to-voxel) was performed in order to measure the functional connectivity between the caudate nuclei and brain regions. The selection of regions of interest (ROI) for analysis in the region of the caudate nuclei was caused by the results of the previous study [208], which used voxel morphometry and revealed statistically significant difference in the caudate nuclei volume when comparing the subject groups with high and low social intelligence level. Spherical masks with radius of 5 mm localized in the region of the bodies and heads of the caudate nuclei were used as ROI in accordance with the study of Seitzmann et al. [22]. The selection of ROI was based by the anatomical division of the caudate nuclei. ROI in the region of the tail of the caudate nucleus were not used because of their anatomical peculiarities: this structure is represented by a narrow stipe of the gray matter and is characterized by the position near the lateral ventricle wall as a result of which its ROI localization is subject to the effect of partial volume [260].

The functional connectivity maps between the signal within ROI (averaged by all voxels of the analyzed region of interest) and other voxels of functional images were formed for each subject by transformation of Pierson correlation coefficients r to z-values. The multiple regression analysis with the help of the general lineal model (implemented in CONN package) was used to reveal correlation between the social intelligence level and FC between the caudate nuclei and other brain regions. The total assessment of the social intelligence was transformed into z-values and used as a variable of interest. Raw score distribution according to the Guilford is presented in Figure (Fig. 2.4). The gender and age were used in the analysis as ignorable variables. The functional connectivity of the caudate nuclei at rest was analyzed additionally. Two t-contrasts for a respective variable were used to reveal the positive and negative correlations between z-values of the assessment of the social intelligence and FC between ROI in the caudate nuclei and other voxels of the functional images. Statistical parametric maps were constructed using the uncorrected threshold of $p < 0.001$ at the voxel level with subsequent correction for multiple comparisons at the cluster level according to the Family-Wise error (FWE) method with the threshold of $p < 0.5$ (see section Methods in the report of [303]). The analysis results were visualized using the MRIcron software package.

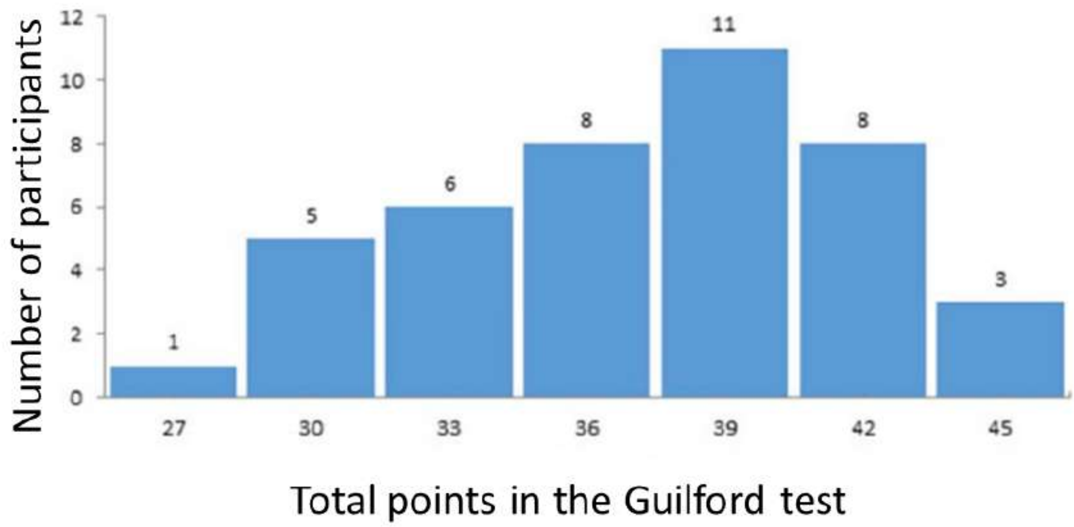


**Figure 2.4.** Guilford test values distribution obtained from the healthy subjects.

**2.4.2. fMRI investigation of the local activity and modulated human brain functional connectivity in social interactions under conditions of the Taylor test task**

The study involved 42 healthy right-hand volunteers (26 females and 13 males at the age of 24.5 ± 3.6 years) without history of psychiatric or neurological disorders and currently not taking drugs. Manual dextrality was assessed using the Oldfield test [219]. All study participants signed the free informed consent form before beginning of the study. All procedures were performed according to Helsinki Declaration and approved by the Ethics Committee of Bekhtereva Institute of Human Brain of the Russian Academy of Sciences. After the investigation the subjects filled in questionnaires concerning their strategy and opinion about the opponent.

***2.4.2.1. The test task of the fMRI investigation for social interactions under conditions of Taylor aggression paradigm***

This study used a modified version of the test task, which is known from the studies of aggression and called Taylor aggression paradigm, hereinafter referred to as TAP-investigation [121, 130]). The investigation participants were informed of the fact that they would play a game for response rate with an opponent. The test task was divided in four sessions. A volunteer played with an anonymous (Anon) opponent in two of them and with a known (Known) opponent in other two sessions. Each test (game round) consisted of four phases (see Fig. 2.5).

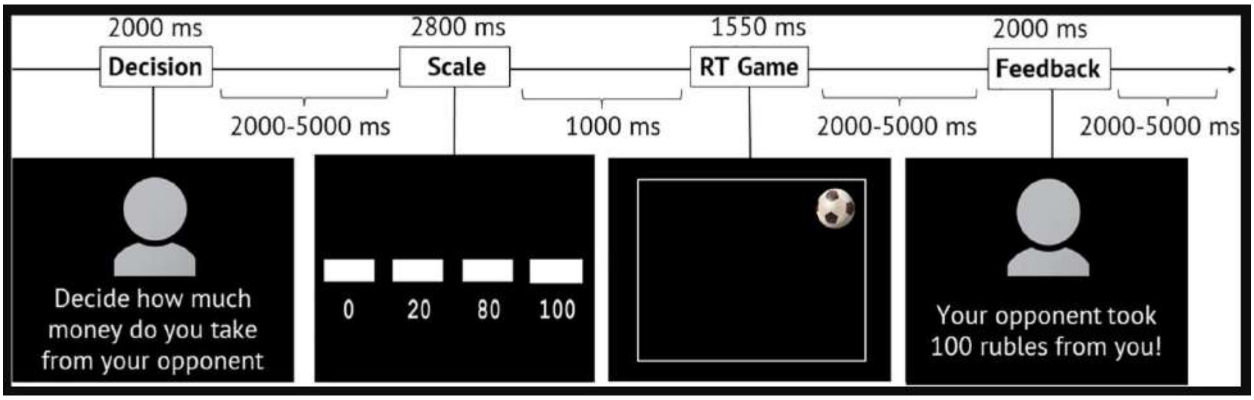


**Figure 2.5.** Taylor aggression paradigm task scheme.

In the first phase (hereinafter referred to as “Decision” phase) the monitor screen showed avatar of anonymous opponent or photo of an actual opponent done before beginning of the investigation on the day of scanning, and a message: “Decide how much money you will take away from your opponent”. During the “Decision” phase, according to the instruction, a volunteer had to select that amount which he wished to take away from the opponent in case of victory in this round. During the second phase (hereinafter referred to as “Scale” phase), the monitor screen showed a gradually filling scale with amounts of 0, 20, 80, 100 roubles. At that moment, when the scale corresponded to the amount, selected earlier during the “Decision” phase, a volunteer pressed a manipulator button with the right index finger. During the third phase (hereinafter referred to as “Game” phase) the image of a football appeared at random in one of the four angles of the playing ground on the monitor screen. The task for the volunteer was to press the button with the right index finger quicker than his opponent having seen the ball but at the same time he should not press the button prematurely (before appearance of the ball). During the fourth phase (hereinafter referred to as “Feedback” phase) the monitor screen showed avatar of the anonymous opponent or photo of the actual opponent and a message: «The opponent took 0/20/80/100 away from you!» or «You won 50 roubles!».

According to the instruction, the selection of the amount by the volunteer in the beginning of the round influenced the fact of how much roubles the opponent would lose in case of the volunteer's win. In its turn, the amount which was taken away from the volunteer in case of his defeat depended on the selection of his opponent. The prize of the volunteer and opponent did not depend of their selection. The prize was fixed and equal to 50 roubles.

Actually, the number of tests with the prize of 50 roubles and loss of 0/20/80/100 roubles was preprogrammed by the researchers and did not depend on the volunteer. These tests were presented at random. The number of tests with the win among all four sessions was 60, the number of tests with loss of 0 and 100 roubles was 24 each, with loss of 20 and 80 roubles – 26 each. The number of tests could change only in case, when the volunteer did not press the button when catching the ball. In such case 0 or 20 roubles was always taken away from the volunteer in the "Feedback" phase.

The duration of the "Decision" phase was 2 s, duration of the "Scale" phase was 2.8 (the first amount of the scale appeared at second 1, three subsequent amounts at millisecond 600); the duration of "Game" phase was 1.55 s (absence of the ball in the screen for 700–1,200 ms, the ball appeared in the screen at millisecond 600), the duration of "Feedback" phase was 2 s. The interval between the "Decision" and "Scale" phases varied from 2 to 5 s and was 3.5 s on average. The interval between "Scale" and "Game" phases was 1 s. The interval between "Game" and "Feedback" phases varied from 2 to 5 s and was 3.5 on average. The interval between the tests varied from 2 to 5 s and was 3.5 on average.

***2.4.2.2. Statistical analysis of fMRI data obtained in the studies aimed at revealing the elements of brain systems providing for socially significant information processing under conditions of the Taylor test task***

The specifications of fMRI data collection and also the stages of its preparation to statistical analysis are presented above in section 2.3.1.3, chapter 2.

Firstly, statistical analysis was performed for each participant separately and individual general linear models (GLM) were generated. The same GLM models with 11 regressors representing time characteristics of the experimental phases were generated for anonymous and known opponents. The events were classified similarly to GLM generated by Wagels et al. [121] who also used version of TAP task which was compatible with fMRI. Namely, the event were modelled with occurrence in the beginning of the experimental phase and duration equal to zero. The "Feedback" phase (provocation) corresponded to three regressors of GLM: low provocation (loss of 0 and 20 roubles), high provocation (loss of 80 or 100 roubles) and absence of provocation (prize). The "Decision" and "Scale" phases were sorted in accordance with provocation in the previous test: low, high and absence of provocation. A separate regressor corresponded to the "Game" phase. GLM included also individual regressors corresponding to the first tests and mistakes being of no interest and six regressors for six parameters of the head movement obtained during preprocessing at the stage of realignment [195]. Then regressors were convoluted with the standard hemodynamic response function (HRF).

Secondly, beta-values of regression coefficients for regressors in GLM were assessed at the individual analysis level. We calculated linear contrasts of beta-coefficients for each game phase and initial BOLD-signal level which were used as a variable for the analysis of the second (group) level. When analyzing the random effects of the second level, the models were constructed for each interesting game phase ("Decision", "Scale" and "Feedback") separately and included two factors with two levels: "provocation" (high and low) and "opponent" (known and anonymous). F-contrasts for the main effect of the opponent, main effect of provocation and interaction of two factors were calculated.

Finally, the obtained F-contrasts were used for the statistical conclusion by voxels at the group level. Uncorrected threshold of $p < 0.001$ was used at the level of voxels, and the threshold of $p < 0.05$ with correction for multiple comparisons by the Family-Wise error method (FWE) was used at the level of clusters. The mask of the gray substance generated using segmented structural images was used for selection of voxels within the gray matter in all objects. Xjview Toolbox2[1] was used to determine anatomical position of voxels with significant changes in the local neuronal activity. The REX set of tools was used for illustration of differences in beta-coefficient values in obtained clusters of BOLD-signal changes.

The generalized analysis of psychophysiological interactions (gPPI-analysis) using the program for SPM12 was performed in order to assess the influence of the opponent anonymity on changes in modulated functional connectivity between the brain regions [20]. This method allows to discriminate context-dependent changes of the functional interaction force from simple coactivations and correlations of spontaneous signal fluctuations observed in the rest condition. The regions of interest (ROI) were selected basing on two criteria. Firstly, ROI should be a TOM network node. Secondly, ROI should be characterized by differential neuronal activity during interaction with the known anonymous opponent obtained in the present study. One cluster including the right inferior frontal gyrus (IFG) met the above criteria because it was characterized by differential activity in our study and was referred to the TOM network in previous meta-analyses [183, 224]. Besides that, the local BOLD-signal in the right IFG was intensified when observing provocation on the part of the anonymous opponent as compared to the known opponent: the contrast “Anonymous opponent” > “Known opponent” calculated to the phase “Feedback” (see The influence of the opponent anonymity on changes in the local brain activity when obtaining social provocation [”Feedback” phase in section 3.2). Thus, we selected UFG cluster with center in coordinates MNI x = 57, y = 11, z = 14 as a e ROI in gPPI-analysis.

In gPPI-analysis, specific GLM described above included additional regressors: physiologic regressor and PPI regressors. Physiological regressor Xphysio(t) represents a temporal series of BOLD-signals in ROI. In order to generate PPI-regressor XPPI(t), the temporal series of BOLD-signal from ROI were subjected to deconvolution (⊗^-1) with HRF(t) in order to reveal the underlying

[1] https://www.nitrc.org/projects/xjview

neuronal activity Zphysio(t): $Zphysio(t) = Xphysio(t) \otimes$ ^-1 HRF(t) [191]. The obtained signal was multiplied by the temporal characteristics of experimental events Zpsy(t). The result of this multiplication was the psychophysiological interaction at the level of neuronal activity. In order to model this interaction at the level of the BOLD-signal is was subject to the procedure of convolution with $XPPI(t) = (Zphysio(t) \cdot Zpsy(t)) \otimes HRF(t)$. PPI-regressors were generated separately for anonymous and known opponents for regressors of interest including the “FeedBack” phase with low and high provocation. The analysis was performed for the “FeedBack” because considerable changes in the local BOLD-signal were recorded for this phase of obtaining provocation from the anonymous opponent.

Similarly to the analysis of changes in BOLD-signal, group models included two factors with two levels: “provocation” (high and low) and “opponent” (known and anonymous). F-contrasts for the main effect of the opponent, main effect of provocation and interaction of two factors were calculated.

The uncorrected threshold $p < 0.001$ was used at the voxel level and the corrected FWE threshold $p < 0.05$ was used at the cluster level. The mask of the gray matter generated of segmented structural images was used for selection of voxels within the gray matter in all subjects. xjView Toolbox[1] was used to determine the anatomical position of voxels with significant changes in the local neuronal activity. In order to interpret and illustrate the results from viewpoint of the fact which clusters obtained by analysis of the whole brain are localized in the TOM neuronal system, we used statistical maps of seven regions associated with TOM (right temporoparietal junction (rTPJ) and left TPJ, precuneus, dorsal, medial and ventral components of the medial prefrontal cortex and the region of the right superior temporal sulcus) [267] downloaded from https://saxelab.mit.edu/use-our-theory-mind-group-карты/. The results obtained in the current study were superimposed on the regions obtained by [267]. Only those clusters, which coincided with TOM regions by their localization, were interpreted as ones localized in the TOM system.

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[1] https://www.nitrc.org/projects/xjview

The REX[1] tools were used to illustrate differences of regression coefficients in the obtained clusters of changes in the functional interactions.

### 2.4.3. fMRT investigation for revealing the elements of the brain system providing for executive control processes performed under conditions of resolving lexical ambiguousness in healthy subjects

fMRI investigations involved 48 healthy volunteers (20 males and 28 females at the age of 26.7 ± 5.3 years (the data of four of them was excluded later from the analysis)) [285]. All subjects were right handed, and manual dextrality was assessed using the Oldfield inventory [219]. The performance of the study was approved by the Ethics Committee of Bekhtereva Institute of Human Brain of the Russian Academy of Sciences. All study participants signed the informed consent form for participation in the study.

#### *2.4.3.1. The test task aimed at revealing the elements of the brain systems providing for executive control processes, using the model for studying lexical ambiguousness resolution processes*

The task for the subjects consisted in the necessity to end the pairs adjective-noun with dropped letters in Russian. E.g., the fragments *с-хое ви-о* or *с-хое -ино (-ry wi-e)* were shown in the screen and the participants had to determine the dropped letters saying the word combination: *сухое вино (dry wine).* The subjects were instructed to say the first occurring solution in order to induce the implicit processing and avoid realization of several solutions. There was always only one solution for adjectives. Nouns had one or two solutions depending on the experimental condition but the adjective prioritized one of them in each fragment. In the above examples, *ви-о* (wine) can be ended only as “вино" (wine) (control condition), but *-ино* can be also ended as “кино” (film) (not single meaning condition).

The phrases adjective-noun used as stimuli were generated as follows. At first we used the StimulStat database [34] to select noun pairs differing in only one letter, e.g. “вино” (wine) and “кино” (film). All nouns consisted of 4–5 letters, their frequency varied from 5 to 100 incidence per million (ipm) (according to frequency

[1] http://www.nitrc.org/projects/rex/

dictionary [432]). The difference in frequency between two nouns in each pair never exceeded 50 inches per minute. For each noun we selected an adjective which is often combined with it and is incompatible in the pair with another noun. E.g., for the noun “вино” (wine) we selected “сухое” (dry) and for “кино” (film) we selected “интересное” (interesting).

We performed the pilot study involving 22 volunteers (adult healthy Russian native speakers who gave the informed consent), in order to check whether selected adjectives were actually closely associated with one noun in the pair but not with another. They did not participate in the main experiment. During this study, fragments adjective-noun in ambiguousness condition were shown in the computer screen one after another at random. The participants were asked to end them as soon as possible but time limitations were not included in the experimental procedure. As a result, 48 sets of stimuli (consisting of two nouns and two adjectives) were selected basing on the following inclusion criteria: more than 70% of correct answers for both combinations adjective-noun within 5 second interval after presentation of the fragment.

Out of these 48 sets 15 included noun pairs differing in the first letter. The last letters of nouns were different in 7 sets; the difference in the middle letter was in other 26 sets. For each set, 4 fragment stimuli were generated: two in ambiguousness condition (e.g., *с-хое -ино (dry wine)*, *и-тересное -ино (interesting film*) and two in the control condition (e.g., *с-хое ви-о (dry wine)*, *и-тересное ки-о (interesting film*)). The noun-stimuli were identical in two ambiguous fragments (e.g., -*ино*). So, if one of them is presented after another, it is possible to investigate, how the same ambiguous stimulus is processed the first and the second time in two different contexts (generated by adjectives).

During the fMRI investigation each participant was offered to complete 96 fragments, i.e. all adjective and noun combinations generated by us (in one of the two experimental conditions). Two word combinations from the same set were always separated by three other stimuli and demonstrated in the same condition, i.e., those subjects, who saw *с-хое ви-о (dry wine)*, also saw *и-тересное к-но* (interesting film) (both fragments in the control condition); those, who received *с-хое -ино (dry wine)* saw also *и-тересное -ино* (interesting film) both fragments in ambiguousness condition). This provides us four variants for each set of stimuli: e.g., presentation of the fragment "вино" (wine) before or after fragment "кино" (film) in ambiguousness or control condition. We generated four experimental lists using the principle of Latin square. We generated three different sequences of stimuli presentation for each list making sure that two fragments from each set were separated by three stimuli. The more detailed information concerning the lists of used word combinations is presented in appendix to the publication of the study results [285].

So, we obtained four types of experimental tests (Fig. 3.1):

– Ambig1st – the first fragment from the set in ambiguousness condition (e.g., *с-хое -ино (dry wine)*);

– Ambig2ndt – the second fragment from the set in ambiguousness condition (e.g., *и-тересное -ино (interesting film)*);

– Control1st – the first fragment from the set in control condition (e.g., *с-хое ви-о (dry wine)*);

– Control2nd – the second fragment from the set in control condition (e.g., *и-тересное ки-о (interesting film)*).

In the tests Ambig1st, the noun can be ended in two different ways but the context (i.e., adjective) favors unconscious selection of one variant (e.g., the word "вино" (wine) in Fig. 3.1). In order to check, whether the second variant (the word "кино" (film)) was suppressed as a result of such selection, the tests Ambig1st were compared with tests Control1st, in which one could not expect suppression (but the same adjectives and nouns were used in order to avoid any mixed factors). To check also, whether the selection process in the test Ambig1st complicated the selection of presumably suppressed variant in the next test Ambig2nd, i.e. negative aftereffect, we performed the additional analysis. For this purpose, the tests Ambig2nd were compared with tests Control2nd, in which one could not expect effects of previous suppression. The interval of three tests was selected as relatively short but not immediate.

| Trial type | First occurrence | Second occurrence | Variants of noun completion |
|---|---|---|---|
| **Ambiguous** condition: | *s-hoe -ino* 'dry wine' **Ambig1st** | *i-teresnoe -ino* 'interesting movie' **Ambig2nd** | **TWO** |
| **Unambiguous** condition: | *s-hoe v-no* 'dry wine' **Control1st** | *i-teresnoe k-no* 'interesting movie' **Control2nd** | **ONE** |

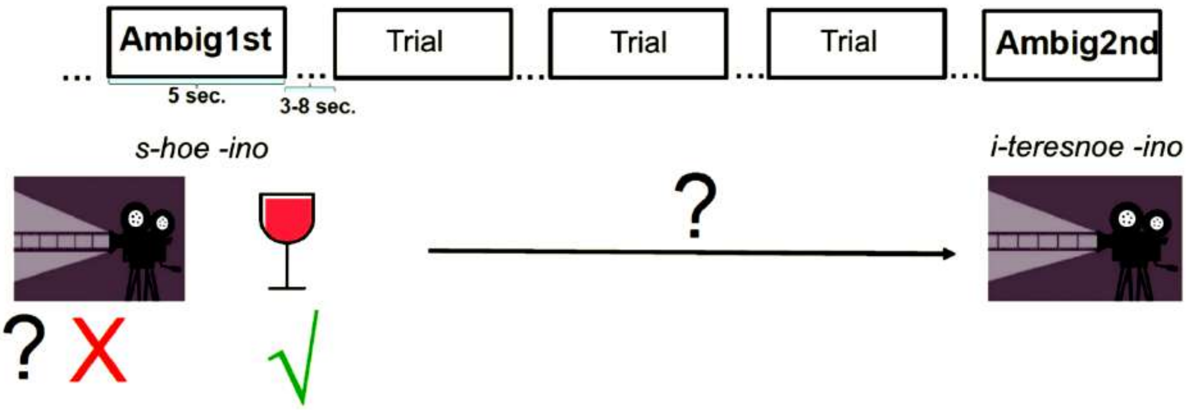


**Figure 2.6.** The experimental design of the fMRI study. The table illustrates four different trial types. The pictures in the lower part illustrate two variants of completion of the noun -ino (vino 'wine' or kino 'movie').

Each fragment adjective-noun was presented in the screen for 5 s. The participant had to press the button of the MR-compatible controller and say an ended phase within this time. Pressing the button was included into the task in order to measure possible changes in the response time as we expected potentially negative consequence in the condition Ambig2nd caused by the supposed suppression of unselected ending in the condition Ambig1st. Verbal answers were recorded and later analyzed for revealing mistakes in finding solutions for word fragments. It was expected that memory blocking effects would be associated with intrusion mistakes, i.e. with repeating the solution found for the fragmented noun in the condition Ambig1st but irrelevant for condition Ambig2nd.

The stimulus did not disappear after pressing the button and remained in the screen for 5 s. A fixation cross was presented in the screen during inter-stimulus intervals. In order to improve the sampling frequency of hemodynamic function response its length varied at random from 3 to 8 s with equally probable increment of 500 ms. The total duration of one fMRI session was 16.8 min.

After completing the investigation, the participants received a printed list of all stimuli (in the order of presentation) and indicated for which ambiguous fragments they understood that two variants of ending were possible. The participants reported very small number of such cases which we excluded from the subsequent analysis. Of course, we could not guarantee that they remembered accurately all such cases but we wished to make every efforts to exclude them, because we were specially interested in unconscious processes of ambiguousness resolution in this investigation.

***2.4.3.2 Statistical analysis of fMRI data obtained in the investigation aimed at revealing the elements of the brain systems providing for executive control processes, using the model for studying lexical ambiguousness resolution processes***

The specifications of fMRI data collection and also the stages of its preparation to statistical analysis are presented above in section 2.3.1.3, chapter 2.

This analysis type was carried out in two stages. At the first stage the brain activity associated with performing the test tasks was determined individually for each volunteer. The general linear model (GLM) [279] included regressors corresponding to four variants of the experimental conditions described above (see Fig. 2.6): Ambig1st and Ambig2nd and also Control1st and Control2nd. In addition to these regressors, we included a regressor in the form of parametric modulator (hereinafter referred to as PM) reflecting response time (times of pressing the button by the subject before saying a phase ending variant were used).

Additionally, basing on the questioning results after the investigations, the tests of Ambig1st type, in which the subjects noted availability of two noun completion variants, were isolated as a separate regressor (“DoubleMeaning”). Also the tests, in which the subjects gave incorrect answers (i.e. not corresponding to the adjective) and tests, in which the subjects did not answer, were isolated as a separate regressor ("Mistake"). Six regressors of the head position shifts calculated at the stage of realignment, were introduced to GLM additionally to consider the influence of movement artifacts [195].

The standard function of hemodynamic response and stimulus screen presentation time were used to construct regressors. The differences of beta-coefficients obtained at the individual level, when calculating the linear contrasts of the kind "Type of experimental test" > "Rest condition", reflecting changes in the BOLD-signal in relative units, were used as variables for the second, group stage of the statistical data analysis. The group data analysis was performed in voxel-based regimen taking into account the inter-subject variability (random effect analysis). The statistical conclusion was made using Bayesian statistics with log posterior odds threshold > 5 (posterior probability of obtaining the effect 0.99) what corresponds to "very strong" effect and also the effect size Hz > 0.

The contrasts of Ambig1st>Control1st type and Ambig1st<Control1st type (experimental test) were analyzed in order to check the above hypotheses on the mechanisms of the brain provision for unconscious word meaning selection processes. It was supposed that, if the hypothesis on the determinant role of selection processes (without involvement of suppression) was true, significant changes in the BOLD-signal should be revealed only in the comparison Ambig1st>Control1st, as when presenting a noun with a dropped letter with several completion variants, several meanings were actualized (activated), out of which meaning was selected which was the most appropriate to the context. It was supposed that such BOLD-signal changes would be observed in the prefrontal cortex structures which are associated with provision of selection processes and also in the temporal and prefrontal brain regions associated with provision of semantic word analysis.

If the hypothesis is true, in accordance with which during unconscious selection of one meaning there occurs suppression of other meaning, it was supposed to reveal in the contrast Ambig1st>Control1st intensification of BOLD-signal in the brain structures associated with inhibition provision (e.g., the right supplementary motor cortex or right dorsolateral prefrontal cortex).

### 2.5. Analysis of the human brain functional connectivity in the operational rest condition using the regions of interest revealed at previous study stages within the limits of a clinical model of GAD-associated changes in the brain provision of control functions

The control group included fMRI data in the operational rest condition of 100 healthy subjects without neurological pathology (the ratio of males and females = 50:50, average age: 24.7 ± 4.2 years), and the group of patients with generalized anxiety included 25 persons (9 males and 16 females, average age: 37.2 ± 11.9 years). All study participants were right-handed. Manual dextrality was assessed using the Oldfield inventory [219]. The performance of the study was approved by the Ethics Committee of Bekhtereva Institute of Human Brain of the Russian Academy of Sciences. All study participants signed the informed consent form for participation in the study.

#### 2.5.1. Statistical processing of fMRI data obtained in the operational rest condition

The specifications of collection and preparation of fMRI data in the operational rest condition are presented in 2.4.1.1.

For additional control of the movement artifacts in functional images, the image volumes with maximum shift (> 0.5 mm) and maximum change in the global signal intensity (z-value of global signal intensity > 3) were determined for each subject; they were not taken into account when calculating individual values of functional connectivity. The subjects, for whom the number of outlier dynamic images exceeded 25% (> 30) were excluded from the further analysis. Additionally, the framewise displacement (FD) [277] was calculated for each subject; it was used as an ignorable variable in the intergroup analysis.

The analysis of functional connectivity between regions of interest – the brain structures of and analyzed brain systems and other brain voxels – was performed for the following regions of interest:

1.1. Brain structures providing for nonselective inhibitory control (under conditions of Go/NoGo test) (see sections 4.1.2–4.1.4, chapter 4).

1.2. Brain structures providing for socially significant information processing in social interactions (see section 4.2.1, chapter 4).

1.3. Brain structures providing for executive control of cognitive activity when resolving ambiguousness (see section 4.2.2, chapter 4).

Regions of interest (ROI) represented spheres with diameter of 10 mm, whose coordinates of center corresponded to coordinates of cluster peak obtained in the studies described above. Before determination of the region of interest, a group mask of gray matter was formed so that ROI should contain only gray matter. The following was used additionally as ROI: 1) Collection of anatomical charts aal3 (automated anatomical labeling) [47], 2) set of 300 spherical ROI according to Seitzman et al. [22].

Both the analysis of FC between ROI (ROI-to-ROI) and analysis of FC between ROI and other voxels of functional images (ROI-to-voxel) were used to reveal differences in the degree of functional connectivity (FC) between groups of patients with anxiety disorder and healthy subjects. Two-sample t-test was used to compare groups; gender, age and FD parameter were used as ignorable variables. The following was used for the first type of analysis: 1) statistical threshold $p < 0.05$ with correction for multiple comparisons by the false discovery rate method (FDR) at the level of separate relationships and 2) $p < 0.05$ without correction for multiple comparisons at the level of separate relationship with subsequent correction for multiple comparisons by the FDR method at the cluster level with threshold $p < 0.05$. For the second type of analysis, statistical parametric maps were constructed with the voxel-based uncorrected threshold $p < 0.001$, with subsequent correction for multiple comparisons by the FDR method at the cluster level ($p < 0.05$).

If clusters were revealed, in which the functional connectivity values differed significantly between two compared patient groups with anxiety disorder as compared to health subjects, correlation analysis was performed using the data of psychometric investigations of the patient group with anxiety. The functional connectivity values expressed in the form of Pierson correlation coefficient were transformed into Fischer z-values and averaged for such clusters. The obtained values were used as variables for calculation of Pierson correlation coefficient with values of psychometric parameters and Kerdo index.

# CHAPTER 3 RESULTS OF OWN STUDIES. PSYCHOLOGICAL INVESTIGATION OF HIGHLY QUALIFIED SPORTSMEN

## 3.1. Results of psychological investigations of women gymnasts

### 3.1.1. Personal characteristics of investigated women gymnasts

Our analysis of literature data [532] showed that coping with action of stressor factors associated both with strain of training processes and result pressure during competitions could be materialized due to changed anxiety condition [19, 349, 404] or, according to English reports, sports anxiety [276]. The anxiety as a personality feature is associated with genetically determined properties of the human brain functional activity and, as a rule, high anxiety is often caused by the intensified sensation of emotional arousal and anxiety emotions [349, 478] which tell upon the quality (efficiency) of sports activities [255, 276].

According to opinion of some authors, the increased anxiety level can be considered as one of the main markers of lowered efficiency and productivity of the competitive activities [184]. The increased anxiety level often has a negative influence on the sportsmen's capabilities self-assessment and productivity of their activities [255, 276, 394].

The problem of relationship between efficiency of implementation and productivity of sports activities and anxiety level still remains one of controversial issues in sports medicine and psychology [276, 337]. E.g., increased personal anxiety level is not certainly an unfavorable factor promoting unsuccess in competitions.  On the contrary, according to Yerkes–Dodson law [411], there exists the individual optimum level of "useful anxiety" at which anxiety has a mobilizing action on the sportsman stimulating the fulfillment of the set tasks and achievement of the best result [370]. Moreover, both increase of anxiety and lowering of the activities implementation efficiency are observed as motivation grows (see Fig. 3.1).

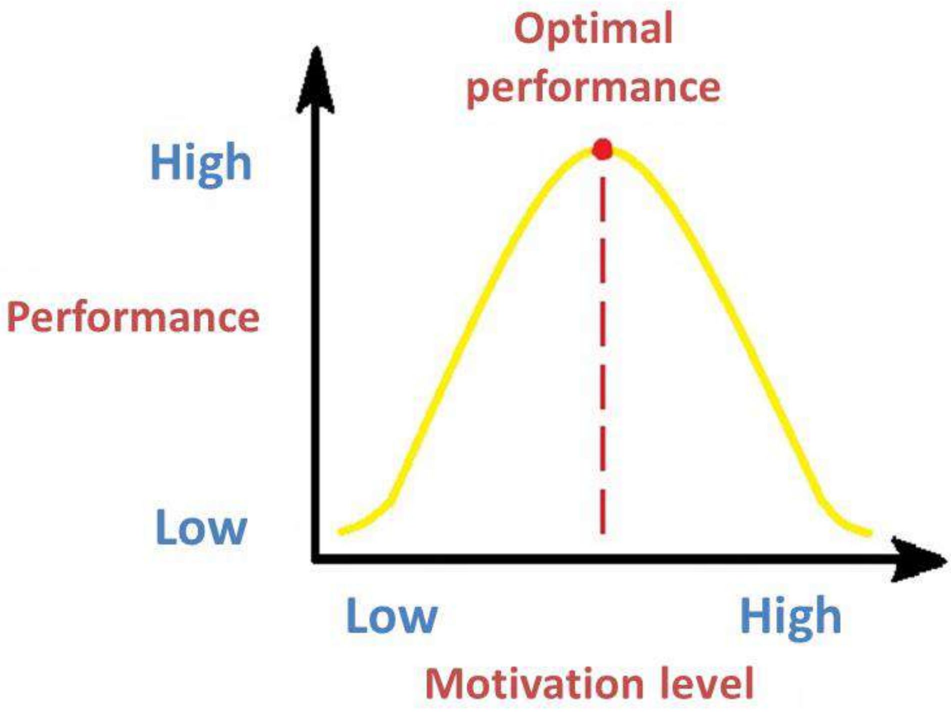


**Figure 3.1.** Schematic representation of the Yerkes-Dodson law

As the results of experimental studies show, this law reflects the relationship between changes in anxiety levels and sports productivity and also training efficiency [441] and are evidence of existence of a certain optimum. This correlates to a significant extent with the Khanin's theory of individual zones of optimal functioning [146] when the efficiency peak of sports activities is achieved when a certain individual ratio between excitability and anxiety is present. The more complex picture of cognitive and somatic anxiety aspects is considered within the limits of the Martens multidimensional anxiety theory [184] when lowered efficiency of sports activities is observed in case of cognitive manifestation of increased anxiety level and the inverted U-relationship is noted in case of somatic/vegetative manifestation how it is established in Yerkes–Dodson law.

At the same time, one can find reports in the literature, according to which linear growth of the sports activities efficiency is observed when competitive anxiety (associated with sports activities) increases [152]. Or, e.g., it is considered that somatic anxiety is correlated with sports activities according to Yerkes–Dodson law only at low individual anxiety levels (it its cognitive aspect) (see Hardy and Parfitt catastrophe theory [147]).

Basing on the above one can conclude that the problem of relationship between sports activities productivity and anxiety remains unsolved [276, 337]. But the available data of the experimental studies on this problem are quire contradictory [74], which is, probably, associated with a relatively small number of neurobiological/psychophysiological studies and, as a consequence, lack of neurophysiological objectivization of the principles developed in the above theories and laws.

At the same time it should be mentioned that regulatory requirements set in the "Procedure for Organization of Medico-Biological Support of Sportsmen from the Sports Representative Teams of the Russian Federation" imperatively determine "Measures of Psychological Nature" [11], which include: 1) psychological and psychophysiological diagnostics (individual, group) of personal features and professionally important characteristics of sportsmen; 2) psychological training aimed at prevention of deadaptation conditions and improvement of sportsmen's professionally important qualities determining success of the sports activities; 3) psychological and psychophysiological correction of unfavorable changes in psycho-emotional conditions, prenosologic psychosomatic and deadaptation disorders in sportsmen; 4) psychologic rehabilitation after injuries and diseases. But, as it was mentioned above in chapter 2, the regulatory requirements of departmental orders did not find proper scientific substantiation yet.

Our psychodiagnostical investigation showed [532] the increased level of personal anxiety (PA), as it was mentioned above, reflecting individual-specific features was significantly higher in women sportsmen from the representative team of SPb (score: $46.3 \pm 2.6$ vs. $37.8 \pm 2.3$, $p < 0.05$). When assessing the prevalence of the high and low PA level is was found that the high PA level was observed in 33.3% of female sportsmen from the representative team of SPb vs. 10% in female sportsmen from the representative team of RF (see Table 3.1).

**Table 3.1.** Indicators of the anxiety level among the examined gymnasts (points)

| Anxiety | Groups of sportsmen | | |
|---|---|---|---|
| | **Team SPb (п = 13)** | **Team Russia (п = 18)** | **Significance of differences (t Student)** |
| Situational | 40,9 ± 3,0 | 33,5 ± 1,7 | p<0,05 (2,15) |
| Personal | 46,3 ± 2,6 | 37,8 ± 2,3 | p<0,05 (2,45) |
| Competitional | 22,3 ± 1,3 | 16,1 ±0,8 | p<0,01 (4,06) |

Situational anxiety (SA) characterizing peculiarities of the personality condition in a specific behavioral situation (including situation, which is difficult for the personality) also proved to be confidently higher in female sportsmen from the representative team of SPb (score: 40.9 ± 3.0 vs. 33.5 ± 1.7, $p < 0.05$). Similarly to personal anxiety, the prevalence of confidently higher competitive anxiety level was found in female sportsmen for SPb 33.3% vs. 5.5% in the representative team of RF (1 women gymnast MSIC, 17 years old, $p < 0.05$) (Table 3.2).

**Table 3.2.** Analysis of the occurrence of athletes with high and low anxiety in the examined group of gymnasts

| Anxiety | Team SPb (п = 13) | | Team Russia (п = 18) | |
|---|---|---|---|---|
| | **High** | **Low** | **High** | **Low** |
| Personal | 33,3* | - | 11 | 22,2 |
| Situational | 33,3* | 7,7 | 5,5 | 33,3 |
| Competitional | 77* | 7,7 | 17 | 28 |

Note: significance of differences between groups * - p<0.05, all values are expressed as a percentage of the total number of study participants

Our literature analysis [532] suggests that Martens Competitive Personal Anxiety (CPA) Scale adapted by Yu.L. Khanin can be used effectively in in studies of anxiety in sportsmen going in for different sports [388, 417, 492, 506]. The use of this questionnaire allows to parametrize personal characteristics of sportsmen’s reacting to stressor conditions of competitions in terms of the anxiety level. This psychodiagnostical tool is specialized just for assessment of the sportsmen’s condition and can be used as an additional test of generalized (personal) anxiety. The results of our studies [532] (Table 3.2) show relatively higher level of competitive anxiety in women gymnasts from the representative team of St. Petersburg (77% of investigation participants) as compared to women gymnasts from the representative team of the country (17% of investigation participants).

The obtained results allow to conclude that high sports productivity making it possible to achieve the level of the representative team of the country is linked with mean anxiety level. According to Yerkes Dodson law, this is in compliance with the optimum anxiety level while increase of this level is associated with lowered productivity.

### 3.1.2. Investigation results of psychological defenses and coping-strategies in women gymnasts

The concept of coping-strategy, by its content is close to the concept of psychological defense. The main difference of protective mechanisms consists in unconscious or conscious activation of the coping-strategy mechanism of psychological defense [410]. The psychological defense mechanism based on coping-strategy is a complicated response to action of stressogenic factors (including those of psychological nature). The issue on dynamics of psychological processes considered within the limits of coping-strategy is associated directly with the prognosis problem of some or other human behavior in stress situation. The long-term action of a stressogenic factor can exhaust the coping-resource at a certain time moment and, in spite of the fact that coping-strategy of the protective behavior is aimed at optimization of the personality's adaptation possibilities, this process can result in deadaptaion [377]. The issue of psychologic defense efficiency is associated directly with the concept and characteristics of coping-strategies. Thus, coping-strategies can be defined as a totality of approaches and way with the help of which there takes place the process of conscious and unconscious overcoming a stress situation [395].

Basing from the above, we studied basic coping-strategies in the sportsmen contingent involved in the study of anxiety: highly qualified female sportsmen of the RSG representative team of RF (18 women gymnasts) and representative team of SPb (13 women gymnasts). The analysis of questionnaire data showed that coping-strategy "solving problems" is observed significantly more often in the group of adult sportsmen as compared to women sportsmen of the representative team of SPb (score: 28.9 ± 0.5 vs. 26.4 ± 1.1, $p < 0.05$) and, on the contrary, such non-constructive coping-strategy as "avoidance" is found significantly rarer (score: 17.8 ± 0.5 vs. 19.8 ± 0.8, $p < 0.05$) (Table 3.3).

**Table 3.3.** Comparative analysis of basic coping strategies among the examined highly qualified representatives of sports requiring complex (M ± m)

| Coping-strategies, points | Team Russia (n = 18) | Team SPb (n = 13) | Significance of differences |
|---|---|---|---|
| Problem solving | 28,9 ± 0,5 | 26,4 ± 1,1 | p<0,05 |
| Seeking social support | 22,8 ± 1,0 | 22,7 ± 1,3 | p>0,05 |
| Escapism | 17,8 ± 0,5 | 19,8 ± 0,8 | p<0,05 |

Thus, basing on the obtained data it is possible to note a complex coping-strategy pattern characterizing, most likely, a possible trend to such their combination in relatively higher-level sportsmen, in which the levels of "solving problems" are maximized and the degree of avoidance coping-strategy is minimized. It should be specified regarding the above that gymnastic training begins in young age, when psychological defense mechanisms are not finally formed yet, what, on the one hand, can increase probability of psychological defense inefficiency (what can cause psychological adaptation) and, on the other hand, can leave little chances for development of their optimum combination in the process of moving into adulthood. This determined the necessity to control these parameters for timely correction both in young and adult highly qualified women gymnasts.

The analysis of the obtained data within the limits of this procedure showed that there were no significant differences by the parameter of total strain of basic psychological defenses between female sportsmen of the representative teams of SPb and RF (Table 3.4).

**Table 3.4.** Profiles of psychological defenses intensity among the examined athletes

| Types of psychological defenses, points | Team Russia (n = 18) | Team SPb (n = 13) | Significance of differences |
|---|---|---|---|
| Displacement | 26,2 ± 2,6 | 20,2 ± 3,3 | p>0,05 |
| Regression | 28,3 ± 3,1 | 31,1 ± 2,9 | p>0,05 |
| Substitution | 21,5 ± 3,9 | 25,4 ± 3,8 | p>0,05 |
| Negation | 42,2 ± 2,7 | 48,3 ± 3,3 | p>0,05 |
| Progection | 62,1 ± 3,1 | 53,2 ± 3,9 | p>0,05 |
| Compensation | 51,5 ± 2,9 | 42,3 ± 3,8 | p>0,05 |
| Hypercompensation | 38,5 ± 3,2 | 30,7 ± 4,6 | p>0,05 |

### 3.1.3. The emotional burnout parameters and peculiarities in quality of life self-assessment in highly qualified representatives of precise sports

The study results showed that signs of emotional burnout were in average less pronounced in female sportsmen from the representative team of RF than in female sportsmen from the representative team of SPb due to lower values of strain and exhaustion phases (scores: 16 ± 2.1 and 23 ± 2.9 vs. 26.6 ± 2.8 and 31.3 ± 3.1, $p < 0.01–0.05$) (Table 3.5). It should be mentioned that, as a rule, “unsatisfaction with oneself” and “sensation of being entrapped in a cage” and “personal disengagement” are not typical of leading women gymnasts.

**Table 3.5.** Indicators of emotional burnout among the examined athletes

| Phases of emotional burnout, points | Groups of sportsmen | | Significance of differences |
|---|---|---|---|
| | Team SPb (n = 13) | Team Russia (n = 18) | |
| Tension | 26,6 ± 2,8 | 16 ± 2,1 | p<0,01 (T=3,03) |
| Resistence | 46,85 ± 6,6 | 37 ± 4,3 | p>0,05 (T=1,25) |

| | | | |
|---|---|---|---|
| Burnout | 31,3 ± 3,1 | 23 ± 2,9 | p<0,05 (T=1,95) |
| Total | 20,9 ± 21,7 | 154 ± 17,2 | p<0,05 (T=1,98) |

The analysis results of health self-assessments in both respondent groups were approximately at the same level and did not differ significantly between the compared groups. Similarly, we did not find differences also in current health self-assessment, role limitations due to emotional problems (RE) and relationship between physical and psychic components of quality of life (QL).

Thus, our results show that increased emotional burnout levels in less productive female sportsmen are combined with increased anxiety level.

**3.1.4. The correlation analysis results of the women gymnasts' psychological status**

The assessment of highly qualified female sportsmen's psychological status using correlation analysis showed that the members of the representative team of RF had statistically significant positive correlation ($r = 0.83$, $p < 0.05$) between situational anxiety and exhaustion phase of emotional burnout syndrome. The obtained result suggests possible interrelationship between these parameters and is in compliance with the analysis results of the emotional burnout levels. Correlations were revealed also between situational anxiety and competitive anxiety parameter values ($r = 0.66$, $p < 0.05$) and also strain phase ($r = -0.51$, $p < 0.05$) and resistance ($r = 0.58$, $p < 0.05$). At the same time our data shows that there was not a single statistically significant correlation for the personal anxiety parameter. At the same time, in spite of this fact, competitive anxiety in the considered group correlates with situational anxiety ($r = 0.65$), exhaustion phase ($r = 0.66$) and also strain phase ($r = 0.40$).

A different correlation pattern between psychodiagnostical parameters was revealed for women gymnasts from the representative team of St. Petersburg: positive correlation was revealed between all anxiety types – personal and situational anxiety ($r = 0.7$, $p < 0.05$) and also between personal and competitive anxiety ($r = 0.75$, $p < 0.05$). It was found additionally that competitive anxiety correlated with emotional burnout parameters – resistance phase ($r = 0.58$, 0.05) and strain phase ($r = 0.49$, 0.05).

The performed analysis of the psychodiagnostical investigation data reflecting the anxiety level suggests that that the personal, situational and competitive anxiety level in female sportsmen of the representative team of RF is lower than in women gymnasts from the representative team of St. Petersburg. While this can be caused by the factors associated with the psychologist's work, more strict selection to the representative team and intense competition schedule, to our opinion, the obtained data can be considered also as evidence in favor of the fact that sportsmen at the level of the representative team of the country are characterized by relatively more effective adaptation to stressor psycho-emotional loads. This is in compliance with the provision on the necessity to adapt not only to physical but also to psychological loads in the process of the training and especially competitive activities.

Thus, our studies found that emotional burnout in female sportsmen from the representative team of RF was less pronounced than in female sportsmen from the representative team of SPB with lower values of strain and exhaustion phases. The correlations between the anxiety level and emotional burnout syndrome have their peculiarities in female sportsmen from the representative team of RF and SPb. So, competitive anxiety in the members of the representative team of RF did not correlate with personal anxiety but at the same time it had positive correlation with the exhaustion phase of burnout syndrome. The competitive anxiety in the members of the representative team of SPb correlates with resistance phase and with personal anxiety. Moreover, the competitive anxiety in all women gymnast groups has strong positive correlation with situational anxiety being its specific case.

At the same time, our results of psychological investigation allow to conclude that even with the same level of sports mastery, the most productive female sportsmen training in the representative team of RF, have signs of more effective adaptation to stressor psychic loads. This can be evidence of the fact that a considerable role in the practice of selection and preparation of the reserve for high performance sports is played by the sportsman's psychophysiological status determining the sports productivity. And the psychophysiological status monitoring can be of great diagnostic importance in the sportsman's preparation process. Moreover, the results of our study suggest the important role of anxiety levels.

The study of revealed correlations between strain of psychological defenses with characterological features of women gymnasts demonstrated that parameters of the coping-strategy "solving problems" in the representative team of RF correlate negatively with both emotional stability parameter values ($r = -0.62$, $p < 0.05$) and introversion levels ($r = -0.52$, $p < 0.05$). The women gymnasts preferring the coping strategy "search for social support" show positive correlation with parameter values of of coping strategy "avoidance" ($r = 0.54$, $p < 0.05$). The female sportsmen characterized by relatively high extraversion levels exhibit positive correlation with neurotism parameter levels ($r = 0.58$, $p < 0.05$). Moreover, introverts ($r = 0.52$, $p < 0.05$) and emotionally stable sportsmen ($r = 0.50$, $p < 0.05$) are characterized by correlations with psychological defense strain levels.

A somewhat another correlation pattern is observed in the members of the representative team of SPb, because all significant correlations with the considered parameters were inverse (negative) and their number was relatively less (3 vs. 6). But it is important to mention that absence of statistically significant effects is not the evidence in favor of absence of analyzed statistical relationships [244]. So, female sportsmen from the representative team of SPb preferring the constructive coping strategy "solving problems" are characterized by negative correlation with psychological defense strain ($r = -0.55$).

The performed analysis of correlations between anxiety level parameters and personal characteristics of the investigated sportsmen cohort demonstrates the complex nature of their structure. Moreover, if it is difficult to describe psychological mechanisms of formation of these parameters without contradictions only basing on our psychological data, the study results demonstrate confidently the necessity to consider these parameters anyway associated with anxiety with the purposes of the sportsman's psychological condition monitoring. At the same time it is known that implementation of physical qualities in the sports activities is impossible without high quality professional interdisciplinary control of psychic functions. Basing on the above, we can speak of the fact that the development of a procedure for psychological preparation individualization taking into account specifics of precise sports is a very urgent scientific and practical problem at all preparation stages of the sports reserve and representative teams of the country [342, 355, 441].

The results obtained by us at the stage of the psychological investigation are in compliance with modern concepts of the anxiety influence on characteristics of sports activities and on the results of experimental studies of the relationship between anxiety condition and productivity of sports activities. Notwithstanding the available contradictions in the experimental data of medico-psychological investigations of sports activities, the obtained results suggest concordantly that the influence of the anxiety factor is nonuniform for different sports, i.e. the influence nature of the increased anxiety level is manifested differently in various sports. So, e.g., high requirements to anxiety condition are noted for those sports, where the key role is played by subjective officials' assessments (e.g, gymnastics or figure skating) and also in individual sports as compared to commend sports [87]. It is known also that the higher the traumatism of sports activities is, the higher the prevalence of anxiety is, what is typical for contact sports (box, football) [82, 84].

In addition to sport-specific factors, the influence of the anxiety condition on sports activities depends on personal characteristics. E.g., it is known that relatively higher anxiety levels and lower levels of confidence in own forces are demonstrated by female sportsmen (as compared to males) and also relatively less experienced and younger sportsmen (as compared to more experienced and older sportsmen) [92]. Moreover, elite sportsmen control better anxiety condition as compared to other highly qualified professional sportsmen [114].

An important aspect of influence exerted by anxiety consists in its connectivity with the sportsman's traumatic experience – athletes with history of injuries or brain concussion [85] are characterized the increased personal anxiety levels [276, 305]. It is known that diagnostics of anxiety is associated not only with possible limitation of the sportsman's potential but also with increased risk of musculoskeletal injuries. [276, 305]. Thus, if anxiety level is increased, besides changes in sports activities efficiency, a situation of vicious circle can be formed, when increased anxiety level causes the risk of traumatization, and injuries, in their turn, promote the development of anxiety condition. This is especially important in connection with the fact that competitive anxiety can be characterized by comorbidity with generalized anxiety disorder [255]. This aspect is of importance because the development of diseases anyway associated with the development of anxiety conditions may vary considerably for different sports (it is important to take this into account when organizing medico-biological monitoring of sportsmen). E.g., several recent studies showed that relatively higher risk of generalized anxiety disorder is observed in individual sports as compared to team sports: 13% vs. 7%, respectively [87, 294]. Besides that, the higher risk of such diseases is observed in such sports where aesthetics is important (gymnastics, figure skating) [245]. A similar trend is observed also for female sportsmen [245].

Basing on the above, it becomes clear why the results of the performed psychological studies enable us to speak of the fact that relatively more effective sportsmen (of the level of the country representative team) are characterized by relatively less pronounced anxiety levels. Although, strictly speaking, the use of the correlation analysis method does not allow to establish cause-effect relationships between the personal parameters and anxiety levels. But, taking into account the necessity to search for a potential diagnostically effective parameter of the psychophysiological status, the obtained results can be considered as evidence suggesting the possible existence of such association. Therefore, their use is justified within the limits of the present thesis study as pivotal data for search for a suitable clinical model to develop an approach to psychophysiological monitoring of the sportsman's condition. Thus, taking into account the contradictory nature of experimental data and continuing discussions on psychological patterns underlying the association between the development of competitive anxiety and productivity of sports activities, the search for psychophysiological markers of increased anxiety level is one of the possible areas for further studies.

From this viewpoint, the patterns of anxiety level change in sportsmen of different productivity degree (and also their correlations with other psychodiagnostical parameters) revealed in our study allow to select generalized anxiety disorder (GAD) as a key element in the clinical model of changes in the brain provision for control functions within the limits of our thesis study. Thus, search for neurophysiological manifestations of increased anxiety level, which would suggest the possible association between GAD and structural and functional organization of the brain human activities control systems can be used, in its turn, to establish potentially diagnostically significant signs of changes in the control functions which can be evidence of possible lowering of activity control efficiency and its productivity. Moreover; such search cannot fail to consider the complicated nature of established correlations between personal anxiety and other personal characteristics (coping-strategies, emotional burnout), which are manifested differently depending on qualification of the analyzed groups of highly qualified sportsmen (women gymnasts of the city representative team vs. country representative team). This warrants broadening of studies for search for the brain substrate beyond the limits of brain activities control systems, the focused psychophysiological monitoring of which would be suitable for objectives of the present thesis study. Moreover, it is important to broaden a set of potential targets for such monitoring up to brain structures which can be associated with provision of behavior aspects which are significant for provision of skills and actions, which are important for sports activities, and possible modulating influence of anxiety (resulting, in some cases, in the development of disease according to vicious circle principle). The socially significant information processing and cognitive activities executive control processes were selected as such aspects of activities in this thesis study.

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Thus, the results obtained at the psychological stage of the present thesis study allow to state the demand for the development of potential markers of the sportsman's psychophysiological condition associated with those behavioral aspects, which can be modified due to change in anxiety level.

An important methodical study aspect consists in selection of the optimum psychophysiological monitoring method taking into account limited time for the investigations of highly qualified sportsmen due to the intense schedule of training cycles. Functional MRI at rest (operational condition according to Ukhtomsky [514], is one of the methods widely used in modern psychophysiological investigations of the healthy and sick human brain. During such fMRI investigations BOLD-signal fluctuations recorded in the operational rest condition are used to analyze the correlation between two temporal series of BOLD-response from different brain regions (called regions of interest (ROI)). The correlation parameters obtained in such a way are called as functional connectivity reflecting functional integration between large-scale brain regions in the operational rest condition [136]. Many important and new facts on the brain integrative activity were obtained since introduction of this analysis method. So, wide use of fMRI method in studying the operational rest condition basing on the functional connectivity data allowed to reveal several unions of human brain structures (called as networks or systems). It is considered that availability of correlations between separated sets of structures has functional sense. So, e.g. the DMN-default mode network [515], sensorimotor system, executive control network (ECN), visual, auditory, speech systems, etc. are distinguished [251].

In contrast to the activation approach, as follows from the name, fMRI in the operational control condition is performed without use of a test task, what makes it easier to a significant extent to perform this procedure in a wide range of patients. The activation investigations often use a test task making certain requirements to the subject's involvement which can be fulfilled not always in conditions of neurological or psychological deficit. So, e.g., the prevalence of aphasic disorders in patients with glial mass lesions according to some studies is up to 48% being the most frequent neurological disorder in this cohort [241]. Severe aphasic disorders can make it impossible to perform test tasks within preoperative mapping of functionally significant verbal zones using activation fMRT [316]. In addition to specific function disorder (speech or sensorimotor), barriers to use of activation fMRI in the clinical practice include also patient’s age (in particular, children) and long scanning duration requiring high attention concentration and correct performing the test task what is not always possible, e.g., psychiatric patients [251]. It is possible to overcome the above defects of activation fMRT using fMRI in the operational rest condition.

Besides that, a so-called pathoconnectivity model becomes more and more common recently [151]. This model assumes existence of different human brain networks, changes in which are associated with the development of one or another disease symptom. The above networks consist of a set of anatomical structures which can be included in composition of different networks. At the initial stages of the disease one or several networks are partially affected by pathologic changes which spread then gradually inside the network. This disturbs normal functioning of the network, what results in occurrence of a specific symptom. Moreover, if several networks are involved in the pathologic process (through disturbed function of common nodes), a symptom complex will be associated with it, what, possibly, will lead to development of typical syndrome or clinical diagnosis of concomitant diseases. Thus, the use of fMRI in the operational rest condition in order to assess the condition of these networks can be of importance both in diagnostics of individual diseases and in estimation of their prognosis, because the analysis of functional connectivity in the operational rest condition allows to obtain information both on the interaction strength (functional connectivity) and direction (effective connectivity) of connection between all human regions [128].

Basing on the above and peculiarities of the present study tasks, just the operational rest condition was selected as conditions for fMRI scanning for establishing potential neuromarkers of the sportsmen’s psychophysiological conditions basing on the neurovisualization studies using a clinical model of GAD-associated changes in the brain provision for control functions. The results of these studies are presented in the next chapter.

# CHAPTER 4 RESULTS OF OWN STUDIES. PSYCHOPHYSIOLOGICAL INVESTIGATIONS OF HEALTHY VOLUNTEERS AND PATIENTS WITH GENERALIZED ANXIETY DISORDER

At the first stage of a psychophysiologic investigation series, we tested the hypothesis on the fact that patients with generalized anxiety disorder (GAD) have changes in functioning of the brain inhibitory control system as compared to healthy subjects. Basing on the fact that one of GAD aspects consists in uncertainty intolerance, we supposed that such change in anxiety level concerns the brain provision for nonselective inhibitory control processes of actions. As it is known that nonselective inhibiting is involved in provision of behavior control processes, when there is no certainty regarding the fact which action should be implemented (or suppressed). For this purpose, we used the Go/NoGo test task with equally probable presentation of control Go and NoGo stimuli what allows to model the uncertainty conditions. Besides that, the selection of just this test task variant was associated with the fact that the possibility of involvement of the brain nonselective inhibitory control (NSIC) system was demonstrated earlier exactly using such modification of the Go/NoGo test [118, 156]. The hypothesis tested at this stage of studies is substantiated by the fact that, as it was discussed above, change in personal anxiety level can influence the behavior not only in psychoneurological disease but in the conditional norm, i.e. in the healthy human (including a person engaged in professional sports activities). This is in compliance with the fact that anxiety factor is one of considerable regulatory factors influencing the efficiency of professional sportsmen's activity implementation [87, 276, 425]. Taking into account that the brain nonselective inhibitory control system, the existence of which was directly proven in experimental studies [118, 156], is involved in providing for both suppressed and implemented actions, it was supposed that the increased anxiety level could not fail to interfere with the function of this system. One should emphasize once more that the latter aspect is of special importance because so-called uncertainty intolerance is observed under conditions of anxiety disorders. In accordance with concepts of psychologic GAD mechanisms, uncertainty intolerance is manifested as trend to emotional negative waiting associated with an uncertainty situation which provokes avoidance of such situation [67, 163]. If there is a minimum chance to obtain a negative action result, such action is perceived as unsuccessful what results in permanent search for an ideal solution (which, as a rule, is not an action or is its suppression (situations were observed with probability of 50%)).

Thus, considering the above, we revealed the elements of the neuronal NSIC system in a patient group with anxiety using fMRI data recorded under conditions of the two-stimulus Go/NoGo test task with equally probable presentation of Go and NoGo stimuli. As it was demonstrated earlier in the studies involving healthy subjects [118] and patients with obsessions [156], such test task design allows in principle to model the uncertainty situations and is effective in determining the element composition of NSIC. Besides that, to solve this task, we used the developed statistical approach based on interval statistics and Bayesian data analysis allowing to reveal the brain regions demonstrating statistically significant practically equivalent level of fMRI signal [244], i.e. ROPE mapping [1] [496]. At the first stage, to classify the brain regions revealed by such ROPE mapping as structures providing for just action inhibition, we compared statistical practical equivalence maps of fMRT signal in the Go and NoGo tests with the results meta-analysis published in the literature (statistical map constructed based on literature data) dedicated to studying the brain substrate of nonselective inhibitory control using the comparable experimental conditions [118, 156]. At the next stage, the obtained result was compared with the findings of the similar analysis performed only for a healthy subject group [118, 437].

Simultaneously with fMRI data analysis, we assessed behavior parameters of efficiency when fulfilling the Go/NoGo test task within the limits of intergroup comparison of patients with generalized anxiety disorder and healthy subjects: the analysis included values of response time and number of mistakes with incorrect

[1] https://github.com/Masharipov/Bayesian_inference

pressing the button during the NoGo tests and failures to press the button in the Go tests.

Thus, this stage of our study required answers to the following questions: 1) does generalized anxiety disorder tell upon the efficiency of activities implementation, 2) does varying efficiency of activities implementation agree with varying characteristics of the autonomic nervous system condition, 3) with which peculiarities in brain functioning during fulfillment of the Go/NoGo test task can the lowered activities efficiency in case of change in personal anxiety levels in GAD be associated.

At the next stage a question arose for us, whether change in the brain provision of cognitive functions implementation at increased anxiety levels is accompanied by changes in functioning of the neuronal nonselective inhibitory control system and/or brain structures related to providing processes of inhibition and cognitive/executive activities control. For this purpose, we performed direct intergroup comparison of fMRI signal level during fulfilling the Go/NoGo test task by healthy subjects and patients with generalized anxiety.

Also the studies were performed to investigate signs of changed functioning of the brain systems providing for cognitive functions in GAD in the operational rest condition using fMRI data. To solve this task we used the data on element composition of: 1) neuronal nonselective inhibitory control system (basing on the data of statistical parametric maps constructed when analyzing fMRI findings obtained under conditions of the Go/NoGo test task); 2) neuronal socially significant information processing system determined by the data of statistical parametric maps constructed when analyzing fMRI findings during assessment of the influence exerted by social intelligence level on the functional connectivity in rest condition and fMRI findings obtained under conditions of Taylor paradigm; 3) neuronal cognitive activity executive control system established basing on the data of statistical parametric maps constructed using fMRI data obtained under conditions of resolving lexical ambiguity.

In order to investigate the nature of influence exerted by GAD on the integrative activity patterns of revealed elements of the above brain systems according to fMRI data recorded in the operative rest condition, we analyzed correlations between psychodiagnostical and neurophysiological signs of generalized anxiety and the functional connectivity level. Besides the question associated with study of the possible contribution of changed brain provision of inhibitory control to GAD pathogenesis, this stage of the study was called upon to assess potential possibilities to use fMRI in operational rest condition for practical diagnostics of signs of lowered activities efficiency and productivity. We had to answer a question whether it is possible to use this method for diagnostics or revealing signs of changed functioning of the brain systems providing for cognitive activities, the activity of which is modulated by changed anxiety level and which could be used in the practical medico-biological support of sportsmen.

At the final stage of the psychophysiological investigation we compared directly the data of functional connectivity basing on fMRI findings in the operational rest condition between healthy subject group and patient group with generalized anxiety disorder.

## 4.1. Revealing the elements of the brain nonselective inhibitory control system in patients with generalized anxiety disorder

### 4.1.1. Behavioral data of the Go/NoGo test task in patients with GAD and healthy subjects

At the beginning of the psychophysiological stage we analyzed behavioral data obtained when fulfilling the two-stimulus Go/NoGo test task. Our studies revealed that direct intergroup comparison of behavioral data of patients with GAD with health subjects regarding the response rate when fulfilling the Go tests did not allow to establish statistically significant differences. The mean response rate values in the healthy subject group and patient group with anxiety disorder and the results of their statistical analysis are presented in Table 4.1 and Fig. 4.1.

**Table 4.1.** Results of intergroup comparison of Go/NoGo task performance

| | t-value | p-value | Average difference | Cohen's d |
|---|---|---|---|---|
| Average reaction time | 1,293 | 0,201 | 22,833 | 0,341 |
| Errors Go | -0,945 | 0,349 | -0,851 | -0,249 |
| Errors NoGo | 0,665 | 0,509 | 0,127 | 0,175 |
| Errors Ignore | -1,050 | 0,298 | -0,155 | -0,277 |

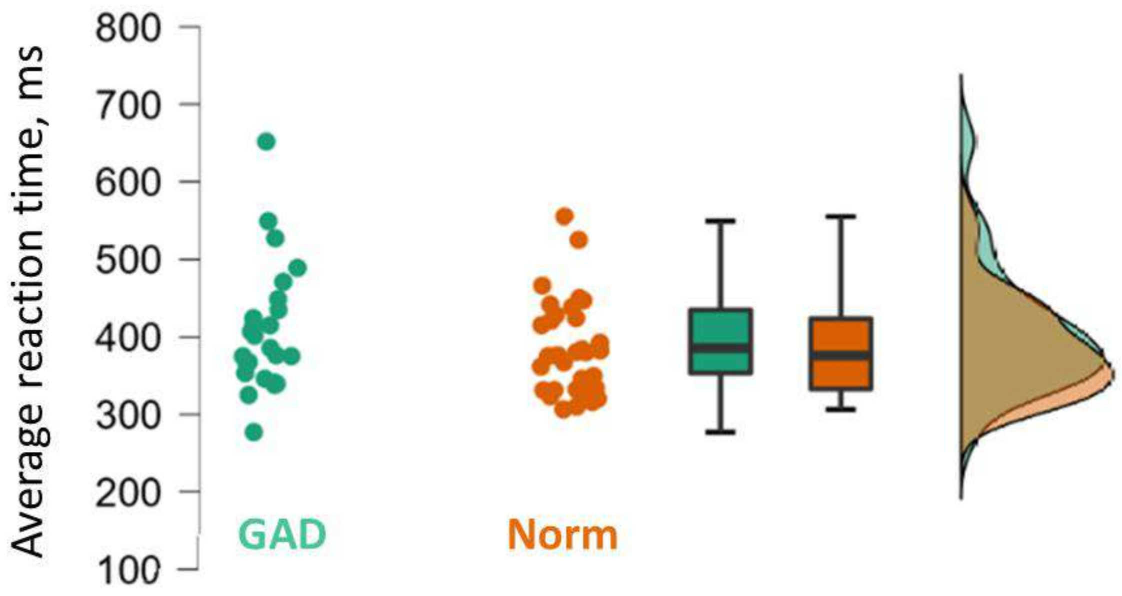



**Figure 4.1.** Average reaction time in a group of healthy subjects and patients with generalized anxiety disorder (GAD). GAD – data from a group of patients with GAD, Norm – data from a group of healthy subjects.

We also did not find statistically significant differences between the compared groups regarding the number of mistakes in the Go, NoGo and Ignore tests (see Table 4.1).

Thus, we did not reveal signs of lowered activities efficiency in the terms of slowed response time when performing the Go/NoGo test task at the intergroup analysis level of the behavioral data (response time and number of mistakes), i.e., when comparing the healthy subject group and patient group with generalized anxiety. The obtained results are in compliance with the results of previous behavioral studies of inhibitory control in patients with GAD using the Go/NoGo test task [74], which was similar to the Go/NoGo test variant used in the present study. This is evidence of the fact that patients with GAD did not show rough behavioral disorders associated with relatively simple activities for suppression and implementation of actions. At least, this is true for conditions of Go/NoGo test by the behavioral data of which one can judge about the efficiency of action inhibitory control. So, e.g., it is known that in patients with obsessions, where increased personal anxiety levels are ones of the frequently observed symptoms, the lowered activities efficiency is manifested as increased response time in the Go tests [132, 156].

As a result of comparing the behavioral data of the Go/NoGo test with psychodiagnostic data in patients with generalized anxiety disorder, a significant correlation was found between these parameters. So, patients with GAD showed significant negative correlation between the number of mistakes in the NoGo tests and Kerdo index (correlation coefficient = 0.57 ($p < 0,05$). At the same time any significant correlations were not detected between other parameters of the test task and psychometric parameters including response time in the GO tasks of Go/NoGo tests.

### 4.1.2. Analysis results of fMRI data obtained when fulfilling the Go/NoGo test in patients with anxiety disorder as compared to the norm: analysis of changes in local activities and functional connectivity

As a result of our direct intergroup comparison of the brain activity in the equally probable Go and NoGo tests (analyzed in combination) in patients with GAD as compared to healthy volunteers we revealed statistically significant BOLD-signal decrease in the following brain structure: left caudate nucleus, thalamus, primary motor cortex and premotor cortex and also bilaterally in the visual cortex (cuneus, lingual gyrus), supplementary motor cortex and anterior cingulate gyrus (see table 4.2, Fig. 4.2).

**Table 4.2.** Areas of the brain that show decreased activity in patients with GAD compared to healthy subjects for the contrast «Go + NoGo > baseline»

| № | Cluster size, mm³ | pFWE cluster level | Location (L – left hemisphere, R – right hemisphere) | t-value of local max | Local max coordinates in MNI | | |
|---|---|---|---|---|---|---|---|
| | | | | | x | y | z |
| 1 | 14985 | 0,0001 | L/R: SMA, Pre-SMA, Primary motor cortex, Premotor cortex | 4,79 | 9 | -1 | 68 |
| | | | L/R: ACC | 4,72 | -3 | 23 | 32 |
| 2 | 18819 | 0,0001 | L/R: Visual cortex (cuneus, lingual gyrus) | 4,48 | 0 | -70 | 20 |
| 3 | 5724 | 0,047 | L: Head of the caudate nucleus | 4,33 | -18 | 8 | 17 |
| | | | L/R: Thalamus | 4,20 | -3 | -19 | 14 |

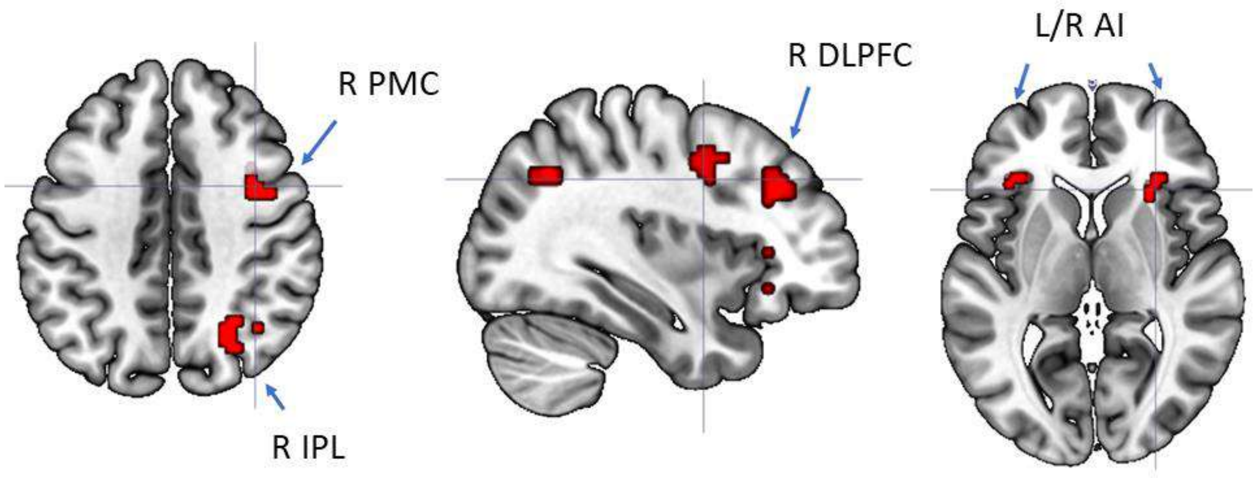



**Figure 4.2.** Areas of the brain that show decreased activity in patients with GAD compared to healthy subjects for the contrast «Go + NoGo > baseline». PMC

– premotor cortex; IPL – inferior parietal lobule; DLPFC – dorsolateral prefrontal cortex; AI – anterior insula; L/R – left/right hemisphere.

The lowered local brain activity revealed by separate analysis of the Go and NoGo tests was observed also in patients with GAD as compared to the data of healthy subjects. When analyzing the Go tests, lowering was found in the left caudate nucleus, left and right thalamus, left primary motor cortex and premotor cortex, left superior parietal lobule (associative somatosensory cortex), and also bilaterally in the cerebellum, visual cortex, supplementary motor cortex and anterior cingulate cortex (see Table 4.3, Fig. 4.3).

**Table 4.3.** Areas of the brain that show decreased activity in patients with GAD compared to healthy subjects for the contrast «Go > baseline»

| **№** | **Cluster size, mm$^3$** | **pFWE cluster level** | **Location (L – left hemisphere, R – right hemisphere)** | **t-value of local max** | **Local max coordinates in MNI** | | |
|---|---|---|---|---|---|---|---|
| | | | | | **x** | **y** | **z** |
| 1 | 29160 | 0,0001 | L/R: Thalamus | 5,10 | -3 | -19 | 14 |
| | | | L/R: Visual cortex (cuneus, lingual gyrus) | 4,17 | -3 | -70 | 11 |
| | | | L/R: Cerebellum | 4,05 | 3 | -64 | -16 |
| | | | L: Head of the caudate nucleus | 3,84 | -18 | 17 | 17 |
| 2 | 8748 | 0,008 | L/R: SMA, Pre-SMA, Primary apical cortex, Premotor cortex | 4,92 | 6 | -1 | 68 |
| | | | L: Superior parietal lobule | 3,58 | -24 | -40 | 53 |
| 3 | 8262 | 0,011 | L/R: ACC | 4,46 | -3 | 23 | 32 |

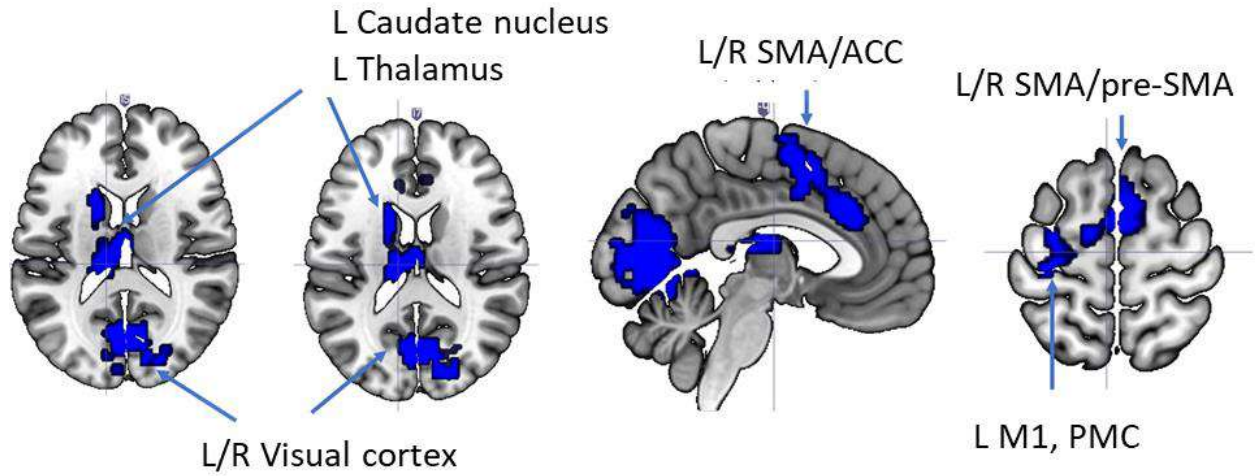



**Figure 4.3.** Areas of the brain that show decreased activity in patients with GAD compared to healthy subjects for the contrast «Go > baseline». SMA – supplementary motor area; ACC – anterior cingulate cortex; M1 – primary motor area; PMC – premotor cortex; L/R – left/right hemisphere.

We found that separate analysis of NoGo tests revealed statistically significant lowering of BOLD-signal level in patients with GAD (as compared to the norm) which was localized bilaterally in the visual cortex, additional motor cortex and anterior cingulate cortex (see Table 4.4, Fig. 4.4).

**Table 4.4.** Areas of the brain that show decreased activity in patients with GAD compared to healthy subjects for the contrast «NoGo > baseline»

| | **Cluster size, mm$^3$** | **pFWE cluster level** | **Location (L – left hemisphere, R – right hemisphere)** | **t-value of local max** | **Local max coordinates in MNI** | | |
|---|---|---|---|---|---|---|---|
| | | | | | **x** | **y** | **z** |
| | 12285 | 0,001 | L/R: Visual cortex (cuneus, lingual gyrus) | 4,45 | 0 | -70 | 23 |
| | 10233 | 0,003 | L/R: SMA, Pre-SMA | 4,36 | 6 | 8 | 59 |
| | | | L/R: ACC | 4,12 | -3 | 23 | 32 |

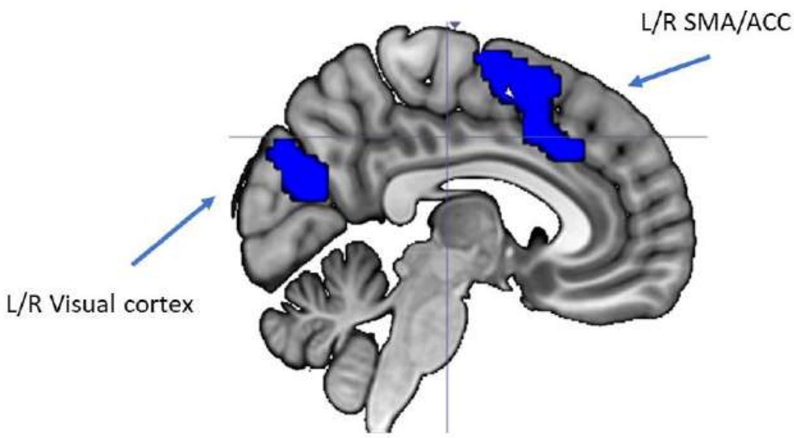



**Figure 4.4.** Areas of the brain that show decreased activity in patients with GAD compared to healthy subjects for the contrast «NoGo > baseline». SMA – supplementary motor area; ACC – anterior cingulate cortex; L/R – left/right hemisphere.

Thus, our comparative analysis shows that lowering of the local brain activity in GAD does not involve NSIC elements revealed in this patient group. This is evidenced by absence of crossings between the brain regions which showed lowered brain activity in patients with generalized anxiety disorder (as compared to the norm), and the brain regions referred to the NSIC system.

This, firstly, suggests that very pronounced changes in the functioning of this system are not observed in GAD.

Secondly, basing on the obtained data one cannot conclude that hypoactivation observed in GAD under conditions of implementation and suppression of prepared actions during fulfilling the Go/NoGo test task, concerns the brain structures providing for involvement of nonselective inhibition processes, i.e. possible inhibition control process deficit in GAD does not concern NSIC.

At the same time, in the anterior cingulate cortex, our studies revealed crossing between the brain structures, in which the lowered activity is observed in patients as compared to the norm for contrasts “Go > baseline” and “NoGo > baseline”, and the brain regions providing for action inhibitory control according to meta-analysis of 20 fMRI studies using the Go/NoGo task [**118**] (see Fig. 4.5), which was used in the present study to reveal the NSIC structures as potentially associated with inhibition processes.

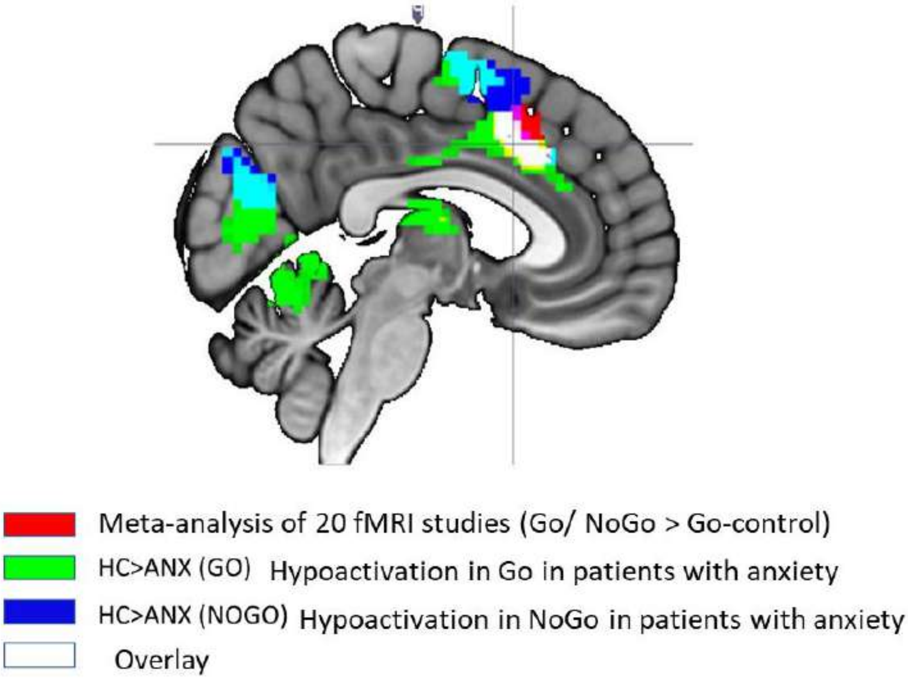



**Fig.4.5.** Spatial overlap of human brain areas in which there is a decrease in activity in patients with GAD compared to healthy subjects for the contrasts "Go > baseline" and "NoGo > baseline", which are as well related to the inhibitory control system according to a meta-analysis of 20 fMRI studies (contrast "Go /NoGo > Go-control"). SMA – supplementary motor area; ACC – anterior cingulate cortex.

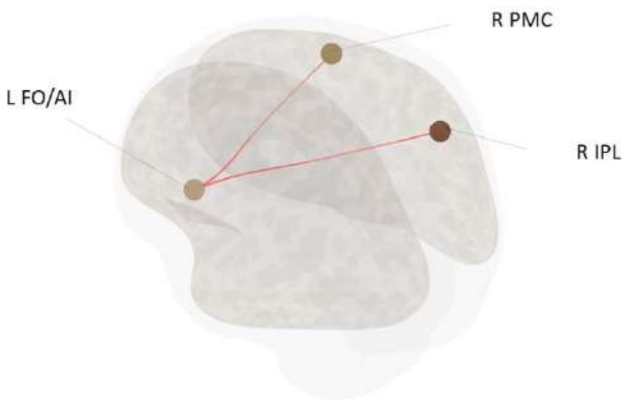
Thus, basing on our data it is possible to conclude that GAD is accompanied by changes in the brain structure function in the anterior cingulate cortex associated with provision of inhibitory control (NoGo tests) and executive control (Go tests). Because of the fact that revealed BOLD-signal changes do not correspond to NSIC elements by localization, the obtained results can be considered as reflection of the deficit in provision of the activities control in GAD not associated with disturbed functioning of the neuronal nonselective inhibitory control system. Taking into account the fact revealed by us that NSIC in GAD is wider by its element composition as compared to standard values the observed characteristics of BOLD-signal changes can suggest the compensatory nature of such NSIC element composition extension. This is in accord with the fact that anxiety can result in increased activities control. The content of this extension consists of additional involvement of the insular cortex and dorsolateral prefrontal cortex of the right hemisphere. It should be mentioned that, in accordance with the available literature data, just these brain structures are quite often mentioned because of their involvement in provision of anxiety feeling in GAD. In particular, exactly these activity patterns of insular cortex are associated with the effect of uncertainty intolerance [132] and also fear emotions in case of specific types of phobias (when they are provoked in the experiment) and so-called social anxiety [117, 210]. Our result is also in accord with literature data on the fact that insula is of the human brain structures which exhibits lowered brain gray substance density in GAD [193, 214]. It is known also that anxiolytic action of citalopram is manifested as a suppressing influence on insula hyperactivation in response to speech stimulation provoking the anxiety feeling [19]. It is important to mention also that increased functional connectivity between the anterior cingulate cortex and anterior regions of the insula and medical dorsolateral prefrontal cortex, which is similar by its localization with our study results, was observed earlier when anxiety was provoked by the method of threatening image presentation [272]. The increased activity of the insula and dorsolateral prefrontal cortex was also observed when presenting faces expressing a threat (expression of malice) [320].

At the next stage of the study, fMRI data was used to analyze the functional connectivity parameters between the elements of the nonselective inhibitory control system, which were compared between the GAD patient group and healthy subjects: 1) the NSIC elements were established in a separate investigation including fulfillment of the Go/NoGo test task; 2) the functional connectivity was analyzed for two sessions of the Go/NoGo test task (see section 2.3.1.4, chapter 2).

Our analysis of the functional connectivity between NSIC elements, when comparing healthy subjects and patients with anxiety disorder fulfilling different sessions of the Go/NoGo test task, revealed three correlations, the strength of which differed between comparison groups.

So, we showed that in GAD the functional connectivity is lowered between the left insula/frontal operculum and two structures located in the right hemisphere (see

Fig. 4.6): 1) frontal motor field/premotor cortex; 2) inferior parietal lobule. Moreover, the multidirectional changes were observed in the functional connectivity between the structures of the right dorsolateral cortex and right temporoparietal junction. The relative lowering of the functional connectivity in GAD as compared to the norm was observed for a relatively less difficult AAGO test task variant, and, on the contrary, growth of the functional connectivity in GAD as compared to the norm was found for relatively more difficult APGO test task variant.



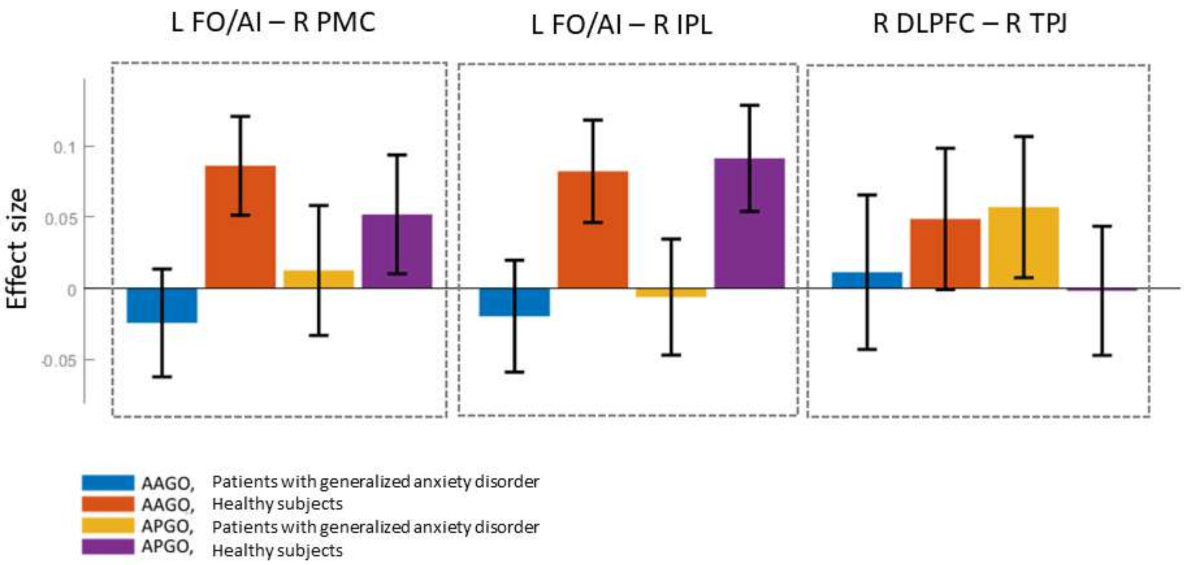




**Figure 4.6.** The effect size for the identified statistically significant changes in the functional connectivity between the nodes of the NSIC in patients with GAD, compared with healthy subjects. PMC – premotor cortex; IPL – inferior parietal lobule; DLPFC – dorsolateral prefrontal cortex; AI – anterior insula; FO – frontal operculum; TPJ – temporo-parietal junction; L/R – left/right hemisphere.

### 4.1.3. The NSIC elements revealed in patients with generalized anxiety disorder when fulfilling the Go/NoGo test

We determined the brain regions belonging to NSIC system in patients with generalized anxiety disorder using spatial overlap of statistical parametric maps calculated as a result of statistical meta-analysis of literature data which compared the experimental conditions of type Go/NoGo>Go-control and Bayesian ROPE analysis of contrast NoGo = Go (basing on the data of our fMRI investigation). The revealed NSIC structures, among others, included the following: right dorsolateral prefrontal cortex, inferior parietal lobule, frontal oculomotor field, premotor cortex, left and right anterior insula/frontal operculum (see Table 4.5., Fig. 4.7).

**Table 4.5.** Human brain regions related to the NSIC system in patients with generalized anxiety disorder

| | **Location (L – left hemisphere, R – right hemisphere)** | **Cluster size, mm$^3$** | **Local max coordinates in MNI** | | |
|---|---|---|---|---|---|
| | | | **x** | **y** | **z** |
| | R: Inferior parietal lobule | 1107 | 28 | -60 | 40 |
| | R: Dorsolateral prefrontal cortex | 756 | 32 | 36 | 32 |
| | R: Frontal oculomotor field, premotor cortex | 675 | 38 | 4 | 44 |
| | R: Anterior insula, frontal operculum | 378 | 28 | 28 | 4 |
| | L: Anterior insula, frontal operculum | 243 | -36 | 30 | 4 |
| | R: Dorsolateral prefrontal cortex | 162 | 26 | 54 | 16 |

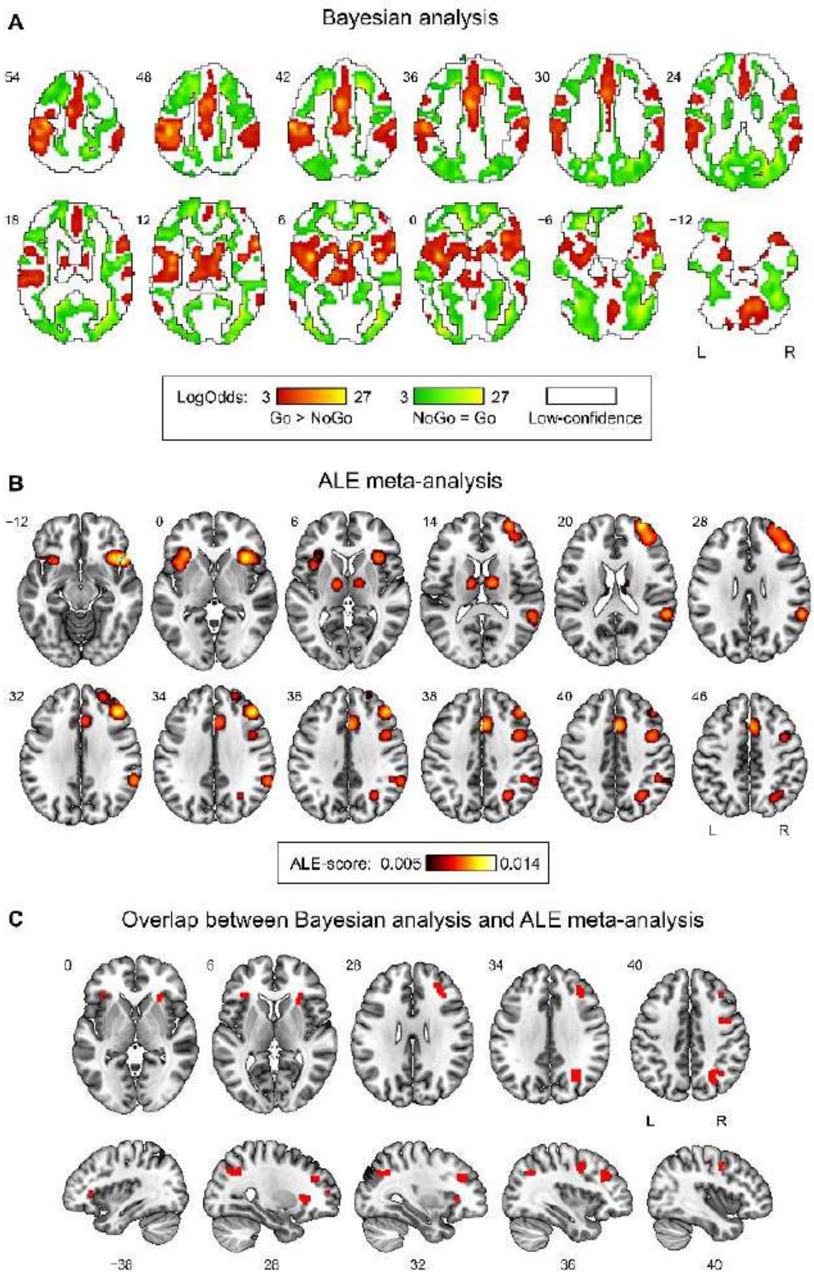



**Figure 4.7.** Human brain regions related to the NTSK system in patients with generalized anxiety disorder. FOF – frontal oculomotor field; PMC – premotor cortex; IPL – inferior parietal lobule; DLPFC – dorsolateral prefrontal cortex; AI – anterior insula; FO – frontal operculum; TPJ – temporo-parietal junction; L/R – left/right hemisphere.

Thus, the NSIC system in patients with anxiety disorder includes the same elements as in the norm but it also includes additionally the element in the right anterior insula/frontal operculum. The obtained result can be considered as a specific sign evidencing of both GAD presence and possible change in the brain provision of inhibitory control associated with lowered activities efficiency and productivity.

Moreover, as compared to NSIC element distribution in healthy subjects, the elements of this system in patients with GAD are localized either in adjacent brain regions, or occupy an anatomically large territory, or are located in the brain structures not revealed in healthy volunteers. So, the additional NSIC elements in GAD as compared to the norm, are observed in the right insula and right dorsolateral prefrontal cortex (see Fig. 4.8). This, GAD is characterized by NSIC network extension as compared to the norm.

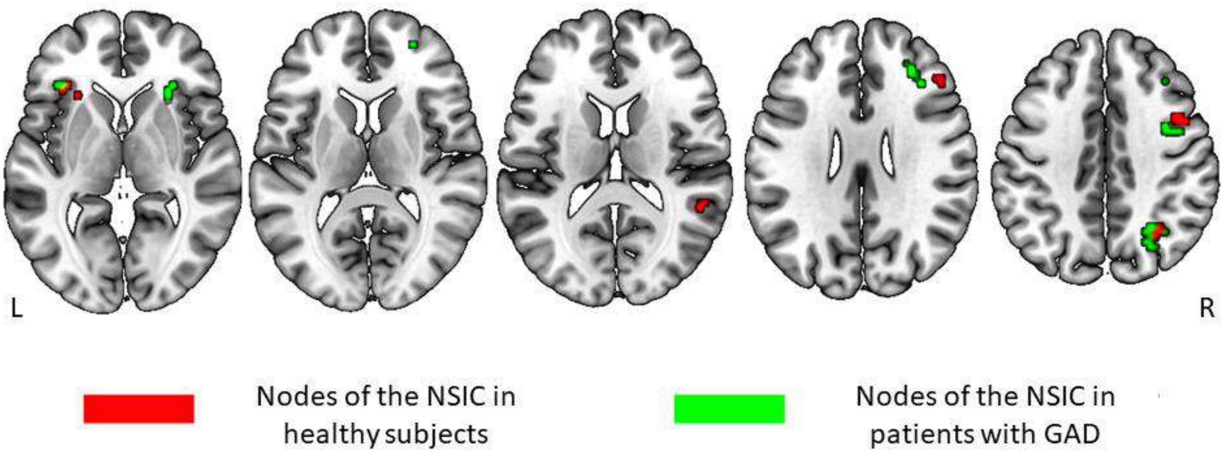



**Figure 4.8.** The comparison of localizations of NSIC nodes in healthy subjects and patients with GAD. Green indicates brain regions that are part of the neural system of NSIC, identified in patients with GAD; Red indicates brain regions of the NSTC neural system in healthy subjects; L – left hemisphere; R – right hemisphere.

**4.1.4. The relationship between the human brain activity during fulfillment of the Go/NoGo test in patients with generalized anxiety disorder and their behavioral, psychodiagnostic data and autonomic nervous system activity parameters**

The relationship between the brain activity during fulfillment of the Go/NoGo test and behavioral and psychodiagnostic parameters of personal anxiety level and also Kerdo index was determined in our studies by analyzing the BOLD-signal level in certain regions of interest (basing on the data of the previous study stage) and also with the help of voxel-based analysis.

We selected as regions of interest the brain regions, whose belonging to the NSIC system in patients with GAD was established by us above (see Fig. 4.7, Table 4.5 presented above) and also the region of lowered local brain activity in GAD (as compared to the norm) overlapped with meta-analysis results for revealing structures-candidates to NSIC elements (see Fig. 4.5).

It is important to mention that in the NSIC system statistically significant relationships between local element activity and both behavioral and psychodiagnostic data were revealed by us only for two brain structures: 1) significant negative correlation was observed between the activity in the right inferior parietal lobule and mean response rate ($r = -0.41$, $p < 0.05$); 2) significant positive correlation was found between the activity in the right frontal operculum/anterior insula and internality parameters ($r = 0.397$, $p < 0.05$).

The same picture of statistical relationships was revealed also when studying the brain activity in the NoGo tests associated with inhibition. Our analysis allowed to establish correlations for the following two regions of the NSIC system: 1) negative correlation was revealed between the activity in the right dorsolateral prefrontal cortex and number of mistakes in Ignore tests ($r = -0.42$, $p < 0.05$); 2) positive correlation was detected between the activity in the right frontal operculum/anterior insula and both the number of mistakes in Go tests ($r = -0.4$, $p < 0.05$) and psychodiagnostic internality parameter ($r = 0.43$, $p < 0.05$).

Taking into account a large number of compared variables in the correlation analysis, the results of which are presented above, later we were especially interested in the results obtained in the voxel-based analysis because the methods for statistical correction for multiple comparisons, allowing to reduce significantly the number of false-positive findings, were used for their obtaining.

The voxel-based correlation analysis revealed clusters with significant negative correlation between the brain activity in patients in the Go tests and the anxiety Hamilton scale score (see Table 4.6; Fig. 4.9).

Any other statistically significant correlations between the brain activity and behavioral parameters and also psychometrical parameters and Kerdo index were not revealed.

**Table 4.6.** Areas of the human brain in which a negative correlation is observed between the level of the BOLD-signal in patients with GAD in Go tests and the anxiety rating on the Hamilton scale

| | **Cluster size, mm$^3$** | **pFWE cluster level** | **Location (L – left hemisphere, R – right hemisphere)** | **t-value of local max** | **Local max coordinates in MNI** | | |
|---|---|---|---|---|---|---|---|
| | | | | | **x** | **y** | **z** |
| | 14040 | 0,0001 | L: Posterior insula, putamen | 5,84 | 36 | -25 | 20 |
| | | | L: Precentral gyrus | 4,25 | 36 | -10 | 44 |
| | 5859 | 0,025 | L: Anterior cingulate cortex | 5,70 | 15 | 11 | 47 |

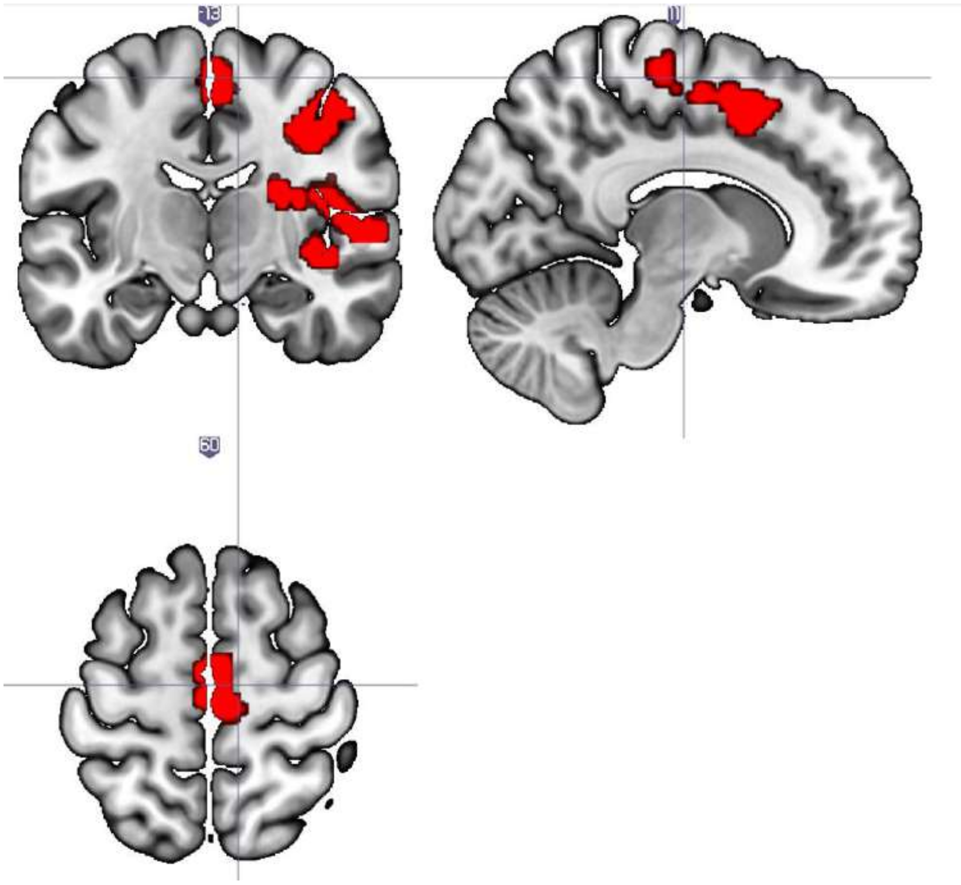


**Figure 4.9.** Negative correlation between the level of the BOLD-signal in patients with GAD in Go tests and anxiety scores on the Hamilton scale.

Besides that, we should mention our comparison of obtained correlation analysis results and changes in the local activity in GAD, which revealed partial spatial overlap between the cluster with negative correlation between BOLD-signal and Hamilton scale score and cluster of GAD-associated BOLD-signal lowering in the anterior cingulate cortex (see **Fig. 4.10**).

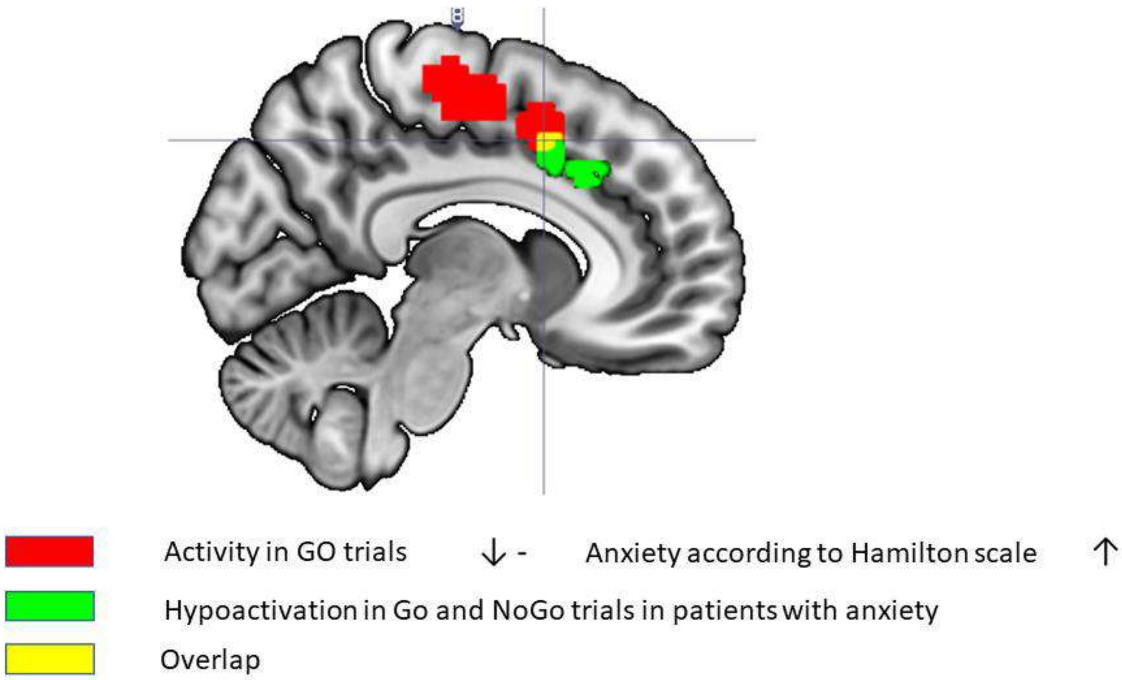



**Figure 4.10.** The location of brain regions in patients with GAD in which there is a decrease in the BOLD-signal relative to healthy subjects for all contrasts: “Go > baseline”, “NoGo > baseline”, and brain regions in which a correlation was found between the BOLD-signal and anxiety scores on the Hamilton scale.

Our results of correlation analysis between functional connectivity for separate sessions of the Go/NoGo test task (AAGO and APGO) between revealed NSIC elements and psychodiagnostic, behavioral parameters revealed only negative correlation with vigilance questionnaire score (Melbourne Decision Making Questionnaire): the higher these values were, the more functional connectivity parameter value lowered between the right insula and frontal oculomotor field/premotor cortex ($r = -0.52$, $p < 0.05$, Fig. 4.11).

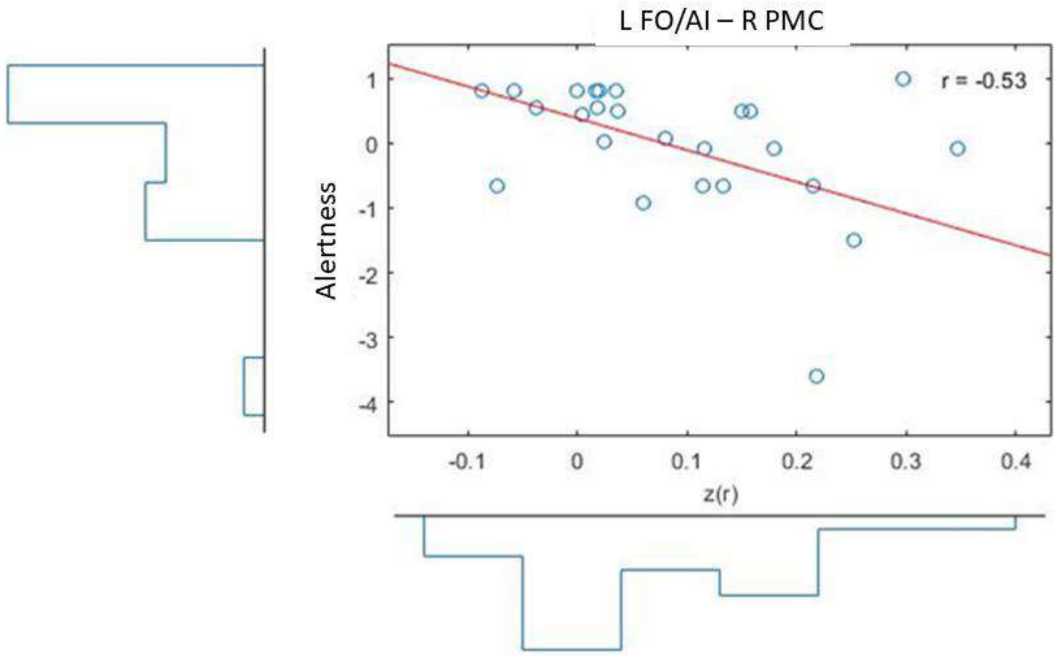



**Figure 4.11.** Scatterplot of the psychological indicators on the strength of human brain functional connectivity between the nodes of the NSIC system in patients with anxiety disorder. Abbreviations: FOF – frontal oculomotor field; PMC – premotor cortex; AI – anterior insula; FO – frontal operculum; L/R – left/right hemisphere; r – Pearson correlation coefficient.

Summarizing the interim results of this study stage we can conclude that we established the element composition extension of the brain nonselective inhibitory control system for the first time in studying neurobiology of the modulating effect exerted by anxiety on the activities control. As it is known, this brain system is involved in suppression of prepared actions and their implementation. The obtained results are evidence of the fact the brain NSIC system is extended in GAD by additional involvement of the insular and dorsolateral cortex of the right hemisphere, i.e. brain structures associated closely with functional brain activity when worry, emotional response and anxiety are provoked in patients with GAD (as compared to the norm). Most likely, such extension is compensatory as intergroup comparison of patients with GAD and healthy subjects revealed lowered brain functional activity in GAD under conditions of action implementation and suppression (in case of their combined and separate analysis) in the brain structures associated also with provision of inhibitory control but not included in NSIC. Basing on this, one can speak of the fact that the observed extension of the NSIC element composition in GAD reflects a typical effect of increased activity control, which is spread not only to suppression but also to implementation of actions, what is important.

So, the result demonstrated by us in the clinical model of GAD- associated changes in the brain provision of control functions is an example of the possible implementation mechanism of the modulating influence exerted by anxiety on the brain provision of the activities leading to behavior hypercontrol what, in its turn, tells negatively upon the implementation efficiency and productivity of precise motor activity types which are typical of sports activities. The effect revealed by us is confirmed additionally by the data on lowered functional connectivity at the moment of activities implementation between NSIC elements and inverse correlation of their local activity and functional connectivity with psychodiagnostic parameters. The characteristics established by us are obtained for the first time and are in accord with modern understanding of the fact that frequently observed emotional-affective behavioral and neuronal signs of GAD can be the result of GAD-associated changes in the brain control functions on the whole and, in particular, inhibitory control [19, 37, 193].

### 4.2. The results of the study series involving healthy subjects for selection of human brain structures associated with socially significant information processing and executive control of cognitive activities

At this stage of the psychophysiolocal investigation using fMRI in independent healthy subject groups we established the brain structures: 1) changing significantly the functional connectivity level depending on social intelligence, 2) involved in the executive control processes of cognitive activity for modelling of which we used speech activity for verbal completion of ambiguous phrases with dropped letters. The brain structures revealed at this stage of the thesis study were selected by us to form regions of interest, the functional connectivity of which was assessed in the comparative intergroup analysis of healthy subjects and patients with GAD. The selection of exactly social interactions as a test task was caused by great importance of opponent's intentions perception processes and the role in games-based sports. It is known that the brain structures providing for executive control of the cognitive activity play an important role in ensuring any types of highly professional activity associated with the high requirements to coordination of the motor acts (sports, dances, playing musical instruments). Thus, the revealed involvement of these brain structures in the processes related to GAD- associated FC change in the operational rest condition can be used for extension of a diagnostically significant set of brain regions (targets) for psychophysiological condition monitoring of sportsman's control functions.

### 4.2.1. The human brain structures associated with provision of behavior under conditions of social interactions

#### *4.2.1.1. The social intelligence level and human brain functional connectivity pattern in the operational rest condition*

At this investigation stage we established characteristics of the human brain functional connectivity in healthy subjects in the operational rest condition depending on the social intelligence level according to the Gielford-Sullivan test [220].

Analyzing the functional connectivity of the regions of interest (ROI) in the head of the right caudate nucleus revealed positive and negative correlations with z-values of Gielford-Sullivan test score [303]. The positive correlation between these scores and FC level with the right caudate nucleus was revealed for the following human brain structures: right superior temporal gyrus, precuneus of the right and left hemispheres, right precentral gyrus and left postcentral gyrus (Table 4.7). Moreover, the negative correlation between the social intelligence level and FC of the right caudate nucleus head was established for the pole of the right occipital lobe. After correcting for multiple comparisons at the cluster level using FWE method with threshold $p < 0.05$, the results for only two clusters (right superior temporal gyrus, precuneus) were statistically significant (Fig. 4.12). Fig. 4.13 also presents scattering diagrams for FC values between the region of interest and above clusters and z-values of Gielford-Sullivan test scores with the purpose of visualization.

**Table 4.7.** Results of functional connectivity analysis for the region of interest in the head of the caudate nucleus in the right hemisphere of the human brain

| № | Location (L – left hemisphere, R – right hemisphere) | Local max coordinates in MNI | | |
|---|---|---|---|---|
| | | x | y | z |
| 1 | R: caudate nucleus | 11 | 6 | 9 |
| 2 | R: superior temporal gyrus | 64 | -40 | 16 |
| 3 | R, L: precuneus | 6 | -48 | 44 |

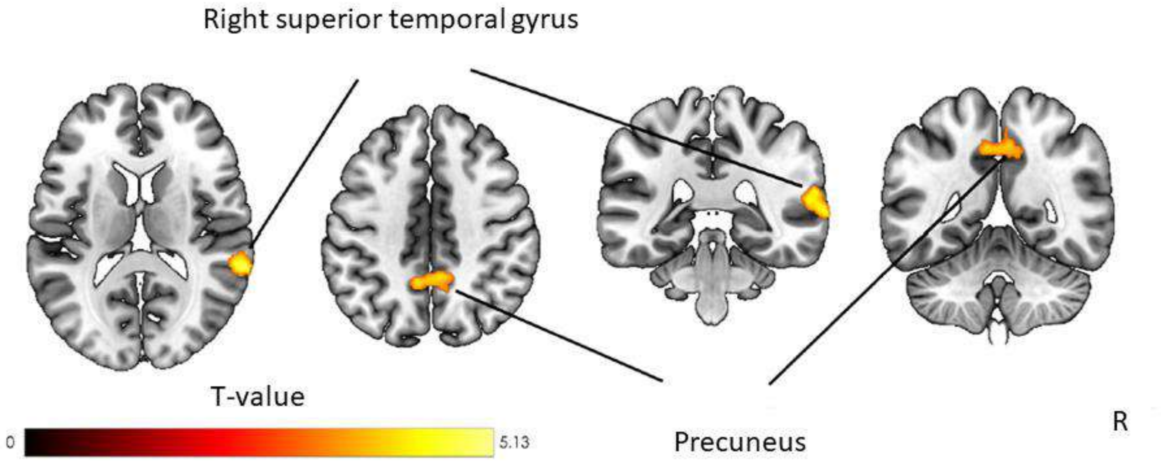



**Figure 4.12.** Statistical parametric maps of correlation analysis results between z-scores according to the Guilford-Sullivan test and functional connectivity values for the region of interest in the head of the right caudate nucleus and the remaining voxels of functional images, p<0.001 at the voxel level without correction for multiple comparisons, p<0.05 at the cluster level with the FWE correction for multiple comparisons.

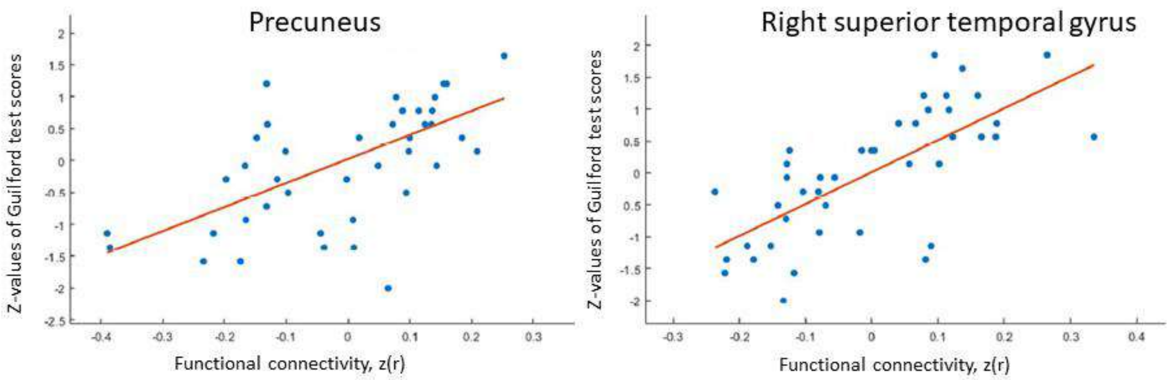



**Figure 4.13.** Scatterplots between Guilford-Sullivan test z-scores and functional connectivity between regions of interest in the head of the right caudate nucleus and 1) precuneus, 2) right superior temporal gyrus. Red – trend line.

The analysis of functional connectivity for ROI in the body of the right caudate nucleus revealed only positive correlation between z-values of Gielford-Sullivan test score and functional connectivity between this ROI and the right postcentral gyrus, right cerebellar hemisphere (VIII), left cerebellar hemisphere (Crus I), right superior occipital gyrus. The negative correlation was obtained for cluster in the right angular gyrus. But after correcting for multiple comparisons using FWE method with threshold $p < 0.05$ at the cluster level, these clusters became not significant.

Similarly for ROI in the head of the left caudate nucleus with uncorrected threshold $p < 0.001$ we revealed negative correlation between z-values of Gielford-Sullivan test score and functional connectivity between ROI and the right angular gyrus; the revealed cluster also proved to be statistically insignificant after correcting for multiple comparisons at the cluster level using the FWE method with threshold $p < 0.05$.

The analysis of functional connectivity for ROI in the body of the left caudate nucleus revealed (with uncorrected threshold) negative correlation between z-values of Gielford-Sullivan test score and functional connectivity between ROI and the left cerebellar hemisphere (IV–V). The revealed cluster also proved to be statistically insignificant after correcting for multiple comparisons at the cluster level using FWE method with threshold $p < 0.05$.

As it was already mentioned above, our results were used later to form regions of interest applied for analysis of the functional connectivity in patients with anxiety disorder in the rest condition. The information on localization and coordinates in the standard anatomical space of the Montreal Neurological Institute for those clusters, which were corrected for multiple comparisons is presented in Table 4.7.

#### *4.2.1.2. Revealing the human brain structures associated with provision of social interactions under conditions of Taylor test task*

At the first stage of analysis we assessed the influence exerted by the opponent's anonymity factor on changes in the human brain local activity when making a decision on the penalty amount for the opponent in case of his defeat ("Decision" phase, see Fig. 2.5 and section 2.4.2.1., chapter 2) [270].

The influence exerted by the factor "opponent" on BOLD-signal change at the stage of making a decision was observed. This stage of the test task included time, when the participant thought about the money amount which should be taken away from the opponent having seen his provocation. The mental selection of response to provocation of the known opponent was associated with increased BOLD-signal in the fusiform gyrus bilaterally as compared to the anonymous opponent (see Fig. 4.14 and Table 4.8). Not a single one of analyzed voxels of fMRI images demonstrated significant BOLD-signal increase when the participants thought about the amount which should be taken away from the anonymous opponent. The study did not reveal statistically significant changes in relation to the factor "provocation" (high or low) and interaction of the factors "opponent" and "provocation" at the "Decision" phase.

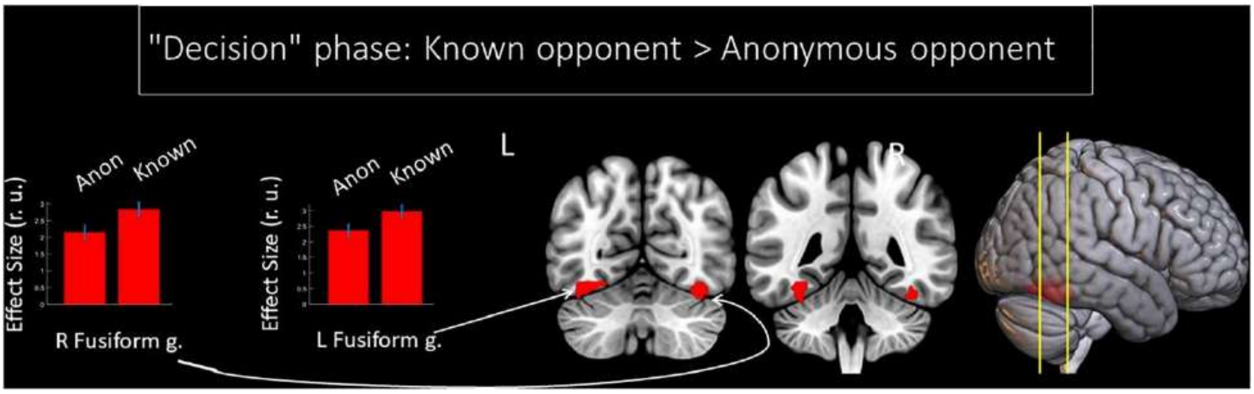



**Figure 4.14.** Results of the group-level BOLD signal analysis. Clusters of increased BOLD signals associated with decision-making after being provoked for the F-contrast "Known opponent vs. Anonymous opponent" (uncorrected $p < 0.001$ at the voxel level, FWE-corrected at the cluster level $p < 0.05$, $k = 15$). Plots show effect sizes with 95% confidence intervals. L/R, left/right hemisphere; g., gyrus; Anon, anonymous opponent; Known, introduced opponent.

**Table 4.8** Results of the group-level analysis of the BOLD signal associated with decision-making after being provoked (uncorrected p<0.001 on the voxel level, FWE-corrected at the cluster level p<0.05, and k = 15)

| | **Cluster** | | **Peak** | | | **Peak MNI coordinates** | | |
|---|---|---|---|---|---|---|---|---|
| **Brain area** | **p(FWE-corr.)** | **k** | **p(unc.)** | **F** | **Z** | **x** | **y** | **z** |
| ***'Decision' phase: Known opponent > Anonymous opponent*** | | | | | | | | |
| L Fusiform g. | < 0.001 | 160 | <0.001 | 36.21 | 5.47 | -36 | -46 | -19 |
| R Fusiform g. | 0.001 | 143 | <0.001 | 34.71 | 5.37 | 39 | -64 | -16 |
| ***No significant changes were obtained for the 'Decision' phase: Anonymous opponent > Known opponent*** | | | | | | | | |

**Denotations:** k – cluster size in voxels; FWE – familywise error correction; L/R – left/right hemisphere; g. – gyrus.

Then the study assessed the influence exerted by the money amount of provocation on changes in the human brain local activity when selecting the punishment (“Scale” phase). The influence exerted by the factor “punishment” on the BOLD-signal change at the stage of selecting punishment was observed. Taking away a large money amount (80 or 100 roubles) was associated with increased BOLD-signal in the left putamen (see Table 4.9) as compared to a small amount (0 or 20 roubles), irrespective of the opponent type. The study did not reveal a significant increase of BOLD-signal when selecting a small amount as compared to a large amount. Any statistically significant changes related to the factor “Opponent” or factor interaction for “Scale” phase were not revealed.

**Table 4.9.** Results of the group-level analysis of the BOLD signal associated with selection of punishment (uncorrected p<0.001 at the voxel level, FWE-corrected at the cluster level p<0.05, and k = 15)

| | **Cluster** | | **Peak** | | | **Peak MNI coordinates** | | |
|---|---|---|---|---|---|---|---|---|
| **Brain area** | **p(FWE-corr.)** | **k** | **p(unc.)** | **F** | **Z** | **x** | **y** | **z** |
| ***'Scale' phase: High provocation > Low provocation*** | | | | | | | | |
| LPutamen | 0.018 | 106 | < 0.001 | 26.49 | 4.73 | -18 | 11 | 8 |
| ***No significant changes were obtained for the 'Scale' phase: Low provocation > High provocation*** | | | | | | | | |

**Denotations:** k – cluster size in voxels; FWE – familywise error correction; L/R – left/right hemisphere.

Then we analyzed the influence exerted by the opponent's anonymity on changes in the human brain local activity when a social provocation ("Feedback" phase) was received. The influence of the factor "opponent" on the BOLD-signal change at the stage of observing the provocation was assessed. Receiving the provocation from the anonymous opponent was associated with increased BOLD-signal in the right IFG as compared to the known opponent (see Fig. 4.15 and Table 4.10). As compared to anonymous opponent, receiving the provocation from the known opponent was associated with the increased BOLD-signal in the right fusiform gyrus similarly to the results observed during the "Decision" phase. We did not find also any statistically significant changes related to factor interaction for "Feedback" phase.

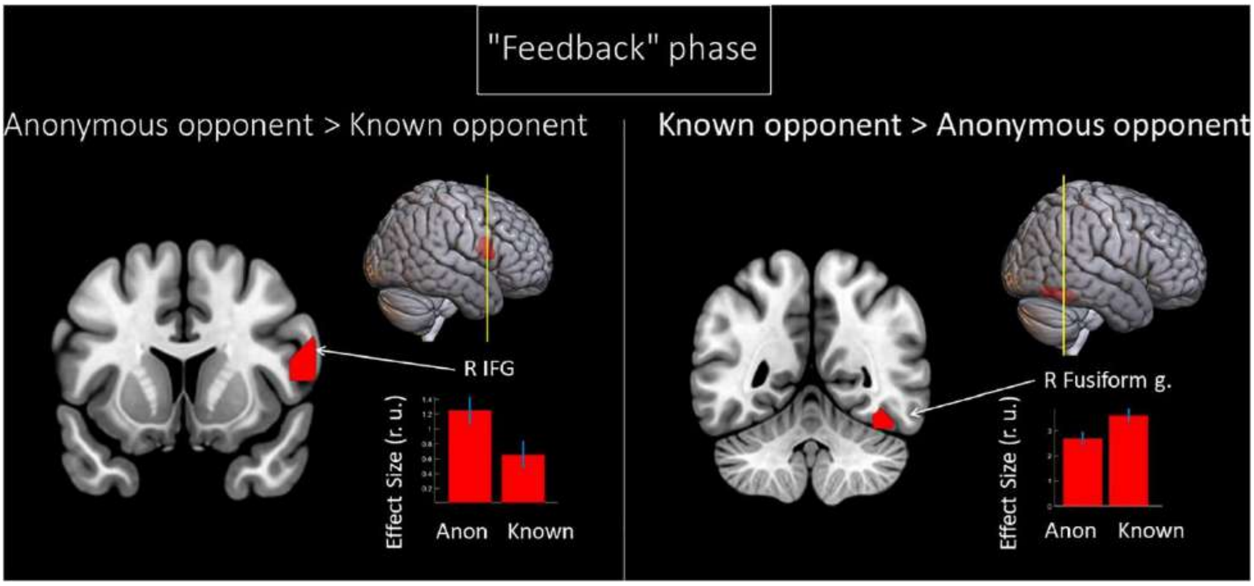



**Figure 4.15.** Results of the group-level BOLD signal analysis. Clusters of increased BOLD signals associated with the observation of provocation for the F-contrast "Anonymous opponent vs. Known opponent" (uncorrected $p < 0.001$ at the voxel level, FWE-corrected at the cluster level $p < 0.05$, and $k = 15$). Plots show effect sizes with 95% confidence intervals. L/R, left/right hemisphere; g., gyrus; IFG, inferior frontal gyrus; Anon, anonymous opponent; Known, introduced opponent.

**Table 4.10.** Results of the group-level analysis of the BOLD signal associated with the observation of provocation (uncorrected p<0.001 at the voxel level, FWE corrected at the cluster level p<0.05, and k = 15)

| | **Cluster** | | **Peak** | | | **Peak MNI Coordinates** | | |
|---|---|---|---|---|---|---|---|---|
| **Brain area** | **p(FWE-corr.)** | **k** | **p(unc.)** | **F** | **Z** | **x** | **y** | **z** |
| ***'Feedback' phase: Anonymous opponent > Known opponent*** | | | | | | | | |
| **R Inferior frontal g.** | 0.009 | 111 | < 0.001 | 29.65 | 4.99 | 57 | 11 | 14 |
| ***'Feedback' phase: Known opponent > Anonymous opponent*** | | | | | | | | |
| **R Fusiform g.** | 0.005 | 126 | < 0.001 | 58.47 | 6.76 | 39 | -52 | -19 |

**Denotations:** k – cluster size in voxels; FWE – familywise error correction; L/R – left/right hemisphere; g. – gyrus.

Then the influence exerted by the money provocation size on changes in the brain local activity, when receiving social provocation ("Feedback" phase), was analyzed. The analysis revealed statistically significant influence exerted by the factor "provocation" on BOLD-signal change at the stage of selecting punishment.

When observing the provocative feedback, the high provocation level (taking away 80 or 100 roubles) was associated with increased BOLD-signal in the angular gyrus and supplementary motor cortex as compared to low provocation level (taking away 0 or 20 roubles) irrespective of the opponent type (see Table 4). As compared to the high provocation, receiving the low provocation was associated with increased BOLD-signal in the right medial frontal gyrus, left IFG, left angular gyrus and right precuneus (see Table 4.11). Among these human brain structures, the right angular gyrus, left angular gyrus and right precuneus are localized inside the right TPJ, left TPJ and right precuneus included in the TOM system [267, 270]. Any statistically significant changes related to factor interaction for “Feedback” phase were not revealed.

**Table 4.11.** Results of the group-level analysis of the BOLD signal associated with the observation of provocation (uncorrected p<0.001 at the voxel level, FWE-corrected at the cluster level p<0.05, and k = 15)

| | **Cluster** | | **Peak** | | | **Peak MNI coordinates** | | |
|---|---|---|---|---|---|---|---|---|
| **Brain area** | **p(FWE-corr.)** | **k** | **p(unc.)** | **F** | **Z** | **x** | **y** | **z** |
| ***‘Feedback’ phase: High provocation > Low provocation*** | | | | | | | | |
| R Angular g. | < 0.001 | 502 | < 0.001 | 48.33 | 6.23 | 48 | -52 | 29 |
| R SMA | 0.001 | 173 | < 0.001 | 40.66 | 5.77 | 6 | 11 | 62 |
| ***‘Feedback’ phase: Low provocation > High provocation*** | | | | | | | | |
| R Middle frontal g. | < 0.001 | 749 | < 0.001 | 48.12 | 6.21 | 39 | 20 | 44 |
| L Angular g. | 0.001 | 166 | < 0.001 | 29.15 | 4.95 | -54 | -58 | 38 |
| L Inferior frontal g. | 0.001 | 176 | < 0.001 | 24.95 | 4.60 | -39 | 20 | 32 |
| R Precuneus | 0.002 | 151 | < 0.001 | 24.84 | 4.59 | 6 | -55 | 41 |

**Denotations:** k – cluster size in voxels; FWE – familywise error correction; L/R – left/right hemisphere; g. – gyrus; SMA – supplementary motor area.

The further analysis was related to searching for changes in functional connectivity of the right inferior frontal gyrus of the human brain depending on the influence exerted by the opponent's anonymity factor on receiving social provocation during the "Feedback" phase. As compared to the known opponent, receiving the feedback from the anonymous opponent was associated with increase in the functional connectivity between the right and left IFG (see Fig. 4.16 and Table 4.12). But any significant change in functional connectivity of the right IFG for the known opponent was not revealed as compared to the anonymous opponent.

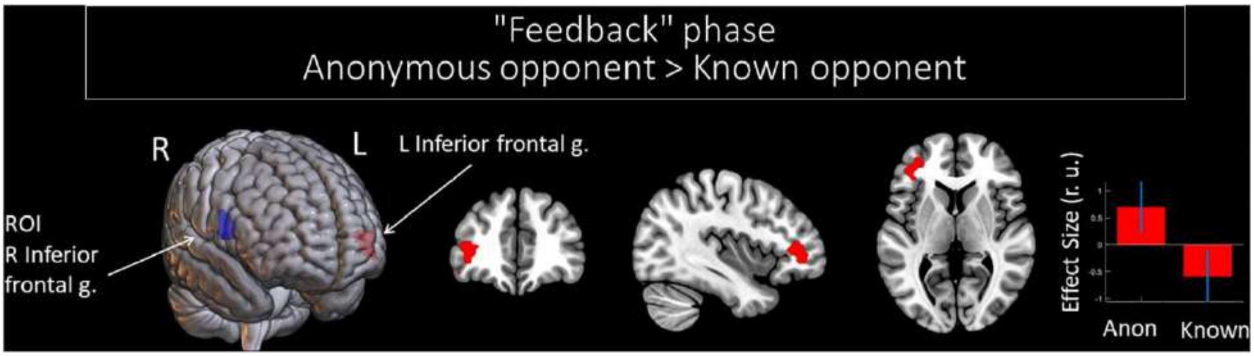



**Figure 4.16.** Results of the group-level gPPI analysis with the ROI in the right IFG. Clusters of significant changes in functional connectivity, with the right IFG associated with the anonymity of the opponent (uncorrected $p < 0.001$ at the voxel level, FWE-corrected at the cluster level $p < 0.05$, and $k = 15$), are shown in red. The ROI in the right IFG is presented in blue. The plot shows effect sizes with 95% confidence intervals. L/R, left/right hemisphere; g., gyrus; ROI, the region of interest; Anon, anonymous opponent; Known, introduced opponent.

**Table 4.12.** Results of the group-level gPPI analysis with the ROI in the right IFG, associated with the observation of provocation from anonymous and known opponents (uncorrected p<0.001 at the voxel level, FWE-corrected at the cluster level p<0.05, and k = 15)

| | **Cluster** | | **Peak** | | | **Peak MNI coordinates** | | |
|---|---|---|---|---|---|---|---|---|
| **Brain area** | **p(FWE-corr.)** | **k** | **p(unc.)** | **F** | **Z** | **x** | **y** | **z** |
| ***'Feedback' phase: Anonymous opponent > Known opponent*** | | | | | | | | |
| L Inferior frontal g. | 0.011 | 91 | < 0.001 | 22.20 | 4.34 | -39 | 41 | 5 |
| ***No significant changes were obtained for the 'Feedback' phase: Known opponent > Anonymous opponent*** | | | | | | | | |

**Denotations:** k – cluster size in voxels; FWE – familywise error correction; ROI – region of interest; L/R – left/right hemisphere; g. – gyrus.

The analysis of changes in functional connectivity of the right inferior frontal gyrus in the human brain established the influence pattern exerted by the provocation level on receiving social provocation during the "Feedback" phase. In accordance with the obtained data when observing the provocation feedback, low provocation (0 or 20 roubles) was associated with increased functional connectivity of the right IFG with the right superior temporal gyrus and left cerebellum as compared to high provocation (80 or 100 roubles) irrespective of the opponent (see Table 4.13). At the same time we did not reveal any significant changes in functional connectivity of the right IFG when low provocation from the opponents was received as compared to high provocation.

**Table 4.13.** Results of the group-level gPPI analysis with the ROI in the right IFG, associated with the observation of different levels of provocation (uncorrected p<0.001 at the voxel level, FWE-corrected at the cluster level p<0.05, and k = 15)

| | Cluster | | Peak | | | Peak MNI coordinates | | |
|---|---|---|---|---|---|---|---|---|
| **Brain area** | **p(FWE-corr)** | **k** | **p(unc)** | **F** | **Z** | **x** | **y** | **z** |
| ***'Feedback' phase: Low provocation > High provocation*** | | | | | | | | |
| R Superior temporal g. | 0.054 | 59 | <0.001 | 22.87 | 4.41 | 51 | -10 | -4 |
| L Cerebellum | 0.002 | 133 | <0.001 | 20.36 | 4.16 | -6 | -49 | -4 |
| ***No significant changes were obtained for the 'Feedback' phase: High provocation > Low provocation*** | | | | | | | | |

**Denotations:** k – cluster size in voxels; FWE – familywise error correction; ROI – region of interest; L/R – left/right hemisphere; g. – gyrus.

Then we assessed changes in functional connectivity of the right inferior frontal gyrus: interaction between opponent's anonymity and provocation level when social provocation during the "Feedback" phase was received. As a result of the study we revealed significant changes in functional connectivity for ROI in the right inferior frontal gyrus (IFG) associated with interaction between the "opponent" and "provocation" factors [270]. The right inferior frontal gyrus changed functional connection with bilateral cerebellum, precentral gyrus and supplementary motor region; left fusiform gyrus and superior temporal gyrus; right medial frontal gyrus, insular cortex, precuneus and angular gyrus (see Table 4.14). Among these structures, the right angular gyrus and right precuneus are localized in rTPJ clusters and precunei of the TOM system in accordance with masks developed by Dufour et al. [267] (see Fig. 4.17). When provocation from the anonymous opponent was perceived, functional interactions increased between the right IFG and the above regions under conditions of high provocation (as compared to low provocation). Moreover, this interaction was inverse when provocation from the known opponent was observed. We did not observe any significant results for other comparison directions.

**Table 4.14.** Results of the group-level gPPI analysis with the ROI in the right IFG for the interaction between the level of observed provocation and the anonymity of the opponent during the 'Feedback' phase (uncorrected p<0.001 at the voxel level, FWE-corrected at the cluster level p<0.05, and k = 15).

| | **Cluster** | | **Peak** | | | **Peak MNI coordinates** | | |
|---|---|---|---|---|---|---|---|---|
| **Brain area** | **p(FWE-corr.)** | **k** | **p(unc.)** | **F** | **Z** | **x** | **y** | **z** |
| R cerebellum | < 0.001 | 457 | < 0.001 | 57.83 | 6.72 | 9 | -37 | -22 |
| L cerebellum | 0.019 | 80 | < 0.001 | 48.98 | 6.26 | -30 | -58 | -34 |
| R angular g. | 0.001 | 150 | < 0.001 | 48.16 | 6.22 | 42 | -61 | 29 |
| R middle frontal g. | 0.054 | 59 | < 0.001 | 45.84 | 6.08 | 30 | 32 | 44 |
| L precentral g. | < 0.001 | 195 | < 0.001 | 38.10 | 5.60 | -36 | -16 | 50 |
| R insula | < 0.001 | 363 | < 0.001 | 37.96 | 5.59 | 36 | 8 | 2 |
| R SMA | 0.010 | 95 | < 0.001 | 36.68 | 5.51 | 12 | 8 | 47 |
| L fusiform g. | 0.041 | 64 | < 0.001 | 26.57 | 4.74 | -30 | -49 | -16 |
| L superior temporal g. | < 0.001 | 232 | < 0.001 | 26.46 | 4.73 | -51 | 2 | -13 |
| R precuneus | < 0.001 | 190 | < 0.001 | 25.84 | 4.68 | 12 | -58 | 53 |
| R precentral g. | 0.020 | 79 | < 0.001 | 24.47 | 4.55 | 39 | -4 | 50 |
| L SMA | 0.002 | 127 | < 0.001 | 20.80 | 4.21 | 0 | -10 | 56 |

**Denotations:** k – cluster size in voxels; FWE – familywise error correction; ROI – region of interest; L/R – left/right hemisphere; g. – gyrus; SMA – supplementary motor area

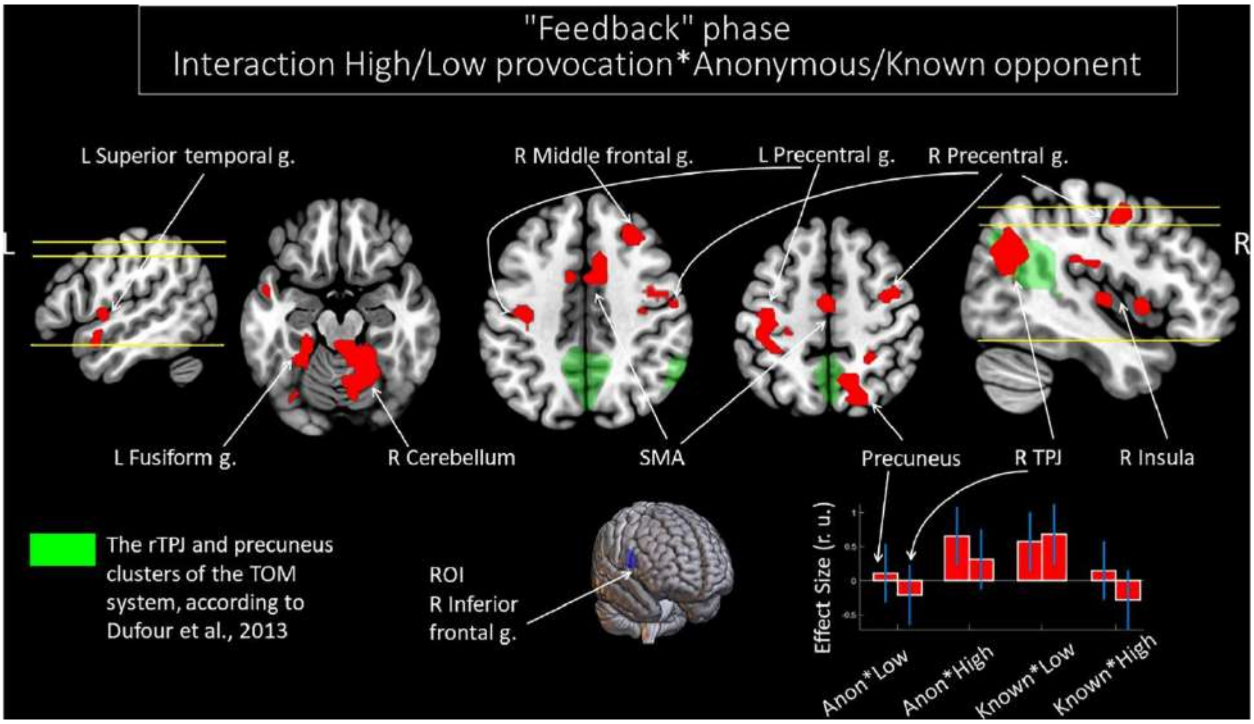



**Figure 4.17.** Results of the group-level gPPI analysis with the ROI in the right IFG. Clusters of significant changes in functional connectivity with the right IFG, associated with the interactions between the level of observed provocation and the anonymity of the opponent (uncorrected $p < 0.001$ at the voxel level, FWE-corrected at the cluster level $p < 0.05$, and $k = 15$), are shown in red. The TOM system clusters are presented in green according to the results of Dufour et al. [267]. The plot on the lower right side indicates effect sizes with 95% confidence intervals. L/R, left/right hemisphere; g., gyrus; TPJ, temporoparietal junction; SMA, supplementary motor area; ROI, region of interest; Anon, anonymous opponent; Known, introduced opponent; High, high provocation; Low, low provocation.

Thus, we established a set of human brain structures associated with provision of socially significant information processing. Firstly, this is the set of brain structures associated with provision of the opponent’s intention formation processes (the so-called theory of mind) [238, 259], whose functional connectivity correlates positively with the social intelligence [303]. Our result for the first time demonstrated and proved in the experiments the existence of connection between the brain activity associated with the capability to attribute thoughts and intentions to the opponents (so-called theory of mind) and human social intelligence parameters. Taking into account special significance of these processes for a quite wide range of sports activities types, the human brain structures revealed at this stage were selected as the regions of interest, i.e. potential brain structures – candidates for psychophysiological monitoring tested at the next stage of intergroup comparison of patients with GAD and healthy subjects in the rest condition. Besides that, it is important to emphasize here that so-called social anxiety disorder (SAD) is one of disorders closely associated with GAD; it can also develop in sportsmen by the "vicious circle" mechanism. Taking into account the public character of some sports activities types, and especially the sports being assessed like sportive gymnastics (as also figure skating), the use of data on localization of brain structures revealed by us at this study stage demonstrated their diagnostic potential at the next stage of the thesis study.

### 4.2.2. Human brain structures associated with provision of executive control processes during cognitive activity under conditions of ambiguous speech stimulus processing

At this stage of studies, the investigational model of ambiguity resolution negative aftereffect was selected to reveal the brain structures associated with provision of the executive control of cognitive activity. The experimental modelling of these processes was carried out using the developed test task for completion of fragmented phrases with dropped letters [285].

The analysis if the response rate (RR) using using non-parametric Mann–Whitney U test did not reveal any significant differences between Ambig1st and Control1st tests (group medians: 1,777 ms and 1,730 ms, $p = 0.75$), between Ambig2nd and Control2nd (group medians: 1,907 and 1,665 ms, $p = 0.053$) and also between Ambig1st and Ambig2nd tests ($p = 0.22$).

In our studies the number of "ambiguous" tests, in which the subject reported that they noted that the presented fragmented noun has two solutions did not differ significantly between conditions Ambig1st and Ambig2nd (group mean percentage of the total test number for Ambig1st and Ambig2nd: 4.2% and 3.8%, $p = 0.53$).

While analyzing mistakes of completion, we divided them in: (1) misses, i.e. not giving the answer within the time allowed (both at the first and second appearance of the fragmented noun); (2) intrusion, i.e. repeating the previous solution which is irrelevant in the new context; (3) incorrect solutions, i.e. solutions not associated with the previously presented and orthographically close fragmented noun. The number of incorrect solutions was significantly larger under conditions Ambig1st (mean for the group: 7.7%, standard deviation (SD) 6.7%) that under conditions Control1st (mean for the group: 1.9%, SD 3.3%) according to assessment using Mann–Whitney U test ($z = 4.93$, $p < 0.001$). A similar analysis of mistakes related to misses revealed significantly greater ($z = 2.5$, $p = 0.01$) frequency of mistakes under conditions Ambig1st (mean for the group: 7.7%, SD 6.8%) as compared to Control1st (mean for the group: 4.5%, SD 5.4%).

The mistakes under condition Ambig2nd related to repeating the solution from the condition Ambig1st were observed in 36 subjects while other 12 subjects did not have intrusion mistakes at all. Mean percentage of mistakes of this type i the group was 7.7% with SD = 7.9%. The mistakes of this type can be expected only under condition Ambig2nd, therefore, instead of comparing their frequency under different conditions, we compare intrusion mistakes with other incorrect solutions below. Incorrect solutions under conditions Ambig2nd and Control2nd did not differ significantly and were observed relatively rarely with means for the group being 1.1% (SD 2.1%) and 1.6% (SD 3.3%), respectively. The miss mistakes under conditions Ambig2nd (mean for the group: 8.1%, SD 8.3%) were significantly more numerous ($z = 2.4$, $p = 0.02$) as compared to condition Control2nd (mean for the group: 4.5%, SD 6.6%). The frequency of miss and intrusion mistakes did not differ considerably under condition Ambig2nd but both types were more common than incorrect solutions ($z = 5.38$, $p < 0.001$ and $z = 5.21$, $p < 0.001$, respectively). Finally, there was no significant difference between Ambig1st and Ambig2nd regarding miss mistakes.

#### *4.2.2.1. The results of fMRI investigations of human executive control processes during cognitive activity under conditions of ambiguous speech stimulus processing*

Significant BOLD-signal changes were revealed in the linear contrast Control1st>Ambig1st using Bayesian inference [285]. Searching for solutions for fragmented word pairs, in which nouns had two possible completions, was characterized by decreased BOLD-signal in the anterior part of hippocampus, amygdaloid body and planum temporale bilaterally, in the right supplementary motor cortex, putamen and insular cortex, cuneus and cerebellum and also left precuneus, superior parietal lobe and precentral gyrus (Fig. 4.18, Table 4.15). The inverse linear contrast Ambig1st>Control1st did not reveal any significant changes in BOLD-signal. The additional analysis of psychophysiological interactions of human brain caudate nuclei revealed lowed functional connectivity of this structure with prefrontal cortex when solving the task for completion of the fragmented phrase having several variants for completion (Ambig1st) as compared to control test (Control1st) [246].

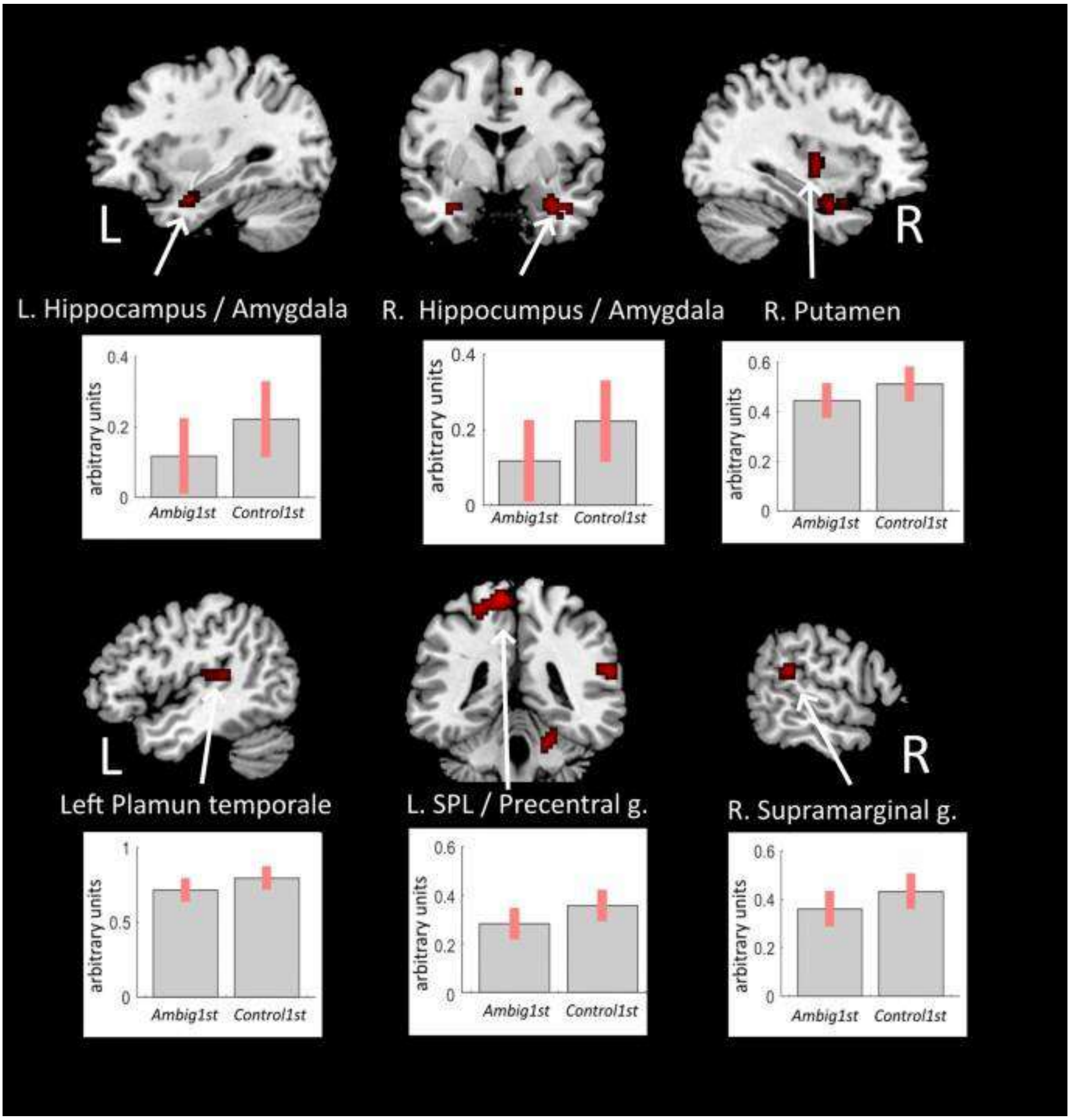



**Figure 4.18.** Changes in the BOLD signal associated with processing of a non-selected non selected solutions for the word pair fragments. Clusters of significant t-contrast Control1st > Ambig1st presented over a template brain image. Blue color bar represents the value of Log Odds Bars represented the sizes of effect in arbitrary units describing the PPI-parameters.

**Table 4.15.** Decreases in the BOLD signal associated with processing of a non-selected meaning revealed in the *Control1st > Ambig1st* contrast.

| **Brain Region** | **k** | **Log Odds** | **peak MNI coordinates** | | |
|---|---|---|---|---|---|
| | | | **x** | **y** | **z** |
| ***Contol1st > Ambig1st*** | | | | | |
| Left hippocampus / amygdala | 14 | 6.6 | -30 | -4 | -25 |
| Right hippocampus / amygdala / ITG | 51 | 6.9 | 39 | 8 | -25 |
| Right SMA /Precentral gyrus | 31 | 7 | 12 | -13 | 50 |
| Right Putamen / Insula | 18 | | +33 | -10 | 2 |
| Right planum temporale / supramarginal gyrus | 28 | 7.2 | 60 | -37 | 20 |
| Left SPL / precentral gyrus | 189 | 8.8 | -24 | -43 | 62 |
| Left planum temporale / Heschl`s gyrus / parietal opeculum | 24 | 5.9 | -42 | -25 | 14 |
| Left precuneous | 28 | 6.25 | -17 | -73 | 17 |
| Right cuneal cortex | 39 | 5.9 | 18 | -73 | 23 |
| Right cerebellum | 18 | 6.3 | 18 | -40 | -28 |

Denotations: L/R – left/right hemisphere; k – cluster size in voxels;; ITG – inferior temporal gyrus, SMA – supplementary motor area, SPL - superior parietal lobule

Searching for solution for the second appearance of the fragmented noun in pair with a new fragmented adjective under condition Ambig2nd as compared to condition Control2nd revealed increased BOLD-signal in the frontoparietal, temporal region of human brain and also basal ganglia including: the inferior frontal gyrus (IFG), frontal gyrus (MFG), insular cortex and caudate nucleus bilateral and also left superior and medial frontal gyri, left precuneus and thalamus (Fig. 4.19, Table 4.16). Our inverse linear contrasting Ambig2nd >Control2nd did not reveal any significant changes in BOLD-signal.

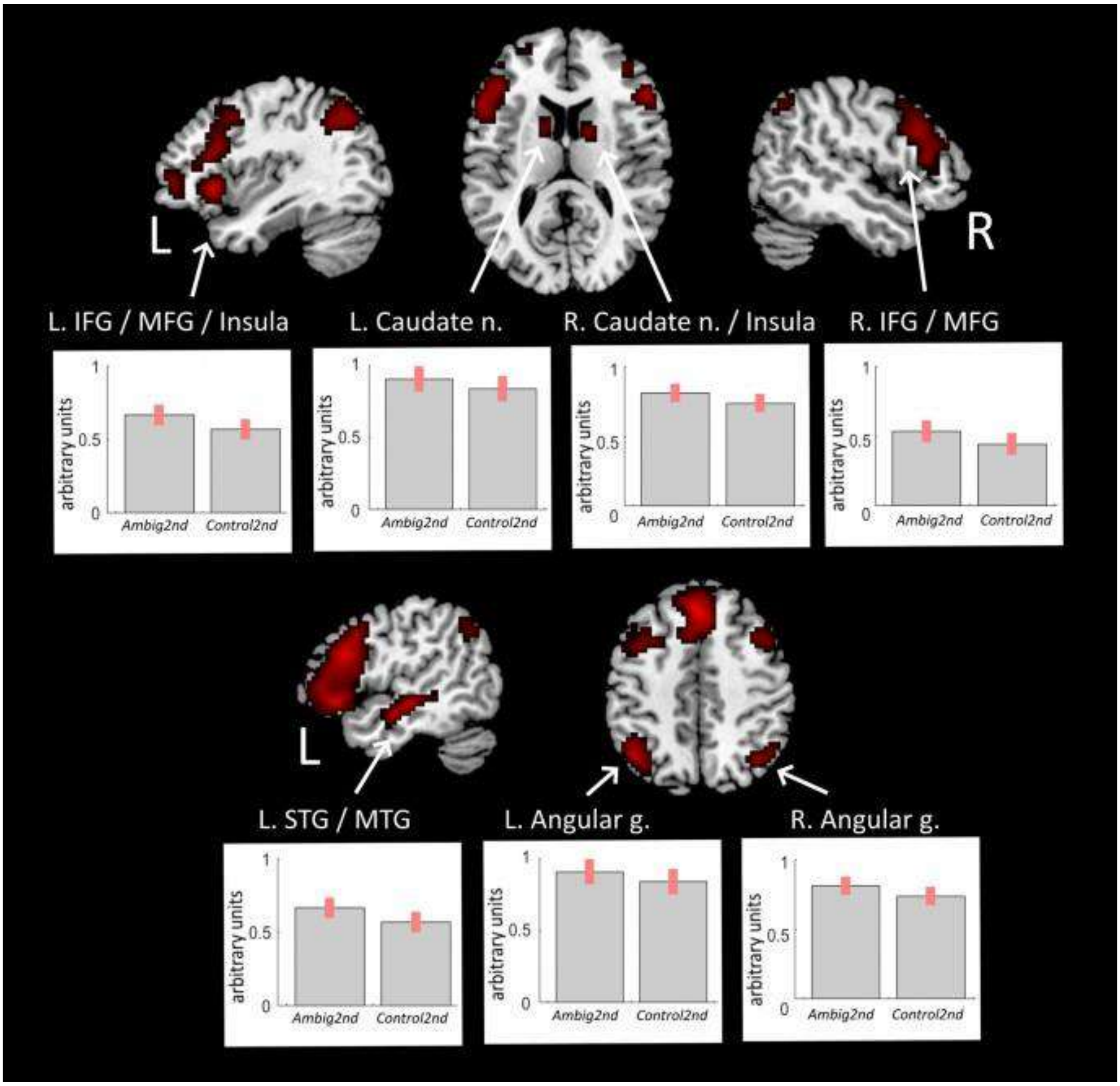



**Figure 4.19.** Enhanced BOLD signal associated with finding solution in Ambig2nd condition when fragmented noun having two solutions was paired with new fragmented adjective making previous solution to this nous inappropriate. Denotations: *L/R* left/right hemisphere, *IFG* inferior frontal gyrus, *MFG* middle frontal gyrus, *STG* superior temporal gyrus, *MTG* middle temporal gyrus, *g*. gyrus, *n*. nucleus.

**Table 4.16.** Increases of the BOLD signal associated with proactive interference between the previously chosen solution inappropriate in the new context and the correct alternative solution for fragmented word pairs in the *Ambig2nd* condition.

| Location | k | Log odds | Local max coordinates in MNI | | |
|---|---|---|---|---|---|
| | | | x | y | z |
| *Ambig2nd > Control2nd* | | | | | |
| L inferior/middle frontal gyrus (BA 44/45)/insula | 897 | 13.4 | -51 | 26 | -7 |
| L Middle frontal gyrus/paracingulate gyrus | 424 | 14.4 | 0 | 32 | 47 |
| R inferior/middle frontal gyrus (BA 44/45) | 289 | 10 | 54 | 29 | 14 |
| R water the frontal lobe | 13 | 5.9 | 39 | 44 | 14 |
| R Insula / caudate nucleus | 104 | 9.6 | 36 | 23 | 2 |
| L caudate nucleus | 38 | 6.7 | -12 | 8 | 8 |
| L superior/middle temporal gyrus (BA 21) | 109 | 12.3 | -51 | -22 | -7 |
| L Anterior cingulate cortex | 11 | 7.6 | -3 | -10 | 29 |
| L thalamus | 13 | 6.5 | -3 | -28 | 5 |
| L angular gyrus/lateral occipital cortex | 157 | 11.4 | -42 | -61 | 44 |
| P angular gyrus/lateral occipital cortex | 64 | 8.6 | 36 | -67 | 50 |
| L precuneus/superior parietal lobe | 13 | 5.9 | -6 | -70 | 35 |

Denotations: *L/R* left/right hemisphere, *k* cluster size in voxels, *BA* Brodmann area, *IFG* inferior frontal gyrus, *MFG* middle frontal gyrus, *STG* superior temporal gyrus, *MTG* middle temporal gyrus, *SPL* superior parietal lobule.

Thus, basing on the obtained data, a set of the regions of interest was formed for the analytical cohort study using the fMRI data in the operation rest, i.e. comparing the data obtained in patients with generalized anxiety and healthy subjects (see section 4.3.3, chapter 4). In particular, the obtained result reflects the involvement of the human brain structures associated with provision of executive control processes engaged in solving a task for completion of phrases with dropped letters. This effect reflects aftereffect of the solution found earlier, which prevents (interferes with) solution of the current task. In other words, when the solution for a certain word found earlier is not suitable for solution in the current context, we speak of a negative priming situation. It is necessary to suppress the previous solution in such situation. The revealed pattern of BOLD-signal changes corresponds to the data obtained earlier on the characteristics of local activity changes under conditions of negative aftereffect of the solutions found earlier [99, 340]. In accordance with this data, such negative aftereffect is accompanied by increased local activity in the region of the left dorsolateral cortex (including the inferior frontal gyrus), superior and medial temporal gyri and also in the region of basal ganglia in the human brain. Besides that, the above structures are often involved in semantically ambiguous word processing what reflects interference or competition processes between several senses of ambiguous verbal information (see, e.g., [254, 263]).

Thus, the revealed effect of BOLD-signal increase in the above structures can be associated with involvement of executive control required for resolving the conflict between dominating solution (but not appropriate for the current context) and relevant value (suppressed earlier). Basing on the tasks of the present study and also considering the association of the revealed structures with provision of the activity executive control, we selected this set of structures to use it at the next stages of the study as regions of interest for comparative analysis of fMRI data in the operational rest condition between healthy subjects and patients with GAD.

### 4.3. The intergroup analysis results of functional connectivity in healthy subjects and patients with generalized anxiety disorder in the operational rest condition

At the next stage of our thesis study, the regions of interest selected at the previous stages of the psychophysiological investigation were used as potential candidates for the role of diagnostics targets in the intergroup comparison of patients with GAD and healthy subjects.

#### 4.3.1. GAD-associated changes in the human brain functional connectivity between the elements of the brain nonselective inhibitory control system in the operational rest condition

We revealed both lowering and increase of functional connectivity between brain structures included in the brain nonselective inhibitory control system and other brain regions in the operational rest condition in the patient group with generalized anxiety disorder. So, lowered functional connectivity was revealed between the orbital part of the right inferior frontal gyrus of the human brain and several clusters with significant FC change localized in the region of the left medial and superior frontal gyrus, right precentral gyrus, right occipital pole, right cerebellar hemisphere (Fig. 4.20). The anterior regions of NSIC element localized in the region of the right insula/frontal operculum demonstrated, on the contrary, increased FC with pole of the right frontal lobe and right medial temporal gyrus of the human brain (Fig. 4.21). The obtained results are presented in Table 4.17.

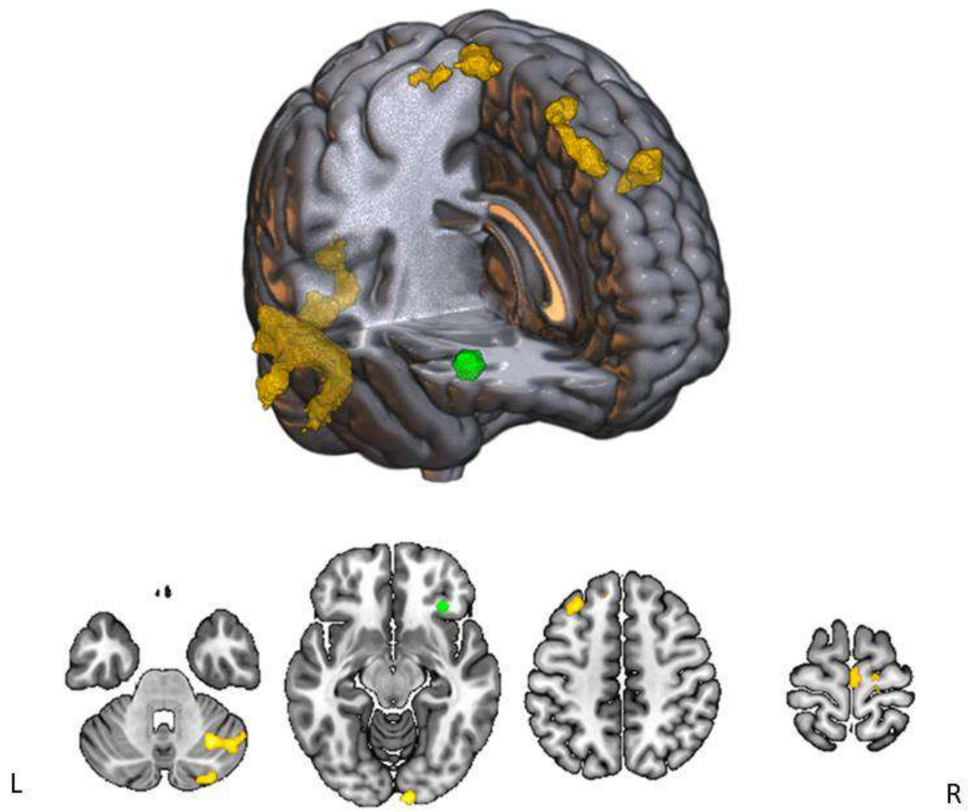



**Figure 4.20.** Areas of decreased functional connectivity with the non-selective inhibitory control system (green sphere), localized in the orbital part of the right inferior frontal gyrus, in patients with generalized anxiety disorder, compared to healthy subjects (pFDR(cluster)<0.05, minimum cluster size – 30 voxels). R – right hemisphere, L – left hemisphere.

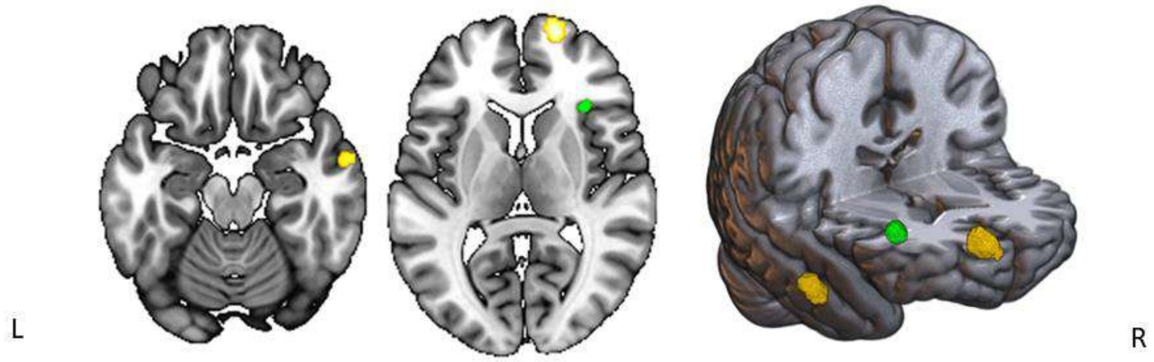



**Figure 4.21.** Areas of increased functional connectivity with the non-selective inhibitory control system (green sphere), localized in the anterior insula/frontal operculum in the right hemisphere, in patients with generalized anxiety disorder, compared to healthy subjects (pFDR(cluster)<0.05, minimum cluster size – 30 voxels). R – right hemisphere, L – left hemisphere.

Our correlation analysis between functional connectivity of revealed clusters with FC changes and psychodiagnostic parameter values of patients with GAD allowed to establish only negative correlations. So, FC between the orbital part of the right inferior frontal gyrus and several revealed clusters (left medial frontal gyrus, right precentral gyrus, left superior frontal gyrus) correlated negatively with Kerdo index (Fig. 4.22–4.25). FC between right anterior regions of the insula/frontal operculum and the right medial temporal gyrus correlated negatively with the situational anxiety level in patients with GAD according to Integrative Test for Anxiety (Fig. 4.22).

**Table 4.17**. Areas of changes in functional connectivity with parts of the non-selective inhibitory control system in patients with GAD, pFDR(cluster)<0.05, minimum cluster size - 30 voxels.

| **№** | **Location (L – left hemisphere, R – right hemisphere)** | **p-FDR cluster level** | **Cluster size** | **Local max coordinates in MNI** | | |
|---|---|---|---|---|---|---|
| | | | | **x** | **y** | **z** |
| **Decreased functional connectivity<br>Region of interest: orbital part of the right inferior frontal gyrus** | | | | | | |
| 1 | P: cerebellum | <0,001 | 958 | +42 | -66 | -28 |
| 2 | L: middle frontal gyrus | 0,012 | 195 | -34 | 24 | 42 |
| 3 | P: precentral gyrus | 0,0173 | 164 | +02 | -20 | 74 |
| 4 | L: superior frontal gyrus | 0,02 | 148 | -06 | 34 | 54 |
| 5 | P: occipital pole | 0,043 | 114 | +08 | -100 | -12 |
| **Increased functional connectivity<br>Region of interest: right anterior insula/frontal operculum** | | | | | | |
| 1 | P: frontal pole | 0,025 | 157 | +18 | 66 | 8 |
| 2 | P: middle temporal gyrus | 0,034 | 121 | +58 | -2 | -22 |

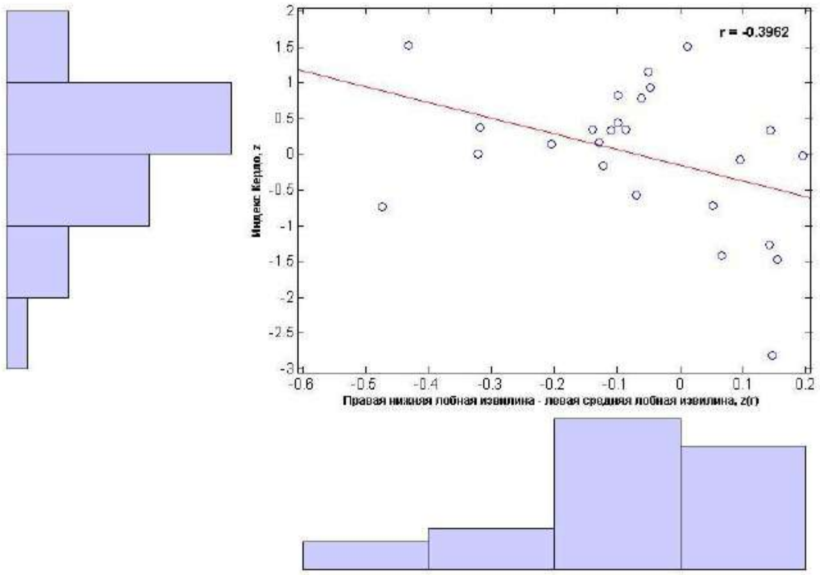



**Figure 4.22.** Scatterplot of the values of the resting state functional connectivity between the right inferior frontal gyrus and the left middle frontal gyrus and the Kerdo index of patients with GAD. The red line is the trend line, r is the Pearson correlation coefficient.

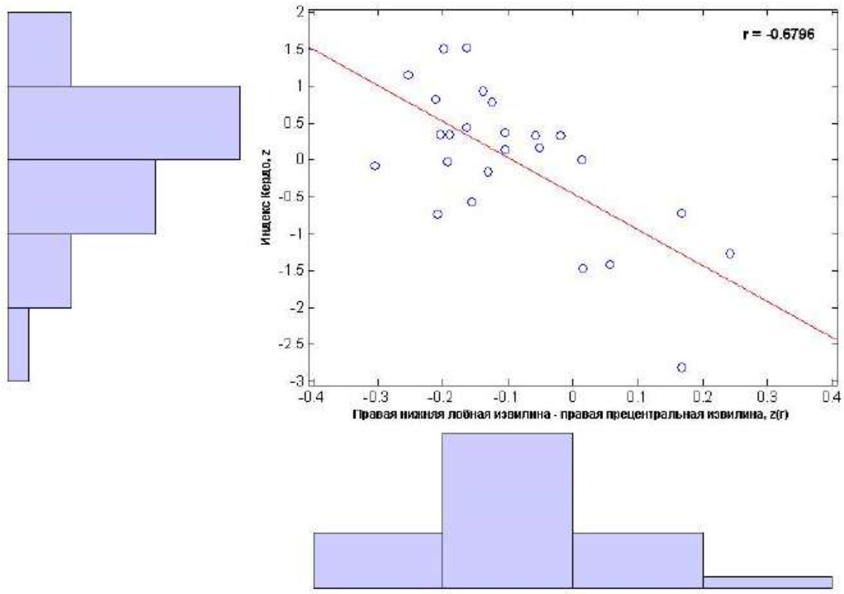



**Figure 4.23.** Scatterplot of the values of the resting state functional connectivity between the right inferior frontal gyrus and the right precentral gyrus

and the Kerdo index of patients with GAD. The red line is the trend line, r is the Pearson correlation coefficient.

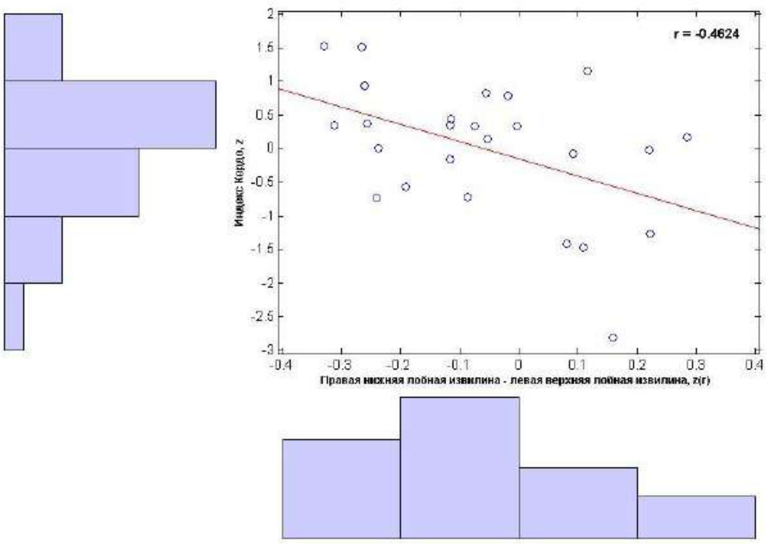



**Figure 4.24.** Scatterplot of the values of the resting state functional connectivity between the right inferior frontal gyrus and the left superior frontal gyrus and the Kerdo index of patients with GAD. The red line is the trend line, r is the Pearson correlation coefficient.

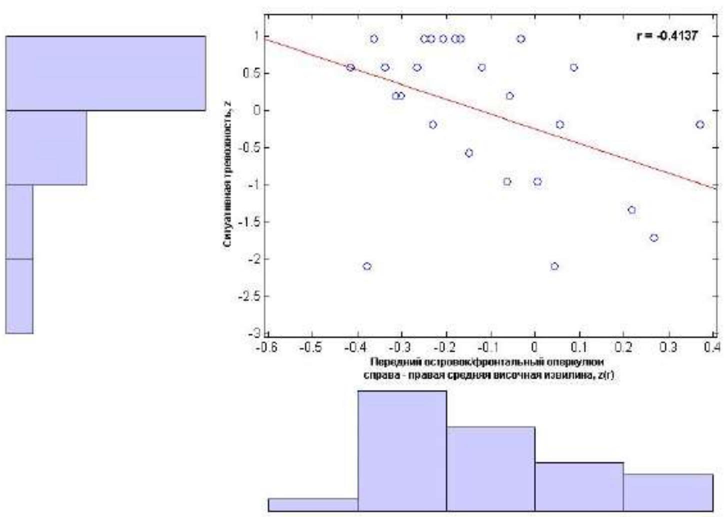



**Figure 4.25.** Scatter plot of the resting state functional connectivity values between the right anterior insula/frontal operculum and the right middle temporal gyrus and anxiety scores according to the Integrative Anxiety Test of patients with GAD. The red line is the trend line, r is the Pearson correlation coefficient.

Thus, it was found that an additional (respective to standard values) NSIC element in the region of the anterior insula and opercular region of the inferior frontal gyrus of the human brain, appearing in the generalized anxiety disorder was characterized by increased FC levels. This suggests the compensatory involvement of this additional element. Moreover, correlation analysis shows that high functional connectivity values are accompanied by relatively low situational anxiety levels what can be evidence of individual varying of compensatory NSIC involvement. This is in accord to a great degree with known literature data showing that lowered FC of the cingulo-opercular system structures is observed in case increased personal anxiety levels [53,138].

### 4.3.2. GAD-associated changes in the human brain functional connectivity between the elements of the system providing for socially significant information processing associated with social intelligence

Patients with generalized anxiety disorders had lowered FC between ROI localized in the right caudate nucleus (FC of which demonstrated correlation with the social intelligence level [303]) and several anatomical human brain regions including the supramarginal gyrus bilaterally, right post- and precentral gyri, right cerebellar hemisphere and its vermis, left inferior temporal and medial frontal gyri (Fig. 4.26, Table 4.18).

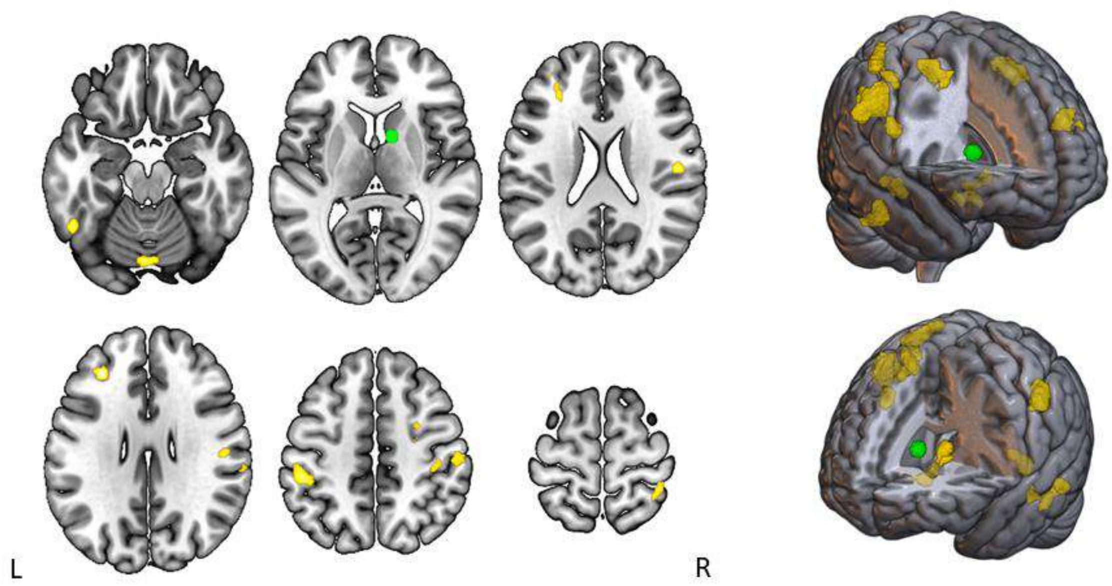



**Figure 4.26.** Areas of decreased human brain functional connectivity between a node of the system involved in a processing of socially significant information

(green sphere), localized in the right caudate nucleus, in patients with generalized anxiety disorder, compared to healthy subjects (pFDR(cluster)<0.05, minimum cluster size – 30 voxels). R – right hemisphere, L – left hemisphere.

**Table 4.18.** Areas of decreased functional connectivity between the ROI localized in the right caudate nucleus and the remaining functional images' voxels in patients with anxiety disorder (pFDR(cluster) <0.05, minimum cluster size – 30 voxels).

| **Location (L – left hemisphere, R – right hemisphere)** | **p-FDR cluster level** | **Cluster size** | **Local max coordinates in MNI** | | |
|---|---|---|---|---|---|
| | | | **x** | **y** | **z** |
| R Supramarginal gyrus | <0,0011 | 546 | 58 | -22 | 38 |
| R Postcentral gyrus | 0,008 | 194 | 40 | -42 | 64 |
| L Supramarginal gyrus | 0,008 | 184 | -48 | -34 | 46 |
| L Inferior temporal lobule | 0,013 | 158 | -50 | -52 | -18 |
| R Precentral gyrus | 0,013 | 151 | 28 | -8 | 58 |
| R Cerebellum | 0,027 | 117 | 42 | -42 | -32 |
| Cerebellar vermis | 0,027 | 113 | -6 | -78 | -24 |
| L Middle frontal gyrus | 0,027 | 110 | -30 | 34 | 26 |

The correlation analysis revealed negative correlation between functional connectivity of the right caudate nucleus with the right postcentral gyrus and Kerdo index (Fig. 4.27), and also positive correlation between FC of the right caudate nucleus and cerebellar vermis and Vigilance Scale score of Melbourne Decision Making Questionnaire (Fig. 4. 28).

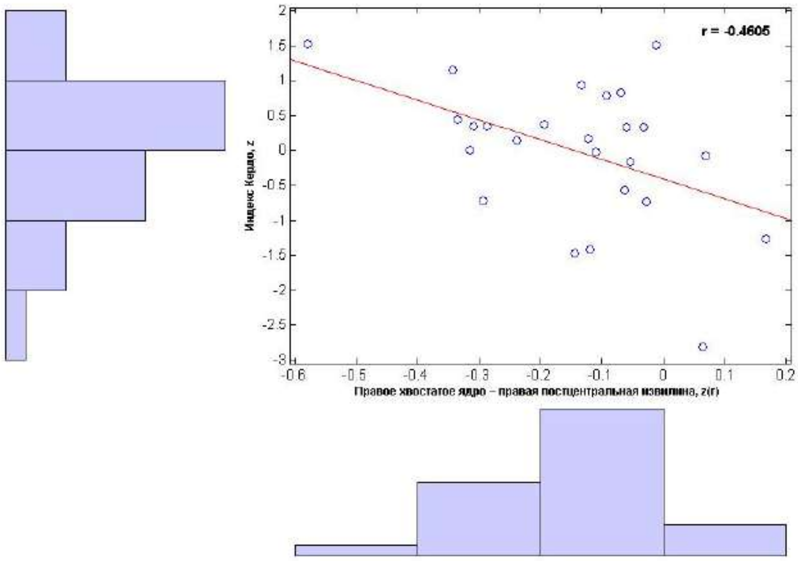



**Figure 4.27.** Scatterplot of functional connectivity values of the right caudate nucleus with the right postcentral gyrus and the Kerdo index of patients with GAD. The red line is the trend line, r is the Pearson correlation coefficient.

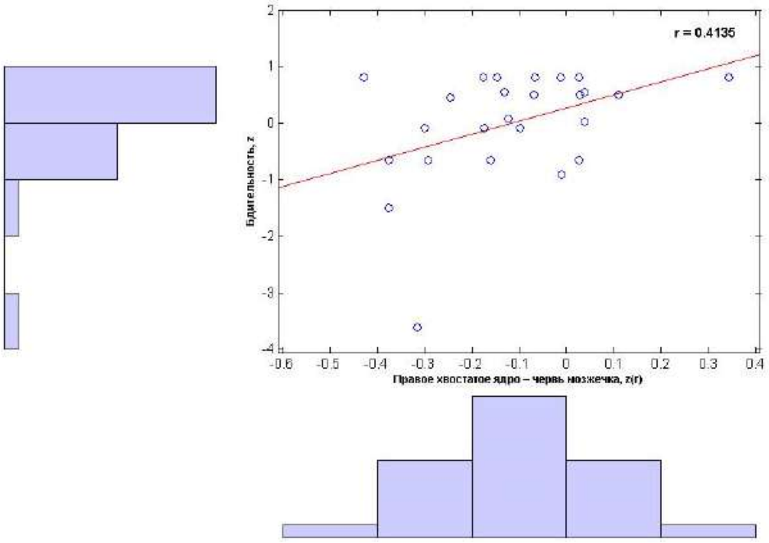



**Figure 4.28.** Scatterplot of functional connectivity values of the right caudate nucleus with the cerebellar vermis and Melbourne Decision Making Questionnaire (MDMQ) Alertness scale scores of patients with GAD. The red line is the trend line, r is the Pearson correlation coefficient.

Our analysis of functional connectivity between ROI selected according to results of activation investigation and gPPI-analysis using TAP-paradigm [270] and other image voxels did not reveal statistically significant differences between the patient group with anxiety disorders and healthy subjects.

### 4.3.3. GAD-associated changes in the human brain functional connectivity between the elements of the brain executive control provision systems of cognitive activity in the operational rest condition

Patients with generalized anxiety disorder were characterized by lowered functional connectivity between elements of the systems providing for executive control processes revealed at the previous stage of our studies [285] and several brain regions including the right superior and medial frontal gyri, left supramarginal gyrus, right precuneus (Fig. 4.29, 4.30, Table 4.19).

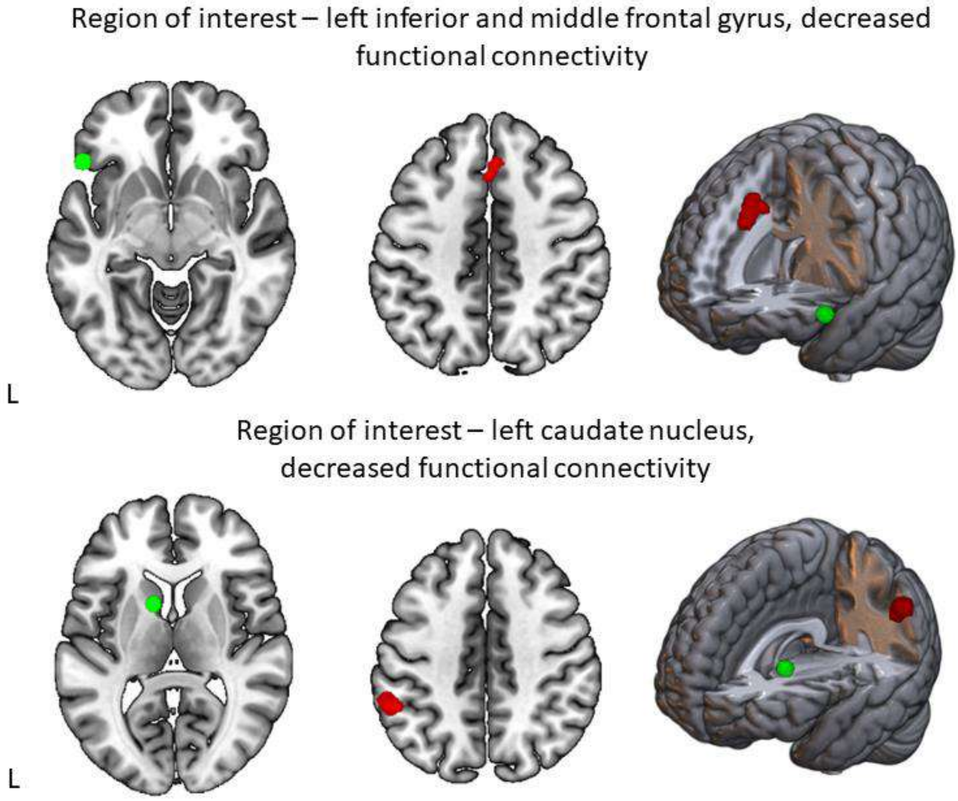



**Figure 4.29.** Areas of decreased functional connectivity with nodes of the system underlying executive control of cognitive activity for areas of interest in the left caudate nucleus and left inferior frontal gyrus (green spheres) in patients with generalized anxiety disorder, compared to healthy subjects (pFDR(cluster)<0.05, minimum cluster size – 30 voxels). R – right hemisphere, L – left hemisphere.

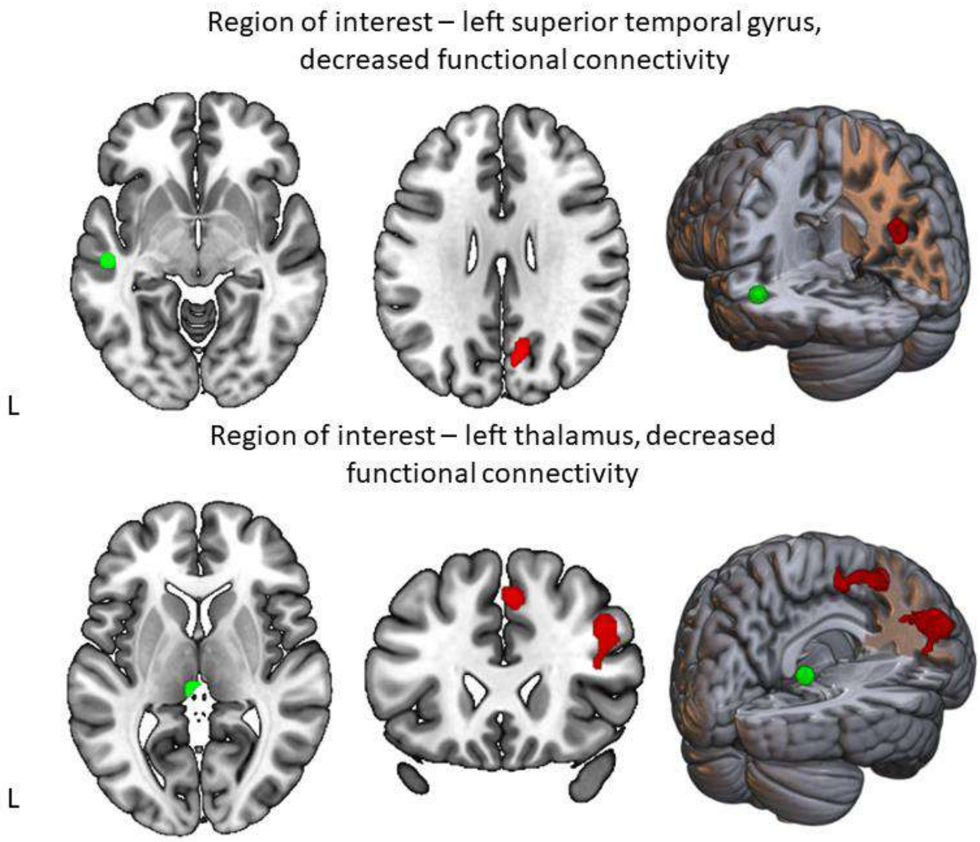



**Figure 4.30.** Areas of decreased functional connectivity with nodes of the system underlying executive control of cognitive activity for areas of interest in the left superior temporal gyrus and left thalamus (green spheres) in patients with generalized anxiety disorder, compared with healthy subjects (pFDR(cluster)<0.05, minimum cluster size – 30 voxels). R – right hemisphere, L – left hemisphere.

**Table 4.19.** Areas of functional connectivity changes with nodes of the system underlying executive control processes in patients with generalized anxiety disorder (pFDR(cluster)<0.05, minimum cluster size – 30 voxels)

| **№** | **Location (L – left hemisphere, R – right hemisphere)** | **p-FDR cluster level** | **Cluster size** | **Local max coordinates in MNI** | | |
|---|---|---|---|---|---|---|
| | | | | **x** | **y** | **z** |
| **The decrease of functional connectivity** | | | | | | |
| **Region of interest – left inferior and middle frontal gyrus** | | | | | | |
| 1 | R superior frontal gyrus | 0,028 | 164 | 2 | 26 | 48 |
| **Region of interest – left caudate nucleus** | | | | | | |
| 1 | L Supramarginal gyrus | 0,031 | 168 | -52 | -46 | 40 |
| **Region of interest – left superior temporal gyrus** | | | | | | |
| 1 | R Precuneus | 0,032 | 164 | 10 | -70 | 26 |
| **Region of interest – left thalamus** | | | | | | |
| 1 | R Middle frontal gyrus | 0,001 | 306 | 48 | 28 | 30 |
| 2 | R Superior frontal gyrus | 0,002 | 243 | -2 | 34 | 44 |

Our analysis of correlations between Kerdo index and vigilance level according to Melbourne Decision Making Questionnaire and GAD patients' functional connectivity between regions of interest in the caudate nucleus and superior temporal gyrus of the left human brain hemisphere and revealed clusters in the left supramarginal gyrus and right precuneus revealed only negative correlations (Fig. 4.31, 4.32).

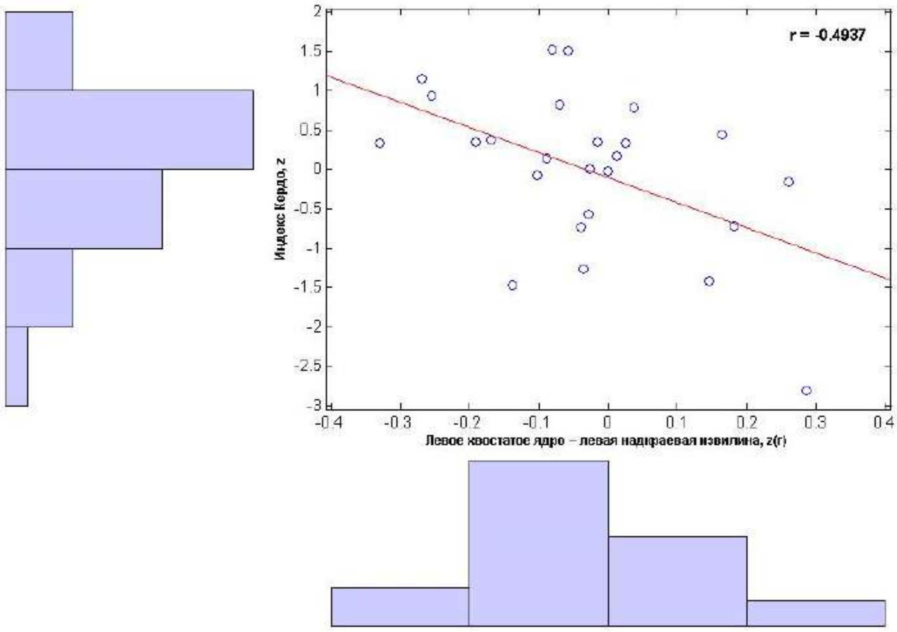



**Figure 4.31.** Scatterplot of the values of functional connectivity between of the left caudate nucleus with the left supramarginal gyrus and the Kerdo index in patients with GAD. The red line is the trend line, r is the Pearson correlation coefficient.

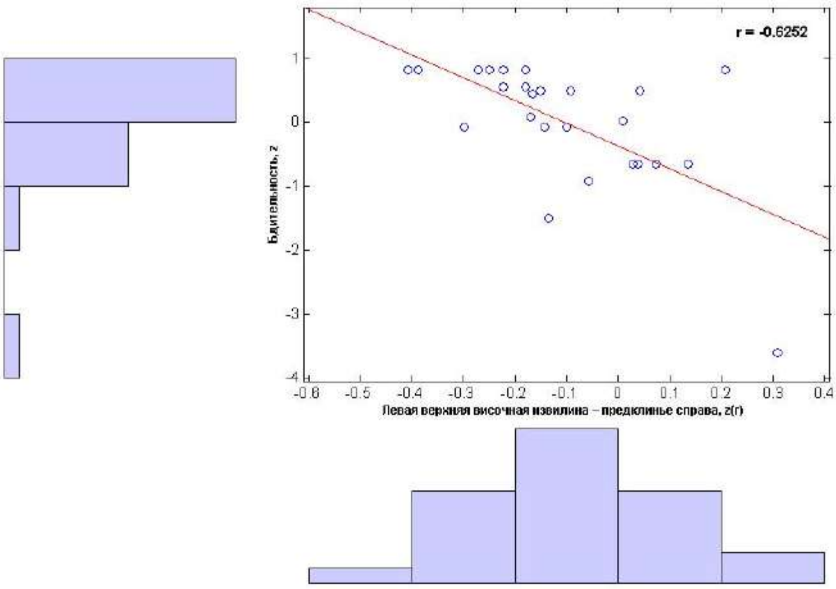



**Figure 4.32.** Scatterplot of the values of functional connectivity of the left superior temporal gyrus with the right precuneus and scores on the Alertness scale of the Melbourne Decision Making Questionnaire in patients with GAD. Red line – trend line, r – Pearson correlation coefficient

Equally with correlation analysis, the revealed FC changes were contrasted with the results obtained by intergroup comparison of fMRI data of patients with GAD and healthy subjects regarding local activity changes when fulfilling the Go/NoGo test task and functional connectivity changes for NSIC elements and the neuronal system providing for social interactions. The results showed that GAD-associated FC decrease observed between ROI in the left thalamus and medial surface of the left superior frontal gyrus (Fig. 4.30) coincided by its localization with the cluster of GAD-associated lowered BOLD-signal in case of inhibition of prepared actions (NoGo tests, see Fig. 4.5). Localization of this crossing is presented in Figure 4.33 and corresponds to the medial surface of the medial frontal gyrus. According to the meta-analytical Internet resource “Neurosynth” [175] the above brain structure is included in the frontoparietal executive and cognitive control system is detected as activated under a wide range of test conditions varying from emotional reacting [109, 174], speech activity [68, 180] to working memory [190, 308] and cognitive interference [204, 296] or actual or imagined motor activity [59].

Basing on the literature data it will be correctly to acknowledge the revealed supramodal nature of functional specialization of this region what suggests directly the association of this structure with executive control of the current activity.

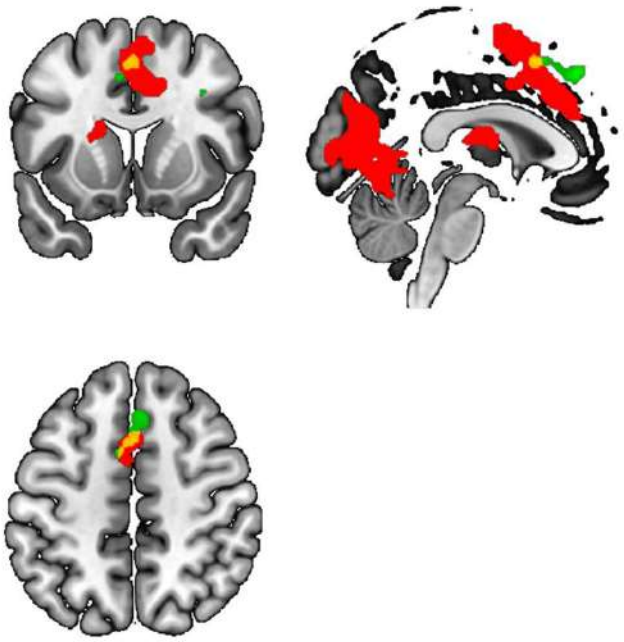


**Figure 4.33**. Spatial intersection of the GAD-induced decrease in local human brain activity during suppression of prepared actions (NoGo test) and the GAD-induced decrease in functional connectivity between ROIs in the left thalamus. Legend: red indicates clusters of decreased BOLD-signal when comparing “NoGo > baseline” contrasts between patients with GAD and healthy subjects (see Fig. 4.5); green indicates clusters with reduced functional connectivity values in patients with GAD relative to healthy subject according to the resting state fMRI-data for the region of interest in the left thalamus (see Fig. 4.30); yellow indicates the intersection between the two clusters described above, localized on the medial surface of the superior frontal gyrus (with coordinates x = -2, y = 11, z = 49).

#### 4.3.4. GAD-associated changes in human brain functional connectivity in the operational rest condition between regions of interest covering the whole brain

The analysis of functional connectivity between ROI covering the whole brain volume according to collection of anatomical charts aal3 [47] revealed that patients with anxiety disorder were characterized by lowered FC between the caudate nuclei bilaterally and the right cerebellar hemisphere (Fig. 4.34, Table 4.20).

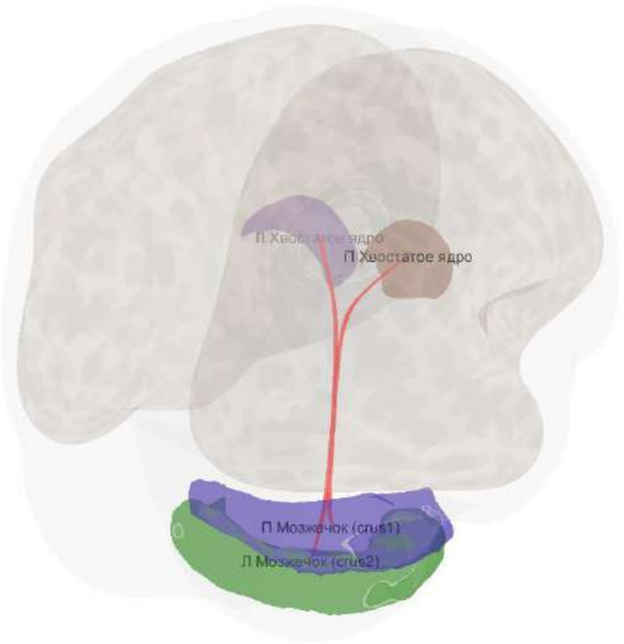



**Figure 4.34.** Decreased functional connectivity (red lines) between brain regions, revealed by pairwise comparisons of regions of interest covering the entire brain without attribution to preselected brain structures, in patients with generalized anxiety disorder compared with healthy subjects (pFDR(cluster)<0.05, minimum cluster size is 30 voxels). R – right hemisphere, L – left hemisphere

**Table 4.20.** Decrease in functional connectivity between ROIs covering the entire volume of the brain according to the atlas of the CONN software package in patients with anxiety disorder (p(connection)<0.05 without correction for multiple comparisons, pFDR(cluster)<0.5).

| **The decrease of functional connectivity (FC) in GAD between caudate nuclei and cerebellum** | | **F/T values** |
|---|---|---|
| Cluster | | F = 7,24 |
| 1 | FC «right caudate nucleus – right cerebellar hemisphere (Crus1)» | T = 2,61 |
| 2 | FC «left caudate nucleus - right cerebellar hemisphere (Crus2)» | T = 2,44 |
| 3 | FC «left caudate nucleus - right cerebellar hemisphere (Crus1)» | T = 2,16 |

The correlation analysis performed by us between the functional connectivity degree and psychodiagnostic parameters of patients with GAD did not reveal any significant correlations.

The obtained result is in accords with the literature data suggesting GAD-associated lowering of functional connectivity between the cerebellum in the operational rest condition and the following structures: right dorsolateral cortex [25.], posterior cingulate gyrus [250], right right cerebellar tonsil [155].

As it was shown in previous studies of topographic organization of the human cerebellum basing on fMRI data in the operational rest condition, the cerebellum region crus1 could be associated with provision of executive control functions [101, 102]. Basing from this, we can conclude that the revealed lowering of FC of this region with the caudate nuclei can reflect changes in control functions and, that our result supplements the previous data on the nature of integrative activity of NSIC elements in the operational rest condition in GAD.

Besides that, functional connectivity lowering revealed by us is also in compliance with a similar effect found in GAD when FC was analyzed in the mode “region of interest – all other image voxels” (see previous section 4.3.2): between the region of interest in the caudate nucleus and cluster in the cerebellum where lowered FC was also detected.

It is important to specify here that the region of interest in the right caudate nucleus of the human brain was selected basing on the analysis results of a relationship between FC in this structure and the social intelligence level [303]. As judged by the available literature data, a similar effect of cerebellum FC lowering in the operational rest condition was observed in numerous studies of social anxiety (GAD variant with involvement of emotion regulation processes) including FC with prefrontal cortex [69], basal ganglia (putamen) and right thalamus [283] and also right cerebellar tonsil [155].

Thus, our result not only clears up the potential commonality between brain processes providing for social intelligence, social anxiety and generalized anxiety, but suggests also the potential of revealed brain structures (cerebellum and caudate nuclei) as candidates for psychophysiological monitoring of control function disorder.

***

Summarizing the psychophysiological stage of our study we should conclude that when solving the set tasks of this stage we established previously unknown patterns of involvement of the brain nonselective inhibitory control system (NSIC) elements in provision of action control processes associated with generalized anxiety.

We showed for the first time that extension of the element composition of the brain NSIC system is observed in generalized anxiety disorder under conditions of uncertainty when previously prepared actions are suppressed and implemented (the Go and NoGo tests), as compared to the norm.  This extension occurs due to additional involvement of the elements localized both in the region of the right anterior insula and frontal operculum and in the region of orbito-frontal cortex of the right brain hemisphere.  The literature dedicated to studying neurophysiological manifestations of GAD attaches the critical importance in pathogenesis of this disease to the human brain region including the anterior regions of the insula and frontal opercular cortex in which our study revealed GAD-associated NSIC link [40, 117, 225]. Besides the established extension of the NSIC element composition, significant overlapping is observed between other links of the NSIC system in patients with GAD and NSIC elements revealed earlier in healthy volunteer group (see [188]).

It should be mentioned that the experimental search in such studies is focused to changes in the recorded brain activity (more often, its lowering relative to the norm) in changes of the brain functioning associated with the pathologic formation process of generalized anxiety disorder.  In contrast to this, our study used a principally new methodical approach aimed at statistical analysis of practical equivalence of the brain activity parameters [244] and tested when studying functioning patterns of the brain NICS system in obsessions [156]. This allows to consider brain activity characteristics ignored earlier in the tomographic investigations of the brain. i.e to reveal those brain structures which demonstrate statistically verified absence of changes in their activity. As a result exactly such approach used in this study allowed to establish new elements of the neuronal nonselective inhibitory control system whose activity level does not differ from the norm.  It should be mentioned also that another location pattern of the brain NSIC system elements is observed and local lowered activity of these elements is recorded [156] in obsessive compulsory disorder under the same test conditions of activities implementation. This is in compliance with concepts of different pathophysiological neurobiological principles of GAD and obsessions.

At the same time, GAD-associated changes in the functional activity were found by us also for other brain structures: our studies showed lowered local activity in the anterior cingulate cortex when it was involved in provision of action implementation (Go tests) and their suppression (NoGo tests). Moreover, the higher individual anxiety levels were, the more the BOLD-signal in this region decreased. Our results are in accord with the known literature data because it is known that the anterior cingulate cortex is one of the brain structures whose activity changes are associated with GAD pathogenesis and are part of the cingulo-opercular neuronal network (sometimes this neuronal network is considered in the literature as salience network (neuronal network providing for processing/perception processes of behavioral significance)). So, lowered activity in the anterior cingulate cortex is explained by disturbance of descending control influences (including regulation of emotional experiences) in GAD [23] and this structure is an important element in their brain provision.

Thus, this effect of relatively lowered involvement of the anterior cingulate cortex in action control processes in GAD was demonstrated by us for the first time for experimental conditions implying involvement of action inhibitory control processes under uncertainty conditions modelled by the Go/NoGo test task. The previous studies of other authors observed brain structure activity changes in GAD comparable by their nature only under conditions of provoking anxiety or emotional experiences and there were no purposeful studies focused to investigation of the brain provision of inhibitory control in GAD using tomographic neurovisualization methods. Our result complies with modern understanding of GAD brain base and evidences correctness of the hypothesis on GAD-associated lowering of the capability to control actions not only in situations associated with emotional experiences but also when controlling actions under emotionally neutral conditions.

Besides that, the presence of brain activity change pattern in GAD revealed by us is in accord with the concepts of the association between control functions and psychodiagnostic parameters of personal anxiety which is manifested in GA clearly and consistently: a respective brain activity parameter is lowered with growth of personal anxiety. Thus, the results of our correlation analysis additionally suggest the potential diagnostic value of neurophysiological activity parameters of revealed GAD-associated set of structures which can be useful for psychophysiological monitoring of control functions.

At the same time we did not observe lowered activities efficiency in patients with GAD at the behavioral level in terms of response time to Go-stimuli or number of mistakes. Our result reproduced data of single previous studies of motor (Go/NoGo test) and cognitive (using Stroop test) inhibition processes in GAD, in which GAD was manifested not only in increased response time and number of mistakes in Stroop test (see, e.g., [74]). To our opinion, this can be caused by compensatory involvement of additional (relative to the norm) elements of the neuronal nonselective inhibitory control system revealed in our study, namely GAD-associated NSIC element in the anterior insula and frontal operculum.

To our opinion, the compensatory nature of extension of NSIC element composition in GAD (due to involvement of the anterior region of insula of the right brain hemisphere) is confirmed additionally by the data obtained by us when analyzing functional connectivity in the operational rest condition. So, it was established that functional connectivity of GAD-associated NSIC element localized in the region of the anterior insula/frontal operculum is characterized by increased (relative to the norm) FC parameter values with the pole of the frontal lobe and medial temporal gyrus of the right hemisphere. It should be mentioned also that AI/FO is the only one brain structure of all analyzed regions of interest which demonstrates increased FC in GAD relative to the norm in the operational rest condition. Moreover, it demonstrates inverse correlation with the personal anxiety level.

Besides that, in GAD the effect of increased functional connectivity of GAD-associated NSIC element was observed with simultaneous lowering of functional connectivity of both other NSIC elements and elements of other brain systems analyzed in our study: neuronal systems of socially significant information processes [303] and cognitive activity executive control [285]. To our opinion, the nature of revealed correlation between FC of this NSIC element with individual situational anxiety levels in patients with GAD can be an additional evidence suggesting its compensatory role in the behavioral control: relatively low FC of this GAD-associated element in the operational rest condition was observed at high anxiety levels. It is important to emphasize that before obtaining the results of our study, previous studies interpreted the functional role played by involvement of the anterior region of the insular cortex in GAD pathogenesis from viewpoints of providing the affective aspect of anxiety disorders (see, e.g., [225]). In such studies the matter concerned that part of the insular cortex, which, along with the anterior cingulate cortex, is included in the cingulo-opercular neuronal network composition (so-called salience network). Our analysis of literature data shows also that elements of this system are characterized exactly by another type changes in brain functional activity parameters in GAD, namely, lowering of FC parameter values and local activity level in GAD [61, 126]. It is important to emphasize here once more that GAD-associated NSIC element detected for the first time, was revealed thanks to a new method of brain function mapping [244] developed within the limits of our thesis study.

Functional specialization of this element relatively to control functions is confirmed not only by coincidence with the meta-analysis results obtained in fMRI investigation of inhibitory control but also by comparison with meta-analysis study findings using larger literature data body associated with investigations of the executive control brain provision.  So, it is known that the region of insular cortex (together with anterior cingulate cortex) included in the neuronal network associated with provision of behavioral significance (so-called salience network) demonstrates, as a rule, lowered FC parameter values and local activity level in GAD [61, 126].

Our analysis comparing localization of GAD-associated NSIC element in the anterior insula and neuronal executive network, visualized using the Neurosynth.org meta-analytical software [175], shows that this element coincides by its localization with the brain structures included in the neuronal executive control system. This suggests additionally the conclusion on the compensatory role played by involvement of GAD-associated element in AI/FO in providing nonselective inhibitory control processes for action control under conditions of the Go/NoGo test task.

Besides the compensatory nature of the anterior insular cortex involvement, the extension of NSIC element composition itself can suggest the increased activities control level which can lead to certain choking.  As it was mentioned above, the chocking phenomenon can be associated with increased activity control what can result in confusing action in case of excess development of these phenomena, especially in sportsmen going in for technically complex sports [364, 409]. Moreover, the increased anxiety factor can result in increased control of the current activities implementation, neuronal manifestations of which are observed in our study, most likely, as NSIC element composition extension.

As it was already mentioned above, other analyzed regions of interest related to neuronal nonselective inhibitory control system demonstrate lowered functional connectivity in the operational rest condition in GAD as compared to the norm.  This was confidently demonstrated for GAD-associated neuronal NSIC system element localized in the right orbitofrontal cortex.  In combination with the data on lowered local activity in the anterior cingulate cortex when fulfilling the Go and NoGo tests, one can state the complicated nature of action control brain systems restructuring demonstrated in the clinical model of GAD-associated changes in control functions. Thus, one of the key brain systems providing for behavior control, i.e. nonselective inhibitory control system, is characterized in GAD by additional (relative to the norm) inclusion of elements with multidirectional values of functional connectivity in the rest condition.

The patterns revealed by us can be considered as neurobiological signs of changes in control functions which can be required in practice of psychophysiological monitoring within the limits of TME of sportsmen.

Thus, two brain regions revealed in the present study, being GAD-associated elements of the brain nonselective inhibitory control system involved in provision of action control under uncertainty conditions can be considered as candidates for the role of regions of interest which can be used for psychophysiological monitoring of changes in the control functions as potentially associated with lowered efficiency of the current activities implementation (Fig. 4.35).

Besides the above brain structures, the results obtained by us in the clinical model of GAD-associated changes in the brain provision of executive control allow to suggest additional regions of interest as candidates for diagnostics of control function changes. So, one of GAD variants, so-called social anxiety, is closely connected with sports in which productivity depends on the experts' external assessment, or so-called spectator sports attracting large masses of observers. In this connection, the finding seems promising, which suggests involvement in GAD pathogenesis of the brain structures associated with providing for socially significant behavior aspect processing/perception. So, we found lowered functional connectivity between the caudate nuclei and cerebellum in the operational rest condition in patients with GAD as compared to the norm using two independent methods for analysis of fMRI data in the operational rest condition. In one case GAD-associated FC lowering between these structures was observed in the operational rest condition when the caudate nuclei were selected as regions of interest as ones associated with neuronal processes supporting the social intelligence level [303]. In other case, this effect was demonstrated in paired comparison of all regions of interest covering the brain without preliminary selection of a region of interest in any brain structure (see section 4.3.4). It is important to emphasize in this respect that, basing on the literature data, the lowered FC of the cerebellum in the operational rest condition is a reproducible effect not only in GAD but also in case of social anxiety what determines the selection of the caudate nuclei and cerebellum as candidates for potential regions of interest for diagnostics of control function changes caused by anxiety (see Fig. 4.35).

The comparison of the patterns found by us with the literature data analyzed within the limits of the purposeful meta-analytical study for revealing the brain structures providing for inhibitory action control [118] showed that lowered functional activity with simultaneously high anxiety levels was observed in the anterior cingulate and supplementary motor cortex (ACC/SMC) which are associated with provision of central inhibition processes (but these brain structures are not included in NSIC). It should be mentioned here that ACC is one of those brain structures which are closely connected with GAD pathogenesis and changes in its functioning are associated with emotion dysregulation in GAD [290]. It was found additionally that GAD-associated local activity lowering on the medial surface of the medial frontal gyrus during action suppression was combined with GAD-associated functional connectivity lowering with the region of interest in the left thalamus in the operational rest condition. To our opinion, taking into account the polyfunctional specialization of this brain structure and its element belonging to the frontoparietal executive control system, the effect revealed by us is also the reflection of control function changes caused by generalized anxiety disorder. Basing on the above, the regions of the anterior cingulate cortex and medial surface of the medial frontal gyrus are suggested as candidates to target structures for psychophysiological monitoring of control function changes (see Fig. 4.35).

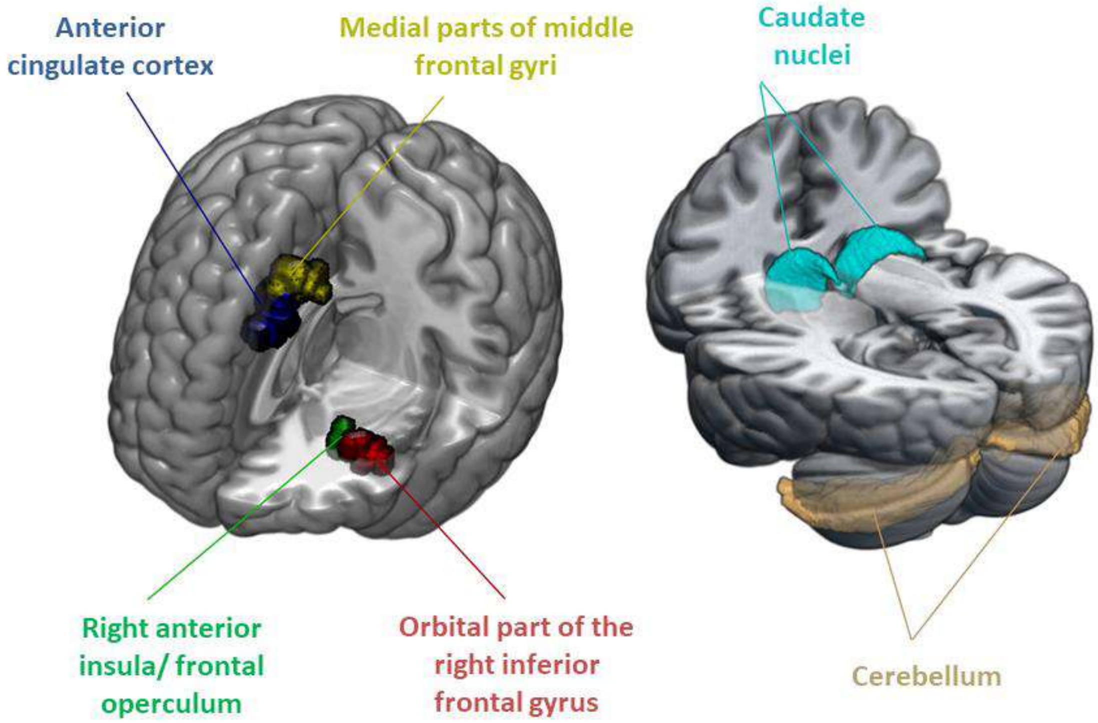



**Figure 4.35.** Human brain structures as a result of our research selected as target structures for psychophysiological diagnostics of changes in the brain mechanisms of executive functions. Functional activity parameters in these areas can be used as objective indicators of a possible decrease in the effectiveness of the implementation and performance of sports activities within the framework of athletes' mental training.

Thus, changes of the brain provision of behavior control processes in case of increased anxiety level are much wider and are not limited to the NSIC brain system. The obtained experimental data suggest the possible unidirectional restructuring nature of neuronal provision of the brain activities control mechanisms in generalized anxiety notwithstanding absence of rough behavioral disorders and statistically significant deviations of behavioral activity efficiency parameters from the standard values. Thus, the pattern of changes established by us indicates hypoactivity of the brain structures providing for control functions in GAD.

Weakening of distant functional interactions in the operational rest condition, which is similar in its pattern, was revealed by us for the elements of the executive control system localized in the structures associated with cognitive control processes.

The global analysis of our data shows that local lowering of the brain structure functional activity associated with provision of behavioral control in its different aspects and weakening of distant interaction combined with it suggest generalized character of the influence exerted by increased anxiety on functioning of the analyzed brain systems. Weakening of distant functional connections between the brain structures revealed in GAD using the fMRI data obtained in the operational rest condition in practically all analyzed regions of interest (except for GAD-associated NSIC element in the right insula/operculum of the frontal cortex) indicates the high potential for diagnostic use of the information on these brain structures activity.

In order to check the above at the next stage of our thesis study, the formed set of the brain structures selected as target structures for fMRI monitoring was used to test a data analysis method which allows to consider differences between group parameter values of the functional brain activity (patients with GAD and healthy subjects) in individual diagnostics. To solve this task and achieve the objectives of our thesis study, the fMRI data body used at the previous study stages was processed in order to obtain the data of another modality (as compared to that used at the previous study stage). The fMRI data recorded by us in the operational rest condition was used to obtain another parameter of the brain functional condition, i.e. the amplitude of low-frequency fluctuations of BOLD-signal in the operational rest condition (ALFF) [31]. This brain activity parameter is calculated as square root of low frequency activity power spectrum (0.01–0.1 Hz) and, as considered in the literature, is an index of brain spontaneous neuronal activity level which reflects its functional condition [90]. The covariation approach based on principal component method (so-called PCA-based scaled subprofiled model (SSM-PCA)) was applied to use ALFF values of all human brain structures from the set suggested by us in individual diagnostics. Initially this approach was suggested to analyze positron emission tomography data [256] and allowed to consider glucose accumulation levels in all image voxels, i.e. it is essentially a kind of multivariate analysis. Later this approach was successfully used for analysis of fMRI data [223, 274]. Application of SSM-PCA to analysis of group data (e.g., when comparing fMRI images of healthy subjects and patients) allows to obtain the change pattern of the recorded signal in the scanned brain volume, the degree of which can be assessed in an individual patient or study participant. Thus, this statistical approach allows to pass from the assessment of group differences to individual diagnostics. So, the use of this method in our thesis study is substantiated by the need to achieve its objective.

### 4.4. Individual diagnostics of functional condition of the brain structures providing for control functions using rest fMRI data in healthy subjects and patients with generalized anxiety disorder

At the final stage of our thesis study, a task was solved to test a fMRI data processing method which would allow to use the intergroup comparison data (within our clinical model of GAD-associated changes in the brain provision of control functions) in individual fMRI diagnostics of possible changes in control functions associated with possibly productivity lowering. The positron emission tomography using 18-fluorine deoxyglucose (FDG PET) is today a golden standard in diagnostics of the functional brain condition. But the use of PET under conditions of existing radiation safety standards when investigating the diseases, accompanied by the disturbed functional brain condition, is restricted by several factors one of which consists in presence of the effective dose for the patient. This restricts the use of PET in practice of TME of sportsmen. But the literature contains a sufficient number of studies which show high correlation between fMRI data in the operational rest condition (including ALFF) and FDG PET results using different radiopharmaceuticals (18-FDG, 15-H2O both in the healthy population [311] and in case of pathologic conditions [60, 317]. As follows from the modern literature data, the fMRI method in the operational rest condition can be used for obtaining the the parameter of human brain functional condition not only in patients but also in healthy subjects, therefore, it is applicable in principle to assessment of the sportsmen's functional condition.

Taking account the above, the final stage of our thesis study included: 1) methodical testing of the method for individual diagnostics of the functional brain condition basing on PCA/SSM applicably to PET data which allows in principle to use the results of intergroup comparison between the reference and target group of study participants (e.g., patients (and healthy subjects)), for which purpose we used PET data from the database of the Institute of Human Brain of RAS obtained in diagnostics of schizophrenia [222], 2) adaptation of this method for analysis of fMRI data obtained in the operational rest condition and testing such method in the clinical model of GAD-associated change in the brain provision of control functions, using the amplitude of low-frequency fluctuations of BOLD-signal recorded in the patient group with generalized anxiety order and healthy subject group with low and medium anxiety scores according to Spielberger-Khanin test [522].

The SSM-PCA method includes Scaled Subprofile Model (SSM) and principal component analysis (PCA). SSM-PCA decomposes the obtained data to group mean profile (GMP), individual residual profile (SRP) and scalar value of global scaling factor (GSF) [275]:

$$P_{sv} = GSF_s*(GMP_v+SRP_{sv})$$

where P – matrix s×v (s – total number of subjects, v – number of voxels in one 3D image after using the mask).

SRP, in its turn, can be considered as product of vectors group invariant subprofiles (GIS) by scalar values of subprofile scaling factor (SSF) [256].

According to literature data [256, 273, 275] the use of SSM-PCA method consists of the following stages:

1. Transformation of 3D image for each subject into vector with length v. Formation of matrix P with size s×v, each line of which is a totality of all voxels of one subject after using the mask.

2. Logarithm data transformation

$P_{sv} \rightarrow \text{Log } P_{sv}$

3. Data centering by lines. At this stage mean for this stage is substracted from each value in the line. After that data is deviation from the mean value of the line.

$Q_{sv} = \text{Log } P_{sv} – \text{mean}_v(\text{Log } P_{sv})$

where Q is matrix with data centered by lines.

4. Date centering by columns is performed similarly to centering by lines. Initially a column is a totality of values of the given voxel in each subject after taking logarithms and centering by lines.

$SRP_{sv} = Q_{sv} – GMP_v$

where $GMP_v$ = mean $_s(\text{Log } Q_{sv})$.

5. The principal component analysis is used to decompose the obtained matrix of SRP (individual residual profiles) to vectors GIS (principal components) and their respective scalar values of SSF.

6. The pattern is a product of respective vector GIS by square of its singular value. Notwithstanding the fact that GIS and its respective SSF can be used already as pattern and expression values for specific patients, respectively, this step allows to effectively compare different patterns between each other taking into account their explained variance.

7. The pattern expression for a specific subject is scalar product of SRP by respective pattern.

Our analysis of literature data shows that pattern expression values are used, as a rule, for studying differences between the control healthy subject group and patient group. E.g., expression values of obtained patterns can be used as variables within the standard methods for statistical testing of null hypotheses: it is considered that the pattern with statistically significant difference of scalar values between the groups reflects spatial covariance structure associated with the disease [273]. As a rule, in such cases t-test for independent samples is used: for test and control group, respectively. The pattern was considered significant if p-value was less than 0.05 in the intergroup comparison.

As a rule, SSM-PCA method is described in the literature as an effective way for differential diagnostics of change in the functional brain basing on neurovisualization data (fMRI or PET). Different authors reported in their studies on obtaining and validation of SSM-PCA diagnostic pattern of Parkinson's disease [28, 97], multiple system atrophy, progressive supranuclear palsy [83], behavior disorder in sleep phase with rapid eye movements [306], diffuse Lewy body disease, Alzheimer's disease [188, 298] and other diseases [322]. It was shown that quantitative expression values obtained for each subject correlated significantly with disease severity which was reflected by this pattern [107; 202].

Basing on the above, we performed the study to assess the possibilities of SSM-PCA method in precise differential diagnostics of drug-induced parkinsonism with the purpose of methodical testing of this method using PET data [222]. For this purpose we used fluorine-deoxyglucose (18F) PET data allowing to map the brain energy metabolism. Basing on this data, we used PCA-SSM method to suggest a diagnostic tool (in the form of regression component contribution pattern) allowing to forecast the possible development of drug-induced parkinsonism in patients with schizophrenia [222]. It is known that drug-induced parkinsonism is one of the common side effects caused by pharmacotherapy of psychic disorders including psychoses which can make the treatment quite difficult and lower its efficiency [189, 265]. But diagnostic and prognostic criteria of drug-induced parkinsonism have been not developed today what is associated to a great degree with insufficient knowledge of its pathogenetic mechanisms. When performing the methodical testing of the SSM-PCA method, new data was obtained, on the base of which it became possible to determine that PET-pattern expression typical of idiopathic Parkinson's disease can be used as a neuromarker of drug-induced parkinsonism [222]. In addition to the fact that the obtained result opens a new potential for PER-diagnostics and prognosis of drug-induced parkinsonism, the successful methodical testing of the SSM-PCA method determined its application to fMRI data for achieving the objectives of our thesis study.

The advantage of the SSM-PCA method applicably to the data of patients with generalized anxiety consists in the fact that manifestations of generalized anxiety in fMRI are extremely variable [126]. The point is that the use of SSM-PCA neutralizes the influence of the mean inside the group and between brain regions and, thus, the possibility of error associated with different functional activity profiles in different subjects (belonging to different groups) is ruled out. The principal component assay (PCA) allows to construct the pattern reflecting spatial distribution of variance associated with a certain attribute – presence of GAD disease in our study. Moreover, comparing pattern expression in different groups, in its turn, makes it possible to isolate the pattern corresponding to a differential attribute such as presence of generalized anxiety disorder which can be used in the individual analysis. The degree of such pattern allows to determine objectively presence of such manifestation of brain activity changes which indicates presence of GAD or changes in control functions.

In accordance with the above, in order to obtain 3D images of voxel-based distribution of BOLD-signal amplitude of low-frequency fluctuations (ALFF), temporal BOLD-signal series from each voxel were subject to fast Fourier transform with subsequent determination of BOLD-signal fluctuation spectrum power in low-frequency range (0.01–0.1 Hz).

Similarly to our analysis of human brain functional connectivity basing on fMRI data in the operational rest condition, the patient group with GAD included data for 25 participants with generalized anxiety disorder. The control group involved 33 healthy subjects with low and medium personal anxiety levels, which was determined by the data of Spielberger-Khanin psychodiagnostic test [522]; these subjects were selected out of 100 healthy subjects, whose data was used at the previous stages of our thesis study (see section 4.3). The clustering algorithm k-means++ [44], tested by us successfully earlier in the analysis of psychodiagnostic data obtained in the Dark Triad Questionnaire [91], was applied with this purpose to psychodiagnostic data of personal anxiety. The peculiarity of this method consists in principal possibility to use it in small samples (but not less than 50) what allows to cluster any data, including psychodiagnostic data. Earlier when testing the application of this method to analysis of psychodiagnostic data, we used the clustering algorithm k-means++ for analysis of psychological data obtained by the Dark Triad Questionnaire in healthy subjects for their dividing in comparison groups in order to use them for performing the morphometric analysis of structural MRI data [91]. It was decided to use the experience of successful testing of this clustering method in our thesis study. As a result, the use of the method k-means++ allowed to isolate the group of 33 persons with medium and low anxiety levels out of the group of 100 healthy subjects whose data was used at the previous stages of out thesis study for analyzing the brain functional connectivity.

At the next stage, the BOLD-signal amplitudes of low-frequency fluctuation in the operational rest condition were obtained for these subjects for each voxel of fMRI images. The selection of this parameter for suggesting a diagnostic tool was determined by both close association of this parameter with functional brain condition and necessity to use independent data not connected with that, which was used for selection of a set of diagnostically significant brain regions.

In accordance with the above, before using SSM-PCA, our ALFF data was spatially normalized and smoothed using Gaussian function (point size = 14 mm). Smoothing and normalization of 3D images were performed in the SPM-12 software application in MATLAB R2023a medium for Windows (Mathworks Inc, Sherborn, MA). In order to process the data using the SSM-PCA method and perform t-tests of obtained pattern expression values, we wrote a software code in Python 3.11.5 language, fulfilled in the local web-interface Jupyter Notebook 6.5.4. The code was checked by generating test patterns based on the brain gray and white matter and also by comparing with ScAnVP/SSM-PCA software application (www.feinsteinneuroscience.org), which is widely used as a method for obtaining the functional activity pattern [75, 307]. Then a so-called 3D mask was generated to apply the SSM-PCA method to ALFF data obtained only in the brain structures which were selected as a result of our neurophysiological fMRI investigations (see Fig. 4.36).

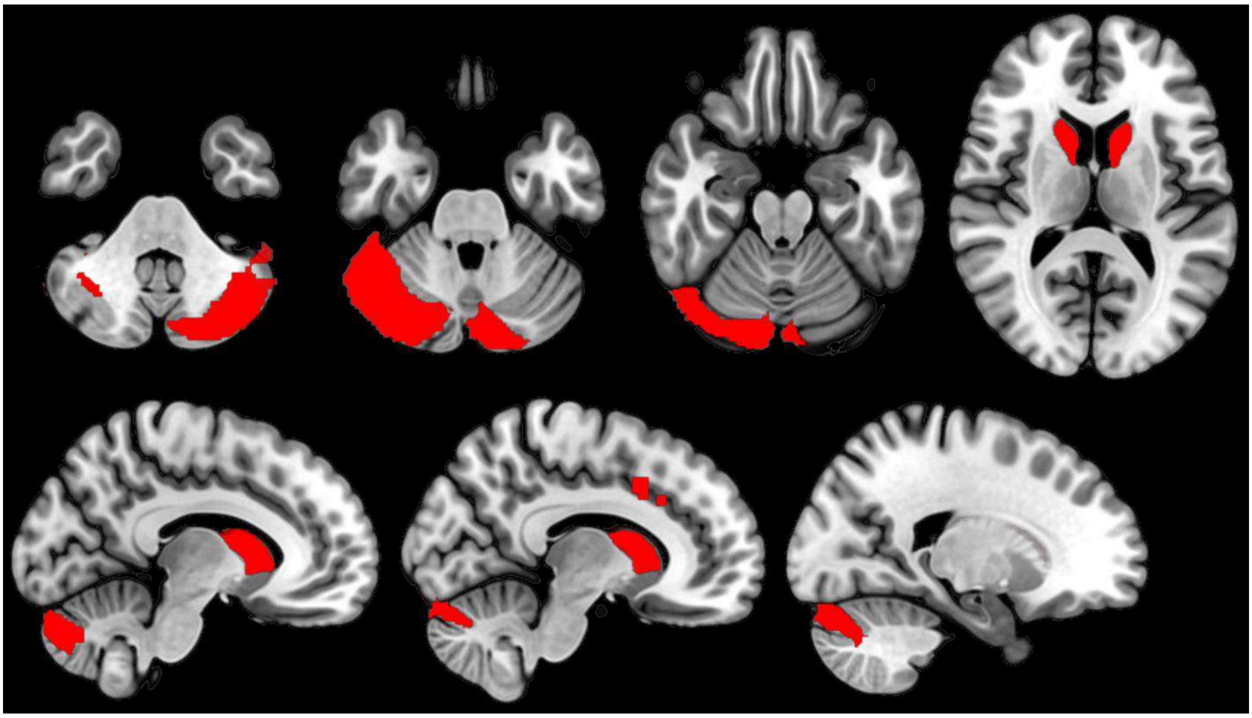


**Figure 4.36.** The mask used during SSM-PCA (axial slice coordinates: Z = -40, -30, -22, 12; sagittal slice coordinates: X = -10, 10, 20).

As a result of our analysis of the amplitude of low-frequency fluctuations of the brain structures BOLD-signal selected by us a diagnostically significant ones at the previous stage of the thesis study, we used the SSM-PCA method to obtain several patterns which were ranked in accordance with explained variance. So, e.g., we obtained expression values of each pattern for each patient with GAD and each healthy object from respective groups and after that we performed two-sample t-test for respective pattern expression values.  As a result it turned out that only first pattern could be determined as significant (explained variance 6.3% at p = 0.002). In other words, we calculated the SSM-PCA pattern (see Fig. 4.37), expression values of which differed significantly between GAD patient and healthy subject groups.  In particular, patients with G=GAD were characterized by: 1) increased pattern expression values (first model component) in the caudate nuclei, insula, medial part of the cingulate cortex and cerebellum (human brain regions designated by red color in Fig. 4.37); lowered pattern expression values in the cerebellum bilaterally (human brain regions designated by blue color in Fig. 4.37) as compared to healthy subjects.

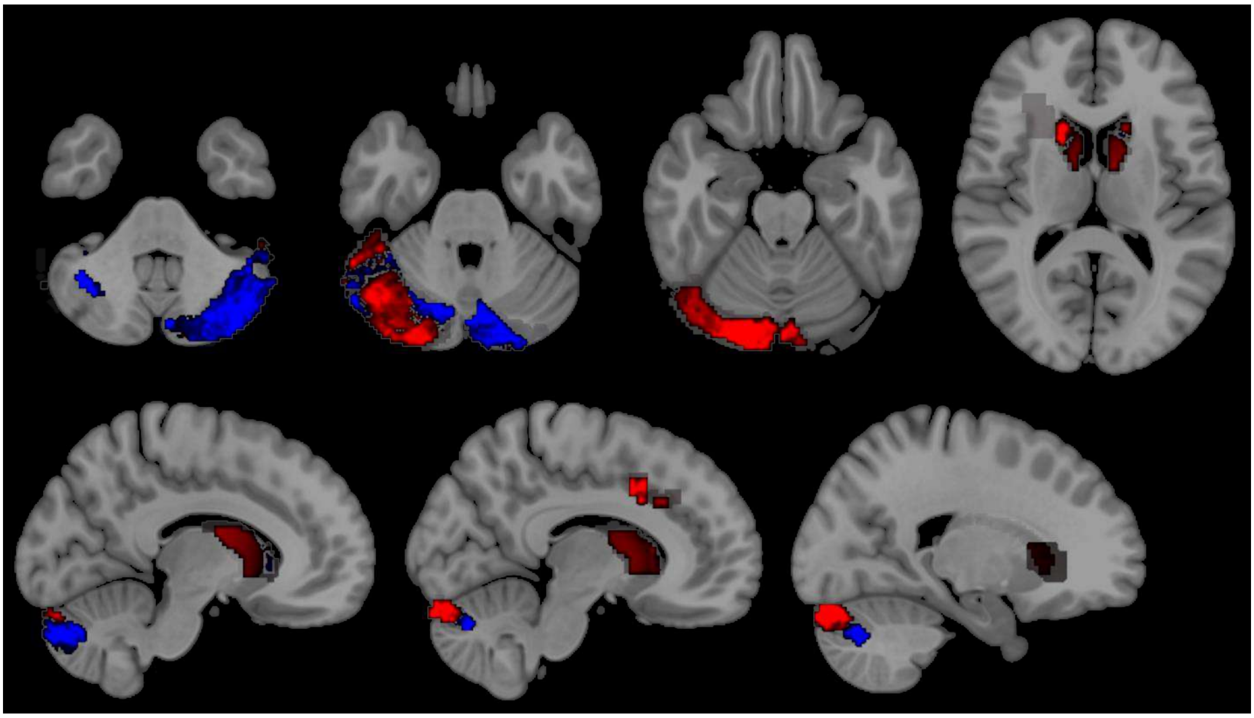


**Figure 4.37.** The pattern of changes in the amplitude of resting state low-frequency oscillations of BOLD-signals obtained as a result of comparing patients with generalized anxiety disorder and healthy subjects. Designations: coordinates of axial sections – Z = -40, -30, -22, 12; coordinates of sagittal slices – X = -10, 10, 20).

At the next stage of our study, in order to determine BOLD-signal ALFF value for regions with different expression degree of the first model component in patients with GAD, we obtained averaged ALFF values for the above clusters comprising the revealed pattern. The averaged BOLD-signal ALFF values in the human brain region, which demonstrated high values of the revealed component expression in patients with GAD (as compared to the data of healthy subjects) are presented in Fig. 4.38. Basing on ALFF data distribution it is seen that there are not significant differences between patients with GAD and healthy subjects what is confirmed by the statistical analysis results (p = 0.92).

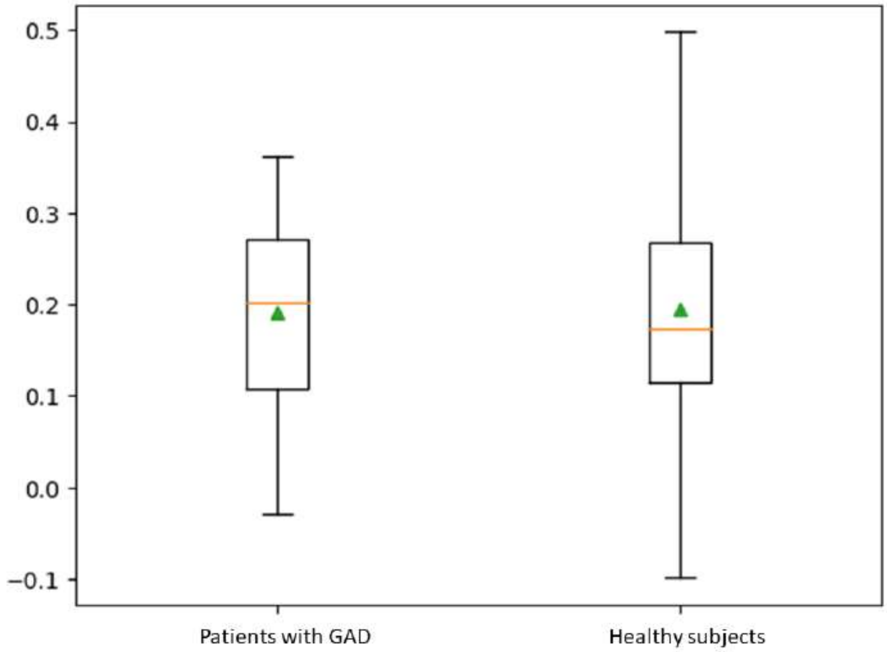



**Figure 4.38.** Averaged values of the low-frequency BOLD-signal oscillations amplitude for human brain areas that demonstrated greater expression values of the identified component (according to SSM-PCA analysis) in patients with GAD, compared to healthy subjects. Designations: along the ordinate axis – values of the low-frequency BOLD-signal oscillations amplitude (ALFF), green triangle – group average ALFF values, horizontal line – median of ALFF values

The similar analysis of averaged BOLD-signal ALFF values in the human brain regions (the cerebellum regions designated by blue color in Fig. 4.37), which demonstrated negative values of the first component expression in SSM model for patients with GAD (designated by blue color in Fig. 4.37), revealed significant differences between healthy subjects and patients with GAD ($p = 0.015$, see Fig. 4.39). The obtained results are in accordance with previous data of other researchers, in which ALFF values were increased in patients with GAD as compared to the data of healthy subjects [26] and reproduce the effects of ALFF decrease in the cerebellum in GAD revealed earlier [159]. At the same time, a recent review published in the end of 2023 [24] states an insufficient number of the studies using ALFF for investigating the functional human brain condition in GAD.

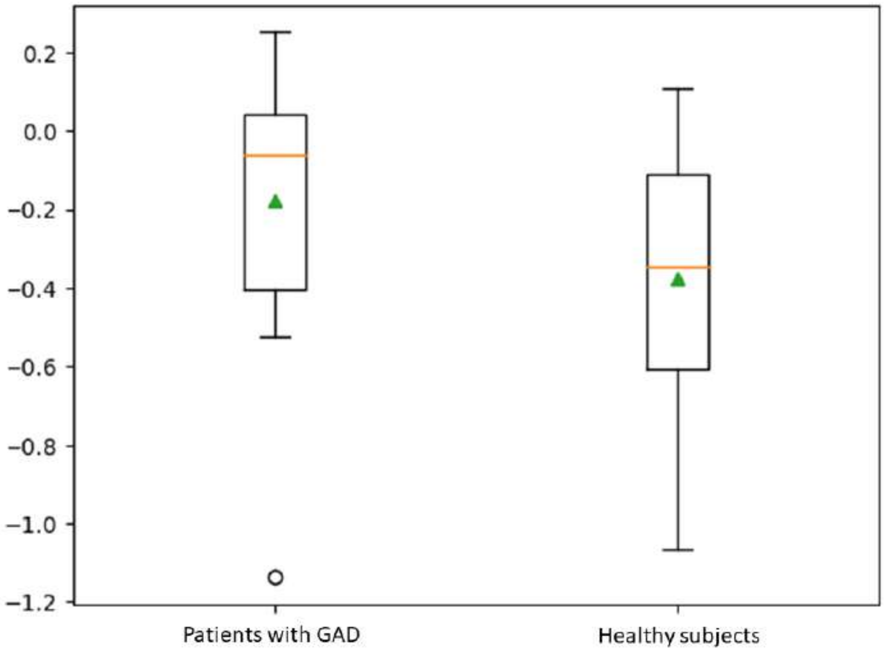



**Figure 4.39.** Averaged values of the low-frequency BOLD-signal oscillations amplitude for human brain areas that demonstrated lower expression values of the identified component (according to SSM-PCA analysis) in patients with GAD, compared to healthy subjects. Designations: along the ordinate axis – values of the low-frequency BOLD-signal oscillations amplitude (ALFF), green triangle – group average ALFF values, horizontal line – median of ALFF values

Thus, basing on fMRI data on the functional human brain condition, its structures associated with control function provision, we obtained the diagnostic SSM-PCA pattern, the expression level of which can be used as an objective marker of the sportsman’s functional condition. The obtained result is not only in compliance with the results of independent studies performed by other authors but it also outlines further field for future studies for specifying and developing the procedure for individual diagnostics of the functional human brain condition linked with control functions. The issue of introducing the suggested diagnostic method in practice of thorough medical examination of sportsmen is a subject for future and purposeful studies (including longitudinal ones).

**SUMMARY**

Our study is dedicated to analyzing the modern situation concerning the use of medical and medico-biological monitoring (MBM) technologies assessing the sportsman's functional condition in connection with scientific medical studies in the field of sports medicine and also searching for and development of new diagnostical approaches to psychophysiological monitoring. The conceptual limits of the technology within the limits of medico-biological and especially psychological studies can be defined as a science on the mastery to carry out transformations in the preset space of problems, objects, knowledge or information. In this connection MBM is an integral part of the more general concept of "control" designating the process of change in the condition of some biological object or system resulting in achievement of a certain target [455, 459]. Basing on this, the main task for MBM, as applicable to control in sports medicine, can be considered as achievement of a desired or predetermined effect in a controlled biological objector system. The effect achieved by this can be training, preventive, therapeutic or rehabilitation [455, 459]. Our analysis of the state-of-art of MBM in our country suggests a problem of delay in introduction of the scientific study results into practice of thorough medical examination (TME). While accumulation of the scientific data results in gradual increase of the list of diagnostic methods, we have to acknowledge lack of parallelism between these processes. This is clearly seen by the example of the data on functioning of the sportsman immune [351, 352] and cardiovascular system [399, 530], which remained for long time without normative consolidation. In particular, the literature data accumulated over the recent years and results of our own studies of lipid metabolism, endothelial dysfunction and autoimmune processes shows that high physical and psycho-emotional loads influencing the organism of highly qualified sportsmen cause considerable immunological readjustment as a result of which, diagnostic signs in intensified tissue destroying are observed because of autoimmune response, therefore, the sportsman's heart is under constant autoimmune shock all the year round [351, 352, 353, 531]. In spite of the fact that the totality of accumulated scientific data suggests convincingly the necessity to

include diagnostics of endothelial dysfunction in the thorough medical examination this did not receive due attention in any Procedure version beginning from 2010 [531, 351, 352, 353, 462].

Such situation of a certain disagreement between the level and results of modern scientific studies and content of the documents regulating medical examinations of sportsmen is even more pronounced regarding TME associated with participation of a medical psychologist/psychotherapist in diagnostic investigation of the psycho-emotional status. Traditionally, the dominating approach in diagnostics and control of the sportsman's functional condition within the limits of MBM is associated with an emphasis on somatometry parameters, assessment of clinical-and-laboratory and functional-and-diagnostic parameters of the organism focusing on health preservation and providing for sports implementation of the sportsman's main physical qualities (endurance, strength, coordination, flexibility, speed) and basic functional systems. By the regulated extent of diagnostic investigations, the assessment of the sportsman's physical (somatic) condition, when implementing the "Procedure for Healthcare Delivery", takes more than 99%, and psychological investigations take only 1%. This contradicts the most important principle of Olympic sports stated by Pierre de Coubertin according to which "Psychology wins in the struggle of equal rivals". While it is evident that achievement of the sports result, provided that the somatic and psychic health parameters are preserved, is possible only in case of the sportsman's certain psychophysiological condition in most sports, the instructions in the "Procedure of TME" concerning the necessity to investigate the psycho-emotional status do not describe its content. This suggests high urgency of evidence-based selection of diagnostic procedures both from viewpoint of their methodical organization [455, 459], and from viewpoints of their neurophysiological and psychophysiological content.

Thus, today a situation has been formed, in which it is evident that achievement of the preset sports result is possible in case of high quality and evidence-based assessment of the sportsman's psychological condition and carrying out monitoring of his functional condition. In this situation its negative role is played by a known problem of insufficient objective parameters showing the human psychological condition, the so-called neuromarkers. This problem is closely associated with absence of generally accepted non-contradicting understanding of the relationship between psychic activity patterns and its brain provision what cannot fail to influence introduction of methods for objective assessment of the sportsman’s psychophysiological condition into the regulated practice of TME.

Although investigating the associations between characteristics of the psychic activity course and efficiency of the sports activities implementation is, as earlier, a focus for a large number of psychological and neurophysiological studies what allows in principle to outline several investigational directions having the potential for inclusion in TME. Nevertheless, the selection of a target function, the objective psychophysiological assessment of which would allow to suggest possible candidates for the role of effective diagnostic criteria (whether an individual parameter of the brain total electric activity or characteristic of the neurophysiologic activity in a specific brain region) is difficult to a certain degree due to absence of a consensus regarding the nature of some or other psychic processes or mechanisms associated with such function.

Thus, the work performed within the limits of our thesis study included, on the one hand, selection of such target function and, on the other hand, analysis of the informal description of processes and psychologic operations attributed to such function and also their neurobiological provision. Considering the above, the present study was aimed at the development of potential candidates for the role of diagnostically significant parameters of the brain functional activity reflecting such condition of its structures regulating the current activities and behavior, which can be evidence of a possible change in the sportsman’s psychophysiological condition associated with potentially worsened implementation of the sports activities and lowered productivity.

The studies within the limits of this thesis performed using the material of the psychological investigation of professional sportsmen group who are representatives of precise sports – women gymnasts from the representative team of Russia and representative team of St. Petersburg, allowed to determine the target function and factors telling upon the efficiency of its implementation. Our psychological investigation showed that the efficiency of the women gymnasts' sports activities implementation could be influenced by the personal anxiety level which is closely associated with the activities control function.

Thus, the results of our study allowed to form a specific request for performing an independent psychophysiological investigation in order not only to assess the neurophysiological base of association between anxiety level and control functions but to suggest also a set of potential markers which can be useful in assessment of the sportsman's psychophysiological condition associated with those behavior control processes which can be altered due to change in personal anxiety level.

In order to solve the set task, it is necessary to select a procedure for recording the human brain activity which later could be applicable in practice of thorough medical examination taking into account time deficit and complex organization of the highly qualitied sportsmen' training process. Then we had to perform a series of psychophysiological investigations in a clinical model, which would allow to suggest evidence-based parameters for psychophysiological monitoring. As a result, functional magnetic resonance tomography was selected as such method within the limits of this study; we planned to assess its use under experimental conditions of the operational rest from viewpoint of possible diagnostic application. The essence of this approach consists in analysis of the functional connectivity between the analyzed brain regions (correlation of fMRI signal changes between selected regions of interest). This approach is widely used not only with the investigational but also diagnostic and prognostic purposes.

In addition to the tested procedure for psychophysiological monitoring, it was necessary to select a clinical model, which would allow to perform the evidence-based assessment of the suggested approach. Taking into account the results of the psychological investigation, we selected a clinical model of change in the brain provision of control functions in generalized anxiety disorder (GAD). At the next stage it was necessary to select experimental test conditions which should be adequate to the selected clinical model.

Taking into account the association between change in anxiety levels and control functions, the inhibitory control processes were used as a study object; in order to model their involvement we used the Go/NoGo test task, which was used earlier not only when studying the action control processes, but also in the studies of the correlation between sports activities characteristics and individual levels of the cognitive/inhibitory control capability. The modification with equally probable presentation of Go and NoGo stimuli used by us allowed also to model the uncertainty conditions of activity implementation, which, on the one hand, are observed often in the situation of sports activities implementation, and on the other hand, are important for investigating the anxiety, because uncertainty intolerance is one of the typical symptoms of GAD. Besides that, the uncertainty situation creates conditions for studying the brain nonselective inhibitory control system (NSIC system) discovered relatively not long ago, which is known to be involved in provision of both implementation and suppression of actions under conditions of uncertainty. The latter circumstance is especially important for the tasks of our thesis study because, in accordance with one of probable hypotheses, the lowered efficiency of the current activities implementation can be caused by the excessive control, which can be provided for also as a result of NSIC involvement.

As a result of the performed fMRI investigations of patients with GAD and healthy subjects we showed for the first time that in GAD implementation and suppression of the prepared actions under conditions of uncertainty was characterized by extension of the element composition of the neuronal NSIC system due to additional (relatively to the norm) involvement of the human brain structures localized in the anterior region of the insula (adjacent with the frontal opercular cortex) and orbital part of the inferior frontal gyrus of the right hemisphere. Moreover, the pattern of correlations between individual anxiety levels and the brain activity level in these NSIC elements involved additionally suggested the compensatory nature of the anterior insula involvement. It should be mentioned that the activity level of these brain structures did not differ significantly when comparing patients with GAD and healthy subjects. At the same time, we found lowered (relative to the norm) local brain activity during action implementation under conditions of the Go/NoGo test task in patients with GAD in several brain structures functionally associated with provision of the reactive inhibitory control and executive functions in different types of cognitive activities, among which one should mention the adjacent regions of the anterior cingulate cortex and medial surface of the superior and medial frontal gyri. The comparison of our results with the literature data allowed to consider the revealed brain activity change patterns in GAD as signs of changes in the control functions. This enabled us to select, on the base of the obtained experimental data, the brain regions as regions of interest – candidates for the role of targets for testing at the third stage of the thesis study using the experimental fMRI findings in the operational rest condition.

It is evident that the sports activities go beyond the limits of a narrow task for inhibition and implementation of actions modelled during the neurovisualization study. Therefore, besides the regions of interest associated with functioning of the brain nonselective inhibitory control system in a series of independent fMRI investigations of healthy subjects, we selected additionally the brain structures associated with provision of: 1) processes of social interactions and socially significant information processing, 2) executive control processes of cognitive activities (when solving cognitive tasks associated with verbal multi-meaning).

Our testing of the selected set of regions of interest in the intergroup comparison of fMRI findings in the operational rest in patients with GAD and a large sample of healthy subjects provided new data on characteristics of the functional connectivity at rest of the elements of neuronal NSIC systems, systems providing social interactions and executive control.

So, the additional evidences were obtained in favor of compensatory involvement of GAD-associated element of the neuronal NSIC system, localized in the anterior region of the right insula, in provision of action suppression and implementation processes because in the operational rest condition this structure proved to be only one which demonstrated intensified functional connectivity in GAD. At the same time, functional connectivity of all other analyzed regions of interest was characterized by lowering in GAD relative to the norm. This effect was seen also for the regions of interest localized on the caudate nuclei and cerebellum of the human brain, which, as our studies showed, are associated with provision of social intelligence and demonstrated, according to known literature reports, the same pattern of functional connectivity in case of social anxiety (FC lowering relative to the norm). A similar effect was obtained also for regions of interest associated with provision of executive control during realization of cognitive activities localized in the medial part of the medial frontal gyrus demonstrating also lowered local activity in patients with GAD during action suppression in NoGo tests of the Go/NoGo test task.

Thus, when summarizing our clinical data it is possible to state that lowering of functional connectivity in the operational rest condition in the basal ganglia structures, cerebellum, anterior cingulate gurus, medial surface of the medial frontal gyrus and orbital part of the right inferior frontal gyrus, which is recorded against a background of the compensatorily intensified functional connectivity of the element in the neuronal nonselective inhibitory control system in the anterior region of the right insula in the human brain, is a diagnostic sign of lowered efficiency of activity implementation and productivity in GAD. Basing on our data, an evidence-based set of regions of interest is formed which is recommended for use in practice of the thorough medical examination of sportsmen with the purpose of psychophysiological monitoring of the brain provision for control functions.

Thus, the totality of our results allows to determine a set of human brain structures whose parameters of functional activity in the operational rest condition can be used as signs showing change in the control functions associated potentially with lowered efficiency of the activities implementation and productivity. Within the limits of our work, a diagnostic approach is suggested, which allows to use the data of intergroup comparison in individual diagnostics of the functional condition of the human brain structures selected in out study. The results obtained when applying the statistical methods of multidimensional modeling to the data on amplitude of low-frequency fluctuations of BOLD-signal allowed to receive a diagnostic pattern of its redistribution, the degree of which can be used in the individual monitoring of the brain provision for control functions. Our results not only suggest the expediency of including fMRI monitoring in the MBM program of sportsmen in order to reveal neurophysiological signs of changes in the sportsmen's functional condition potentially associated with lowered productivity but also allow to suggest diagnostic tools for carrying out such monitoring.

Detecting in a sportsman fMRI signs coinciding with parameter values of the brain activity which were demonstrated by us in a clinical model of GAD-associated changes in the brain provision for control functions can be the grounds for thorough psychological investigation of a sportsman and possible correction of revealed disorders. Besides that, our results allow to establish the area for practice-oriented studies in order to develop new diagnostic fMRI criteria and psychophysiological monitoring programs and also determine ways for further studying the practical use of the functional MRT method in TME of sportsmen.

**CONCLUSIONS**

1. The systemic analysis of the structure and content of the "Procedure for Healthcare Delivery to Sportsmen" (three versions) revealed the following problems:

- the list of procedures has clear disbalance in favor of parameters characterizing working capacity, physical qualities and somatic health;

- the rapidness and substantiation of new scientific data transfer retards considerably both by somatic and, especially, by psychophysiological parameters;

- the volume of fundamental studies and knowledge transformed into medical technologies, especially in the field of neuropsychology, is very limited.

2. The results obtained in the psychological investigation of highly qualified representatives of precise sport (rhythmic-sportive gymnastics) demonstrate the important role of personal anxiety level as an indicator of efficiency of the sports activities implementation and productivity and suggest the significance of the control function assessment: levels of personal anxiety in women-gymnasts from the representative team of the country were lowered as compared to women-gymnasts from the representative team of St. Petersburg.

3. We showed for the first time in the clinical model of GAD-associated changes in the brain provision of control functions that the high anxiety is associated with involvement of the neuronal system of nonselective inhibitory control (NSIC).

4. Our results showed neurophysiological significance of GAD-associated changes in the brain functional activity observed earlier under experimental conditions implying anxiety provocation or emotion generation and also allowed to establish that emotional reacting dysregulation in GAD is caused by the changes in the brain provision of inhibitory control processes.

5. It is shown that in generalized anxiety disorder there takes place extension of the element composition of the neuronal nonselective inhibitory control system, which is one of the key neuronal systems for action control, which is active both during implementation and during inhibition of prepared actions. Such extension is realized due to additional (relatively to the norm) elements which are localized in

the anterior region of insula and orbital part of the inferior frontal gyrus of the right human brain hemisphere.

6. Changes in the brain provision of control functions in generalized anxiety disorder are accompanied by lowering of the brain functional activity in the prefrontal cortex structures associated with the reactive inhibitory and executive control.

7. We demonstrated for the first time the compensatory nature of involvement of the element of the brain nonselective inhibitory control system, localized in the anterior insula region of the right human brain hemisphere, in processes providing for actions in GAD. This is confirmed by GAD-associated increase of functional connectivity of this element in operational rest condition correlating positively with personal anxiety level.

8. The study revealed for the first time different direction of GAD-associated changes in functional connectivity in the operational rest condition of those elements of the brain nonselective inhibitory control system, which are localized in the anterior insula/frontal operculum and orbital part of the inferior frontal gyrus in the right hemisphere.

9. It is shown for the first time that in the operational rest condition GAD is characterized by unidirectional and combined changes in the local activity and functional connectivity of the brain structures associated with provision of processes of nonselective inhibitory control, executive control and socially significant information processing.

10. The study found the human brain structures and diagnostic signs of their functional condition associated with change in control functions, lowered efficiency of the activity implementation and productivity.

**Practical recommendations**

1. In order to determine signs of changes in the brain provision of sportsmen’s control functions it is recommended to perform studies for scanning the brain activity in the operational rest condition (in wake state) using functional MRI with duration from 5 to 10 minutes.

2. Performing the fMRI-investigation in the operational rest condition with collection of functional T2*-images should be combined with obtaining structural 3D-T1-weighted images with subsequent export of the obtained images from the working station.

3. The obtained functional and structural images are converted using the dii2nifti module of the mricron software package to NIFTI-format and after that they are assessed visually for artefacts.

4. In order to obtain the correct data on the brain functional activity the obtained fMRI data should be corrected regarding: 1) slice realignment with counting of six parameters of head shift relative to the initial position; 2) slice-timing correction; 3) determination of outlier scans by the maximum spatial shift (2 mm) and change of global signal intensity ($z > 5$); 4) structural image segmentation to gray and white matter, cerebrospinal fluid; 5) normalization of structural and functional images to the standard anatomical space (MNI152); 6) smoothing of functional images with diameter of convolution nucleus of 8 mm.

5. Preprocessed functional images are subject to the procedure for physiologic denoising using a multiple regression model: regressors are the following: a) the first 5 main signal components from the white matter and b) from cerebrospinal fluid, c) 6 parameters of the head shift and their first-order derivatives, d) outlier scans by the maximum movement or change of global signal intensity; then a band pass filter is applied to functional images to isolate low-frequency fluctuations (0.01–0.1 Hz).

6. Then the amplitude of low-frequency fluctuations (ALFF) maps corresponding to the power of BOLD-signal fluctuation spectrum in the low-frequency range (0.01–0.1 Hz) are calculated.

7. In order to reveal signs of changes in the brain provision of control functions, it is necessary to calculate the pattern expression developed basing on results of our thesis study using the multidimensional modeling methods as applicable to comparative analysis of fMRI date in the operational rest obtained in patient with generalized anxiety disorder.

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**List of abbreviations**

NSIC – non-selective inhibitory control

GAD – generalized anxiety disorder

fMRI – functional magnetic resonance imaging

PET - positron emission tomography

TME – thorough medical examination

SM – sport medicine

MT – medical technology

MBS – medical-biological support

EEG – electroencephalography

ROI – region of interest

FC – functional connectivty