4.3. RESEARCH OBJECTIVE 3 -THERAPY OF MENTAL DISORDERS AND THEIR RELATIONSHIP TO THE NEUROTRANSMISSION OF GLUTAMATE

4.3.1. Abstract

Cognitive deficit is one of the main symptoms of neuropsychiatric and neurodegenerative disorders such as schizophrenia, bipolar disorder, obsessive-compulsive disorder and mild cognitive impairment s. The deficit is manifested in varying degrees of severity, according to the type and length of the disorder. If we look at cognitive deficit from a neurobiological perspective, the key role is played by glutamatergic transmission. As the most frequent excitation neurotransmitter, glutamate is responsible precisely for the higher brain functions, which include cognitive functions (e.g. memory, speed of information processing and executive function), and the attendant cognitive strategies and functioning in everyday life. Despite the heterogeneity of the aforementioned disorders, the incidence of cognitive deficit in connection with impaired glutamatergic transmission is the main connecting link between these disorders.

For this reason, glutamatergic psychopharmaceuticals are currently the subject of intensive investigation in connection with a number of neuropsychiatric disorder s. It is not only the pro-cognitive effect of non-competitive NMDA receptor antagonists such as memantine that is coming to the forefront of attention, but also the antidepressant effect of the NMDA antagonist ketamine for the treatment of depression.

In addition to pharmacological therapy targeting the regulation of glutamatergic transmission, an improvement of cognitive functions may take place also by means of non-pharmacological methods, in particular long-term and intensive training of diminished domains of cognitive functioning . From a neurobiological perspective, the basis of cognitive training is the principie of synaptic plasticity of the neuronal syste m, in which long-term positive changes may take place in affected areas of the brain thanks to long-term potentiation (LTP) processes, with an attendant renewal of the diminished cognitive functions in connection therewith. Complex cognitive training, or cognitive remediation, may thus contribute to an augmentation of pharmacological therapy. Modern technologies, for example virtual reality games and connected aids for 3D imaging, today enable us to create cognitive tasks which are close to real life situati ons, which increase their ecological validity. However, an integral component of cognitive remediation is diverse technical aids such as a calendar or other tools serving as a reminder of various tasks. Furthermore, training of cognitive functions may be augmented by the use of stimulation methods in the affected regions of the brain (repetitive transcranial magnetic stimulation - rTMS, trascranial direct current stimulation - tDCS).

The target of this research objective is to observe glutamatergic transmission in selected neuropsychiatric and neurodevelopmental disorders, in connection with pharmacotherapy and non-pharmacological approaches in clinical practice.

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The research programme will be implemented during the entire term of the Project (from 1. 1. 2018 to 31. 12.2022).

Principal investigator

- NIMH (National Institute of Mental Health)

4.3.2. Current state of knowledge

Cognitive deficit afflicting for example memory, attention or decision-making capacity is an integral component of several neuropsychiatric and neurodegenerative disorders such as schizophrenia (SCH), bipolar affective disorder (BAD), obsessive-compulsive disorder (OCD) or mild cognitive impairment (MCI) . The form and intensity of the deficit is highly heterogeneous. Whereas complex deficit occurs especially in SCH, MCI and Alzheimer's disease (AD), in the case of other disorders only certain cognitive functions may be impaired . ln the case of OCD, this for example concerns impairment of inhibition control and cognitive flexibility (Chamberlein et al, 2006). Furthermore, cognitive deficit may occur already during the prodromal phase of the disorder (e.g. in SCH or AD), where as a rule it afflicts the decision-making capacity, mental performance and flexibility of the individua! and memory. The depth of the deficit also differs . Especially upon a comparison of schizophrenia and bipolar disorder, it has been demonstrated that differences in cognitive deficit are of a quantitative rather than a qualitative nature (Stefanopoulou et al., 2009). ln comparison with neurodegenerative disorders, the deficit in neuropsychiatric disorders often progresses slowly , nevertheless the presence of symptomatology has an influence on its profile. ln the case of BAD, performance is emotion -dependent or "hot" , and emotion-independent or "cold" (Roiser et al., 2009) . From a neurobiological perspective, a key role for us is played by glutamate, which as the most frequent excitation neurotransmitter is responsible for the regulation of higher cognitive functions such as learning or memory. The glutamatergic (AMPA and NMDA) receptors play a key role in the regulation of cognitive functions on the level of synaptic transmission. The NMDA (N-methyl D-aspartate) receptors regulate the power of the glutamatergic synapses with the aid of transduction of the intensity and time coincidence of pre- and post-synaptic acti vati ons. The NMDA receptor thus serves as a "coincidence detecto r", which weakens or strengthens synaptic activity and thereby also the plasticity of the neuronal system (Tabone, Ra maswami, 2012) . lt is precisely this mechanism that is the molecular basis of the adaptive capacity of the brain crucial for cognitive tr ai ning, primarily in connection with learning and memory. With regard to pro-cognitive effects, psychopharmaceuticals modulating glutamatergic transmission are coming to the forefront of preclinical and clinical research (Olivares et al, 2012) .

Despite the substantial heterogeneity in the field of neuropsychiatry and neurology, dysregulation of glutamatergic transmission is probably the basis of cognitive deficit in several of these disorders. Glutamatergic dysregulation may lead to the above-described changes in the area of cognitive capacities in the form of complex deficit (e.g. in SCH, BAD and AD) or an impairment of specific capabilities (e.g. cognitive inhibition in OCD).

ln patients with schizophrenia, positive symptoms typically respond to standard pharmacological treatment, whereas negative and cognitive symptoms often persist and contribute to chronic invalidity. Schizophrenia is linked with extensive neurocognitive deficits - including disorders in the domain of executive functions, learning, memory and speed of processing. Cognitive deficit is considered a

fundamental characteristic of the disorder and may precede the development of the acute phase of the disease. Current pharmacological therapy is based on the dopamine model of schizophrenia, which assumes dopamine dysfunction to be the basis of the symptoms and development of cognitive defi cit. Even though this model is effective in the treatment of certain patients, the majority of these patients manifest persisting afflíction despite having received the best available treatment.

Over the course of the last two decades, scientists have developed alternative conceptual models of SCH based on the psychotomimetic effects of compounds such as phencyclidine (PCP) and ketamine. These compounds function primarily by blocking glutamate of the type N-methyl-D-aspartate (NMDA) (NMDARs), which has led research workers to focus on glutamatergic neurotransmission and NMDAR as a basis for the new development of pharmaceuticals. In the case of schizophrenia, the development of typical symptoms of the disorder is explained on the basis of glutamatergic dysregulation. Results of studies using magnetic spectroscopy confirm glutamatergic dysregulation in schizophrenia in the cortical and subcortical regions with the aid of MRI spectroscopy (Meritt et al., 2016). The administration of NMDA glutamatergic receptor antagonists (e.g. ketamine) in healthy individuals leads to a simulation of symptoms similar to schizophrenia, not only positive symptoms, but also symptoms of cognitive deficit (Bubeníková-Valešová, 2008).

Non-competitive NMDA receptor antagonists such as memantine influence glutamatergic transmission in Alzheimer's disease, and provide the best evidence that glutamate plays a key role in impaired memory processes in Alzheimer's disease. Memantine blocks the chronic stimulation of the NMDA receptors by abnormally high concentrations of glutamate in resting state. On the other hand, the physiological activation of the NMDA receptors must be maintained, which is necessary for learning and remembering. This therefore concerns partial antagonism. Memantine acts on two connected processes: 1) it influences the proportion of the signal and noise on the post-synaptic neuron and 2) reduces increased inflow of calcium into the neuron. In physiological conditions the synaptic activation by glutamate creates a signal that is registered in the existing background noise, if there is a sufficient proportion between the size of the signal and the noise. This secures learning and the formation of memory traces. In the case of Alzheimer's disease, however, background noise is increased, which hampers detection of the signal. Memantine has a beneficial intervention in this condition by reducing background noise and thus renewing learning and formation of memory. Furthermore, by means of a partial blockade it also reduces the inflow of calcium into the neuron, which reduces the excitotoxic effect of glutamate, and for this reason the neuroprotective effect of memantine is also under consideration (Bartoš and Roth, 2015).

Preclinical and clinical trials focusing on the modulation of glutamatergic transmission are no exception also in the case of disorders distinguished by a deficit of inhibition processes (cognitive, motoric and behavioural inhibition), including bipolar affective disorder (BAD), obsessive-compulsive disorder (OCD), attention deficit disorder with hyperactivity, Tourette's syndrome, trichotillomania and other related neurotic disorders (Grados et al, 2015). OCD ranks among the psychological disorders in which the effectiveness of traditional biological therapy, influencing in particular monoaminergic neurotransmission (serotonin and dopamine) is generally not very high and does not bring about remission in all patients. For this reason also, today attention is being focused on glutamatergic dysregulation, which contributes to the development of OCD symptoms. However, the study of glutamatergic drugs (e.g. memantine, ketamine, D-cycloserine, glycine, N-acetylserine, lamotrigine and others) has not yet brought fully satisfactory results (Pittenger et al., 2015) .

Dysregulation of glutamatergic transmission is also being observed in connection with depression, in which despite the wide range of available pharmaceuticals, only one half of patients respond to the first chosen monoaminergic antidepressant, and only 10-20% of patients have a chance of achieving remission following repeated therapeutic attempts (Rush et al., 2006, Trivedi, 2013). A larger proportion of patients with depression thus remain exposed to the adverse neurobiological impacts of the disorder, and remain at an increased risk of suicidality, especially in the period of the lengthy wait for the antidepressant medication to take effect. In recent years we have seen a shift in the research paradigm in the sense of expected resistance to regular antidepressants in a direction toward alternative pathophysiological mechanisms using neuroplasticity. Glutamate, now considered the primary mediator of affective disorders (Sanacora et al., 2012), as well as the proportion of immune mechanisms as potential modulators of neuroplasticity, are coming to the centre of interest. The majority of neuroplastic changes take place in glutamatergic neuronal circuits, and clinical evidence of glutamatergic dysregulation as a pathophysiological mechanism of depression has been increasing sharply in recent years - in particular a positive correlation has been demonstrated between the plasmatic level of glutamate and the severity of depressive symptomatology (Kendel et al., 2005, Mitani et al., 2006, Sanacora et al., 2012), as well as a decrease in the serum level of glutamate following successful depression therapy (Kucukibrahimoglu et al., 2009). Spectroscopic studies also confirm an increase in extracellular levels of glutamate in the occipital, frontal and cingulate cortex of depression patients (Sanacora et al., 2004, Hasler et al., 2007, Grimm et al., 2012). One of the turning points in research into depression was the finding of the prompt antidepressant effect of molecules of ketamine, an NMDA antagonist first described in humans in the year 2000 (Berman et al., 2000).

Pharmacotherapy of neuropsychiatric disorders is frequently not sufficiently effective, and in the case of several diagnoses it alone does not lead to full remission (e.g. in BAD, OCD) or to the rectification of cognitive deficit (in the case of MCI/AD and SCH). For this reason, in addition to pharmacotherapy also other non-pharmacological approaches are applied in the treatment of neuropsychiatric disorders, such as cognitive remediation and stimulation methods (rTMS, tDCS), as well as various forms of structured psychotherapy (e.g. KBT).

Cognitive remediation in particular is an important component of the treatment of neuropsychiatric and neurodegenerative disorders, in which a complex or partial cognitive deficit occurs. This intervention has been demonstrated to be an effective method which can be used to positively influence not only cognitive deficit, but also psychosocial functioning in everyday life (e.g. Wykes et al., 2011; Huckans et al., 2013). As demonstrated by a range of scientific studies (e.g. Willis, Tennstedt, Marsiske et al., 2006; Mowszowski, Batchelor, Naismith et al, 2010; Buschert, Friese, Taipei et al., 2011; Buschert, Giegling, Teipel et al., 2012; Woods, Aguirre, Spector et al., 2012), persons with MCI and persons in the preclinical stage may profit above all from cognitive training and cognitive rehabilitation. In some cases, through appropriate and timely intervention we can defer progression into dementia and improve the quality of life of patients (e.g. Willis, Tennstedt, Marsiske et al., 2006; Mowszowski, Batchelor, Naismith et al, 2010; Buschert, Friese, Taipei et al., 2011; Buschert, Giegling, Teipel et al., 2012; Woods, Aguirre, Spector et al., 2012). Cognitive remediation also manifests a long-term effect in the form of a beneficial influence on relapses of the disorder (lower number of relapses and larger intervals between them), the application of the clients within society - studying or finding employment (Tao et al., 2015), and alleviating symptoms (e.g. Cella et al., 2016; Huckans et al., 2013). The results of cognitive intervention are favourable, but heterogeneous. The reason for this heterogeneity is primarily the method of intervention, but this also differs in the targeted regions. It is precisely the use of observations hitherto concerning the role of

glutamatergic transmission on cognition that promises a new approach in cognitive training. The targeted regions should be memory and executive functions, speed of processing, inhibition and mental flexibility.

Long-term and intensive training of diminished cognitive functions may bring about positive changes on a number of levels. For example, upon training of verbal memory {e.g. in SCH, BAD and MCI), long-term improved results may be attained in this cognitive domain thanks to the principie of long-term potentiation of existing synaptic connections . Changes observed in cognitive abilities after undergoing cognitive remediation are reflected not only in the form of an improvement of results in neurocognitive tests, but also on the level of modulation of impaired neurotransmission, increased functional connectivity of target regions of the brain and therefore also the engagement of large neural networks (DMN, SN and CEN), or an increase in the intrahemispheric transmission of information in task solving burdening this domain {Penadés et al. 2013).

Today considerable attention is also being devoted to the utilisation of new technologies in the therapy of mental disorders. The most common methods include especially the creation of therapeutic games within a virtual reality {VR) environment, which is applied in the cognitive remediation of impaired cognitive functions, and also as a means of exposure therapy, especially in anxiety disorders {Fajnerova et al, 2016).

One of the further approaches to improving cognitive functioning is direct influencing of cortical excitability and metabolism {e.g. rTMS, TDCS) in the affected regions of the brain (Mohr et al...). These methods may have potential as potentiation in the treatment of neuropsychiatric and neurodegenerative disorders. However, stimulation parameters in particular differ markedly between studies, and will probably subsequently influence the effectiveness of treatment {Elder, Taylor, 2014). A new unifying paradigm may clarify the effectiveness of these interventions.

The importance of mutual linkage of pharmacotherapy with non-pharmacological approaches is noted not only by clinical, but also by preclinical trials. In preclinical trials the effect of NMDA glutamatergic receptor analysis has been extensively tested, as a supplement to cognitive remediati on. A comparison of D-cycloserine (partial agonist) and D-serine (full agonist) demonstrated that D-serine is more effective in increasing the function of the NMDA receptors, and therefore also for cognitive remediation focused on working memory and recognition in mice. The observed improvement was linked with a measurable increase in hippocampal D-serine. The need for combined pharmacotherapy with non-pharmacological methods has been pointed out also by further studies, e.g. in connection with the treatment of symptomatolgy in OCD. Praško (2008) points especially to the suitability of a combination of pharmacotherapy and psychotherapy in the form of cognitive-behavioural therapy (CBT), and states that if a desirable effect of pharmacotherapy is not achieved, it is possible to combine individua! antidepressants and augment them with the method of EEG biofeedback or rTMS.

The present state of knowledge indicates the role of glutamatergic transmission both in clinical and cognitive symptoms. According to the findings so far, it appears that this transmission may be influenced both pharmacologically and non-pharmacologically (Medeiros et el. 2012). The target of this research objective is to observe glutamatergic transmission in selected neuropsychiatric and neurodevelopmental disoders in connection with pharmacotherapy and with non-pharmacological approaches in clinical practice .

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4.3.3. Link to the current research of the applicant and project partners

A key role in the solution of research objective 1 will be played by the National Institute of Mental Health (NUDZ), which has been engaged over the long term in research into the neurobiology of mental disorders in preclinical experiments and the issue of the synthesis of substances influencing the activity of the CNS. In this research, emphasis is placed on a translational approach. The proposed research activities are targeted at a whole spectrum of psychological disorders, but above all concentrate on research into psychotic disorders, in particular schizophrenia, affective disorders, anxiety disorders and dependencies. In human experiments we focus on the study of neurobiological correlates in the brain with the aid of neuro-display methods, such as functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) or their simultaneous registration, and a subsequent analysis with the aid of advanced methods (connectivity, entropy etc.). At the same time the project studies parameters of neurocognitive functions, correlated with biochemical biomarkers, analysis of polymorphisms etc . We are an entirely unique centre in the Czech Republic and one of a few centres worldwide to conduct clinical trials on healthy volunteers and patients with the use of glutamatergic pharmaceuticals, primarily ketamine, both with the aim of understanding the neurobiology of the disorder and with a therapeutic objective. Preclinical experiments then enable us to study the neurobiology of mental disorders from a molecular-genetic level, via a microscopic and biochemical level up to complex behavioural paradigms, advanced electrophysiological experiments and neuro-display studies with MRI. The project shall follow on from the research grants listed below, which have been or are being realised in our centre, and expands upon them in a fundamental manner. The table below presents an overview of some of the most significant of these:

	Affective response to visual art: a linkage of the fine arts and neuroscience perspective
	Project for excellence in the sphere of the neurosciences
	Utilisation of machine teaching in data analysis from magnetic resonance imaging for the purpose of improving timely diagnosis of schizophrenia and bipolar disorder
	Efficacy and functional changes in the brain in treatment of depression using translational direct current simulation (tDCS) in comparison with venlafaxine
	Prediction of therapeutic response in patients with depression with the aid of new methods of EEG analysis
	Endophenotypes of psychotic disorders
	Genetic and functional study of **NMDA** receptors focusing on the potential diagnosis and treatment of schizophrenia
	Physis in the sphere of improving human cognitive capabilities

	An animal and human serotonergic model of schizophrenia: validity assessed with the aid of qEEG and fMRI.
	The role of metabotropic mGlu2/3 and AMPA glutamate receptors in the neurobiology of schizophrenia
	The glutamatergic theory of schizophrenia in an animal and human model of disconnection, tested by a comparison with a population of schizophrenia patients
	Creation of standards for determining the degree of influence on drivers following the use of cannabis based drugs: an assessment of the level of cannabinoids in blood with respect to the time of use, psychomotor performance, vigilance and influence on brain activity
	Development of a Novel FGL Therapy and Translational Tests for Regenerative Treatment of Neurological Disorders
	The role of mTOR (mammalian target or rapamycin) signal pathway in the antidepressant effect of ketamine and antidepressants in patients with depression: a translational study
	Changes in QEEG cordance and EEG connectivity following the application of a subanaesthetic dose of ketamine in patients with depression - a randomised, double-blind, placebo-controlled cross-over trial
	Centre for neuropsychiatric studies of the CNS

Milestones of research aim 3

- Milestone 1: 12/2018: Developing an online platform for cognitive patient training in the home environment with the goal of long-term maintenance of the effect of remedial programs, and the creation of a remedial program in combination with pacing methods; Pilot testing and preparation of methods for analyzing the effectiveness of ketamine administration
- Milestone 2: 12/2019: pilot testing of the whole remedial program, recruitment of the first subjects, adjustment of the remediation parameters for each diagnosis, presentation of the results in the peer review, continuation of the recruitment of subjects, testing of a group of at least 100 healthy volunteers (cohort of young and older volunteers, 80 years) to determine normative performance in each CoR task . Inclusion of virtual games and FLEXIKOG aids into long-term cognitive training programs of individua! diagnostic groups (Objective 3) and monitoring the effectiveness of comprehensive training; Recruitment of the first group of patients suffering from depression and data evaluation; Presentations of present results at conferences and in the peer-reviewed publication;
- Milestone 3: 06/2021: continuing recruitment, ongoing evaluation of results; The inclusion of patients with FMR and healthy volunteers in the remedial program to evaluate the effectiveness of a new type of program, to continue the long-term cognitive remediation program and to evaluate its effectiveness, to include additional remedial methods in the KBT program and to recruit OCD patients. The traditional form of KBT, the analysis of normative data in a healthy population for each age group, and analysis of data obtained during cognitive rehabilitation of patients. Comparison of individual diagnostic groups, continuous evaluation of results
- Milestone 4: 12/2022: Final Data Analysis; Evaluation of studies; Preparing and submitting applications for certified methodologies; Development of cooperation with actors in the sphere of application in health and social innovation.

Expected outcomes of research aim 3

- 9 publications in IF journals
- presentation of results at international scientific conferences
- at least 3 certified methodologies and verification of the use of research results in clinical practice
- subsequent establishment of cooperation with the application sphere in the field of health and social innovation and submission of international grant projects.

4.3.5. Experimental verification of the research results practical applicability, including the intellectual property treatment

The optimal form of research results crystallizes during the implementation of the project. At the moment, a whole portfolio of research results ranging from personalized sessions led by a qualified expert, through personalized digital service to on-line services, is being considered . This will give rise to a specific form of clinical verification of the possible practical application of the research results.

Advantages of research results for their experimental verification of possible practical application will be the concept specifically focused on the needs of patients suffering from cognitive disorders or mental illnesses. In verifying the practical application, the key clinical role of the NUDZ Clinical Centre, which is a reference workplace for the mental health area in the Czech Republic with an international reputation, will play a key role. Comprehensive backgrounds guarantee high-quality and future-proof investors a trusted verification of the possible practical application of research results. The Clinic Centre

and the NUDZ clinic itself represent a major provider of health services.

Due to the nature of the product - software, diagnostic and therapeutic procedures - protection based on the principles of industrial property protection (patent law) cannot be assumed; copyright protection, trademark registration or protection of unspecified know -how are considered. Based on the verification and evaluation of the possible practical application of the specific properties of the research results, the possibility of product protection will be considered by certifying the methodology that is its basis.

Indicator 2 20 11 International patent applications (PCT) created by supported entities	**9**
Other result that is not reflected in indicators: possible partial outcomes of implementing the activities are the result s, which are defined according to the Definitions of types of research and experimental development results for the RIV database. (Please give the type of result of planned target value)	**3**
Other result, which is not reflect in indicators. (Please give the type of result of planned target value)	**4**