Research objective 2 - Non-pharmacological effects of glutamatergic neurotransmission in the therapy of neurogenerative disorders: mechanisms and efficacy of cognitive remediation and stimulation methods

Activity 1 - Options of cognitive remediation using a progressive cognitive training for schizophrenia and bipolar disorder

SCH and DP are chronic diseases with presence of a cognitive deficit. The deficit is present in all cognitive domains to a lesser or larger extent, has an impact on the general quality of life and endures even at the time of remission (Stefanopoulou et al., 2010). Glutamate is responsible for higher brain functions, such as cognitive flexibility, memory and learning. It is through the "glutamate theory" that the cognitive deficit in schizophrenia patients is explained. Antagonists of NMDA receptors, i.e. receptors for glutamate, are capable of stimulating the cognitive deficient in schizophrenia patients (and, in addition, positive symptoms). Furthermore, results of studies using the magnetic spectroscopy reveal a certain glutamate metabolism in cortical and sub-cortical regions in schizophrenia patients (Meritt et al., 2016). Pharmacological procedures are not sufficient for remedying the cognitive deficit (quotation). In accordance with current studies, cognitive remediation appears to be a good candidate for non-pharmacological interventions for the cognitive deficit.

A clinically significant improvement for most remediation procedures, including computer-based procedures, has been proven at the psychometric level by two most recent large-scale meta-analyses for schizophrenia (McGurk et al., 2007; Wykes et al., 2011), and by individual studies for the bipolar disorder (e.g. Deckersbach et al., 2010; Egamal et al., 2007). Improvement has been shown for complex approaches covering both the cognitive remediation and psychiatric rehabilitation (McGurk et al., 2007) and for approaches targeted solely at cognition (e.g. Wykes et al., 2011, Egamal et al., 2007). Cognitive remediation in schizophrenia is well established. For bipolar disorders, so far no targeted remediation programmes of cognitive deficit have been established, but certain complex programmes with a positive effect are being verified at present (Torrent et al., 2013).

Neurophysiologic studies for schizophrenia using fMRI have repeatedly shown functional changes in the frontal cortical region (Wexler et al., 2000; Wykes et al., 2002; Wexler and Bell, 2005) and, as a novelty, an increased density of grey matter after two years of remediation (Eack et al., 2010). In another area of neurobiological research, a genetic study monitoring an influence of catechol-O-methyltransferase morphism (an enzyme regulating the activity of dopamine) has proven a significant correlation between the presence of Met alela and a better response to cognitive remediation, in particular as regards flexibility and working memory (Bosia et al., 2007). In order to use a computer as an auxiliary remediation tool for schizophrenia patients, the studies of Burda et al. (1994) brought results, at that time considered very

encouraging, showing improvement in the performance of cognitive functions in patients with chronic schizophrenia and schizoaffective disorder during an eight-week training by means of computers. Today, the use of computers is considered an integral component of complex remediation programmes (e.g. Eack et al., 2010).

Cognitive remediation is a therapeutic intervention that accomplishes general criteria similar to psychotherapy, pharmacotherapy and other treatment approaches, since it is based on a theoretical and methodological framework, takes into consideration individual requirements of patients, is characterized by certain regularity and a sustaining effect in the practical life ("generalization effect").

The knowledge gained so far implies the objective of this activity. The objective is to prepare a complex and progressive 6-month programme of remediation of cognitive functions in patients treated either for schizophrenia or bipolar disorder. The programme encompasses three phases:

Phase 1 the intensive treatment phase occurs twice a week over a two-month period. Patients will be placed in the programme during hospitalization. The training will have a form of a group practice and individual training exercises. Computer-based methods will be applied along with pencil-and-paper method. In this phase, attention will be paid in particular to weakened areas which are considerably influenced by positive symptoms (especially the speed of processing and cognitive flexibility) in patients hospitalized for a psychotic disease, and in case of bipolar disorder patients, the training will be adjusted to the results gained from the previous neuropsychological examination.

Phase 2 the treatment phase takes place once a week over a two-month period. The participants placed in the programme come from the ranks of outpatients who have undergone the first phase. The objective of this phase is to optimize cognitive functions in everyday life circumstances. The training during this phase will be focused on the speed of information processing and cognitive flexibility, memory functions and control or executive functions. In addition, this phase will introduce a training of everyday skills that might be difficult for the patient to manage in connection with his or her disease (e.g. areas of social relationships or functional skills in the sense of planning of everyday activities). The training will be conducted on the premises of NUDZ [National Institute of Mental Health]. The participants will be informed of the use of "online remediation". For the rest of the week, the participants will accordingly practise the speed of information processing and flexibility, using the newly developed hardware "FlexiKog" (see Objective 3, Activity 1).

Phase 3 the after-treatment phase. This phase consists in a maintenance treatment in line with the objective to extend the effect of intensive training and to increase the independency of a person who has undergone the above training. Participants train three times a week for the period of two months. This phase is conducted from home. The training takes place online in NEUROKOG programme. The complex online programme consists of a set of games focused on all cognitive functions. The programme enables each patient to set up his or her personal account; a therapist is assigned to each patient. The patient and therapist communicate with each other via "online chat or e-mail messages directly inside the system." The patient will be notified by messages sent by the system if the patient does not train often enough. During this maintenance phase, all functions are trained at various levels, using the hardware FlexKog. The programme is currently tested on patients suffering from SCH and BD, including tasks that train inhibitory control.

Throughout the whole period, subjects learn new problem solving strategies, and practise metacognitive exercises and exercises oriented at social cognition.

Subjects: The focus group will comprise patients with diagnoses according to MKN F20 and F30. Their ages will range from 18 to 40. The control group will consist of people with a similar disease who will not undergo the intervention since they will be unable to participate in all of the three phases for personal reasons.

During the period of training in NUDZ, no person placed in any of the groups may participate in any other regular cognitive activity that might affect results of the research. There will be three examinations of cognitive functions: before commencement of the training, immediately after the termination thereof and after expiry of six months, when continuation of the effect will be monitored. Participants will be examined using a neuropsychological battery. Methods where a significant learning effect has been proven will be replaced with alternative versions in the following two measurements.

The efficacy of the programme will be measured before and after the termination of a six-month programme, and subsequently after another six-month period with the aim of verifying a long-term effect of the training. Repeated examinations will be conducted by means of a battery of cognitive tests and MRI imaging methods (chiefly spectroscopic measurement of the concentration of glutamate in prefrontal regions, functional connectivity of prefrontal cortex (PFC), activity of large neural networks and structural characteristics of PFC).

Activity 2 - Options of cognitive remediation by means of a progressive cognitive training for a mild cognitive impairment - Bartoš, Rodriguez

With the population of developed countries growing older, incidence of Alzheimer's disease (AD) is on the increase. Before this disease reaches the dementia phase, the patient goes through a phase of mild cognitive impairment (MCI), which usually encompasses several years. In the MCI stage, the patient is entirely self-sufficient; however, presence of the cognitive deficit may be objectively observed in such patient, at least in one cognitive domain, which usually regards early memory impairment, gradually intensified over time. The early phase of the disease affects in particular the episodic memory for recent events from the patient's own life, and only later the semantic memory is impaired (Seidl, Lueken, Thomann, Geider & Schröder, 2011). Apart from the memory impairment, also speech may be affected during the early stage (especially the ability to name objects), visual and spatial and executive functions, and the psychomotor tempo slows down. The MCI phase is preceded by a pre-clinical phase, which progresses asymptomatically in objective terms. Nevertheless, even in this phase, the patient may issue subjective complaints of his or her memory abilities. These persons are justified in requiring intervention processes from medical personnel.

The causal treatment of AD remains unavailable. AD is currently treated by two groups of symptomatic treatments, which may not stop the disease, but at least slow down a decline in memory abilities, improve the quality of life, extend the period of self-sufficiency and, at the same time, reduce the burden imposed on the patient's family and other carers (Bartoš and Roth, 2015): 1) inhibitors of acetylcholinesterase in the brain, 2) non-competitive NMDA receptor antagonists (memantine). Apart from the pharmacological treatment, a number of non-pharmacological treatments are applied. A suitable and timely intervention (in particular in form of a cognitive training and cognitive rehabilitation) may in some cases delay the progression in dementia, thus improving the quality of life of these patients. A cognitive training in MCI as such consists of two basis components: restorative (regeneration of premorbid functioning of cognition) and compensatory (efforts to ensure that a loss of functioning of cognition has as

little impact on the patient's practical life as possible). A more intensive effect is achieved by the restorative component (Sitzer, Twamley et Jeste, 2006), which typically includes various practical exercises aimed at strengthening of individual cognitive functions. In case of persons suffering from MCI due to AD, the most effective exercises are those that focus on training of memory, especially if more elements are targeted (such as short-term, long-term, visual, verbal memory) (Rap, Brenes et Marsh, 2010). As a suitable method of training of the short-term memory for amnestic MCI patients, Herrera, Chambon, Michel et al (2012) refer to a mechanism of progressive prolongation of the interval over which the material acquired should be recalled. Even though the patients in the above programme trained recalling from memory only by means of recognition, they showed an improvement in free recall at the end of the programme. According to Willis, Tennstedt, Marsiske et al. (2006), even untrained elements of cognition are improved, but the above-named authors point out that this transmission works only in the framework of one domain only (e.g., the semantic memory may improve by strengthening of the episodic memory, but it is probable that executive functions will not be improved). The aforesaid implies that to train more cognitive domains is necessary in the scope of a complex training. The efficacy of generally formed cognitive trainings in comparison with strictly specialized trainings is also confirmed by other studies (e.g. Sitzer, Twamley et Jeste, 2006). The mechanism of effects of a restorative cognitive training is usually perceived in plasticity in the brain, as regards both healthy people and MCI people (Mahncke, Bronstone, et Merzenich, 2006). Compensatory methods include, inter alia, the use of various aids, such as a calendar, timer, or objects used for remembering different tasks. The study by Willis, Tennstedt, Marsiske et al (2006) maintains that a cognitive training may have a long-term effect. According to this study, which was conducted on healthy seniors, trained persons retain better functions of cognition than persons from the control group, specifically for a five-year period. However, with the interval from the period of the study getting longer, differences between both groups would fade away. An important condition for efficiency of a cognitive training is therefore its regularity and long-term perspective. This implies considerable demands on the development of suitable training methods. A clear advantage is presented in this case by computer programmes, which may be used in the home environment. Computer programmes are also beneficial for the feedback provided after each practice; this feedback has a motivational effect.

We intend to focus the project on the development of a complex programme of cognitive remediation on the premises of NUDZ [National Institute of Mental Health] and the development of an electronic version of memory exercises, which would be made available to senior persons, also for them to use at home. We believe that current training programmes do not adjust adequately to options of the senior population (size of texts, key information is not presented in a well-arranged manner), training games are not operated easily and are generally unaffordable. The objective of this part of the study is to create a database of cognitive exercises to comply with needs of the senior population, and these exercises will practise cognitive domains that are typically disrupted in case of incipient AD (i.e. chiefly various types of memory, speech, visual and spatial and executive functions and concentration). These exercises will be based on our clinical and research experience in the field of cognitive disorders. Needless to say, we have at our disposal a database of senior persons, with healthy and ill volunteers, who will help us verify the user accessibility to the programme for the senior population. The efficacy of the exercises such created will be verified in detail on a group of healthy seniors and a group of MCI seniors. Each research group will consist of at least 50 volunteers. The group of MCI patients will include persons who suffer from MCI due to AD, and patients with a high probability of development thereof in the future. In other words, this group will comprise amnestic MCI persons and multiple-domain MCI persons. Both groups of volunteers will be examined for cognitive functions by means of a neuropsychological battery at the beginning of the study.

Subsequently, these groups will undergo the same training programme, divided into three phases by training intensity:

The first phase will be engaged in an intensive training. The training will be conducted in groups twice per week for the period of two months. In this phase, persons will be trained by means of a software programme and also by the pencil-and-paper method under the supervision of a psychologist.

The second phase - treatment phase - will focus on training of persons once a week during another two-month period under the supervision of a psychologist. Activities of this phase follow up on the previous intensive training and seniors will be prepared for the third phase training.

The third phase is an after-treatment phase, during which researched persons will train three times a week from home on loaned tablets. At the end of the entire programme, the volunteers will undergo another psychological diagnostic of cognitive functions. The continuation of the effect will be monitored after the expiry of another six months, when the third examination of cognitive functions will be conducted. Methods for which a significant effect of learning has been proven will be replaced with alternative versions in the two subsequent measurements. A control group, also consisting of 50 persons, will be assigned to the group of healthy volunteers. Similarly to persons from the control group, these persons will go through all examinations of cognitive functions (i.e. at the beginning of their placement in the study, in six months' time, and after 1 year of their placement in the study). In the meantime, however, they will undergo no cognitive training. No control group will be assigned to the group of MCI persons for ethical reasons, since it would be incorrect not to provide treatment care to those who are in need of such treatment. After the research is concluded, healthy persons from the control group will be offered a participation in the same programme beyond the scope of the research proposal. In total, a minimum of 150 old-aged persons are expected to participate in this part of research. During the training in NUDZ, no person placed in any of the groups may participate in any other regular cognitive activity that might affect results of the research. In addition to the development of the training software as such, we expect that various compensatory aids will be created, especially on the basis of the use of new technologies. The efficacy of the programme will be measured before and after the end of the six-month programme and then subsequently after six months with the aim of verifying a long-term effect of the training. A repeated examination will be performed by means of a battery of cognitive tests and also MRI imaging methods (especially spectroscopic measurement of the concentration of glutamate in the central temporal lobe, connectivity of hippocampal formation (HPC), activity of large neural networks and structural characteristics - volume and connectivity of HPC).

Activity 3 - Augmentation (enhancer) of pharmacotherapy using non-pharmacological methods– influencing of glutamatergic transmission in target areas of the brain (stimulation methods - rTMS, tDCS)

Stimulation methods are new procedures used for the treatment of selected psychiatric diseases (e.g. for the treatment of pharmacoresistant depression). These are non-invasive, painless methods working on the principle of a long-term potentiation resulting in reinforcement of synaptic connections. The repetitive transcranial magnetic stimulation (rTMS) is a neurophysiologic technique to induce an electrical current in the brain tissue by a magnetic field that goes through the soft tissue and skull safely and painlessly. In rTMS, stimuli are applied to the same area of the brain several times per second continuously for a period of several seconds. Procedures might differ in the number of stimuli per second, strength of stimuli, duration of stimulation, interval between the individual series (trains) of stimuli, total

number of series and total number of stimuli in the given session and the position of the brain against the coil. For schizophrenia patients, this method is traditionally verified in research especially in order to mitigate aural hallucinations or reduce the impact of the cognitive deficit. Results of current studies vary to a great extent; cognition was strengthened in some groups of patients; however, certain studies have found no effect on cognition in connection with the application of rTMS. This heterogeneity of results may be caused by different methodologies. For bipolar disorder patients, stimulation methods are most often used to mitigate manic or depressive symptoms. Current work tries to identify a suitable place of stimulation which would bring a long-term effect.

Transcranial direct-current stimulation (tDCS) modulates the neuronal activity of large-scale networks, or cortical excitability, by delivering a low direct current (0.5-2mA) between electrodes on the scalp. The passing current influences the membrane potentials depending on the polarity and position of electrodes. It has been shown that if an anode is positioned above or directly on the cortex, the subliminal stimulation results in an increase of spontaneous neuronal activity, whereas the use of a cathode induces a contrary phenomenon. Short-term changes are probably caused by non-synaptic mechanisms, when resting membrane potentials are depolarized. On the other hand, the long-term effect has been explained by changes of NMDA-receptor circuits, which are similar to the long-term potentiation and long-term depression (LTP and LTD). The continuation of the effect of tDCS stimulation is greatly conditional on the intensity and duration of stimulation, and it appears that regular application (on a weekly basis) may extend the continuation of the stimulation effect and increase significantly the positive effect on behavioural manifestation of the underlying disease.

In connection with the reinforcement of cognitive functions, the area of dorsolateral prefrontal cortex (DLPFC) is stimulated in patients with a psychotic disease or a bipolar disorder. The level of cognitive functions is most often measured before and after the application of stimulation methods. Cognitive training is either not conducted at all, or takes place outside of sessions. An interconnection of these two approaches shows as the most effective method, i.e. the performance of cognitive tasks directly during stimulation, which gives rise to a complex remediation. In our study, we intend to stimulate the area of DLPFC using rTMS, with 20 sessions held during a four-week period. High-frequency stimulation (10Hz) would be applied. For tDCS, current studies have shown as adequate 15 sessions in 3 weeks, with stimulation of 1-2mA.

The efficacy of a remediation programme that makes use of a combination of stimulation methods and a cognitive training will be measured before and after the termination of the programme, and subsequently after six months with the aim of verifying a long-term effect of the training. A repeated examination will be carried out by means of a battery of cognitive tests and MRI imaging methods (chiefly spectroscopic measurement of the concentration of glutamate in prefrontal regions, functional connectivity of prefrontal cortex (PFC), activity of large neural networks and structural characteristics of PFC).