Research objective 3 - Development of new methods using virtual reality for a cognitive remediation for neuropsychiatric disorders in connection with the glutamatergic transmission

<u>Activity 1 - Development of applications for remediation of a disrupted speed of information processing</u> (flexibility, psychomotor tempo, cognitive coordination)

The speed of information processing is related to a psychomotor tempo, which is usually affected in case of a number of neuropsychiatric disorders, but there also exists a connection with the ability respond flexibly to changes and to coordinate cognitive skills when solving more complex tasks. The deficit of cognitive coordination at the level of cell and neuronal structures is related to glutamatergic transmission and is typically disrupted in case of a number if diseases (SCH, BD, MCI, AD and OCD). Accordingly, our objective is to develop a set of tasks targeted at training of the speed of information processing and metal flexibility.

A certain portion of these tasks is to use the technology of virtual reality (VR), which, in comparison with simple computer tasks, enables its user to create environments similar to if not comparable with the real environment. It is our experience of "being present in VR" that helps us forget that the situation we are in is a test only. It is therefore possible to gain a better insight into the client's typical behaviour and, as a result, to influence and train the client more intensively. Moreover, we have a full control over the form and complexity of presented stimuli and over the measurement of the client's answers. The aim is to develop tasks targeted at the speed of processing and mental flexibility, with an increasing complexity of the environment and a growing demand factor (e.g. the speed of presentation of stimuli and frequency of changes that the patient must adjust to).

In addition to VR tasks, the project objective consists in the development of a hardware tool for training the flexibility and speed of processing of information - FLEXIKOG. This tool will allow for an efficient training by means of simple signalling elements and controllers of the connection of visual, aural and tactile modalities and their interconnection with the coordination of motor abilities.

Activity 2 - Development of virtual games for a cognitive training with a focus on memory functions

The deficit of a declarative memory is a part of the complex cognitive deficit mainly with respect to schizophrenia, bipolar disorder, mild cognitive impairment and Alzheimer's dementia. This deficit is closely connected with glutamatergic dysregulation in the area of hippocampal formation and prefrontal cortex, and, as such, affects both the learning process and recall of information from memory as a consequence of a disrupted consolidation. What is more, the learning process is strongly disrupted due to the disruption of executive functions in form of cognitive strategies applied to the arrangement of material remembered. The memory deficit often affects both verbal and audio-visual components.

A targeted therapy of the deficit of memory functions therefore plays a key role in remediation programmes of the aforementioned diseases. Our objective is to develop a set of memory tasks in virtual reality, with a focus on training of the declarative memory. We intenci to develop already conceived methods that concentrate on training of the verbal memory (shopping in a virtual supermarket using a shopping list) or the episodic-type memory for episodes experienced in everyday life (what happened, when and where). In addition, we will prepare tasks for training of the spatial memory and navigation in the virtual space of a hospital and the whole city. All types of tasks will be based on the principie of a progressive increase in the level of demands in line with performance of individual patients.

Furthermore, our intention is to focus on tasks that require the transmission of information among the individua! sensual modalities, where, by way of example, information is communicated verbally (a list of





words), recalled visually (by a selection from a set of presented objects, and similar). This process will secure the interconnection of both hemispheres in the processes of learning and recall. Each task will be developed in several variants of the virtual environment, ranging from an environment of a small fiat or office to a complex environment of a virtual town. This approach will ensure that complexity, i.e. also cognitive demands of the environment where learning is conducted, will grow. Another beneficial contribution of alterations of a virtual environment is that motivation of a trained patient is retained during a repeated presentation of tasks. In addition, we intenci to adjust the load purposely and accurately in line

with requirements of a trained person and increase the same gradually in order to ensure that his or her motivation is not lost. Another valuable advantage of VR technology is the increase in ecologic validity, which represents the ability to transfer the skills learnt during rehabilitation in a virtual environment to a practical life.

<u>Activity 3 - Development of new methods for a cognitive training for obsessive-compulsive type disorder</u> with a focus on inhibitory control

The typical feature of the obsessive compulsive disorder is presence of compulsive thoughts obsessions and compulsive behaviour - compulsions. However, the effectiveness of traditional monoaminergic pharmacotherapy is normally insufficient for reaching a complete remission of OCD patients. Pharmacotherapy is therefore combined with non-pharmacologic methods, in particular the cognitive behaviour therapy (CBT). At the forefront, there is also glutamatergic dysregulation in OCD, described mainly in the region of anterior cingulate (ACC), which results in disruption of inhibitory control in OCD, and for this reason, it probably leads to development of typical symptoms (obsessions and compul sions). Our primary objective is therefore to develop techniques oriented at inhibitory processes and cognitive flexibility in OCD with the aim of increasing the efficacy of traditional CBT programmes. Since the inhibitory control is disrupted also in case of a number of other anxiety disorders, and the bipolar affective disorder too, the developed methods may be used for other diagnostic groups as well.

Consequently, the aim of this activity is to develop tasks in VR that would purposefully influence the ability to inhibit undesired responses. For this purpose, a set of tasks will be prepared to train the inhibitory control during a response to simple stimuli, where the task of a trained person is to respond to most of the presented stimuli and to refrain from responding to a specifically selected type of stimuli ("Go/no-to tasks"). These tasks will progressively increase the range of complexity, beginning from responses to simple stimuli and proceeding to tasks requiring making a decision between several types of stimuli and selecting an adequate answer. Moreover, certain tasks will represent a complex exposition therapy, in form of dreaded situations and stimuli, specific for a certain type of OCD (such as a fear of dirt and infection, need for symmetry, checking repeatedly if electrical appliances are switched off, etc.). These complex tasks performed in a virtual space (household, workplace, town) will gradually present a specific situation feared by the given patient, with the aim of suppressing a stress-induced behavioural answer of the patient (compulsion).

Supplementary methods using VR technologies will be incorporated in the on-going therapeutic programme of Department 1 and daily care centre 1, establishment NUDZ [National Institute of Mental Health], which programme is conducted in a closed group of no more than 19 participants over a six and a half-week programme. The programme is based on a group cognitive and behavioural therapy, involves also life-experience groups and is complemented by a practice of assertiveness, ergotherapy and motor therapy. A group cognitive and behavioural therapy systematically focuses on working with manifestations of stress, anxiety and depression. The main treatment method for OCD patients is to expose them to



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triggers, with subsequent inhibition of compulsion, ritual or neutralizati on. Subject to the condition of individua! patients, the group CBT is completed with rational pharmacotherapy, which reflects modern procedures in the treatment of anxiety disorders and OCD. After the therapy is completed, a part of patients will be placed in a follow-up programme, enabling them to continue using VR techniques within NUDZ or from home for the next two months.

Moreover, the study is to evaluate the effect of the combined BT and cognitive training in comparison with the CBT traditional programme. The progress in treatment is monitored every week using subjective scales - Beck's Depression Inventory (BDI) and Anxiety Inventory (BAi), patients with obsession compulsive disorders are evaluated at the beginning and at the end by Y-BOCS questionnaire (Young - Brown scale for evaluating obsessions and compulsions). A group of ODC patients undergoing the combined CBT therapy with inhibition training will be compared with a group of patients who go through the CBT therapy only, and a control group of healthy volunteers. The efficacy of the programme will be measured before and after the six-month programme and subsequently after another six months with the aim of verifying a long-term effect of training. A repeated examination will be carried out by means of a battery of cognitive tests and MRI imaging methods (in particular, spectroscopic measurement of glutamate in the region of anterior cingulated (ACC), connectivity of ACC, activity of large neural networks and structural characteristics - volume and connectivity of ACC).



