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Remediace kognitivního deficitu u neuropsychiatrických poruch pomocí úloh ve virtuální realitě

Cognitive remediation using virtual reality in neuropsychiatric disorders

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Abstract

Theoretical background: This dissertation investigates the feasibility of virtual reality (VR) for cognitive remediation in neuropsychiatric patients. The main goal was to create VR tasks appropriate for this purpose, assess the characteristics of the applied VR media, and investigate the validity and efficacy of the developed program in the target population. **Method:** In Study 1, healthy seniors (*n* = 36) and young adults (*n* = 25) participated in a newly developed Virtual Supermarket Shopping Task (VSST) in immersive VR (IVR) or non-immersive VR (non-IVR) to investigate their characteristics. Study 2 assessed validity (*n* = 21) and reliability (*n* = 8) of a novel VR task focused on psychomotor speed called Flies. In Study 3, VSST was administered to 20 patients with schizophrenia (SZ) and 20 healthy controls (HC) to investigate its validity. Finally, in Study 4, 28 patients with schizophrenia or depression participated in the proposed VE program and standard paper-pencil remediation approach to investigate feasibility and efficacy. **Results**: In Study 1, the seniors performed significantly worse in IVR than in non-IVR, cognitive performance in young adults was stable across different VR media, the young adults preferred IVR over non-IVR. Study 2 found a significant correlation between the Flies and standard cognitive measures, and the test-retest reliability was above 0.7. In Study 3, the patients' performance in VSST was significantly worse than in HC in all VSST measures, and we reported significant correlations with standard metrics of delayed recall. In Study 4, neither standard treatment nor VE program resulted in improvement in standard cognitive measures. However, patients significantly improved in the VE task and rated both programs as beneficial and enjoyable. **Conclusions:** VR offers specific advantages valuable for remediation purposes, as it is the ability to track participants' performance, automatic difficulty adaption, or the possibility to simulate real-life scenarios. Nevertheless, to fully capitalize on the VR potential, the intervention approaches should reflect the VR affordances and cognitive remediation principles.

Abstrakt

Teoretická východiska: Tato práce zkoumá obecnou uplatnitelnost virtuální reality (VR) pro kognitivní remediaci u neuropsychiatrických pacientů. Hlavním cílem práce bylo vytvořit VR úlohy vhodné pro tento účel, posoudit vlastnosti různých VR platforem a stanovit validitu a efektivitu vyvinutého programu u cílové populace. **Metoda**: Ve studii 1 se zdraví senioři (*n* = 36) a mladí dospělí (*n* = 25) zúčastnili nově vyvinuté úlohy Virtual Supermarket Shopping Task (VSST) v imerzivní VR (IVR) nebo neimerzivní VR (non-IVR) za účelem zkoumání jejich charakteristik. Studie 2 hodnotila validitu (*n* = 21) a spolehlivost (*n* = 8) Much, nové VR úlohy zaměřené na psychomotorickou rychlost. Ve studii 3 byl VSST administrován 20 pacientům se schizofrenií (SZ) a 20 zdravým kontrolám (HC), aby se vyhodnotila jeho validita. Ve studii 4 se 28 pacientů se schizofrenií nebo depresí zúčastnilo VE programu a standardního programu tužka-papír, aby byla ověřena uplatnitelnost a efektivita obou metod. **Výsledky**: Ve studii 1 si senioři vedli výrazně hůře v IVR než v non-IVR, kognitivní výkon u mladých dospělých byla stabilní napříč platformami, mladí dospělí preferovali IVR před non-IVR. Studie 2 zjistila významnou korelaci mezi Mouchami a standardními kognitivními testy a test-retest reliabilita přesahovala hodnotu 0,7. Ve studii 3 byl výkon pacientů ve VSST ve všech VSST metrikách výrazně horší než u HC a zároveň VSST významně korelovala se standardními testy oddálného vybavení. Ve studii 4 nevedla ani standardní léčba ani program VE ke zlepšení sledovaných kognitivních funkcí. Pacienti se však výrazně zlepšili ve VE úkolu a oba programy hodnotili jako prospěšné a zábavné. **Závěry**: VR nabízí specifické výhody cenné pro účely kognitivní remediace, například schopnost sledovat výkon účastníků, automatické přizpůsobování obtížnosti nebo možnost simulovat scénáře ze skutečného života. Aby však bylo možné plně využít potenciál VR, intervence využívající VR by měly odrážet možnosti VR společně s principy kognitivní remediace.

List of abbreviations

AD – Alzheimer's disease

ADHD – Attention deficit hyperactivity disorder

BAI – Beck Anxiety Inventory

BD – Bipolar disorder

BDI – Beck Depression Inventory

CEN – Central executive network

CPT – Continuous performance test

DMN – Default mode network

ES – Effect size

HC – Healthy control

HMD – Head-mounted display

IVR – Immersive virtual reality

LM – Logical memory

MDD – Major depressive disorder

ND – Neuropsychiatric disorder

NMDA - N-Methyl-D-aspartate

Non-IVR – Non-immersive virtual reality

OCD – Obsessive-compulsive disorder

VE – Virtual environment

VR – Virtual reality

VSST- Virtual Supermarket Shopping Task

RAVLT – Rey Auditory Verbal Learning Test

SD – Standard deviation

SN – Salient network

SRT – Simple reaction time

SZ – Schizophrenia

WMS – Wechsler Memory Scale

1. Introduction

Neuropsychiatric disorders (ND) are currently among the diseases with one of the highest Global Burden of Disease resulting in patients' reduced quality of life, disability, and premature mortality (Rehm & Shield, 2019). Neuropsychiatric disorders lie on the border of neurological and psychiatric illness and can be classified as mental disorders with etiology in the disruption of nervous systems (Hyman, 2008). Typical examples of neuropsychiatric disorders are schizophrenia, bipolar disorder, major depressive disorder (MDD), attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), or Alzheimer's disease (Hyman, 2008; Stuchlik & Sumiyoshi, 2014). Neuropsychiatric disorders are typically highly prevalent, have a strong heritability component, onset at a young age, or have relapse-remitting courses (Hyman, 2008). Furthermore, cognitive impairment was shown to be a core symptom of many ND, e.g., schizophrenia, Alzheimer's disease, or OCD (Stuchlik & Sumiyoshi, 2014). Due to the rising prevalence, MDD is now the leading cause of mental health-related disease burden, currently affecting around 6 % of the population worldwide (Bromet et al., 2011). Schizophrenia has a prevalence of 1 %, but its chronic, relapse-remitting course and profound neurocognitive deficit make it one of the most burdening mental diseases (Charlson et al., 2018).

Cognitive functions play a crucial role in our everyday lives as they enable us to successfully adapt to constantly changing environments (Sternberg, Sternberg, & Mio, 2012). Cognitive processes encompass various psychological functions, including attention, perception, speech, executive functions, and memory abilities. Unfortunately, our cognitive abilities can be negatively affected not only by various neuropsychiatric, neurological, or even somatic diseases but also during physiological processes of aging (Harada, Natelson Love, & Triebel, 2013).

Cognitive impairments vary in their extent (affecting more functions) and magnitude (how severely the function is impacted). Memory abilities are especially vulnerable to impairment as significant memory deficits are present in heterogeneous neurological and mental disorders including schizophrenia, (Achim & Lepage, 2005; Forbes, Carrick, McIntosh, & Lawrie, 2009), mood disorders (Emre Bora & Pantelis, 2015; Rock, Roiser, Riedel, & Blackwell, 2014), obsessive-compulsive disorder (Olley, Malhi, & Sachdev, 2007), mild cognitive impairment (Costa, Caltagirone, & Carlesimo, 2011), Alzheimer disease (Bäckman, Jones, Berger, Laukka, & Small, 2005; Celone et al., 2006), Parkinson disease (Whittington, Podd, & Kan, 2000) or multiple sclerosis (Lafosse, Mitchell, Corboy, & Filley, 2013).

As cognitive functions enable us to navigate in our daily life and manage our social interactions, their impairment can significantly reduce the quality of life not only in neuropsychiatric disorders, such as schizophrenia (Alptekin et al., 2005; Savilla, Kettler, & Galletly, 2008) and major depressive disorder (Toyoshima et al., 2019) but also in the aging population (N. L. Hill et al., 2017). Furthermore, current findings imply that deficits in cognitive functions and social cognition are strong predictors of psychosocial functioning. Psychosocial functioning includes a different aspect of daily living, e.g., community functioning, independent living, social interaction, or work-life (Sanchez-Moreno et al., 2009) and is often disrupted in patients with schizophrenia (Green, 1996; Green, Kern, & Heaton, 2004) and with mood disorders (Green, 2006; Jiménez-López et al., 2018; Simonsen et al., 2010; Torres et al., 2011).

Currently, cognitive remediation is considered a method of choice for cognitive intervention in ND (Lejeune, Northrop, & Kurtz, 2021; Revell, Neill, Harte, Khan, & Drake, 2015; Wykes, Huddy, Cellard, McGurk, & Czobor, 2011) typically using standard paper-pencil approaches. However, the transfer of these rehabilitation programs into patients' real life has been questioned (Moreau & Conway, 2014; Neisser, 1978). The greater availability of new technological approaches, e.g., virtual reality (VR), together with the need for more ecologically valid approaches, resulted in skyrocketing application of VR in cognitive neuroscience, including cognitive assessment and remediation (Bouchard & Rizzo, 2019; Riva, Wiederhold, & Mantovani, 2019).

Therefore, this thesis focused on investigating the feasibility and efficacy of VR in cognitive remediation in patients with NDs. It explored how the program should be designed, what media should be used, and how the target population perceives it compared to standard treatments.

1.1. Cognitive deficit in schizophrenia and mood disorder

Schizophrenia (SZ) is a complex chronic psychiatric illness with onset in early adulthood mainly manifested by the presence of so-called positive and negative symptoms (Kahn et al., 2015). Positive symptoms include hallucinations, delusions, or disorganized speech and behavior; negative symptoms consist of, e.g., social withdrawal, abulia, anhedonia, or affect flattening (Khoury, Kogan, & Daouk, 2017). Besides positive and negative symptoms, neurocognitive deficit represents a core syndrome in schizophrenia pathology, which is closely related to the functional outcome in SZ patients (Reichenberg et al., 2014). Some findings suggest that neurocognitive deficits are good candidates for the schizophrenia endophenotype (Snitz, Macdonald, & Carter, 2006). Endophenotype is a reliable, measurable, and heritable illness phenotype (Gottesman & Gould, 2003), enabling more successful identification of genes associated with the specific illness (Flint & Munafò, 2007).

The cognitive impairment in SZ can be reported in the premorbid phase of the illness – even years before the manifestation of clinical symptoms (Keshavan et al., 2010; Sørensen, Mortensen, Parnas, & Mednick, 2006), and it further progresses with clinical symptoms. The deficits are believed to stabilize during the first psychotic episode (E. Bora, Binnur Akdede, & Alptekin, 2017; Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009).

Concerning the magnitude and extent of the deficit, the impairment is considered large, effect size (ES) > 0.8 (Fioravanti, Bianchi, & Cinti, 2012) and broader than deficits reported in other psychotic disorders (Sheffield, Karcher, & Barch, 2018) - affecting all cognitive domains. Verbal memory, executive functions, and processing speed are argued to be the most impaired subdomains (E. Bora et al., 2017; Dickinson, Ramsey, & Gold, 2007; Mesholam-Gately et al., 2009). Deficits in verbal memory and processing speed were reported as the most prominent cognitive impairment in premorbid phase and ultra-high risk participants (Emre Bora & Pantelis, 2015; Keshavan et al., 2010). Impaired processing speed can further deteriorate verbal memory abilities, impacting the rehearsal loop (Brébion et al., 2000). The magnitude of cognitive deficit together with the presence of negative symptomatology has an adverse effect on patients psychosocial functioning also presented in impaired activities of daily living (ADL), for instance, shopping, food preparation, or handling finances (Bowie et al., 2008; Green, 1996; Samuel, Thomas, & Jacob, 2018).

Major depressive disorder (MDD) is a debilitating disease characterized by depressive mood, diminished interest, and loss of pleasure (Khoury et al., 2017). Besides vegetative symptoms, e.g., loss/increase of appetite or disturbed sleep, impairment in cognitive functions is a common manifestation of MDD (Otte et al., 2016). Psychotic features can accompany moderate and severe MDD, e.g., hallucinations or delusions (Dold et al., 2019; World Health Organization, 2004), which further aggravate the magnitude of cognitive deficits (Schatzberg et al., 2000; Sheffield et al., 2018). On average, the neurocognitive impairment in MDD is less severe in comparison to schizophrenia (Hammar & Ardal, 2009; Liang et al., 2018; Sheffield et al., 2018).

The meta-analysis by Rock et al. (2014) confirmed moderate deficits in memory, executive functions, and attention. Furthermore, according to the same study, these impairments are also present in patients in remission (Rock et al., 2014). Patients diagnosed with mood disorders, including bipolar disorder and MDD, suffer from profound deficits in verbal memory similar to schizophrenia patients (Mesholam-Gately et al., 2009; Rock et al., 2014).

1.2. Cognitive decline in healthy aging and its common pathways with neuropsychiatric disorders

Due to demographic aging (Corselli-Nordblad & Strandell, 2020), cognitive decline in the elderly is a pressing issue, especially in the USA and European Union. Furthermore, the cognitive decline pattern, with memory deficit being the most prominent (Rönnlund, Nyberg, Bäckman, & Nilsson, 2005) and most concern in the complaints by elderly (Harada et al., 2013), is similar to the impairment pattern in NDs. Apart from memory deficit, most of our fluid cognitive abilities, especially processing speed, executive functions, attention, visuospatial abilities, face age-related cognitive decline before 60 years (Salthouse, 2009).

This deterioration is linked to the brain changes that occur during the aging process. Primarily, the volume of grey matter is progressively reduced with aging (Hafkemeijer et al., 2014). This is especially prominent in the structures responsible for high cognitive functions, e.g., hippocampus or posterior cingulate cortex associated with default mode network (DMN) (Raichle, 2015). Disturbance in the DMN structures, responsible for the resting state of the brain, was repeatedly reported in neurodegenerative disorders (Seeley, Crawford, Zhou, Miller, & Greicius, 2009) and NDs, including mood disorders (Wise et al., 2017) and schizophrenia (Hu et al., 2017). DMN functional connectivity was repeatedly linked to the robustness of cognitive impairments (Petrella, Sheldon, Prince, Calhoun, & Doraiswamy, 2011; Rocca et al., 2010). Some studies even imply that the disruption in DMN can distinguish patients with mild cognitive impairment (MCI) who are at risk of developing Alzheimer's disease (Eyler et al., 2019). In SZ, not only disruption in DMN activity but also in the central executive network (CEN) and salience network (SN) was observed (Nekovarova, Fajnerova, Horacek, & Spaniel, 2014), emphasizing the role of the triple brain network. In contrast to the DMN, the CEN is active when mental activity focuses on external stimuli (for example, when performing a cognitively demanding task). Third, the SN ensures the "switching" between DMN and CEN and their anti-correlation activity. Activation of CEN typically reduces DMN activity and vice versa (Spaniel et al., 2016). The model shows that dysfunctional switching between the three main networks (Nekovarova et al., 2014).

Healthy aging also leads to changes in levels of specific neurotransmitters linked to normal cognitive functioning, e.g., serotonin (Buhot, Martin, & Segu, 2000) and dopamine (Nieoullon, 2002). A progressive decline in dopamine levels was linked to cognitive and motor functioning deficits in healthy aging (Bäckman, Nyberg, Lindenberger, Li, & Farde, 2006). Together with brain-derived neurotrophic factors, serotonin plays an essential role in synaptogenesis and neuroplasticity (Mattson, Maudsley, & Martin, 2004). Disruptions in dopamine and serotonin, together with glutamate and its N-methyl-d-aspartate (NMDA) receptors, are a crucial part of schizophrenia pathophysiology as well.

1.3. Pharmacology treatment of cognitive deficit

Standard medical intervention in schizophrenia results in a successful decrease of positive symptoms is antipsychotic medication (Huhn et al., 2019; Leucht et al., 2009; Uchida, Suzuki, Takeuchi, Arenovich, & Mamo, 2011). Nevertheless, according to the current findings, the first-generation antipsychotics (e.g., haloperidol or chlorpromazine) that successfully treat positive symptoms do not affect patients' cognitive functioning (Davidson et al., 2009). Similarly, despite the optimistic preliminary findings concerning that the second generation of antipsychotics (e.g., clozapine or olanzapine) would be able to restore cognitive impairment in SZ, the results show only a small effect of atypical antipsychotics (ranging from 0.12 to 0.26) (Keefe et al., 2007; Leucht et al., 2009). Thus, in contrast to the magnitude of the neurocognitive deficit described above, this effect cannot sufficiently improve patients' quality of life. Furthermore, a more recent meta-analysis showed no significant difference between the second and first antipsychotic on its impact on cognitive functioning (Nielsen et al., 2015).

MDD is commonly treated with antidepressants. Even though the positive effect of antidepressants on depressive mood is mediated through enhancing neurogenesis and plasticity pathways signaling (D'Sa & Duman, 2002), their impact on cognitive functioning is only minimal (Prado, Watt, & Crowe, 2018) or none (Rosenblat, Kakar, & McIntyre, 2015; Shilyansky et al., 2016). The most significant effect was reported for selective serotonin reuptake inhibitors (SSRIs) (Shilyansky et al., 2016). Nevertheless, as Keefe et al. (2017) proposed, these small improvements could also be attributed to the practice effect. Experimental application of pharmacotherapy approved for the Alzheimer's disorder treatment (i.e., cholinesterase inhibitors, e.g., donepezil or NMDA receptor antagonist memantine) did not prove to improve cognitive functions in schizophrenia or MDD (Keefe et al., 2008; Sani et al., 2012).

1.4. Virtual reality in cognitive assessment

Virtual reality (VR) is a digitally rendered three-dimensional representation of the virtual environment (VE) (Lombard & Ditton, 1997). VR enables researchers to create complex, authentic, and possibly highly interactive virtual experiences to assess real-time cognitive, emotional, behavioral, or even physiological reactions (Bouchard & Rizzo, 2019). As shown by Rizzo and Buckwalter's review from 1997, VR is not, against common presumptions, an entirely new tool in assessment and rehabilitation. Even though VR has been present in rehabilitation for more than 30 years, the constant development of VR technology implies a need for continuous replication of the published findings. Nevertheless, the application of VR in psychiatry is slightly more recent (Bisso et al., 2020; Hejtmánek & Fajnerová, 2019; Parsons, 2015; Parsons, Gaggioli, & Riva, 2017).

One of the reasons for such an increase in VR application in cognitive neuroscience is the assumed low ecological validity of standard paper-pencil methods in neuropsychological assessment, rehabilitation, and research. This issue was firstly introduced by Neisser (1978) and led to further discussion in the scientific community (Banaji & Crowder, 1989; Chaytor & Schmitter-Edgecombe, 2003; Kothgassner & Felnhofer, 2020). High hopes are put into the VR application in cognitive neuroscience to solve the need for high internal validity (tied to controlled laboratory setting) and to increase ecological validity (Kothgassner & Felnhofer, 2020; Parsons, 2015; Parsons et al., 2017). Thus VR found its place in the neuroscientific research and clinical application as it allows us, for example, to:

- Investigate complex emotional and cognitive processes with high ecological validity and in a highly controllable environment while measuring behavioral or physiological outcomes. VR enables precise stimuli presentation together with real-time behavior recording. For example VR was successfully applied in the research of human navigation (Hejtmánek, Oravcová, Motýl, Horáček, & Fajnerová, 2018; Weibel et al., 2018) or memory abilities (Reggente et al., 2018).
- Simulate Activities of Daily Living (ADLs; e.g. doing groceries or cooking) and assess patients' real-life functioning (Corriveau Lecavalier, Ouellet, Boller, & Belleville, 2018; Ouellet, Boller, Corriveau-Lecavalier, Cloutier, & Belleville, 2018). For example, Greenwood

(2016) created a VR supermarket for the assessment of ADLs in patients with schizophrenia. According to the validity study, the performance in the VR supermarket significantly improved the prediction of the real-life behavior made by standard cognitive measures (Greenwood et al., 2016). Furthermore, the real-time recording of the participants' performance allows us to conduct a further qualitative assessment, for example, to investigate disruption in problem-solving or mnemonic strategies (Josman, Schenirderman, Klinger, & Shevil, 2009).

- Mimic behavioral tasks used in animal models of NDs in complex VEs and develop models with higher predictive validity (Fajnerová et al., 2014).

1.4.1. Immersive and non-immersive virtual reality

VEs can be presented in a low or high level of immersion. Immersion can be understood as a technological quality of used media (Cummings & Bailenson, 2015); the higher the quality of the system, the higher the level of immersion (for example, the size of the field of view or the graphic quality). Immersive VR (IVR) is almost interchangeably used with head-mounted displays (HMDs) technology; in contrast, non-immersive VR (non-IVR) corresponds to "flat screens," e.g., a desktop presentation using a laptop or monitor screen. Importance of immersion roots in the term presence – feeling of being present in the VE (Slater, Usoh, & Steed, 1994) that is reported to be higher in IVR (Cummings & Bailenson, 2015). Due to an increased sense of presence, IVR creates experiences that are very close to our real-life experiences (Blascovich & Bailenson, 2011).

Despite the theoretical benefits of HMD technology that are summarized in Table 1. The empirical findings of the impact of immersion on cognitive performance are inconclusive. Some studies show superior performance on behalf of IVR (Bowman, Sowndararajan, Ragan, & Kopper, 2009; Murcia-López & Steed, 2016) others result in better cognitive outcomes with non-IVR (Mania & Chalmers, 2001; Ruddle et al., 1999; Sousa Santos et al., 2009). More consistent results were found in usability, showing greater enjoyment and intrinsic motivation in IVR than non-IVR (Makransky, Terkildsen, & Mayer, 2019; Sousa Santos et al., 2009).

Table 1 Advantages and disadvantages of immersive (IVR) and non-immersive virtual reality (non-IVR) (adapted from (Plechatá, Nekovářová, & Fajnerová, 2021)**.**

Category	Description	Non-IVR	IVR
	Advantages		
VE environment	Realistic virtual environments enable training and assessment in real-life situations in a safe environment.	PARTIAL	YES
	Enable investigation of the neural correlates of task-related behavior and neuroplasticity changes as an effect of the therapy.	YES	PARTIAL
Interaction	Realistic and intuitive interaction	NO	YES
Stimuli control	Combination of the maximal control over the stimuli and realistic environment	PARTIAL	YES
	Engaging multiple sensory channels - making the experience more realistic	PARTIAL	YES
	Incorporating number, form or combination of stimuli which would not be possible in the real world	PARTIAL	YES
	Disadvantages		
Vision	Compression of estimated distances (depth perception)	YES	PARTIAL
	Narrow field of view (FOV)	YES	YES
	Distortion of angular declination (determining the angle between the visual target and the height of the viewer's eye) and restrictions of oculomotor cues	YES	PARTIAL
	Lack of binocular depth cues	YES	NO
	Faster fatigue and overloading of the visual apparatus	PARTIAL	YES
Vision/side effects	Discomfort is caused by the curvature of the lenses, which are primarily designed for eyes looking forward, as the head movement is used to control the rotation of FOV directly.	NO	YES
	Visual strain and dry eyes problem	YES	YES
Movement	Complete absence or only limited movement prevents the vestibular and proprioceptive system from receiving positional information	YES	PARTIAL
	Head/body rotations disconnected from rotations in the virtual environment	YES	NO
Side effects	Motion sickness is due to sensory conflict, the discrepancy between information coming from external (mostly visual information about motion in VR) and internal sources (proprioception and the vestibular system informing us of our position in the real world).	YES	YES

1.5. Cognitive remediation in neuropsychiatric disorders

Cognitive remediation is currently the method of choice for treating cognitive deficits in NDs, including schizophrenia or MDD. The terms cognitive remediation and cognitive rehabilitation are often used interchangeably. Cognitive remediation is more often linked to cognitive intervention in psychiatric disorders, especially schizophrenia (Wykes et al., 2011), and cognitive rehabilitation is commonly referred to the treatment of patients after stroke or traumatic brain injury (TBI) (Alashram, Annino, Padua, Romagnoli, & Mercuri, 2019). Cognitive remediation consists of systematic behavioral interventions aiming to improve cognitive functioning (Benedict et al., 1994; Medalia & Choi, 2009). As cognitive remediation often contains repetitive exercises, computerized cognitive remediation is a very suitable approach as it allows precise recording of participant's performance and automatized adaptation of difficulty (Medalia & Choi, 2009). The fact that the drill-practice approach is the most prevalent in clinical trials (Paquin, Wilson, Cellard, Lecomte, & Potvin, 2014), results in the increasing popularity of the computerized approach, as shown by a recent meta-analysis by Prikken et al. consisting of 24 studies (2019). Another cognitive remediation approach is strategy-based interventions, combining repetitive exercises with strategy learning and its generalization across the tasks (Wykes & Spaulding, 2011). Additionally, cognitive remediation can be divided into the restorative and compensatory approaches (Medalia & Choi, 2009), where restorative remediation adopts drill-practice techniques to remediate the impaired functions, and compensatory interventions focus on learning compensatory strategies. The meta-analysis by Prikker et al. (2019) shows that computerized remediation applying the drill-practice approach can effectively improve cognition in schizophrenia patients (ES ranging from 0.31 to 0.38). Wykes et al. (2011) found slightly more positive results reporting a moderate effect of cognitive remediation on global cognitive functioning (ES = 0.45). However, the most recent meta-analysis reports more conservative results of small to moderate (ES = 0.19-0.33) improvements (Lejeune et al., 2021).

Consistently with a critique of limited ecological validity of standard neuropsychological approaches, the standard drill-practice approach was linked with low impact on functional outcome in contrast with the strategy-based approach (McGurk, Twamley, Sitzer, McHugo, & Mueser, 2007; Prikken et al., 2019; Wykes et al., 2011).

The efficacy of cognitive remediation in MDD is not that well studied as in the schizophrenia population. However, according to a recent meta-analysis (Thérond et al., 2021), the improvement is slightly more significant in MDD patients than in SZ, showing effect sizes ranging from 0.3 to 0.6. Nevertheless, as only eight studies of heterogeneous methodology were included in the analysis, more evidence is needed to generalize these findings.

1.5.1. Virtual reality in cognitive remediation

The major challenge in cognitive remediation is the insufficient evidence of the transferability of the training outcomes in the patients' everyday life and the improvement of their functional outcomes (Jahn, Skovbye, Obenhausen, Jespersen, & Miskowiak, 2021; Prikken et al., 2019; Wykes et al., 2011). In addition, functional outcomes in NDs patients can be improved by accommodating training of everyday life skills and compensatory strategies in cognitive remediation (Jahn et al., 2021; Lejeune et al., 2021; Lewandowski et al., 2017).

Besides the benefits of computerized programs (i.e., precise task administration, stimulus presentation, automatic response recording, adaptive difficulty levels, etc.), VR enables presenting three-dimensional and complex VE and creating realistic training scenarios. According to Rizzo and colleagues (A. A. Rizzo, Schultheis, Kerns, & Mateer, 2004), creating an environment that looks like the real world and also incorporates its other characteristics and challenges of our everyday functioning can significantly improve the ecological validity of the training programs. Consequently, VR training could result in the more effortless transfer of the training outcomes in the real-life (Rose et al., 2000; Tieri, Morone, Paolucci, & Iosa, 2018). As mentioned above, VR can easily simulate ADLs and train everyday skills in a safe environment (Faria, Andrade, Soares, & Badia, 2016; Gamito et al., 2019), making a perfect media to bridge a gap between the training settings and real-life.

Another reason for applying new technologies in cognitive remediation is that many cognitive remediation programs fail to successfully motivate participants resulting in high attritions rates (Lewandowski et al., 2017). This can be a challenge, especially in patients with schizophrenia suffering from negative symptoms, including abulia and apathy (Barlati et al., 2018). VR, especially when designed in an interactive and gamified manner, can lead to highly engaging experiences that could motivate the patients to perform better in these programs (Jahn et al., 2021).

1.5.2. Current state and challenges

VR technology was proven to be especially suitable for motor rehabilitation in the TBI, and stroke patients, e.g., for balance training, showing promising results (Alashram et al., 2019; Corbetta, Imeri, & Gatti, 2015; Howard, 2017; Lee, Park, & Park, 2019). Later on VR was also applied in cognitive rehabilitation (Cano Porras, Siemonsma, Inzelberg, Zeilig, & Plotnik, 2018) with positive findings in healthy and pathological aging (García-Betances, Jiménez-Mixco, Arredondo, & Cabrera-Umpiérrez, 2015; La Corte, Sperduti, Abichou, & Piolino, 2019). Moreover, reviews confirm that the VR-based cognitive interventions result in a more positive attitude and increased motivation, especially in aging populations (N. T. M. Hill et al., 2017; La Corte et al., 2019). The VR application in the remediation of memory abilities in NDs and healthy aging are summarized in Table 2. The table is adapted from Plechatá et al. (2021), reporting only results for target populations.

Table 2 Summary of virtual reality-based cognitive interventions in neuropsychiatric disorders (Plechatá, Nekovářová, & Fajnerová, 2021)

Memory domain	Reference	Study sample	Training task	Technology/device	Control group/treatment	Results
visuospatial memory and verbal memory	Schreiber,1999	Mildly to moderately cognitively impaired adults (aged 65 years or above) alternately assigned to a training (*n* =7) and control group (*n* =7)	The VE tasks consisted of a simulation of real-life tasks simulated in a virtual environment of an apartment.	non-immersive/monitor and joystick	a chat with a psychologist to keep social stimulation comparable	The training group improved more on immediate recall and retention of topographical information. The control group showed neither improvement nor decline in performance.
verbal memory, free/cued recall, implicit/explicit learning	Hofmann et al., 2003	Patients with the diagnosis of probable AD (*n* = 9), patients with a major depressive episode (*n* = 9), healthy subjects (*n* = 10)	The VE training compromised of daily living activities. The participant had to find a predefined shopping route, buy three items, and answer ten questions.	non-immersive/touch-screen	control group N/A	Training resulted in a significant reduction of mistakes. Moreover, training effects were sustained until follow-up three weeks later. However, no significant improvement was found for the outcome measures of cognitive performance.
verbal and spatial memory	Optale et al., 2010	Older adults with memory deficits were randomly assigned to the VR group (*n* = 15) and control group (*n* = 16)	The VE training involved remembering taken routes and their orientation.	immersive/HMD and joystick	music therapy in the control group	VR group showed significant improvements in memory tests, especially in long-term recall and several other cognition aspects. In contrast, the control group showed a progressive decline.
semantic and episodic memory	Man, Chung & Lee, 2012	adults (65 years or above) with questionable dementia randomly assigned to VR group (n = 20) and therapist-led memory training group (*n* = 24)	The VR training included tasks to memorize certain items, place them in the right places, or search and buy requested items in a shop.	non-immersive/monitor and keyboard/joystick	therapist-led training similar to the VR, but with color-print images that matched the VR images	The results demonstrated positive training effects in both groups. The VR group showed more significant improvement in objective memory performance, and the non-VR group showed better subjective memory results.
prospective memory	Yip & Man, 2013	adults with acquired brain injury were randomly assigned to the VR group (*n* = 19) and control group (*n* = 18)	The VR training consisted of event-based tasks completed in a VR convenience store. The participants were required to remember and perform tasks in the VR store.	non-immersive/monitor and keyboard and mouse/joystick	reading and table games activities during the treatment phase	The VR group significantly improved in VR-based assessment and in the real-life prospective memory test, prospective memory measures, frontal assessment, and verbal fluency. No significant difference was found in any outcome measure in the control group.
working memory, visuospatial memory, and navigation	Gamito et al., 2014	stroke patients were randomly assigned to the desktop VR group (*n* = 8) and the HMD VR group (*n* = 9).	The VR training was compromised of daily living activities conducted in the virtual town.	non-immersive/monitor and keyboard and mouse + immersive/HMD	control group N/A	The results showed increased working memory and sustained attention from initial to final assessment regardless of the VR device used.

working memory tasks, visuospatial memory, recognition	Gamito et al., 2015	20 stroke patients were randomly assigned to the experimental group (*n* = 10) and the wait-listed control group (*n* = 10)	The VR tasks constituted of daily living activities, e.g., shopping or finding VE characters dressed in specific colors in a virtual town.	immersive/HMD and keyboard and mouse (not specified)	waiting list	The results showed significant improvements in attention and memory functions in the experimental group but not in the controls.
prospective memory	Mathews et al., 2016	15 stroke patients	The participants were taught visual imagery to improve memory. After that, participants practiced their memory skills using VE games where they could perform the tasks.	non-immersive/monitor and joystick	control group N/A	The prospective memory skills of participants have improved significantly after the treatment. The improvement was stable 4 weeks after training.
visuospatial memory and navigation	Amado et al., 2016	7 patients with schizophrenia	The VR training consisted of daily living activities conducted in VR town, e.g., shopping or memorizing the route to the supermarket.	non-immersive/monitor and joystick	control group N/A	The results showed improvement in attention, working memory, prospective and retrospective memory benefits. No improvement was found in planning.
verbal memory	Dehn et al., 2018	37 patients with depressive disorders were assigned to the VR-environment group (*n* = 21) and the desktop group (*n* = 19)	The VE training consisted of a VE simulation of grocery shopping.	non-immersive/the OctaVis - eight LCD-touch-screens surrounding participant and non-immersive/monitor	control group N/A	The results did not show significantly greater improvement using more immersive technology. Both groups improved in visuospatial memory; phasic alertness improved only in the desktop condition in contrast to mental rotation, which showed improvement only in the more immersive group.
working memory and auditory memory	Gamito et al., 2019	25 healthy participants in age 65–85	The VE training was compromised of several daily living activities, e.g. selecting ingredients to bake a cake, shopping, remembering news from TV.	non-immersive/monitor	control group N/A	A significant improvement was found in visual memory, attention, and cognitive flexibility. Results also suggest that participants with lower baseline cognitive performance levels improved most after these sessions.
working memory and navigation	Shema-Shiratzky, 2019	14 non-medicated school-aged children with ADHD	The VE training combined walking on a treadmill with cognitive tasks. The training focused on sustained and divided attention, navigation and memory.	non-immersive/motion capture camera, screen, and treadmill	control group N/A	There was a significant improvement in social issues and psychosomatic behavior after the training. Executive function and memory were improved post-training while attention was unchanged. Long-term training effects were maintained in memory and executive function.
verbal working memory and visuospatial memory	Park, 2019	26 adults aged 65 years and older diagnosed with MCI were randomly allocated into two VR group (*n* = 10) and in the control group (*n* = 11).	The VR training consisted of several tasks conducted in a virtual home setting scenario in four different rooms.	immersive/ HMD with hand tracking and heat cameras (augmented reality)	conventional computer-assisted cognitive training system	The results showed significant improvement in the VR group in comparison to the control group only in visuospatial working memory (d=1.14) but not in other measures of memory or different cognitive functions.

Step by step, VR is also implemented in cognitive remediation in psychiatric disorders (Dellazizzo, Potvin, Luigi, & Dumais, 2020; Jahn et al., 2021). Here we describe studies applying VR tasks in cognitive remediation in SZ and MDD patients:

La Paglia and colleagues performed two studies applying IVR in cognitive remediation in schizophrenia (La Paglia et al., 2016, 2013) with control groups attending psychotherapy. Both studies focused on attention (catching a virtual ball or picking up different flowers in the distracting environment) and executive functions (picking up a specific type of bottle while conducting a set of additional new activities). In the second study, a virtual supermarket task was also included in the training. In both studies, authors found improvement in both groups, control, and VR.

A non-IVR study by Amado et al. (2016) focused on training ADLs, e.g., shopping and memorizing spatial routes, in a complex virtual city. The authors reported significant improvement in attention, working memory, and prospective and retrospective memory. Nevertheless, the pilot study was conducted with only seven patients with no control group. Dehn et al. (2018) investigated the efficacy of a VR program designed to train grocery shopping in a group of patients with MDD. The training was administered to 37 participants who were randomly divided into more (eight LCD-touch-screens surrounding participants) and less immersive conditions (desktop). Both groups showed a significant increase in visuospatial memory. Nevertheless, phasic alertness increased only in the less immersive condition. Conversely, mental rotation improved more in the more immersive group.

As can be seen from reviewed studies, current findings bring only preliminary results. Moreover, the sample sizes are very small, with a relatively poor methodology of the majority of the studies. That also indicates a high to moderate risk of publication bias (Jahn et al., 2021).

2. Aims and objectives

According to current findings, cognitive deficits in neuropsychiatric disorders (NDs), especially in schizophrenia, major depressive disorder, and healthy aging, severely impact the functional outcome and quality of life. As available pharmacotherapy cannot sufficiently influence these deficits, non-pharmacological interventions, specifically cognitive remediation, are a method of choice. Despite the reported positive impact of the standard behavioral interventions on cognition, the transfer of these changes to functional outcomes is scarce. Virtual reality (VR) allows us to simulate daily life challenges and creating realistic scenarios with higher ecological validity. Despite the potential, the findings of the efficacy and feasibility of VR cognitive remediation for patients with SZ or MDD (Jahn et al., 2021) are just preliminary and not consistent.

This work aimed to study how VR can be successfully applied in the cognitive remediation of NDs. As the research on VR cognitive remediation was in its infancy at the beginning of this thesis, the first goal was to create VR tasks feasible for this purpose. The development required intensive testing of the designed program and standardization of the individual tasks in healthy populations. As the objective was to develop a program that would be applicable in different target populations (taking into consideration resources necessary for such a task), the tasks were standardized also in the healthy aging population. To shed more light on the discussion about the impact of different levels of immersion on cognitive performance, we have conducted a VR media comparison study of non-IVR and IVR versions of a virtual memory task. After successful standardization, testing in the targeted population was necessary to assess the validity and adjust program difficulty before launching the study with repeated exposure. Finally, it was essential to implement the developed program in cognitive remediation of target psychiatric populations to assess its feasibility and compare its outcomes with a standard paper-pencil program.

3. SECTION 1: DEVELOPMENT OF VIRTUAL TASKS AND VIRTUAL REALITY MEDIA COMPARISON

The main goal of this work was to design and develop virtual reality (VR) tasks to create a complex rehabilitation program for neuropsychiatric patients. A thorough literature review and testing were necessary in order to develop tasks that would be feasible for the targeted group and the clinical personnel. Thus, the first fundamental step was to apply the methods in healthy young adults and the elderly to investigate the program validity and understand which cognitive processes are involved when solving the tasks. The feasibility of the methods was tested together with applied media – immersive VR (IVR) and non-immersive VR (non-IVR) to understand its benefits and drawbacks. After developing the first model tasks focused on declarative memory, which is the most impaired cognitive function in neuropsychiatric disorders (NDs) and healthy aging, we present the following tasks designed as part of a complex training program.

Aims and goals:

- Development of VR tasks and their standardization in healthy young adults and seniors
- Feasibility of IVR and non-IVR media in memory assessment
- Memory performance in IVR and non-IVR media

3.1. Study 1: Age-related differences with immersive and non-immersive virtual reality in memory assessment

Published as: **Plechata**, A., Sahula, V., Fayette, D., & Fajnerova, I. (2019). Age-related differences with immersive and non-immersive virtual reality in memory assessment. *Frontiers in Psychology*, *10*, 1330. IF (2019) = 2.067

3.1.1. Materials and methods

3.1.1.1. Participants and procedure

Thirty-six seniors (23 females, *M* = 69.47; *SD* = 7.39; age range = 60-91) and 25 young adults (16 females, *M* = 25.4; *SD* = 5.13; age range = 19-39) voluntarily participated in this study. The participants performed VSST in two conditions with different levels of immersion according to the platform applied: HMD and desktop. During the experiment, we counterbalanced both the order of the platforms (HMD/desktop) and the two Virtual Supermarket Shopping Task variants (A/B - sets of the lists to remember) to minimize the practice effect on repeatedly measured performance.

Before the experiment, all participants were assessed using standard neuropsychological methods to evaluate their cognitive performance, particularly learning and declarative memory, psychomotor speed, and mental flexibility. We used the Czech version of the Rey Auditory Verbal Learning Test (RAVLT) (Rey 1964; Preiss 1999) to evaluate learning and declarative memory. To assess psychomotor speed and attention, we used the Czech version of the Trail Making Test A and B (TMT) (Reitan and Wolfson 1985; Preiss and Preiss 2006). After completion of the Virtual Supermarket Shopping Task, all participants filled out a task usability questionnaire.

3.1.1.2. The Virtual Supermarket Shopping Task

The Virtual Supermarket Shopping Task (VSST) was designed to diagnose and rehabilitate memory deficits in ecologically valid VE. VSST is created in VE, resembling a grocery store and simulating ADL of shopping (see Figure 1).

Figure 1 Virtual Supermarket Shopping Task preview from the first-person perspective.

The participant was supposed to remember a shopping list (verbal, written instruction) and later find and collect recalled items in the virtual supermarket. Prior to the testing, the participant had time to explore the VE and become familiar with the control system. The length of the *exploration phase* differed according to the platform used (10 minutes for HMD and 4 minutes for desktop). Each VSST trial consisted of two phases: the *acquisition phase* (presentation of the shopping list) and the *recall phase* (testing the recall of the shopping list by picking up the items in the virtual supermarket). The length of the acquisition phase increased automatically by five seconds for each item added to the list (i.e., 15s for three items; 25s for five items; 35s for seven items; 45s for nine items). The recall phase was not time-limited. After completing each recall phase, the results (number of errors, trial time, and trajectory) were presented to the participant. Moreover, participants were instructed to play a visuospatial game (non-verbal) for three minutes as a distraction task between the acquisition and recall phases. In this experiment, VSST had four consecutive levels of increasing difficulty (requiring remembering three, five, seven, and nine items on the shopping list).

In order to allow for the repeated assessment using VSST, two task variants of the shopping list were created for each difficulty level (variant A and variant B). The primary outcome VSST measures were: **errors** (sum of omissions – missing items, and intrusions – additional items), **time** spent solving the task (recalling and picking up the item), and **trajectory** length (distance traveled in VE).

3.1.1.3. Materials

The experiment was conducted in an NIMH VR lab which was a 7 m long x 5 m wide x 3.5 m high open space. HTC VIVE was used as the **HMD platform**, with a 1080 x 1200 pixels per eye display resolution. The movement in VE was enabled using teleport on the HTC VIVE controller (trackpad) and also by physically walking around the room (limited by the room parameters, participants were encouraged to limit their physical movement). The controller trigger was used for the selection of objects. For the **desktop platform**, a 24-inch monitor with a display resolution of 1920×1080 pixels was used. The participants controlled their movements and pick-up/drop actions using the keyboard arrows and a computer mouse.

3.1.2. Results

3.1.2.1. Results of the cognitive evaluation

For the purposes of comparison, raw data acquired from the cognitive evaluation were transformed to percentiles according to the scoring manual (Preiss, Rodriguez, & Laing, 2012). The normative cognitive performance of seniors in RAVLT and TMT did not differ from that of young adults (see statistics in Table 3).

Table 3 Results of the cognitive assessment.

		Group of SENIORS (N=36)	**Group of YOUNG ADULTS (N=25)**	**SENIORS VS YOUNG**	
		Mean score (SD)		Mann-Whitney U	p
Rey Auditory Verbal Learning Test (RAVLT)					
RAVLT (I-V)	*words recalled*	51.06 (6.89)	56.96 (9.74)		
	percentile	58.06(22.43)	46.24(26.15)	271.5	.114
RAVLT delayed	*words recalled*	11.15 (2.5)	12.08 (2.44)		
	percentile	56.44(23.6)	49.84(29.37)	305.5	.322
Trail Making Test (TMT)					
TMT-A	*time (seconds)*	36.77 (14.16)	26.2 (9.88)		
	percentile	40.76(28.94)	55.2(30.39)	308.5	.073
TMT-B	*time (seconds)*	84.99 (26.28)	62.88 (29.73)		
	percentile	54.63(27.16)	52.36(32.88)	386.5	.682

3.1.2.2. The virtual Supermarket Shopping Task performance

In VSST, we were mainly interested in the number of errors to measure the recall accuracy crucial for assessing memory abilities. In the statistical comparison, we analyzed cumulative errors consisting of combined omission and intrusion errors made during three levels of task difficulty (for five, seven, and nine items on the list). We used a generalized linear model (GLM) with

ANOVA for repeated measures with the *platform*, *group*, and *order of platforms* as within-subject factors to analyze VSST errors.

The analysis revealed the main effect of the *platform* – the difference between the mean of HMD errors 8.31 (*SD* = 5.21) and the mean of desktop errors 6.98 (*SD* = 4.88) is significant, F(1,57) = 7.474, p = .008. The Tukey post-hoc test revealed that seniors made significantly more errors in HMD (*M* = 11.43, *SD* =4.23) in comparison to the desktop (*M* = 9.08, *SD* = 4.64), p = .001. Conversely, the performance of the group of young adults did not differ across the platforms (p = 0.998). A significant main effect was found also in terms of *group* (F(1,57) = 45.814, p < .001), confirming that seniors performed significantly worse in VSST (*M* = 20.5, *SD* = 8.03) than young adults (*M* = 7.8, *SD*=5.02) (see Figure 2).

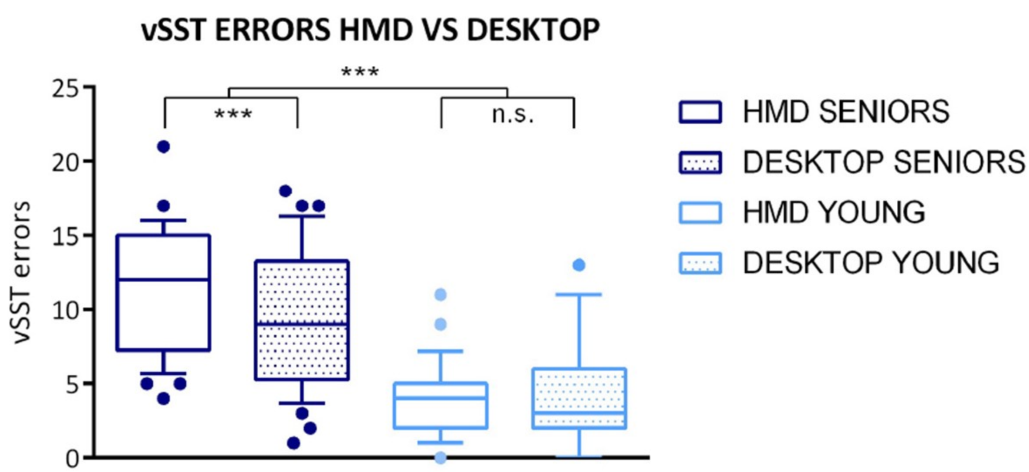

Figure 2 Boxplot for cumulative VSST errors (group/platform). *Boxplot for cumulative vSST errors (group/platform). The VSST errors are presented separately for specific age groups and according to the used platform. Legend: Boxplots represent the following information: the line is plotted at the median, the box extends from the 25th to 75th percentiles, the whiskers are drawn up/down to the 10th and 90th percentile, and points represent the outliers. The results of statistical analysis are visualized as follows: full line markers represent the group effect and group*platform interaction, dashed line markers represent platform effect, significance levels are presented as ***; p-value < .001; n.s.: p-value > .05.*

3.1.2.3. Usability Questionnaire

The analysis revealed a main effect of group on usability score, specifically that seniors rated the experience lower than young adults (*M* = 105.29; *SD* =11.71 & *M* = 114.64; *SD* = 6.40) regardless of the applied platform, ($F(1,56) = 10.986$, $p = .002$). Furthermore, the analysis revealed only one interaction effect for platform*group ($F(1,56) = 6.148$, $p = .016$). Post-hoc analysis showed that young adults (*M* = 59.72, *SD* = 5.86) rated HMD experience significantly higher than seniors (*M* = 50.49, *SD* = 11.29), $p < .001$); the user experience with the desktop platform showed no group effect ($p = .999$). There was no significant difference between the platforms' usability scores in either of the age groups.

Additionally, we analyzed the results for individual items of the Usability questionnaire. After Bonferroni correction for repeated statistical comparison ($\alpha = .01$), we observed a significant difference between the platforms only in the group of young adults. Specifically, the young adults preferred HMD (mean = 4.2, SD=1.11) over the desktop platform (mean 2.04, SD=0.97), $Z=-3.42$, $p<0.001$. The young adults also enjoyed the HMD (*M* =4.32, *SD* =0.9) significantly more than the desktop (*M* = 2, *SD* = 0.81), $Z = -3.98$, $p < .001$).

3.1.2.4. Cybersickness

The reported cybersickness symptoms (e.g., nausea, dizziness, eye strain, and headache) effects were minor, and no participant wanted to terminate their participation in the study.

3.1.2.5. Normative data

A total of 128 respondents were examined using the VSST task. Seniors aged 65-91 consisted of 100 respondents; 28 respondents were aged 18-40 years. These data were used to calculate normative data, part of the VSST manual (Plechatá, 2020). For the purposes of the normative study, we tested four selected levels of difficulty with an increasing number of objects to remember (see Figure 3)

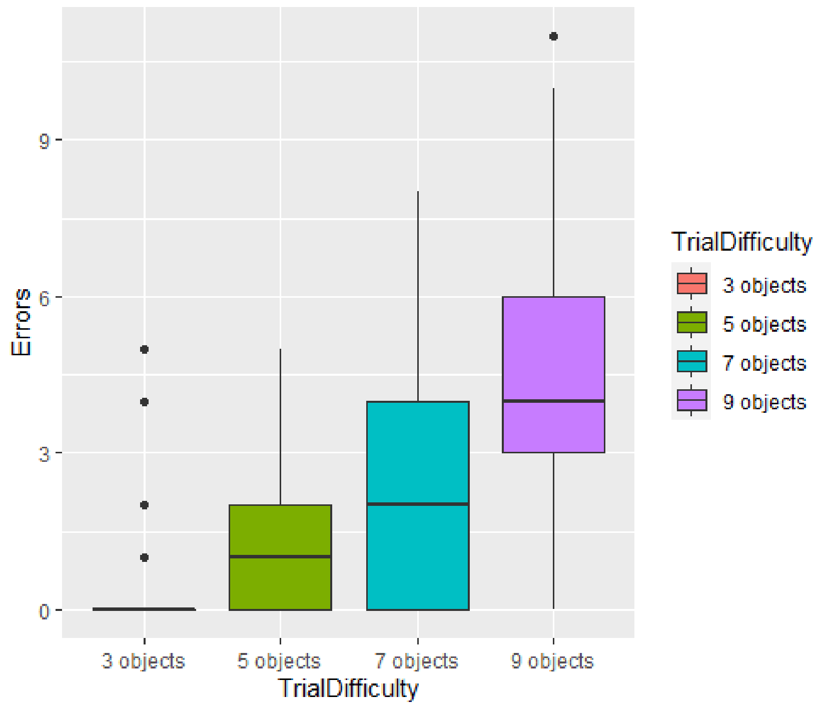

Figure 3. Results of selected VSST levels show the number of errors increasing according to the increasing level of difficulty of the task.

3.1.3. Author contribution

The manuscript is the result of my project financed by Charles University Grant Agency no. 1832218. Thus, I was responsible for the funding and project management. I collected a significant part of the dataset, and I coordinated undergraduate students during the data collection. I was responsible for the designing VSST task and for the study methodology under the supervision of Dr. Fajnerová. I performed all analyses presented in the study. I wrote the manuscript under Dr. Fajnerová's supervision.

3.2. Study 2: Virtual city for cognitive rehabilitation – complex training system

Study two was published as two proceedings papers. The first paper describes the development of a VR city system and contains characteristics of the individual VR tasks (Fajnerová, Plechatá, Sahula, Hrdlička, & Wild, 2019). The second paper investigates the validity of the VR task focused on psychomotor speed and visual attention in healthy elderly (Fajnerová, Hurych, Plechatá, Vorel, & Wild, 2021). Submission of the full papers is planned for the end of the year 2021.

Published as:

Fajnerová, I., Hurych, J., **Plechatá, A.,** Vorel, F., & Wild, J. (2021). Flies - a serious virtual game for cognitive assessment and rehabilitation. *Proc. 13th Intl Conf. on Disability, Virtual Reality and Assoc. Technologies, ICDVRAT with ITAG*.

Fajnerová, I., **Plechatá, A.,** Sahula, V., Hrdlička, J., & Wild, J. (2019). Virtual City system for cognitive training in elderly. In P. J. Standen, S. Cobb, D. Brown, P. Gamito, Appiah, & Kofi (Eds.), *Proc. IVR 2019 International Conference on Virtual Rehabilitation (ICVR)* (pp. 1–2).

3.2.1. Methods and Materials

VR city is a complex training system aiming at cognitive functions most impaired in ND and healthy aging. Even though the developed VR city consists of various tasks (including VSST described above) focused on navigation, planning, memory, or flexibility, here we describe only those tasks that were further investigated and applied in cognitive remediation within this thesis.

Objects. This task is focused on the rehabilitation of episodic memory. It was inspired by episodic-like memory tasks (Fajnerova et al., 2017). Each trial has two phases - the acquisition phase and the retrieval phase. In the acquisition phase, the participant is guided towards virtual items (objects) that have to be collected in a virtual home environment. The participant's task is to remember the collected items (What), their order (When) in which they were collected, and their location (Where). In the retrieval phase, the participant is asked to select the remembered objects from various items and then be instructed to place them in their original positions and order.

Figure 4. Preview of the task Objects (arrow navigating towards an item during the acquisition).

Shooting gallery. The task is a variant of a standard Go / No-go task (Donders, 1969) that focuses on attention, psychomotor speed, and inhibiting the behavioral response. The task requires the participant to distinguish targets (e.g., a dangerous animal such as a wolf, shark. etc.) from non-targets (e.g., dog, or fish) (see Figure 5). The participant is asked to "shoot" (press a button, no aiming required) the target stimuli and to ignore non-targets. Fast recognition and reaction are crucial for success in the task.

Figure 5 Preview of the Shooting gallery from the first-person perspective.

Flies. The task is focused on psychomotor speed, attention, and visuomotor coordination. During the task, the participant is located in a virtual kitchen and is instructed to swat flies that are flying around and sitting on the kitchen counter (see Figure 6). At the end of each trial, the player gets information about the accuracy.

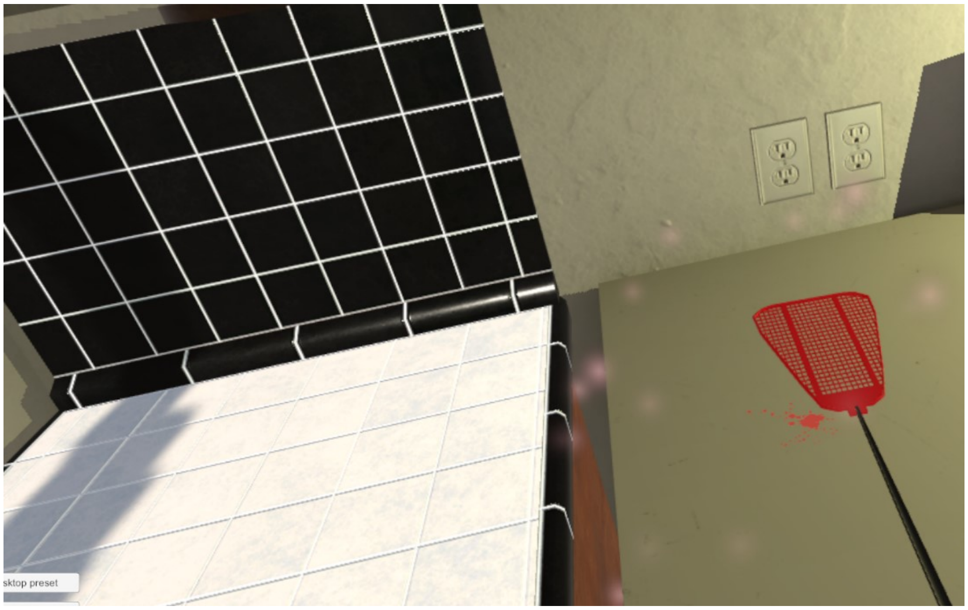

Figure 6 Preview of the task Flies from the first-person perspective.

3.2.1.1. Flies – Task validity and reliability

The study presents two experiments to preliminary evaluate the validity and reliability of the VR task *Flies*. The first experiment assessed validity in the sample of 21 healthy participants (13 females) with ages ranging from 21 to 60 years (*M* = 31.05, *SD* = 8.22). Prior to *Flies,* all participants performed a set of neurocognitive tests aimed to evaluate abilities potentially addressed by the task:

1. reaction time and focused attention - hit reaction time in Conners' Continuous performance test 3 (Conners, Epstein, Angold, & Klaric, 2003); simple response time (SRT) in PEBL 2.0 (Mueller & Piper, 2014)
2. psychomotor speed and executive functioning - Trail making test (Preiss & Preiss, 2006)
3. visuospatial scanning - Bell test - total time (Gauthier, Dehaut, & Joanette, 1989)

The second experiment investigating task reliability was completed by eight healthy volunteers (4 females) aged 16-34 years (mean = 24.75, SD = 6.58). First participants performed an approx. 10 minutes long task in *Flies* consisting of a tutorial and two levels. During the task, two dependent variables were measured: **hit reaction time** and **hit distance error**. Spearman's rho consequently tested the averages of these for correlations between test and retest assessments.

3.2.2. Results

In terms of task validity, Spearman's correlation analysis revealed a significant positive association between the **hit reaction time** measureand the performance in the Bell test (total time) and the TMT-A. Conversely, no significant correlation was identified between hit reaction time and CPT and SRT reaction time (see Table 4).

Table 4. Descriptive statistics and correlations (Spearman's rho) of measured variables.

Variable	M	SD	TMT_A	TMT_B	Bell	SRT	CPT	Level1	Level2	Level3
TMT_A	27.07	9.84								
TMT_B	71.89	21.55	0.365							
Bell	130.07	38.41	0.127	0.212						
SRT	280.6	32.04	0.044	0.129	0.168					
CPT	362.8	33.12	**0.456***	0.344	0.095	0.401				
Level1	0.909	0.199	0.321	0.227	0.26	0.128	0.289			
Level2	0.604	0.173	**0.515***	0.022	**0.527***	-0.083	0.236	**0.662****		
Level3	1.176	0.536	**0.439***	0.018	0.248	-0.336	-0.003	0.328	**0.598****	
Level4	0.994	0.239	**0.517***	0.211	0.406	-0.031	0.187	**0.561****	**0.712****	**0.725****

Note: M and SD represent mean and standard deviation in seconds. Levels 1-4 represent averaged hit reaction times in Flies (in seconds); * indicates $p < .05$. ** indicates $p < .01$.

Concerning the task's reliability, the test-retest reliability of *hit reaction time in Level A* was $r = 0.762$ $(p = .038)$ and for the Level B the reliability was $r = 0.810$ $(p = .022)$.

Furthermore, participants in both experiments found the VR task enjoyable (Experiment 1: M = 5.13, SD = 0.64; Experiment 2: M = 4.86, SD = 1.2; measured on 6-point scale). One participant reported moderate cybersickness, and five participants experienced mild symptoms of cybersickness.

3.2.3. Author contribution

Together with Iveta Fajnerová, I prepared the design of VR-tasks described in the manuscript. I was responsible for the testing and participated in the communication with the software developers. Together with Dr. Fajnerová, I supervised the undergraduate student Jan Hurych. I worked on the experiment methodology and collected part of the study data. I wrote one of the manuscripts together with Dr. Fajnerová (Fajnerová et al., 2019).

4. SECTION 2: VALIDATION IN SCHIZOPHRENIA PATIENTS

The next phase of the program development was to validate the proposed method in the target population. We, therefore, conducted an experimental study comparing the performance of patients with schizophrenia diagnosis in the model VR task with healthy participants matched for age, sex, and level of education.

Our main goals were:

- To investigate VSST construct validity using the convergent and divergent approach.
- To compare patients' performance with healthy participants.

4.1. Study 3: Virtual Supermarket Shopping Task for cognitive rehabilitation and assessment of psychiatric patients: Validation in chronic schizophrenia

Published as: **Plechatá**, A., Hejtmánek, L., & Fajnerová, I. (2021). Virtual Supermarket Shopping Task for Cognitive Rehabilitation and Assessment of Psychiatric Patients: Validation in Chronic Schizophrenia. *Ceskoslovenska Psychologie*, *65*(1), 14–30. (IF 0.471)

4.1.1. Materials and methods

We tested a total of 40 participants, 20 patients suffering from chronic SZ (F20.X), and 20 healthy participants (HC) paired to the experimental group according to their age, gender, and education level. Participants completed neuropsychological evaluation and evaluation with Virtual Supermarket Shopping Task (VSST). One patient was excluded due to an unfinished protocol. Our final sample had 15 female participants (eight HC, seven patients) and 24 male participants (12 healthy, 12 patients). Given the matched pairs design, there was no age difference between the groups (M = 34.74 (SD = 10.23), t(36.97) = 0.19, p =.851). Before the experiment, we collected participants' essential demographic characteristics (age, education, and gender) and inquired about their gaming experience (yes/no).

4.1.1.1. Clinical and cognitive evaluation

Patients' clinical status was assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987), Beck Depression Inventory (BDI-II) (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), Beck Anxiety Inventory (BAI)(Beck, Epstein, Brown, & Steer, 1988) and Global Assessment of Functioning (GAF) (Hall, 1995).

All participants were evaluated with standard neuropsychological measures to assess their declarative memory, learning abilities, sustained attention, psychomotor speed, and executive control.

Rey Auditory Verbal Learning Test (RAVLT) was used to measure episodic memory and verbal learning (Preiss, 1999; Rey, 1964). RAVLT is a test that has a similar rationale as VSST and was chosen as the gold standard for the convergent validity of VSST.

Logical Memory I, II (LM) is a subtest of Wechsler Memory Scale III for episodic memory assessment (Wechsler, 2002).

Trail Making Test (TMT) is used to measure psychomotor speed, attention, and mental flexibility (Preiss & Preiss, 2006; Reitan & Wolfson, 1985).

PEBL Continuous performance task (PCPT) is a vigilance test from PEBL test battery (Mueller & Piper, 2014)

4.1.2. Results

4.1.2.1. VSST measures and group comparisons

Our first aim was to evaluate the VSST measures and their alterations in the SZ group to select task difficulties to focus on. As we expected, the differences between groups in *item performance* – the ratio between correctly picked items and the number of items on the shopping list, became more apparent with increasing difficulty. Mixed effect model with group and difficulty as fixed factors and participant as a random factor showed that the task difficulty had a negative impact on item performance ($b = -0.07$, 95% CI [-0.09, -0.05], $t(92.1) = -7.35$, $p < .001$) meaning that with increasing difficulty (number of items on the list) participants made more mistake. We also found an interaction between the experimental group and the trial difficulty - the decline in the performance with increasing difficulty is steeper in patients than in HC, b = −0.04, 95% CI [-0.07, -0.02], t(92.77) =−3.21, p = 0.002, see Figure 1).

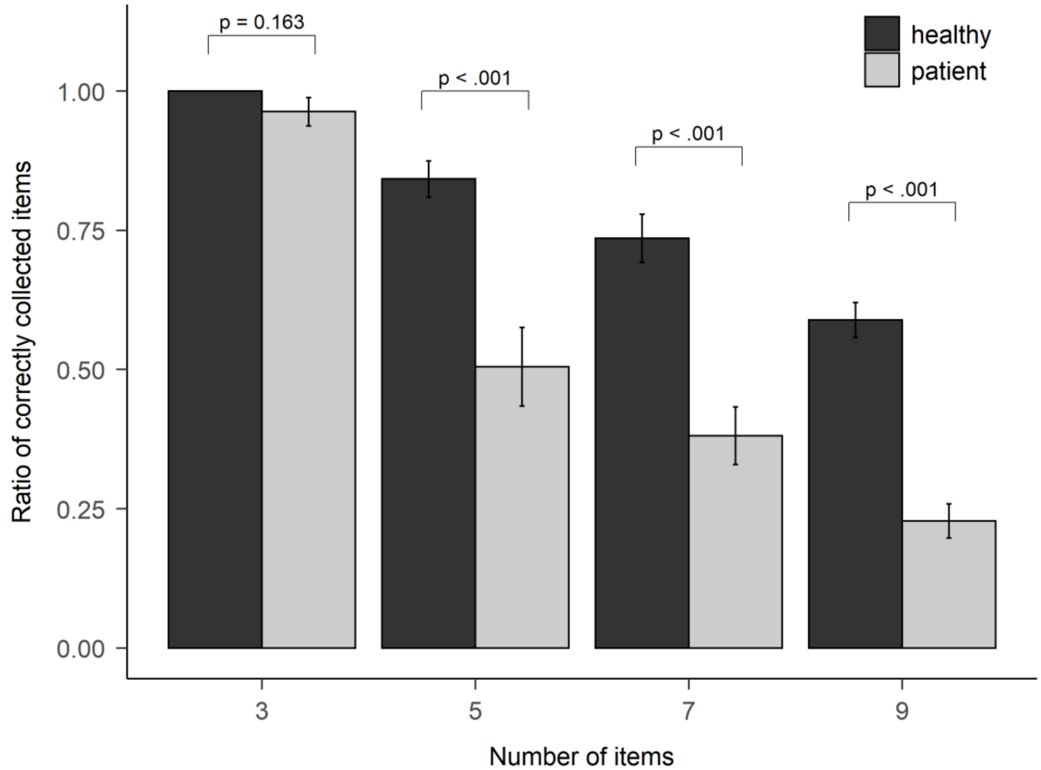

Figure 7. Average item performance (ratio of correctly collected items) with SEM error bars for all VSST trials at increasing difficulties (number of items) split by group. *Groups were compared at each difficulty using two-sample t-tests.*

This suggests that what best differentiates healthy participants from patients is the rate of item performance decline with the increasing difficulty rather than overall performance. We found no difference in VSST measures between patients and healthy subjects in the lowest difficulty (3 items). At this difficulty level, groups did not differ in the number of correctly collected items (t(17) = 1.46, p =.163), extra items collected (t(34.76) = −0.04, p =.970), nor trial distance (t(28.82) = −0.56, p =.578), although they differed in trial time (t(22.75) = −2.59, p = .016). Running the same mixed model but predicting the *extra items,* we have found an increased number of *extra items* being picked up with increasing difficulty (b=0.19, 95% CI [0.09, 0.29], t(93.22) = 3.69, p

< .001), but no group by difficulty interaction (b=0.07, 95% CI [-0.08, 0.22], t(93.72) = 0.94, p = .35).

To study the effects of difficulty on item collection more closely, we fitted a linear regression separately for patients and controls to model the total number of collected items (correct items + additional items) as a function of difficulty. We observed a significant increase of number of items collected in healthy controls (b = 0.55, 95% CI [0.46, 0.65], t(76) =11.70, $p < .001$), but not in SZ patients (b = 0.12, 95% CI [−0.03, 0.27], t(71) = 1.64, p = .105). This suggests that patients were collecting approximately 3 items in each trial regardless of difficulty (i.e. number of items on the list) (see Fig 2).

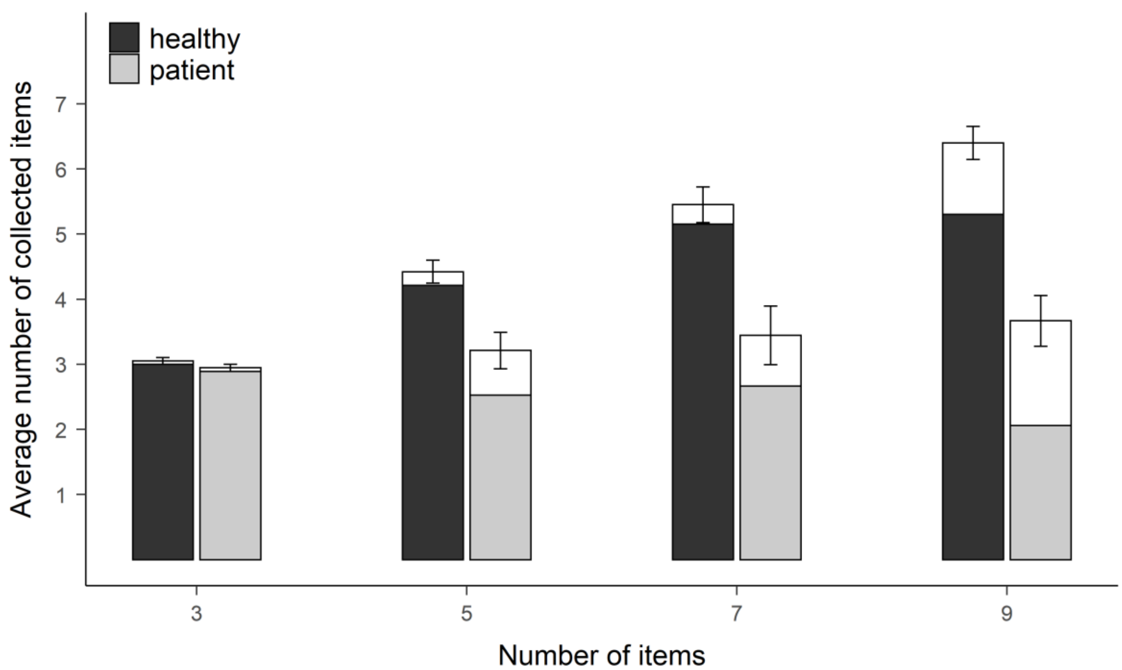

Figure 8. Average number of all collected items (correct + additional) separated by groups and shaded by the item type. *The darker section on the bottom represents correct items, and the lighter section on top represents extra items. Error bars represent SEM of the total.*

4.1.2.2. VSST distance and time

Using a mixed effect model, we modeled the trial distance as a function of task difficulty and the group as fixed effects and the participant as a random effect. We found a significant effect of task difficulty (b = 17.54, 95% CI [8.76, 26.31], t(92.97) = 3.92, $p < .001$) on the trial distance and the interaction between task difficulty and group (b = -14.51, 95% CI [-27.45, -1.57], t(93.39) = -2.2, $p = .03$), suggesting that with more items on the shopping list the increase was steeper in HC. But comparing trial distances between groups at each difficulty using t-tests, we found no differences except at the highest difficulty (t(29.74) = 3.20, $p = .003$), where the traveled distance was significantly longer in HC.

Modelling the distance as a function of time and group with participant as a random effect, we found a significant effect of trial time (b = 1.06, 95% CI [0.83, 1.29], t(104.23) = 9.13, $p < .001$) and group by time interaction (b = −0.71, 95% CI [-0.99, -0.44], t(109.75) = −5.07, $p < .001$), but no group effect (b=60.7, 95% CI [-9.46, 130.86], t(69.83) = 1.7, $p = 0.094$). In other terms, for healthy subjects, the distance increased more steeply as a function of trial time than for patients, as can be seen in Figure 9. meaning that patients move more slowly than HC, but as the speed in VSST was constant, this difference was due to patients' pauses in movement. Scatter plot of trial distance (in virtual units) and trial time (in seconds) split by group. Grey areas represent the 95% confidence interval of the fitted linear regression slopes.

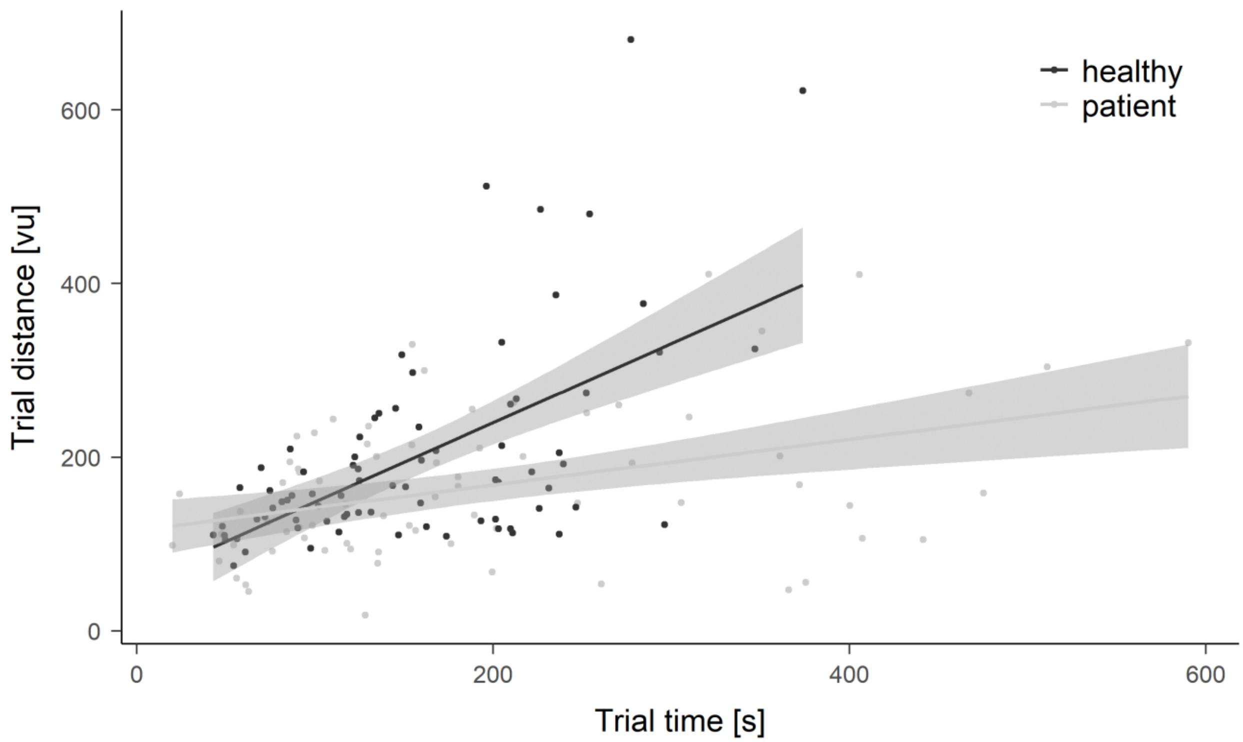

Figure 9. Scatter plot of trial distance (in virtual units) and trial time (in seconds) split by group. *Grey areas represent the 95% confidence interval of the fitted linear regression slopes.*

4.1.2.3. VSST convergent and divergent validity

As VSST differentiates groups better with increasing difficulty, and groups' performance often did not differ in lower difficulties, we decided to focus solely on the performance from the two most difficult trials (7 and 9 items) to reduce the possibility of false negatives. Although other metrics also demonstrate differences between the groups, we decided to further discuss and analyze the *item performance* as the best and most consistent measure of participant's performance.

We assessed the convergent validity and divergent validity of VSST *item performance* measure, by obtaining Pearson correlation coefficient against neuropsychological measures. We did so for the average of the two most difficult trials (e.g., 7 and 9 items). CPT measure detectability d' – the ability to differentiate non-target from targets should not be related to the VSST performance. Thus, it was used to assess divergent task validity. RAVLT and LM delayed recall measures were used to assess the VSST convergent validity. The correlation coefficients can be found in Table 5. We did not find any significant correlation with patients' clinical status measures.

Table 5 Correlation of VSST item performance (average for 7 and 9 items) and neuropsychological and clinical measures split by the group.

Test/correlation	*Healthy*	*Patient*
Convergent validity		
RAVLT delayed	$r = 0.63, p = .003$*	$r = 0.61, p = .005$*
LM delayed	$r = 0.48, p = .031$	$r = 0.74, p < .001$*
TMT A time	$r = -0.12, p = .617$	$r = -0.11, p = .667$
TMT difference score (B-A)	$r = -0.16, p = .489$	r = -0.46, $p = .046$
Divergent validity		
PCPT Detectability d'	$r = 0.08, p = .768$	$r = 0.11, p = .18$
Mental status		
PANSS negative scale	-	$r = -0.41, p = .088$
PANSS positive scale	-	$r = -0.09, p = .732$
PANSS general psychopathology	-	$r = -0.23, p = .36$
GAF	-	$r = 0.42$, p = .077

Legend: RAVLT (Rey Auditory Verbal Learning Test) delayed recall, LM (Logical Memory) delayed recall, PEBL CPT - PEBL Continuous Performance Task, TMT (Trail Making Test) difference B-A - TMT B and TMT A time difference, PANSS - Positive and Negative Syndrome Scale. GAF - Global Assessment of Functioning scale. After applying Bonferroni correction on multiple comparisons in each section we set the alpha to 0.0125. The asterisk symbol marks statistically significant correlations at this level.

4.1.3. Author contribution

I designed and prepared the methodology of the experiment under Dr. Fajnerová's supervision. I collaborated with the psychiatric institutions to recruit the study participants and I collected all data used in this study. In collaboration with Lukáš Hejtmánek, I wrote the manuscript under the supervision of Dr. Fajnerová and interpreted the results analyzed by Lukáš Hejtmánek.

5. SECTION 3: EFFICACY OF COGNITIVE REMEDIATION IN VIRTUAL ENVIRONMENT

The final goal of my thesis was to evaluate the developed virtual environment (VE) program in cognitive remediation of neuropsychiatric disorders, specifically in schizophrenia (SZ) and major depressive disorder (MDD). For these purposes, we conducted a cross-over pilot study with a sample of patients with SZ or MDD and compared it with the cognitive and feasibility outcomes of the standard paper-pencil program (Plechatá, Hejtmánek, Bednářová, & Fajnerová, 2021).

Our aims were to:

- Evaluate the participants' progress in the VR tasks.
- Compare the cognitive outcomes of the VE cognitive remediation program and standard paper-pencil approach (referred to as standard treatment program).
- Compare and further investigate the feasibility of both programs.

5.1. Study 4: Cognitive remediation in virtual environments for patients with schizophrenia and major depressive disorder: a feasibility study

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5.1.1. Materials and Methods

The participants were recruited from the outpatients attending the Psychotherapeutic Day Center for psychotic patients in the town Karviná. A total of 35 participants were recruited. Only those participants who completed at least one program were included in the subsequent analyses: 28 in total, 17 male (*M* = 35.391, *SD* = 8.033), 11 female (*M* = 36.909, *SD* = 13.172). Twenty-two participants were diagnosed with SZ or other primary psychotic disorders, and six were diagnosed with MDD (World Health Organization, 2018). The mean duration of the illness was 6.19 years (*SD* = 6.3), and it ranged from 0.5 to 20 years. The level of education ranged from elementary education (*n* = 9), vocational school (*n* = 9), high school (*n* = 9) to university education (*n* = 1). The participants were excluded from the study in case of:

- Severe visual impairment
- Neurological disorder or comorbid psychiatric diagnosis
- Physical handicap preventing the participant from participating in the VE program
- Refusal to give informed consent

5.1.1.1. Procedure

Before the beginning of the rehabilitation program, all participants completed a baseline cognitive assessment. Participants were then randomly assigned to the first rehabilitation program: VEs program or standard treatment. Equal randomization was not possible due to the insufficient number of laptops available for the VE program. After the first program completion, participants were retested with the cognitive battery and then assigned to the second program: standard treatment or VEs program. After completing the second program, the participants were assessed with a cognitive battery and filled out a brief evaluation questionnaire. The questionnaire had 17 questions about participant's enjoyment and perceived difficulty of the programs, their task preferences, willingness to participate in the program again, and their perception of achieved cognitive enhancement. In some cases, participants did not complete the program due to relapse-related hospitalization or due to the adverse epidemiological situation associated with the coronavirus disease, SARS-CoV-2.

5.1.1.2. Virtual Environments (VEs) Program

The virtual tasks were administered on 17.3" laptops. Participants interacted with the VEs using a keyboard and a mouse. Participants attended 12 computer sessions during 6–12 weeks. Each session lasted 30 min and consisted of a set of three VEs tasks. For the VE program, we adopted a drill–practice approach and progressively increased the difficulty of the task according to the participant's performance. During the first session, participants were explained how to interact with the virtual environment and how to control specific tasks. During the following sessions, participants were instructed to train for approximately 5 minutes with the Shooting gallery and then continue for 10 minutes with Virtual Supermarket Shopping Task (VSST) and 10 minutes with Objects.

5.1.1.3. Standard Treatment Program

Participants in the standard cognitive rehabilitation program (referred to as a standard treatment) attended a total of 12 paper-pencil sessions over 6–12 weeks. Each session lasted 45 min. The session started with a warm-up game and then continued with a set of paper-pencil tasks focusing on attention, fine motor skills, recall, short-term and long-term memory, verbal fluency, visual search, cognitive flexibility, abstraction, and executive functions, and numerical abilities. The tasks were adapted to each participant's own abilities.

5.1.1.4. Cognitive Assessment

The participants' cognitive abilities were assessed before cognitive rehabilitation, after completing the first program, and after finishing the second program. This allowed us to precisely track their performance over long periods and evaluate the effect of each program individually.

The **Repeatable Battery for the Assessment of Neuropsychological Status (RBAN**S) was previously standardized in schizophrenia patients (Gold, Queern, Iannone, & Buchanan, 1999). RBANS is easy and fast to administer, which eliminates the burden placed on participants during the assessment and it covers most impaired cognitive domains in schizophrenia (E. Bora et al., 2017). Its alternative forms (A, B, C, D) allow for repeated testing after the cognitive remediation program, which is fitting for the purposes of our study.

5.1.2. Results

5.1.2.1. Adherence to the treatment

From the initial number of 35 participants, seven did not finish any rehabilitation program, 28 completed at least one program, and 17 completed the entire program (see Figure 10 for details).

Two participants refused to attend the VE program because they did not find it beneficial and one participant felt that they could not perform well in the program. This makes the total VEs program *refusal rate* 8.6 %. In contrast, no participant quit or refused the standard treatment.

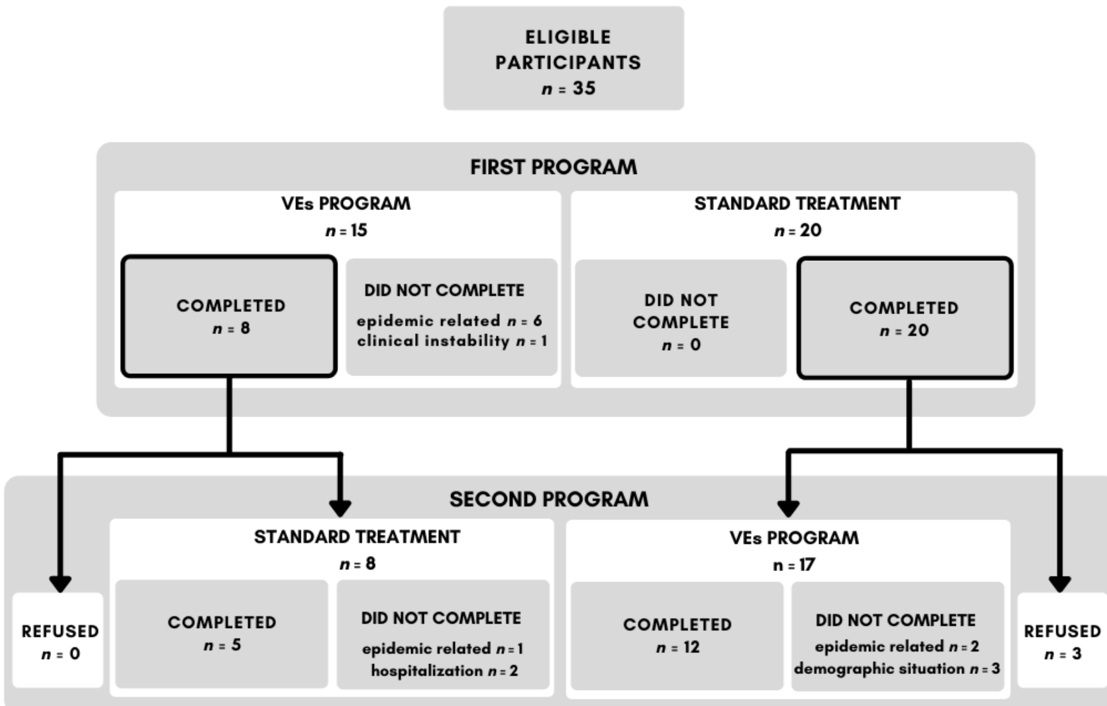

Figure 10. Adherence to the treatment and study procedure flow chart.

5.1.2.2. Feedback Questionnaire

The questionnaire aimed to assess participants' subjective perception of the program regarding difficulty, enjoyment, or subjective improvement. We found no significant differences between the standard treatment and the VE program in either category. Nevertheless, participants seem to slightly prefer the standard treatment in terms of their willingness to repeat it in the future ($t(48.38) = -1.91$, $p = 0.062$). Generally, the participants perceived both programs as enjoyable (standard treatment mean = 4.26, VE program mean = 4.04) and beneficial (standard treatment mean = 4.26, VE program mean = 4.08). Note that the treatment was rated on a 5-point Likert scale.

5.1.2.3. Virtual Supermarket Shopping Task

Using linear mixed effect models, we looked at how patients learned VSST as the cognitive training progressed. We defined **maximum difficulty achieved** as the highest difficulty level (number of items on the list) participants had reached during the session. We observed that participants were continuously able to improve and proceed to more difficult trials as the training progressed (b = 0.09, 95% CI [0.04, 0.13], t(156.74) = 4.04, $p < 0.001$) (see Figure 3), although the rate of improvement was low.

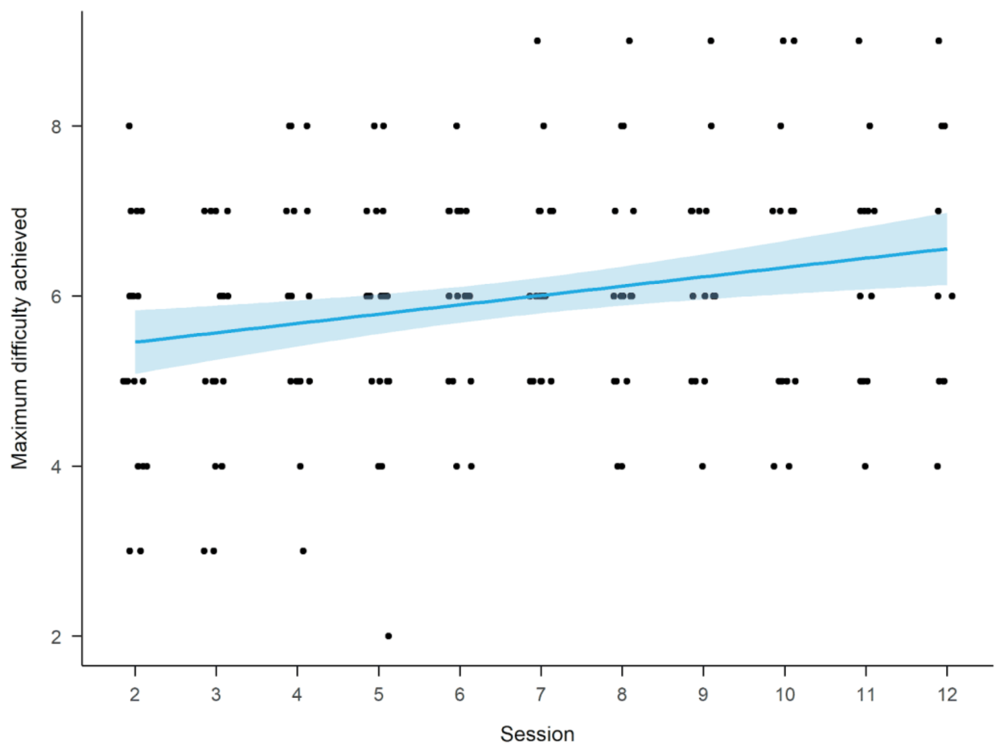

Figure 11. Maximum difficulty achieved in Virtual Supermarket Shopping Task plotted as an effect of the session.

As the **trial trajectory** and **trial time** are dependent on the participant's performance and task difficulty (to pick up more items, participants need to walk longer trajectory), we modeled the **trial**

time and **trajectory** with both session and trial difficulty as a predictor. We observed that participants improved in both of these measures as the remediation program progressed. With each new session we saw a decrease in length of **trial trajectories** (b = −5, 95% CI [−6.84, −3.16], t(1268.04) = −5.33, $p \leq 0.001$) and **trial times** (b = −5.61, 95% CI [−6.79, −4.42], t(1269.06) = −9.29, $p \leq 0.001$). That implies that patients were able to reach higher levels and were able to solve the task faster and more efficiently.

5.1.2.4. Cognitive Assessment

As expected, we have observed that patients who have schizophrenia scored lower in all RBANS domains and had significantly worse baseline performance than patients with MDDs in the language domain and RBANS total index score (Table 5). This was one of the reasons we opted for the linear mixed effect models in our subsequent analyses, as the method is able to control for the effect of the diagnosis implicitly.

Table 6. Baseline results of RBANS cognitive domains index scores presented separately for both diagnoses and group comparison using an independent t-test.

RBANS domain	**Depressive disorder (*n* = 6)**	**Schizophrenia (*n* = 22)**	**t-test**
	Mean (SD)		
Delayed memory	77(19.411)	61.909(18.296)	t(23.42) = 1.50, $p = 0.147$
Immediate memory	85.667(18.129)	72.5(17.88)	t(23.27) = 1.65, $p = 0.112$
Attention	86.5(14.293)	78.273(18.224)	t(24.43) = 1.95, $p = 0.063$
Language	93.5(6.504)	82.182(14.634)	t(35.27) = 2.88, $p = 0.007$
visuospatial/constructional	73.667(7.501)	70.409(9.854)	t(26.42) = 1.51, $p = 0.144$
RBANS TOTAL INDEX SCORE	78.5(11.467)	66(13.238)	t(24.09) = 2.51, $p = 0.019$

Legend: RBANS—Repeatable Battery for the Assessment of Neuropsychological Status.

Using linear mixed effect models we explored the effect of the intervention (see Figure 4) and the session on RBANS scores, with the participant being a random effect.

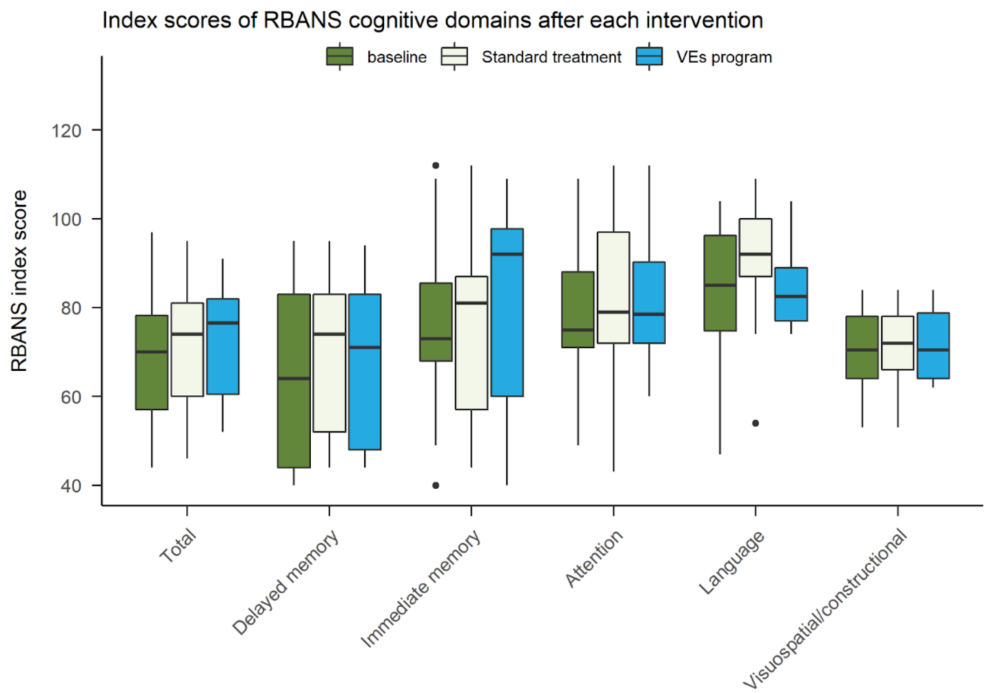

Figure 12. Summative results for RBANS cognitive domains (index scores) for each treatment. *Boxplots represent the following information: the line is plotted at the median, the box extends from 25th to 75th percentiles, the whiskers are drawn up/down to the 10th and 90th percentile, and points represent the outliers.*

We have not found any effect of the intervention, neither positive nor negative, on either RBANS domain (see Table 3). Furthermore, we only found a negative effect of the third session on the normalized total RBANS score (b = −0.31, 95% CI [−0.55, −0.06], t(15.41) = −2.47, p = .026) with participant's scoring marginally worse at the end of the study (RBANS form C, both interventions completed) than after the first interventions. Thus, we did not find significant improvement in any cognitive measures regardless of the intervention type.

Table 7. The effect of the intervention (standard treatment/VE program) on cognitive performance. *The beta signifies the effect of the VE program on the normalized score in the given domain while controlling for the session and participant effects.*

RBANS Standardized Domain	**Linear Mixed-Effect Model Result Of The Virtual Environment Program in Comparison to Standard Treatment Program**		
	Beta	95% Confidence interval	Statistic
Immediate memory	0.19	−0.1, 0.49	t(16.56) = 1.27, p = 0.221

Delayed memory	−0.14	−0.34, 0.07	t(15.89) = −1.3, *p* = 0.212
Attention	−0.03	−0.4, 0.33	t(16.16) = −0.18, *p* = 0.862
Language	0.25	−0.21, 0.71	t(17.07) = 1.06, *p* = 0.302
Visuospatial/constructional	−0.37	−0.93, 0.19	t(20.09) = −1.29, p = 0.210
RBANS TOTAL SCORE	0.02	−0.22, 0.26	t(15.7) = 0.16, *p* = 0.875

Legend: RBANS—Repeatable Battery for the Assessment of Neuropsychological Status.

Although linear effects models are suited to control for individual differences and, therefore, participants' diagnoses, participants with MDD could perform differently from those with SZ. We modeled the cognitive performance in each RBANS standardized domain as a function of the diagnosis, session, and their interaction as fixed effects and participant as a random effect. We did not find any significant interaction between the diagnosis and the session on any RBANS domain (see Table 4).

Table 8. Interaction between the diagnosis and session on cognitive performance. *The beta signifies the interaction effect of schizophrenia and session in each RBANS domain while controlling for the participant effect.*

RBANS standardized domain	**Beta**	95% Confidence interval	Statistic
immediate memory	0.19	−0.16, 0.54	t(43.78) = 1.08, *p* = 0.285
delayed memory	0.21	−0.08, 0.5	t(43.69)=1.44, *p* = 0.157
attention	0.07	−0.34, 0.49	t(43.94) = 0.34, *p* = 0.732
language	−0.18	−0.72, 0.35	t(44.39) = −0.68, *p* = 0.502
visuospatial/constructional	−0.1	−0.56, 0.36	t(43.94) = −0.42, *p* = 0.675
RBANS TOTAL SCORE	0.13	−0.14, 0.4	t(43.4) = 0.95, *p* = 0.346

Legend: RBANS - Repeatable Battery for the Assessment of Neuropsychological Status.

5.1.3. Author contribution

I was responsible for collaborating with the Day Care Center for psychotic patients in Karviná and I coordinated the study procedure. Under the supervision of Dr. Iveta Fajnerová, I designed the cross-over trial and prepared the methodology. I also supervised the undegraduate student, Markéta Slezáková who transcribed the RBANS data. Together with Lukáš Hejtmánek, I wrote the manuscript under the supervision of Dr. Fajnerová and interpreted the results analyzed and visualized by Lukáš Hejtmánek.

6. Discussion

6.1. Media comparison (Study 1)

Study 1 presented the first virtual environment (VE) task called Virtual Supermarket Shopping Task (VSST) that simulates everyday activity, shopping, with four levels of increasing difficulty. The task was tested in healthy young adults and seniors in two levels of immersion using a within-subject design. By counterbalancing the platforms and task variants applied, we controlled for possible effects of fatigue and practice effect. We have identified age-related differences in terms of cognitive performance in the presented task and user experience.

6.1.1. Cognitive performance

The main finding of this study was that the performance of seniors and young adults differed across the tested platforms (HMD vs desktop). Specifically, the memory performance assessed by the number of errors in VSST (number of incorrectly picked items and forgotten items from the shopping list) was higher in more immersive virtual reality (IVR) than in non-immersive virtual reality (non-IVR) in healthy elderly. Conversely, the VSST performance was stable across the applied VR media in healthy adults. These findings were contrary to our a priori hypothesis that IVR would be able to increase performance due to its ability to shield participants from the outside world's distractors and enhance participants' motivation. Nevertheless, our results are consistent with findings from other media studies, which we also summarize in a recent review (Plechatá, Nekovářová, & Fajnerová, 2021). In addition, media studies show that a higher level of immersion is associated with a higher level of presence (the feeling of being present in the VE) (Cummings & Bailenson, 2015).

Nevertheless, immersive media can often lead to decrease cognitive performance, e.g., in terms of spatial memory (Sousa Santos et al., 2009), episodic memory (Mania & Chalmers, 2001; Rand et al., 2005; Rohrbach et al., 2019) but also in learning (Frederiksen, Sørensen, Konge, Svendsen, & Andersen, 2019; Makransky, Terkildsen, et al., 2019). The worse cognitive outcome linked to higher immersion was explained with higher levels of so-called extraneous cognitive load, i.e., higher cognitive demands arising from the way task is presented (Sweller, 2011). In IVR, for example, complex three-dimensional models can increase demands on our working memory and result in lower performance (Richards & Taylor, 2015). The association between working memory and cognitive load also helped us explain the difference between young adults and seniors; as the working memory capacity declines with age, the elderly population can be more susceptible to cognitive overload (Cantin, Lavallière, Simoneau, & Teasdale, 2009; Plechata, Sahula, Fayette, & Fajnerova, 2019). Previous studies also measured the higher cognitive load linked to the IVR using an electroencephalogram (Makransky, Terkildsen, et al., 2019). Moreover, the following findings indicate that the effect of cognitive load is not influenced by the level of experience with VR and cannot be accountable to the novelty of the technology (Frederiksen, Sørensen, Konge, Svendsen, & Andersen, 2019).

Conversely, some studies focusing on spatial memory or navigation tasks (Murcia-López & Steed, 2016) showed increased performance in IVR compared to non-IVR, for example, when applying the method of memory palaces (Krokos, Plaisant, & Varshney, 2019) or when remembering spatial layout (Ruddle et al., 1999). These possible beneficial effects of immersion can be linked to the advantages described above, e.g., active movement, more naturalistic rotation, or larger field of views, highlighted in the tasks demanding spatial abilities. Moreover, studies focusing on learning in IVR show that when instructional design principles are successfully applied, the IVR can result in better outcomes in terms of learning performance (Makransky & Petersen, 2021). A recent meta-analysis consistently showed that IVR media has a slight advantage over non-IVR platforms in learning outcomes (Wu, Yu, & Gu, 2020). We will discuss the implications for cognitive rehabilitation in a later section.

6.1.2. User experience

To address the acceptance of IVR in the aging population, we analyzed the differences in user experience among the applied media. When investigating the summative results of the usability questionnaire, we identified that the seniors rated the overall experience as less favorable than young adults regardless of the applied media. That could be related to general lower experience with new technology in seniors in comparison to young adults. In general, seniors could experience the whole procedure as more stressful or demanding when considering the differences in cognitive abilities among the tested groups (Plechata et al., 2019). However, the summative usability scores showed no significant preference for HMD or desktop platforms in the young adult or senior participants. Analyzing the individual items, we have discovered that young adults enjoyed the experience significantly more when presented on HMD. This is in line with previous and also with subsequent studies that repeatedly confirmed that more immersive media could effectively elicit more enjoyment, interest, and motivation (Adamo-Villani & Wilbur, 2008; Makransky, Borre-Gude, & Mayer, 2019; Makransky, Terkildsen, et al., 2019; Sousa Santos et al., 2009). Despite the missing preference of IVR reported in our study, usability studies show that IVR is overall well-accepted by the elderly (Tuena et al., 2020). This was, in general, our case as well, as the reported adverse effects were very low (including cybersickness), and no respondent quit the study prematurely. As none of the older participants had previous experience with IVR, it can be expected that repeated exposure would lead to a reduction of adverse symptoms (Taylor, Harm, Kennedy, Reschke, & Loftin, 2011) to increase enjoyment due to reduced anxiety.

6.2. Standardization in healthy controls (Study 1 and 2)

In Study 1 and 2, we present the developed VR-based methods that are part of the Virtual City project (including VSST). All presented VR tasks focus on training cognitive functions in high fidelity environments and with arguably high ecological validity due to their resemblance with real-life challenges. In Study 1, VSST was tested in the group of healthy seniors and young adults. Study 1 confirmed that with increasing difficulty, the participants' (young and elderly) performance is decreasing – they are making more mistakes in terms of memory recall accuracy. Moreover, the performance between groups significantly differed as healthy seniors were making significantly more mistakes than young adults, consistent with findings of cognitive decline pronounced in memory abilities in physiological aging reported with standard cognitive measures (Harada et al., 2013; Rönnlund et al., 2005). We also presented results from a normative study conducted on more than 100 subjects; these data confirm that the difficulty levels are appropriate and well-designed. Furthermore, it enables us to use this normative data to track the participants' progress during the cognitive remediation.

In Study 2, we tested the reliability and validity of Flies, an IVR task focused on psychomotor speed and attention, in two experiments conducted with healthy volunteers. Study results indicate that the task of swatting a fly in high fidelity immersive VEs can be a valid measure of visuospatial scanning and visuomotor coordination. Furthermore, the findings reflect the complexity of the task, as the performance in the task was not related to a simple measure of reaction time in a standard measure of vigilance (Conners et al., 2003; Fajnerová et al., 2021). Despite the task's higher complexity and high interactivity, preliminary findings from the pilot experiment indicate sufficient test-retest reliability. Study 2 also shows that the highly interactive task can be enjoyable for the participants. The high levels of enjoyment can be crucial for increasing participants' intrinsic motivation to engage in cognitive training and possibly prevent drop out from the programs (Jahn et al., 2021). Unfortunately, as we did not compare the two interventions, we cannot conclude the role of interactivity and immersion on the level of enjoyment. Nevertheless, current findings seem to be consistent in showing that immersive and interactive tasks can promote a high level of presence and agency that increases motivational and affective factors (Makransky, Borre-Gude, et al., 2019; Makransky, Terkildsen, et al., 2019; Plechata et al., 2019; Sousa Santos et al., 2009) necessary for the effective learning outcomes (Makransky & Petersen, 2021).

6.3. Validation of virtual reality task in schizophrenia (Study 3)

Our goal in Study 3 was to use the model memory task – VSST, presented in Study 1 in patients with SZ to address its construct validity. We administered the VR task and standard cognitive measures to patients with SZ and healthy controls matched for sex, age, and education. We administered the task at the same level of difficulty as in Study 1. To compare the patients and healthy controls, we established a new measure of VSST performance – item performance, the ratio between correctly picked items, and the number of items on the shopping list. This measure differentiated the patients and healthy volunteers in all difficulties except for the first trial with three items on the list. Thus, this level could be considered as a training trial in future studies (Plechatá, Hejtmánek, & Fajnerová, 2021). Notably, the findings showed that the decline in the performance during the increase in difficulty is more pronounced in the patients; their performance is deteriorating more steeply. These findings agree with previous studies confirming profound deficit in memory abilities in SZ assessed by standard neuropsychological measures (E. Bora et al., 2017; Cirillo & Seidman, 2003) and also in VR-based memory tasks (Huang et al., 2021; Man et al., 2018). These findings, similar to findings from Study 1, confirm VSST construct validity. Moreover, detailed analyses revealed that the patients collected significantly fewer items than healthy controls. Meaning, regardless of the number of items on the list (= how many items participants were supposed to collect), patients with SZ collected on average three items. Besides possible inability to encode more than three items, this can be linked to different aspects: patients are in general less motivated due to negative symptoms (e.g., apathy or abulia) (Blanchard & Cohen, 2006; Buchanan, 2007; Fervaha et al., 2015), also deficits in attention can limit patients ability to focus on the progressing levels, or patients can be inhibited by higher anxiety levels and fear of collecting the wrong items.

Furthermore, when analyzing the trial distance as a function of time, we found that another aspect that differentiated the healthy controls and patients with SZ was longer and more frequent pauses when completing VSST. Basically, in comparison to healthy controls, patients walked shorter distances for the same time period. This can be accounted for the slower psychomotor speed observed in patients with SZ that can also be associated with SZ negative symptoms (Morrens, Hulstijn, & Sabbe, 2007). A further qualitative analysis could be beneficial to investigate these specific differences. Clinicians could also use the possibility to track patients' movement to observe their progress in the remediation and investigate in more detail what could be the most important aspects of the individual patient deficit for their real-life functioning (Plechatá et al., 2021).

In terms of tasks validity, we found a correlation between the item performance and standard memory measures of delayed recall – Rey Auditory Verbal Learning Task (RAVLT) (Preiss, 1999; Rey, 1964) and Logical memory (LM) (Wechsler, 2002). Specifically, we found strong correlations between RAVLT delayed recall and LM delayed recall (r = 0.61, 0.74 respectively) in SZ patients. In healthy controls, we similarly found a strong correlation with RAVLT delayed memory (r = 0.63), correlation with LM did not pass the corrections for multiple comparisons (r = 0.48). These results support the construct validity of VSST as a memory measure.

Nevertheless, due to assumed multifacetedness of VSST and the deficit in encoding in SZ patients being related to a deficit in a semantic organization and use of mnemonic strategies, we expected a correlation with measures of processing speed or executive functions (Plechatá et al., 2021). Our results confirmed a moderate correlation between the item performance and the Trail Making Test difference measuring the level of executive functioning (Sánchez-Cubillo et al., 2009). Even though the correlation did not survive the multiple comparison correction, we believe it points out the importance of the executive function for successful VSST completion. The deficit in executive functioning in SZ (E. Bora et al., 2017) also plays an essential role in memory deficits. It influences the ability to organize the encoded material and apply mnemonic strategies (Bonner-Jackson & Barch, 2011; Brébion et al., 2000). The missing link between the TMT B-A difference in cognitively healthy adults can suggest that participants without memory deficits do not need to engage executive functions to solve VSST. Similarly, as in previous studies aimed at memory deficits in SZ (Bezdicek et al., 2020), the correlation between the clinical symptoms and VSST performance was not significant. However, given the magnitude of correlation (r = 0.41) and the fact that studies conducted on chronic patients report the modest correlation between cognition and negative symptoms (Keefe et al., 2007), the missing significance can be related to the small sample size.

6.4. Cognitive remediation in virtual environments (Study 4)

In the final study, we applied all tasks presented in previous studies in a novel cognitive remediation program applied in patients with SZ and MDD. The study compared the efficacy and usability of the developed VR-based program with standard paper-pencil treatment in a cross-over trial. Initially, we recruited 35 participants to complete 12 sessions of each treatment due to epidemiological situations related to the covid-19 pandemic and also clinical instability of the patients; the final sample consisted of 28 patients who participated in at least one treatment. The results from the feedback questionnaire showed that patients perceived both programs as similar in terms of benefit, difficulty, enjoyment, or perceived cognitive improvement after the program. Nevertheless, the attrition rate was slightly higher for the VR-based program as 8.6% of patients did not want to participate after completing the standard training. High attrition rates and low motivation, especially in severe mental illnesses as is SZ, is a crucial issue in remediation settings. Some studies report attrition rates as high as 50 % (Bowie, 2019). Considering that the VE cognitive program was much more demanding and required independent work, we considered the attrition rate reasonable. In general, the participants rated both programs as enjoyable and beneficial.

Nevertheless, in terms of standardized cognitive outcome, neither the VE program nor standard treatment improved cognitive functions measured at the beginning, after the first and second program. We did not find positive change at the end of the whole program (after 24 sessions), and the impact did not differ among the applied programs. This is in contrast to preliminary findings, which show that VR can significantly improve cognitive performance in SZ patients (La Cascia et al., 2020); nevertheless, the studied sample size was very small *(n* = 5). More importantly, these findings contradict the meta-analyses reporting significant cognitive improvement (small to moderate) in SZ after cognitive remediation (Cella et al., 2020; Grynszpan et al., 2011; Prikken et al., 2019; Wykes et al., 2011). Nevertheless, Revell et al.'s (2015) meta-analysis showed significant improvement only in verbal memory in early episode SZ patients. Some randomized controlled trials also failed to find significant improvement in cognition (Kidd et al., 2020; Mahncke et al., 2019).

Although the majority of previous meta-analyses reports significant improvement in different cognitive abilities in SZ after cognitive remediation (Cella et al., 2020; Grynszpan et al., 2011; Wykes et al., 2011), the meta-analysis by Revell (2015) was conducted in patients with early SZ showed only a non-significant small effect of cognitive remediation on global cognition and other cognitive domains. In addition, (Bryce, Sloan, Lee, Ponsford, & Rossell, 2016; Kidd et al., 2020; Mahncke et al., 2019; Rass et al., 2012), as we personally experienced how difficult it could be to get negative findings published. Especially when the risk of publication bias is often omitted in the published meta-analyses (Bryce et al., 2016) e.g., a recent meta-analysis (Cella et al., 2020) pointed out a high risk for file-drawer effect in attention and vigilance and executive functioning.

Published meta-analyses are often contradictory also in terms of the impact of participant and treatment factors on the cognitive outcome. For example, Wykes et al. (2011) reported that the treatment characteristics (approach, intensity, or length) did not influence the magnitude of cognitive improvement. Prikken et al. (2019) also confirmed that the drill-practice approach is effective in terms of cognitive outcome. Nevertheless, the most recent meta-analysis (Lejeune et al., 2021) reports a significantly larger improvement in verbal and visual learning in strategy-based approaches than drill practice. The recommendation to incorporate strategy learning is consistent with findings reporting disruption in mnemonic strategies as a core factor in SZ's memory deficit (Bonner-Jackson & Barch, 2011; Cirillo & Seidman, 2003; Gsottschneider et al., 2011).

In our study, both programs, VE program and standard treatment, adopted drill-practice approach. Lejeune et al. (2021) further pointed out the importance of the “bridging” strategy in order to enhance global cognition and verbal memory. Lejeune's term bridging describes discussion focused on how the trained exercise can be applied in real life and it was applied in 13 studies in the reported meta-analyses (Lejeune et al., 2021; Medalia & Choi, 2009). Therefore, due to its resemblance to real-world challenges, we believe that the VEs program would be very suitable to provide strategic training and an efficient tool for bridging discussions. This should be addressed in future studies.

As mentioned above, the cognitive deficit has a similar pattern in MDD and SZ; nevertheless, the magnitude of impairment is larger in SZ (Emre Bora & Pantelis, 2015; Sheffield et al., 2018). This is consistent with our results, as patients with SZ scored lower in total RBANS score than MDD patients. The interaction between the diagnosis and outcome measures showed that the treatment affected both groups similarly.

The major advantage of using computerized methods is the ability to automatically and precisely record participants' performance. This allows researchers and clinicians to run a post hoc analysis of the patients' progress or use the information to qualitatively analyze the performance and target the treatment according to the specific deficit. In this study, despite the missing impact of the treatment on the RBANS measures, we have found improvement in most VSST measures. Importantly, patients significantly improved in terms of difficulty achieved – to which VSST level they made it without a mistake during each training session. Even though the improvement rate was small ($b = 0.09$, 95% CI [0.04, 0.13], $t(156.74) = 4.04$, $p < .001$) it shows that the patients could actually benefit from the treatment. Besides their VSST memory performance, the patients were able to solve the virtual shopping task more quickly and with a shorter trajectory, pointing out increased efficiency in solving the task. These results are promising to imply that a more intense program could result in improvement with a larger effect size.

6.5. Limitations and challenges

Reported studies have several limitations. As the main reasoning behind applying VR in cognitive assessment and remediation is limited transfer of standard neuropsychological tools (Neisser, 1978; Parsons, 2015), future research should be able to confirm that VR tasks outcome can transfer into real-life. Therefore, the major limitation of reporting higher ecological validity is that we never compared the results to the measures of real-life performance. Nevertheless, some studies confirm that the virtual shopping task can successfully predict real-life behavior in a supermarket (Greenwood et al., 2016; Grewe et al., 2014), indicating the high ecological validity of this approach. Similarly, for the rehabilitation outcome in Study 4, it would be valuable to measure also the quality of life or ability to remember a shopping list in real life to indicate positivity transfer into everyday functioning. The preliminary findings (Rose et al., 2000) showing that VR-based training can result in the same or even better outcomes as training the skill in real-life should be confirmed by future studies focusing on cognitive remediation.

Furthermore, despite the potential benefits of IVR for training purposes (Jahn et al., 2021; Makransky, Borre-Gude, et al., 2019), we never tested the impact of IVR in rehabilitation settings. There are several reasons for that. Firstly, at the time of launching the remediation study, there was insufficient evidence about the usability and safety of the IVR in psychotic patients. Nevertheless, recent findings suggest that the application of IVR media should be well-accepted by patients with SZ (Bisso et al., 2020; Jahn et al., 2021). Secondly, in the context of the recent adverse epidemiological situation around the covid-19 pandemic, it was more challenging to use HMDs – the most common immersive technology at the time the study was conducted, as the headsets had to be disinfected after each participant and there is a higher risk of infection transmission than in desktop devices that are easier to keep sterile. Thirdly, although IVR technology is currently more available, the VR headsets are still cost demanding and require more space to safely conduct the training (at least 2x1.5m per participant in case of HTC Vive headset). As a result of this limitation, we never tested the Virtual City tasks designed solely for IVR, e.g., Flies, in a remediation setting in the neuropsychiatric population (except for a small unpublished pilot study).

It should be noted that even though VE tasks can be applied in the cognitive assessment, they should never be used as a sole indicator of a participant's cognitive status. As shown in our validation studies (Study 2 and 3), the isolated cognitive functions (e.g., memory recall) cannot be assessed with the current task design due to the higher complexity of tasks. Thus, the primary purpose of the developed tasks should not be standard neuropsychological assessment but training or evaluation of the everyday functioning after applying specific treatment. Moreover, the sample size in Study 2 is too small to draw any conclusion about the Flies task, and the findings should be considered preliminary. Concerning Study 3, the larger sample size would help us identify the trending relationships regarding the differences in patients' trajectory and time than healthy controls in more detail.

Regarding the outcomes of cognitive remediation Study 4, follow-up studies would be necessary to generalize our findings. First of all, even though the cross-over design and applied statistical models should control the fact that the treatment groups were not balanced, as we did not randomize the RBANS test forms (A-C), some bias still remains. Moreover, as both treatments were focused on enhancing cognitive functions, a washout period (period without any treatment) should have been applied (Sibbald & Roberts, 1998). Furthermore, due to the lack of technical equipment, complete randomization of the participants was not possible, raising the risk of bias. Nevertheless, the partially randomized technique, e.g., patients preference trials, should not compromise the internal validity of the trial outcome (Wasmann, Wijsman, van Dieren, Bemelman, & Buskens, 2019). Additionally, the sample of participants in Study 4 was rather heterogenic, as it consisted of the patients suffering from first-episode or chronic SZ, which could prevent us from generalizing our results. Nevertheless, recent findings show no effect of clinical status on the cognitive outcome (Reser, Slikboer, & Rossell, 2019). Moreover, adopting a mixed-model approach should control for the individual differences in the sample (Cnaan, Laird, & Slasor, 1997).

According to recent findings (Lejeune et al., 2021), strategy-based approaches show to be more efficient in improving memory functions in SZ patients. The importance of strategy-based approaches, especially in combination with drill practice, was previously pointed out by example by (Medalia & Choi, 2009) and was also associated with larger functional outcomes. Moreover, Lejeune et al. (2021) showed that the efficacy could be increased by discussing how the training tasks apply to real life. This method was already proposed in The Neuropsychological Educational Approach to Cognitive Remediation (NEAR) (Medalia & Freilich, 2008). Therefore, we believe that complex VE could be suitable media for applying these methods in cognitive remediation, and future studies should compare its efficacy with standard drill-practice approaches applied in most clinical trials (Paquin et al., 2014). Medalia & Choi (2009) also proposed that the training intensity in SZ should be higher, at least two to three times per week. Nevertheless, the training intensity in our study was lower (1-2 sessions per week), as patients finished the program in 6 to 12 weeks according to their attendance at the Daily Center.

Moreover, future studies should focus on replicating the studies in different NDs or SZ patients in early diagnosis, as the objective was to develop a remediation program suitable for diverse diagnoses.

6.6. Implications for VR in cognitive remediation

This work presents several studies focusing on developing and applying novel remediation methods using VR technology. The main aim was to apply media with specific advantages, e.g., the ability to present complex environments, automatic recording of participants' performance, automatized difficulty increase, etc., in cognitive intervention. It was repeatedly proposed that VR can increase ecological validity and transfer of cognitive outcomes of cognitive remediation in psychiatric patients (Kothgassner & Felnhofer, 2020; Parsons, 2015; Parsons et al., 2017). In addition, IVR can significantly increase intrinsic motivation, enjoyment, and interest which would be really beneficial for rehabilitation purposes, especially in participants with low motivation (Jahn et al., 2021; Plechata et al., 2019).

However, up to this date, experimental data from clinical trials and pilot studies do not show the advantage of IVR over non-IVR or other treatment methods, as we summarize in a recent systematic review (Plechatá, Nekovářová, & Fajnerová, 2021). As shown in recent educational psychology studies, the question should not be if the IVR is an effective tool, but how we should use it in order to be effective (Makransky, 2021; Makransky & Petersen, 2021). We believe that VR, especially in its immersive form, can surpass other media applied in cognitive remediation if it is applied with the remediation approach that can benefit from VR characteristics. For example, complex VE will not be efficient applying standard drill practice without really using the potential of the real-life setting, e.g., explaining how the ability to encode words is essential for doing groceries. Moreover, IVR can be the perfect media for strategy learning, as it allows us to simulate real-life scenarios and practice in a safe environment. Moreover, another key IVR affordance is interactivity, which can be successfully applied when combining cognitive training with physical activity (Faria et al., 2018) and can increase the feeling of agency, further increasing participants' self-efficacy (Makransky, 2021; Makransky & Petersen, 2021).

Thus, future studies and clinicians using VR should keep in mind the specific media affordances that can help training outcomes, the essential instructional design principles important for successful cognitive remediation, e.g., NEAR (Medalia & Freilich, 2008) together with neuroplasticity principles as the basis of successful restoration, e.g., repetition, intensity, salience, and transfer (Kleim & Jones, 2008) in order to capitalize on the full VR potential.

7. Conclusions

To conclude, this thesis presents some crucial implications for using virtual reality (VR) in cognitive remediation. First, immersive VR (IVR) can increase extraneous cognitive load, and thus, it can result in decreased memory performance compared to non-immersive VR (non-IVR). Second, consistent with current findings, this work confirms that IVR can enhance enjoyment from completing the task and, therefore, be suitable for rehabilitation purposes where the motivational aspect can be crucial to reduce attrition rates. Third, our results show that the developed VR cognitive tasks had high construct validity despite their interactivity and higher complexity. Fourth, our findings indicate that neither standard treatment nor novel VR-based program was successful in improving patients' cognitive performance in standard cognitive measures. Nevertheless, the patient's VR task performance significantly enhanced during the training, and patients accepted the program well. Finally, considering recent findings of cognitive remediation outcome predictors and the role of the applied method when learning in VR, different remediation approaches, specifically strategy learning, should be further investigated in this context.

8. Summary

Cognitive impairment is a core symptom of all neuropsychiatric disorders (NDs), and it has a profound impact on patients' quality of life; the deficits are especially profound in schizophrenia patients (SZ). Due to the inefficiency of pharmacological treatment in influencing cognitive impairment, cognitive remediation is a method of choice in treating cognitive impairment. However, there is only limited evidence of transferability of cognitive remediation into patients' everyday life. Therefore, virtual reality (VR), due to its ability to provide complex experiences resembling real-life challenges, was proposed as effective media to increase the transfer of cognitive remediation outcomes in patients' everyday functioning.

In this thesis, I described the development of novel remediation methods in virtual environments for patients with NDs and the process of evaluating its feasibility, validity, and potential efficacy. The developed tasks were tested and validated in the healthy young adults and healthy elderly. Furthermore, the model memory task – Virtual Supermarket Shopping Task (VSST) was used in a VR media comparison study, where the implications of using immersive and non-immersive VR in the cognitive assessment were drawn. I also presented the validation study results conducted on patients with chronic schizophrenia, confirming the construct validity of VSST as a memory task. Finally, I presented a cross-over trial investigating the efficacy and usability of the developed VR program in patients with schizophrenia and major depressive disorder. The developed program was well-accepted by patients and perceived as enjoyable and beneficial. Nevertheless, neither the standard treatment nor novel VR program resulted in cognitive improvement in the standard cognitive measures, suggesting a low impact of the applied drill-practice approach. Nevertheless, the patients improved in the VSST training task. Thus, the implication of the aspects of treatment applied using VR media were further discussed.

9. Shrnutí

Kognitivní porucha je základním symptomem všech neuropsychiatrických poruch (NP) a má hluboký dopad na kvalitu života pacientů; deficit je obzvláště výrazný u pacientů se schizofrenií (SZ). Vzhledem k neúčinnosti psychofarmakologie v léčbě kognitivních poruch má kognitivní remediace v terapii kognitivního deficitu v zásadní postavení. Existují však pouze omezené důkazy o přenositelnosti efektu kognitivní remediace do každodenního života pacientů. Proto je aktuálně virtuální realita (VR), díky své schopnosti simulovat komplexní zážitky připomínající situace z reálného života, zkoumána jako potenciálně efektivní médium pro zvýšení transferu dopadů kognitivní remediace do každodenního fungování pacientů.

V této práci popisuji vývoj nových remediačních metod ve virtuálním prostředí pro pacienty s neuropsychiatrickým onemocněním a proces zhodnocení jejich uživatelské přívětivosti, validity a potenciální efektivity v remediaci. Vytvořené tréninkové úkoly byly testovány a validovány na zdravých mladých dospělých a u zdravé stárnoucí populace. Dále práce předkládá srovnávací studii dvou VR médií – imerzivní a neimerzivní VR, ve které byla využita modelová paměťová úloha - Virtual Supermarket Shopping Task (VSST). Studie přináší poznatky o důsledcích použití imerzivní a neimerzivní VR v diagnostice. Uvádím zde také výsledky validační studie provedené na pacientech s chronickou schizofrenií a zdravých dobrovolnících potvrzující validitu VSST jako paměťového úkolu. Na konci práce popisuji cross-over trial zkoumající efektivity a uživatelskou přívětivost vyvinutého VR programu u pacientů se schizofrenií a depresivní poruchou. Navržený program byl pacienty dobře akceptován a vnímán jako zábavný a prospěšný. Nicméně ani standardní léčba, ani nový VR program nevedly ke kognitivnímu zlepšení měřenému pomocí standardních kognitivních testů. Výkon pacientů se však signifikantně zlepšil ve VSST. Proto je dále diskutována implikace aspektů remediace pomocí VR.

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Publications not related to the Ph.D. thesis:

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Diondet, S., **Plechatá, A.,** Adámková, J., Fajnerová, I. & Bartos, A., (2020). Attitudes of seniors toward computerized memory training. *Psychiatrie*. 24(3), 108-113. ISSN 1211-7579.

APPENDIX - Original publications related to the thesis