

Efficacy of Virtual Reality Treatment with NIBS for Schizophrenia

Sashvathkumar Krishnakumar¹, Rajagopal Appavu[#] and Jothsna Kethar[#]

¹Cox Mill High School, Concord, NC, USA

[#]Advisor

ABSTRACT

Technology plays a more significant role in healthcare today than it has ever done before. Technologies such as Artificial Intelligence and neurotechnology have advanced healthcare by leaps and bounds that wouldn't have even been dreamt about 50 years ago. In recent years, virtual reality technology has advanced along with these technologies and medical professionals have taken an interest in its applications, especially in the treatment of treatment-resistant mental health conditions. Research on whether virtual reality is a viable option for psychotherapy is an ongoing process that is highly influential in the medical world. VR enables therapies that may be more accessible, need less delivery time, and have more ecological validity. While NIBS has the ability to directly modify activity in social brain regions in order to promote neuroplasticity, build neural connections, and improve brain function linked to social cognitive behaviors. This paper will aim to examine the benefits virtual reality along with NIBS (Non-invasive Brain Stimulation) has over today's conventional treatment method for Schizophrenia through analyzing past case studies and discussing it in the context of a new virtual technology, Metaverse. As a result, it was concluded that virtual reality treatment is a better alternative to standard treatment today.

Introduction

Schizophrenia, a major mental disorder that affects approximately 1 in every 300 people, is one of the top 15 leading causes of disability worldwide. It can lead to a 15-20 year reduction in life expectancy yet it still continues to be treated with standard therapy and medicine. Is Virtual Reality (VR), along with NIBS (Non-Invasive Brain Stimulation), a better alternative treatment? To begin understanding the issue at hand, it is imperative to define schizophrenia as a type of mental illness. Mental illnesses can be categorized into many groups. The main ones are mood disorders, anxiety disorders, personality disorders, and psychotic disorders. Schizophrenia is considered a psychotic disorder due to the nature of its symptoms bringing about psychotic behavior in a diagnosed patient. These include hallucinations, delusions, and more.

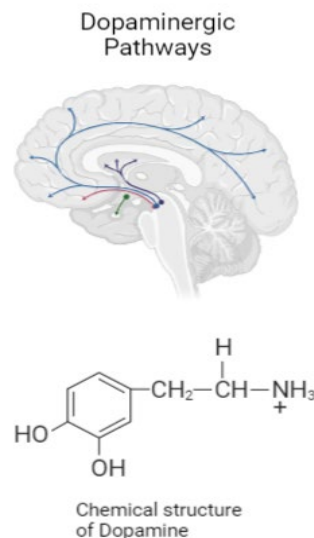
The treatment method this paper will aim to analyze is Virtual Reality (VR), a 3-dimensional computer-simulated environment that a patient interacts with through a head-mounted display (HMD) and controller. The use of virtual reality allows the patient to be immersed in a virtual environment where different scenarios can be portrayed, allowing for greater response and motivation toward treatment. NIBS encompasses a group of neuromodulatory techniques that cause activity changes in targeted regions of the brain. It is implemented during treatment by using a stimulator coil to generate a brief electrical current or magnetic pulse that passes through the hair, skin, and skull to the brain, stimulating that portion of the brain VR training benefits by administering NIBS to social cognition-relevant brain areas concurrently with VR. to help increase or decrease activity in that region. As a result, it may be able to expedite and incre

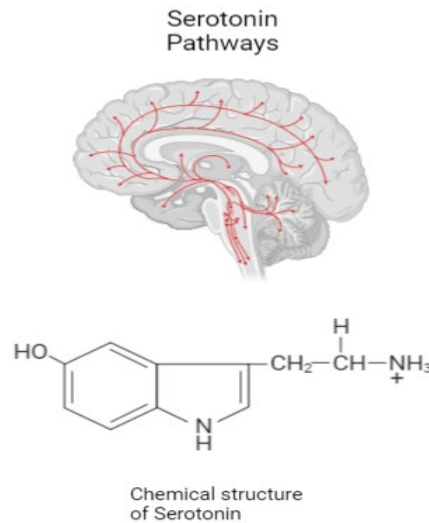
Ultimately, NIBS combined with VR might become a more accessible, less time-consuming, and more effective treatment than currently available solutions. This research paper intends to explore the potential role

of these technologies in the treatment of schizophrenia compared to the conventional therapy that is commonly used today. We will do this by reviewing past studies and research conducted using virtual reality as a treatment method for schizophrenia. This is an important topic as schizophrenia and psychological disorders are an ever-growing occurrence as a result of many factors, such as the pandemic. Learning how to treat such disorders efficiently and effectively will help numerous people struggling with not only schizophrenia but mental disorders in general.

Causes and Symptoms of Schizophrenia

It's important to know how a person is affected by Schizophrenia in their day-to-day life and what factors cause it. "The average age of onset tends to be in the late teens to the early 20s for men, and the late 20s to early 30s for women" (What Is Schizophrenia? | NAMI: National Alliance on Mental Illness, n.d.). The exact causes of Schizophrenia are unknown but researchers suggest that a combination of physical, genetic, psychological, and environmental factors can put a person at increased risk for developing Schizophrenia (NHS website, 2021). Neurotransmitters, chemicals that carry messages between brain cells, are known to have a connection with Schizophrenia because drugs that alter the level of neurotransmitters oftentimes relieve the symptoms of Schizophrenia (NHS website, 2021). Research suggests that a chemical imbalance between 2 neurotransmitters, dopamine, and serotonin, may be the root cause of Schizophrenia. Dopamine is widely considered to be the neurotransmitter responsible for motivation and plays an integral role in the brain's reward system.. Serotonin is responsible for regulating attention, behavior, and body temperature. In contrast, others have found that a change in the sensitivity towards neurotransmitters is part of the cause.





Figures 1 & 2. Shows the chemical structure of Dopamine and Serotonin. It also shows the pathways where Dopamine and Serotonin travel throughout the brain. Created and Copyright by Sashvathkumar

People diagnosed with Schizophrenia are affected by a multitude of symptoms such as “delusions, hallucinations, disorganized thinking, disorganized or abnormal motor behavior, and negative symptoms” (Schizophrenia - Symptoms and Causes, 2020). They are also affected by a decrease in executive functioning skills (EF) and social cognition impairment which makes it significantly harder to make or maintain relationships with people, consequently making it more difficult to stay employed. Teens affected by Schizophrenia express similar symptoms to adults. However, they also incur different symptoms like withdrawal from friends and family, drop in performance, trouble sleeping, depressed mood, and lack of motivation.

How Does It Affect the Brain?

Schizophrenia is a disorder that greatly affects the brain. First, Schizophrenia is associated with changes and alterations in the structure and functioning of numerous key cognitive systems, including the prefrontal and medial temporal lobe regions which relate to working memory and declarative memory respectively. Theory of mind (ToM) and emotion recognition are the two most typically damaged social cognitive domains in schizophrenia (Horan & Green, 2017; Kurtz, Gagen, Rocha, Machado, & Penn, 2016; Tan et al., 2018). The former is concerned with understanding and forecasting the intentions, beliefs, and behaviors of others, whereas the latter is concerned with identifying, understanding, managing, and interpreting emotions (Green et al., 2008). Social perception (awareness of and adherence to social and societal rules), social knowledge (awareness of what rules characterize and guide interactions), and attributional bias (how people infer causes of situations) are also domains of social cognition, but they have received less attention in schizophrenia (Green et al., 2008; Kurtz et al., 2016).

Current Diagnosis and Treatment Methods

Virtual reality not only has many benefits in the treatment aspect of Schizophrenia, but it also has numerous benefits in the diagnosis of the disorder. Before we discuss the edges virtual reality has, it's essential to know how diagnosis and treatment are being carried out today. As there is no biomarker for Schizophrenia, patients are diagnosed through physical exams, tests, and screenings such as an MRI or CT scan, and Psychiatric evaluation where a psychiatrist observes a patient's actions while asking them questions about their “thoughts, moods, delusions, hallucinations, substance use, and potential for violence or suicide”. This long and tedious

process causes patients to be unmotivated and uncooperative with medical professionals, some even refusing treatment. This is why Schizophrenia is a particularly great condition to be treated by VR due to it being engaging and eliciting motivation from patients. It's also possible for therapy to result in adverse effects like the emergence of new symptoms such as suicidality, therapy dependence, and more. Moreover, this method is unreliable as each patient manifests different subsets of symptoms which even expert observers can misinterpret. Patients can be diagnosed with Schizophrenia by being put in a virtual environment and having their actions and responses observed and compared to those of a normal control group. One instance of this is a study conducted in 2004, testing the Executive functioning (EF) skills of a group of 39 patients diagnosed with Schizophrenia compared to a group of 21 healthy comparison subjects (control group) matched by gender, age, and education level. Both groups of people were placed into a virtual reality maze where the goal was to get to the end of the game through a series of doors composed of different elements that were placed to distract the patients. Through this method, it was possible to accurately distinguish patients who were previously diagnosed with Schizophrenia from those who weren't by observing the results accumulated within each category tested. This can also help identify the symptoms a patient may develop as each patient diagnosed with Schizophrenia manifest different symptoms from each other.

Because Schizophrenia is a chronic condition, it "requires lifelong treatment, even when symptoms have subsided". Treatment is usually guided by a psychiatrist experienced in treating Schizophrenia, along with other medical professionals such as "a psychologist, social worker, psychiatric nurse and possibly a case manager to coordinate care". Medications are a crucial part of treatment, specifically antipsychotic medications which are thought to control symptoms by influencing the neurotransmitter dopamine. Medications aim to "effectively manage ... symptoms" using the least possible dosage. Antidepressants and anti-anxiety pills may also help manage symptoms. After psychosis recedes, the use of medications and intervention becomes particularly important. Some forms of therapy include Individual therapy, Social skills training, Family therapy, and Vocational rehabilitation. Although treatment is an important process that one with Schizophrenia needs to partake in, less than a 1/3 of people affected are treated. If not treated, one's mental health can worsen and one can even develop other mental disorders such as Obsessive Compulsive Disorder (OCD), Anxiety disorders, and Depression (Schizophrenia - Diagnosis and Treatment - Mayo Clinic, 2020).

Alternate Treatments

Although social and psychological intervention along with medications is the main form of treatment used today, there are alternative treatments and methods being used. Alternatives can be useful if standard therapy isn't helping and patients receive relief from these alternates. One such example of this is the use and consumption of B vitamins. Recent studies have shown that patients who have taken supplements of these vitamins with their antipsychotic medication, experienced fewer symptoms than those who've taken only the medication. Another form of alternative treatment being used is Deep Brain Stimulation (DBS). DBS is implemented through surgery where electrodes are implanted within a patient's brain tissue, which then activates brain areas through electrical stimulation that helps control motivation and logical reasoning. Closely related to this are Non-invasive Brain Stimulation (NIBS) and Virtual Reality, the focus of this research paper. Another important topic is the Metaverse and although it isn't currently being used for the treatment of Schizophrenia, it holds immense potential for psychotherapy in general and can possibly be a substantial tool later down the line.

How Does Virtual Reality Work?

Virtual Reality is an up-and-coming form of treatment for Schizophrenia, but what is virtual reality? Virtual reality is a computer-generated environment that a user is placed into and can interact with through specialized

equipment. An example of this equipment is an Oculus Quest and a handheld controller. Virtual Reality can be integrated with a patient’s treatment while they continue with standard treatment carried out by a psychiatrist. With the use of virtual reality, patients can be placed into specific scenarios chosen by a psychologist, helping them get over fears they may experience in public places or situations. It would be possible to collect data from the patient through conversation time, facial emotion recognition, and social anxiety exhibited by the patient while they are in a virtual environment. An adaptation algorithm that could change the virtual environment and tailor it towards the patient’s needs can also be implemented. It also provides a patient with a drug-free treatment option if they prefer not to consume medications. Virtual Reality works by creating the illusion that the reality the patient experiences within virtual reality is the only reality because it feels so real. ““Even if you know intellectually that you’re not at the beach, your brain can’t live in two realities at once. Instead, the brain accepts [the input] it’s given””, making it harder for patients to focus on other stimuli from the outside world such as pain or anxiety (Virtual Reality in Medicine, 2021). This is what causes the intense immersion when you enter Virtual Reality and why many psychologists find Virtual Reality to be a viable option.

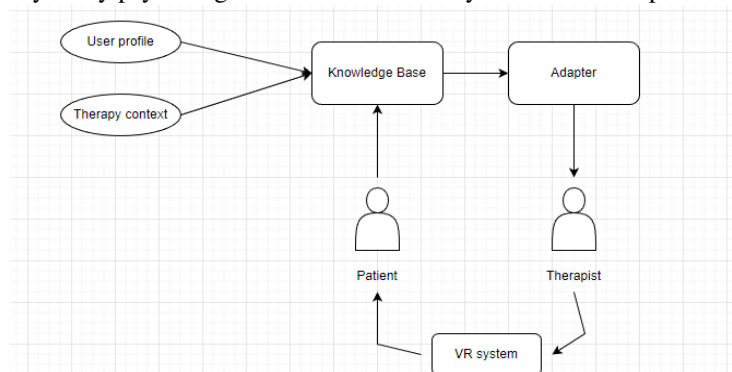


Figure 3. Shows the process of the treatment of Schizophrenia using Virtual Reality. Created and Copyright by Sashvathkumar

How Does VR Compare to The Traditional Therapy Used Today?

The advantages of virtual reality are numerous and have a notable effect on the well-being of the patient. Some of these advantages include being able to personalize treatment for the unique needs of each patient, allowing patients greater control over their exposure, providing a drug-free solution, can offer improved cost-effectiveness compared to conventional treatment programs, offering a more immersive and authentic experience, encouraging patients to continue treatment from their home, and many more.

Several studies with VR have shown promising results;

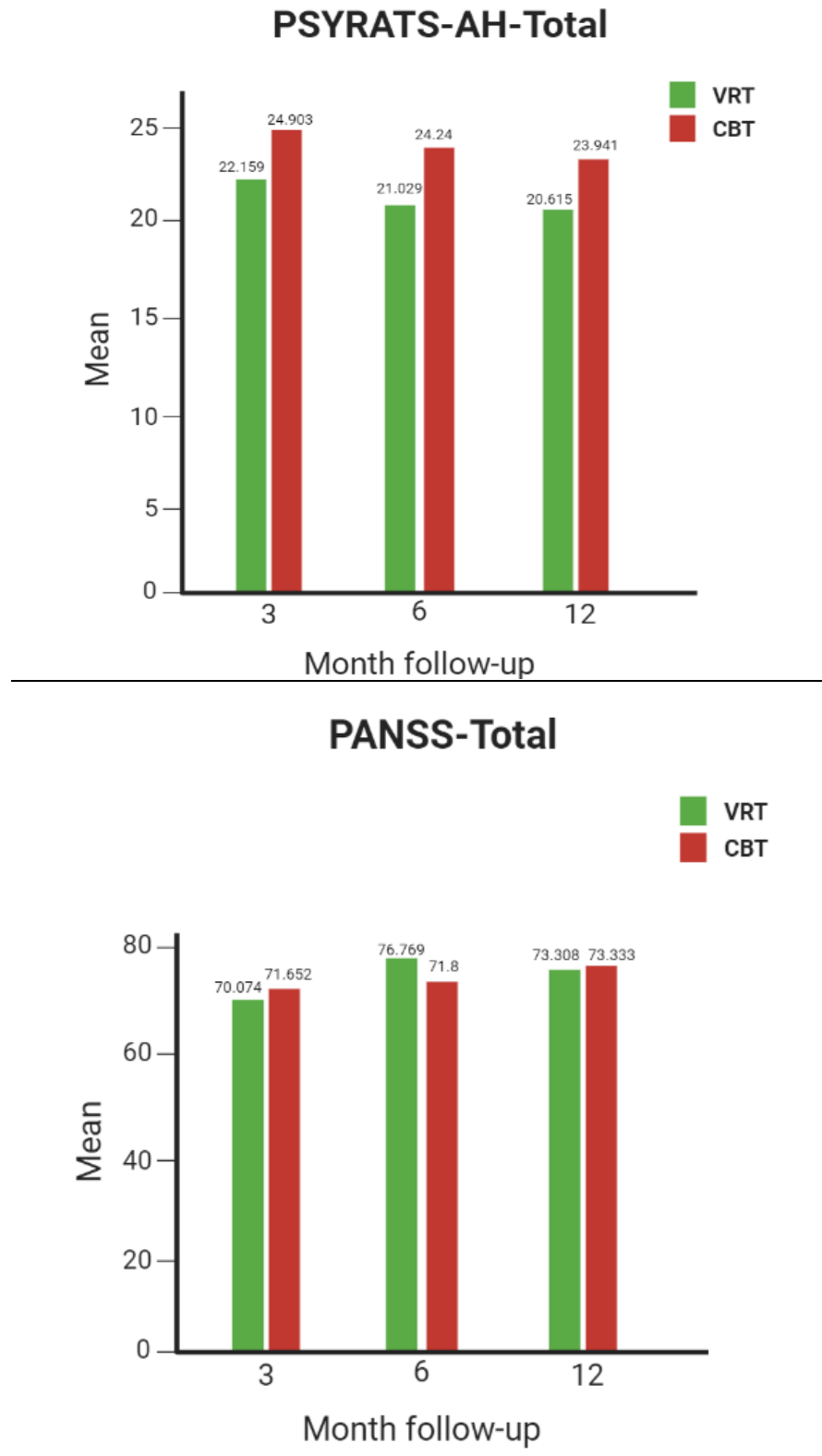
- Diagnosis and treatment of a number of disorders (i.e. anxiety, phobias, eating disorders, addiction, autism, and Alzheimer's disease; Riva, Wiederhold, & Mantovani, 2019).
- Virtual reality exposure therapy (VRET) for phobias and anxiety disorders (Cardos, David, & David, 2017; Maples-Keller, Yasinski, Manjin, & Rothbaum, 2017; McCann et al., 2014),
- Post-traumatic stress disorder ([PTSD], Maples-Keller et al., 2017),
- Eating disorders (De Carvalho, Dias, Duchesne, Nardi, & Appolinario, 2017)
- Addiction (Park et al., 2014);

From a schizophrenia perspective, there has been research on treating and improving the understanding of hallucinations and paranoia (Glanz, Rizzo, & Graap, 2003; Rus-Calafell et al., 2018).

Table 1. Synthesis matrix of results from different studies conducted comparing Virtual Reality treatment with traditional methods.

Author	Park et al., 2011 South Korea	Tsang and Man, 2013 Hong Kong	Smith et al., 2015 USA	Adery et al., 2018 USA
Participants	64 schizophrenia inpatients; 33 VR social skills training (SST-VR); 31 traditional roleplay social skills training (SST-TR)	75 schizophrenia inpatients; 25 VR vocational training (VRG); 25 Therapist-administered Group (TAG); 25 Conventional treatment (CG)	32 schizophrenia; 21 VR job interview training (VR-JIT); 11 Traditional methods;R	16 schizophrenia
Experimental Duration	10 sessions across 5 weeks.	10 sessions over 5 weeks.	10hrs VR-JIT over 5 visits	10 sessions social skills training game
Final Result	SST-VR group showed - more interest in training - better generalization - better assertiveness - better conversational skills than SST-T	VRG improved executive function performance (WCST) and self-efficacy score over TAG and CG	VR-JIT improved in job interview skills and self-confidence. At the 6-month follow-up, VR-JIT was more likely to receive job offers	Reduced negative symptoms and high user satisfaction rate

Previous studies prove its efficacy such as a one-year randomized trial conducted in 2021. In this study, patients were randomly assigned to Virtual reality-assisted therapy (VRT) or cognitive behavioral therapy (CBT) in a 1:1 ratio. They completed 7 to 9 sessions of intervention and were assessed by trained psychiatric nurses 3,6 and 12 months later. The table below shows the mean of 2 different types of assessments between CBT and VRT. It is possible to derive that since VRT had lower values on average, patients who received VRT experienced fewer symptoms after treatment compared to patients who underwent CBT.



Figures 4 & 5. Created and Copyright by Sashvathkumar

This graph shows the mean value of PSYRATS-AH (Psychotic Symptoms Rating Scale–Auditory Hallucinations) and PANSS (Positive and Negative Symptom Scale) of patients treated by VRT (Virtual Reality-assisted therapy) and CBT (cognitive-behavioral therapy) after 3,6 and 12-month follow-ups. PSYRATS-

AH is a survey used to measure the severity of hallucinations and delusions while PANSS is a medical scale used to measure the severity of symptoms in Schizophrenics. Due to there being no statistically significant difference, more research may be needed to reconcile this difference

Use of NIBS

The use of NIBS hand in hand with virtual reality can help maximize the potential of treating patients with Schizophrenia. There consists of 2 types of NIBS, transcranial magnetic stimulation (rTMS) which utilizes magnetic pulses to stimulate a part of the brain, and transcranial direct current stimulation (tDCS) which uses a weak electrical current. The application of these currents is carried out by a magnetic coil that's placed over the region of interest. Both modalities aim to increase or decrease activity in a region of the brain which allows for brain rewiring. This can help alleviate the symptoms of Schizophrenia. Proof of NIBS effectiveness is a meta-analysis conducted that included 31 randomized-controlled trials on transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) compared to sham. Sham is “an inactive form of stimulation (e.g., a very brief or weak one) that is used in research to control for the placebo effect”, and used frequently in clinical trials (About tCS - Neuroelectric's Wiki, n.d.). After analyzing the 31 randomized-controlled trials, it was concluded that both tDCS and rTMS were superior to sham in alleviating the symptoms of schizophrenia.

TMS and tES (e.g., tDCS, tACS) have mechanisms of action that make them potentially acceptable for use with VR, however, their simplicity of usage in this context varies significantly. TMS works by delivering a magnetic pulse to specific brain locations, causing brain cells to activate and, as a result, directly modifying brain activity (Rossi, Hallett, Rossini, & Pascual-Leone, 2009). TMS effects have been demonstrated to linger for more than an hour after a single stimulation session, indicating that TMS might be a helpful method for priming brain activity prior to VR intervention (Bütefisch, Khurana, Kopylev, & Cohen, 2004). Indeed, such an approach has previously been successfully utilized in VR studies, including stroke and spider phobia (Zheng, Liao, & Xia, 2015). (Deppermann et al., 2016). Online TMS testing. TMS online (i.e. at the same time as VR instruction) presents certain issues. TMS makes noises and evokes feelings that may be distracting when completing VR training and may influence performance and immersion in virtual worlds, in addition to practical challenges with huge, expensive machines that are not portable. The existing practical limits of TMS in conjunction with VR would need in-clinic treatments, which may limit its accessibility as a possible home-based combined treatment. tES methods are intriguing for usage with VR because to their low cost, mobility, safety, and usefulness (Boggio, Rêgo, Marques, & Costa, 2016). While tES approaches create scalp sensations during stimulation, they are usually restricted to slight tingling on the head. As a result, tES is less distracting and more appropriate for usage 'online' in conjunction with VR training.

Virtual Reality + NIBS Treatment

NIBS can be implemented alongside virtual reality in many different variations such as using NIBS after virtual reality treatment or vice versa. Very few studies with this combination of VR and NIBS are available; one is addressing spider phobia using an accelerated type of TMS called theta-burst stimulation ([TBS], Deppermann et al., 2016), and another is treating PTSD with tDCS and VR (van 't Wout-Frank, Shea, Larson, Greenberg, and Philip, 2019). Both studies show reduced negative symptoms and a high user satisfaction rate. Another study conducted in 2020 analyzed 16 articles that explored the combination of VR and NIBS in such variations. These articles were categorized into 5 major groups; the treatment of stroke rehabilitation, phobia and PTSD, cerebral palsy, neuropathic pain, and multiple sclerosis. In all 5 groups, NIBS plus Virtual reality had a more positive effect than sham, mainly using both simultaneously.

To be integrated with virtual reality treatment for Schizophrenia, NIBS can be used simultaneously alongside virtual reality. Virtual reality could also be used 5-10 minutes after treating a patient with NIBS which is another method that led to positive effects in alleviating symptoms. While these data sets give preliminary evidence for integrating VR and NIBS in therapy development, a number of questions remain. As technology progresses and more research is conducted to merge various technologies, a variety of difficulties and possibilities must be explored. One critical aspect for clinical or at-home use would be to ensure that both professionals and patients feel appropriately supported and trained to use combined VR and NIBS therapies (Kellmeyer, 2018). As medical technology therapy becomes more frequent, it will be critical to identify the skills and training required in this setting and begin to modify clinical training accordingly.

Context in Psychotherapy

Successfully implementing virtual reality as a prominent treatment method for Schizophrenia will help patients diagnosed with Schizophrenia and numerous other patients diagnosed with different types of mental disorders. Although virtual reality was initially designed to combat phobias, it's expanded to mental disorders such as "posttraumatic stress disorder, substance-related disorders, eating disorders, psychosis, and autism spectrum disorder" (Emmelkamp & Meyerbröker, 2021). Virtual reality has had major success in the treatment of phobias also. In a clinical study conducted, students at the University of Otago repeatedly exposed images of patients' fears to them through a VR headset over a time period of 6 weeks. This led to a 75% decrease in phobia symptoms across the 129 patients within the study.

The Metaverse

A similar concept to Virtual Reality is the Metaverse. The Metaverse is an up-and-coming digital world that is said to be the "next iteration of the internet" (Metaverse Medicine and the Doctor, Patient Avatars Ahead, 2022). It's predicted that 25% of people will spend at least 1 hour a day in the Metaverse by 2026. Recently, researchers and medical professionals have been showing interest in the use of the Metaverse in medical practice. It has possible uses in surgery practice, and more importantly for this research paper, social and psychological therapy.

Before we learn how the Metaverse can be integrated with Schizophrenia treatment, it's essential to know the difference between the Metaverse and Virtual Reality. The Metaverse allows for more interaction and socialization between people, an important factor for therapy. Moreover, Metaverse is decentralized, meaning that the community decides what they want to do and users have the freedom to control their experience. On top of all of this, the Metaverse doesn't go offline when you log off as it is always running while connected to a cloud and people can join at any time.

How can Metaverse help treat Schizophrenia and mental disorders? Because the Metaverse allows for more socialization and customizability compared to virtual reality by creating a world similar to real life where users can sing, play, games, watch movies, go shopping, and more, patients can overcome their social anxiety by talking and socializing with other people within Metaverse. The Metaverse also allows for more interactive therapy sessions between the psychologist and the patient as they are both able to see and communicate with each other within the virtual world. Metaverse is even being implemented today in the form of Metaverse clinics. Metaverse clinics are virtual clinics with physicians that are able to examine and consult with patients in real-time. "It is a 3D version of an online consultation where users can see, touch, hear and feel gestures and movements while communicating with physicians like they would in a face-to-face consultation" (Epazz DeskFlex Will Launch Metaverse Virtual Clinics, the Next-Generation Telemedicine for Physicians and Health Care Facilities, 2022). Metaverse also offers the potential for increasing the integration of Schizophrenia patients by providing a controlled setting.

Conclusion

Combining VR with NIBS has the potential to solve the limits of existing social cognitive therapies by allowing neuromodulation of brain activity while immersing users in life-like, safe, therapeutic virtual settings that might allow direct translation to real-world functioning. After reviewing several studies of treating Schizophrenia with Virtual Reality and NIBS, it is clear that Virtual Reality with NIBS is a potential alternative to conventional treatment today due to its increased efficacy in alleviating Schizophrenics of their symptoms. Today's therapy has become ineffective because of its reliance on human analysis and patient motivation. Virtual Reality is a solution that solves these problems. This paper also highlights the potential Metaverse holds in the treatment of Schizophrenia and mental disorders due to its ability to allow patients increased freedom and sociability. In conclusion, Virtual Reality and the Metaverse hold immense potential for the future of virtual healthcare and serves as an outstanding treatment method for Schizophrenia.

Acknowledgments

I would like to thank my advisor for the valuable insight provided to me on this topic.

References

- "Gainsford, K., Fitzgibbon, B., Fitzgerald, P. B., & Hoy, K. E. (2020). Transforming treatments for schizophrenia: Virtual reality, brain stimulation and social cognition. *Psychiatry research*, 288, 112974."
- About tCS - Neuroelectric's Wiki. (n.d.). https://www.neuroelectrics.com/wiki/index.php/About_tCS
- Aderly, L.H., Ichinose, M., Torregrossa, L.J., Wade, J., Nichols, H., Bekele, E., Park, S., 2018. The acceptability and feasibility of a novel virtual reality based social skills training game for schizophrenia: Preliminary findings. *Psychiatry Research* 270, 496–502. <https://doi.org/10.1016/j.psychres.2018.10.014>.
- Bisso, E., Signorelli, M. S., Milazzo, M., Maglia, M., Polosa, R., Aguglia, E., & Caponnetto, P. (2020). Immersive Virtual Reality Applications in Schizophrenia Spectrum Therapy: A Systematic Review. *International journal of environmental research and public health*, 17(17), 6111. <https://doi.org/10.3390/ijerph17176111>
- Boggio, P., Rêgo, G.G., Marques, L.M., Costa, T.L., 2016. Social psychology and noninvasive electrical stimulation. *Journal of European Psychologist* 21 (1), 30–40. <https://doi.org/10.1027/1016-9040/a000247>.
- Business Wire. (n.d.). Retrieved November 6, 2022, from <https://www.businesswire.com/news/home/20220201006263/en/Epazz-DeskFlex-Will-Launch-Metaverse-Virtual-Clinics-the-Next-Generation-Telemedicine-for-Physicians-and-Health-Care-Facilities>

- Bütefisch, C.M., Khurana, V., Kopylev, L., Cohen, L.G., 2004. Enhancing Encoding of a Motor Memory in the Primary Motor Cortex By Cortical Stimulation. *Journal of Neurophysiology* 91 (5), 2110–2116. <https://doi.org/10.1152/jn.01038.2003>
- Cardoş, R.A., David, O.A., David, D.O., 2017. Virtual reality exposure therapy in flight anxiety: A quantitative meta-analysis. *Computers in Human Behavior* 72, 371–380. <https://doi.org/10.1016/j.chb.2017.03.007>.
- Complementary Treatments for Schizophrenia. (2018, November 1). WebMD. <https://www.webmd.com/schizophrenia/schizophrenia-complementary-treatments>
- De Carvalho, M., Dias, T., Duchesne, M., Nardi, A., Appolinario, J., 2017. Virtual reality as a promising strategy in the assessment and treatment of bulimia nervosa and binge eating disorder: A systematic review. *Behavioral Sciences* 7 (4), 43. <https://doi.org/10.3390/bs7030043>.
- Dellazizzo, L. (2021, February 12). One-year randomized trial comparing virtual reality-assisted therapy to cognitive-behavioral therapy for patients with treatment-resistant schizophrenia. *Nature*. https://www.nature.com/articles/s41537-021-00139-2?error=cookies_not_supported&code=404dec89-55be-4a53-9f11-fdce00b5183e
- Deppermann, S., Notzon, S., Kroczeck, A., Rosenbaum, D., Haeussinger, F.B., Diemer, J., Zwanzger, P., 2016. Functional co-activation within the prefrontal cortex supports the maintenance of behavioural performance in fear-relevant situations before an iTBS modulated virtual reality challenge in participants with spider phobia. *Behav Brain Res* 307, 208–217. <https://doi.org/10.1016/j.bbr.2016.03.028>.
- Florida Behavioral Health. (2019, November 11). What Can Happen if Schizophrenia Goes Untreated. Behavioral Health Florida. <https://www.behavioralhealthflorida.com/blog/what-can-happen-if-schizophrenia-goes-untreated/>
- Glanz, K., Rizzo, A.S., Graap, K., 2003. Virtual reality for psychotherapy: Current reality and future possibilities. *Psychotherapy: Theory, Research, Practice, Training* 40 (1- 2), 55–67. <https://doi.org/10.1037/0033-3204.40.1/2.55>.
- Green, M.F., Penn, D.L., Bentall, R., Carpenter, W.T., Gaebel, W., Gur, R.C., Heinsen, R.J., 2008. Social cognition in schizophrenia: An NIMH workshop on definitions, assessment, and research opportunities. *Schizophr Bull* 34 (6), 1211–1220. <https://doi.org/10.1093/schbul/sbm145>.
- Heyse, J., Depreeuw, B., Daele, T. V., Daeseleire, T., Ongenaes, F., Backere, F. D., & Turck, F. D. (2022, August 19). An adaptation algorithm for personalised virtual reality exposure therapy. *Computer Methods and Programs in Biomedicine*. Retrieved November 10, 2022, from <https://www.sciencedirect.com/science/article/abs/pii/S0169260722004588#>
- Horan, W.P., Green, M.F., 2017. Treatment of social cognition in schizophrenia: Current status and future directions. *Journal of Schizophrenia Research* 203, 3–11. <https://doi.org/10.1016/j.schres.2017.07.013>.

- Howell, J. (2022, August 23). Metaverse vs. Virtual Reality: Key Differences. 101 Blockchains. <https://101blockchains.com/metaverse-vs-virtual-reality/>
- Hwang, J. (2019, January 28). The Cutting Edge of Schizophrenia Research: VR as Treatment for Psychosis. Psychiatry Advisor. <https://www.psychiatryadvisor.com/home/schizophrenia-advisor/the-cutting-edge-of-schizophrenia-research-vr-as-treatment-for-psychosis/>
- Kurtz, M.M., Gagen, E., Rocha, N.B.F., Machado, S., Penn, D.L., 2016. Comprehensive treatments for social cognitive deficits in schizophrenia: A critical review and effect-size analysis of controlled studies. Clin Psychol Rev 43, 80–89. <https://doi.org/10.1016/j.cpr.2015.09.003>.
- Maples-Keller, J.L., Yasinski, C., Manjin, N., Rothbaum, B.O., 2017. Virtual reality-enhanced extinction of phobias and post-traumatic stress. Neurotherapeutics 14 (3), 554–563. <https://doi.org/10.1007/s13311-017-0534-y>.
- Mead, T. (2022, July 15). Fear factor: Study shows virtual reality can cure phobias. 1 News. <https://www.1news.co.nz/2022/07/14/fear-factor-study-shows-virtual-reality-can-cure-phobias/>
- Metaverse Medicine and the Doctor, Patient Avatars Ahead. (2022b, August 12). WebMD. <https://www.webmd.com/a-to-z-guides/news/20220812/metaverse-medicine-doctor-patient-avatars-ahead>
- NHS website. (2021b, November 18). Causes - Schizophrenia. nhs.uk. <https://www.nhs.uk/mental-health/conditions/schizophrenia/causes/>
- Noninvasive Brain Stimulation Program. (n.d.). Mount Sinai Health System. <https://www.mountsinai.org/locations/abilities-research-center/programs-technologies/brain-stimulation-program>
- Orellana, G., & Slachevsky, A. (2013). Executive functioning in schizophrenia. Frontiers in psychiatry, 4, 35. <https://doi.org/10.3389/fpsy.2013.00035>
- Osoegawa, C., Gomes, J. S., Grigolon, R. B., Brietzke, E., Gadelha, A., Lacerda, A. L. T., Dias, Á. M., Cordeiro, Q., Laranjeira, R., Jesus, D. de, Daskalakis, Z. J., Brunelin, J., Cordes, J., & Trevizol, A. P. (2018, February 4). Non-invasive brain stimulation for negative symptoms in schizophrenia: An updated systematic review and meta-analysis. Schizophrenia Research. Retrieved November 10, 2022, from <https://www.sciencedirect.com/science/article/abs/pii/S0920996418300318#!>
- Park, C.-B., Choi, J.-S., Park, S.M., Lee, J.-Y., Jung, H.Y., Seol, J.-M., Kwon, J.S., 2014. Comparison of the effectiveness of virtual cue exposure therapy and cognitive behavioral therapy for nicotine dependence. Cyberpsychology, Behavior, and Social Networking 17 (4), 262–267. <https://doi.org/10.1089/cyber.2013.0253>.
- Park, K.M., Ku, J., Choi, S.H., Jang, H.J., Park, J.Y., Kim, S.I., Kim, J.J., 2011. A virtual reality application in role-plays of social skills training for schizophrenia: A randomized, controlled trial. Psychiatry Research 189 (2), 166–172. <https://doi.org/10.1016/j.psychres.2011.04.003>.

- Psychiatry Online. (n.d.). The American Journal of Psychiatry. Retrieved November 6, 2022, from <https://ajp.psychiatryonline.org/action/cookieAbsent>
- Riva, G., Wiederhold, B.K., Mantovani, F., 2019. Neuroscience of virtual reality: From virtual exposure to embodied medicine. *Cyberpsychol Behav Soc Netw* 22 (1), 82–96. <https://doi.org/10.1089/cyber.2017.29099.gri>.
- Rossi, S., Hallett, M., Rossini, P.M., Pascual-Leone, A., 2009. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology* 120 (12), 2008–2039. <https://doi.org/10.1016/j.clinph.2009.08.016>.
- Schizophrenia and Your Brain. (2015, December 24). WebMD. <https://www.webmd.com/schizophrenia/schizophrenia-and-your-brain>
- Schizophrenia - Diagnosis and treatment - Mayo Clinic. (2020b, January 7). <https://www.mayoclinic.org/diseases-conditions/schizophrenia/diagnosis-treatment/drc-20354449>
- Schizophrenia - Diagnosis and treatment - Mayo Clinic. (2020c, January 7). <https://www.mayoclinic.org/diseases-conditions/schizophrenia/diagnosis-treatment/drc-20354449>
- Shpancer, N. (2020, March 7). When talking doesn't cure: Negative outcomes in therapy. *Psychology Today*. Retrieved November 10, 2022, from <https://www.psychologytoday.com/us/blog/insight-therapy/202003/when-talking-doesnt-cure-negative-outcomes-in-therapy#:~:text=They%20include%20treatment%20failure%20and,undermining%20of%20self%E2%80%90efficacy.%22>
- Smith, M.J., Fleming, M.F., Wright, M.A., Roberts, A.G., Humm, L.B., Olsen, D., Bell, M.D., 2015. Virtual reality job interview training and 6-month employment outcomes for individuals with schizophrenia seeking employment. *Schizophr Res* 166 (1-3), 86–91. <https://doi.org/10.1016/j.schres.2015.05.022>.
- Srivastava, K., Das, R. C., & Chaudhury, S. (2014). Virtual reality applications in Mental Health: Challenges and perspectives. *Industrial psychiatry journal*. Retrieved November 11, 2022, from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4361984/>
- Tan, B.L., Lee, S.A., Lee, J., 2018. Social cognitive interventions for people with schizophrenia: A systematic review. *Asian J Psychiatr* 35, 115–131. <https://doi.org/10.1016/j.ajp.2016.06.013>.
- Tsang, M.M.Y., Man, D.W.K., 2013. A virtual reality-based vocational training system (VRVTS) for people with schizophrenia in vocational rehabilitation. *Schizophr Res* 144 (1), 51–62. <https://doi.org/10.1016/j.schres.2012.12.024>
- van 't Wout-Frank, M., Shea, M.T., Larson, V.C., Greenberg, B.D., Philip, N.S., 2019. Combined transcranial direct current stimulation with virtual reality exposure for posttraumatic stress disorder: Feasibility and pilot results. *Brain Stimul* 12 (1), 41–43. <https://doi.org/10.1016/j.brs.2018.09.011>.

Vassev, N. (2022, May 25). How the Metaverse Will Reshape Mental Health Therapy. Entrepreneur. <https://www.entrepreneur.com/science-technology/how-the-metaverse-will-reshape-mental-health-therapy/427930>

What causes schizophrenia? Mind. (n.d.). Retrieved November 10, 2022, from <https://www.mind.org.uk/information-support/types-of-mental-health-problems/schizophrenia/causes/>

What is Schizophrenia? | NAMI: National Alliance on Mental Illness. (n.d.-b). Retrieved November 6, 2022, from <https://www.nami.org/About-Mental-Illness/Mental-Health-Conditions/Schizophrenia>

Your Guide to the Metaverse. (2022, October 25). Ledger. <https://www.ledger.com/academy/your-guide-to-the-metaverse>

Zheng, C.-J., Liao, W.-J., Xia, W.-G., 2015. Effect of combined low-frequency repetitive transcranial magnetic stimulation and virtual reality training on upper limb function in subacute stroke: a double-blind randomized controlled trial. Journal of Huazhong University of Science and Technology [Medical Sciences] 35 (2), 248–254. <https://doi.org/10.1007/s11596-015-1419-0>