SEMMELWEIS EGYETEM

DOKTORI ISKOLA

Ph.D. értekezések

3257.

ERDŐS SÁNDOR

Gyermekkori betegségek klinikuma, élettana és prevenciója

című program

Programvezető: Dr. Szabó Attila, egyetemi tanár

Témavezető: Dr. Horváth Klára, egyetemi adjunktus

USING VIRTUAL REALITY TO MANAGE STRESS IN CHILDREN AND YOUNG ADULTS

PhD thesis

Sándor Erdős, MD

Károly Rácz Conservative Medicine Division

Doctoral College Semmelweis University

Supervisor: Klára Horváth MD, DPhil

Official reviewers:
Edit Haluska-Vass, PhD
Máté Bence Szondy, PhD

Head of the Complex Examination Committee:
András Kiss MD, PhD, DSc

Members of the Complex Examination Committee:
Dóra Krikovszky MD, PhD
Katalin Müller MD, PhD
Mónika Csóka MD, PhD

Budapest
2025

TABLE OF CONTENTS

1. Introduction 6

1.1. Fundamentals of Stress 6

1.1.1. Definition 6

1.1.2. Pathomechanism 7

1.2. Coping with stress 10

1.3.1. Measurement 10

1.3.2. Treatment 11

1.4. Virtual reality in medicine 12

1.4.1. Definition and presence 12

1.4.2. Side effects 15

1.4.3 Fields where VR could be revolutionised 17

1.5. VR in acute stress management 20

1.5.1. Mindfulness-based VR interventions 20

1.5.2. VR for stress reduction during procedures 22

2. Objectives 28

2.1. Project I. 28

2.2. Project II. 28

2.3 Project III. 29

3. Methods 31

3.1. Project I. 31

3.1.1. Participants 31

3.1.2. Procedure 31

3.1.3. Measures 32

3.1.4. Data Analyses 32

3.2. Project II. 33

3.2.1. Participants 33
3.2.2. Procedure 34
3.2.3. Measures 35
3.2.4. Data Analyses 36
3.3. Project III. 37
3.3.1 Participants 37
3.3.2 Sample size 38
3.3.3. Procedure 38
3.3.4. Measures 40
3.3.5. Statistical analysis 40
4. Results 42
4.1. Project I. 42
4.2. Project II. 43
4.2.1. Phase I. 43
4.2.2. Phase II. 46
4.3. Project III. 48
5. Discussion 54
6. Conclusion 59
7. Summary 61
8. References 62
9. Bibliography of the candidate's publications 73
9.1. Bibliography related to the thesis 73
9.2. Bibliography not related to the thesis 73
10. Acknowledgements 74

LIST OF ABBREVIATIONS

BP	Blood pressure
CBT	Cognitive behavioural therapy
CRH	Corticotropin-releasing hormone
DBP	Diastolic blood pressure
EDA	Electrodermal activity
GA	General anaesthesia
GAD	Generalised anxiety disorder
GI	Guided imagery
HMD	Head-mounted display
HPA	Hypothalamic-pituitary-adrenal
HR	Heart rate
HRV	Heart rate variability
MBSR	Mindfulness-Based Stress Reduction
PSS	Perceived Stress Scale
PTSD	Post-traumatic stress disorder
RCT	Randomised controlled trial
SAD	Social anxiety disorder
SAM	Sympathetic-adreno-medullary
SBP	Systolic blood pressure
SCI	Spinal cord injury
SCL	Skin conductance level
STAI	State-Trait Anxiety Inventory
VAS	Visual analogue scale
VR	Virtual reality
VRET	Virtual reality exposure therapy
VRT	Virtual reality therapy

1. INTRODUCTION

As psychological stressors continue to rise, it is essential to find innovative solutions that can mitigate stress responses, improve well-being, and complement existing therapeutic methods. The purpose of this dissertation is to explore the application of virtual reality (VR) technology as a tool for managing stress in children and young adults. The introduction begins with an overview of the background and significance of stress, emphasising its biological and psychological components. Next, the role of VR in medicine is presented, detailing its capacity to create engaging, customizable environments that can enhance the sense of presence and help reduce stress levels. The discussion then transitions to the specific application of VR for stress reduction during acute medical procedures and in mindfulness-based interventions. This framework sets the stage for the subsequent detailed examinations of three major research projects.

Project I examines the effects of mindfulness-based VR exercises on young adults. This project compares VR-delivered mindfulness sessions with tablet-based meditation, hypothesising that the immersive quality of VR may lead to greater anxiety reduction. Project II focuses on children undergoing chemotherapy. This study employs a crossover design to assess the impact of a VR experience on both psychological outcomes and physiological markers of stress. Project III investigates the efficacy of VR as a preparatory tool for children facing MRI examinations. Through an ongoing randomised controlled trial, this study assesses whether VR-based preparation can reduce the need for anaesthesia and alleviate pre-procedure distress compared to traditional educational booklets or standard care. The beginning of the thesis lays the groundwork for an in-depth exploration of VR's potential to transform stress management in clinical practice.

1.1. Fundamentals of Stress

1.1.1. Definition

Stress is a complex biological and psychological process that has been defined in various ways. Hans Selye proposed the earliest and most widely recognised definition of stress: "Stress is the non-specific response of the body to any demand" (1). According to behavioural scientists, stress is "the perception of threat, resulting in anxiety, discomfort, emotional tension, and difficulty in adjustment" (2). From a biological perspective,

specifically neuroendocrinology; “stress is any stimulus that provokes the release of ACTH and adrenal glucocorticoids”, which definition comes from Eugene Yates (3) Another essential definition comes from Richard Lazarus, who defined stress as a “particular relationship between the person and the environment that the person appraises as taxing or exceeding his or her resources and endangering his or her well-being” (4). In the following section, the potential classifications of stress will be examined.

First, stress can be categorised into acute and chronic forms. Acute stress is short-term and typically occurs in response to immediate threats, such as accidents, moving, or exams. It contributes to the body's fight-or-flight response, which triggers temporary physiological changes, including a rise in heart rate (HR) and the release of adrenaline. Acute stress is often adaptive, aiding in task performance and survival. However, when stressors are prolonged or repeated over time, such as in long-term hospitalisation, it is referred to as chronic stress. It is detrimental to both physical and mental health, contributing to various disorders such as cardiovascular disease, depression, and anxiety (5). Secondly, it is crucial to distinguish between positive stress (eustress) and negative stress (distress). Eustress refers to stress perceived as manageable and motivating, leading to improved performance and resilience. It occurs when individuals perceive challenges as exciting, achievable, and beneficial for personal development, such as a promotion at work (6). Distress results when demands exceed an individual’s coping ability, causing emotional and physiological strain. It often appears when losing a job or the death of a family member, and leads to anxiety, reduced performance, and potential burnout (4). The individual’s perception of the stressor, their coping resources, and the context in which stress occurs all play key roles in determining whether stress will have positive or negative outcomes. Based on the different forms and definitions of stress, physiological and psychological factors play crucial roles in understanding the effects of stress.

1.1.2. Pathomechanism

The stress response is regulated through a complex interaction of nervous, endocrine, and immune mechanisms, involving the activation of the sympathetic-adreno-medullary (SAM) axis, the hypothalamic-pituitary-adrenal (HPA) axis, and the immune system (7). SAM plays one of the most prominent roles, which activation increases

norepinephrine and epinephrine release from the adrenal medulla and sympathetic nerves, elevating norepinephrine levels in the brain. These hormones interact with α- and β-adrenergic receptors in the central nervous system and on smooth muscle cells, initiating a signalling pathway that quickly activates cellular responses. This results in smooth and cardiac muscle contractions, causing elevated blood pressure (BP), HR, glucose levels, oxygen consumption, reduced intestinal motility, and bronchiolar dilation. Additionally, SAM activation boosts behaviours such as alertness, vigilance, focus, and pain tolerance (8). Another important biological factor in understanding stress development is HPA axis activation, where corticotropin-releasing hormone (CRH) is released from the hypothalamus and induces adrenocorticotropic hormone (ACTH) release from the pituitary gland. ACTH then stimulates the adrenal cortex to secrete cortisol, the main glucocorticoid hormone, often referred to as the stress hormone. Cortisol helps the body manage stress by mobilising energy reserves, supporting cardiovascular function, and controlling inflammation. Cortisol also affects brain areas like the hippocampus and amygdala, influencing memory, mood, and emotional processing (9). Generally, a stressful situation triggers the SAM and HPA axis, initiating the fight-or-flight response. This acute response is driven by epinephrine, norepinephrine, and cortisol; therefore, this change increases BP, redirects blood flow to muscles, raises blood glucose, and enhances muscle strength and mental alertness, preparing the body for intense physical activity. Once the threat subsides, physiological functions return to normal.

Stress significantly impacts multiple bodily systems, with both acute and chronic forms eliciting distinct physiological responses. One of the most well-documented consequences of stress is its impact on the cardiovascular system. Acute stress increases HR and redirects blood flow to muscles, while chronic stress elevates cortisol and epinephrine levels, leading to oxidative stress and atherosclerosis and heightening cardiovascular risk (10). The respiratory system also reacts to stress with bronchial hyperresponsiveness and altered breathing, potentially exacerbating asthma and COPD due to immune system compromise. In the gastrointestinal system, stress hormones delay gastric emptying, reduce blood flow, and disrupt gut motility, contributing to symptoms like IBS and impairing gut barrier integrity (11). Stress-mediated dysregulation of the gut-brain axis worsens gastrointestinal diseases via two-way communication between the central nervous system and gut microbiota (12). Chronic stress affects the

musculoskeletal system by causing muscle tension and reducing bone density, increasing susceptibility to conditions like tension headaches and fibromyalgia. Under chronic stress, the immune system experiences suppression, raising susceptibility to infections and promoting inflammatory conditions (13). Chronic stress induces systemic inflammation by upregulating inflammatory mediators, contributing to the development of chronic inflammatory disorders (14). The reproductive system is also affected by disrupted hormone regulation, leading to menstrual irregularities, infertility, and sexual dysfunction (15). Finally, early-life stress has been linked to the development of a wide range of chronic conditions in later life, including cardiovascular diseases, metabolic disorders, and immune dysfunction (16).

The physiological and psychological effects of stress are equally significant. According to Lazarus, there is no clear distinction between physical stressors, which affect biological tissue systems, and psychological stressors (4). Stress influences the brain's structure and function, particularly in regions involved in memory, learning, and emotional regulation, such as the hippocampus, amygdala, and prefrontal cortex. Chronic stress leads to elevated cortisol levels, which, over time, can result in hippocampal atrophy, impairing memory and cognitive function (17). Stress also affects the prefrontal cortex, the brain region responsible for higher-order cognitive functions such as planning, impulse control, and emotional regulation. Prolonged stress can weaken the connections between the prefrontal cortex and other brain regions, impairing decision-making and emotional reactivity (18). Individuals experiencing chronic stress may adopt maladaptive coping mechanisms, such as overeating, substance misuse, or social withdrawal. Maladaptive behaviours may initially provide relief but can ultimately increase psychological strain and lead to dependency (19). Stress has a profound impact on both depression and anxiety, two of the most prevalent mental health conditions worldwide. Previously mentioned mechanisms of stress in relation to depression and anxiety are interlinked, involving both neurochemical changes in the brain and psychological responses that exacerbate these conditions. Chronic stress alters brain chemistry, particularly by affecting neurotransmitters such as noradrenaline, which are crucial for mood regulation. A study by Kendler et al. demonstrated that individuals exposed to stressful life events are more likely to develop depressive symptoms, especially those with a genetic predisposition (20). This relationship is partly mediated by dysregulation

of the HPA axis, leading to increased cortisol levels that disrupt mood balance. Additional studies indicate that stress-induced changes in the hippocampus, a region associated with memory and emotional regulation, can contribute to depressive symptoms due to impaired cognitive function and emotional processing (21). Elevated cortisol levels also contribute to feelings of hopelessness, helplessness, and anhedonia, which are core features of depression (22). Stress also plays a critical role in the development and maintenance of anxiety disorders. Prolonged stress exposure can lead to hyperactivity in the amygdala, the brain's fear centre (23). Consequently, individuals under chronic stress are more prone to heightened anxiety, panic, and excessive worry, all of which contribute to generalised anxiety disorder (24). While acute stress may cause temporary anxiety, chronic stress tends to establish a feedback loop that perpetuates and intensifies anxiety symptoms. Depression and anxiety often interact with stress in a cyclical manner, where each condition amplifies the other. Anxiety heightens perceived stress levels by increasing sensitivity to everyday challenges, while stress can deepen depressive symptoms. As noted by Hammen et al., individuals suffering from both depression and anxiety typically report higher levels of perceived stress, making them more vulnerable to further stressors (25).

1.2. Coping with stress

1.3.1. Measurement

There are several opportunities to measure stress using psychological and physiological approaches. One of the main methods involves measuring stress hormone levels (cortisol, epinephrine, and norepinephrine) in blood, saliva, and urine. These tests offer objective metrics for assessing physiological stress responses. These biomarkers represent the functional activity of the HPA axis and the SAM system. Another effective method is the measurement of heart rate variability (HRV), which evaluates the variations in time intervals between successive heartbeats, offering insights into the autonomic balance between the sympathetic and parasympathetic systems. A reduced HRV typically indicates sympathetic predominance and elevated stress, while a higher HRV correlates with greater stress resilience and improved cardiovascular function. Another method that measures cardiac outputs involves monitoring shifts in blood pressure and HR, providing valuable information on cardiovascular responses to stress (26). Electrodermal activity

(EDA), assessed via skin conductance, tracks changes in sweat gland activity due to sympathetic nervous system arousal. Increased EDA signifies increased autonomic activation associated with stress (27). Finally, evidence indicates that the human body temperature shifts in response to stress (28).

Another way to measure stress levels involves self-reported questionnaires, providing a practical yet subjective assessment of stress. Several validated questionnaires are used daily in clinical practice. These instruments can capture both general and specific aspects of stress, including perceived stress levels, frequency of stressors, and personal coping strategies. One widely recognised tool is the Perceived Stress Scale (PSS), developed by Cohen et al., which assesses how different situations affect participants' feelings and perceived stress. The PSS is comprised of a 10-item, 5-point Likert scale, valid in many languages (29). Another well-established measure is the State-Trait Anxiety Inventory (STAI) developed by Spielberger et al., which measures state anxiety (temporary condition of emotional arousal) and trait anxiety (stable tendency to experience anxiety). Although primarily designed for anxiety, the STAI provides insight into stress responses, as anxiety often coexists with stress reactions, offering clinicians a more nuanced understanding of stress-related affective states (30).

1.3.2. Treatment

Coping refers to a person's cognitive and behavioural efforts to manage specific external and internal demands appraised as taxing or exceeding the person's resources (4). These efforts can involve addressing stressful situations directly, modifying their emotional responses, or finding ways to avoid the stressors altogether. There are several psychotherapeutic methods which can improve individuals' coping skills. One of the most common is cognitive behavioural therapy (CBT), which focuses on identifying and modifying negative thought patterns and behaviours contributing to stress. By helping individuals develop healthier coping strategies and improve emotional regulation, CBT can reduce stress levels and prevent stress from escalating into chronic conditions such as anxiety or depression (31). CBT can be applied in various settings (individual, group, or online). However, it requires a time commitment and active participation, which may be difficult for individuals experiencing high-stress levels. Another technique that can help individuals focus on the present moment, improving awareness and reducing the

physiological and psychological impacts of stress, is mindfulness. Mindfulness has been shown to reduce cortisol levels, improve emotional regulation, and enhance overall well-being (32). Mindfulness is a cost-effective, accessible technique that can be practised independently or in a structured group setting. On the other hand, there is individual variability in finding mindfulness techniques effective and easy to incorporate into their daily routine. In addition to psychotherapeutic tools, there are other options for reducing stress. One is regular physical activity, which can be the most effective way to manage stress. Exercise reduces levels of the body's stress hormones, such as cortisol. Activities like running, swimming, and cycling have been shown to improve mental health by reducing anxiety and improving mood (33). It also provides a targeted psychological treatment that may be especially effective for patients who find more traditional psychological interventions less acceptable. Moreover, exercise is widely accessible and can be adapted to individual preferences and abilities, although it can be challenging or painful for those with physical limitations. Finally, pharmacological approaches such as anxiolytics (e.g., benzodiazepines) and antidepressants (e.g., selective serotonin reuptake inhibitors) are often prescribed to manage stress-related conditions, especially when stress leads to anxiety disorders or depression. These medications can help stabilise mood, reduce anxiety, and improve sleep, thus helping individuals cope with stress more effectively (34). With pharmacotherapy agents, rapid relief of stress-related symptoms is available, especially for individuals who cannot attend psychotherapy methods because of their severe symptoms. All medications can have side effects (gastrointestinal issues, sedation, sexual dysfunction), and long-term use, like benzodiazepines, carries the risk of dependency.

1.4. Virtual reality in medicine

1.4.1. Definition and presence

VR is an immersive technology that simulates a computer-generated, three-dimensional environment where users can interact in real time. Typically, VR systems include a combination of hardware (head-mounted displays - HMDs and controllers) that track the user's movements and adjust the virtual environment accordingly (see Figure 1). This creates the sensation of physical presence in a virtual world, allowing users to interact with objects or scenarios as if they were in the real world (35). VR aims to

transcend reality and provide environments that might be impossible, impractical, or unsafe to recreate in the real world. For these reasons, it is suitable for specific therapeutic purposes. The effectiveness of a VR system largely depends on the user's sense of immersion and the intensity of their perceived presence within the virtual environment (36). Presence goes beyond simple engagement; it is a deeper cognitive and emotional state wherein the virtual world feels genuinely real, allowing users to interact with and react to virtual stimuli as if they were tangible. This sense of presence can lead to deeper engagement, enhanced memory retention, and heightened emotional responses compared to traditional media (37, 38). For example, VR is more effective in creating emotional responses during experiences such as simulated public speaking, leading to better training outcomes for anxiety management (39). VR's ability to create tailored environments is another notable advantage. Unlike traditional methods, VR environments can be customised to meet specific user needs, making them versatile tools across disciplines, such as an operating room for surgery education or a snowy landscape for burn victims.

Figure 1. VR system in action (own photograph).

Researchers often distinguish between different types of presence in virtual environments. Physical presence refers to the sensation of being physically located within the virtual world (40). Users experience this form of presence when they feel like they are truly inside the simulated environment, moving and interacting with virtual objects as they would in the real world (41). Based on another definition, presence is described as a subjective psychological experience composed of three key elements: the feeling of being there, responding to what is there as if it were real and recalling the environment as a familiar place, much like real life (42). Witmer and Singer proposed that increased

involvement and immersion in virtual environments correlate with heightened levels of presence (43). This type of presence is particularly crucial in applications such as surgical VR training, where realistic simulations can significantly enhance learning outcomes.

Another form of presence in VR is social presence, which involves perceiving other virtual characters or avatars as real individuals. Short, Williams, and Christie introduced the concept of social presence to explore how different communication media compare to face-to-face interactions and how well each conveys social cues (44). They defined social presence as the degree to which one feels the presence of others during interaction, significantly influencing interpersonal relationships. The main idea across these theories is that social presence increases as the quality of the medium improves, with face-to-face communication typically offering the highest sense of presence. Social presence makes virtual interactions feel more real, helping users feel connected to others within a virtual space. It can be important in VR simulations to place patients in social scenarios that provoke anxiety, such as group gatherings. Patients can practice managing their responses to social situations by interacting with virtual characters in a controlled and safe environment.

Beyond the basic idea of "just being there" or simply being present in the virtual world, researchers have introduced a related concept called co-presence, which focuses on a deeper psychological feeling of togetherness (45). Originating from Goffman's work, co-presence describes a sense of shared space in a virtual environment where people become available, visible, and able to interact (46). Co-presence includes sensing the presence of others and perceiving their awareness of oneself, fostering a sense of belonging to a group (46). While social presence is more about the medium's quality and the user's perception of others, co-presence emphasises a direct, psychological connection between people (47). Co-presence is valuable in therapeutic VR settings, such as group therapy or support groups, where individuals benefit from mutual awareness and emotional support.

Several factors influence user experiences of presence in virtual environments. Technological immersion has a moderate impact, with evidence suggesting that higher levels of user tracking, stereoscopic visuals, and wider fields of view significantly enhance presence more effectively than improvements in visual and auditory content alone (48). Additionally, a consistent and coherent virtual world, free from unrealistic or

contradictory elements, sustains higher levels of presence (39). User engagement also plays a crucial role; prior experience with VR, individual spatial abilities, and current mental states significantly influence perceived immersion. Presence relies on focused attention and is driven by the interaction of sensory stimuli and environmental factors that foster immersion and engagement. Witmer et al. developed the Immersive Tendencies Questionnaire to assess individual variations in experiencing presence. Users familiar with immersive technologies or open to new experiences typically report higher presence levels (49). Conversely, individuals experiencing greater simulator sickness tend to perceive lower presence levels compared to those with fewer symptoms.

1.4.2. Side effects

While VR offers numerous benefits, it also presents several challenges and potential negative consequences. These downsides come from both the technological limitations of VR systems and the psychological, social, and physical effects on users. Understanding these negative aspects is crucial for the responsible development and use of VR technologies, especially as their adoption becomes more widespread. One of the most well-documented negative side effects of VR is cybersickness, a condition similar to motion sickness. The pathomechanism of cybersickness is not exactly known; however, it is possibly connected to the vestibular system. It often occurs when the user's eyes perceive movement in the virtual world, but their body remains stationary. Common symptoms of cybersickness include nausea, dizziness, headaches, and fatigue (50). Prolonged exposure to VR can exacerbate these symptoms, limiting the time users can comfortably spend in virtual environments. Technological advancements, such as improving frame rates, reducing latency, and optimising motion tracking, have helped mitigate cybersickness. Extended use of VR systems can also lead to physical discomfort. Eye strain is common, as users spend long periods focusing on screens close to their eyes, leading to visual fatigue and discomfort. In addition, musculoskeletal strain can result from holding VR controllers or maintaining certain postures during VR sessions. VR's immersive and engaging nature also brings the potential for addiction or overuse. The addictive potential of VR apps, as they currently exist, is scarcely distinct from other online activities rooted in traditional media, such as video games or social networking platforms. However, the fact that feelings of embodiment predict addictive VR use

suggests that future applications utilising more immersive technologies could become even more addictive for users (51).

There are some cases when the use of VR is contraindicated because the side effects can cause serious health problems. Research indicates that individuals with a history of epilepsy, especially photosensitive epilepsy, are at increased risk of seizure when exposed to VR stimuli. VR heavily relies on multisensory integration; thus, severe visual impairments (e.g., monocular vision or significant uncorrected visual deficits) or auditory impairments can limit the VR experience and, in some cases, compromise safety. VR use following head injuries can lead to exacerbated symptoms, including dizziness, headaches, and cognitive strain. Most companies set an age limit above 10 to use VR devices; however, based on several studies in a controlled environment, it is possible to use VR safely for those above 4 years old (52). Finally, there are some psychiatric disorders like psychosis or serious mental retardation which prevent to use VR.

The cost-effectiveness of VR in various applications, including healthcare, presents a complex, ambivalent picture. On one hand, high-quality VR hardware, such as HMDs, can be expensive, with significant upfront costs required for hardware, software development, and maintenance. These costs may initially pose a financial barrier. For instance, purchasing a VR system for therapeutic purposes involves the equipment and the training of professionals to implement it effectively. However, when considering long-term use and scalability, VR can become more cost-effective than traditional methods, particularly in therapeutic and educational settings. For example, in psychological therapy, the cost of a single session with a psychologist can be high, especially for long-term or intensive treatments. VR-based therapeutic tools, once developed, can offer scalable solutions that allow for repeated, guided, self-administered therapy at a fraction of the cost of in-person sessions. We now have a much clearer understanding of which therapeutic techniques are most effective. However, a shortage of suitably trained therapists remains, and maintaining quality control is a persistent concern. VR and related technologies could help address this challenge by making the best therapeutic techniques accessible to a broader audience. Nevertheless, VR's potential extends beyond merely enhancing psychological treatment delivery. VR enables experimentation with approaches that would be challenging to implement in real-world settings (53).

1.4.3 Fields where VR could be revolutionised

One of the most prominent applications of VR is in surgical training. VR surgical simulations allow surgeons to refine their skills and gain experience with complex procedures before performing them on actual patients. Results suggest that HMD provide enhanced immersion, spatial awareness, and interactivity, aligning with motor skill acquisition and constructivist educational theories. Nevertheless, issues including limited system fidelity, operational difficulties, and physical discomfort were identified. Many studies reported comparable or superior outcomes to traditional methods, highlighting the significance of social interaction (54).

VR has also proven to be valuable in training emergency medical personnel. Virtual simulations can replicate real-world emergency scenarios, such as trauma cases or mass casualty incidents, allowing healthcare workers to practice rapid decision-making and team coordination under pressure. These simulations provide a safe space for learning, enabling medical teams to rehearse responses to critical situations without putting patients at risk. According to the results, the students have high, sustained acceptance and ease of use. Most students find VR engaging and valuable for learning emergency medicine skills. Notably, the occurrence of motion sickness was minimal. These results suggest that VR can significantly enhance medical education by enabling immersive, high-fidelity training in emergency and high-pressure clinical contexts (55).

VR has also shown great promise in pain management, particularly for chronic pain patients or those undergoing painful medical procedures. With a sense of presence, VR can offer distraction-based therapies that reduce pain perception by engaging patients in immersive virtual environments. These VR experiences act as a form of cognitive distraction, diverting attention away from pain and towards a more engaging virtual world. VR pain relief has been applied in various contexts, including burn wound care, physical therapy, and during labour. Spiegel et al. created a prospective, randomised, comparative effectiveness trial conducted in hospitalised patients. Patients in the experimental group experienced 21 VR sessions delivered through an HMD, while control patients viewed specialised television programming focused on health and wellness. The primary outcome was patient-reported pain, measured using a numeric rating scale and recorded by nursing staff during routine care. Results showed that VR significantly reduce pain compared to an active control condition in hospitalised patients,

with the greatest effect observed in cases of severe pain (56). Patients with chronic pain endure long-term discomfort that adversely impacts their daily lives and mental health. Pharmacological treatments for chronic pain and pruritus may involve side effects, leading to a search for non-invasive, non-pharmacological options. Wong et al. conducted a systematic review that included seventeen peer-reviewed articles. In the analysed studies, 1 to 20 VR sessions were used, each lasting between 1 and 120 minutes. Furthermore, patients were able to experience the positive effects of VR at home in two of the studies. Patients suffering from phantom limb pain, chronic headache, chronic neck pain, and chronic low back pain have shown improved pain outcomes with VR (57). Furthermore, VR is a feasible, acceptable, and safe intervention for children and adolescents with chronic pain across a range of conditions, offering promise as an adjunctive treatment to enhance pain management and quality of life (58).

VR is increasingly being utilised in rehabilitation, offering interactive, task-specific therapy for patients recovering from strokes, spinal cord, or musculoskeletal injuries. In traditional rehabilitation, patients often engage in repetitive exercises to restore movement, strength, and function. VR enhances this process by providing engaging, goal-oriented activities within a virtual environment that simulate real-life tasks. The use of VR in rehabilitation has been shown to improve patient motivation, as the immersive environments make the exercises feel more like games than repetitive, monotonous tasks. Additionally, VR systems can track patients' progress in real-time, providing immediate feedback on performance and allowing therapists to adjust treatment protocol. For instance, spinal cord injury (SCI) is a prevalent neurological condition characterised by damage to the spinal cord. In neurological rehabilitation, VR is increasingly utilised to assess and address the physical limitations associated with SCI. VR has demonstrated the potential to improve walking ability and balance in individuals with SCI (59). Additionally, VR-based therapy effectively complements physical therapy within anterior cruciate ligament (ACL) rehabilitation programs, as it reduces pain and enhances knee function, strength, range of motion, and dynamic balance following ACL injury (60).

Mental health is the field where VR technology is most used. One of the most researched fields is phobias. In traditional exposure therapy, patients are gradually exposed to anxiety-provoking stimuli in a controlled environment to desensitise them to

these stimuli. VR enhances this process by enabling therapists to create highly realistic and customizable virtual environments where patients can confront their fears in a safe and controlled setting. The results showed a positive effect on VR-based exposure therapy in treating most phobias (61). Similarly, for post-traumatic stress disorder (PTSD) patients, VR exposure therapy allows them to re-experience traumatic events in a therapeutic environment. Unlike in vivo exposure, where real-world settings might be difficult or impossible to recreate, VR can simulate these traumatic experiences with high fidelity. For instance, soldiers can relive battlefield scenarios, or accident survivors can re-experience the traumatic event under the guidance of a therapist. Heo et al.'s findings demonstrated the superiority of using VR for PTSD symptoms compared to controls, highlighting the importance of immersive treatments for PTSD (62). VR is suitable for developing diagnostic procedures (for example, attention deficit hyperactivity disorder - ADHD) as well as therapeutic methods. Recent studies on VR-assisted psychiatric assessments have been conducted to validate VR environments (63). In virtual environments, physicians can examine patients' mental symptoms in real-time. For instance, a Spanish company developed a classroom with many exciting stimuli for children who are diagnosed with ADHD (64). In this virtual classroom, psychiatrists can observe hyperactivity, lack of inhibitory functions, and a continuous urge to speak. VR can be helpful in reducing generalised anxiety disorder (GAD) and social anxiety disorder (SAD) symptoms. Malbos et al. evaluated the effectiveness of VR combined with relaxation for GAD, comparing VR relaxation therapy with standard mental imagery exposure. This study randomly assigned participants to one of the therapies, each delivered in six weekly 30-minute-long sessions. VR participants could choose from six relaxing virtual environments to apply their techniques. Results showed significant improvements in anxiety, worry, mood, and positive functioning in both groups, though no significant difference was found between them (65). Kampmann et al. conducted a study with patients diagnosed with SAD, randomly assigning them to individual virtual reality exposure therapy (VRET) (n=20), individual in vivo exposure therapy (n=20), or a waiting list (n=20). The treatments consisted of ten 90-minute-long sessions twice weekly, with VRET including virtual one-to-one and group scenarios designed to trigger anxiety. Results showed symptom improvement from pre- to post-assessment in both

VRET and in vivo exposure therapy groups; however, greater symptom reduction was observed in the in vivo exposure therapy group (66).

1.5. VR in acute stress management

Acute stress is a significant challenge in medical settings, where patients often face fear, uncertainty, and discomfort related to medical procedures, diagnoses, and treatments. Stressful events such as diagnostic imaging and chemotherapy can elicit both psychological and physiological stress responses (67, 68). These acute stress reactions can negatively affect patient outcomes and increase the need for sedative or analgesic medications (67, 69). As a result, healthcare professionals are increasingly exploring innovative interventions to mitigate stress, enhance patient experience, and improve overall well-being. One promising approach is the use of technology innovations like VR technology.

VR, through its sense of presence, provides patients with immersive, interactive environments that can distract them from stress-inducing stimuli in medical settings, such as the sights, sounds, and sensations associated with medical procedures. By transporting patients to calming virtual worlds, VR can reduce stress and anxiety, making medical procedures more tolerable (70). Furthermore, VR is extremely suitable for education (71). In many cases, the source of stress is a lack of knowledge. Specialists can create specific virtual environments, such as a radiotherapy machine or an MRI scanner, so patients can relive the experience before the real procedure (72, 73).

In the following studies, our main goal was to mitigate stress with virtual reality in real-life medical settings. Therefore, the final section of the introduction will explore specific areas where we conducted investigations into reducing acute stress with VR. These settings included diagnostic imaging (MRI scans) and chemotherapy treatments. Additionally, we investigated how virtual reality can complement traditional psychology methods such as mindfulness.

1.5.1. Mindfulness-based VR interventions

Mindfulness-based interventions have long been recognised as effective tools for treating stress, anxiety, cancer-related symptoms, and depression (74). Traditionally, mindfulness practices, such as meditation, breathing exercises, and body scans, have been

conducted in physical environments through structured programs like Mindfulness-Based Stress Reduction (MBSR) (75). However, with the advent of VR technology, mindfulness practices have been given a new, immersive dimension that enhances the engagement and accessibility of these interventions.

VR exhibits promising features for supporting mindfulness practice, particularly with immersive and multisensory experiences. Most studies indicate that VR facilitates greater relaxation self-efficacy, decreases cognitive drift, and promotes the maintenance of attentional focus (76). Tarrant et al. compared a brief nature-based mindfulness VR experience to a resting control condition in anxious participants. Self-reported anxiety symptoms and resting-state EEG were recorded across intervals of quiet rest or the VR intervention. Results showed that both the quiet rest control and VR meditation significantly reduced subjective anxiety reports, aligning with a physiological reduction in anxiety. This pilot study offers preliminary evidence supporting the therapeutic potential of VR for anxiety management and stress reduction programs (77).

Another study investigated 44 participants at a mindfulness conference who wore an HMD, experiencing a calm, 3D-generated virtual river while listening to specific, digitised mindfulness training instructions. VR supports mindfulness development by minimising real-world distractions, enhancing the sense of presence, and providing an engaging environment for mindfulness practice. Participants reported increases in mindfulness states and decreases in negative emotions. After VR, they noted significantly reduced sadness, anger, and anxiety, along with a notable increase in relaxation. These findings offer promising preliminary evidence for the feasibility and acceptability of VR-based mindfulness training based on expert clinical feedback (78).

VR can establish virtual scenarios that support mindfulness practice, as shown in the Modrego-Alarcón randomised controlled trial that examined the effects and acceptability of mindfulness-based VR environments among university students. Specifically, a single group (n = 93) underwent an intervention consisting of six brief VR mindfulness sessions. Participants' mindfulness and emotional state were measured immediately before and after each VR environment session. VR is an appealing, immersive environment that aids participants in visualising complex ideas, creating interactive simulations, and mastering practical skills within a controlled setting. These insights align with research indicating that immersive technologies in higher education

encourage active, engaging learning among students. Overall, the sample of 93 university students responded positively to VR as a mindfulness technique, reporting high initial expectations and, upon completing the intervention, expressing high satisfaction and perceived usefulness (79).

The same mindfulness meditations delivered via VR and computer were compared in a between-subjects study. The study aimed to enhance exam performance, potentially by reducing pre-exam anxiety. Students exposed to the VR-based meditation benefited more from this relaxation technique than the video-based control group. VR technology may facilitate deeper immersion in meditative environments for learners, thereby promoting greater relaxation and improved performance (80). In a pilot randomised trial by Poetar et al., desktop-based mindfulness meditations were also compared. This study evaluated the effects of negative and positive emotions using the Positive and Negative Affect Schedule questionnaire (81). Both VR and computer-based mindfulness practices effectively reduced negative emotions. Notably, positive emotions significantly increased only in VR, with no significant reports of cybersickness. These findings suggest potential advantages of VR-based mindfulness meditation over computer-based approaches, particularly enhancing positive emotions.

Several design concepts suggest that VR could introduce interactive and body-centred innovations to mindfulness practice. The latest developments in VR systems allow for personalised mindfulness environments tailored to the individual's preferences, thereby increasing patient engagement and intervention efficacy. As VR systems become more accessible and cost-effective, their integration into routine healthcare practices could become more feasible, broadening mindfulness interventions' reach to patients needing psychological support during treatment.

1.5.2. VR for stress reduction during procedures

1.5.2.1. Reducing stress during chemotherapy treatment.

Chemotherapy is often lengthy and uncomfortable, and it is one of the most emotionally and physically taxing experiences for children with chronic illnesses. In paediatric oncology, children face multiple layers of stress: the pain and side effects of treatment, fear of medical procedures, disruption of daily routines, and prolonged hospitalisation. These factors can lead to elevated anxiety, a sense of helplessness, and

long-term emotional consequences. Moreover, the unfamiliar and clinical hospital environment often intensifies distress, especially in younger patients who may not fully understand the purpose of their treatment. According to a cross-sectional study, more than a quarter of participants experienced anxiety or depression. Psychological symptoms were more frequently observed among those who had received a lower number of chemotherapy sessions (82). These difficulties affect not only the child but also the entire family system. Chronic parental stress has been linked to lower emotional, physical, and social functioning in paediatric patients (83). Given these challenges, there is a growing need for supportive interventions that help children cope with the emotional burden of chronic illness. As a result, existing guidelines like the Pediatric Psychosocial Standards of Care advocate for a multimodal therapeutic approach. (84). A key recommendation is the routine assessment and management of stress using age-appropriate, non-pharmacological methods such as cognitive-behavioural strategies, play therapy, psychoeducation, and family-centred care. VR could be a new element of this comprehensive approach during chemotherapy.

Several studies have investigated the effects of VR technology on physiological and psychological variables in adult patients. In a study involving 66 women with breast cancer undergoing adjuvant chemotherapy, the intervention group viewed beach and nature scenes through VR glasses for 30 minutes, while the control group received standard care. Data was collected using an Introductory Information Form, the State Anxiety Scale, and the Cancer Fatigue Scale, with assessments conducted for each cycle across four cycles. Results showed a reduction in mean post-application anxiety scores in the intervention group compared to their pre-test scores, with their anxiety levels continuing to decrease from the first to the last cycle. Additionally, the intervention group's mean post-test anxiety scores were consistently lower across all four cycles compared to those of the control group (85). Another randomised controlled trial included 80 breast cancer patients. They were randomly allocated to either a VR group or a control group. Results indicated that a single session combining immersive VR with morphine significantly reduced self-reported pain and anxiety scores compared to morphine alone. The use of VR as an adjunct to traditional pharmacological treatment was more effective than morphine alone and demonstrated a higher safety profile than pharmacological options (86). Besides pain and anxiety reduction, Schneider et al. investigate the impact

of VR on time perception during intravenous chemotherapy. Each participant underwent two matched chemotherapy sessions, one of which involved the use of VR as a distraction-based intervention. The findings suggest that VR is a non-invasive tool that can improve the tolerability of chemotherapy by altering patients' perception of time (87).

Biological variables can increase the evidence of VR's positive effect. Ioannu evaluated whether VR can improve mood and biophysical parameters in cancer patients through interaction with an immersive environment; a comparison was made with patients experiencing a Guided Imagery (GI) intervention. Patients in the VR group showed greater significant improvements in mood across all mood sub-scales compared to those in the GI group. Systolic blood pressure (SBP) decreased from baseline in both groups, with a progressive decline observed across successive interventions for the GI-VR group. Similar patterns were noted for diastolic blood pressure (DBP) and HR (88).

Children often perceive the stress, nausea, and fatigue linked to treatment as more distressing than the illness itself (89). A randomised controlled trial was conducted to investigate the feasibility and acceptability of using immersive virtual reality to manage anxiety, nausea, and vomiting in paediatric cancer patients undergoing their first chemotherapy. Paediatric patients in China undergoing their initial intravenous chemotherapy were enrolled and randomly assigned to either the intervention group (three immersive virtual reality sessions) or the control group (standard care). The results indicated that the intervention was feasible, demonstrated by a high consent rate and low withdrawal rates. The intervention group showed significantly greater improvement in anxiety and a more substantial reduction in acute nausea compared to the control group.

Another randomised controlled trial included 41 children, aged 7 to 16, receiving chemotherapy in a university hospital's paediatric haematology and oncology wards. Data were collected using the Child Anxiety Scale-State, Child Fatigue Scale-24-Hours, and Visual Fatigue Scale in both groups before and during the first three days of chemotherapy treatment. A statistically significant difference was observed between the intervention and control groups' mean anxiety and fatigue scores across group, time, and group–time interaction (90).

Cancer patients often endure severe pain due to their illness, the stages of chemotherapy they undergo, and its side effects, which can increase stress levels and decrease daily activities. Sharifpour et al. aimed to assess the impact of virtual reality

therapy (VRT) on pain variables in 30 adolescents with cancer during chemotherapy. The experimental group participated in eight 30-minute VRT sessions once a week over 2 months, while the control group was placed on a waiting list. Results showed significant differences in pain variables between the experimental and control groups. Additionally, the effects of the treatment were sustained during the first and second follow-up periods (91).

VR is increasingly recognised as an effective tool for alleviating the physical and psychological burden of chemotherapy. Research demonstrates that VR interventions can significantly reduce anxiety, pain, fatigue, and nausea in adults undergoing treatment (92). VR has been shown to enhance the effectiveness of pharmacological treatments and offer sustained benefits over time (91, 93). While the feasibility and acceptability of VR in clinical settings are well-documented among adults, further research is needed to explore its effects in children. Moreover, there is a lack of studies investigating the impact of VR on physiological variables. Our aim is to examine the effectiveness of VR among children undergoing chemotherapy, which Project II will later address in Chapter 3.2. Understanding the underlying mechanisms and optimising its application could solidify VR's role in improving the chemotherapy experience for children.

1.5.2.2. Reducing stress during MRI scans

The unfamiliar environment of MRI procedures can be highly stressful for children and their parents, often causing significant anxiety. Patients are enclosed in a narrow, noisy tube and must remain still for extended periods. Claustrophobia is a notable concern during MRI, with approximately 1 in 100 patients requiring premature scan termination due to claustrophobic reactions (94). According to a study by Shanbari et al., of the 465 participants had undergone an MRI (95), over half (55.9%) reported moderate MRI-related anxiety. While 74% desired more specific information, 48% experienced breathing difficulties and 51% reported panic. This discomfort and anxiety can increase minor movements during the scan, resulting in poor-quality MRI images or failed scans. As a result, general anaesthesia has become a core part of MRI procedures for children. A study found that the use of general anaesthesia in children’s MRI procedures increased between 2011 and 2014 (96). However, general anaesthesia is not risk-free, with common side effects such as nausea, headache, and dizziness as well as potential severe reactions like respiratory distress, allergic reactions, or arrhythmias (97). Anaesthesia also adds

considerable costs due to the need for specialised equipment and personnel. Since anxiety has been associated with higher doses of anaesthetic drugs, reducing anxiety may lessen anaesthesia-related complications, especially for dose-dependent side effects, such as those linked to opioids (98).

Research has shown that adequate preparation and information can reduce the need for general anaesthesia in MRI procedures. Various methods, such as step-by-step instructional videos and MRI models, have been used to prepare children. (99) Rothman et al. reported that fewer children needed anaesthesia when they received comprehensive instruction (booklet, movie, and simulator practice) than when they received only booklet-based preparation, suggesting that proper preparation may ease anxiety and make anaesthesia unnecessary or reduce its required dosage (100).

A few studies have explored VR use for MRI preparation, though they have involved small samples. One study involved adults (n=20) who experienced VR and a mock MRI scan. Anxiety, comfort, and relaxation were assessed at five time points, with no significant differences in anxiety or comfort between the conditions, and participants reported both experiences as equally real. VR offers advantages over mock MRI equipment, including lower space requirements and cost-effectiveness. Furthermore, an awake MRI was successfully completed in 4 out of 5 children who would otherwise have required general anaesthesia for the procedure under routine care (69). Another study with 4-12-year-old children (n=23) used a 360-degree interactive VR experience before MRI. Four of the five children who typically require anaesthesia completed an awake MRI. All children reported feeling more positive about the MRI experience and stated they would recommend VR preparation to others. Stunden et al. conducted a randomised controlled trial with 92 children aged 4-13 divided into VR, brochure, and no-preparation groups in a simulated MRI setting. Questionnaires measured anxiety and procedural knowledge, and movement was recorded. No significant differences were found among the groups, although a correlation was noted between children's and parental anxiety (68).

Studies highlight that proper preparation, using tools like instructional videos, booklets, and mock MRI simulators, may reduce anxiety and the need for anaesthesia. (99, 100) Emerging evidence suggests that VR could be a promising alternative for MRI preparation. Few studies have demonstrated that VR experiences can reduce anxiety, occasionally eliminating the need for general anaesthesia (GA) (68, 69). However, high-

quality randomised trials comparing VR to other preparation methods have yielded mixed results and did not investigate the GA need as a primary objective. Therefore, we have initiated a randomised controlled trial (RCT, Project III) to explore the need for anaesthesia as a primary outcome and to measure the psychological variables of children and their parents too. Positive results can contribute to replacing or complementing traditional preparation methods for children's psychological well-being.

2. OBJECTIVES

Our research focuses on the stress-reducing effects of VR technology among children and young adults. We conducted three studies examining the relationship between VR and stress. First, we studied the effects of mindfulness-based virtual experiences among young adults (Project I), and then we conducted a study among children with cancer undergoing chemotherapy (Project II). Finally, our research centred on reducing the stress associated with MRI examinations in children (Project III).

2.1. Project I. – Effects of a VR-based mindfulness exercise on young people

While the number of studies investigating VR-based mindfulness interventions is growing (101, 102), very few have directly compared VR with other digital modalities, such as tablet or desktop devices. Most notably, prior comparative studies (80, 81) used between-subject designs with limited outcome scopes. In contrast, our study used a within-subject design to compare VR and tablet-based mindfulness, reducing interindividual variability. It uniquely combined psychological, physiological, and time perception measures to assess immersion, flow state and emotional impact, offering a more comprehensive view of the user experience than prior studies.

Based on these findings, we hypothesised that the VR condition contributed to a significant reduction in anxiety compared to the tablet condition. Additionally, we investigated whether VR would promote greater parasympathetic dominance reflected in lower HR, stabilised body temperature, and reduced EDA both during and after the intervention. Finally, we expected that participants immersed in the VR experience would perceive the duration of the exercise as shorter than its actual length.

2.2. Project II. – The impact of VR on children undergoing chemotherapy

To date, very few studies have explored the application of VR for stress reduction during paediatric chemotherapy (103, 104). Among those, none to our knowledge has used a within-subject design, which significantly reduces noise from between-subject variability arising from different diagnoses and temperament. Another novel aspect is the inclusion of physiological data, such as EDA and peripheral temperature, which offer

objective insights into stress response. The VR content was also custom-developed, which may maximise the stress reduction effect of VR in phase II.

To complement these findings, we created a study which investigated the impact of VR in chemotherapy-treated children. It had two phases; the first phase examined the effects of an interactive VR experience and a mobile phone condition through a crossover design on multiple psychological and physiological variables during chemotherapy, assessing its potential to enhance patient well-being within a clinical context. We hypothesised that VR sessions would reduce anxiety, nausea, and fatigue while also improving mood during chemotherapy. Additionally, we anticipate that VR would attenuate sympathetic nervous system activity, as evidenced by reductions in HR, SBP, and EDA. A crossover design was again utilised in the second phase of the investigation. We developed a custom-made VR experience and compared it to the VR experience used in Phase I. We hypothesised that the specifically developed VR experience would reduce anxiety, HR, EDA, and peripheral temperature more effectively than a freely available VR game.

2.3 Project III. – Efficacy of a VR-based simulation in preparing children for MRI examinations

Most existing studies on MRI preparation in children have been limited by small sample sizes, lack of randomised controlled designs, and implementation in experimental settings. Furthermore, while passive interventions such as videos, role play, or mock scanners are commonly used, immersive virtual reality tools remain underexplored (68, 69, 100).

In contrast, we designed a randomised controlled trial with a specifically developed VR experience to evaluate the efficacy of a VR-based preparatory approach in children before MRI examinations. We hypothesised that a smaller proportion of children in the VR group would require anaesthesia for MRI compared to those in the booklet and control groups. Furthermore, we expected that children in the VR group would show more significant improvements in fear, mood, and distress and a higher level of familiarity with the MRI procedure. We also anticipated a stronger preference for the VR intervention among children compared to the booklet and control groups and an increased willingness among VR group participants to undergo future MRI scans. Additionally, we

hypothesised that the VR intervention has the potential to reduce the required dose of anaesthesia in comparison to the control groups.

3. METHODS

3.1. Project I. – Effects of a VR-based mindfulness exercise on young people

3.1.1. Participants

Participants were recruited via social media, specifically through Facebook groups, to reach young adults who met the specified eligibility criteria. Inclusion criteria specified that participants were to be between 18 and 30 years of age, self-reporting basic proficiency in English, and either currently enrolled in or having completed university studies. A total of 50 volunteers (26 females and 24 males, with 47 being university students) were selected, with ages ranging from 19 to 28 years (M = 23, SD = 1.93 years). All participants were able to attend both scheduled mindfulness sessions. The sample sizes were informed by similar earlier studies in the literature.

3.1.2. Procedure

The study received ethical approval from the Semmelweis University Regional and Institutional Committee of Science and Research Ethics. (registration date: 8.01.2021; registration number: 183/2020) Data collection was carried out between October 2020 and June 2021. This randomised crossover trial examined and compared the effects of two device-assisted mindfulness interventions on time perception, physiological responses, and psychological states in young adults. Each participant engaged in two mindfulness sessions: one delivered via a VR headset (experimental condition) and the other via a tablet device (control condition). The sequence of conditions was randomised, using a pre-generated random sequence, ensuring that 25 participants commenced with VR and 25 with the tablet. Due to the nature of the interventions, neither the participants nor the experimenter was blinded to the conditions. Before the first session, participants were informed about the study, and written consent was obtained.

Mindfulness sessions were administered using an Oculus Go VR headset (Oculus VR LLC, California, USA, 2018) and a Samsung Galaxy Tab A tablet (Samsung Electronics, Suwon, South Korea, 2019) equipped with an Acer Predator Galea 311 headset (Acer Inc., New Taipei City, China, 2020). The Guided Meditation VR™ experience (Cubicle Ninjas, Chicago, USA, 2018) provided a 20-minute English-

language relaxation program on a virtual beach without background music. Participants were guided by a female voice through breathing exercises, body scanning, and visualisation (e.g., imagining birds flying in virtual surroundings). The VR session was recorded using the device's internal system and downloaded as a 20-minute video. The tablet version featured visuals and audio identical to those of the VR application.

Sessions were held in a quiet room within an office setting to provide a calm environment. Upon arrival, participants wore an Empatica E4 device on their left wrist. After, they had the initial 20 questions of the STAI-Y to assess state anxiety. Following the survey, they participated in the mindfulness session via the assigned device. Upon completing the session, participants filled out the STAI-Y once more and responded to a brief question about time perception. No methodology or outcome measures changes occurred after the study's initiation.

3.1.3. Measures

Physiological data were collected using an Empatica E4 wristband (Empatica Inc., Cambridge, USA) same as in Project I, measuring HR (average HR values calculated over 10-second intervals), body temperature (recorded in Celsius at a sampling rate of 4 Hz), and EDA (measured in μS at 4 Hz). Data were uploaded to Empatica's Web Portal, E4 Connect, for visualisation and download in CSV format. The STAI-Y is a validated psychological instrument for assessing anxiety levels in young adults; we employed the Hungarian version (105). This self-report scale is used to gauge momentary (state) feelings, with the internal consistency coefficient being $\alpha = 0.91$. The questionnaire was completed independently by participants. Time perception was measured with the question: "How long do you think the exercise lasted?"

3.1.4. Data Analyses

Metrics for pre- and post-intervention states were calculated by averaging data over two-minute intervals immediately before and after the mindfulness session, while data collected during the session were also averaged. State anxiety scores were determined based on the STAI-Y Manual.

The raw HR, body temperature, and EDA data were processed using R Statistical Software (v4.3.2, R Core Team, 2021). (106) Due to substantial individual variability in EDA, a bandpass filter with a 0.01 μS to 100 μS range was applied as in Project I. No HR

and body temperature filtering was necessary as values remained within physiological limits. All HR, body temperature, and EDA signals underwent visual inspection to identify any instability during data capture. No data were excluded due to poor signal quality. Statistical analyses involved averaging data over two-minute periods before and after the mindfulness sessions. A repeated-measures ANOVA analysis was conducted, with paired t-tests for post-hoc analysis. Dependent variables included physiological measures and STAI-Y scores, with time and condition as within-subject factors. Additionally, sign tests were performed separately for the VR and tablet conditions to assess whether time underestimation or overestimation differed significantly from zero. Bonferroni correction was applied to control for multiple comparisons, setting the significance threshold at P = .025.

3.2. Project II. - The impact of VR on children undergoing chemotherapy

3.2.1. Participants

The study involved thirty-five children, aged 10 to 18, undergoing chemotherapy treatment. Participants were recruited from the oncology units of the Second Department of Paediatrics, Semmelweis University, between August 2018 and February 2020. Of forty-three children approached, eight declined to participate for various causes (e.g., lack of interest, feeling unwell). Although VR devices are typically recommended for individuals aged 13 and above, we concluded that this age limit could safely be lowered in a controlled setting. Children aged eight years and older were included, as they demonstrated sufficient maturity to understand the tasks and independently use the VR device and controllers. The inclusion requirements were active chemotherapy treatment, inpatient status at an oncology unit, age 8-18, and stable participation condition (as evaluated by nursing staff). Exclusion criteria were the following: visual impairments, eye movement disorders, primary neurological conditions, or intellectual disabilities.

Phase II was in the same oncology units at Semmelweis University from September 2020 to July 2022. Thirty children were recruited for the investigation, and seven declined to participate for different reasons. Inclusion and exclusion criteria remained the same. The sample sizes of both studies were guided by previous similar research.

3.2.2. Procedure

A crossover design was utilised in phases I and II, where all participants were enrolled in experimental and control conditions. The sequence of conditions was randomised across participants, with a pre-determined random sequence indicating the starting session for each participant. Sessions were scheduled to ensure that each child received the same chemotherapeutic agents in both conditions, thereby controlling for the varying effects of different drugs. Research protocols were authorised by the Semmelweis University Regional and Institutional Committee of Science and Research Ethics (Phase I - registration number: 79/2018, registration date: 22.05.2018; Phase II – registration number: 184/2020, registration date: 0.10.2020). The children and their parents were informed that participation was voluntary and that they could withdraw without providing a reason. Written consent was obtained from the parents at the beginning of the study.

The experimental VR condition utilised the full version of A Night Sky (Coatsink Software LTD, UK, 2017) in phase I. This game was chosen because it avoids sudden positional changes, reduces the risk of cybersickness, and features an interactive design that enables children to manipulate the virtual environment using a controller, potentially enhancing immersion and a sense of control. In the game, participants connect stars in an Arctic landscape, with successful star-linking rewarded by the appearance of mythical creatures. The game was demonstrated on a Samsung Gear VR (Samsung Galaxy S7 Edge, Samsung Electronics Co., Seoul, South Korea, 2016) or Oculus Go (Oculus VR LLC, California, USA, 2018) device, each featuring a 5.5-inch display with 2560 x 1440 resolution and a 3-degrees-of-freedom motion detection system, allowing orientation tracking but not position tracking, so that children could look around but not move in the virtual experience. The VR environment was mirrored onto a computer screen, enabling the experimenter to monitor and guide the children. All devices were thoroughly sanitised using antiseptic wipes before and after each use. In the phase I control condition, children were allowed to choose a mobile game on their own device, selecting one that suited their current state, which helped reduce individual variability.

In phase II, the control condition was the A Night Sky VR experience (phase I experimental condition). After six months of planning and collaboration between doctors, psychologists, and IT specialists, we created a VR experience for phase II. Because there is no formal guidelines currently exist on what constitutes an effective or child-friendly

VR experience. Our design was informed by developmental and clinical considerations. We prioritised ease of use, environments that clearly contrast with hospital settings, and included metaphorical elements related to recovery. (e.g. pills) The game features a low-poly design, and it is customisable to give the child back control; for example, children can change the character. The game has a short storyline where patients assist a dragon whose island has been overrun by various enemies, symbolising the challenges of hospitalisation (see Figure 2). These enemies can be defeated through logical and action-based mini-games where patients can use medical tools to win.

Initially, we encountered technical difficulties such as unstable screen mirroring and headset calibration issues. However, advances in standalone VR technology, particularly the release of Oculus Go have significantly improved usability and screen mirroring also helped the experimenter to support children in a virtual environment. With this device, the systems are quick to set up (under 5 minutes) and can be managed by our volunteers after a brief 45–60-minute training. However, the use of the device necessitates a trained volunteer for the safety of the experience. Devices are disinfected between uses and are easily portable, allowing flexibility across different wards and examination rooms. The research procedure, including the tools and design used, remained consistent in all phases.

Figure 2. Specifically developed "OncoVR game" beginning scene (own photograph).

3.2.3. Measures

Phase I HR and SBP were evaluated with an automatic blood pressure monitor on the upper arm. EDA was examined with an Obimon device featuring a 22-bit analogue-to-digital converter, a zero-drift operational amplifier, and a constant voltage EDA

method, with electrodes attached directly to the device. The Obimon device collected EDA data every 125 ms. Psychological variables (including happiness, joy, fear, nervousness, anxiety, alertness, patience, pain, and nausea) were evaluated using an 11-point Likert scale. Physiological data were collected immediately before and after each session, beginning with HR and SBP, followed by a 3-minute EDA measurement taken from the palm with the Obimon device while the child stayed seated. Following these measurements, the children filled out the questionnaire with verbal support from a researcher if needed. Each session, held in the afternoon at the child's hospital bedside, lasted no longer than 30 minutes. The exact measurements (HR, SBP, EDA, and questionnaire) were repeated post-session.

Empatica E4 wristband (Empatica Inc., Cambridge, USA) was used in phase II to collect physiological data. It is a wearable device for real-time physiological data collection commonly used in research settings (107). It features multiple sensors, including a photoplethysmography that captures blood volume pulse, enabling HR and inter-beat interval analysis. Moreover, it has an EDA sensor, a 3-axis accelerometer, and an optical thermometer that measures skin temperature, providing insights into the vegetative nervous system. The E4 wristband was applied 2 minutes before the intervention and taken off after 2 minutes at the end of the game. During this period, EDA (sampling rate was 4 Hz, measured in μS), HR and peripheral temperature (calculated every 10 seconds) were measured continuously. The psychological variable was determined by the STAI-Y questionnaire in phase II. This is a psychological tool designed to assess anxiety by distinguishing between temporary emotional states, known as state anxiety, and enduring personality characteristics, referred to as trait anxiety. It comprises 40 items, split evenly between these two forms of anxiety, with responses rated on a 4-point Likert scale. This inventory is widely used in clinical psychology and research to evaluate stress responses, the effectiveness of interventions, and the psychological impact of various conditions (108). Only the first 20 items (state anxiety) were employed in the study. Before and after the intervention, children completed the STAI-Y questionnaire.

3.2.4. Data Analyses

In phase I and II statistical analyses, the EDA artefacts were manually excluded based on criteria set out by Kocielnik et al. (109). Second-to-second fluctuations

exceeding 0.5 μS in baseline skin conductance levels (SCL) were omitted. Due to individual variability, SCL filters of 0.01 μS (minimum) and 100 μS (maximum) were applied. HR and body temperature data were not filtered, as all values fell within physiological limits. Visual inspection was performed on all HR, body temperature, and EDA signals to identify irregularities or inconsistencies during data collection. No data were excluded due to signal quality concerns. Statistical analyses were performed by averaging the data before and after the intervention.

All phase statistical analyses were conducted using R (R version 3.6.1, R Core Team) (110). Normality was assessed through visual inspection. A square transformation was applied to variables with right-skewed distributions (e.g., happiness), while left-skewed variables (e.g., EDA) underwent a square-root transformation for analysis. Multiple two-way repeated measures ANOVAs were conducted to compare questionnaire responses and physiological parameters before, after, and during (in phase II) the intervention by condition, using time and condition as independent variables via the `anova_test` function in the *rstatix* package. Repeated measures ANOVA accounted for interdependent data from the crossover design. Post-hoc paired t-tests revealed significant interaction effects. Changes in pain and nausea were categorised into three categories (decreased, unchanged, and increased) and analysed through ordinal logistic regression in phase I. Time perception values were investigated with paired t-tests during phase II analyses.

3.3. Project III. – Efficacy of a VR-based simulation in preparing children for MRI examinations

3.3.1 Participants

Participants were recruited from the two departments of the Paediatric Centre at Semmelweis University, who were scheduled for anaesthetised MRI examinations. A few days before their examination, patients were pre-screened for inclusion and exclusion criteria. All inpatient or outpatient children aged 4 to 18 at the Paediatric Centre of Semmelweis University who are fluent in Hungarian were eligible for the study. Parents were required to provide informed consent, indicating their willingness to participate. Exclusion criteria included severe visual impairment or hearing loss, major face or cranial deformities, wounds on the face and head and severe intellectual disability that would

hinder participation in the VR and booklet experience. In the case of epilepsy, the treating physician will be contacted to obtain permission to include the children in the study. Children receiving inpatient care will be excluded if the treating physician determines they are too unwell to participate in the study.

3.3.2 Sample size

Our sample size was determined based on the primary endpoint: the proportion of children requiring general anaesthesia. To our knowledge, no prior study had investigated the impact of VR-based MRI preparation on anaesthesia need. Therefore, we based our assumptions on a randomised controlled trial by Rothman et al. (100), which compared a multimodal preparation protocol (booklet, simulation, and interactive session) to booklet-only preparation. In that study, 27% of children in the intervention group required anaesthesia, compared to 47% in the control group (OR = 0.42). Using these proportions, we calculated the required sample size for a chi-square test with 80% power and $\alpha = 0.05$, resulting in a minimum of 91 participants per group. To allow for a 5% dropout or crossover, we planned to enrol 96 children per group, for a total of 288 participants.

3.3.3. Procedure

This study investigated the clinical efficacy of a newly developed VR with a three-arm randomised controlled trial. On the day of the examination, a research assistant approached the caregivers of eligible patients to explain the study and obtain written consent from the caregiver as well as verbal assent from the child. Pre-intervention questionnaires (T0) were completed via a custom-made online platform, which was also used to facilitate a randomisation process. Participants were randomly assigned to one of three groups: VR, booklet, or passive control. Using a computer-generated blocked randomisation schedule (R `blockrand` package), children were allocated to the groups with a 1:1:1 ratio, stratified by age (4–6 years and 7–18 years). Participants underwent the preparation assigned to their group once, on the day of their MRI scan. Adverse effects and intervention times were monitored. Upon arrival for the MRI, a second, blinded research assistant administered post-intervention questionnaires (T1) via tablet in the online platform. The anaesthesiology team was also blinded to group assignments. The decision to perform general anaesthesia during MRI was made independently by the clinical anaesthesia team. GA were carried out by rotating teams of anaesthesiologists;

thus, multiple teams were involved throughout the study. After the MRI, the second assistant collected anaesthesiology records, including details about anaesthesia use, medication doses, adverse events, and administered post-procedure questionnaires (T2). The study design is illustrated in a flow chart, as shown in Figure 3.

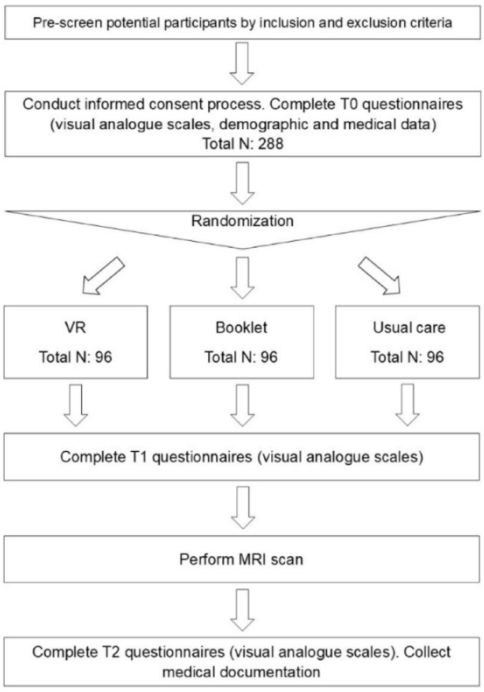

Figure 3. Flow chart of the study design (111).

The VR group experienced a custom-developed 360° VR environment designed to prepare children for MRI scans. The experience ranged from 16 to 25 minutes, depending on the child's needs and familiarity with VR. The environment comprised two parts: The first session focused on enhancing familiarity, awareness, and a sense of control, while the second session taught children techniques-based ACT to stay calm during the MRI scan. VR experience developed for Meta Quest 2 or 3 (Reality Labs, USA) VR headset provided a high-quality, immersive experience. Parents and the research assistant could observe the child's VR session via online streaming to a laptop using the Side Quest (2020, Side Quest Media, USA) application.

The booklet condition functioned as an active control, utilising a custom-made educational booklet to prepare children for the MRI examination through colourful illustrations and simple, easy-to-understand sentences. The passive control condition represented the standard care provided in participating departments, typically consisting of a brief verbal explanation of the MRI procedure by staff.

The Semmelweis University Regional and Institutional Committee of Science and Research Ethics approved the study protocol (registration number: 202/2021). The trial was registered on ClinicalTrials.gov under the identification number NCT06132854 on 11/06/2023 and was updated on 26/02/2024. The reason for the update is that the introduction of Oculus Quest 3 VR headsets has provided the opportunity to lower the age limit from 6 years to 4 years, as the device is lighter, and its design is more suitable for younger children.

For the current thesis, we made an interim data analysis on the data collected between November 2023 and November 2024.

3.3.4. Measures

Data on the use of anaesthesia and medication doses were collected from the anaesthesiology records. At three data collection points, 100-unit visual analogue scales (VAS) were used to measure the children's nervousness, fear, and mood. Furthermore, introducing them to the MRI machine in a virtual environment makes them familiar with the challenges of a real MRI examination, such as loud, mechanical noises and the confined space; thus, we measured familiarity with the MRI examination using VAS as well. To evaluate children's preference for VR preparation over traditional methods, VAS was used to measure their willingness to participate in a future MRI examination and how much they liked the preparation method. Children completed questionnaires on their own, with verbal support from a researcher if needed. Enhanced parental well-being and familiarity with procedures may improve cooperation with medical staff and have a calming effect on children. VAS was used to assess parents' nervousness, fear, mood, and familiarity in three data collection points. Similarly, using VAS, parents evaluated their children's nervousness, fear, mood, and familiarity with the MRI.

3.3.5. Statistical analysis

We compared the need for anaesthesia across the three groups using logistic regression. Univariate regression models were applied to assess age, gender, previous MRI experience, parental education, and MRI region to identify covariates for the final multivariate model (included if P-values $\leq .25$). Age and gender were included as covariates due to their potential influence on interest in gaming and technology. Previous MRI experience may affect familiarity, while parental education could influence a child's

sensitivity to the techniques used, and brain MRI might reveal neurological deficits that could alter the intervention's effects. Additionally, brain MRI may cause increased distress, especially as the scanner covers the child's head.

Children, parents, and data provided by parents about their child's mood, fear, nervousness, and familiarity were analysed using ANCOVA to examine the main effects of time and intervention on mean differences, as well as the interaction between intervention and changes in VAS scores. If significant main effects or interactions were identified, post-hoc t-tests were conducted to determine pairs that differed. For covariate selection, univariate repeated measures ANOVA models were applied to factors such as age, prior MRI experience, gender, previous VR exposure, parental education level, familial history of MRI examinations, and brain MRI. Predictors with a P-value $\leq .25$ were included in the final multivariate model.

Linear regression was used to analyse the likelihood of participating in a future MRI examination, incorporating age, gender, parental education, and MRI region as potential covariates. Covariate selection for the final model followed the approach described above.

4. RESULTS

4.1. Project I. - Effects of a VR-based mindfulness exercise on young people

4.1.1. Baseline Characteristics of Patients

The two mindfulness sessions were scheduled approximately one week apart (M = 7.04 days, SD = 0.35 days), with each session lasting between 23 and 32 minutes, including 20 minutes of mindfulness exercise and additional time for the STAI-Y questionnaire and time perception question (M = 27.80 minutes, SD = 1.77 minutes). The average age of the 50 participants (female = 26, male = 24) was 23.02 years (SD = 1.92 years). Only one participant reported mild dizziness and a headache following the VR-based mindfulness session, but was able to complete the exercise without any interruption.

4.1.2. Psychological and physiological variables

One participant was excluded from the analysis due to a misunderstanding of the STAI questionnaire, which was only reported post-session. Analysis revealed no significant main effect of condition ($F(1, 48) = .76$, $p = .39$) or interaction effect ($F(1, 48) = .06$, $P = .81$) between the VR ($M_{before} = 37.10$, $SD_{before} = 8.13$; $M_{after} = 29.41$, $SD_{after} = 5.78$) and tablet ($M_{before} = 36.66$, $SD_{before} = 8.52$; $M_{after} = 28.30$, $SD_{after} = 6.20$) conditions concerning state anxiety. However, there was a significant reduction ($F (1, 48) = 164.47$, $P < .001$, $\eta^2 = 0.23$) between pre-exercise ($M = 47.46$, $SD = 7.35$) and post-exercise ($M = 40.40$, $SD = 5.35$) measures, indicating both mindfulness sessions effectively reduced anxiety.

With data from 47 participants analysed, a sign test showed a significant difference in positive and negative deviations from zero in the VR condition ($p = 0.006$) but not in the tablet condition ($P = .39$). Specifically, there were nine positive and 26 negative deviations in the VR condition, indicating a consistent tendency to underestimate intervention time, whereas in the tablet condition, there were 14 positive and 20 negative deviations.

A repeated-measures ANOVA showed no significant main effect of condition for HR ($F (1, 45) = 1.31$, $P = .26$), body temperature ($F (1, 46) = 3.33$, $P = .07$), or EDA ($F (1, 46) = .007$, $P = .93$). Similarly, there was no significant interaction effect for HR (F

(2, 90) = 0.31, P = .73), body temperature (F (1.21, 55.57) = 2.18, P = .14), or EDA (F (1.32, 60.84) = .59, P = .49).

A significant main effect of the session was observed for HR (F (2, 90) = 10.58, P < .001, η^2 = .03). Post-hoc t-tests revealed a lower HR during the mindfulness session compared to both pre-session (t (91) = 4.14, P < .001, d = 0.17) and post-session (t (91) = 3.37, P = .001, d = 0.25) measures, with no significant difference between pre-and post-session HR (t (91) = 1.70, P = .09). The session had no significant effect on EDA (F (1.33, 61.21) = 2.32, P = .13).

For body temperature, a significant main effect of the session was found (F (1.09, 50.36) = 60.93, P < .001, η^2 = 0.09). Post-hoc tests indicated significant increases between pre- and intersession (t (93) = 9.05, P < .001, d = .46), intersession and post-session (t (93) = 6.74, P < .001, d = .36), and pre- and post-session (t (93) = 8.87, P < .001, d = 0.75). Table 4 shows the means and standard deviations of the variables.

Table 1. Means and standard deviations by condition before, during and after the mindfulness practice (107).

	VR			**Tablet**		
	Means (SD)			**Means (SD)**		
	before	**during**	**after**	**before**	**during**	**after**
Anxiety (score)	37.1 (8.13)		29.41 (5.78)	36.66 (8.52)		28.3 (6.2)
HR (bpm)	83.06 (12.03)	77.63 (14.42)	80.55 (10.42)	79.88 (10.15)	75.68 (14.78)	78.91 (9.22)
Body temperature (°C)	32.25 (2.13)	33.27 (1.92)	33.75 (2.0)	31.33 (2.91)	32.54 (2.4)	33.34 (2.14)

4.2. Project II. - The impact of VR on children undergoing chemotherapy

4.2.1. Phase I.

4.2.1.1 Baseline Characteristics of Patients

Data from 29 children (8 females, 21 males) were analysed. Six children, consisting of three females and three males, were excluded from further analysis for the following reasons: one due to cybersickness, one due to a hospital transfer, and four due to incomplete questionnaires. The mean age of excluded children was 13.66 years (SD =

3.61 years). Four children withdrew following the control condition, while two discontinued after the VR condition.

The mean age of participants was 15.28 years (SD = 2.44 years, range 10.28–18.69 years). Patients were undergoing chemotherapy for the following diagnoses: acute lymphoblastic leukaemia (ALL) in nine cases, Hodgkin lymphoma in eight, osteosarcoma in four, Ewing sarcoma in three, non-Hodgkin lymphoma in two, germ cell tumour in two, and rhabdomyosarcoma in one. Additionally, four participants had relapsed disease. Participants were randomly allocated to start with either the control condition (n = 10) or the VR condition (n = 19). The median interval between sessions was 27 days (IQR = 24 days). The mean session duration was 22.5 minutes (SD = 3.43 minutes). The mean time since diagnosis was 106.3 days (IQR = 54 days), and the mean hospital stay immediately before intervention was 2.45 days (IQR = 2 days). These data suggest that participants were midway through their treatment regimens.

Table 2. Summary of the main and interaction effects of the repeated measures ANOVA on psychological and physiological variables in Phase I (112).

	Main effects						Interaction effect		
	Condition			Time			Condition x Time		
	F	P	Eta squared	F	P	Eta squared	F	P	Eta squared
Happiness	0.04	0.838		16.54	< .001	0.046	10.56	0.003	0.031
Joy	0.28	0.602		9.07	0.005	0.036	6.68	0.015	0.01
Fear	4.78	0.037	0.029	3.4	0.076		2.16	0.153	
Nervousness	0.41	0.528		2.94	0.098		0.1	0.759	
Anxiety	2.7	0.112		11.43	0.002	0.03	1.08	0.307	
Alertness	0.44	0.514		1.67	0.207		0.18	0.673	
Patience	3.43	0.075		6.66	0.015	0.019	0.001	0.97	
Heart rate (minutes^{-1})	0.617	0.439		0.06	0.916		0.71	0.407	
SBP (Hgmm)	0.07	0.787		0.09	0.772		1.51	0.23	
EDA (µS)	1.78	0.193		7.16	0.012	0.008	4.97	0.034	0.008

df = 1, 28; Eta squared is not presented if the effect was not significant.

4.2.1.2. Effects of VR on Psychological and Physiological Variables

For happiness and joy, a significant main effect of time was found (happiness: $F(1,28) = 16.54$, $P < .001$, $\eta^2 = 0.046$; joy: $F(1,28) = 9.07$, $P = .005$, $\eta^2 = 0.036$) along

with a significant time-by-condition interaction (happiness: $F(1,28) = 10.56$, $P = .003$, $\eta^2 = 0.031$; joy: $F(1,28) = 6.68$, $P = .015$, $\eta^2 = 0.01$). Post-hoc tests indicated a significant increase in happiness ($P < .001$) and joy ($P = .003$) exclusively in the VR condition. The main effect of the condition was not significant for either measure. The interaction effect is demonstrated in Figure 4.

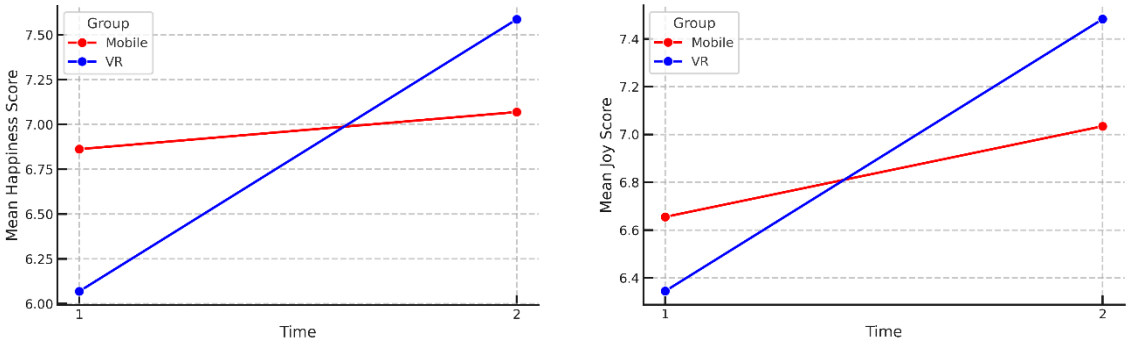

Figure 4. Interaction effects of group and time on happiness and joy.

For fear, a significant main effect of condition was noticed ($F(1,28) = 4.78$, $P = .037$, $\eta^2 = 0.029$), while the interaction between time and condition and the main effect of time were non-significant. Post-hoc analyses revealed that children exhibited greater fear before the VR intervention than before the control condition ($P = .005$), with no significant difference between conditions after the intervention ($P = .276$).

For anxiety and patience, a significant main effect of time was detected (anxiety: $F(1,28) = 11.43$, $P = .002$, $\eta^2 = 0.03$; patience: $F(1,28) = 6.66$, $P = .015$, $\eta^2 = 0.019$), but no significant interaction between time and condition or main effect of condition was observed. These findings suggest that anxiety decreased, and patience increased similarly across both conditions. No significant main effects or interaction effects were observed for nervousness or alertness.

Regarding physiological variables, no significant main or interaction effects were observed for HR and SBP. A significant main effect of time ($F(1,28) = 7.16$, $P = .012$, $\eta^2 = 0.008$) and a time-by-condition interaction ($F(1,28) = 4.97$, $P = .034$, $\eta^2 = 0.008$) were observed, while the main effect of condition was non-significant for EDA. Post-hoc analysis revealed a significant reduction in EDA in the control condition ($P = .005$), but no significant change in the VR condition ($P = .993$). A three-way mixed ANOVA was performed on all variables to assess potential order effects; however, no significant interactions were found. All main effects, interaction effects, and mean differences with 95% confidence intervals are presented in Tables 1 and 2.

Changes in pain and nausea scores were analysed using ordinal regression. Condition was not a significant predictor of changes in nausea (β = −0.14, P = .81, OR = 0.87, 95% CI = 0.26–2.81) or pain (β = 0.31, P = .698, OR = 1.37, 95% CI = 0.28–7.53).

Table 3. Mean differences with 95% confidence intervals by condition and post-hoc paired t-tests on psychological and physiological variables in Phase I. (112)

	VR			Control		
	MD	**95% CI**	**P-value**	**MD**	**95% CI**	**P-value**
Happiness[1]	22.21	11.39, 33.03	< .001	2.34	-3.8, 8.49	0.441
Joy[1]	16.59	6.09, 27.08	0.003	5.14	-1.19, 11.47	0.108
Anxiety[1,2]	15	2.78, 27.22	0.018	6.9	-1.21, 15	0.092
EDA (μS)[3]	0.02	-5.18, 5.23	0.993	-10.2	-17.03, -3.32	0.005

[1.] Squared for analysis, [2.] Reversed scale, [3.] Square root transformed for analysis

4.2.2. Phase II.

4.2.2.1. Baseline Characteristics of Patients

Data from 19 children (15 females, 4 males) were analysed. Six children (5 females and 1 male) were excluded from further analysis due to incomplete questionnaires. The mean age of excluded children was 13.16 years (SD = 2.31 years). Six children dropped out after the first occasion involving a specifically developed VR game.

The mean age of participants was 14.5 years (SD = 2.1 years). Patients were receiving chemotherapy for ALL (9), Hodgkin lymphoma or non-Hodgkin Lymphoma (6), Ewing sarcoma (3), and germ cell tumour (1). Participants were randomly assigned to begin with either the specifically developed VR game or the control VR condition (10 and 9, respectively).

4.2.2.1 Effects of Specific VR Intervention on Psychological and Physiological Variables

Investigating psychological variables, we found a significant main effect of time for STAI-Y ($F(1,18) = 25.06$, $P < .001$, $\eta^2 = 0.097$). Neither the condition nor the time-by-condition interaction showed significant results. Post-hoc tests demonstrated a significant decrease in anxiety levels in both specific-developed ($P = .001$, ($M_{before} = 34.10$, $SD_{before} = 8.93$; $M_{after} = 29.90$, $SD_{after} = 6.80$) and control VR conditions ($P < .001$,

(M_{before} = 34.10, SD_{before} = 8.86; M_{after} = 28.50, SD_{after} = 5.43). A summary of the main and interaction effects can be seen in Table 3.

We examined whether repeated gameplay influenced the anxiety-reducing effect. Therefore, we conducted a two-way ANOVA to examine the effects of condition and occasion (playing a VR game for the first or second time during chemotherapy treatment) and their interaction on STAI change scores. The results indicated that the occasion had no significant effect on change scores. (F (1,34) = 0.089, P = .767). Similarly, the main effect of condition was not significant (F (1,34) = 0.754, P = .391). Additionally, the interaction effect between occasion and condition was also non-significant. (F (1,34) = 0.789, P = .381) Consequently, whether the child played the VR game for the first or second time did not affect the reduction in STAI scores.

Time perception values were analysed with paired t-tests. The results showed no significant differences (t = -1.57, P = .124, 95% CI = -6.02-0.75) between the developed VR experience and the control VR game.

Table 4. Effects of condition and time on Anxiety and Physiological Responses: Summary of Repeated Measures ANOVA Results in Phase II.

	Main effects					Interaction effect	
	Condition		Time			Condition x Time	
	F	P	F	P	η^2	F	P
STAI-Y score	0.226	0.64	25.07	< .001	0.97	1.437	0.246
Peripheral temperature (°C)	0.439	0.516	12.24	< .001	0.481	0.243	0.643
Heart rate ($minutes^{-1}$)	2.086	0.152	0.478	0.621		0.094	0.91
EDA (μS)	0.072	0.789	1.963	0.146		0.12	0.887

Statistical analysis with EDA and HR values did not have main or interaction effects for physiological variables. A significant main effect of time was found for peripheral temperature (F (2,36) = 12.24, P < .001, η^2 = .037). The post-hoc test presented a significant increase in peripheral temperature (decreased sympathetic nervous activity) in the control VR experience (P = .016, M_{before} = 33.40, SD_{before} = 1.85; M_{after} = 34.30, SD_{after} = 1.39) with no significant difference in the specifically developed VR game (P = .213, M_{before} = 33.70, SD_{before} = 1.27; M_{after} = 34.30, SD_{after} = 1.68).

4.3. Project III. – Efficacy of a VR-based simulation in preparing children for MRI examinations

4.3.1. Baseline Characteristics of Patients

Data from 120 participants (65 males and 55 females) were analysed. The mean age was 6 years (SD = 2.06 years). Twenty-six participants were classified as the 7-18 age group, and 94 as the 4-6 age group. Patients were undergoing MRI examination for diagnosis or follow-up of a cancer disease (59), neurological disease (25), orthopaedic-rheumatology disease (8), endocrine disease (7), blood vessel malformation (7), gastroenterological disease (4), ophthalmology causes (2), and other reasons (8). After randomisation, 36 children had a VR session, 40 went through the educational booklet, and 44 were in the control condition. Seventeen participants had prior experience with VR, while 103 had no previous exposure. Additionally, 90 participants had undergone an MRI before, whereas 30 had not. 64 mothers and 49 fathers had higher education. Furthermore, 48 mothers and 57 fathers hold a secondary education qualification. 10 mothers and 14 fathers had elementary school or less. Out of 121 children, 17 participants reported having used VR before, and only 7 participants reported having a VR device at home.

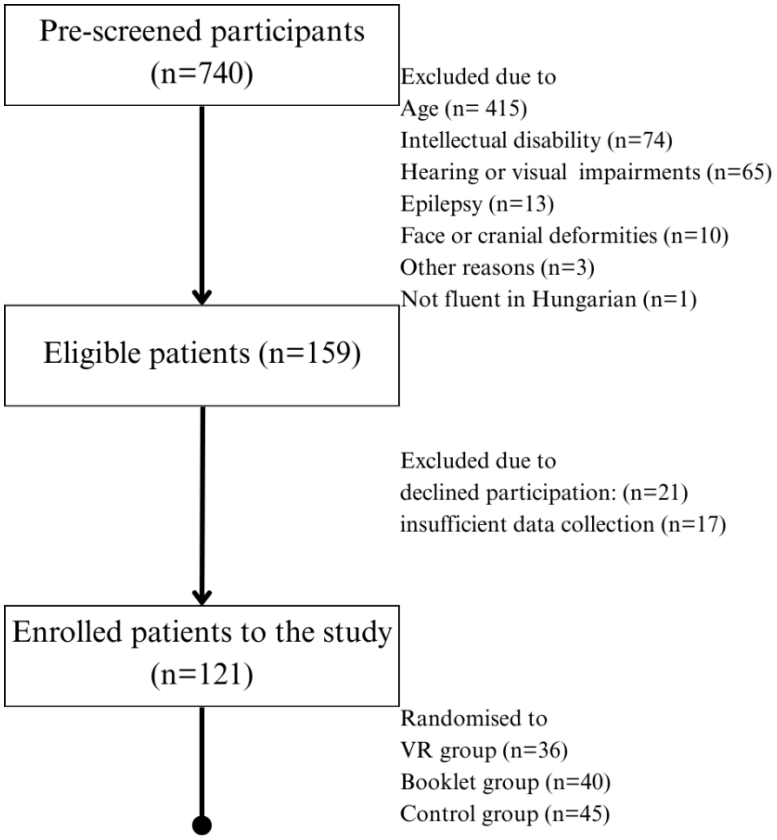

Figure 5. Participant flowchart (111).

The duration of interventions varied across the groups. Participants in the VR session had an average intervention time of 25.80 minutes (SD = 8.93), while those who read the educational booklet spent an average of 8.29 minutes (SD = 4.56). The mean duration of MRI scans across all participants was 35.45 minutes (SD = 9.89). During the VR intervention, it was necessary to pause the session on 12 occasions for various reasons, including participant discomfort or technical issues. Reported side effects of the VR intervention included eye strain (10 cases), nausea (8 cases), vomiting (4 cases), and headache (5 cases). Participant enrolment and attrition rates are illustrated in Figure 5.

4.3.2. Psychological and physiological variables

It is important to highlight that our current findings are reported approximately halfway to the total sample size. A logistic regression analysis was conducted to examine the factors predicting the need for anaesthesia during MRI. Univariate regression models are used to assess age, gender, previous MRI experience, parental education, and MRI region to identify covariates. Condition, age, father's and mother's education levels were

identified as relevant covariates (P ≤ .25) and incorporated into the final multivariate analysis. Results of univariate analysis can be seen in Table 5.

Table 5. Univariate logistic regression analysis predicting the need for anaesthesia in Project III.

Predictor		OR	95% CI	P
Condition	Booklet	3.51	1.21, 10.24	0.021
Condition	VR	2.13	0.78, 5.82	0.142
Age		0.85	0.7, 1.02	0.083
Mother's education	Primary education qualification	4.7×10^{7}	$1.7*10^{16}$ $9.7*10^{14}$	0.987
Mother's education	Secondary education qualification	9.27	0.87, 98.57	0.065
Mother's education	Higher education qualification	7.24	0.7, 74.54	0.096
Father's education	Primary education qualification	9	0.24, 473	0.213
Father's education	Secondary education qualification	3.23	0.19, 55.31	0.418
Father's education	Higher education qualification	1.69	0.1, 28.88	0.718
Gender	Female	0.85	0.37, 1.96	0.708
Previous MR occasions		1.35	0.57, 3.2	0.501

A significant effect was found for the booklet condition compared to the control condition (OR = 3.84, 95% CI = 1.24, 13.17, P = .024), indicating higher odds of requiring anaesthesia in condition B. In booklet condition, anaesthesia was required in 31 out of 37 cases. In the control group, 25 out of 42 participants received anaesthesia. In the VR group, anaesthesia was administered in 25 out of 33 cases. However, the VR condition did not differ significantly from the reference condition (OR = 2.05, 95% CI = 0.67, 6.67, P = .22). Table 6 summarises the multivariate logistic regression analysis predicting the necessity for anaesthesia.

Table 6. Multivariate logistic regression analysis predicting the need for anaesthesia in Project III.

Predictor		P	OR	95% CI
Condition	Booklet	.02	3.84	1.24, 13.17
Condition	VR	.22	2.05	0.67, 6.67
Age		.06	0.82	
Mother's education	Primary education qualification	.99	1.51×10^{22}	
Mother's education	Secondary education qualification	.99	1.44×10^{15}	
Mother's education	Higher education qualification	.99	2.29×10^{15}	
Father's education	Primary school education	.99	2.65×10^{-8}	
Father's education	Secondary education qualification	.99	1.28×10^{-15}	
Father's education	Higher education qualification	.99	4.61×10^{-16}	

The likelihood of taking part in a future MRI examination and preference for the preparation method were measured on a 100-unit-long visual analogue scale after the MRI examination, and compared between the three arms with linear regression, with potential covariates. The model included the preparation age as a covariate for the likelihood of future MRI participation. The analysis did not reveal a significant effect of the condition (Booklet: β = 1.74, 95% CI = -18.74, 22.22, P = .87; VR: β = -2.39, 95% CI = -22.79, 18.02, P = .82). However, age was significantly associated with a lower likelihood of future MRI participation (β = -4.46, 95% CI = -8.34, -0.57, P = .02). For the preference for the preparation method, the model included the father's and mother's education levels as covariates. As shown in Table 7, no significant effects were found for any of the predictors, indicating that the preparation condition, mother's, and father's education did not significantly influence participants' preference for the preparation method.

Table 7. Linear regression analysis of factors influencing reference for the preparation method in Project III.

Predictor		Beta	P value	95% CI
Condition	Booklet	7.99	0.31	-4.89, 26.10
Condition	VR	3.42	0.66	-12.63, 18.92
Mother's education	Primary education qualification	-40.79	0.11	-40.79, 110.17
Mother's education	Secondary education qualification	21.59	0.06	-16.17, 134.79
Mother's education	Higher education qualification	-29.88	0.24	-29.88, 123.37
Father's education	Primary school education	-44.18	0.19	-44.18, 63.23
Father's education	Secondary education qualification	-62.33	0.41	-62.33, 29.28
Father's education	Higher education qualification	-51.52	0.31	-51.52, 41.99

Repeated measures ANOVA was used to evaluate the main effects and the interaction effects of mood, anxiety, fear, and familiarity. In the case of patients' anxiety, a significant main effect of time was observed (F (2, 166) = 3.43, P = .034, η^2 = 0.039), while no interaction effect was detected. However, no significant interaction effect between condition and time was found (F(4, 166) = 0.7, P = .6), and the main effect of condition was not significant either (F(2, 85) = 2.63, P = .08). Post-hoc tests indicated that children's anxiety decreased significantly between the T0 and T1 measurements (M_{T0} = 64.63, SD_{T0} = 36.30; M_{T1} = 70.93, SD_{T1} = 36.69, P = .04). There was a marginally significant decrease between T0 and T2 (*P* = .07), but no significant change between T1 and T2 (*P* = .96). No statistically significant pairwise differences were observed when

examining the condition's effect within each time point. A significant main effect of time was found in the parental anxiety (F (2, 196) = 6.37, P = .002, $\eta^2 = 0.06$), indicating that parental anxiety levels changed over the three measurement points. However, neither the main effect of condition (F(2, 98) = 0.90, P = .41) nor the interaction effect between condition and time (F(4, 196) = 0.84, P = .50) reached statistical significance. According to the post-hoc t-test, parents' anxiety decreased significantly between T0 and T2 (M_{T0} = 48.94, SD_{T0} = 36.25; M_{T2} = 60.66, SD_{T2} = 34.55, P = .024), while the comparisons between T0 and T1 (p = .140) and between T1 and T2 (P = .28) did not yield statistically significant results.

In analysing the child's familiarity values with the upcoming MRI examination, which can be an important predictor of children's mental state, as familiarity with the environment may reduce anxiety. We observed significant main effects of time (F (2, 160) = 7.034, P = .001, $\eta^2 = 0.07$) and time-by-condition interaction effect (F (4, 160) = 3.725, P = .006, $\eta^2 = 0.07$). The main effect of condition was not significant (F(2, 83) = 1.504, P = .228). Post-hoc tests revealed the advantage of VR before MRI scanning (M_C = 68.2, SD_C = 39.8; M_{VR} = 78.7, SD_{VR} = 35.7, P = .02) compared to the control condition. Furthermore, the informational booklet condition demonstrated significant differences from the control condition after MRI scanning. (M_C = 61.1, SD_C = 42.8; $M_{Booklet}$ = 78.6, $SD_{Booklet}$ = 35.7 P = .003) At T0, no significant differences were found between groups (P =.78). Additionally, within-subject post-hoc comparisons across time points (averaged across conditions) revealed a significant increase in familiarity was noticed between T0 and T1(P = .001) and between T0 and T2 (P = .003) time points (M_{T0} = 58.42, SD_{T0} = 40.45; M_{T1} = 71, SD_{T1} = 39.50; M_{T2} = 68.88, SD_{T2} = 39.69). There was no significant difference between T1 and T2 (P = 7.933). The mood and fear analysis revealed no significant main or interaction effects. Detailed statistics for anxiety, mood, fear, and familiarity outcomes are presented in Table 8.

Table 8. Summary of repeated measures ANOVA results on psychological variables in Project III.

	Effect	Df	Sum Sq	Mean Sq	F	P
Anxiety	Condition	2	2.73	1.37	0.57	0.57
	Time	2	7.98	3.99	3.34	0.04
	Condition-Time	4	4.75	1.19	0.99	0.41
Mood	Condition	2	1.22	611.9	0.42	0.66
	Time	2	7	3.5	0.00	1.00
	Condition-Time	4	1.88	470.1	0.59	0.67
Fear	Condition	2	3.13	1.57	0.72	0.49
	Time	2	6.7	3.35	2.82	0.06
	Condition-Time	4	4.93	1.23	1.04	0.39
Familiarity	Condition	2	6.612×10^{7}	33.06	1.50	0.23
	Time	2	1.627×10^{8}	81.36	7.03	0.00
	Condition-Time	4	1.723×10^{8}	43.08	3.73	0.01

5. DISCUSSION

Stress is highly prevalent across populations; therefore, improving coping strategies and treatment opportunities is crucial. Besides classic psychological and pharmacological methods, VR appears to be a highly relevant option for mitigating stress levels in clinical settings. Beyond health education, pain management and rehabilitation, mental health is the area where VR technology finds its most significant applications, and it has proven to be a versatile tool in stress management, especially in clinical and therapeutic settings. This dissertation examines its use in paediatric oncology, mindfulness-based interventions, and preparation for MRI procedures in children.

In Project I, fifty young adults aged 18–30 participated in this randomised crossover trial comparing VR and tablet-based mindfulness. Physiological responses (HR, peripheral temperature, and EDA) and time perception were measured. Furthermore, the STAI-Y questionnaire was filled out to investigate anxiety before and after each session. This project hypothesised that VR would reduce anxiety, change time perception, and cause a parasympathetic nervous system dominance effect compared to the tablet.

Our findings indicate that VR positively influences the perception of time, not only in chemotherapy-treated patients, as demonstrated in prior studies, but also in young, healthy volunteers. (87) The results highlight that VR can effectively modify time perception, where individuals perceive time as passing more quickly, enhancing the overall experience. This approach can significantly enhance long-term adherence to meditation practices, as it creates an engaging and immersive experience that encourages individuals to return to the activity consistently over time. Furthermore, it may help individuals attain a deeper and more intense meditative state, as observed in previous studies. (80) About the additional variables examined in this study, our findings are consistent with previous research, which demonstrated that mindfulness interventions supported by electronic devices effectively reduce stress. (80, 81)

This stress reduction was evidenced by decreases in self-reported anxiety levels and measurable physiological changes. Specifically, participants exhibited reduced HR and increased body temperature during mindfulness exercises, changes that align with a parasympathetic nervous system response. These physiological outcomes are consistent

with those observed in prior meditation studies, further reinforcing the calming effects of mindfulness practices. (77) While one participant reported experiencing mild cybersickness characterised by dizziness and a headache during the VR session, this side effect did not prevent them from completing the meditation exercises. All participants completed the VR-based meditations without encountering significant difficulties, providing strong evidence for the safety and feasibility of VR as a tool for facilitating mindfulness practices. These findings underscore the potential of VR technology as a reliable and accessible medium for enhancing meditation experiences and promoting stress reduction in diverse populations.

In Project II, we examined two phases to explore the impact of VR on children undergoing chemotherapy. A crossover design was implemented in both phases (VR-mobile game and custom-made VR experience condition) to reduce the variability induced by interindividual differences. Variables were compared regarding the children's emotional states, anxiety levels and physiological measurements of stress response (e.g. HR, SBP, EDA). Both phases hypothesised that VR would positively influence physiological variables and a reduction of physiological stress markers.

Our findings confirmed our objectives regarding two variables related to mood. Children reported increased scores in both happiness and joy following the intervention in the VR condition. However, no changes were observed in the mobile condition. These results are similar to those of Ioannou et al., in which patients reported improvements in mood scales filled out by adults after attending a VR experience compared to a GI intervention. (88) In phase I, anxiety values, which were measured with the Likert scale, decreased in both conditions, suggesting that VR provides no additional benefit compared to the control, which was a mobile session. We confirmed this result in phase II using the STAI questionnaire, where both VR and a specifically developed VR experience could reduce anxiety levels. These results imply the anxiety-reducing effects of VR and are consistent with the research where anxiety reduction was demonstrated before. (85, 89, 90, 93) In Phase II, the change in STAI scores was not dependent on whether the children played with the VR experience for the first- or second time during chemotherapy treatment. This suggests that the anxiety-reducing effect of VR remained constant. This observation was also noted by Sharifpour et al.(91). Back to Phase I results, patience increased in both conditions following the intervention. Additionally, greater fearfulness

was observed before the VR condition, while no significant differences were found after the interventions. Notably, both anxiety and fearfulness scores remained relatively low throughout the interventions. Thus, the higher levels of anxiety and fear, as well as the lower patience levels before the intervention, may be attributed to the excitement experienced by the children. However, it is also plausible that the interventions reduced anxiety and increased patience through the presence effects of either the games or the interaction with the experimenter.

Although there are results that VR can reduce pain during chemotherapy treatment, we did not find significant main or interaction effects in children. (86) Time perception, pain, and nausea did not differ between the conditions and did not change after the interventions. VR did not provoke cybersickness symptoms in most cases; however, one child withdrew due to such symptoms.

Regarding physiological parameters, our investigations attempted to assess information about the state of the autonomic nervous system. In Phase II, a significant main effect of time was noted in peripheral temperature. This result is consistent with our hypothesis and previous investigation that VR could contribute to decreasing stress-related psychological variables. (88) In contrast, EDA significantly decreased in the Phase I control condition, but no change was observed after the VR session. This may reflect excitement before the session, like the other psychological parameters (anxiety and patience). The fact that the children chose a familiar mobile game and the novelty of VR, may affect the physiological measurements. In Phase I, there was no increase in SBP, nor was there any change in EDA during Phase II. We did not observe significant changes in HR, possibly because HR reductions are typically reported in studies involving invasive procedures (113). A single VR session may have a more prominent effect in reducing an acute stress reaction than a more chronic type of stress.

Furthermore, our goal was to understand how VR could be integrated into paediatric oncology centres effectively. Overall, our experience was positive; children were enthusiastic about VR and quickly mastered the necessary skills. Additionally, parents and staff were supportive of our research program. Although we did not collect objective data on this, we had the subjective impression that our intervention did not interfere with any hospital routines, allowing us to incorporate the VR sessions into everyday hospital life seamlessly.

Project III evaluates the efficacy of a VR-based preparatory method in children undergoing MRI scans. This study is a randomised controlled trial, where 120 children aged 4-18 participated in three arms: VR, an educational booklet and a passive control. Psychological and physiological variables, such as anxiety, familiarity, mood, and fear, were assessed three times to evaluate the effectiveness of the interventions. We hypothesise that the VR arm will result in the lowest proportion of children requiring anaesthesia, alongside more significant improvements in emotional states and better familiarity with the MRI procedure.

It is important to note that Project III results were reported approximately halfway through the study, meaning that conclusions cannot be drawn at the current stage. According to our interim results, conditions may induce changes in the number of general anaesthesia cases and can change psychological variables such as anxiety and familiarity. The research is expected to be completed in December 2026. (69) Although mild side effects, such as eye strain, nausea, and headaches, were reported among participants in the VR group, these effects were generally transient. They did not significantly hinder the children's ability to fully engage with or complete the intervention. This outcome highlights not only the tolerability of the VR experience but also its practicality as a tool for preparation in medical settings.

5.1. Limitations

There are some limitations to our projects. The most significant limitation was that the experimenter was not blinded to the participants' condition or the studys' aim in any of the studies. This might have led to an unconscious influence on some participants. However, masking the participants' condition with the help of a research assistant would have been impossible in these studies. Another limitation of this study was that most participants were unfamiliar with VR technology, which could have triggered a sympathetic response in their bodies and potentially influenced our findings. Another key limitation is the wide range of ages. We also used the same VR experience for the six- and seventeen-year-old children; however, their psychological needs may differ.

In Project I, the significance of this phenomenon should be evaluated, considering that most MBSR programs typically span 8 weeks with at least 1 hour per week (114). Our study was designed as an exploratory trial, where our primary aim was to examine whether a single VR session could already lead to measurable changes in stress and

emotional state. Because this was a new area of application in our clinical settings, we prioritised practicality and feasibility. We aim to extend our research with additional sessions and prolonged mindfulness practices to obtain more robust results regarding mental health impact and overall well-being. Furthermore, due to the pilot nature of our study and the constraints on personal interactions imposed by the COVID-19 pandemic, we did not conduct follow-up assessments with home practice to determine the long-term sustainability of these effects. Additionally, the mild immersion effect of the meditation program used in our experiment could have influenced our measures. (115) A more immersive meditation program could have caused a significant difference between the VR and tablet devices regarding psychological and physiological measures. It could have caused a more significant difference regarding time perception. In Project II, the second condition was later in the chemotherapy treatment process. Therefore, participants might have been in varying mental states and experienced different side effects at that stage. However, we counterbalanced the order of the interventions and confirmed that the order did not influence our results. Additionally, due to errors in data collection, detailed information about the children who declined participation is unavailable. In Project III, the main limitations were the complexity of evaluating psychological states in young children. VAS are widely used and valuable tools for quick and straightforward assessments of psychological variables, but they come with certain limitations. VAS relies heavily on self-reporting, making the data subjective, and it may lack the precision needed to capture subtle differences in psychological states. Despite these constraints, no better validated measuring tool exists for evaluating psychological variables in this age group.

6. CONCLUSION

Stress is a complex process with significant physiological and psychological impacts. The findings of this thesis highlight the pressing need for innovative interventions to mitigate stress. (7) VR emerges as a promising, state-of-the-art tool for stress management in clinical settings, offering immersive and engaging experiences that extend beyond traditional psychological and pharmacological methods. (70)

Project I explored the application of VR in mindfulness-based interventions for young adults. The results showed that VR significantly enhanced time perception, creating a sense of accelerated time passage during meditation sessions. This effect has implications for improving long-term adherence to mindfulness practices. Physiological measurements, including reduced heart rate and increased peripheral temperature, confirmed the calming effects of VR-mediated mindfulness, indicating parasympathetic nervous system dominance, although the reduction was similar to that of the control group. No side effects were reported by participants. These findings demonstrate the potential of VR to enrich meditation experiences safely, reduce stress, and promote mental well-being in young adults.

In Project II, which investigated the impact of VR on children undergoing chemotherapy, VR interventions demonstrated notable benefits for emotional states. Children reported increased happiness and joy following VR experiences, while anxiety reduction was comparable between VR and mobile-based interventions. Fearfulness decreased, and patience improved after interventions, potentially influenced by the games and experimenter interactions. VR did not cause significant cybersickness, although one child withdrew due to this issue, and no changes were observed in pain, tiredness, or nausea. In Phase II, the custom-developed VR experience produced an anxiety reduction effect as the control group (standard VR game). However, the anxiety relief effect did not change over time, indicating VR could be effective in the long term. Physiological findings showed a decrease in peripheral temperature, indicating reduced stress, while other measures, such as HR and EDA, remained unaffected. Importantly, VR was well-received, easily integrated into clinical routines, and supported by children, parents, and staff. These findings suggest that VR is a feasible tool for mood enhancement and stress management in paediatric oncology.

Project III evaluated the efficacy of a VR-based preparatory method for children undergoing MRI scans. Since this is only an interim analysis, no definitive conclusions can be drawn. However, based on the data, the conditions may have the potential to modify the number of general anaesthesia cases, and VR may positively influence children's anxiety levels and familiarity. These findings may validate the psychological benefits of VR-based preparation in a real-world medical diagnostic context, demonstrating its potential to enhance the MRI experience for children and their parents.

Across all projects, VR was shown to be a practical and well-tolerated tool, with mild and transient side effects reported in a minority of participants. We did not observe any seizure-like events during the studies. The findings highlight the feasibility of integrating VR into clinical settings, complementing traditional stress management methods and enhancing patient experiences. Several significant findings have been achieved regarding the role of VR in stress management in adults. Our current study contributes to the growing body of research on paediatric populations, providing positive outcomes on its practical applications. Future research should prioritise large-scale, multi-centre, randomised controlled trials focusing on specific clinical populations (e.g., paediatric oncology patients or children before a medical procedure) to validate the efficacy of VR interventions in reducing psychological and physiological variables. Longitudinal studies are also needed to assess the sustained impact of VR on stress reduction, providing insights into long-term benefits and the necessity of repeated sessions. Developing personalised VR content tailored to age, cultural background, and specific needs could enhance engagement and outcomes.

7. SUMMARY

Stress is a significant contributor to poor physical and mental health, with acute and chronic stress linked to conditions such as cardiovascular disease, depression, and anxiety. Addressing stress effectively is crucial for improving health outcomes, particularly in vulnerable populations such as children and young adults. VR, a technology offering immersive and interactive experiences, has shown promise in reducing stress in medical contexts.

This thesis explores the role of VR in stress management through three key projects. In paediatric oncology, children undergoing chemotherapy often face heightened levels of anxiety and discomfort. Project I investigated VR-assisted mindfulness exercises in young adults compared to traditional tablet-based exercises. Both methods effectively reduced state anxiety, but the VR intervention provided modified time perception, likely due to its immersive features. MRI is often stressful for children, necessitating general anaesthesia in many cases. In Project II, a crossover study evaluated the effects of VR experiences on stress markers. Compared to standard mobile games, the VR experience led to a significantly enhanced mood. Compared to another VR game, both conditions resulted in significant anxiety reduction, and the anxiety reduction did not change over time. These results support the feasibility of this technology in hospital settings. Mindfulness practices are well-established interventions for stress reduction, but their accessibility can be limited. In Project III, a three-arm randomised controlled trial examined the impact of VR preparation on reducing pre-procedure anxiety compared to educational booklets and standard care. Initial findings indicate that VR significantly decreases anxiety levels and increases familiarity. However, it does not affect the need for GA.

The findings suggest that VR can be a powerful tool for mitigating stress in medical environments. Its applications extend from enhancing mindfulness practices to improving patient preparedness for stressful procedures. We observed a few mild side effects when using VR, and overall, it was well-tolerated and safe to use during projects. Future directions include optimising VR content and conducting large-scale studies to further validate its efficacy in clinical settings. VR has the potential to transform stress management, offering scalable, cost-effective, and engaging solutions for diverse populations.

8. REFERENCES

1. Selye H. A syndrome produced by diverse nocuous agents. Nature. 1936;138(3479):32-.
2. Fink G. Fink G. Stress, Definitions, Mechanisms, and Effects Outlined: Lessons from Anxiety. In: Fink G, ed. Stress: Concepts, Cognition, Emotion, and Behavior, Volume 1 of the Handbook of Stress Series. San Diego: Elsevier Inc., 2016: 3-11. 2016.
3. Fink G. Stress: Definition and history. Stress Sci. 2010:3-9.
4. Lazarus RS. Stress, appraisal, and coping: Springer; 1984.
5. Vogelzangs N, Seldenrijk A, Beekman ATF, van Hout HPJ, de Jonge P, Penninx BWJH. Cardiovascular disease in persons with depressive and anxiety disorders. Journal of Affective Disorders. 2010;125(1):241-8.
6. Selye H. Stress without Distress. New York: New American Library. 1975.
7. Mifsud KR, Reul J. Mineralocorticoid and glucocorticoid receptor-mediated control of genomic responses to stress in the brain. Stress. 2018;21(5):389-402.
8. Joëls M, Baram TZ. The neuro-symphony of stress. Nat Rev Neurosci. 2009;10(6):459-66.
9. Khoo B, Boshier PR, Freethy A, Tharakan G, Saeed S, Hill N, et al. Redefining the stress cortisol response to surgery. Clin Endocrinol (Oxf). 2017;87(5):451-8.
10. Hinterdobler J, Schunkert H, Kessler T, Sager HB. Impact of Acute and Chronic Psychosocial Stress on Vascular Inflammation. Antioxidants & Redox Signaling. 2021;35(18):1531-50.
11. Söderholm JD, Perdue MH. Stress and gastrointestinal tract. II. Stress and intestinal barrier function. Am J Physiol Gastrointest Liver Physiol. 2001;280(1):G7-g13.
12. Chuang JY. Stressor-Specific Microbiota Intervention. Front Nutr. 2022;9:870665.
13. Engler-Chiurazzi E. B cells and the stressed brain: emerging evidence of neuroimmune interactions in the context of psychosocial stress and major depression. Front Cell Neurosci. 2024;18:1360242.
14. Miller E, Apple C, Kannan K, Funk Z, Plazas J, Efron P, et al. Chronic Stress Induces Persistent Low-Grade Inflammation. The American Journal of Surgery. 2019;218.

15. Agarwal A, Gupta S, Sharma RK. Role of oxidative stress in female reproduction. Reprod Biol Endocrinol. 2005;3:28.
16. Heim CM, Entringer S, Buss C. Translating basic research knowledge on the biological embedding of early-life stress into novel approaches for the developmental programming of lifelong health. Psychoneuroendocrinology. 2019;105:123-37.
17. Huang C-W, Lui C-C, Chang W-N, Lu C-H, Wang Y-L, Chang C-C. Elevated basal cortisol level predicts lower hippocampal volume and cognitive decline in Alzheimer's disease. Journal of Clinical Neuroscience. 2009;16(10):1283-6.
18. Arnsten AF. Stress signalling pathways that impair prefrontal cortex structure and function. Nat Rev Neurosci. 2009;10(6):410-22.
19. Chaaya R, Sfeir M, Khoury SE, Malhab SB, Khoury-Malhame ME. Adaptive versus maladaptive coping strategies: insight from Lebanese young adults navigating multiple crises. BMC Public Health. 2025;25(1):1464.
20. Kendler KS, Karkowski LM, Prescott CA. Causal relationship between stressful life events and the onset of major depression. Am J Psychiatry. 1999;156(6):837-41.
21. Sapolsky RM. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. Arch Gen Psychiatry. 2000;57(10):925-35.
22. Ahmed S, Moussa F, Moustafa A, Ayoub D. Cortisol level in depressed patients and its relation with suicidal risk and anhedonia. The Egyptian Journal of Neurology, Psychiatry and Neurosurgery. 2016;53:193.
23. Roozendaal B, McEwen BS, Chattarji S. Stress, memory and the amygdala. Nat Rev Neurosci. 2009;10(6):423-33.
24. Patriquin MA, Mathew SJ. The Neurobiological Mechanisms of Generalized Anxiety Disorder and Chronic Stress. Chronic Stress. 2017;1:2470547017703993.
25. Hammen C. Stress and depression. Annu Rev Clin Psychol. 2005;1:293-319.
26. Albright GL, Andreassi JL, Brockwell AL. Effects of stress management on blood pressure and other cardiovascular variables. International Journal of Psychophysiology. 1991;11(2):213-7.
27. Kasos K, Zimonyi S, Gonye B, Köteles F, Kasos E, Kotyuk E, et al. Obimon: An open-source device enabling group measurement of electrodermal activity. Psychophysiology. 2019;56(8):e13374.

28. Vinkers CH, Penning R, Hellhammer J, Verster JC, Klaessens JHGM, Olivier B, et al. The effect of stress on core and peripheral body temperature in humans. Stress. 2013;16(5):520-30.
29. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav. 1983;24(4):385-96.
30. Ferreira R, Murray J. Spielberger's State-Trait Anxiety Inventory: Measuring Anxiety with and without an Audience during Performance on a Stabilometer. Perceptual and Motor Skills. 1983;57(1):15-8.
31. Hofmann SG, Asnaani A, Vonk IJ, Sawyer AT, Fang A. The Efficacy of Cognitive Behavioral Therapy: A Review of Meta-analyses. Cognit Ther Res. 2012;36(5):427-40.
32. Goyal M, Singh S, Sibinga EM, Gould NF, Rowland-Seymour A, Sharma R, et al. Meditation programs for psychological stress and well-being: a systematic review and meta-analysis. JAMA Intern Med. 2014;174(3):357-68.
33. Salmon P. Effects of physical exercise on anxiety, depression, and sensitivity to stress: a unifying theory. Clin Psychol Rev. 2001;21(1):33-61.
34. Baldwin DS, Waldman S, Allgulander C. Evidence-based pharmacological treatment of generalized anxiety disorder. Int J Neuropsychopharmacol. 2011;14(5):697-710.
35. Slater M. Immersion and the illusion of presence in virtual reality. Br J Psychol. 2018;109(3):431-3.
36. Baños RM, Botella C, Alcañiz M, Liaño V, Guerrero B, Rey B. Immersion and emotion: their impact on the sense of presence. Cyberpsychology & behavior. 2004;7(6):734-41.
37. Makowski D, Sperduti M, Nicolas S, Piolino P. “Being there” and remembering it: Presence improves memory encoding. Consciousness and Cognition. 2017;53:194-202.
38. Tang Q, Wang Y, Liu H, Liu Q, Jiang S. Experiencing an art education program through immersive virtual reality or iPad: Examining the mediating effects of sense of presence and extraneous cognitive load on enjoyment, attention, and retention. Front Psychol. 2022;13:957037.

39. Reeves R, Curran D, Gleeson A, Hanna D. A Meta-Analysis of the Efficacy of Virtual Reality and In Vivo Exposure Therapy as Psychological Interventions for Public Speaking Anxiety. Behavior Modification. 2021;46(4):937-65.
40. Sheridan TB. Musings on telepresence and virtual presence. Presence Teleoperators Virtual Environ. 1992;1(1):120-5.
41. Lee KM. Presence, Explicated. Communication Theory. 2004;14(1):27-50.
42. Witmer A, Slater M. Measuring Presence: A Response to the Witmer and Singer Presence Questionnaire. Presence (Camb). 1999;8.
43. Witmer BG, Singer MJ. Measuring presence in virtual environments: A presence questionnaire. Presence. 1998;7(3):225-40.
44. J. Short EWaBC. "The Social Psychology of Telecommunications," London: John Wiley & Sons, ; 1976.
45. Nowak K. The Effect of the Agency and Anthropomorphism on Users' Sense of Telepresence, Copresence, and Social Presence in Virtual Environments. Presence Teleoperators &amp Virtual Environments. 2003;12:481-94.
46. Lenz K. Behavior in Public Places. Notes on the Social Organization of Gatherings. Goffman-Handbuch: Leben–Werk–Wirkung: Springer; 2022. p. 291-7.
47. Nowak K. The Influence of Anthropomorphism and Agency on Social Judgment in Virtual Environments. Journal of Computer-Mediated Communication. 2004;9.
48. Cummings JJ, Bailenson JN. How Immersive Is Enough? A Meta-Analysis of the Effect of Immersive Technology on User Presence. Media Psychology. 2016;19(2):272-309.
49. Witmer BG, Singer MJ. Measuring Presence in Virtual Environments: A Presence Questionnaire. Presence: Teleoperators and Virtual Environments. 1998;7(3):225-40.
50. Davis S, Nesbitt K, Nalivaiko E. A Systematic Review of Cybersickness. Proceedings of the 2014 Conference on Interactive Entertainment; Newcastle, NSW, Australia: Association for Computing Machinery; 2014. p. 1–9.
51. Barreda-Ángeles M, Hartmann T. Hooked on the metaverse? Exploring the prevalence of addiction to virtual reality applications. Frontiers in Virtual Reality. 2022;3.
52. Tychsen L, Foeller P. Effects of Immersive Virtual Reality Headset Viewing on Young Children: Visuomotor Function, Postural Stability, and Motion Sickness. American Journal of Ophthalmology. 2020;209:151-9.

53. Freeman D, Reeve S, Robinson A, Ehlers A, Clark D, Spanlang B, et al. Virtual reality in the assessment, understanding, and treatment of mental health disorders. Psychol Med. 2017;47(14):2393-400.
54. Qi Z, Corr F, Grimm D, Nimsky C, Bopp MHA. Extended Reality-Based Head-Mounted Displays for Surgical Education: A Ten-Year Systematic Review. Bioengineering (Basel). 2024;11(8).
55. Einloft J, Meyer HL, Bedenbender S, Morgenschweis ML, Ganser A, Russ P, et al. Immersive medical training: a comprehensive longitudinal study of extended reality in emergency scenarios for large student groups. BMC Med Educ. 2024;24(1):978.
56. Spiegel B, Fuller G, Lopez M, Dupuy T, Noah B, Howard A, et al. Virtual reality for management of pain in hospitalized patients: A randomized comparative effectiveness trial. PLoS One. 2019;14(8):e0219115.
57. Wong KP, Tse MMY, Qin J. Effectiveness of Virtual Reality-Based Interventions for Managing Chronic Pain on Pain Reduction, Anxiety, Depression and Mood: A Systematic Review. Healthcare (Basel). 2022;10(10).
58. Singleton H, Mahato P, Arden-Close E, Thomas S, Ersser S, Holley D, et al. Virtual reality used to distract children and young people with long-term conditions from pain or pruritus: A scoping review using PAGER. J Clin Nurs. 2024;33(2):469-80.
59. Wang L, Zhang H, Ai H, Liu Y. Effects of virtual reality rehabilitation after spinal cord injury: a systematic review and meta-analysis. J Neuroeng Rehabil. 2024;21(1):191.
60. Cortés-Pérez I, Desdentado-Guillem JM, Camacho-Delgado MS, Del Rocío Ibancos-Losada M, Obrero-Gaitán E, Lomas-Vega R. Virtual reality-based therapy after anterior cruciate ligament injury effectively reduces pain and improves knee function, movement patterns, and dynamic balance: A systematic review and meta-analysis. Knee Surg Sports Traumatol Arthrosc. 2024.
61. Freitas JRS, Velosa VHS, Abreu LTN, Jardim RL, Santos JAV, Peres B, et al. Virtual Reality Exposure Treatment in Phobias: a Systematic Review. Psychiatr Q. 2021;92(4):1685-710.
62. Heo S, Park JH. Effects of Virtual Reality-Based Graded Exposure Therapy on PTSD Symptoms: A Systematic Review and Meta-Analysis. Int J Environ Res Public Health. 2022;19(23).

63. Geraets CNW, Wallinius M, Sygel K. Use of Virtual Reality in Psychiatric Diagnostic Assessments: A Systematic Review. Front Psychiatry. 2022;13:828410.
64. Cibrian FL, Monteiro EM, Lakes KD. Digital assessments for children and adolescents with ADHD: a scoping review. Front Digit Health. 2024;6:1440701.
65. Malbos E, Borwell B, Lançon C, weindel g, Chichery N, Seimandi J. Virtual Reality for Relaxation in the Treatment of Generalized Anxiety Disorder : a Comparative Trial. Annual Review of CyberTherapy and Telemedicine. 2020;18:206.
66. Kampmann IL, Emmelkamp PM, Hartanto D, Brinkman W-P, Zijlstra BJ, Morina N. Exposure to virtual social interactions in the treatment of social anxiety disorder: A randomized controlled trial. Behaviour research and therapy. 2016;77:147-56.
67. Hardardottir H, Aspelund T, Fall K, Broström E, Sigurdsson B, Cook E, et al. Psychobiological stress response to a lung cancer diagnosis: a prospective study of patients in Iceland and Sweden. Acta Oncologica. 2023;62:1338-47.
68. Stunden C, Stratton K, Zakani S, Jacob J. Comparing a Virtual Reality-Based Simulation App (VR-MRI) With a Standard Preparatory Manual and Child Life Program for Improving Success and Reducing Anxiety During Pediatric Medical Imaging: Randomized Clinical Trial. J Med Internet Res. 2021;23(9):e22942.
69. Ashmore J, Di Pietro J, Williams K, Stokes E, Symons A, Smith M, et al. A Free Virtual Reality Experience to Prepare Pediatric Patients for Magnetic Resonance Imaging: Cross-Sectional Questionnaire Study. JMIR Pediatr Parent. 2019;2(1):e11684.
70. Kondylakis H, Giglioli IAC, Katehakis D, Aldemir H, Zikas P, Papagiannakis G, et al. Stress Reduction in Perioperative Care: Feasibility Randomized Controlled Trial. J Med Internet Res. 2025;27:e54049.
71. Ahmad M, Tran MT, Ahmad B, Kavallieros K, Shalhoub J, Davies AH. Virtual Reality Versus Simulation in the Management of Trauma Based Scenarios-A Systematic Review. Health Sci Rep. 2024;7(12):e70216.
72. Nakarada-Kordic I, Reay S, Bennett G, Kruse J, Lydon AM, Sim J. Can virtual reality simulation prepare patients for an MRI experience? Radiography (Lond). 2020;26(3):205-13.
73. Tennant M, Anderson N, Youssef GJ, McMillan L, Thorson R, Wheeler G, et al. Effects of immersive virtual reality exposure in preparing pediatric oncology patients for

radiation therapy. Technical innovations & patient support in radiation oncology. 2021;19:18-25.

74. Zhang D, Lee EKP, Mak ECW, Ho CY, Wong SYS. Mindfulness-based interventions: an overall review. Br Med Bull. 2021;138(1):41-57.

75. Marciniak R, Šumec R, Vyhnálek M, Bendíčková K, Lázničková P, Forte G, et al. The Effect of Mindfulness-Based Stress Reduction (MBSR) on Depression, Cognition, and Immunity in Mild Cognitive Impairment: A Pilot Feasibility Study. Clin Interv Aging. 2020;15:1365-81.

76. Arpaia P, D'Errico G, De Paolis LT, Moccaldi N, Nuccetelli F. A Narrative Review of Mindfulness-Based Interventions Using Virtual Reality. Mindfulness. 2022;13(3):556-71.

77. Tarrant J, Viczko J, Cope H. Virtual Reality for Anxiety Reduction Demonstrated by Quantitative EEG: A Pilot Study. Front Psychol. 2018;9:1280.

78. Navarro-Haro MV, López-Del-Hoyo Y, Campos D, Linehan MM, Hoffman HG, García-Palacios A, et al. Meditation experts try Virtual Reality Mindfulness: A pilot study evaluation of the feasibility and acceptability of Virtual Reality to facilitate mindfulness practice in people attending a Mindfulness conference. PLoS One. 2017;12(11):e0187777.

79. Modrego-Alarcón M, Morillo H, Campos D, Navarro-Gil MT, Montero-Marín J, Monreal-Bartolomé A, et al. Effects and acceptability of virtual reality to facilitate mindfulness practice in university students. Journal of Computing in Higher Education. 2023.

80. Kaplan-Rakowski R, Johnson KR, Wojdynski T. The impact of virtual reality meditation on college students' exam performance. Smart Learning Environments. 2021;8(1):21.

81. Poetar C-R, Bradley N, Voinescu A. Immersive virtual reality or computerised mindfulness meditation for improving mood? Preliminary efficacy from a pilot randomised trial. Frontiers in psychology. 2023;14:1157469.

82. El Kheir DYM, Ibrahim AHM. Epidemiological assessment of distress during chemotherapy: who is affected? J Taibah Univ Med Sci. 2019;14(5):448-53.

83. Hamner T, Latzman RD, Latzman NE, Elkin TD, Majumdar S. Quality of life among pediatric patients with cancer: Contributions of time since diagnosis and parental chronic stress. Pediatr Blood Cancer. 2015;62(7):1232-6.
84. Wiener L, Kazak AE, Noll RB, Patenaude AF, Kupst MJ. Standards for the Psychosocial Care of Children With Cancer and Their Families: An Introduction to the Special Issue. Pediatr Blood Cancer. 2015;62 Suppl 5(Suppl 5):S419-24.
85. Uslu A, Arslan S. The Effect of Using Virtual Reality Glasses on Anxiety and Fatigue in Women with Breast Cancer Receiving Adjuvant Chemotherapy: A Pretest-Posttest Randomized Controlled Study. Semin Oncol Nurs. 2023;39(5):151503.
86. Bani Mohammad E, Ahmad M. Virtual reality as a distraction technique for pain and anxiety among patients with breast cancer: A randomized control trial. Palliative and Supportive Care. 2019;17(1):29-34.
87. Schneider SM, Kisby CK, Flint EP. Effect of virtual reality on time perception in patients receiving chemotherapy. Support Care Cancer. 2011;19(4):555-64.
88. Ioannou A, Paikousis L, Papastavrou E, Avraamides MN, Astras G, Charalambous A. Effectiveness of Virtual Reality Vs Guided Imagery on mood changes in cancer patients receiving chemotherapy treatment: A crossover trial. Eur J Oncol Nurs. 2022;61:102188.
89. Hedström M, Haglund K, Skolin I, von Essen L. Distressing events for children and adolescents with cancer: child, parent, and nurse perceptions. J Pediatr Oncol Nurs. 2003;20(3):120-32.
90. Gerçeker G, Bektaş M, Önal A, Kudubeş AA, Çeçen RE. The Effect of Virtual Reality Distraction and Fatigue Training on Anxiety and Fatigue Levels in Children with Cancer: A Randomized Controlled Study. Semin Oncol Nurs. 2024:151725.
91. Sharifpour S, Manshaee GR, Sajjadian I. Effects of virtual reality therapy on perceived pain intensity, anxiety, catastrophising and self-efficacy among adolescents with cancer. Couns Psychother Res. 2021;21(1):218-26.
92. Chirico A, Lucidi F, De Laurentiis M, Milanese C, Napoli A, Giordano A. Virtual Reality in Health System: Beyond Entertainment. A Mini-Review on the Efficacy of VR During Cancer Treatment. J Cell Physiol. 2016;231(2):275-87.

93. Bani Mohammad E, Ahmad M. Virtual reality as a distraction technique for pain and anxiety among patients with breast cancer: A randomized control trial. Palliat Support Care. 2019;17(1):29-34.
94. Munn Z, Moola S, Lisy K, Riitano D, Murphy F. Claustrophobia in magnetic resonance imaging: A systematic review and meta-analysis. Radiography. 2015;21(2):e59-e63.
95. Al Shanbari NM, Alobaidi SF, Alhasawi R, Alzahrani AS, Bin Laswad BM, Alzahrani AA, et al. Assessment of Anxiety Associated With MRI Examination Among the General Population in the Western Region of Saudi Arabia. Cureus. 2023;15(2):e34531.
96. Uffman JC, Tumin D, Raman V, Thung A, Adler B, Tobias JD. MRI Utilization and the Associated Use of Sedation and Anesthesia in a Pediatric ACO. J Am Coll Radiol. 2017;14(7):924-30.
97. Harris M, Chung F. Complications of general anesthesia. Clin Plast Surg. 2013;40(4):503-13.
98. Maranets I, Kain ZN. Preoperative anxiety and intraoperative anesthetic requirements. Anesth Analg. 1999;89(6):1346-51.
99. de Bie HM, Boersma M, Wattjes MP, Adriaanse S, Vermeulen RJ, Oostrom KJ, et al. Preparing children with a mock scanner training protocol results in high quality structural and functional MRI scans. Eur J Pediatr. 2010;169(9):1079-85.
100. Rothman S, Gonen A, Vodonos A, Novack V, Shelef I. Does preparation of children before MRI reduce the need for anesthesia? Prospective randomized control trial. Pediatr Radiol. 2016;46(11):1599-605.
101. Arpaia P, D'Errico G, De Paolis L, Moccaldi N, Nuccetelli F. A Narrative Review of Mindfulness-Based Interventions Using Virtual Reality. Mindfulness. 2022;13:1-16.
102. Ma J, Zhao D, Xu N, Yang J. The effectiveness of immersive virtual reality (VR) based mindfulness training on improvement mental-health in adults: A narrative systematic review. Explore. 2023;19(3):310-8.
103. Lee Wong C, Li CK, Choi KC, Wei So WK, Yan Kwok JY, Cheung YT, et al. Effects of immersive virtual reality for managing anxiety, nausea and vomiting among paediatric cancer patients receiving their first chemotherapy: An exploratory randomised controlled trial. Eur J Oncol Nurs. 2022;61:102233.

104. Tennant M, Youssef GJ, McGillivray J, Clark T-J, McMillan L, McCarthy MC. Exploring the use of Immersive Virtual Reality to enhance Psychological Well-Being in Pediatric Oncology: A pilot randomized controlled trial. Eur J Oncol Nurs. 2020;48:101804.
105. Sipos K, Sipos M. The development and validation of the Hungarian Form of the State-Trait Anxiety Inventory. Series in Clinical & Community Psychology: Stress & Anxiety. 1983;2:27-39.
106. Team RC. R: A language and environment for statistical computing. 2013.
107. Chandra V, Priyarup A, Sethia D, editors. Comparative Study of Physiological Signals from Empatica E4 Wristband for Stress Classification. Advances in Computing and Data Sciences; 2021 2021//; Cham: Springer International Publishing.
108. Spielberger C. State-trait anxiety inventory for adults. Mind Garden. 1983.
109. Kocielnik R, Sidorova N, Maggi FM, Ouwerkerk M, Westerink JHDM, editors. Smart technologies for long-term stress monitoring at work. Proceedings of the 26th IEEE International Symposium on Computer-Based Medical Systems; 2013 20-22 June 2013.
110. Team RC. RA language and environment for statistical computing, R Foundation for Statistical. Computing. 2020.
111. Erdős S, Papik F, Dorottya N, Schlosser K, Topa K, András M, et al. Comparing virtual reality-based simulation, booklet-based and standard preparation methods for pediatric magnetic resonance imaging (MR-VR): study protocol for a randomized clinical trial. Virtual Reality. 2025;29(3):95.
112. Erdős S, Horváth K. The Impact of Virtual Reality (VR) on Psychological and Physiological Variables in Children Receiving Chemotherapy: A Pilot Cross-Over Study. Integr Cancer Ther. 2023;22:15347354231168984.
113. Gershon J, Zimand E, Lemos R, Rothbaum BO, Hodges L. Use of virtual reality as a distractor for painful procedures in a patient with pediatric cancer: a case study. Cyberpsychol Behav. 2003;6(6):657-61.
114. Ito Y, Browne CA, Yamamoto K. The Impacts of Mindfulness-Based Stress Reduction (MBSR) on Mindfulness and Well-being for Regular and Novice Meditators. Mindfulness. 2022;13(6):1458-68.
115. Best P, Meireles M, Schroeder F, Montgomery L, Maddock A, Davidson G, et al. Freely Available Virtual Reality Experiences as Tools to Support Mental Health Therapy:

a Systematic Scoping Review and Consensus Based Interdisciplinary Analysis. Journal of Technology in Behavioral Science. 2022;7(1):100-14.

9. BIBLIOGRAPHY OF THE CANDIDATE'S PUBLICATIONS

9.1. Bibliography related to the thesis Σ IF: 6,4

1. **Erdős S,** Horváth K. The impact of virtual reality (VR) on psychological and physiological variables in children receiving chemotherapy: a pilot cross-over study. Integr Cancer Ther. 2023;22. doi:10.1177/15347354231168984. **IF: 2.9**
2. Olasz O, **Erdős S,** Horváth K. The effects of virtual reality-based mindfulness exercises on the perception of time, psychological and physiological states of young people: a randomized crossover trial. Mindfulness. 2024;15:2347–2354. doi:10.1007/s12671-024-02438-y. **IF: 3.5**

9.2. Bibliography not related to the thesis Σ IF: 5,0

3. **Erdős S,** Papik F, Nyáry D, Schlosser K, Topa K, András M, et al. Efficacy of virtual reality based simulation in the preparation of children for magnetic resonance imaging examinations (MR-VR): study protocol for a randomized clinical trial. Virtual Reality. **IF: 5,0**

10.ACKNOWLEDGEMENTS

At the conclusion of my doctoral thesis, I would like to extend my heartfelt thanks and appreciation to everyone whose support was essential to my scientific endeavours.

First, I express my deepest gratitude to my supervisor. I am grateful that I met with Klára Horváth as a third-year medical student. I am honoured that she allowed me to explore the healthcare applications of VR and introduced me to this rapidly evolving, innovative world. Her advice and valuable comments have guided me throughout my work and helped my development to practice science to a high standard. My PhD thesis would not have been possible without her exemplary attitude and extensive knowledge.

I would like to thank Professor Gábor Kovács. As the previous chair of the Department, he allowed me to start my research career. I am grateful that he let me explore the usage of VR technology in healthcare.

I want to express my gratitude to the Chair of the Department, Professor Attila Szabó, for the great support and advice. I am grateful for the opportunity he provided me to expand my knowledge and continue my career at the Department.

I would like to thank all the children and parents who contributed to exploring the possibilities of using VR in healthcare. Furthermore, I am deeply grateful to all the healthcare professionals whose innovative approach contributed to the realization of our research.

I am deeply grateful to Digital Thinkers Ltd., which supported the creation of unique VR experiences with their work as software developers. I would like to especially thank their chief executive officer, Balázs Máramarosi, who always supported our work with their expertise and ideas. Another important company is Appy Nonprofit Kft. I would like to thank its leader, Tünde Schranc, and Judit Oprics, who generously dedicated their time to supporting our work.

I would like to thank all members of our labour who helped me with their outstanding skills and attitude. I am honoured to be supported by Dorka Aschenbrenner, Anna Petró, Balázs Hauser, Dorottya Nyáry, Edit Varga, Flóra Papik, Gábor Jakus, Kristóf Topa, Károly Schlosser, Márton Szabados, Orsolya Juhász, Orsolya Olasz, Szilveszter Papp, Zsuzsanna Korponay.

Finally, I would like to thank my family, friends, and colleagues. Their unwavering patience and selfless dedication in supporting me have reminded me why I chose this path. A special thanks goes to my wife, who encouraged me to never give up. I am deeply grateful to my late father, whose unwavering support and belief in me continue to inspire my journey. This achievement would not have been possible without his encouragement and love.