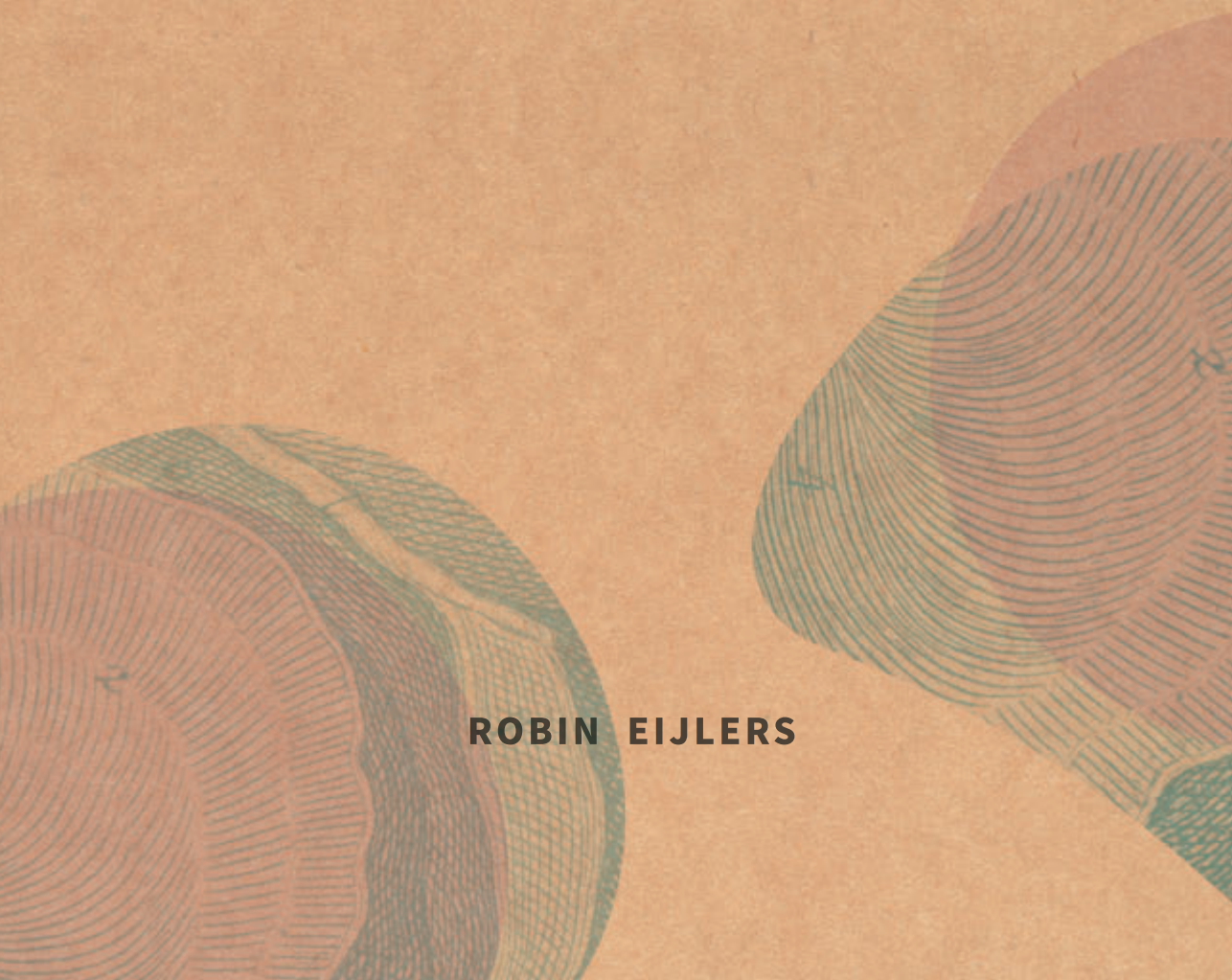
VIRTUAL REALITY EXPOSURE TO PREPARE CHILDREN FOR SURGERY:

EFFECTS ON ANXIETY AND PAIN



ROBIN EIJLERS

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COLOFON

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Virtual Reality Exposure to Prepare Children for Surgery: Effects on Anxiety and Pain

Virtual Reality Exposure voor kinderen ter voorbereiding op een operatie: effecten op angst en pijn

Proefschrift

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General introduction

PART I: VIRTUAL REALITY TO PREPARE CHILDREN FOR SURGERY: EFFECTS ON ANXIETY AND PAIN

Preoperative anxiety in children

Undergoing surgery can be a very stressful situation for children. On the day of surgery, up to 70% of children experience anxiety, which gradually increases and usually peaks during induction of anesthesia [1-5]. Anxiety can be due to uncertainty and is often related to 'the unknown', including the unfamiliar surgical environment and procedures, unknown people, and feelings of loss of control [1, 6]. Moreover, younger children (one to six years) are often afraid of being separated from their parents, whereas older children (over six years) tend to be more afraid of bodily harm and consequences of surgery [1]. The method of anesthesia induction, i.e., intravenous or inhalation, also plays a role in the level of anxiety children experience, but there is no agreement regarding which type of anesthesia induction method leads to the most satisfying experience for children [7, 8]. A child's operation is also a stressful experience for parents, as they often experience feelings of worry and helplessness [9, 10]. Child and parental anxiety have been shown to reciprocally influence each other [11, 12].

Consequences of anxiety during anesthesia induction

Children express preoperative anxiety in different ways. While some verbalize it, others may protest and show resistance during anesthesia induction [13]. Children can be so anxious that they even try to escape from the operating theatre [13, 14]. When anxiety causes children to be less compliant during induction of anesthesia, anesthesiologists sometimes need to use physical restraint and pharmacological interventions, which can lead to a traumatic experience and prolonged recovery time after surgery [5, 14, 15].

Preoperative anxiety in children is related to a range of maladaptive consequences in the direct postoperative period, such as increased anxiety, intensified pain, and poorer recovery [13, 16-18]. For example, in a study by Kain et al. [17], including 241 5-to-12-year-old children, anxious patients had significantly higher levels of pain in the recovery room, as well as during the first three days after adenoidectomy and tonsillectomy. As a result, anxious children also needed more analgesics (pain medication) [17]. Preoperative anxiety is also associated with the occurrence of emergence delirium [19, 20]. Emergence delirium is a common postoperative complication, encompassing unintentional and purposeless motions (e.g., kicking),

hypersensitivity to stimuli, not recognizing surroundings, and being inconsolable [21-23]. It typically starts quickly after emergence from general anesthesia and is mostly of short duration, i.e., less than 15 minutes [23-25].

Highly anxious children are also at risk for developing psychological problems in the two weeks after surgery, such as anxiety, nightmares, eating and sleeping disturbances, and apathy [17, 19, 26-28]. Moreover, it has been found that undergoing elective daycare surgery can result in mild posttraumatic stress symptoms in children aged 6 to 18 years that may persist up to six months [27]. Finally, negative hospital experiences, including anxiety, pain, and low satisfaction with health care could lead to lower adherence to medical treatment and avoidance of health care, even later in life [29-34].

Interventions to reduce anxiety during anesthesia induction

Over the past decade, patient-and family-centered care has become more of a focus in hospitals [35]. Objectives of patient- and family-centered care are, amongst others, collaboration between patients/families and professionals, joint decision making, building on family strengths, and supporting children in participating in medical treatment [35-37]. Paying attention to the psychological wellbeing of children and their families, including interventions to reduce anxiety levels, should be an integral part of pediatric health care [36]. Therefore, at our hospital, the Erasmus MC Sophia Children's Hospital, all children who need to undergo surgery, are first scheduled for a preoperative visit with a pediatric anesthesiologist. During this visit, the anesthesiologist will provide children and parents elaborate education concerning general anesthesia. In addition, an age-appropriate informative movie about general anesthesia is available on the website of our hospital, which children and parents can watch at home.

In scientific literature, many non-pharmacological interventions to reduce preoperative anxiety have been proposed, such as distraction during anesthesia induction and psychological preparation for anesthesia and surgery [38-40]. Distraction is a commonly applied technique in pediatric health care. The theory behind distraction is that by directing attention away from the painful procedure and redirecting it to something fun and engaging, less attention is available for the perception of pain and anxiety [41, 42]. Examples of distraction techniques during induction of anesthesia are playing hand-held videogames, watching cartoons or videos, distraction by parents

or nurses, playing with toys, and listening to music [38, 43-45]. According to literature reviews [38, 46], distraction *can* be an effective method to reduce anxiety and pain, but results are mixed and its efficacy depends on different factors, such as the method that is used and the amount of engagement and activity of a child.

Distraction interventions often target *pain* and have, therefore, often been applied during *painful* procedures, e.g., burn wound treatment, venipuncture, and cancer treatment [47-49]. However, during anesthesia induction, the main focus is to reduce *anxiety*, which can be achieved via psychological preparation. Successful psychological preparation of children for surgery can minimize preoperative anxiety, which in turn can prevent its negative consequences [17, 19, 39]. Psychological preparation strategies for children undergoing surgery can be divided into providing information, teaching skills, or exposure. Examples of strategies are: educational programs [50], therapeutic play, including a doll demonstration of anesthesia induction [10], acquiring coping skills [51], and education via leaflets [52], videos [53], websites [54], or smartphone applications [55]. Mixed results have been found for these preparation strategies. According to a meta-analysis on audiovisual interventions as a preparation tool for children undergoing surgery, internet programs seem to have limited efficacy, whilst interactive games have the most potential to reduce preoperative anxiety in children [46]. The effectiveness of these techniques is also dependent on timing and duration of the intervention, the engagement of children, and involvement of parents [56].

Exposure is a behavioral technique to become gradually familiar with a situation, place, or person [57]. Scientific literature has shown that exposing children to anxiety-evoking situations is more effective in reducing anxiety, for example for the treatment of panic disorders and specific phobias, than redirecting attention (distraction) [57, 58]. Therefore, a possible intervention to reduce preoperative anxiety in children would be to expose them, prior to surgery, to all preoperative and postoperative aspects. Li et al. [10] took children and their parents on a live tour through the holding area, operating room, and recovery room, where they were encouraged to explore the surroundings. The authors found that this way of exposure reduced anxiety prior to and after surgery, compared to the control group, which received only routine information. Unfortunately, exposing children to all preoperative and postoperative aspects at the hospital is often not feasible, due to busy clinical practice and the daily use of surgery rooms. Virtual reality (VR)

might offer a solution, because this way, children can be exposed to the operating environment and anesthetic procedures, *virtually*, in a very realistic manner.

Virtual reality

VR comprises a computer-generated environment, in which orientation and three-dimensional (3D) interaction are possible. Because VR systems use motion tracking, users can move around in the virtual environment, at their own pace [59, 60]. The virtual environment is projected directly in front of the user's eyes via an advanced head-mounted display (HMD) (Figure 1), creating a wide field of view. The stimuli that substitute the real-world sensory information are visual, aural, and sometimes even tactile. These multimodal stimuli in combination with being occluded from the real world contribute to experiencing the feeling of being present in the virtual world and being able to move and act inside it. Modern VR systems are able to create *full* immersion. Immersion is "the objective level of sensory fidelity a VR system provides" [59, 61, 62], but the *feeling* of presence remains subjective [62, 63].

Virtual reality to prepare children for surgery

Over the past two decades, VR has gained popularity in health care and has been applied in different ways. For example, VR has been used as a distraction tool for pediatric patients during medical procedures, e.g., burn dressing changes [64] or blood draw [65]. It has been hypothesized that VR might be more effective than traditional methods of distraction because it may increase patients' engagement [66, 67]. Moreover, VR has been used effectively as an exposure tool for anxiety disorders, e.g., social phobia or spider phobia [68-70]. Recently, VR exposure (VRE) has expanded its reach in health care from treating anxiety disorders to preventively reducing anxiety concerning medical procedures. VRE can be used to make patients feel more comfortable and to increase their familiarity with and understanding of different procedures and environments [71, 72]. Thus, VRE can be used as an exposure tool to reduce preoperative anxiety by exposing children to a realistic virtual version of the operating theatre, in which they are in control, allowing them to explore the operating environment at their own pace and get familiar with anesthesia procedures. Whereas different meta-analyses have shown that VRE is effective in treating anxiety disorders [69, 70], until now, only two [73, 74] studies have been conducted on the effectiveness of VRE as preparation for medical procedures (which we will discuss below).

Figure 1 Example of a virtual reality head-mounted display (left) and controllers (right). This is the HTC VIVE system (HTC Corporation, New Taipei City, Taiwan).

The amount of research investigating the effectiveness of VR on alleviating anxiety and pain in pediatric patients has strongly increased over the past years. However, studies are often small and have been focusing on a wide variety of medical procedures [75, 76]. This underlines the need to systematically evaluate the effectiveness of VR in pediatric populations. Some reviews have described the effectiveness of VR on *pain* [75, 76], but the effectiveness of VR on *anxiety* has received little attention. This is remarkable, considering the reciprocal relationship between pain and anxiety [77]. Whereas few meta-analyses have been conducted on VR interventions to alleviate anxiety and pain during medical procedures [78-81], none of them have explicitly focused on pediatric patients. It is important to make this distinction, as children potentially experience more discomfort from medical procedures and VR might be even more engaging for children, as they often become truly captivated by imaginative play [82]. Chapter 2 aims to collate evidence on the effectiveness of VR to alleviate anxiety and pain in children undergoing medical procedures. In this chapter, the outcomes of a systematic review and meta-analysis on this topic are presented.

Virtual reality exposure

The two studies that have applied VRE prior to a medical procedure, used VRE to prepare children for general anesthesia prior to undergoing elective daycare

surgery. In these RCTs (both n = 69), conducted by Ryu et al. [73] and Ryu et al. [74], half of the children, aged 4 to 10 years, were exposed to a virtual version of the operating environment and anesthesia procedures on the day of surgery. In their first study, patients viewed a four minute 360 degree video of the operating theatre through a VR HMD [73], whilst in their second study, patients played a five minute VR game in which they experienced the preoperative procedures [74]. Children in the control conditions received routine information. The authors found that children experienced significantly less distress [73] and were more compliant [73, 74] during induction of anesthesia in the VRE condition compared to the control condition.

These results are promising, but there are some limitations in these studies. First, concerning the outcome measures, the authors did assess *pre*operative, but not *post*operative outcomes [73, 74], whereas preoperative anxiety is known to be related to postoperative maladaptive consequences, such as more anxiety, more pain, a higher need for analgesics, and a higher incidence of emergence delirium [13, 15-17, 19, 20]. Second, concerning the content of the VRE intervention, the authors did expose children to the *pre*operative, but not to the (unfamiliar) *post*operative environment and procedures [73, 74], e.g., fluids being delivered through an intravenous catheter, which may also evoke anxiety. Anxiety in the direct postoperative period is, like preoperative anxiety, related to consequences, such as pain, analgesics, prolonged recovery, emergence delirium, and sleeping problems after surgery [7, 11, 83-86]. Thus, it is important to also take into account postoperative aspects, i.e., to investigate the postoperative effectiveness of VRE and to prepare children for the postoperative environment and procedures. Other limitations are that Ryu et al. [73] and Ryu et al. [74] did not take into account levels of parental anxiety, whereas previous research has shown that child and parental anxiety can intensify one another [11, 12] and that their sample sizes were relatively small. A final limitation is that children in the study by Ryu et al. [73] viewed a 360 degree *video* through a VR HMD, which is not the same as true VR. In true VR, the virtual environment is computer generated, instead of recorded. Non-VR content, like 360 degree videos, are less interactive and create less immersion than VR content, because the user is limited to the filmmaker's movements and progress of the video. Therefore, VR creates a more realistic experience than 360 degree videos [87].

PREVIEW: a randomized controlled trial into virtual reality exposure prior to pediatric daycare surgery

The aim of the current RCT (PREVIEW) was to psychologically prepare children for general anesthesia and elective daycare surgery, through VRE. We were the first to use VR to expose pediatric patients to the preoperative and postoperative environment and procedures. In addition, we were the first to investigate postoperative outcomes of preoperative VRE and to take into account parental levels of anxiety. The VRE intervention consisted of a 15 minute exposure to a highly realistic virtual environment that replicates the operating theater of the Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands. Children could explore the immersive and interactive environment at their own pace. Screenshots of the virtual holding area, corridor to the operating room, operating room, and recovery room are depicted in Figures 2 – 5, respectively.

We have worked together with a specialized team of VR developers, animators, and artists, using professional technologies and equipment to develop the VRE intervention. The result is a state-of-the-art interactive and child friendly virtual environment, in which children can explore the preoperative and postoperative surroundings, will virtually undergo anesthesia induction, and can point at different instruments (e.g., the blood pressure cuff) with the controllers, to receive information about what these instruments are used for. Virtual characters, that are modeled after real personnel, guide the children through the intervention. Children experienced the virtual environment through an HTC Vive (HTC Corporation, Xindian, New Taipei, Taiwan) HMD (Figure 1). An accompanying parent could watch along with the child, as the environment was also presented on a personal computer monitor.

Children in the control condition received care as usual (CAU). CAU consisted of conventional education concerning anesthesia and surgery, provided by anesthesiologists. Moreover, children and parents were encouraged to watch an informative online movie about general anesthesia, at home. Importantly, children in the VRE condition *also* received this information and were *also* encouraged to watch the online movie about general anesthesia. Thus, the VRE condition actually consisted of VRE + CAU. We compared outcomes of children in the VRE condition with the control condition, who *only* received CAU.

Figure 2 The holding area in virtual reality

Figure 3 The corridor to the operating room in virtual reality

Figure 4 The operating room in virtual reality

Figure 5 The recovery room in virtual reality

Outcomes were: levels of anxiety during anesthesia induction (primary outcome), postoperative anxiety, pain, emergence delirium, rescue analgesia, and parental anxiety (secondary outcomes). Furthermore, we wanted to identify predictors of VRE efficacy. We included 200 4-to-12-year-old children undergoing elective maxillofacial, dental, or ear-nose-throat (ENT) surgery in day care. Full details of the study design, including the procedures and the specifications of the hardware, software, and content the VRE are described in Chapter 3. The results and implications of the PREVIEW study are described in Chapter 4.

Identification of highly anxious children

Whilst most children have anxious feelings on the day of surgery, some children are more anxious than others. The most anxious children are at the highest risk of maladaptive psychological and physiological consequences [4]. Therefore, it is important to identify which children will be most likely to experience *intense* levels of preoperative anxiety [19]. Moreover, it is important to identify these children well in advance of anesthesia induction, so that there is enough time to apply interventions to prevent anxiety from escalating [23]. Early identification of highly anxious children is also important considering the fact that it is often not feasible to apply anxiety-reducing interventions to *every* child undergoing surgery, because of busy clinical practice.

In previous research, multiple child characteristics were found to be associated with increased levels of preoperative anxiety. These characteristics include young age (children aged one to five), shyness, and a passive coping style [4, 12, 19, 88, 89]. Moreover, parental anxiety, lower parental education, and negative earlier hospital experiences have been shown to be related to preoperative child anxiety [4, 88-90].

Even though, these studies have provided insights in the vulnerability of children for anxiety, very limited research has focused on investigating standardized ways to identify them. Identifying children who are at increased risk for being highly anxious during anesthesia induction in a standardized way is clinically relevant, because this way, targeted psychological interventions can be provided in order to *prevent* intense levels of anxiety. Using standardized tools to identify children who will be highly anxious during anesthesia induction is also important for scientific research, as this can provide guidelines for future studies.

Berghmans et al. [23] found that, in children aged 1.5 to 16 years, parent-reported anxious and depression symptoms, present in the six months prior to surgery, as assessed with the Internalizing scale of the Child Behavior Checklist (CBCL) [91, 92], were associated with levels of preoperative anxiety. The authors state that the CBCL can possibly be used as an assessment tool to predict anxiety during induction of anesthesia. Fortier et al. [93] also found that the internalizing scale of the CBCL was predictive of anxiety during induction of anesthesia in adolescents (aged 11 to 18) undergoing surgery. The predictive value of the CBCL for anxiety during induction of anesthesia is a rather unexplored research area and it is important to further expand this promising line of research and to focus on identifying high-risk patients in a standardized manner.

While internalizing behavior in the six months prior to surgery may be a good predictor, situational feelings such as state anxiety may be even more predictive of anxiety during induction of anesthesia. State anxiety at hospital arrival has a much closer temporal association with anxiety during induction of anesthesia, a few hours later, than internalizing behavior during the previous six months. Obtaining information on state anxiety directly at hospital arrival, would still provide parents or health care professionals enough time to intervene, before anxiety possibly escalates. This can possibly be achieved by, for example, providing a VRE intervention, in which children can explore the operating environment and procedures at their own pace, so they can become accustomed to it [73, 74].

Chapter 5 focuses on investigating different standardized tools at hospital arrival to identify patients who will be highly anxious during induction of anesthesia in a sample of 100 4-to-12-year-old children undergoing elective daycare surgery.

PART II: ANXIETY IN CHILDREN UNDERGOING MAGNETIC RESONANCE IMAGING

Not only medical *treatment* procedures, but also medical *diagnostic* procedures, such as undergoing magnetic resonance imaging (MRI) can be anxiety provoking. MRI is a sophisticated technique that is considered the primary diagnostic method for numerous clinical problems [94]. MRI techniques have greatly improved our capability to understand both the structure and function of the brain. In contrast to other methods, MRI can obtain high spatial resolution images, without using

ionizing radiation. However, different features of the MRI procedure can be considered a burden. The MR gradients are ramping on and off, which creates loud noises (85 to 110 dB), the MRI bore is a very confined space, and one has to lie still for a long time (approximately 15 to 90 minutes) [95]. Therefore, undergoing an MRI can evoke feelings of anxiety, claustrophobia, and panic [96].

While MRI in children and adolescents is a well-established method, very little research has focused on anxiety levels they experience during the procedure. Studies from the 90's showed that approximately 30% of pediatric patients were anxious during an MRI [97, 98]. However, these studies are dated, considering scanning techniques and procedures have improved over the past 25 years [94]. More recently, Westra et al. [99] found that 50% of 5-to-12-year-old children with non-acute medical conditions undergoing MRI experienced at least some levels of anxiety. In contrast, two other studies have found that undergoing MRI is regarded a minimal burden for children and adolescents [100, 101].

MRI-related state anxiety not only causes discomfort in children, it may also be associated with important methodological issues concerning functional and structural MRI findings. Functional MRI (fMRI) detects changes in blood flow that are associated with brain activity, for example while performing an emotional processing task [102]. fMRI is an often used neuroimaging technique to investigate patterns of brain activity associated with internalizing and externalizing behavior in children and adolescents with psychiatric disorders [103, 104]. According to comprehensive literature reviews, internalizing behavior in children and adolescents is associated with dysfunction in the amygdala and in different regions of the prefrontal cortex, whereas externalizing behavior is associated with, for example, right fronto-striatal dysfunctions [103, 104].

It has been found that state anxiety is associated with activation in the same brain network as trait and pathological anxiety, which may be associated with an overlap in fMRI responses [105-107]. This means that when examining *internalizing* behavior, including trait anxiety, fMRI signals may be potentiated by state anxiety evoked by the MRI procedure. This possible moderating factor of MRI-related state anxiety in studies on internalizing behavior has, however, not been investigated before. Moreover, until now, very little is known about the relationship between *externalizing* behavior and MRI-related state anxiety. A similar methodological

issue may occur in fMRI studies on externalizing behavioral problems, since brain activity induced by MRI-related state anxiety, for example anxiety related to the loud noises and confined space of the MRI scanner, may be incorrectly interpreted as being related to externalizing behavior. This could be especially problematic for etiologically oriented research, because, in contrast to internalizing behavior, externalizing behavior is associated with activation in other brain networks than state anxiety [108-110]. It is important to investigate the associations between both internalizing and externalizing behavior and MRI-related state anxiety, because state anxiety induced by the MRI procedure may distort the interpretation of fMRI results.

State anxiety evoked by MRI procedures may influence not only findings of functional but also of structural MRI studies. For instance, anxious children are possibly less likely to participate in MRI research, either because they are unwilling to participate because they are too scared, or because researchers will exclude them for ethical reasons, as the procedure may exceed the "minimal-risk standard" [111]. Moreover, anxiety may be associated with being less able to lie still in the MRI bore [112, 113]. Movement during image acquisition can lead to motion artifacts, which are the main cause (90%) of image artifacts [113, 114]. Therefore, MRI data from anxious children may be less likely to be of sufficient quality for data analyses, creating a bias in collected and subsequent reporting data. As far as we know, the possible impact of MRI-related state anxiety on MRI participation and image quality in children has not been investigated before.

Apart from scientific studies, MRI-related anxiety can have large consequences for children with a somatic condition, as they do not have the option to decline undergoing an MRI. When a conscious MRI scanning procedure results in non-usable scans, or when children are extremely anxious for medical imaging, they require general anesthesia [115]. This enables the hospital personnel to manage the MRI procedure and to achieve the quality of scans that is needed. However, general anesthesia comes with risks and undergoing MRI under general anesthesia is often related to a delay in diagnostics, due to limited resources [116]. For example, access to inpatient facilities, anesthesiologists, recovery and daycare nurses are needed, which is also related to increased costs compared to conscious MRI [112].

Chapter 6 aims to investigate the associations between internalizing/externalizing behavior and child participation in MRI research. Moreover, the impact of internalizing/externalizing behavior, as well as MRI-related state anxiety on image quality is investigated. We are the first to investigate these associations in a very large prospective population-based cohort sample of 1,070 children (the Generation R Study). These findings may have important implications for future pediatric neuropsychiatric studies concerning the interpretation of (f)MRI results.

OUTLINE OF THIS THESIS

VR is an innovative technique that can be used to reduce anxiety and pain in pediatric patients undergoing medical procedures. The primary aim of this thesis is to investigate the effectiveness of VRE in reducing anxiety and pain in children undergoing elective daycare surgery. However, first we aim to provide insight into the current role of VR for children at the hospital. Chapter 2 provides a systematic review and meta-analysis in which we investigated *in what ways* VR has been applied for children in a hospital setting to reduce pain and anxiety and what the *effectiveness* was of these VR applications. This meta-analysis is the first to collate evidence on the effectiveness of VR in pediatric patients undergoing different medical procedures. Chapter 3, Chapter 4, and Chapter 5 concern the PREVIEW study. In this study we investigate the effectiveness of our VRE tool to reduce preoperative anxiety and postoperative anxiety, pain, rescue analgesia, and emergence delirium in children undergoing elective daycare surgery. In Chapter 3 detailed descriptions are given of the VRE intervention, including technical specifications (hardware and software) and the VRE storyline. Moreover, this chapter entails an elaborate description of the PREVIEW study design, including inclusion and exclusion criteria, patient recruitment, procedures, and outcomes measures. In Chapter 4, we present and discuss the outcomes of the PREVIEW study on preoperative and postoperative measures. We also examine predictors of VRE effectiveness and discuss implications for the clinical practice and for future studies. In Chapter 5 we discuss the possibilities to identify patients at hospital arrival, in a standardized way, who will be *highly* anxious during anesthesia induction. This is important, since especially highly anxious children are at risk of maladaptive psychological and physiological consequences. In this study, we only included children that have been randomly assigned to the *control* condition of the

PREVIEW study. These children, undergoing elective day care surgery, received regular care at the hospital.

A final aim of this thesis is to provide insight in the role of state anxiety induced by an MRI procedure in (f)MRI research on internalizing and externalizing behavior in children. MRI is an important diagnostic method for and is often applied in pediatric neuropsychiatric research. However, it is also known to evoke state anxiety, which can have consequences for the interpretation of (f)MRI outcomes. In Chapter 6, we discuss the results of our study regarding associations between internalizing/externalizing behavior and MRI-related state anxiety in children, as well as the association between internalizing/externalizing behavior and MRI research participation. Additionally, we discuss the effect of internalizing/externalizing behavior and MRI-related anxiety on image quality in children and possible improvements for future studies.

Chapter 7 entails a general discussion concerning the previous chapters, clinical implications of the findings, and directions for future research.

PART I

Virtual reality to prepare children for surgery: *effects on anxiety and pain*

02

Systematic review and meta-analysis of virtual reality in pediatrics: *effects on pain and anxiety*

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ABSTRACT

Background: Medical procedures often evoke pain and anxiety in pediatric patients. Virtual reality (VR) is a relatively new intervention that can be used to provide distraction during, or to prepare patients for, medical procedures. This meta-analysis is the first to collate evidence on the effectiveness of VR on reducing pain and anxiety in pediatric patients undergoing medical procedures.

Methods: On April 25, 2018, we searched EMBASE, MEDLINE, CENTRAL, PubMed, Web of Science, and PsycINFO with the keywords "VR," "children," and "adolescents." Studies that applied VR in a somatic setting with participants ≤21 years of age were included. VR was defined as a fully immersive 3-dimensional environment displayed in surround stereoscopic vision on a head-mounted display (HMD). We evaluated pain and anxiety outcomes during medical procedures in VR and standard care conditions.

Results: We identified 2889 citations, of which 17 met our inclusion criteria. VR was applied as distraction (n = 16) during venous access, dental, burn, or oncological care or as exposure (n = 1) before elective surgery under general anesthesia. The effect of VR was mostly studied in patients receiving burn care (n = 6). The overall weighted standardized mean difference (SMD) for VR was 1.30 (95% CI, 0.68–1.91) on patient-reported pain (based on 14 studies) and 1.32 (95% CI, 0.21–2.44) on patient-reported anxiety (based on 7 studies). The effect of VR on pediatric pain was also significant when observed by caregivers (SMD = 2.08; 95% CI, 0.55–3.61) or professionals (SMD = 3.02; 95% CI, 0.79–2.25). For anxiety, limited observer data were available.

Conclusions: VR research in pediatrics has mainly focused on distraction. Large effect sizes indicate that VR is an effective distraction intervention to reduce pain and anxiety in pediatric patients undergoing a wide variety of medical procedures. However, further research on the effect of VR exposure as a preparation tool for medical procedures is needed because of the paucity of research into this field.

Keypoints

Question: Is virtual reality (VR) effective in reducing pain and anxiety in pediatric patients undergoing medical procedures?

Findings: VR was most often used as a distraction method during medical procedures and was found to be significantly more effective in reducing pain (14 studies) and anxiety (7 studies), with large effect sizes, than care as usual (CAU).

Meaning: VR can be used effectively as a distraction method in clinical practice, but more research is needed to establish evidence on VR exposure as a prepa-ration tool for medical procedures.

INTRODUCTION

Medical procedures often evoke pain, distress, and anxiety [117]. Especially in children, these feelings not only severely affect comfort levels during medical procedures but are also associated with adverse Consequences, such as attempts to escape [13], poor recovery [17], eating and sleeping disturbances [17], and posttraumatic stress symptoms [26]. Furthermore, as pain and anxiety can lead to avoidance of health care [31, 118], interventions are needed to address pain and anxiety in pediatric patients.

Distraction is a commonly applied intervention during medical procedures. For example, the use of music [119, 120] and movies [121, 122] has been proven efficacious in reducing pain and anxiety. Virtual reality (VR) is a relatively new technique to provide distraction and might be more effective than traditional methods. VR consists of a computer-generated environment, in which orientation and 3-dimensional interaction are possible. This environment is projected right in front of the user's eyes via advanced head-mounted displays (HMDs), including a wide field of view and motion tracking systems [59]. VR can create full immersion, which is a feeling of presence in the virtual environment [59, 62]. Importantly, more immersion is related to more pain reduction, because less attention is available for pain perception [63, 123]. VR is especially engaging for children, as they often become truly captivated by imaginative play [82]. Beyond providing distraction, VR can also alleviate pain and anxiety by providing exposure. Recently, VR exposure has been applied in a more preventive manner, to make patients feel at ease and increase their familiarity with the medical procedures and environments [71, 72]. This preprocedural application of VR has not been thoroughly evaluated yet.

While the amount of research investigating the effect of VR on alleviating pain and anxiety has increased over the past years, studies are often small and encompass a wide variety of medical procedures. This emphasizes the need for a systematic evaluation of VR in pediatric populations. Although some reviews are available on the effectiveness of VR on pain [75, 76] the effectiveness on anxiety has received little attention. This is remarkable, because anxiety can intensify pain [77]. Only 1 meta-analysis is available on VR interventions [78], but no meta-analysis has specifically focused on children. This distinction is important, because children are potentially even more affected by discomfort of medical procedures and might experience VR differently than adults.

In this meta-analysis, we will collate evidence on the effectiveness of VR as either a distraction or an exposure tool, compared to standard care, on pain and anxiety in pediatric patients undergoing medical procedures.

METHODS

Reviews and Meta-analyses (PRISMA) guidelines for the reporting of meta-analyses of randomized controlled trials (RCTs) [124].

Selection Criteria

Studies reporting on the effect of VR on reducing pain and/or anxiety in pediatric patients ≤21 years of age undergoing medical procedures were considered eligible for the systematic review. VR was defined as a fully immersive 3-dimensional computer-generated environment displayed in surround stereoscopic vision on an HMD. Studies that used 360° videos, which are not computer generated, displayed on a VR HMD were considered eligible as well. Studies were included in the meta-analysis if they had at least the following data available: a mean or median score for pain or anxiety during the procedure, as well as a measure of dispersion, for both the intervention and standard care groups. If not available, we requested these data by contacting the authors.

Exclusion criteria were the application of VR in non-somatic patients samples, audiovisual glasses that offer visual and audio stimulation but do not allow interaction between the user and the computer-generated world, or no distinction made between pediatric and adult patients. Reviews, meta-analyses, single-case studies, dissertations, conference papers, and abstracts were excluded as well.

Search Strategy

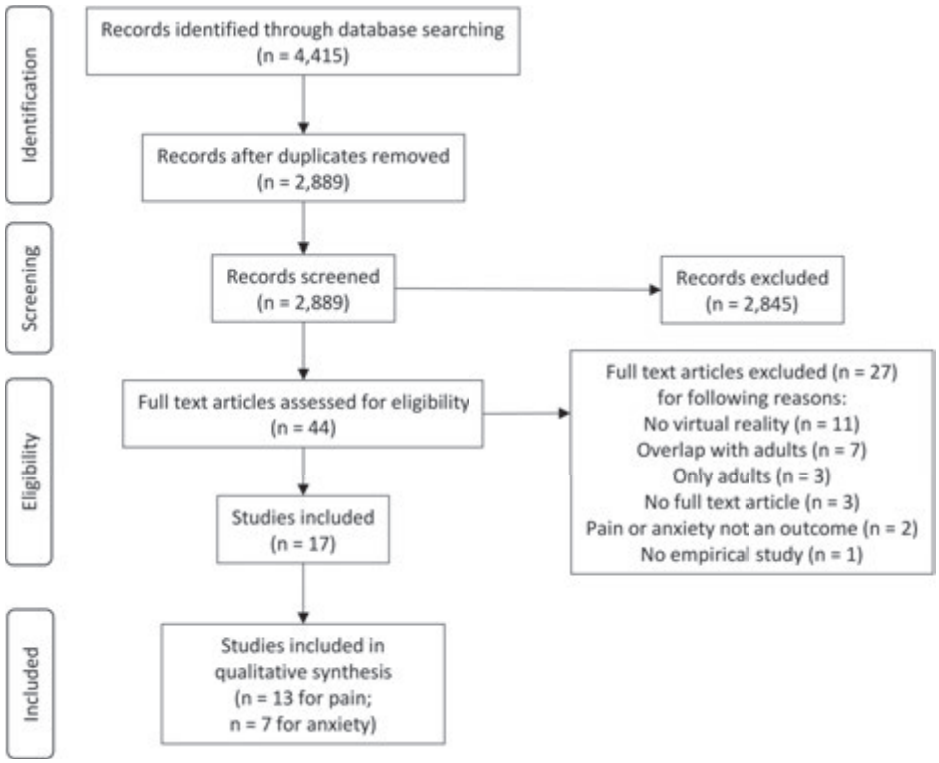
An exhaustive search in the following electronic databases was established and conducted by a biomedical information specialist on April 25, 2018 for articles published in English: EMBASE, MEDLINE, CENTRAL, PubMed, Web of Science, and PsycINFO. No date limit was applied to the search. The search terms “VR” and “children” or “adolescents” were used. For each database, different search strategies were developed. Table 1 gives an overview of the search terms that were used.

Table 1 Literature search terms used for keywords[a].

No.	Keywords	Included
1	Virtual reality	virtual reality, virtual reality exposure therapy
2	Children	boy, child, childhood, girl, infant, kid, pediatrics, preschool, school, toddler
3	Adolescents	adolescence, adolescent, highschool, juvenile, minor, prepubescent, prepuberty, pubescent, puberty, teen, teenager, underaged, youth
	1 AND 2 OR 3	

[a]The following electronic databases were searched: EMBASE, MEDLINE, CENTRAL, PubMed, Web of Science, and PsycINFO.

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flowchart of study selection.



Data Extraction

A detailed overview of the study selection process is shown in Figure 1. The search yielded 2889 articles. Two of the authors (R.E. and P.F.A.d.N.) first assessed the identified studies for compliance with the inclusion and exclusion criteria, independently. Discrepancies (2%) were discussed until consensus was reached. Based on title and abstract, 44 of the 2889 studies were included. Next, both authors screened the full texts of these articles, independently. Discrepancies (16%) were discussed until consensus was reached. We excluded 27 of the 44 studies. Most of these studies (n = 11) were excluded because they did not use VR. Other reasons included, but were not limited to, overlap with a different age group or no inclusion of pediatric patients (see Figure 1). The final 17 studies were included.

Assessment of Study Quality

Two authors (R.E. and P.F.A.d.N.) independently evaluated the included studies with the Delphi list [125] (Table 2) to evaluate their methodologic quality. The Delphi list is often used in systematic reviews and is able to measure internal validity, external validity, and statistical aspects [125]. The Delphi list contains of 9 items, with equal weights, which can be evaluated as satisfactory (yes: scored 1) or non-satisfactory (no: scored 0). Discrepancies in scores (17%) were discussed until consensus was reached.

Table 2 Delphi List for Quality Assessment of Randomized Clinical Trials.

Criteria	Evaluation
1. Treatment allocation: Was a method of randomization performed?	Yes (1)/No (0)
2. Treatment allocation: Was the treatment allocation concealed?	Yes (1)/No (0)
3. Were the groups similar at baseline regarding the most important prognostic indicators?	Yes (1)/No (0)
4. Were the eligibility criteria specified?	Yes (1)/No (0)
5. Was the outcome assessor blinded?[a]	Yes (1)/No (0)
6. Was the care provider blinded?[a]	Yes (1)/No (0)
7. Was the patient blinded? [omitted][b]	
8. Were point estimates and measures of variability presented for the primary outcome measures?	Yes (1)/No (0)
9. Did the analyses include an intention-to-treat analysis?	Yes (1)/No (0)

[a]The applicability of criteria 5 and 6 depends on the moment at which virtual reality was applied. When virtual reality was applied before the medical procedure and outcome assessment, the maximum possible score was 8. When virtual reality was applied during the medical procedure and outcome assessment, the maximum possible score was 6.

[b]Criterion 7 was not applicable.

For our assessment, criterion 7 (“Was the patient blinded?”) was omitted, as it is impossible to be blinded to wearing a VR HMD or not. Consequently, the maximum possible score for studies in this review was 8 points.

Criteria 5 (“Was the outcome assessor blinded?”) and 6 (“Was the care provider blinded?”) also concern blinding but were not omitted, as these criteria could be either applicable (when VR was applied before the medical procedure and outcome assessment) or non-applicable (when VR was applied during the medical procedure and outcome assessment).

Synthesis of Results

For the purpose of this systematic review and meta-analysis, we did not include data on distress, maladaptive behavior, nor physiological measures of arousal, such as heart rate. We only included data on pain and anxiety outcomes based on behavioral observations, self-reports, or questionnaires.

Mean scores and SDs for pain and anxiety during the procedure in VR intervention and standard care conditions were either extracted from articles, calculated using median scores and interquartile ranges, or received from authors. Other non–VR intervention conditions were not taken into account in our analyses. Data were entered into a worksheet in Comprehensive Meta-analysis software version 2 (Biostat Inc, Englewood, NJ) by 2 authors (R.E. and B.D.). The following data were also collated and entered into Comprehensive Meta-analysis: first author, publication year, title of study, sample size per condition, mean age per condition, medical procedure, assessment instruments, quality score, informant, and study design. We used patients as primary source of data within each study, because pain and anxiety are subjective experiences. Observations of pain and anxiety made by caregivers and professionals (eg, nurse or researcher) were also entered into the worksheet. Assessment instruments for pain and anxiety were classed as either visual scales (ie, visual analog, graphic rating, and different faces scales) or questionnaires. Study design was divided into parallel or crossover designs. For crossover designs, data from the first period only, that is, before crossover, were included when available. When authors merely provided combined data from both periods, as if groups were parallel, these data were used. When data were available on different components of pain (eg, cognitive, affective, and sensory pain) the sensory component of pain was used in the meta-analysis.

Pain and anxiety were analyzed separately. Effect sizes were generated as standardized mean difference (SMD) by calculating the mean difference on pain or anxiety outcomes between VR and standard care conditions during the procedure and dividing the result by the pooled SD.

Meta-analyses for either pain or anxiety were conducted for overall effect sizes of VR compared to control conditions. Because of the heterogeneity of studies, a random-effects model was used. Sensitivity analyses were performed by removing the study with the largest effect size and studies with low methodological quality (ie, a quality score of 0–2) from both meta-analyses. Separate sensitivity analyses were run for type of medical procedure. Furthermore, we investigated whether informant affected VR effectivity. To achieve a more reliable estimate of effect sizes, we also excluded outlying and low-quality studies from these analyses. To explore if young children respond differently to VR interventions than older children, a meta-regression analysis was performed with mean age of the study samples as predictor and a random effects model (with methods of moments).

Heterogeneity was assessed using the I^2 statistic, with values ≥75% indicating substantial heterogeneity [126]. In case of substantial heterogeneity, subanalyses were performed to explore sources of heterogeneity. Publication bias was assessed with funnel plot asymmetry and Egger tests [127]. All analyses were performed using Comprehensive Meta-analysis software version 2.

RESULTS

Study Characteristics

Table 3 summarizes the main characteristics and results of the studies. We organized the final 17 studies based on the type of medical procedure. In 16 studies, VR was applied as a distraction technique during dental care (n = 2) [128, 129] burn care (n = 6) [64, 130-134], oncological care (n = 4) [66, 135-137], or venous access (n = 4) [65, 138-140]. Oncological care includes quite heterogeneous procedures (ie, lumbar puncture) [136], port access (piercing of the skin to access a previously implanted catheter in the chest for chemotherapy) [66, 137] or chemotherapy [135]. Only 1 study applied VR preprocedurally, before elective surgery under general anesthesia (n = 1) [73]. The studies were conducted between 1999 and 2018. The number of included patients of the studies varied between 7 and 143, with a median of 38.

Fourteen studies were RCTs, of which 10 used a parallel design and 4 studies a crossover design. All RCTs compared the VR intervention group to care as usual (CAU). CAU was often not well defined. However, CAU varied widely and could involve either no distraction or rather intensive distraction, such as watching television or listening to music. Moreover, not all studies made clear whether or not parents remained present during the procedure, nor which pharmacological analgesia were used. Three RCTs added a third condition to their designs: movie distraction [134], playing a non–VR computer game [137], or applying external cold and vibration [140]. The 3 non–RCTs trials were quasi-experimental, of which 2 did not use randomization [128, 139], while the other study used an interrupted time series design with removed treatment [135].

The age range of participants for 16 of the 17 studies varied between 4 and 21 years. One study reported a mean age of 6.5 years but did not indicate the age range [131]. Studies were heterogeneous regarding VR environments (software) and VR hardware.

Study Quality Assessment

We assessed all included studies with the Delphi list [125] to evaluate their methodologic quality. Blinding of the outcome assessor and caregiver (criteria 5 and 6 of the Delphi list) was only applicable to the study of Ryu et al. [73] because they applied VR before, instead of during, the medical procedure. Therefore, the maximum possible score for this study was 8, while for the other studies, the maximum possible score was 6 (as the 2 criteria regarding blinding were not applicable).

The included studies varied in quality, as the quality scores ranged between 0 and 6 (see Table 3 for quality scores). The average quality score was 3.5 (SD = 1.7). Most studies had moderate quality, whereas 5 studies had high quality (ie, a maximum score, or 1 point below maximum). Four studies had poor quality (ie, a score of 0–2). Even though in 76% (n = 13) a method of randomization was performed, only 18% (n = 3) of the studies guaranteed a concealed treatment allocation. The majority of studies stated that a randomization scheme or table was used, but not enough information was provided to ensure that the allocation procedure was not transparent before assignment. In more than half of the studies, groups were similar at baseline regarding characteristics such as age, sex, and degree of injury (n = 10, 59%). Inclusion and exclusion criteria were not described precisely enough for 6 studies (35%). Seven studies (41%) included intention-to-treat analysis.

Table 3 Characteristics and results of included studies that report on the effectiveness of virtual reality on pain and anxiety in pediatric patients undergoing medical procedures (n = 17).

Medical procedure	Author (year)	Participants *n*	Participants Age	Moment of VR	VR equipment	Treatment conditions[a]	Study design	Key findings	Quality score[b]
Dental care	Sullivan et al. (2000)[128]	30	5-7 y	During restorative treatment	Unknown	VR distraction CAU	Within subjects (not randomized)	• No differences in anxiety based on Koppitz human figure drawing test after procedure	0
	Aminabadi et al. (2012)[129]	120	4-6 y	During restorative treatment	i-glasses 920HR Ilixco inc.	VR distraction CAU	RCT crossover	• Less self-reported pain (FACES) and state anxiety (MCDAS (f)) in VR than CAU during procedure	4
Burn care	Das et al. (2005)[130]	11[c]	5-16 y	During burn dressing change	IO i-glasses	VR distraction CAU	RCT crossover	• Less self-reported pain (Faces scale) during procedure in VR than CAU	3
	Chan et al. (2007)[131]	8	M=6.54 y	During burn dressing change	i-glasses	VR distraction CAU	RCT crossover	• No differences in self-reported pain (FPS-r) during and after procedure	1
	Schmitt et al. (2011)[132]	54	6-19 y	During post-burn physical therapy	nVisor SX VR-1280 ProView XL50 ProView SR80	VR distraction CAU	RCT crossover	• Less self-reported cognitive, affective, and sensory pain (GRS) in VR than CAU during procedure	3
	Kipping et al. (2012)[133]	41	11-17 y	During burn dressing change	eMagin, Z800 3DVisor	VR distraction CAU (TV, stories, or music)	RCT parallel	• Less observed pain (FLACC) during procedure in VR than CAU • No differences in self-reported or parent-observed pain (VAS) during procedure	6
	Jeffs et al. (2014)[134]	28	10-17 y	During burn treatment	Kaiser Optical SR80a on tripod	VR distraction Non-VR distraction (TV) CAU	RCT parallel	• Less self-reported pain (APPT-WGRS) during procedure in VR than in non-VR distraction but not less than CAU	5
	Hua et al. (2015)[64]	56	4-16 y	During burn dressing change	eMagin Z800 3DVisor	VR distraction CAU (toys, TV, books)	RCT parallel	• Less self-reported pain (FACES) during, less parent-observed pain (VAS) before, during, and after, and less researcher-observed pain (FLACC) during and after procedure in VR than CAU	5

Table 3 Continued

Medical procedure	Author (year)	Participants *n*	Participants Age	Moment of VR	VR wequipment	Treatment conditions[a]	Study design	Key findings	Quality score[b]
Oncological care	Schneider et al. (1999) [135]	11	10-17 y	During chemotherapy	Virtual IO	VR distraction CAU	Interrupted time series with removed treatment	• No differences in self-reported state anxiety (STAIC-1) during procedure	2
	Sander Wint et al. (2002)[136]	30	10-19 y	During lumbar puncture	i-O Display Systems LLC	VR distraction CAU	RCT parallel	• No differences in self-reported pain (VAS) during procedure	5
	Gershon et al. (2004) [137]	59	7-19 y	During port access for chemotherapy	Unknown	VR distraction Non-VR distraction CAU (PC game)	RCT parallel	• Less nurse-observed pain (VAS) in VR and non-VR distraction than CAU during procedure • No differences in researcher-observed pain (CHEOPS), self-reported or parent-observed pain or anxiety (VAS) during procedure	4
	Wolitzky et al. (2005)[66]	20	7-14 y	During port access for chemotherapy	Unknown	VR distraction CAU	RCT parallel	• Less researcher observed pain (CHEOPS) in VR than CAU during procedure • No differences in self-reported, parent-observed, or nurse-observed pain or anxiety (VAS) during procedure	4
Venous access	Gold et al. (2006)[138]	20	8-12 y	During intravenous placement for MRI or CT scan	5DT HMD 800 with InterSens InertiaCube2 tracker	VR distraction CAU	RCT parallel	• Less self-reported pain (FPS-r) in VR than CAU during procedure • No differences in self-reported pain measured with FACES during procedure • No differences in self-reported, parent-, or nurse-observed pain (VAS) during procedure	5
	Piskorz and Czub (2017) [139]	38	7-17 y	During blood draw	Oculus Rift DK2	VR distraction CAU	Between subjects design (not randomized)	• Less self-reported pain (VAS) and anxiety (VAS) than CAU during procedure	1

Table 3 Continued

Medical procedure	Author (year)	Participants *n*	Age	Moment of VR	VR wequipment	Treatment conditions[a]	Study design	Key findings	Quality score[b]
	Gerçeker et al. (2018)[140]	121	7-12 y	During blood draw	Samsung Galaxy S5 + Samsung Gear VR	VR distraction External cold and vibration CAU	RCT parallel	• Less self-reported, parent-observed, and nurse-observed pain (FACES) in both VR and external cold and vibration than CAU during procedure • No differences in VR vs. external cold and vibration during procedure	3
	Gold and Mahrer (2018)[65]	143	10-21 y	During blood draw	Samsung Galaxy S6 + 1. Google Pixel Merge VR (10-12) 2. Samsung Gear VR (13-21)	VR distraction CAU (TV)	RCT parallel	• Less self-reported and parent-observed pain (VAS) and anxiety (VAS) in VR than CAU during procedure • Patients with high anxiety sensitivity (CASI) benefit more from VR than with low anxiety sensitivity during procedure	3
Preoperative	Ryu et al. (2017)[73]	69	4-10 y	Before entering the operating theatre	Samsung Galaxy S6 + Samsung Gear VR	VRE CAU (face to face information)	RCT parallel	• Less researcher-observed preoperative anxiety (mYPAS) in VR than CAU	5

Manufacturer information for the equipment noted in the table: i-glasses 920HR (Ilixco, Inc, Menlo Park, CA); i-glasses (i-O Display Systems, LLC, Sacramento, CA); nVisor SX (NVIS, Inc, Reston, VA); VR-1280 (Virtual Research Systems, Inc, Aptos, CA); ProView XL50 (Kaiser Electro-Optics, Inc, Carlsbad, CA); ProView SR80 (Kaiser Electro-Optics, Inc, Carlsbad, CA); eMagin Z800 3DVisor (eMagin Corporation, Hopewell Junction, NY); Kaiser Optical SR80a (on tripod; Kaiser Optical Systems, Inc, Ann Arbor, MI); 5DT HMD 800 (5DT, Inc, Irvine, CA); Oculus Rift DK2 (Facebook Technologies, LLC, Menlo Park, CA); Samsung Galaxy S5 (Samsung Electronics Co, Ltd, Suwon, South Korea); Samsung Gear VR (Facebook Technologies, LLC, Menlo Park, CA); Google Pixel (HTC Corporation, New Taipei City, Taiwan); Merge VR (Merge Labs, Inc, San Antonio, TX); Samsung Galaxy S6 (Samsung Electronics Co, Ltd, Suwon, South Korea).

Abbreviations: APPT-WRGS, adolescent pediatric pain tool - word graphic rating scale; CASI, childhood anxiety sensitivity index; CAU, care as usual; CHEOPS, Children's Hospital of Eastern Ontario pain scale; FLACC, face, legs, activity, cry, consolability; FPS-r, faces pain scale-revised; GRS, graphic rating scale; IV, intravenous; M, mean; MCDA (f), modified child dental anxiety scale (f); m-YPAS, modified Yale preoperative anxiety scale; RCT, randomized controlled trial; VAS, visual analog scale; VR, virtual reality.

[a]In all studies, routine pharmacological analgesia was administered, if applicable. Available information on nonpharmacological care as usual (distraction) is stated in brackets.

[b]Maximum possible score for Ryu et al.[73] is 8. Maximum possible score for all other studies is 6.

[c]Based on 7 unique subjects, who could participate more than once.

Other specific findings that could have influenced study quality were as follows: initially, Das et al. [130] (burn care) only included patients who experienced burns for the first time, but they let some patients participate more than once (ie, 11 trials were undertaken from 7 patients). Piskorz and Czub [139] (venous access) let children play a VR game. If they enjoyed it, these children were included in the VR condition. Afterward, the authors collected data for the control group (who had not tried out the VR game). Gerceker et al. [140] excluded all unsuccessful phlebotomy attempts from their analyses (ie, when there was no blood flow into the tube within 5 seconds during the first attempt). Ryu et al. [73] observed less anxiety during the preoperative period but did not assess anxiety during induction of anesthesia, when anxiety peaks.

Virtual Reality and Pain Management

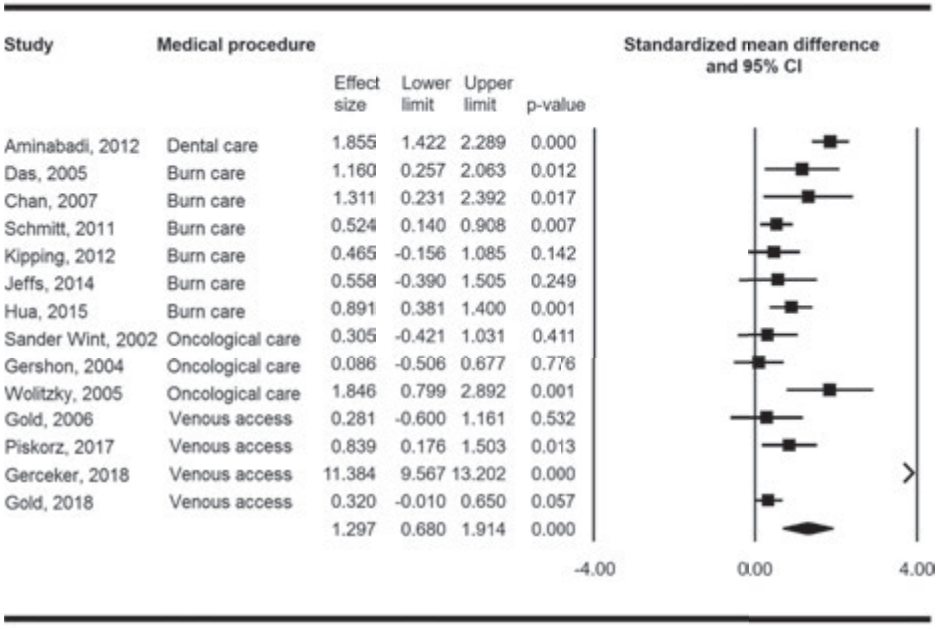
As shown in Figure 2, effect sizes for patient-reported pain could be generated for 14 of the 17 studies. For 2 studies, means and SDs were calculated using median values and interquartile ranges [134, 136]. Calculated effect sizes were positive when VR reduced pain more than CAU. Across all studies, using a random-effects model, the weighted effect size of VR on pediatric pain during a medical procedure was large (SMD = 1.30; 95% CI, 0.68–1.91; $P < .001$). This indicated a substantial clinical benefit, but heterogeneity of study effects was high (I^2 = 93.3%). A sensitivity analysis was performed by excluding the outlying study, that is, the study with the largest effect size (Gerceker et al. [140]) and studies with low methodological quality [131, 139]. This analysis still suggested effects of VR with an attenuated but still medium to large effect size, which indicated a robust effect (SMD = 0.73; 95% CI, 0.35–1.11; $P < .001$). Though, still substantial, this analysis had lower heterogeneity (I^2 = 78.3%).

The following sensitivity analyses were performed after removal of the outlying study [140] and low-quality studies [131, 139] to achieve a more reliable estimate of effect sizes. Sensitivity analyses were run for caregivers and professionals as observers of pediatric pain. We found significant results based on both types of informants (caregivers [64, 65, 133, 137]: SMD = 0.47; 95% CI, 0.22–0.72; $P < .001$; I2 = 0.0%, professionals [64, 133, 137]: SMD = 0.82; 95% CI, 0.48–1.15; $P < .001$; I^2 = 0.0%). Finally, we ran sensitivity analyses on self-reported pain for each type of medical procedure, when data from >1 study were available. We found significant effects for burn care [64, 130, 132-134] (SMD = 0.66; 95% CI, 0.40–0.91; $P < .001$; I^2 = 0.0%)

and venous access [65, 138] (SMD = 0.32; 95% CI, 0.01–0.62; P = .046; I^2 = 0.0%) but not for oncological care [66, 136, 137] (SMD = 0.65; 95% CI, −0.26 to 1.57; P = .159; I^2 = 76.3%). The suggested effect of VR for observed pain and for self-reported pain during burn care and venous access was associated with decreased effect sizes, but also with zero heterogeneity.

A random-effects model (with methods of moments) was used for the meta-regression analysis with age as a predictor. The results suggested that VR interventions for pain reduction were more efficacious for younger than for older children (P = .015). More specifically, the effect size of VR on pain decreased with 0.26 when age increased with 1 year. After removing the study with the largest effect size [140], age was still a significant predictor of the effect of VR on pain (P < .001).

Figure 2 Random-effects meta-analysis for the effect of VR on patient-reported pain during a medical procedure compared to CAU. Note: study effect for Gerceker et al. [140] is out of range. CAU indicates care as usual; VR, virtual reality.

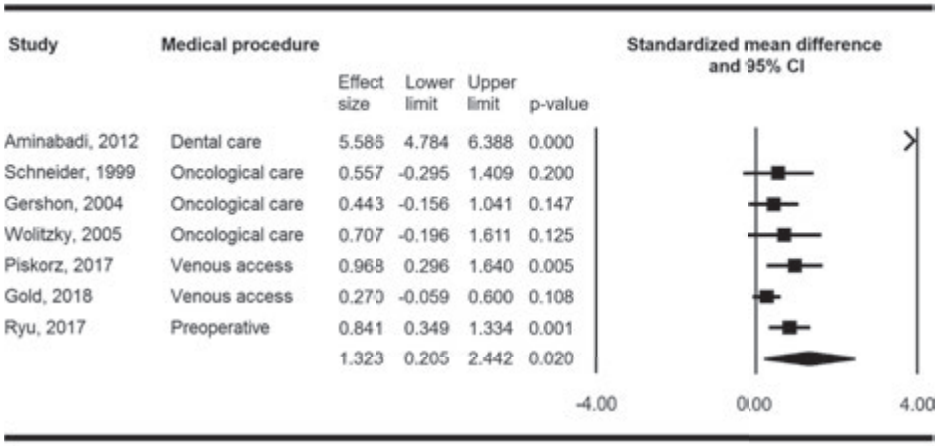


Virtual Reality and Anxiety Management

Effect sizes for patient-reported anxiety could be generated for 7 of the 17 studies (Figure 3). For 1 study, mean and SD were calculated using median value and interquartile range [73]. Using the random-effects model, a large effect size was found for VR on anxiety (SMD = 1.32; 95% CI, 0.21–2.44; *P* = .020). This indicated substantial clinical benefit, but heterogeneity of study effects was high (I^2 = 96.6%). A sensitivity analysis was performed by excluding the outlying study (Asl Aminabadi et al. [129]) and studies with low methodological quality [135, 139]. This analysis still suggested effects of VR (SMD = 0.50; 95% CI, 0.20–0.79; *P* = .001) with an attenuated but still medium effect size, which indicated a robust effect. Moreover, heterogeneity decreased significantly in this analysis (I^2 = 22.4%).

The following sensitivity analyses were performed after removal of the outlying study [129] and low-quality studies [135, 139] to achieve a more reliable estimate of effect sizes. Unfortunately, very limited data were available for caregivers and professionals as observers of pediatric anxiety. We were only able to run a separate analysis for caregiver as informant [65, 137], which did not yield a significant result (SMD = 0.31; 95% CI, −0.02 to 0.63; *P* = .067; I^2 = 0%). Regarding different types of medical procedures, only for oncological care, enough data were available

Figure 3 Random-effects meta-analysis for the effect of VR on patient-reported anxiety during a medical procedure compared to CAU. Note: study effect for Asl Aminabadi et al. [129] is out of range. CAU indicates care as usual; VR, virtual reality.



to run a sensitivity analysis on self-reported anxiety [66, 137], which yielded a significant result (SMD = 0.53; 95% CI, 0.10–0.96; P = .015; I^2 = 0.0%). The effect of VR during oncological care was associated with a decreased effect size but also with zero heterogeneity.

A random-effects model (with methods of moments) was used for the meta-regression analysis with age as a predictor. The results suggested that VR interventions for anxiety reduction were more efficacious for younger than for older children (P = .023). More specifically, the effect size of VR on anxiety decreased to 0.35 when age increased with 1 year. After removing the study with the largest effect size, [129] age was still a significant predictor of the effect of VR on anxiety (P = .037).

Publication Bias and Heterogeneity

Funnel plots for pain and anxiety showed asymmetry, but Egger regression asymmetry tests did not confirm the presence of a significant publication bias for pain (P = .105) nor anxiety (P = .282). Funnel plots indicated that there was one clear outlier for pain [140] and one for anxiety [128]. These outliers correspond to the studies with the largest effect sizes which we have removed from the sensitivity analyses.

As discussed above, substantial heterogeneity of study effects was found for the overall meta-analysis on pain (I^2 = 93.3%) and anxiety (I^2 = 96.0%). We found that the outlying and low-quality studies were important sources of heterogeneity, because removal of these studies was associated with decreased heterogeneity (I^2 = 78.3% for pain and I^2 = 22.4% for anxiety). Moreover, the available data suggested that the different medical procedures were an important source of heterogeneity as well because the study effects of these sensitivity analyses were associated with zero heterogeneity.

DISCUSSION

This is the first systematic review and meta-analysis that specifically focused on VR in pediatric patients. Our meta-analysis, based on 14 studies for pain and 7 studies for anxiety, showed VR to be an effective tool to diminish patient-reported pain (SMD = 1.30) and anxiety (SMD = 1.32) during a range of medical procedures. The effect of VR on pediatric pain was also significant when observed by caregivers or

professionals. For anxiety, limited observer data were available on VR effectivity. Due to small groups, it was difficult to compare VR effectivity indifferent types of medical procedures. VR was most often applied during burn care.

Our results showed that VR interventions for pain and anxiety were potentially more efficacious for younger than for older children. A possible explanation is that younger children tend to have higher levels of anxiety before medical procedures [89, 141]. A different possible explanation is that VR is especially engaging for younger children, as they are often more engaged in magical thinking [142] and become truly captivated by imaginative play [82].

However, because the relationship of age with VR efficacy on pain or anxiety could be different within each study compared to across studies, the relationship shown between age and VR efficacy in the meta-regression may not represent the true relation. This phenomenon is called ecological fallacy [143].

VR was found to be significantly more effective in reducing pain and anxiety than CAU. However, it remains difficult to differentiate between the added value of VR over other forms of distraction, for example, watching television, and no distraction, because CAU was often not well defined. The high weighted effect sizes we found suggest that VR distraction is possibly more effective than other distraction interventions during medical procedures. For example, a Cochrane review [144] found an effect size of 0.61 for the impact of distraction (eg, games, music, and toys) on self-reported pain during needle-related procedures. Similarly, a meta-analysis including trials on music therapy as distraction during different types of medical procedures (eg, dental care, magnetic resonance imaging scans, and venipuncture) showed a significant reduction in pain and anxiety with an effect size of 0.35 [145]. Because VR exposure as a preparation tool for medical procedures is a fairly unexplored area of research, it is not (yet) possible to compare effect sizes for VR preparation to other forms of preparative interventions to reduce pain and anxiety during medical procedures.

The studies in the current systematic review and meta-analysis varied in quality. Most studies applied randomization and clearly described their inclusion and exclusion criteria. However, concealed treatment allocation was often not guaranteed and intention-to-treat analyses were often not performed. Also, very

few studies focused on possible moderating factors of VR effectivity, such as anxiety sensitivity and temperament.

An important area of focus is immersion, which is influenced by interaction with the virtual environment by means of translation (changing position), rotation (changing orientation), point of view (perspective), and field of view [76, 146]. Non–VR content, that is, regular (cartoon) videos or 360° videos, creates less immersion, because the user is limited to the filmmaker's movements and progress of the video. This difference in content is important, as it has been hypothesized that more immersion is related to more pain reduction, because less attention is available for pain perception [63, 123]. Even though some studies included questions about subjective feelings of immersion, it is difficult to objectively analyze this phenomenon. During certain medical procedures, for example, dental treatment, patients were required to keep their head still, which may have limited immersion as well. True VR creates a more compelling illusion of presence in the virtual world than more passive audiovisual glasses and non–VR (360°) videos. However, the supposed superiority of VR over audiovisual glasses and non–VR content regarding efficacy in medical care has yet to be proven [59]. Therefore, the role of immersion should be a focus of future research.

Implications

VR distraction has a large impact on pediatric pain and anxiety during medical procedures, especially for younger children. This easy-to-use tool can be used effectively in clinical practice. More research like the study of Ryu et al. [73] is needed to establish evidence on VR exposure as preparation to reduce pain and anxiety during medical procedures. This is crucial, because anticipatory anxiety can lead to more pain and distress during the medical procedure itself [147, 148].

Limitations

The following limitations should be taken into account when interpreting the results of the current review and meta-analysis. First, effect sizes for patient-reported anxiety could be generated for only 7 studies. Second, limited observer data were available, especially for anxiety outcomes. Third, means and SDs were estimated using median values and interquartile ranges for 3 studies [73, 134, 136]. This was necessary to pool all data, but is unclear how reliable these estimations are. Fourth, substantial heterogeneity was present in the findings. We have identified outlying

and low-quality studies as important sources of heterogeneity. Moreover, there was a difference in effect of VR for different medical procedures, so one should be careful when generalizing the suggested effect for VR to clinical practice. However, in our opinion, the mean pooled effect of all medical procedures still provides the most useful information, especially because certain procedures have not been studied extensively or have not been studied at all, regarding VR interventions. Finally, the included studies applied various kinds of VR software, which could have influenced the amount of immersion and VR effectivity. On the other hand, it is also possible that VR software only plays a small role, as Kenney and Milling [78] found no differences in their meta-analysis between commercially available VR games and VR software that was specifically developed for distraction.

CONCLUSIONS

This systematic review and meta-analysis indicate that pediatric patients undergoing a range of medical procedures benefit from VR as a tool to reduce pain and anxiety. Due to limited available observer data, we could not provide insight into possible differences in perspective between patients, caregivers, and professionals. VR research in pediatrics has mainly focused on VR as a distraction tool. Using VR exposure as a preparation tool could be an innovative way to decrease anxiety and pain before and during medical procedures. However, further research into this field is needed.

Acknowledgements

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03

Development of a virtual reality exposure tool as psychological preparation for elective pediatric day care surgery: *methodological approach for a randomized controlled trial*

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ABSTRACT

Background: Preoperative anxiety in children is highly prevalent and is associated with adverse outcomes. Existing psychosocial interventions to reduce preoperative anxiety are often aimed at distraction and are of limited efficacy. Gradual exposure is a far more effective way to reduce anxiety. Virtual reality (VR) provides a unique opportunity to gradually expose children to all aspects of the operating theater.

Objective: The aims of our study are (1) to develop a virtual reality exposure (VRE) tool to prepare children psychologically for surgery; and (2) to examine the efficacy of the VRE tool in a randomized controlled trial (RCT), in which VRE will be compared to care as usual (CAU).

Methods: The VRE tool is highly realistic and resembles the operating room environment accurately. With this tool, children will not only be able to explore the operating room environment, but also get accustomed to general anesthesia procedures. The PREoperative Virtual reality Intervention to Enhance Wellbeing (PREVIEW) study will be conducted. In this single-blinded RCT, 200 consecutive patients (aged 4 to 12 years) undergoing elective day care surgery for dental, oral, or ear-nose-throat problems, will be randomly allocated to the preoperative VRE intervention or CAU. The primary outcome is change in child state anxiety level between baseline and induction of anesthesia. Secondary outcome measures include child's postoperative anxiety, emergence delirium, postoperative pain, use of analgesics, health care use, and pre- and postoperative parental anxiety.

Results: The VRE tool has been developed. Participant recruitment began March 2017 and is expected to be completed by September 2018.

Conclusions: To our knowledge, this is the first RCT evaluating the effect of a VRE tool to prepare children for surgery. The VRE intervention is expected to significantly diminish preoperative anxiety, postoperative pain, and the use of postoperative analgesics in pediatric patients. The tool could create a less stressful experience for both children and their parents, in line with the modern emphasis on patient- and family-centered care.

Trial Registration: Netherlands Trial Registry: NTR6116

Keywords: virtual reality; pediatric; anxiety; surgery; anesthesia; intervention; exposure; randomized controlled trial

INTRODUCTION

Fifty to 70% of children experience elevated levels of anxiety and distress prior to surgery [4, 10]. Preoperatively, anxious children are more often agitated, sad, emotional, less cooperative, and more resistant compared to children who are not anxious [17, 149]. Preoperative anxiety is also associated with a higher incidence of emergence delirium, more intense and prolonged pain postoperatively, and poorer recovery [17, 150, 151]. A child's operation is also a stressful experience for parents and parental fear has been shown to intensify children's preoperative anxiety [11, 12]. Anxious children undergoing surgery, as well as their parents, are even at risk for a posttraumatic stress disorder [27]. These adverse outcomes underscore the urgent need to develop effective strategies to minimize preoperative anxiety in children.

Education programs have proven to be effective in reducing children's preoperative anxiety. Nonetheless, a recent systematic review by Copanitsanou and Valkeapää indicated that education seems to have a negative effect on younger children's anxiety [152]. Other complementary methods for reducing preoperative anxiety in children predominantly focus on distraction, for instance, watching a video, listening to music, playing video games, or distraction by clowns [43, 45, 122, 153]. However, scientific literature shows that gradual exposure is a much more effective way to reduce anxiety in children than mere distraction [57]. Due to busy clinical practices and the daily use of surgery rooms, exposing children to all pre- and postoperative aspects is often not feasible.

Virtual reality exposure (VRE) offers the possibility to expose children of different ages to a highly realistic virtual environment that mimics the operating theater of a hospital. Children can get accustomed not only to the operating environment, but also to the procedures associated with anesthesia. VRE has already been shown to be effective as a treatment for specific phobias in children, such as a fear of heights or a fear of flying [154]. To the best of our knowledge, the efficacy of VRE to prepare children for general anesthesia and surgery has not yet been studied. Furthermore, Cochrane reviews showed that most studies examining interventions for induction of anesthesia in children are small and of poor quality [144, 155]. As such, high-quality randomized controlled trials (RCTs) are needed.

The aims of the PREoperative Virtual reality Intervention to Enhance Wellbeing (PREVIEW) study are (1) to develop a VRE tool to prepare children for surgery; and (2) to conduct an RCT to test the effectiveness of the VRE tool in children undergoing elective day care surgery.

METHODS

Virtual Reality Design

The VRE tool encompasses a highly realistic virtual environment that replicates the operating theater of the Erasmus MC-Sophia Children's Hospital, Rotterdam, the Netherlands.

A multidisciplinary team, consisting of child life specialists, child psychologists, a child psychiatrist, anesthesiologists, a three-dimensional (3D) acting director, and a 3D project manager designed the script of the VRE. Working together with specialized virtual reality (VR) developers and animators, multiple 3D characters, asset, and environment artists created the scenery and character modeling.

During the design and development phases, team meetings were held to review the process and make any necessary adjustments. Overall, the main goal was to create a dynamic and interactive environment that will prepare children for surgery under general anesthesia, in a realistic and child-friendly manner. Once the VR software was created, it was pilot tested in healthy children (n = 10). Based on the observations and responses of the pilot test, final adjustments were made.

Technical Specifications

Hardware Details

All 3D characters in the virtual environment were modeled after pediatric anesthesiology employees who had undergone motion capture recording with professional Vicon Motion Systems Ltd equipment (Vicon Motion Systems Ltd). Vicon Vantage cameras were used for body motion capture and the Vicon Cara system, including 4 high resolution high speed cameras and a custom head rig, were used for facial motion capture.

The virtual environment is presented via an HTC Vive headset, using room-scale technology, which allows the user to navigate naturally. Real world awareness is

created through a 110 degrees field of view for captivating immersion. The Vive features 32 sensors for 360 degrees motion tracking, a 2160 by 1200 combined resolution, and a 90 Hz refresh rate. With 2 wireless, motion-tracked handheld Vive controllers, each containing 24 sensors, users can interact with precision and experience immersive environments. The headset is connected to a custom computer with an Intel Core i7-5820K processor and a NVIDIA GeForce GTX 1080 graphics card.

Software Details

All software used is of professional quality and well known in the film, game, and VR industry. Vicon Blade II software, which is compatible with the Vicon camera systems, is used for body motion capture, whereas Vicon Cara Live and Vicon Cara Post are used for facial motion capture. Blade II provides real-time visualization, in which multiple range of motion sequences, and thus multiple people, can be captured simultaneously. Cara Live is used during setup and capture, while Cara Post automatically identifies and tracks the markers, applied on a human face, over time, creating a 3D point representation of the markers. With RealityCapture, accurate and realistic 3D models are created out of photographs. 3ds Max and Maya 2016 are digital tools used for creating complex 3D animations and models. Autodesk MotionBuilder 2016 Service Pack 1 is also used for 3D character animation. Mudbox 2016 and Zbrush 4R7 are tools used for high resolution 3D sculpting. Everything comes together in the game engine Unreal Engine 4.13.

Virtual Reality Storyline

The duration of the VRE intervention is approximately 15 minutes. We developed one version for 4- to 7-year-old children and one for 8- to 12-year-old children such that the explanations of the procedures can be attuned to the child's developmental level. We used 8 as the cut-off point between the versions because this age represents a key period in children's brain development with respect to cognitive flexibility and information processing [156].

The VR storyline begins in the holding area, where the child is sitting on a hospital bed (Figure 2, page 15). A receptionist welcomes the child and shows him/her a video with extra information on a virtual tablet. The video explains that one of the child's parents will stay with him/her all the time and shows the hospital gowns the child and parent will be wearing to surgery. After the video, the child

in the hospital bed is transported into the corridor of the operating theater by an anesthesiologist and a nurse anesthetist (Figure 3, page 15). The bed is taken into the operating room via the surgery preparation room. The child can point at different instruments, such as the oxygen saturation monitor, blood pressure cuff, and anesthesia mask, with a motion tracked controller so that the nurse anesthetist can explain what they are used for (Figure 4, page 16). Next, the child moves itself onto the surgery bed where the anesthetic preparation takes place. These preparations are explained at this stage. The program is able to show both intravenous and inhalational induction. After induction, the operating room fades out and the recovery room fades in (Figure 5, page 16). Finally, the anesthetist nurse shows another video on a virtual tablet, which explains what kind of feelings the child might experience after surgery, such as pain or nausea.

Study Design

The PREVIEW study is a single-center, single-blinded RCT carried out in the Erasmus MC-Sophia Children's Hospital, by the departments of Child and Adolescent Psychiatry/Psychology, Pediatric Anesthesiology, and Maxillofacial, Dental, and Ear-Nose-Throat (ENT) Surgery. This RCT involves a psychosocial intervention (VRE preparation) versus care as usual (CAU) in 4- to 12-year-old children undergoing elective day care dental, oral, or ENT surgery (n = 200). CAU involves children being recommended by their anesthesiologist during the preoperative screening consultation to watch the informative online movie of the Erasmus MC-Sophia Children's Hospital about general anesthesia prior to surgery.

Inclusion and Exclusion Criteria

Eligible participants are all consecutive pediatric patients (aged 4 to 12 years) undergoing elective day care surgery (ie, dental, oral, or ENT surgery) at the Erasmus MC-Sophia Children's Hospital, between March 2017 and August 2018. Exclusion criteria are mental retardation, inability of parents to read or write Dutch, epilepsy, visual impairment, or poor general health, indicated by an American Society of Anesthesiologists (ASA) classification of IV or more.

Patient Recruitment and Procedure

Eligible patients and their parents will be informed about the study by phone and, if interested, receive the patient information folder (PIF) by email. Participation will be voluntary and all data will be anonymized. Both parents will be asked to

provide written informed consent. Patients who are 12 years old will also be asked to provide written informed consent themselves. Children under 12 years old will give their permission orally.

After informed consent is provided, children will be randomly allocated to the VRE intervention (n = 100) or CAU (n = 100) group at hospital admission. Randomization will be stratified by age group (4- to 7- or 8- to 12-years-old), and type of surgery (ie, oral and maxillofacial surgeries, tonsil and adenoidectomy, tympanostomy tubes, or other ear surgeries). The researchers and operating staff will be blinded to group allocation. The research assistant will not be blinded, since he/she will be guiding the intervention. This will take place in a separate room, in the presence of an accompanying parent. Un-blinding takes place if patients are excluded from the study and after the final assessment of the last included patient.

Assessments will be carried out at the following time points: (1) T1, admission to the hospital, before possible intervention; (2) T2, after the VRE intervention or after CAU, in the holding area; (3) T3, during induction of anesthesia, in the operating room; (4) T4, postoperatively, in the recovery room; and (5) T5, 3 days after surgery, at home.

Sample Size

To conduct a repeated measures analysis of variance (ANOVA) with 4 time points (ie, T1, T2, T4, and T5) for self-reported child anxiety, Cohen's *f* of 0.25, an alpha of .05 (2-tailed), and a power of .85, a sample size of 200 patients is needed (100 patients per group). To perform regression analyses with 6 predictor variables, a small to medium effect size, and a power of .85, a sample size of 100 patients in the intervention group is sufficient.

Outcome Measures

An overview of the study design and variables at each time point are provided in Figure 5. The primary outcome is change in child state anxiety level between baseline (T1) and induction of anesthesia (T3), evaluated by a psychologist trained in the administration of the modified Yale Preoperative Anxiety Scale (mYPAS) [157, 158]. The mYPAS is a commonly used observational tool consisting of 27 items divided into 5 domains: activity, emotional expressivity, state of arousal, vocalization, and use of parents.

Multiple secondary state anxiety outcomes will be examined. Children will indicate their level of anxiety with a Visual Analogue Scale (VAS) at different time points (T1, T2, T4, and T5) [159]. Moreover, situational parental anxiety, both pre- and postoperatively will be self-reported using the state anxiety form (20 items) of the State-Trait Anxiety Inventory (STAI) at T1 and T3 [160, 161]. Either the psychologist (T1 to T3) or the recovery nurse (T4) will assess parental anxiety with the VAS.

Postoperative pain will be reported with 3 different instruments. The revised Faces Pain Scale (FPS-r) is a self-report measure designed for children to indicate pain intensity [162]. This measure will be used at T4 and T5. A recovery nurse, trained in administering the Face, Legs, Activity, Cry, and Consolability (FLACC) scale, will assess pain intensity at T4 [163, 164]. This scale assesses nonverbal indicators of pain. The Parents' Postoperative Pain Measure (PPPM) will be completed by parents at T5 [165].

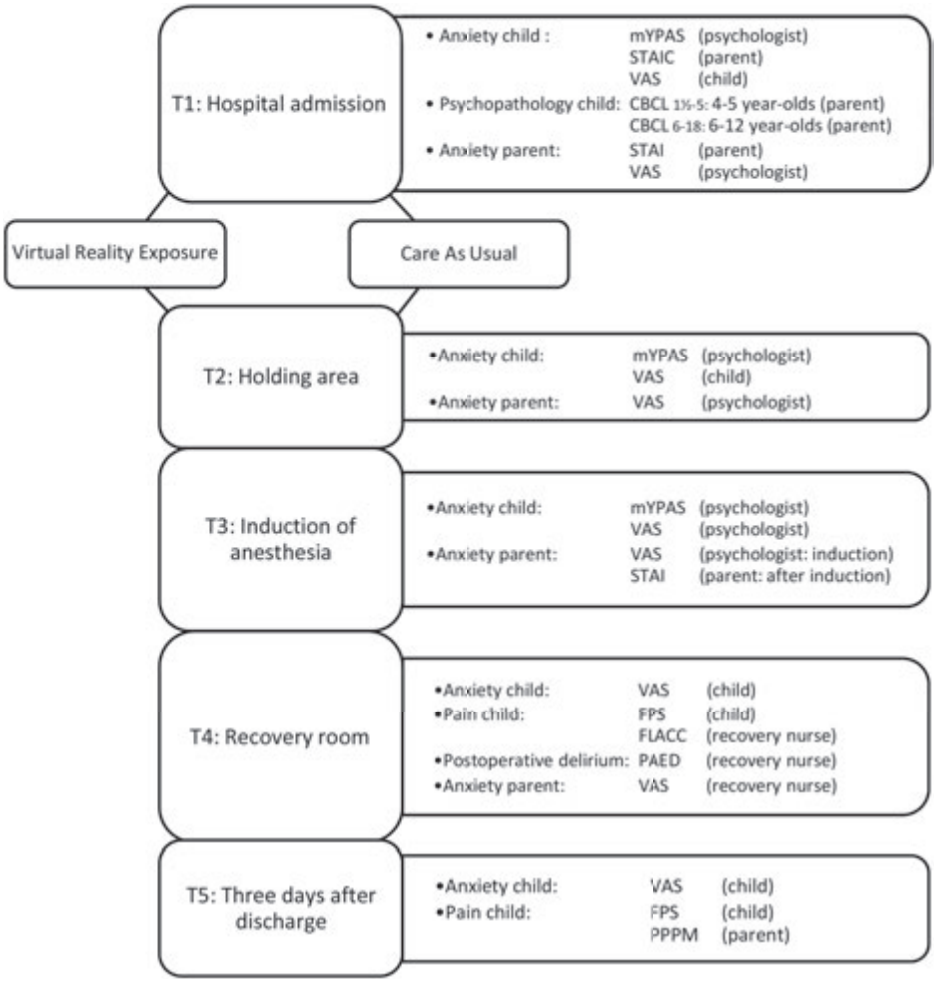
Emergence delirium will be measured with the Pediatric Anesthesia Emergency Delirium (PAED) scale by the recovery nurse at T4 [25, 166]. Finally, information regarding use of analgesics and healthcare use will be extracted from medical records.

Several factors associated with situational anxiety will be assessed because these may influence the efficacy of the VRE. Putative predictors are socioeconomic status, age, sex, type of surgery, preoperative child, and parental trait anxiety. Child trait anxiety will be assessed by parents with the Child Behavior Checklist (CBCL) at T1 [167]. Parental trait anxiety will be self-reported using the trait anxiety form (20 items) of the STAI.

Statistical Analyses

To examine the effect of the intervention on the primary outcome, a repeated measures ANOVA will be conducted with child state anxiety level at T1 (baseline state anxiety) and T3 (anxiety during induction of anesthesia) as within variables and group (VRE versus CAU) as between variables.

Figure 5 Flow chart of the study design with outcomes, instruments, and informants at each time point.



For the secondary outcome measures, repeated measures ANOVA will be conducted with situational parental anxiety at T1 and T3 as within variables and group as between variables. Also, repeated measures ANOVAs will be performed using postoperative pain at T4 (in the recovery room) and T5 (at home) as outcomes, with group as between variables. The effect of the intervention on emergence delirium at T4 will be examined with an analysis of covariance (ANCOVA). Age and sex effects will be accounted for in all analysis.

Multiple linear regression analyses will be performed with change in child state anxiety between T1 and T3 and change in pain between T4 and T5 as outcomes. Predictor variables (ie, socioeconomic status, age, sex, type of surgery, preoperative child, and preoperative parental trait anxiety) will be included into the linear models to identify which factors influence VRE efficacy.

Ethical Considerations

This study has been approved by the Medical Ethics Committee of the Erasmus Medical Center (MEC-2016-626). The study will be conducted according to the Helsinki Declaration.

RESULTS

The development of the VRE tool was finalized and participant recruitment began March 2017. The study to evaluate the efficacy of the VRE will be open for recruitment until September 2018. Data will be analyzed and scientific papers will be submitted for publication in the subsequent year.

DISCUSSION

Principal Findings

There is a need to improve the psychological preparation of pediatric patients, as well as their parents, for surgery since elevated anxiety levels are highly prevalent. VRE has already been shown to be effective as a treatment for specific phobias in children. However, despite the fast-growing field of VR in medical care, the application of a VRE tool to reduce anxiety for surgical procedures in children has not been systematically studied. Since VR is a promising tool for improvement in health outcomes, high quality studies investigating innovative VR interventions are needed.

Here, we describe the development of a psychosocial VR intervention and the PREVIEW trial designed to test its efficacy. We expect the VRE to optimize the preparation of children for surgery under general anesthesia and diminish far-reaching maladaptive consequences, both psychologically and medically.

Strengths and Limitations

In regular medical care, the explanations given to parents and children regarding surgery and anesthesia are mostly verbal of nature. VRE is primarily a visual, non-verbal intervention, so it can have a surplus value for young children, non-verbal children, and for children and parents who do not speak or fully comprehend their second language. Creating a less stressful experience for both children and their parents is in line with the emphasis on patient- and family-centered care [35]. Moreover, if VRE is proven to be effective, this easy to use tool can be implemented into standard medical care, engaging in secondary prevention. We would like to emphasize that, even with the use of modern technology, education provided by healthcare professionals of both pediatric patients and their parents is still absolutely necessary, especially for older children.

A limitation of our study is that it involves children undergoing elective day care surgery (more specifically, dental, oral, and ENT surgery). Therefore, the results of this study might not be generalizable to other types of surgeries.

Conclusion

Preoperative anxiety in children is highly prevalent and there is a need to develop more effective strategies to reduce this anxiety. VRE is a promising tool to prepare pediatric patients for surgery in a child-friendly and efficacious way. We demonstrated that the development of a highly realistic virtual environment that replicates the operating theater is possible with the collaboration of a multidisciplinary team. We are now examining the efficacy of the VRE tool by means of an RCT. By focusing on preparing children for anesthesia and surgery with an innovative VRE tool, instead of distracting them, we hope to improve clinical and psychological outcomes.

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Conflicts of interest

None.

04

Virtual reality exposure before elective day care surgery to reduce anxiety and pain in children: *a randomised controlled trial*

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ABSTRACT

Background: Preoperative anxiety in children is very common and is associated with adverse outcomes.

Objective: The aim of this study was to investigate if virtual reality exposure (VRE) as a preparation tool for elective day care surgery in children is associated with lower levels of anxiety, pain and emergence delirium compared with a control group receiving care as usual (CAU).

Design: A randomized controlled single-blind trial.

Setting: A single university children's hospital in the Netherlands from March 2017 to October 2018.

Patients: Two-hundred children, 4 to 12 years old, undergoing elective day care surgery under general anesthesia.

Intervention: On the day of surgery, children receiving VRE were exposed to a realistic child-friendly immersive virtual version of the operating theatre, so that they could get accustomed to the environment and general anesthesia procedures.

Main outcome measures: The primary outcome was anxiety during induction of anesthesia (modified Yale Preoperative Anxiety Scale, mYPAS). Secondary outcomes were self-reported anxiety, self-reported and observed pain, emergence delirium, need for rescue analgesia (morphine) and parental anxiety.

Results: A total of 191 children were included in the analysis. During induction of anesthesia, mYPAS levels (median [IQR] were similar in VRE, 40.0 [28.3 to 58.3] and CAU, 38.3 [28.3 to 53.3]; $P = 0.862$). No differences between groups were found in self-reported anxiety, pain, emergence delirium or parental anxiety. However, after adenoidectomy/tonsillectomy, children in the VRE condition needed rescue analgesia significantly less often (55.0%) than in the CAU condition (95.7%) ($P = 0.002$).

Conclusion: In children undergoing elective day care surgery, VRE did not have a beneficial effect on anxiety, pain, emergence delirium or parental anxiety. However, after more painful surgery, children in the VRE group needed rescue analgesia significantly less often, a clinically important finding because of the side effects associated with analgesic drugs. Options for future research are to include children with higher levels of anxiety and pain and to examine the timing and duration of VRE.

Trial registration: Netherlands Trial Registry: NTR6116

INTRODUCTION

Preoperative anxiety is very common in children. On the day of surgery, 50 to 70% of children experience anxiety that usually peaks during induction of anesthesia [3, 4]. Preoperative anxiety is associated with problematic induction of anesthesia [17], risk of emergence delirium [17, 19], increased pain and poorer recovery [13, 16]. Anxious children undergoing surgery, and their parents, are also at risk of posttraumatic stress symptoms [26, 27]. These adverse outcomes underscore the urgent need for effective interventions to reduce preoperative anxiety.

A promising innovative intervention is virtual reality. Virtual reality is especially engaging for children, as they often become truly captivated by imaginative play [82]. In our recent meta-analysis on virtual reality interventions in children undergoing medical procedures [168], we found that virtual reality is effective in reducing anxiety and pain. In most studies, virtual reality was used as a distraction tool during medical procedures [168]. However, research has demonstrated that exposure is more effective than distraction in reducing anxiety [57]. Virtual reality exposure (VRE) has already been proven effective in treating anxiety disorders, such as specific phobias (fear of spiders) [69, 70] but very limited research has been conducted on the effect of VRE as preparation for medical procedures.

VRE offers the chance to reduce preoperative anxiety by exposing children to a realistic virtual version of the operating theatre, in which they can get accustomed to the environment and procedures associated with anesthesia. Until now, only two studies [73, 74] have applied VRE prior to surgery. In these studies, both including 69 children, the intervention took place on the day of surgery and consisted of either a 360 degree virtual reality tour of the operating theatre [73] or a virtual reality game in which patients experienced the preoperative process [74]. Children in the control group received conventional education about the preoperative process. Both studies were limited to preoperative outcomes and found that children were significantly less anxious and more compliant in the VRE than in the control group [73, 74]. However, as preoperative anxiety is associated with negative postoperative outcomes, such as increased pain and emergence delirium [13, 16, 17, 19], it is also important to investigate postoperative effects of VRE.

This is the first randomized controlled trial (RCT) to study the effects of VRE on preoperative anxiety, in addition to postoperative outcomes. The objective of the

current study was to compare levels of anxiety during induction of anesthesia (primary outcome), postoperative anxiety, pain, emergence delirium, rescue analgesia and parental anxiety (secondary outcomes) in children receiving VRE, with controls, and to identify predictors of VRE efficacy in children 4 to 12 years old undergoing elective maxillofacial, dental or ear-nose-throat (ENT) day surgery.

MATERIALS AND METHODS

The PREoperative Virtual reality Intervention to Enhance Wellbeing (PREVIEW) study [72] was approved by the Medical Ethics Committee of the Erasmus Medical Centre (MEC-2016-626) on 30 November 2016 and registered at the Netherlands Trial Registry (NTR6116). This single-centre, single-blinded RCT was conducted in accordance with the CONSORT guidelines [169] at the Erasmus MC-Sophia Children's Hospital in the Netherlands, by the Departments of Child and Adolescent Psychiatry/Psychology, Pediatric Anesthesiology, Maxillofacial, Dental and ENT Surgery. Written informed consent was obtained from all parents and from all children aged 12 years. Children aged 11 years and under gave permission orally.

Participants

Eligible participants were consecutive children aged 4 to 12 years undergoing elective maxillofacial, dental or ENT day care surgery between March 2017 and October 2018. Exclusion criteria were mental retardation, inability of parents to read or write Dutch, epilepsy, visual impairment, an American Society of Anesthesiologists (ASA) physical status at least III and need for preoperative anxiolytic medication.

Procedure

Eligible children and their parents were informed about the study by pediatric anesthesiologists during preoperative screening. Those interested received a patient information folder via e-mail. During this screening, the anesthesiologists recommended that all children and parents should watch an informative online film at home about general anesthesia according to the standard hospital protocol.

On the day of surgery, after informed consent was obtained, personal and medical data were collected by the research assistant and baseline anxiety and problem behavior were assessed (T1) (Figure 1). Next, the research assistant randomly allocated children to the VRE intervention, which the children received

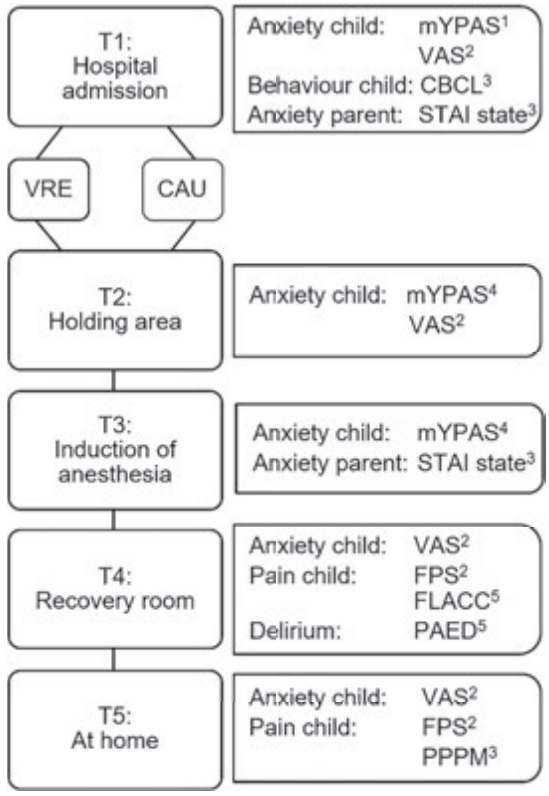
together with usual care, or to the control group, in which children only received care as usual (CAU). Block randomization was performed, stratified by type of surgery: adenoidectomy and/or tonsillectomy, insertion of tympanostomy tubes, maxillofacial and dental procedures or other ENT procedures. After randomization, the VRE intervention took place in a separate room, under the guidance of the research assistant. Afterwards, children were admitted to the day care unit. Children in the CAU group were admitted to the day care unit directly after randomization. Assessments after randomization were performed by the blinded researcher (RE) in the holding area (T2) and during induction of anesthesia (T3), and by a blinded recovery nurse, postoperatively, in the recovery room (T4). One assessment per time point was performed. In the recovery room, assessments took place during later phases of awakening. Parents were present from early phases of awakening (one parent per child). Anesthesiologists were blinded to group allocation. Postoperatively, parents were encouraged and reminded by phone and e-mail to complete online questionnaires at home, via a secure website, on the third day after surgery, but were allowed to do so until 2 weeks after surgery (T5). An overview of the process can be found in Figure 1.

Virtual reality intervention

The VRE tool encompasses a highly realistic virtual environment that is modelled according to the real operating theatre and medical staff. The virtual environment is computer-generated, interactive and child-friendly. It was presented to the child for approximately 15 min via an HTC Vive (HTC Corporation, Xindian, New Taipei, Taiwan) head-mounted display and was also displayed on a personal computer monitor, so the accompanying parent could see what the child was viewing. We developed two versions, for children aged 4 to 7 and 8 to 12 years, in order to attune explanations to a child's developmental level. The storyline begins in the holding area (Figure 2, page 15). A receptionist welcomes the child and shows a video on a virtual tablet that explains that one of the child's parents will stay with him/her until the child is anesthetised and shows the hospital gowns they will be wearing to the operating room. Next, the child is transported, in a hospital bed, into the corridor of the operating theatre by an anesthesiologist and a nurse anesthetist (Figure 3, page 15). After arrival in the operating room, the child can point at different instruments with a motion tracked controller so that the nurse anesthetist can explain what these are used for (Figure 4, page 16). Then, the child moves onto the operating table and preparation for anesthesia takes place. The

programme is able to show both intravenous (i.v.) and inhalational induction. After induction, the operating room fades out and the recovery room fades in (Figure 5, page 16). Here, the nurse anesthetist shows another video that explains what kind of feelings the child might experience after surgery, for example nausea. For a more detailed overview of the storyline, as well as the technical hardware and software specifications, we refer to the trial article [72].

Figure 1 Flowchart of the study design with outcomes and instruments at each time point. Informants are denoted in superscript: 1. Research assistant, 2. Child, 3. Parent, 4. Researcher, 5. Recovery nurse. CAU, care as usual; VRE, virtual reality exposure.



Anesthesia protocol

None of the children received preoperative anxiolytic premedication. EMLA cream (lidocaine/prilocaine) or Rapydan (lidocaine/tetracaine) plasters were applied on the back of the hands, 30 to 60 min before going to the operating room. Induction of anesthesia took place in the operating room in the presence of a parent or a

guardian. Children were lying down or sitting on the operating table but were also permitted to sit on the parent's lap. After placement of the electrocardiography electrodes, pulse oximeter and blood pressure cuff, anesthesia was induced, i.v. or by inhalation if i.v. cannulation was declined or i.v. access was unsuccessful. For i.v. induction, a peripheral i.v. catheter was placed in the back of the hand, and i.v. propofol 2 to 4 mg kg^{-1} and fentanyl 1 to 2 µg kg^{-1} were administered. For inhalation induction, sevoflurane in a mixture of oxygen and air was administered by mask. In these cases, i.v. cannulation took place after induction, after which i.v. fentanyl 1 to 2 µg kg^{-1} was administered. Depending on the surgical procedure, a laryngeal mask airway (LMA) or an endotracheal tube (ETT) was inserted. Before intubation, the child received a muscle relaxant. Anesthesia was maintained with sevoflurane 0.7 to 1.0 minimal alveolar concentration (MAC) in air and oxygen. During surgery, i.v. fentanyl was administered at the discretion of the anesthesiologist. At the end of the procedure, first doses of i.v. paracetamol 20 mg kg^{-1} and diclofenac 1 mg kg^{-1} were administered. If needed, i.v. morphine 0.1 mg kg^{-1} was also administered. After extubation, children were brought to the recovery area. Rescue analgesia, extra morphine, could be administered by the recovery nurse according to perceived clinical need. Standard postoperative analgesics were prescribed: paracetamol 90 mg kg^{-1} per day orally or rectally and diclofenac 3 mg kg^{-1} per day orally or rectally.

Assessment instruments

An overview of the well validated assessment instruments at each time point is provided in Figure 1.

Child anxiety

The primary outcome was child anxiety during induction of anesthesia (T3) assessed with the modified Yale Preoperative Anxiety Scale (mYPAS) [158]. The mYPAS is considered the gold standard in observational instruments to assess preoperative anxiety in children [158] and was completed at three timepoints (T1, T2 and T3). The mYPAS consists of 27 items divided into five domains: activity, emotional expressivity, state of arousal, vocalisation and use of parents. Scores range from 23.33 to 100, with higher scores indicating higher levels of anxiety. The domains have good to excellent interobserver and intra-observer reliability [158]. The research assistant (T1) and blinded researcher (T2 & T3) were trained in administering the mYPAS with standardised instructions. Children indicated their

own anxiety level on a visual analogue scale (VAS) [23] prior to anesthesia and after surgery (T1, T2, T4 and T5).

Child pain and emergence delirium

Postoperative pain was reported by three informants. Children reported their pain intensity (T4 and T5) with the six-faces revised Faces Pain Scale (FPS-r): range 0 to 10 [170]. A blinded recovery nurse assessed pain intensity (T4) with the Face, Legs, Activity, Cry and Consolability (FLACC) scale: range 0 to 10 [163]. Parents assessed their child's pain (T5) by completing the Parents' Postoperative Pain Measure (PPPM): range 0 to 15 [165]. Emergence delirium was assessed (T4) with the Pediatric Anesthesia Emergency Delirium (PAED) scale by a blinded recovery nurse: range 0 to 20 [25].

Child behavior problems

At T1, parents completed the Child Behavior Checklist (CBCL) to assess preoperative emotional and behavioral problems during the past 6 months [91, 92]. Either the 1.5 to 5 years of age version with 100 items (for 4 to 5-year-old participants) or the 6 to 18 years of age version with 113 items (for 6 to 12-year-old participants) was used. T-scores for total scores were computed.

Parental anxiety

The State–Trait Anxiety Inventory (STAI) is a self-reporting instrument that contains two separate scales for trait and state anxiety [160]. Scores on both Likert-type scales range from 20 to 80. Parents completed the state form directly after induction of anesthesia (T3).

Statistical analyses

Intention-to-treat (ITT) analyses were performed for all randomized participants. We used two-way imputation to adjust for missing item data. The Shapiro–Wilk test was used to test the assumption of normal distribution. Non-normally distributed continuous variables were compared between conditions using the Mann–Whitney *U* test. Categorical variables were analysed with the χ^2 test. Continuous non-normally distributed data were reported as median [interquartile range]. Categorical non-normally distributed data were presented as frequency (percentage).

For children in the VRE condition, linear regression analyses were performed with children's state anxiety during induction of anesthesia (mYPAS at T3) and self-reported pain (FPS-r at T4) as outcomes. The following predictor variables were entered simultaneously in the model: sex, age, type of surgery, preoperative state anxiety (mYPAS T1), preoperative problem behavior (CBCL T1) and preoperative parental state anxiety (STAI state T1). All data were analysed with IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp. Armonk, NY). A *P* value less than 0.05 was considered statistically significant.

Sample size calculation

A sample size of 100 patients per group was sufficient to compare the primary outcome, anxiety during induction of anesthesia (mYPAS) between the intervention and control groups, with a Cohen's *d* of 0.4 (small to medium effect size), an alpha of 0.05 (two-tailed) and a power of 0.85. A sample size of 100 patients in the intervention group was sufficient to perform regression analyses with six predictor variables, a small to medium effect size and a power of 0.85.

RESULTS

No significant differences were found between groups in patient and surgical characteristics (all *P*s > 0.05).

Between March 2017 and October 2018, 393 children were assessed for eligibility, of whom 193 children did not participate. Reasons for non-participation were did not meet the inclusion criteria (n = 5), did not want to participate (n = 109) or for other reasons such as inability to contact, postponement or cancellation of surgery before data collection (n = 49) (Figure 3). Two hundred children were enrolled in the study (VRE: n = 100, CAU: n = 100). Nine children were excluded because of accidental unblinding (n = 5), noncompliance with the anesthetic protocol (n = 2), no data collection at T2 and T3, due to logistical reasons (n = 1), or cancelled surgery (n = 1). Therefore, 191 participants were included in the data analyses (VRE: n = 94, CAU: n = 97). Baseline characteristics of all participants are given in Table 1. Twenty-one children in the VRE condition discontinued the intervention by taking off the virtual reality headset. Ad-hoc analyses showed that this group consisted of an equal number of boys (n = 11, 52.4%) and girls (n = 10, 47.6%), with a median age of 5.0 years [4.5 to 6.3]. More specifically, 71.4% of these children were 4 or 5 years old.

For the data collection at T5, most parents (56.0%) had completed the online questionnaires on the fourth day after surgery. On the eighth day after surgery, almost all parents (82.7%) had completed the questionnaires. The final percentage of completed questionnaires after 14 days was 91.6%. No significant correlations (Spearman's *r*) were found between day of completion and postoperative outcomes ($P = 0.228$, $P = 0.577$, and $P = 0.721$, for VAS, FPS-r and PPPM, respectively). Therefore, T5 data from all postoperative days (3 to 14) were combined and included in the analysis.

Figure 3 CONSORT study flowchart. CAU, care as usual; T2, in the holding are; T3, during induction of anesthesia; VRE, virtual reality exposure.

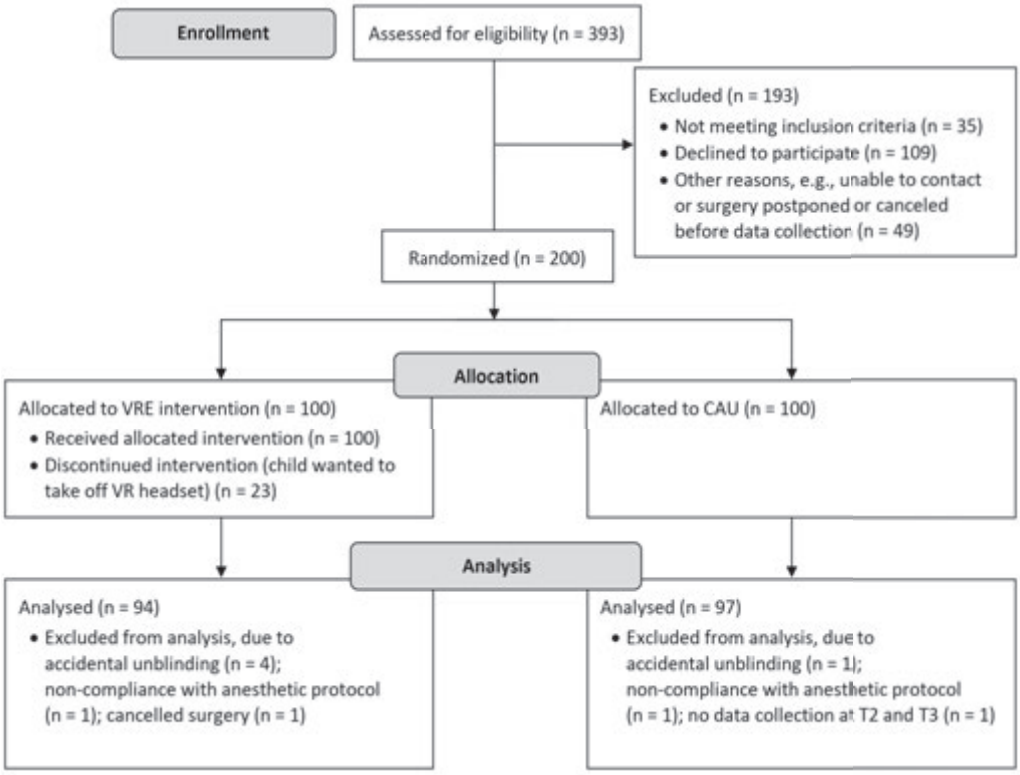


Table 1 Patient and surgical characteristics

	VRE[c] (n = 94)	CAU (n = 97)	P[d]	VRE[e] (n = 73)	P[f]
Age	8 .3 [5.7 to 10.2]	7.5 [5.6 to 10.7]	0.938[a]	9.0 [6.4 to 10.7]	0.064[a]
Sex			0.172[b]		0.149[b]
Male	45 (47.9)	56 (57.7)		34 (46.6)	
Female	49 (52.1)	41 (42.3)		39 (53.4)	
ASA physical status			0.141[b]		0.073[b]
I	72 (76.6)	65 (67.0)		58 (79.5)	
II	22 (23.4)	32 (33.0)		15 (20.5)	
Type of surgery			0.915[b]		0.477[b]
Adenoidectomy and/ or tonsillectomy	20 (21.3)	23 (23.7)		12 (16.4)	
Tympanostomy tubes	23 (24.5)	23 (23.7)		17 (23.3)	
Maxillofacial and dental procedures	23 (24.5)	26 (26.8)		18 (24.7)	
Other ENT procedures	28 (29.8)	25 (25.8)		26 (35.6)	
Induction method			0.499[b]		0.674[b]
Inhalation	54 (57.4)	51 (52.6)		36 (49.3)	
Intravenously	40 (42.6)	46 (47.4)		37 (50.7)	
Total problem behaviour (CBCL)	47.0 [41.0 to 56.0]	46.0 [39.0 to 53.0]	0.251[a]	47.0 [41.0 to 55.0]	0.268[a]
Parental education level			0.442[b]		0.728[b]
Low	5 (5.3)	2 (2.1)		3 (4.1)	
Medium	30 (31.9)	35 (36.1)		25 (34.2)	
High	59 (62.8)	60 (61.9)		45 (61.6)	

Values are median [interquartile range] or frequency (percentage). ASA, American Society of Anaesthesiologists; CAU, care as usual; CBCL, Child Behaviour Checklist; VRE, virtual reality exposure. [a] Mann–Whitney U-test. [b] χ^2 test. [c] Children who were allocated to the VRE condition (n = 94). [d] Intention-to-treat analyses. [e] Children who completed the VRE intervention (n = 73). [f] Per-protocol analyses (ad-hoc).

Table 2 Anxiety, pain, rescue analgesia and emergence delirium levels, and parental anxiety levels in both groups

	VRE[c] (n = 94)	CAU (n = 97)	P[d]	VRE[e] (n = 73)	P[f]
Anxiety					
mYPAS (observed)					
T1	28.3 [23.3 to 31.7]	26.7 [23.3 to 32.5]	0.697[a]	28.3 [23.3 to 30.0]	0.636[a]
T2	28.3 [23.3 to 36.7]	28.3 [23.3 to 41.7]	0.765[a]	26.7 [23.3 to 36.7]	0.129[a]
T3	40.0 [28.3 to 58.3]	38.3 [28.3 to 53.3]	0.862[a]	36.7 [27.5 to 48.3]	0.266[a]
VAS (self-reported)					
T1	3.0 [0.1 to 5.0]	1.5 [0.0 to 5.0]	0.407[a]	3.0 [0.5 to 5.0]	0.209[a]
T2	3.0 [1.0 to 5.5]	3.5 [0.0 to 6.0]	0.753[a]	3.5 [1.0 to 6.0]	0.997[a]
T4	0.0 [0.0 to 2.0]	0.0 [0.0 to 2.0]	0.735[a]	0.3 [0.0 to 2.0]	0.466[a]
T5	0.5 [0.0 to 1.0]	0.3 [0.0 to 2.0]	0.727[a]	0.5 [0.0 to 1.0]	0.620[a]
Pain					
FPS-*r* (self-reported)					
T4	2.0 [0.0 to 4.0]	2.0 [0.0 to 2.5]	0.699[a]	2.0 [0.0 to 4.0]	0.763[a]
T5	0.0 [0.0 to 2.0]	0.0 [0.0 to 2.0]	0.454[a]	0.0 [0.0 to 2.0]	0.551[a]
FLACC (observed, T4)	0.0 [0.0 to 0.0]	0.0 [0.0 to 0.0]	0.669[a]	0.0 [0.0 to 0.0]	0.735[a]
PPPM (observed, T5)	3.0 [0.0 to 5.0]	3.0 [1.0 to 8.0]	0.410[a]	3.0 [0.0 to 5.8]	0.502[a]
Rescue analgesia[g] (T4)					
Overall	28 (29.8)	39 (40.2)	0.131[b]	22 (30.1)	0.175[b]
Adenoidectomy and/ or tonsillectomy	11 (55.0)	22 (95.7)	0.002[b]	6 (50.0)	0.001[b]
Tympanostomy tubes	0 (0.0)	1 (4.3)	0.312[b]	0 (0.0)	0.384[b]
Maxillofacial and dental procedures	4 (17.4)	6 (23.1)	0.622[b]	4 (22.2)	0.947[b]
Other ENT procedures	13 (46.4)	10 (40.0)	0.637[b]	12 (22.2)	0.657[b]
Emergence delirium					
PAED (observed, T4)	7.0 [5.0 to 9.0]	6.0 [5.0 to 9.0]	0.266[a]	7.5 [5.0 to 9.0]	0.223[a]
Parental anxiety					
STAI-state (self-reported, T3)	41.0 [34.5 to 48.5]	40.5 [33.0 to 50.0]	0.753[a]	38.5 [34.0 to 45.8]	0.579[a]
VAS (observed, T3)	3.0 [2.0 to 5.0]	3.5 [2.0 to 5.0]	0.418[a]	3.0 [2.0 to 4.0]	0.171[a]

Values are median [interquartile range] or frequency (percentage). FLACC, Face, Legs, Activity, Cry and Consolability; FPS-r, Faces Pain Scale revised; mYPAS, modified Yale Preoperative Anxiety Scale; PAED, Paediatric Anaesthesia Emergency Delirium; PPPM, Parents' Postoperative Pain Measure; STAI, State-Trait Anxiety Inventory; T1, hospital admission (baseline); T2, holding area; T3, induction of anaesthesia; T4, recovery room, when children were fully awake, in the presence of a parent; T5, at home, within 2 weeks after surgery; VAS, Visual Analogue Scale. [a] Mann–Whitney U-test. [b] χ^2 test. [c] Children who were allocated to the VRE condition (n = 94). [d] Intention-to-treat analyses. [e] Children who completed the VRE intervention (n = 73). [f] Per-protocol analyses (ad-hoc). [g] Need for rescue analgesia (yes or no) was also analysed for each type of surgery, separately.

Child anxiety

At baseline (T1), in the holding area (T2) and during induction of anesthesia (T3), mYPAS scores were similar in CAU and VRE (P = 0.697, P = 0.765 and P = 0.862, respectively). Self-reported VAS scores were also comparable between conditions at different time points (P = 0.407 at T1, P = 0.753 at T2, P = 0.735 at T4 and P = 0.727 at T5) (Table 2).

The only significant predictor of anxiety during induction of anesthesia was preoperative parental state anxiety [F (1,85) = 5.05, P = 0.027]. Higher parental anxiety levels prior to surgery were related to higher child anxiety levels during induction, in the VRE group. The linear regression model accounted for 11.3% of the variance in anxiety during induction of anesthesia [F (6,85) = 1.80, P = 0.109].

Child pain and emergence delirium

No differences in pain levels were found between VRE and CAU, neither when self-reported with FPS-r (P = 0.699 at T4, P = 0.454 at T5), nurse-observed with FLACC (P = 0.669) nor parent-observed with PPPM (P = 0.410). Further investigation of pain levels in the recovery room (T4) indicated that there were no differences between VRE and CAU in the proportion of children experiencing considerable levels of pain (FPS-r > 3 or FLACC > 3) [85, 171], neither when self-reported with the FPS-r (VRE: n = 24, CAU: n = 23, P = 0.211), nor when nurse-observed with the FLACC (VRE: n = 4, CAU: n = 5, P = 0.549). No differences were found in emergence delirium symptoms between conditions (P = 0.266), nor in proportion of children experiencing considerable levels of emergence delirium symptoms (PAED > 10) [25] (VRE: n = 3, CAU: n = 1, P = 0.505). No significant predictors of postoperative pain were found in the model. The linear regression model accounted for 7.4% of the variance in self-reported pain in the recovery room, F (6,81) = 1.07, P = 0.386.

Rescue analgesia

Overall, there was no difference in need for rescue analgesia between VRE and CAU (P = 0.131). When analysing rescue analgesia for each type of surgery separately, 11 out of 20 (55%) children in the VRE group who underwent adenoidectomy and tonsillectomy needed significantly less frequent rescue analgesia than the 22 out of 23 (95.7%) children in the CAU group (χ^2 = 9.91, P = 0.002). No differences in rescue analgesia were found for the other three types of surgery.

Parental anxiety

No differences in parental anxiety during induction of anesthesia were found between groups, either when self-reported (STAI-state) (P = 0.753), or when observed (VAS) (P = 0.418).

Ad-hoc analyses

We did not replace the 21 children who discontinued the VRE intervention, in line with intention-to treat principles. However, because this concerns a substantial number of children, we repeated the analyses per-protocol, in which we compared the children in the VRE group who completed the intervention (n = 73) with children in the CAU group (n = 97). These analyses did not produce significantly different results when compared with the intention-to-treat analyses (Tables 1 and 2; the two columns on the right).

DISCUSSION

This single-blinded RCT, with a sample of 191 children, was designed to investigate the effect of fully immersive VRE in children undergoing elective day care surgery. No significant differences were found between VRE and CAU in child anxiety, pain, emergence delirium or parental anxiety. However, after VRE, children undergoing the most painful surgical procedure [172] needed significantly less rescue analgesia compared with CAU. Lastly, levels of parental anxiety did not differ between VRE and CAU. Virtual reality has previously been investigated as a means of improving health outcomes and previous studies have found that virtual reality reduced pain and anxiety in children undergoing different medical procedures [73, 74, 168]. Most of these studies showed virtual reality being successfully used as a method of distraction [168]. Because these studies were small, often not blinded and lacked standardised assessments, chance findings and a degree of bias could not be ruled out. Previously studied medical procedures that included oncological and burn wound care were more complex and painful [168] compared with the procedures in our study. This is reflected by the relatively small proportion of our patients who experienced substantial levels of pain. It may be possible that VRE is more effective prior to more problematic surgery, with higher levels of anticipated anxiety and pain, compared with elective day care surgery. This is supported by our finding that only children who underwent the most painful type of surgery [172] needed less rescue analgesia after VRE. This finding is of great clinical importance,

because rescue analgesia such as morphine has several side effects, including nausea, vomiting and dizziness [173]. Therefore, administering rescue analgesia may be associated with slower postoperative recovery. In our study, pain levels at T4 were similar in VRE and CAU groups. However, by that time, rescue analgesia would have already been administered if needed. It is possible that, despite substantial pain levels, no treatment effect was found because of adequate pain management. A final explanation for the absence of effects on anxiety and pain is that more time was needed between VRE and surgery for children to process the information. Children require up to 1 week for the processing of information about peri-operative processes [39]. Therefore, VRE may be more effective if taken up no earlier than a week prior to surgery, perhaps even in multiple sessions, or via a mobile application for smartphones [174]. This dispenses with an extra hospital visit and requires no hospital staff for the intervention, resulting in no extra healthcare costs. Considering the intervention only takes 15 minutes, it is achievable to implement VRE even in a busy clinical setting. However, it might be preferable to limit exposure to children who are most at risk for high levels of anxiety and pain, because these are the children who might benefit the most from VRE.

Two studies by Ryu et al. [73, 74], who used VRE prior to elective day care surgery, found positive effects. These studies were methodologically sound and included an acceptable number of participants. We offer several reasons for the discrepancy in results compared with our study. First, during induction of anesthesia, Ryu et al. [73, 74] considered compliance, whereas our study considered anxiety. Compliance and anxiety are known to be different concepts [175], and even though patients were more compliant, [73, 74] they might still have been anxious during induction of anesthesia. This is in line with their finding that distress levels in the operating room were not affected by playing a VR game preoperatively [74]. Second, the VRE group actually consisted of VRE and CAU because all the children in our study, including those in the VRE group, received routine care in a hospital setting that places great emphasis on patient comfort, in line with patient-centred and family-centred care [35]. More specifically, all children and their parents received a preoperative visit from a pediatric anesthesiologist, during which elaborate education was provided along with a suggestion that the child and parents should watch an informative online movie about general anesthesia. In addition, according to routine practice, children were not separated from their parents during anesthetic induction and all parents were with their children throughout the recovery room stay. Successful

routine care, in both the VRE and CAU groups, might have resulted in relatively low anxiety levels. A cut-off score of mYPAS at least 30 indicates high anxiety [158]. In the current study, median anxiety levels in the CAU condition were 26.7 at baseline and 28.3 in the holding area. In comparison, Ryu et al. [73, 74] found substantially higher median levels of anxiety, also measured with the mYPAS, during baseline (CAU: 51.7 [74]) and in the holding area (CAU: 51.7 [73] and 46.7 [74]). Unfortunately, it is not possible to make the same comparison for anxiety during induction of anesthesia, as Ryu et al. [73, 74] did not use the mYPAS during induction. However, the comparisons between studies at admission (baseline) and in the holding area indicate that, overall, anxiety scores in our study were low, making it potentially more difficult to detect treatment effects. Finally, the lack of strong game design elements in our VRE intervention may explain the absence of results. Patients in the most recent study by Ryu et al. [74] faced different challenges and received rewards whilst playing the VR game. These game elements are associated with greater engagement and education [176, 177], so possibly also with a greater anxiolytic effect.

Strengths and limitations

The strengths of this study include the large sample size, limited missing data, use of internationally established standardised assessment tools, blinding of the medical and research staff and the narrow range of surgical procedures (elective day care surgery).

This study also has some limitations. First, in the recovery room, only one assessment took place. Multiple assessments, on entering the recovery room, and again after 5, 10 and 15 min would have provided a more comprehensive insight into the postoperative effects of VRE [23]. Second, we did not include a survey on the subjective experience of the VRE, such as satisfaction, in children or their parents. Third, 21 children discontinued the intervention by taking off the headset. We found that the majority (71.4%) of these children were 4 or 5 years old. Wearing the rather large and heavy headset may have been uncomfortable, or the intervention may have been too lengthy for younger children, who overall have a limited attention span [178]. Finally, by excluding patients who received anxiolytic premedication, we excluded the most anxious children in our study. Hospital policy dictates that anxiolytic premedication is not given unless, for example, it is after a previous

traumatic experience with anesthetic induction. Therefore, these cases can be considered exceptions and excluding them probably did not influence our results.

CONCLUSION

No significant differences were found between VRE and CAU in child anxiety, pain, or emergence delirium, or parental anxiety. However, after VRE, less rescue analgesia was needed after painful surgery. Considering the side effects of rescue analgesia, this means that VRE could be associated with increased patient comfort and a decreased need for postoperative care. It is possible that we did not find an effect of VRE on the other outcomes because we only investigated relatively mild procedures, the VRE intervention and surgery were too close to each other in time, and anxiety levels prior to induction of anesthesia were relatively low. This is in line with the fact that more compelling results have been found in previous studies that either applied virtual reality to more complex procedures or to patient groups with higher levels of anxiety prior to induction.

Future research

On the basis of our results and conclusions, an option for future research is to investigate VRE in children with higher levels of preoperative anxiety or to investigate VRE prior to more complex procedures with higher levels of expected postoperative pain. Second, when investigating postoperative effects of VRE, it would be valuable to make multiple assessments in the recovery room, as well as collecting information on nausea, vomiting and length of stay. Finally, more research is needed on the inclusion of game elements and the timing of VRE in relation to the day of surgery.

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Conflicts of interest

None.

Presentation

None.

05

Predicting intense levels of child anxiety during anesthesia induction at hospital arrival

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ABSTRACT

In children, intense levels of anxiety during anesthetic induction are associated with a higher risk of pain, poor recovery, and emergence delirium. Therefore, it is important to identify these high-risk children at hospital arrival. The current study examined internalizing behavior (Child Behavior Checklist, CBCL) and state anxiety measures (modified Yale Preoperative Anxiety Scale, mYPAS, and State Trait Anxiety Inventory for Children, STAIC) at hospital arrival as predictors of anxiety during induction of anesthesia. One hundred children (aged 4 to 12 years) undergoing elective daycare surgery were included. The STAIC and mYPAS at hospital arrival were significant predictors of anxiety during induction, whereas CBCL was not. The STAIC state form at hospital arrival was the strongest predictor and could be used to identify children who will experience intense levels of anxiety during anesthetic induction, with sufficient to good diagnostic accuracy. Using the STAIC at hospital arrival allows targeted interventions to reduce anxiety in children.

Keywords: General anesthesia, anxiety, child, psychometrics, diagnostic techniques and procedures

INTRODUCTION

To some extent, most children experience anxiety on the day of surgery, but the range of anxiety intensity is wide [4]. Preoperative anxiety peaks during induction of anesthesia and is associated with different maladaptive consequences after surgery. For example, in a study by Kain et al. [17] including 241 5- to 12-year-old children undergoing elective surgery, anxious patients had significantly higher levels of pain in the recovery room, as well as during the first three days after surgery. As a result, anxious children also needed more analgesia. These findings have been replicated by numerous studies [13, 16-18]. Preoperative anxiety is also related to the occurrence of emergence delirium in the recovery room [17, 19, 20, 22, 23], Children experiencing emergence delirium can be extremely agitated, hypersensitive to stimuli, do not recognize surroundings or people, and are inconsolable when emerging from general anesthesia [21]. Previous studies have also found that preoperative anxiety is associated with psychological problems and negative behavioral changes in the two weeks after surgery, including apathy, anxiety, sleeping disturbances, and aggression toward authority [4, 17, 28]. Children experiencing intense levels of preoperative anxiety (defined as one SD above the mean) are particularly at risk for these maladaptive consequences [19]. In addition, Ben-Amitay et al. [27] found that preoperative anxiety in 6- to 18-year-old patients (n = 40) was associated with posttraumatic stress symptoms after elective surgery, which persisted at the follow-up assessments, one month and six months after surgery, in respectively 8% and 5% of all patients. Finally, childhood healthcare experiences have found to be predictive of adolescents' healthcare behavior (e.g., attending checkups). Therefore, negative hospital experiences, including perioperative anxiety and low comfort, could result in low adherence to future medical treatment [30, 33, 34]. These experiences can even impact adult healthcare use, as it has been found that adults with negative memories about childhood hospital experiences are more likely to avoid healthcare as an adult [29].

Considering these adverse consequences of elevated preoperative anxiety levels, it is important to enable clinicians to distinguish high-risk children from other children. Different strategies have been proposed to reduce anxiety during induction of anesthesia [155]. While some non-pharmacological interventions, such as information materials [179] can be easily provided to all children; other interventions, such as comprehensive coping programs [180], come with increased

costs in terms of time and money. Hence, targeted intervention is desirable, but this first requires the identification of high-risk patients.

Fortier et al. [93] found that internalizing behavior in the past six months (e.g., anxiety or depression), as indicated by the widely used Child Behavior Checklist (CBCL), could predict anxiety during induction of anesthesia in adolescents (n = 59). Recently, Berghmans et al. [23] found that internalizing behavior also predicted anxiety during induction in children (*n* = 401). The relationship between internalizing behavior and anxiety during induction of anesthesia is a fairly unexplored research area, so it is important to further expand this promising line of research.

State anxiety at hospital arrival has a much closer temporal association with children's anxiety during anesthetic induction than internalizing behavior in the past six months. Acquiring information on state anxiety directly at hospital arrival (prior to admission) allows parents or healthcare professionals to intervene before anxiety possibly increases. The gold standard for observational assessment of preoperative anxiety is the modified Yale Preoperative Anxiety Scale (mYPAS) [158]. Another well-validated tool to assess state anxiety is the State Trait Anxiety Inventory for Children (STAIC) [181]. This self-report tool is often very difficult to use for young children (≤ 8-year old), as it is considered too lengthy and complex [182]. Parents can complete the questionnaire about their children's state anxiety as an alternative [183].

Identifying high-risk children, well before entering the operating room, may improve induction of anesthesia. Therefore, the aim of the current study was to examine standardized tools (the CBCL, mYPAS, and STAIC) at hospital arrival to identify a high risk population, who would experience intense levels of anxiety during induction (mean mYPAS + 1SD). We hypothesized that levels of internalizing behavior, as measured with the CBCL, as well as state anxiety, as measured with the mYPAS and STAIC, at hospital arrival are predictors of anxiety during induction of anesthesia. Furthermore, we expected that state anxiety at hospital arrival would be a stronger predictor of anxiety during induction of anesthesia, because state anxiety at hospital arrival has a closer temporal association with anxiety during induction of anesthesia than internalizing behavior in the past six months.

METHODS

This study is part of a single blinded randomized controlled trial to investigate the efficacy of a preoperative virtual reality intervention on anxiety, pain, and emergence delirium [72] (Netherlands Trial Registry: NTR6116, https://www.trialregister.nl/trial/5935). For the purpose of this paper, only children who received care as usual (CAU) were included. Preoperative preparation of the intervention group differed considerably from regular care and was thus not included in the current study. The study was conducted at the Erasmus Medical Center, Sophia Children's Hospital in Rotterdam, The Netherlands, and has been approved by the Medical Ethics Committee of the Erasmus Medical Center (MEC-2016-626). Eligible participants were consecutive pediatric patients (aged 4 to 12 years) undergoing elective daycare surgery (i.e., maxillofacial, dental, or ear-nose-throat surgery) between March 2017 and October 2018. Exclusion criteria were intellectual disabilities (i.e., IQ<70), inability of parents to read or write Dutch, epilepsy, visual impairment, poor general health, indicated by the American Society of Anesthesiologists (ASA) physical status ≥ III, or preoperative anxiolytic medication.

Procedure

During the preoperative screening visit, pediatric anesthesiologists informed eligible patients and parents about the study. If they were prepared to cooperate with the study, they received the patient information folder via email. During this preoperative screening visit, anesthesiologists provided comprehensive educational information concerning general anesthesia and recommended that all children and parents should watch an informative online movie at home about general anesthesia, as per the standard hospital protocol. On the day of surgery, at hospital arrival, written informed consent was obtained from all parents, as well as from all children aged 12 years. Children aged 11 years and under provided oral consent for participation in the study.

At hospital arrival (T1), in the main entrance hall, parents completed the CBCL (child's internalizing behavior), STAIC (child's state anxiety), and STAI (own state anxiety). In addition, the research assistant administered the mYPAS and collected demographical/medical data (T1). Parental education (i.e., highest level of education of either parent) was used as an indicator of socioeconomic status (SES) and was categorized into low (=1), middle (=2) or high (=3), according to Statistics

Netherlands (Centraal Bureau voor de Statistiek: https://statline.cbs.nl). Once these data had been collected, the children were admitted to the daycare unit.

After admission, children and one accompanying parent were brought to the preoperative holding area, approximately one and a half hours after hospital arrival. From here, an anesthesiologist and anesthetic nurse transported the child and parent to the operating room. In the operating room, a researcher who was blinded to T1 assessments evaluated anxiety during induction of anesthesia (mYPAS T2). Both the research assistant and researcher were trained in administering the mYPAS with standardized instructions. Interrater reliability was excellent (Cronbach's alpha 0.90, based on 30 double observations).

Anesthesia protocol

Preoperatively, none of the children received anxiolytic premedication. Cream with local anesthetics, e.g., EMLA, was applied on the back of the hands, 30-60 minutes before transportation to the operating room. Anesthetic preparation (i.e., placement of electrocardiography electrodes, pulse oximeter, and blood pressure cuff) took place in the operating room. Anesthetic induction was performed intravenously (IV). If IV placement was not preferred or IV access was not successful, anesthesia was achieved by inhalation induction. For IV induction, a peripheral IV catheter was placed on the back of the hand, and propofol (2-4 mg · kg^{-1} IV) and fentanyl (1-2 mcg · kg^{-1} IV) were administered. For inhalation induction, sevoflurane in a mixture of oxygen and air was administered by mask. In these cases, IV placement took place after induction, after which fentanyl (1-2 mg · kg^{-1} IV) was administered.

Assessment instruments

Modified Yale Preoperative Anxiety Scale

The mYPAS is considered to be the gold standard to assess preoperative anxiety (in the holding area and operating room) [158]. This observational instrument consists of 27 items covering five domains: activity, emotional expressivity, state of arousal, vocalization, and use of parents. Scores range from 23.33 to 100.00, with higher scores indicating higher levels of anxiety. The domains have good to excellent inter-observer and intra-observer reliability and good validity [13, 158]. The mYPAS was administered both at hospital arrival (T1) and during anesthetic induction (T2).

Child Behavior Checklist

The CBCL, concerning emotional and behavioral problems in the past six months, was used to assess internalizing behavior, i.e., anxious/depressed, withdrawn-depressed, and somatic complaints in children [91, 92]. Either the $1^{1/2}$ – 5 years of age version with 100 items (for 4- to 5-year-old participants) or the 6 – 18 years of age version with 113 items (for 6- to 12-year-old participants) was completed by parents at hospital arrival. Response categories range from 0 to 2. Summary scores were computed, with higher scores indicating more problems. As the internalizing scale consists of 36 items for the $1^{1/2}$ – 5 years of age version and of 32 items for the 6 – 18 years of age version, the summary scores of 6- to 12-year-old participants were multiplied by 1.125 (36/32) to obtain a total score of the CBCL for different ages. The widely used CBCL has good to excellent validity and reliability [184].

State Trait Anxiety Inventory for Children

The state anxiety form of the STAIC questionnaire was used to assess situational anxiety at hospital arrival [181]. Twenty questions were answered on a 4-point Likert scale. Scores range from 20 to 80, with higher scores indicating higher levels of anxiety. As the sample included young children, a parent-reported version of the questionnaire was used [183]. The internal consistency of the STAIC in the current sample was excellent (Cronbach's alpha = 0.91).

State Trait Anxiety Inventory

Parents completed the state anxiety form of the STAI questionnaire to assess their own situational anxiety at hospital arrival. The STAI consists of twenty questions with a 4-point Likert scale and has good validity and reliability [160].

Statistical analysis

Baseline characteristics and psychological assessments were reported as mean (SD) or, in case of categorical data, as frequency (percentage). To test for multicollinearity between predictor variables (Pearson's $r \geq 0.8$), a correlation matrix and variance inflation (VIF) factors were computed. Univariate analyses were performed to test for significant associations between predictor and outcome variables.

The aim was to examine whether internalizing behavior and state anxiety at hospital arrival (T1) could predict intense levels of anxiety during induction of anesthesia (T2). First, a hierarchical multiple regression analysis was conducted with mYPAS

at T2 as a dependent variable and CBCL summary scores for internalizing behavior, STAIC, and mYPAS at T1 as the predictors. The model was adjusted for age, sex, and SES. Second, for the strongest predictor in this model, receiver operating characteristic (ROC) curve analyses were performed to determine a cut-off value for high-risk patients, who will experience intense anxiety during induction of anesthesia (mean mYPAS T2 + 1SD). The optimal cut-off point was found using Youden index *J* (sensitivity + specificity – 1). All data were analyzed with SPSS 24.0 for Windows. A *P*-value <0.05 was considered statistically significant.

Sample size calculation

A sample size of 100 patients was sufficient to perform multiple linear regression analyses using 6 predictors at hospital arrival (T1) to predict anxiety during induction of anesthesia (mYPAS T2), with a power of 0.85 and an alpha of 0.05 to detect a small to medium effect size.

RESULTS

Patient characteristics

Between March 2017 and October 2018, 393 children were assessed for eligibility for the overall study. In total, 193 children did not participate, because they did not meet the inclusion criteria (*n* = 35), did not want to participate (*n* = 109), or for other reasons, e.g., unable to get in contact with or their surgery was postponed (*n* = 49). Two hundred children were enrolled (VR intervention: *n* = 100, CAU: *n* = 100) [185] The current study only comprised children in the CAU condition. Two children were excluded either because of non-compliance with the anesthetic protocol (*n* = 1) or because no data were collected during anesthetic induction, due to logistical reasons (*n* = 1). Consequently, 98 participants were included in the data analysis.

Patient characteristics and assessment outcomes are given in Table 1. The mean age of all participants was 8.0 years and 58.2% of the participants were male. The majority of the participants (67.3%) had a physical status of ASA I, whereas 32.7% had a physical status of ASA II. Most participants (66.3%) had never had surgery before. Inhalation and intravenous induction were performed equally often (52.0% and 48.0%, respectively). Most children had parents with high SES (61.2%). No gender differences were found in these patient characteristics.

Univariate analysis

Univariate results are given in Table 2. Pearson's correlation demonstrated that higher levels of state anxiety at hospital arrival (both STAIC T1 and mYPAS T1) were significantly associated with higher levels of anxiety during anesthetic induction (mYPAS T2) (r = 0.32 and r = 0.33, respectively). No association was found between internalizing behavior (CBCL T1) and anxiety during anesthetic induction (mYPAS T2) (r = 0.11).

Multivariate analysis

VIF factors were low (maximum 1.23) and no multicollinearity was found between predictor variables. Parent-reported state anxiety (STAIC, P = 0.001) and observer-reported state anxiety (mYPAS, P = 0.048) at hospital arrival (T1) were significant independent predictors of anxiety during anesthetic induction (mYPAS T2), when correcting for all other variables (R^2 = 0.17, F = 3.20, P = 0.007) (Table 3). Internalizing behavior (CBCL T1) was not a significant predictor of anxiety during induction (P = 0.964). The strongest predictor, associated with the largest standardized beta coefficient, was STAIC (β = 0.35).

Cut-off on anxiety at hospital arrival

As the STAIC was the strongest predictor of anxiety during anesthetic induction, an optimal cut-off value on the STAIC was identified to predict intense levels of anxiety during induction (mean mYPAS T2 + 1 SD = 45.39 + 22.40 = 67.79). A total of 15 children (15.3%) experienced intense levels of anxiety during induction (mYPAS T2 ≥ 67.79). The ROC curve analysis identified a STAIC score of 47.50 as the optimal cut-off value to distinguish these high-risk patients from other patients (area under the curve (AUC) = 0.69, 95% CI = 0.52–0.86, P = 0.021) (Figure 1). An AUC of 0.69 indicates sufficient to good diagnostic accuracy [186]. For this cut-off value, sensitivity was 66.7% and specificity was 79.5%.

Exploratory analysis

No gender differences were found for internalizing behavior (F = 0.539, P = 0.465) or state anxiety, neither at hospital arrival (F = 2.208, P = 0.141 for STAIC and F = 2.554, P = 0.113 for mYPAS) nor during induction of anesthesia (F = 0.086, P = 0.770). Anxiety levels during induction of anesthesia were equal among different types of surgery (F = 0.231, P = 0.875). We have repeated the multivariate analysis in which we

additionally corrected for parental state anxiety at T1 (STAI) and whether patients had previously undergone surgery. These results did not differ from the results of the original analysis (adjusted model 4: R^2 = 0.180, F = 2.438, P = 0.020).

Table 1 Patient characteristics and baseline variables.

	Children (n = 98)	
Age	8.0	(2.8)
Sex		
Male	57	(58.2)
Female	41	(41.8)
ASA physical status		
I	66	(67.3)
II	32	(32.7)
Type of surgery		
Adenoidectomy and/or tonsillectomy	23	(23.5)
Tympanostomy tubes	23	(23.5)
Maxillofacial and dental procedures	26	(26.5)
Other ENT procedures	26	(26.5)
Previous surgery (yes)	33	(33.7)
Induction method		
Inhalation	51	(52.0)
Intravenously	47	(48.0)
SES		
Low	2	(2.0)
Medium	36	(36.7)
High	60	(61.2)
STAI parent (T1)	36.1	(9.5)
CBCL Internalizing behavior (T1)	6.0	(6.8)
STAIC (T1)	41.3	(9.3)
mYPAS (T1)	29.3	(8.2)
mYPAS (T2)	45.4	(22.4)

Values are mean (SD) or frequency (percentage). Abbreviations: ASA, American Society of Anesthesiologists; ENT, ear, nose, throat; SES, socioeconomic status; STAI, State-Trait Anxiety Inventory; CBCL, Child Behavior Checklist; STAIC, State-Trait Anxiety Inventory for Children; mYPAS, modified Yale Preoperative Anxiety Scale. T1: at hospital arrival. T2: during induction of anesthesia.

Table 2 Univariate associations (Pearson's *r*) between predictors and anxiety during induction of anesthesia.

Predictors	**Outcome: mYPAS T2**
Age	- 0.09
Sex	0.03
SES	0.00
CBCL Internalizing behavior T1	0.11
STAIC T1	0.32**
mYPAS T1	0.22*

* $P < 0.05$

** $P < 0.01$

Abbreviations: SES, socioeconomic status; Child Behavior Checklist; STAIC, State-Trait Anxiety Inventory for Children; mYPAS, modified Yale Preoperative Anxiety Scale. T1: at hospital arrival. T2: during induction of anesthesia.

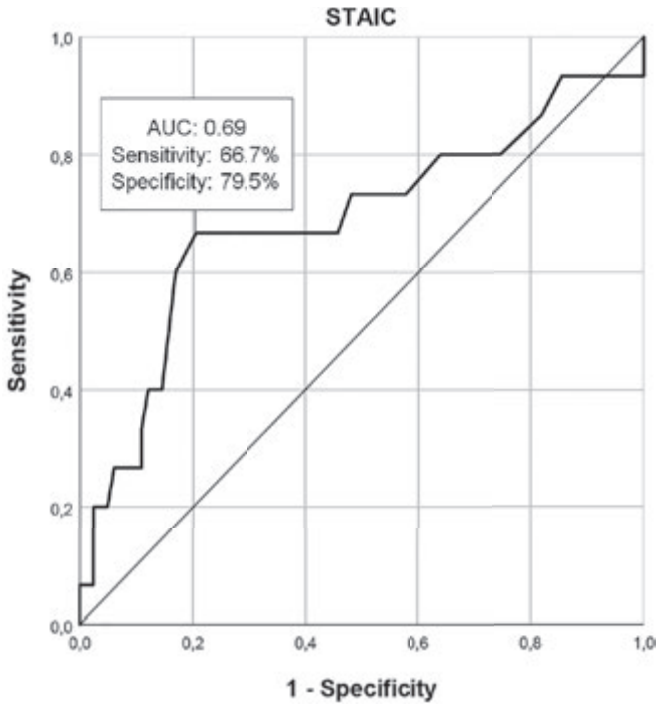
Table 3 Multiple regression: predictors of anxiety during induction of anesthesia

	Outcome: mYPAS T2							
Predictors	**Model 1**		**Model 2**		**Model 3**		**Model 4**	
	B	*β*	*B*	*β*	*B*	*β*	*B*	*β*
Constant	52,070**		47.786**		11.436		-0.586	
Age	-.748	-.093	-.795	-.098	-1.408	-.174	-1.611*	-.199
Sex	1.044	.023	1.003	.022	-1.423	-.031	.141	.003
SES	-.428	-.010	.467	.011	3.042	.073	2.969	.071
CBCL Internalizing behavior T1			.394	.119	.120	.036	.015	.005
STAIC T1					.903**	.373	.847**	.350
mYPAS T1							.550*	.201
R^2	0.009		0.023		0.138		0.174	
R^2 change	0.009		0.014		0.115		0.036	
F	0.292 ($P = 0.831$)		0.544 ($P = 0.704$)		2.944* ($P = 0.016$)		3.202** ($P = 0.007$)	

n = 98, * $P < 0.05$, ** $P < 0.01$

Abbreviations: SES, socioeconomic status; Child Behavior Checklist; STAIC, State-Trait Anxiety Inventory for Children; mYPAS, modified Yale Preoperative Anxiety Scale. T1: at hospital arrival. T2: during induction of anesthesia.

Figure 1 Receiver operating characteristic curve for State-Trait Anxiety Inventory for Children (STAIC) at hospital arrival (T1) for sensitivity and 1 – specificity, including cut-off on the STAIC to distinguish between children who will experience intense levels of anxiety during induction of anesthesia (mYPAS, modified Yale Preoperative Anxiety Scale (mYPAS) T2 ≥ 67.79) and children who will not (mYPAS T2 < 67.79).



DISCUSSION

The aim of the current study was to examine standardized tools (the CBCL, mYPAS, and STAIC) at hospital arrival to identify a high risk population, who would experience intense levels of anxiety during induction of anesthesia. The study was based on a sample of 98 children undergoing elective daycare surgery. Contrary to our hypotheses, internalizing behavior (CBCL) was not a significant predictor of anxiety during induction. However, both parent- and observer-reported state anxiety at hospital arrival (STAIC and mYPAS, respectively) were, as hypothesized, significant predictors of anxiety during induction. The STAIC (state form) was the strongest predictor and could be used to predict intense levels of anxiety (mean mYPAS during anesthesia induction + 1SD), with sufficient to good diagnostic accuracy.

It is important for clinical practice to be able to predict levels of child anxiety during induction of anesthesia, because of the maladaptive postoperative consequences of preoperative anxiety, including increased pain, need for analgesia, and risk of emergence delirium [4, 13, 16-18, 20, 22].

Furthermore, highly anxious children are at risk of developing psychological problems in the two weeks following surgery, including anxiety, apathy, and sleeping disturbances, as well as posttraumatic stress symptoms that may persist up to six months [4, 16, 27, 28]. Finally, these negative experiences may lead to lower adherence to medical treatment and avoidance of future necessary healthcare [30, 33, 34]. These short-term and long-term maladaptive consequences of high levels of preoperative anxiety underscore the importance of identifying high-risk patients. Once these high-risk children have been identified, targeted psychological interventions can be provided. This is important, as it is often not feasible to apply anxiety-reducing interventions to all individual children undergoing surgery, due to the demands on time of clinical staff.

We were not able to replicate previous findings concerning the predictive value of the CBCL for anxiety during induction of anesthesia [23, 93]. It is possible that differences in the distribution of SES played a role in this discrepancy between the findings, since it has been found that lower SES was related to higher CBCL scores [187]. In the current study, parents with high SES were over-represented (61.2%). Age may be another explanatory factor. We focused on a more narrow age range (4 to 12 years) than Berghmans et al. [23] (1.5 to 16 years) and a younger age range than Fortier et al. [93] (11 to 18 years). The nature of preoperative anxiety strongly differs with age. Whereas younger children may have separation anxiety and fear of strangers, older children may fear pain after surgery and may be more aware of potential risks of undergoing surgery [1, 188]. Therefore, the inconsistent results concerning the predictive value of CBCL on anxiety during induction, might indicate a more complex relationship between age, anxiety during induction, and internalizing behavior. These contradictory results indicate the need for replication studies on this relationship.

Another possible explanation for the fact that internalizing behavior, as measured with the CBCL, was not predictive of levels of anxiety during induction of anesthesia is that the CBCL is a relatively broad-band measure, covering a variety of emotional

and behavioral problems. In other words, the CBCL may not be sufficiently sensitive to detect those children who will be highly anxious during induction of anesthesia. Therefore, it would be useful to investigate if narrow-band measures for the assessment of anxiety are able to identify which children will be highly anxious during induction of anesthesia. Examples of such measures are the Screen for Child Anxiety Related Disorders (SCARED) [189] and Multidimensional Anxiety Scale for Children (MASC) [190]. However, a disadvantage of most narrow-band measures for the assessment of anxiety may be that these are focused on disorders (i.e., on DSM criteria). As an alternative, one option could be to specifically assess hospital-related anxiety, for example using the pediatric index of emotional distress (PI-ED) [191], which is modeled on the hospital anxiety and depression scale (HADs) for adults [192]. Future studies are needed to investigate whether narrow-band and hospital-related anxiety instruments would be able to detect anxiety during induction of anesthesia in children.

We hypothesized that state anxiety at hospital arrival would be a stronger predictor of anxiety during induction than internalizing behavior during the past six months, because of a closer temporal association. Our results confirmed this hypothesis, as higher parent- and observer-reported state anxiety at hospital arrival were significantly associated with anxiety during induction of anesthesia. This finding is in line with previous studies that found anxious behavior in the direct preoperative period was related to anxiety during induction of anesthesia [13, 16]. However, at that point, shortly before entering the operating room, anxiety may already have increased significantly. Moreover, not much time is left for professionals or parents to take action at this stage. Consequently, it is important to assess the risk of experiencing intense levels of anxiety during induction early on the day of surgery, i.e., already at hospital arrival. This may allow healthcare professionals to intervene before anxiety increases.

Different non-pharmacological interventions that can be applied on the day of surgery have been shown to reduce anxiety during anesthesia induction in pediatric patients. For example, Brewer, Gleditsch, Syblik, Tietjens, & Vacik [15] found that the psychological preparation of children (aged 5 to 11 years) for elective surgery by a child life specialist was associated with decreased preoperative anxiety. That preparation included exploring and rehearsing with anesthetic equipment, such as the anesthesia mask and pulse oximeter [15]. Another well-known intervention

during induction of anesthesia is to provide distraction. By directing attention away from the procedure and redirecting it to something fun and engaging, less attention is available for the perception of anxiety [41, 42]. Examples of distraction techniques used during induction of anesthesia are playing hand-held videogames, watching cartoons or videos, distraction by parents or nurses, playing with toys, and listening to music [38, 43-45]. An innovative intervention to improve induction of anesthesia in children is providing a virtual reality tour of the operating room environment and the anesthetic procedures, prior to surgery [73, 74, 185]. Using virtual reality to prepare children for what they will see and hear, preoperative anxiety and its postoperative consequences could be reduced. However, according to a recent meta-analysis of virtual reality interventions for pediatric patients, more research is needed to ascertain the effectiveness of virtual reality preparation for surgery [168].

In the current study, we used the STAIC for the between children who will and will not be highly anxious during anesthesia induction, since we found that this assessment tool was the strongest predictor at hospital arrival for anxiety during induction. ROC analyses indicated a STAIC score of 47.50 as the optimal cut-off value to distinguish high-risk patients (associated with a mYPAS score during induction of 67.79) from other patients. In previous studies, mYPAS scores of 30 and 35 have often been used as cut-off values (based on a self-reported STAIC reference score of 37) [158]. For example, recently, Malik et al. [193], using 30 as the mYPAS cut-off score, found that 48% of the 7- to 12-year-old children in their study were anxious shortly before entering the operating room, 72% at parental separation, and 95% during induction. These results indicate that anxiety increases for a significant number of children between hospital arrival and induction of anesthesia. While this is true, this approach ignores the fact that there are considerable variations in the levels of anxiety experienced by children within that 95%. Even though the majority of children have mYPAS scores around 30 or 35, we argue that it is important to focus on those children who experience intense levels of anxiety, as they are considered to be at the highest risk of maladaptive postoperative consequences, such as pain, emergence delirium, and sleeping disturbances [13, 19].

Implementing the parent-reported version of STAIC is relatively easy, given it only takes a few minutes to complete the questionnaire and no hospital staff is needed for the assessment of anxiety. Moreover, involving parents in the healthcare of their children is in line with family-centered care [35]. The results of this study indicate

that completing the STAIC at hospital arrival allows parents, anesthesiologists, and other health care professionals, such as (daycare) nurses or child life specialists, to differentiate between children who will experience intense levels of anxiety during induction and children who will not. Distinguishing between the two categories at this early stage makes more effective targeted interventions possible. This study can also contribute to future studies investigating interventions to reduce preoperative anxiety by indicating how to assess and therefore target those children at highest risk.

Clinical implications

The results of this study are of clinical importance, as completing the STAIC at hospital arrival may help nurses, anesthesiologists, and other clinical personnel identifying highly anxious children. It is well known that preoperative anxiety increases during the day of surgery and peaks during induction of anesthesia [4, 13, 16, 89]. Therefore, being able to predict at an early stage, already at hospital arrival, which children will experience intense levels of anxiety during induction of anesthesia is extremely valuable. Using the STAIC at hospital arrival may make it possible to prevent anxiety from escalating by providing the psychological interventions as described above, such as introducing the child to the anesthetic procedures by rehearsing with anesthetic equipment [15]. We advise using the STAIC as a decision tool to determine whether to apply certain interventions depending upon the specific needs of the child. This may improve compliance during induction of anesthesia and decrease the possible negative short-term and long-term impact of anxiety during induction of anesthesia.

Most children experience some levels of anxiety during induction of anesthesia an intense levels of anxiety in particular are associated with maladaptive consequences [4, 18, 19]. Therefore, as discussed above, we contend that it is important for clinical practice to apply a cut-off score for the STAIC that corresponds with levels of intense anxiety as indicated by the mYPAS. This may help healthcare professionals to pay extra attention to high-risk children. Furthermore, targeting interventions to subgroups of patients, i.e., to patients with high levels of anxiety at hospital arrival, may improve the efficacy of psychological interventions to reduce anxiety during induction of anesthesia.

Strengths and limitations

The strengths of this study include the large sample size, the use of well-validated and easily implemented assessment tools, and its attention to predictors of anxiety during anesthetic induction.

Certain limitations also need to be addressed. First, the children did not complete the STAIC themselves. We used parent reports instead, which could have been influenced by parental anxiety. However, it should be pointed out that reports filled out by children themselves also have validity problems, especially where young children are concerned, because a certain level of cognitive development is needed, particularly in stressful situations [182]. Second, the current study only included children undergoing elective daycare surgery. Therefore, the applicability of the current results to other patient groups has yet to be vindicated.

Conclusion

Most children experience anxiety on the day of surgery, but with a wide range of intensity. At hospital arrival, the CBCL was not a significant predictor of anxiety during induction of anesthesia but the STAIC and the mYPAS were. The STAIC (state form) was considered the strongest predictor and could be used to predict intense levels of anxiety during anesthetic induction. Applying this easy-to-use tool at hospital arrival allows children at high risk to be identified, resulting in the potential for focused interventions by healthcare professionals before induction of anesthesia. By reducing the anxiety of the child a smoother induction may well be possible. However, more research is needed, especially with respect to other patient groups.

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Compliance with Ethical Standards

Conflict of interest: Robin Eijlers, Lonneke M Staals, Jeroen S Legerstee, Johan M Berghmans, Elske M Strabbing, Marc P van der Schroeff, René MH Wijnen, Laura S Kind, Manon HJ Hillegers, Bram Dierckx, and Elisabeth MWJ Utens declare that they have no conflict of interest.

Ethical Approval: This study was approved by the Medical Ethics Committee of the Erasmus Medical Centre (MEC-2016-626) on 30 November 2016 and registered at the Netherlands Trial Registry (NTR6116).

Human and Animal Rights: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5).

Informed Consent: Informed consent was obtained from all patients for being included in the study.

07

General discussion

PART I: VIRTUAL REALITY TO PREPARE CHILDREN FOR SURGERY: EFFECTS ON ANXIETY AND PAIN

Undergoing surgery can be a very stressful situation for children. Anxiety usually peaks during induction of anesthesia [1-5] and is associated with a range of maladaptive postoperative consequences, e.g., increased anxiety, pain, and analgesia [13, 16-19]. The main aim of Part I of this thesis was to investigate the effectiveness of an innovative virtual reality exposure (VRE) intervention on levels of anxiety during anesthesia induction (primary outcome), postoperative anxiety, pain, emergence delirium, rescue analgesia, and parental anxiety (secondary outcomes) in children undergoing elective daycare surgery. In Chapter 2, we presented the results of our systematic review and meta-analysis on the effectiveness of virtual reality (VR) interventions on pain and anxiety for children in a hospital setting. In Chapter 3, the development of our VRE tool for psychological preparation of children undergoing surgery, as well as the design of the PREVIEW study are described. In Chapter 4, the results of the PREVIEW study, a randomized controlled trial (RCT) into the effect of VRE preparation for children undergoing elective day care surgery, are discussed. It is often not feasible or desirable to apply anxiety-reducing interventions at the hospital to *all* children undergoing surgery. Therefore, as described in Chapter 5, we have investigated standardized tools to identify children whose anxiety levels will most likely escalate during induction of anesthesia.

In this chapter, the main findings of our research will be discussed from a broader perspective and implications for clinical practice, as well as recommendations for future research will be provided.

Main findings

Systematic review and meta-analysis

Our systematic review and meta-analysis [168], based on 14 studies for pain and 7 studies for anxiety, showed that VR is an effective tool to reduce child-reported pain and anxiety for a range of medical procedures, e.g., burn care and oncological care. VR was also related to significant reductions of caregiver-observed and professional-observed levels of children's pain (Chapter 2). Because very limited data were available for caregivers and professionals as observers of children's levels of anxiety, we were not able to draw conclusions regarding VR effectiveness on observed levels of anxiety.

These results indicate that VR is more effective than care as usual (CAU) in reducing pain and anxiety. It is important to note, though, that CAU conditions differed between studies. In some studies, children in CAU conditions could watch television or play with toys, since these distraction tools were part of routine care, whereas in other studies, no distraction was used. Moreover, the included studies often did not describe their CAU conditions very clearly. Since all but one study used VR as a distraction tool *during* a medical procedure, the large effect sizes we found in our meta-analysis (1.30 for pain and 1.32 for anxiety) may suggest that VR distraction is more effective than other distraction techniques during medical procedures. For example, a Cochrane review including 39 RCTs on the effectiveness of distraction (e.g., games, music, and toys) on pain during needle-related procedures in children and adolescents, documented a medium effect size of 0.61 [144]. Moreover, a meta-analysis including 19 RCTs on music as a distraction method to control pain in children undergoing a variety of medical procedures (e.g., dental care and venipuncture) resulted in a medium effect size of 0.35 [145]. Another possible explanation for finding large effect sizes for VR in our meta-analysis could be the presence of a publication bias. However, Egger regression asymmetry tests did not indicate the presence of such a bias. Therefore, based on our meta-analysis, it can be concluded that VR has a large impact on pain and anxiety in children undergoing medical procedures.

By using VR distraction *during* a medical procedure, attention is directed away from the procedure and redirected to something fun and engaging (e.g., a VR game). This way, less attention is available for the perception of pain and anxiety during the procedure [38, 46, 75]. VR exposure takes places *prior to* a medical procedure and is aimed at preparing children for undergoing the procedure [73]. By showing children the environments and procedures in VR, they can become gradually familiar with it, which can result in lower levels of anxiety and pain. While the effectiveness of VR as a distraction tool has been well-documented, more research is needed to establish evidence on VR as an exposure tool for children undergoing medical procedures. Indeed, the large effect size of 0.84 found by the one study in our meta-analysis that used VR as an exposure tool [73], indicates the importance of further research on the effectiveness of VRE. Such psychological preparation is important because anxiety prior to a medical procedure can increase anxiety and pain both during and after the procedure [17, 147, 207]. Moreover, according

to scientific literature, preparing children by means of exposure is more effective in reducing anxiety than providing distraction [57, 58].

PREVIEW: a randomized controlled trial into virtual reality exposure prior to pediatric daycare surgery

As discussed above, very limited research has used VR as an exposure tool prior to medical procedures to increase patients' familiarity with and understanding of medical environments and procedures. We were the first to use a computer-generated VR environment to expose pediatric patients to a highly realistic virtual version of both the preoperative and postoperative environment prior to surgery. A computer-generated VR environment, known as *true* VR, is fully immersive, unlike 360 degree videos in which the user is limited to the filmmaker's movements [87]. True VR allows interaction between the virtual environment and the user, creating a realistic experience, in which children are in control.

In the PREVIEW study (Chapter 3 and Chapter 4), children could explore the preoperative and postoperative environments at their own pace and could become familiar with anesthetic procedures. The analyses contained data of 191 of the 200 children that were included in the RCT. Children were randomly allocated to the VRE intervention (n = 94) or to the CAU control group, receiving routine information on general anesthesia (n = 97). We did not find significant differences between the VRE and CAU groups regarding anxiety, pain, or emergence delirium. However, children in the VRE group who underwent the most painful surgery in our study sample, i.e., adenoidectomy/tonsillectomy [172], needed significantly less often rescue analgesia (morphine) (55%) than in the CAU group (96%). Reducing the need for morphine is of clinical importance, because it has several side effects, such as dizziness, nausea, and vomiting. These side effects not only cause discomfort in patients, but could also be associated with a longer hospital stay [173]. As a result, administering rescue analgesia, such as morphine, is also associated with increased costs of care.

Anxiety

In contrast to earlier studies by Ryu et al. [73, 74], we did not find differences between VRE and CAU in levels of preoperative anxiety. There are two possible explanations for this discrepancy in findings. The first explanation concerns routine care for children at our hospital. All children in our study (in the VRE group and

CAU group) received routine care in a specialized children's hospital that strongly focuses on patient comfort, in line with patient- and family-centered care [35]. For example, all children and their parents were scheduled for a preoperative screening visit with a pediatric anesthesiologist. During this visit, children and parents received elaborate education regarding general anesthesia. In addition, all children and parents could watch an online movie about general anesthesia at home. Moreover, on the day of surgery, children were not separated from their parents, since one of the parents stays present during anesthesia induction and during the postoperative recovery room stay. Thus, in both the VRE and CAU groups, extensive family-centered routine care might have resulted in relatively low anxiety levels. This is confirmed by the fact that anxiety levels, assessed with the modified Yale Preoperative Anxiety Scale (mYPAS), were noticeably lower in our CAU group compared to the CAU groups in the studies of Ryu et al. (26.7 versus 51.7 [74] during baseline and 28.3 versus 51.7 [73] and 46.7 [74] in the holding area). Indeed, these anxiety levels in our study sample are below the values that are internationally recognized to indicate high levels of anxiety (mYPAS ≥ 30 or ≥ 35) [158]. Therefore, the low anxiety levels in our study population make it more difficult to detect a potential treatment effect of VRE.

The second explanation for the discrepancy in findings concerns the content of the virtual environment. Our virtual environment replicates the operating room environment and anesthetic procedures in a very realistic way, without additional gaming elements. Possibly, VRE has a stronger effect on preoperative anxiety in children when VRE includes strong game mechanics. Game mechanics have been shown to be associated with stronger engagement and improved education [176, 177] thus, could possibly also result in more profound anxiety-reducing effects. For example, the VRE environment of Ryu et al. [74] did include game-like challenges and children could receive different rewards (consisting of 'health points').

Pain and rescue analgesia

As described in our systematic review and meta-analysis (Chapter 2), VR has been proven effective to reduce pain. In the PREVIEW study (Chapter 4), we found no differences between VRE and CAU in levels of pain, but we did find that half as many children in the VRE group (55%) needed morphine compared with the CAU group (96%), after undergoing the most painful surgery (adenoidectomy/tonsillectomy) [172]. We will discuss several possible explanations for these discrepancies.

First, because all but one study in our systematic review and meta-analysis [168] used VR as a distraction tool during a medical procedure, the pain-reducing effect of VR may only apply to VR distraction and not to VR exposure. However, this is an unlikely explanation, given the finding that, in the PREVIEW study, VRE was associated with a reduced need for rescue analgesia after the painful operations. Second, levels of pain *after* most types of elective daycare surgery are possibly lower than pain *during* most of the previously studied medical procedures, e.g., burn care and oncological care [168]. This is reflected by the relatively small number of children in our study who experienced considerable levels of pain after surgery. Therefore, preoperative VRE is possibly more effective when children undergo more painful types of surgery, experiencing higher levels of postoperative pain. This is supported by our finding that we only found an effect of VRE on need for rescue analgesia for children undergoing the most painful type of elective daycare surgery, namely adenoidectomy/tonsillectomy.

The most plausible explanation for the discrepancy within the PREVIEW study between results on pain levels and need for rescue analgesia concerns the way postoperative pain was assessed. As postoperative pain was not our primary outcome, we assessed pain in the recovery room only once, without standardizing the moment of assessment in time. Usually, this was at the moment when the child was fully awake. According to local protocol, the recovery room nurses could administer morphine to the patient based on their observation and clinical judgement, i.e., when they thought the child was in pain. As a result, at the moment of pain assessment for the PREVIEW study, morphine could already have been administered. In other words, it is possible that we could not detect a treatment effect for pain, because of adequate pain management at the (one) moment of assessing pain in the recovery room.

The current study does not provide enough insight into the underlying mechanism of preoperative VRE to possibly reduce postoperative pain and need for rescue analgesia. Levels of preoperative anxiety cannot explain the effect of VRE on rescue analgesia, since we found no differences in anxiety between the VRE and CAU groups. Therefore, a possible explanation for the effect of VRE on analgesia could be that children were more familiar with the postoperative recovery environment, as they recognized this from the VRE intervention, which may have distracted them from experiencing pain.

Identification of highly anxious children

Most children (up to 70%) experience anxiety to some extent on the day of surgery [3, 4]. Literature has shown that children with the highest levels of anxiety during anesthesia induction are at the highest risk of maladaptive consequences after surgery, such as increased pain and poorer recovery [13, 19]. It is often not feasible to apply interventions to reduce anxiety, like VRE on the day of surgery, to *all* children, because of busy clinical practice. Therefore, it is important for clinical practice to identify children who will experience high levels of anxiety during anesthesia induction. It is important to do this prior to the day of surgery, or *early on* the day of surgery, i.e., at hospital arrival. With early identification, ideally prior to the day of surgery, enough time is available to reduce or to prevent the increase of anxiety levels in children. VRE is a promising intervention to achieve this, allowing children to virtually explore the operating environment and procedures at their own pace, so they can become accustomed to it.

We have examined standardized tools (Child Behavior Checklist (CBCL), State Trait Anxiety Inventory for Children (STAIC), and mYPAS at hospital arrival to identify children that would be highly anxious during anesthesia induction (Chapter 5). We found that internalizing behavior (CBCL) was not a significant predictor of anxiety during anesthesia induction. However, both the STAIC (state form) and mYPAS at hospital arrival, i.e., parent- and observer-reported state anxiety of the child, were significant predictors of anxiety during anesthesia induction. The STAIC was found to be the strongest predictor and could predict intense levels of anxiety (mean mYPAS during induction + 1 SD) with sufficient to good diagnostic accuracy [208]. In previous literature, mYPAS scores of 30 or 35 have been used as cut-off values for preoperative anxiety, whereas mYPAS scores can range from 23 to 100 [158]. For example, recently, Malik et al. [193] found that 95% of the included 7-12 year-old children was anxious during anesthesia induction, based on a mYPAS cut-off score of 30. Using a relatively low cut-off value often results in a large group of children who are considered anxious during anesthesia induction. However, studies have neglected the important difference in the level of anxiety of children within this group. Therefore, for future studies, we argue that it is also important to focus on highly anxious children by using a higher mYPAS cut-off value, indicating more *intense* levels of anxiety. These results are clinically important, since assessing state anxiety at hospital arrival in a standardized way can help health care professionals to apply interventions in a more targeted way.

Our study provides a first indication that completing the parent-reported version of the STAIC at hospital arrival, an easy-to-use tool, allows us to differentiate between children who will experience intense levels of anxiety, thus need extra attention, versus those who do not. It seems plausible that standard preparation for general anesthesia is sufficient for low anxious children, but high anxious children would benefit from more intensive preparation that takes place earlier in advance of surgery. Also considering time constraints, it would be more useful to identify children who will experience intense levels of anxiety during anesthesia induction earlier in advance of surgery. A suitable instrument for this could be the CBCL, a parent-reported measure of internalizing and externalizing behavior in children. Previous studies have found that internalizing behavior as indicated by the CBCL could predict anxiety during anesthesia induction [23, 93], but we could not replicate these findings. A possible explanation for this discrepancy with previous studies is related to differences in the distributions of socioeconomic status (SES). Previous literature has found that lower SES was related to higher CBCL scores [187], whereas in our study, parents with high SES were over-represented (61.2%). Another explanation could be related to differences in age ranges between our study (4-12 years) and previous studies (1.5-16 years [23] and 11-18-years [93]). Because the way children experience and express anxiety strongly differs with age, the relationship between anxiety during anesthesia induction, internalizing behavior (CBCL), and age may be more complex. Replication studies are needed to establish the relationship between internalizing behavior (CBCL) and anxiety during anesthesia induction in children undergoing surgery.

Clinical implications and future research

The possibilities of VR for clinical settings and for research are far-reaching. Different clinical implications arise concerning VR for pediatric patients, based on this thesis. First, VR distraction is an effective way to reduce pain and anxiety in children undergoing painful medical procedures. This can have a large impact on patients' comfort levels and adherence to (future) health care. However, (VR) distraction is sometimes not possible and literature has shown that exposure is more effective in reducing anxiety than providing distraction [57, 58]. Therefore, VRE is a promising solution. There has been concern that patients may habituate to VR(E), which would mean that repeated exposures to the virtual environment would lose its benefits. Different studies, however, have shown that the effects of VR(E) remained stable over time, or may even increase across sessions [69,

209]. Therefore, VR(E) can also be used on the long term in clinical settings to decrease anxiety and pain in children prior to, during, and after a wide range of medical procedures.

As described earlier, more insight is needed into the underlying mechanism of preoperative VRE to possibly reduce postoperative pain and need for analgesia. Therefore, future studies should include multiple postoperative assessments during different phases of awakening, standardized in time [23]. For example, after painful surgery, pain should be assessed every 10 minutes for one hour postoperatively and three times a day until 72 hours postoperatively [210, 211]. Emergence delirium should be assessed directly upon entering the recovery room, 5, 10, and 15 minutes later [23]. Assessing postoperative outcomes more frequently and more elaborately could provide more insights into the temporal postoperative effects of VRE.

While most studies measured *anxiety* during anesthesia induction [17, 52, 55, 168, 174], some studies measured *compliance* [73, 74]. Since anxiety and compliance are different concepts, a child that is anxious can still be compliant, or the other way around [175]. Discrepancies in measures can lead to discrepancies in outcome. Therefore, for future research, it would be useful to include both outcomes [212].

In the PREVIEW study, we found that only a small proportion of children experienced substantial levels of anxiety and pain before or after elective day care surgery. This may have limited the potential impact of our VRE program. Therefore, it would be interesting for future studies to investigate the effectiveness of VRE on anxiety and pain in children undergoing more complex surgery, with higher levels of (anticipated) anxiety and pain (using multiple postoperative assessments, standardized in time). In addition, future studies should not only include children undergoing surgery in a children's hospital, but also in hospitals with a less strong focus on pediatric care. Possibly, these children benefit more from preoperative VRE.

It is important to take into account children's age when investigating VRE interventions. However, it is difficult to define the optimal age range for such interventions. According to previous literature, younger children experience more preoperative anxiety than older children [4, 19, 89]. In line with this, the results

of our meta-regression on VR interventions showed that VR was possibly more effective in reducing pain and anxiety in young children. VR could be more engaging for younger than for older children, as they become more easily captivated by imaginative play and magical thinking [82, 142]. A different explanation is that younger children are more anxious considering medical procedures [89, 141], leaving more room for improvement. For very young children, however, a VR headset is rather large and heavy and may be uncomfortable to wear. This is reflected in our finding that a substantial number of four- and five-year-old children, took off the VR headset. Children of this age also have a limited attention span, thus our intervention (with a duration of approximately 15 minutes) may have been to lengthy for them. In addition, young children are susceptible to believing that the virtual world is the real world, which may lead to difficulties when re-entering the real world [213, 214]. Taken together, we would suggest for future studies on VR *exposure* interventions to include children aged six years and older, using a lightweight VR headset if possible.

An additional important focus point for future studies on VRE as a preparation tool for surgeries should be the timing and number of sessions of VRE. First, it is possible that children need more time between VRE and surgery, because it can take up to one week for children to process information about the perioperative procedures [39]. Li et al. [10], for example, found that a real life tour of the operating theater a week prior to surgery reduced anxiety during anesthesia induction. Second, one VRE session may not provide sufficient exposure. For example, a meta-analysis on VRE therapies for anxiety disorders (including 16 studies) found a trend that suggested that more VRE sessions are related to a stronger reduction in anxiety levels ($p = 0.06$) [69].

The PREVIEW VRE intervention we have studied only takes 15 minutes, so it seems feasible to implement it in a busy clinical setting. However, as discussed above, it may be more effective to allow children to virtually explore the operating environment and procedures multiple times and earlier in advance of surgery. Because of the limited amount of resources available to use VRE in its current form, a solution could be to change the VRE intervention in a way that makes it more easily accessible and implementable. For example, by developing a smartphone application of the VRE program, which parents and children can download themselves and experience through a portable VR headset. The application can be delivered to all children that

need to undergo surgery and it allows them to be exposed more frequently over a longer time period, at home. This could also be more cost-effective, as it does not require a hospital visit and no health care personnel need to be present. In addition, a smartphone application of the VRE program is more easily implementable in other settings, for example in general hospitals, without specialization in children's care or employment of child life specialists. Possibly, children undergoing surgery in these settings will particularly benefit from preoperative VRE. Taken together, research is needed on the effectiveness of smartphone VRE, on the timing of VRE in relation to the day of surgery, and on the number of VRE sessions that are needed. When developing a new VRE program, future studies should consider taking into account strong game mechanics, because, as discussed earlier, game mechanics are associated with stronger engagement and improved education [176, 177].

PART II: ANXIETY IN CHILDREN UNDERGOING MAGNETIC RESONANCE IMAGING

Undergoing magnetic resonance imaging (MRI) can be an anxiety-evoking procedure for children. MRI is considered the primary diagnostic method for numerous clinical problems [94]. Yet, very limited literature is available on levels of anxiety children experience when undergoing MRI and on the methodological issues MRI-related anxiety may cause. Part II of this thesis (Chapter 6), concerning a large prospective population-based cohort study (the Generation R Study), was aimed at investigating the relationship between internalizing/externalizing behavior, as measured with the CBCL, and MRI-related state anxiety in children. In addition, the association between internalizing/externalizing behavior and MRI research participation was investigated. Finally, we have investigated the impact of internalizing/externalizing behavior and MRI-related anxiety on image quality.

Main findings

We found that, combined over three time points (before a mock scanner, after a mock scanner, and during an actual MRI session), internalizing behavior was significantly associated with MRI-related state anxiety, as reported by the child, parent, and researcher. Externalizing behavior, combined over all time points, was only significantly associated with researcher reported MRI-related state anxiety of the child. Additionally, we have found that children with more internalizing or externalizing problems are less likely to participate in an MRI examination. Finally,

more internalizing problems, externalizing problems, and state anxiety during the MRI procedure were associated with poorer image quality.

Clinical implications and future research

These findings have important clinical implications. MRI-related state anxiety may act as an intervening factor between internalizing behavior and functional MRI (fMRI) responses. Because there is an overlap in brain networks that are activated by pathological, trait, and state anxiety [105-107], MRI-related anxiety may possibly exaggerate fMRI results. Because externalizing behavior is associated with activation in *other* brain networks than state anxiety [108-110], MRI-related state anxiety may also result in misinterpretations concerning externalizing behavior. More specifically, fMRI signals related to state anxiety could be attributed to the externalizing behavior under study. Moreover, as a person may habituate to MRI scanning procedures, MRI-related anxiety may reduce across multiple MRI sessions [200]. Therefore, differences in fMRI responses, associated with differences in MRI-related state anxiety, could possibly be interpreted as a treatment effect.

Our findings indicate that children who participated in the mock MRI session but not in the actual MRI session because they were too anxious, had more internalizing and externalizing problems than children who did participate in the actual MRI session. This indicates a participation bias which could lead to a dilution of the number of participants with strong internalizing or externalizing problems in functional and structural MRI studies. This could result in diminished power of studies to find associations between (f)MRI results and psychiatric symptoms and reduced effect sizes.

In addition, we found that more internalizing and externalizing problems, as well as MRI-related state anxiety, were associated with lower image quality. It has been found that up to 90% of artifacts in MRI scans are the result of subject movement [114]. Therefore, a possible explanation for a more profound relationship between MRI-related state anxiety and image quality in children compared to adults may be the lack of children's understanding of MRI procedures, limited coping strategies to manage stressful situation, and low levels of inhibitory control, which makes it difficult to lie still during the MRI [201, 202]. These findings have important implications, since lower image quality can impair diagnostic quality of MRI scans and may introduce information bias [194, 195].

One way of dealing with MRI-related state anxiety in MRI research could be to statistically correct for it. Options are, for example, to add state anxiety as a covariate to analyses, or to stratify analyses by matching levels of state anxiety. More research is needed into these statistical approaches. However, this approach could be associated with concerns of overcorrecting state anxiety, because of high correlations between state and trait anxiety [105].

On the other hand, it is important to focus on *reducing* MRI-related state anxiety in children. This is not only important for research purposes, but also for clinical purposes. In scientific research, children are always offered the opportunity to opt out of the MRI procedure and highly anxious children will be withdrawn by researchers, because of ethical concerns [111]. However, children with somatic symptoms who need to undergo diagnostic MRIs at the hospital do not have the option to decline undergoing an MRI. Extremely anxious children may even need general anesthesia when undergoing MRI, in order to achieve scans that are of sufficient quality [115]. However, undergoing MRI under general anesthesia is often associated with a delay in diagnostics and increase in costs, because of limited available recourses, such as anesthesiologists, recovery nurses, and inpatient facilities that are needed [112, 116].

Examples of psychological interventions to reduce MRI-related anxiety are (repeated) mock MRI sessions [200] or educational videos [203]. Unfortunately, hospitals often do not use a mock MRI to prepare children. Moreover, if they do, the mock MRI is not easily accessible to *all* children. Therefore, VRE is a promising and innovative solution. Through VRE, children can become gradually accustomed to and familiar with the MRI procedures and noises, in a very realistic manner. Recently, Ashmore et al. [204] have developed a VRE smartphone application, including 360 degree videos, to prepare children for undergoing an MRI. Based on their survey (n = 23), patients (aged 4 to 12 years) found the VRE enjoyable, helpful, and easy to use. Its effectiveness for preparation purposes and reducing anxiety has not been investigated yet. Thus, high quality research is needed to establish the effectiveness of VRE as a preparation tool for undergoing MRI. Future studies should especially focus on the usage of computer-generated (or *true*) VR, instead of 360 degree videos, because the first creates a more realistic experience in which children can stay in control [59]. Since computer-generated VR is more immersive than 360 degree videos, it is possibly also more effective.

08

Summary

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SUMMARY

Medical procedures are often associated with anxiety and pain in children and adolescents. Virtual reality (VR) is an innovative intervention that can be used to prepare patients for, or provide distraction during, medical procedures. In part I (Chapter 2 to 5) of this thesis, we first provide insight into the existing role and effectiveness of VR for children and adolescents undergoing medical procedures (Chapter 2). The primary aim of this thesis is to investigate the effectiveness of virtual reality exposure (VRE) in reducing anxiety and pain in children undergoing elective daycare surgery (Chapter 3 and 4). VRE can be used to expose children to a virtual version of the operating environment and anesthetic procedures, so they can be prepared cognitively and emotionally. In addition, we focus on identifying patients at hospital arrival who will be (highly) anxious during anesthesia induction (Chapter 5). Part II (Chapter 6) of this thesis was aimed at investigating the possible impact of magnetic resonance imaging (MRI) related state anxiety on MRI results in children. More detailed information regarding the aims of the studies in this thesis is provided in the general introduction (Chapter 1).

In Chapter 2, a systematic review and meta-analysis is presented on the effectiveness of VR on reducing pain and anxiety in children and adolescents undergoing medical procedures. The 17 studies that we included in our systematic review used VR as a distraction tool (n = 16) during venous access, dental, burn, or oncological care, or as an exposure tool (n = 1) before elective surgery. The meta-analysis resulted in significant effects of VR on reducing self-reported pain, based on 14 studies, and self-reported anxiety, based on 7 studies. The effect of VR on reducing pain was also significant when observed by caregivers or professionals. Taken together, our systematic review and meta-analysis indicates that VR is an effective distraction intervention to reduce pain and anxiety in children and adolescents undergoing a wide variety of medical procedures. However, further research on the promising effect of VR exposure as a preparation tool for medical procedures is needed because of the paucity of research into this field.

In Chapter 3, a detailed description is given of the PREVIEW study: a single-blind randomized controlled trial to investigate the effectiveness of a VRE tool to psychologically prepare children for undergoing elective daycare surgery under general anesthesia. Previous studies have shown that preoperative anxiety in children is highly prevalent and associated with adverse outcomes, including

anxiety, pain, and a higher need for analgesia after surgery. Gradual exposure is an effective and often used way to reduce anxiety. Through VRE, children can become accustomed to all aspects of the operating complex by gradually exposing them to a virtual version of the operating environment and anesthetic procedures. We have developed an immersive, highly realistic, and child friendly VRE tool that resembles the operating room environment of the Sophia Children's hospital very accurately. Chapter 3 also provides a detailed description of the technical specifications (hardware and software) and the VRE storyline.

In Chapter 4, the results of the PREVIEW study are presented. We included two-hundred children, aged 4 to 12 years, undergoing elective day care surgery under general anesthesia at the Sophia Children's Hospital, between March 2017 and October 2018. Children were randomly assigned to the VRE condition (n = 100) or the control condition (n = 100). Children in the control condition received care as usual (CAU). All children, in both conditions, could watch an informative online movie about general anesthesia, at home. On the day of surgery, children in the VRE condition were exposed to the virtual version of the operating theatre, so that they could get accustomed to the environment and general anesthesia procedures, at their own pace. The primary outcome was anxiety during induction of anesthesia, observed by the blinded researcher (modified Yale Preoperative Anxiety Scale, mYPAS). Secondary outcomes were self-reported anxiety, self-reported and observed pain, emergence delirium (delirium when emerging from general anesthesia), need for rescue analgesia (analgesics in addition to standard analgesics, i.e., morphine), and parental anxiety.

A total of 191 children were included in the analysis. During induction of anesthesia, mYPAS levels were similar in VRE and CAU. In addition, no differences between conditions were found in self-reported anxiety, pain, emergence delirium, or parental anxiety. However, after adenoidectomy/tonsillectomy (the most painful type of surgery in our study), children in the VRE condition needed rescue analgesia (i.e., morphine) significantly less often (55.0%) than in the CAU condition (95.7%).

We concluded that in our study, in children undergoing elective day care surgery, VRE did not have an effect on anxiety, pain, emergence delirium, or parental anxiety. This is possibly due to excellent family-centered perioperative care at the Sophia Children's Hospital as standard. However, after a more painful surgery,

children in the VRE condition needed rescue analgesia significantly less often. This finding is clinically important because of the side effects associated with analgesic drugs. For future research, we recommend to include children with high levels of anxiety and pain and to make VRE preparation available at home, e.g., several days prior to surgery, through a smartphone application.

In children, especially intense levels of anxiety during induction of anesthesia are associated with a higher risk of pain, poor recovery, and emergence delirium. Therefore, in the future, it is important to identify these high-risk children at hospital arrival. This allows targeted interventions to prevent or reduce anxiety during induction of anesthesia.

In Chapter 5 of this thesis, we studied the early identification of children who will experience intense levels of anxiety during anesthesia induction. Therefore, we examined internalizing behavior and state anxiety at hospital arrival as predictors of anxiety during induction of anesthesia in 100 children (aged 4 to 12 years) undergoing elective daycare surgery, who had been randomly assigned to the control condition of the PREVIEW study. Internalizing behavior, reported by parents, was assessed with the internalizing scale of the Child Behavior Checklist (CBCL). Situational anxiety at hospital arrival was assessed by a researcher with the modified Yale Preoperative Anxiety Scale (mYPAS). Parents completed the State Trait Anxiety Inventory for Children (STAIC) concerning situational anxiety of their children. The mYPAS and STAIC at hospital arrival were significant predictors of anxiety during induction, whereas the CBCL was not. The STAIC was the strongest predictor and could identify children experiencing intense levels of anxiety during anesthesia induction, preoperatively. This early identification is of importance, since interventions to reduce anxiety can be provided in a targeted way for children with intense levels of anxiety.

Not only medical treatment procedures, but also medical diagnostic procedures, such as undergoing MRI, often evoke anxiety in children. For example, the loud noises and confined space of the MRI scanner can evoke anxiety. In Chapter 6, we discuss the impact of MRI-related state anxiety on MRI-results. In functional MRI studies, signals could be attributed to the behavior under study, while they are likely partially related to state anxiety induced by the MRI procedure. In addition, anxious children may be less likely to participate in MRI research, leading to a

possible selection bias. Moreover, anxious children may be more likely to move during image acquisition, resulting in lower image quality and possible information bias. Therefore, state anxiety can be problematic for functional and structural MRI studies. We included 1,241 six- to ten-year-old children of the Generation R study who underwent a mock MRI. Afterwards, the children underwent an actual MRI (n = 1,070), unless they reported to be very scared during the mock MRI, or in case a parent or researcher observed this. Internalizing and externalizing problems were assessed with the CBCL, prior to the MRI procedure. State anxiety was assessed with a visual analogue scale. Analyses indicated that internalizing and externalizing problems were positively associated with child state anxiety during the actual MRI, as reported by child, parent, and researcher. Internalizing and externalizing problems, as well as MRI-related state anxiety were associated with impaired image quality. In addition, children who did not participate in the actual MRI had more internalizing and externalizing problems than children who did. These results underscore the methodological issues caused by MRI-related state anxiety in children, as well as the importance of statistically correcting for state anxiety. Finally, it is important to develop effective interventions to reduce MRI-related state anxiety.

Chapter 7 provides a general discussion concerning the previous chapters, clinical implications of the findings, and directions for future research. More insight is needed into the underlying mechanism of the postoperative effects of preoperative VRE. Hence, future VRE studies should include multiple assessments postoperatively, standardized in time. In addition, VRE may be more effective when children can explore the virtual environment multiple times and earlier in advance of surgery. Developing a smartphone application of the VRE program, which parents and children can download themselves, for a portable VR headset may offer a solution. This way, children can be exposed more frequently over a longer time period, at home. VRE could also be used to prepare patients for an MRI scan. Therefore, studies are needed to establish the effectiveness of VRE as a preparation tool for undergoing MRI.

SAMENVATTING

Het ondergaan van medische behandelingen en ingrepen gaat vaak gepaard met angst en pijn bij kinderen en adolescenten. Virtual reality (VR) is een innovatieve interventie die ingezet kan worden om patiënten voor te bereiden op, of om afleiding te bieden tijdens, medische behandelingen en ingrepen. In deel I (Hoofdstuk 2 tot en met 5) van dit proefschrift bieden we eerst inzichten in de bestaande rol en effectiviteit van VR voor kinderen en adolescenten die medische behandelingen en ingrepen ondergaan (Hoofdstuk 2). Het primaire doel van dit proefschrift is om de effectiviteit van virtual reality exposure (VRE) te onderzoeken om angst en pijn te verminderen bij kinderen die een electieve operatie ondergaan in dagbehandeling (Hoofdstuk 3 en 4). Middels VRE kunnen kinderen worden blootgesteld aan een virtuele versie van de operatie-omgeving en de anesthesieprocedures. Zo kunnen ze hier cognitief en emotioneel op worden voorbereid. We richten ons tevens op het identificeren van patiënten bij aankomst in het ziekenhuis die (zeer) angstig zijn tijdens de inductie van de anesthesie (Hoofdstuk 5). Deel II (Hoofdstuk 6) van dit proefschrift richt zich op het onderzoeken van de mogelijke impact van magnetic resonance imaging (MRI) gerelateerde situationele angst op MRI resultaten bij kinderen. Gedetailleerdere informatie met betrekking tot de doelen van de studies in dit proefschrift worden omschreven in de algemene introductie (Hoofdstuk 1).

In Hoofdstuk 2 wordt een systematisch review en meta-analyse gepresenteerd over de effectiviteit van VR op het verminderen van pijn en angst bij kinderen en adolescenten die een medische behandeling of ingreep ondergaan. De 17 studies die we geïncludeerd hebben in onze systematisch review gebruikten VR als afleidingsmethode (n = 16) tijdens venapunctie, tand-, brandwonden- of oncologische zorg, of als exposure (blootstelling) methode (n = 1) voorafgaand aan een electieve operatie. De meta-analyse resulteerde in significante effecten van VR op het verminderen van zelfgerapporteerde pijn, gebaseerd op 14 studies, en zelfgerapporteerde angst, gebaseerd op 7 studies. Het effect van VR op het verminderen van pijn was ook significant wanneer deze geobserveerd werd door verzorgers en door medisch personeel. Resumerend, toont onze systematisch review en meta-analyse aan dat VR een effectieve afleidingstechniek is om pijn en angst te verminderen bij kinderen en adolescenten die uiteenlopende medische procedures ondergaan. Echter, meer onderzoek is nodig naar het veelbelovende effect van VR exposure ter voorbereiding op medische procedures, vanwege het gebrek aan onderzoek op dit gebied.

In Hoofdstuk 3 wordt een gedetailleerde beschrijving gegeven van de PREVIEW studie. Dit is een enkelblind gerandomiseerd gecontroleerd onderzoek om de effectiviteit te onderzoeken van een VRE programma om kinderen psychologisch voor te bereiden op het ondergaan van een electieve operatie in dagbehandeling onder algehele anesthesie. Eerder onderzoek heeft aangetoond dat preoperatieve angst bij kinderen vaak voorkomt en geassocieerd is met nadelige uitkomsten, zoals angst, pijn en een grotere behoefte aan pijnmedicatie na de operatie. Geleidelijke exposure is een effectieve en vaak gebruikte manier om angst te reduceren. Middels VRE kunnen kinderen gewend raken aan alle aspecten van het operatiecomplex door ze geleidelijk bloot te stellen aan een virtuele versie van de operatie-omgeving en de anesthesieprocedures. We hebben een zeer realistisch en kindvriendelijk VRE programma ontwikkeld, met hoge mate van immersie (letterlijk: onderdompeling). Hierin wordt de operatie-omgeving van het Sophia Kinderziekenhuis zeer nauwkeurig nagebootst. In Hoofdstuk 3 wordt tevens een gedetailleerde beschrijving gegeven van de technische specificaties (hardware en software) en van de VRE verhaallijn.

In Hoofdstuk 4 worden de resultaten van de PREVIEW studie gepresenteerd. Er zijn tweehonderd kinderen, in de leeftijd van 4 tot en met 12 jaar, geïncludeerd die tussen maart 2017 en oktober 2018 een electieve operatie in dagbehandeling ondergingen in het Sophia Kinderziekenhuis. Kinderen werden willekeurig toegewezen aan de VRE groep (n = 100) of de controlegroep (n = 100). Kinderen in de controlegroep kregen reguliere zorg (care as usual; CAU). Alle kinderen, in beide groepen, konden thuis een informatieve online film bekijken over algehele anesthesie. Op de dag van de operatie werden kinderen in de VRE groep blootgesteld aan de virtuele versie van het operatiecomplex, zodat ze op hun eigen tempo gewend konden raken aan de omgeving en aan de procedures omtrent algehele anesthesie. De primaire uitkomstmaat was angst tijdens inductie van de anesthesie, geobserveerd door de geblindeerde onderzoeker (modified Yale Preoperative Anxiety Scale; mYPAS). Secundaire uitkomstmaten waren zelf-gerapporteerde angst, zelf-gerapporteerde en geobserveerde pijn, emergence delirium (delier na het ontwaken uit de algehele anesthesie), behoefte aan rescue analgetica (analgetica bovenop onderhouds-pijnmedicatie; morfine) en ouderlijke angst.

In totaal werden data van 191 kinderen meegenomen in de analyses. Tijdens inductie van de anesthesie waren mYPAS scores gelijk in de VRE en CAU groep. Er werden

ook geen verschillen gevonden tussen de groepen in zelf-gerapporteerde angst, pijn, emergence delirium, of ouderlijke angst. Echter, na (adeno)tonsillectomie (de pijnlijkste ingreep in onze studie), hadden kinderen in de VRE groep significant minder vaak rescue analgetica (morfine) nodig (55.0%) dan in de CAU groep (95.7%).

We kunnen concluderen dat in onze studie, bij kinderen die een electieve operatie in dagbehandeling ondergingen, VRE geen effect had op angst, pijn, emergence delirium of ouderlijke angst. Dit komt mogelijk door de goede familiegerichte perioperatieve zorg in het Sophia Kinderziekenhuis die standaard wordt toegepast. Echter, na een pijnlijkere operatie hadden kinderen in de VRE groep significant minder vaak rescue analgetica nodig. Deze bevinding is van klinisch belang vanwege de bijwerkingen van analgetica. Voor toekomstig onderzoek bevelen we aan om kinderen te includeren met hoge mate van angst en pijn. Ook bevelen we aan om de VRE voorbereiding thuis te laten plaatsvinden, bijvoorbeeld enkele dagen voorafgaand aan de operatie, middels een smartphone applicatie.

Hoge mate van angst tijdens inductie van anesthesie bij kinderen houdt sterk verband met een hoger risico op pijn, slecht herstel en emergence delirium. Het is daarom voor de toekomst belangrijk om deze kinderen met een verhoogd risico te identificeren bij aankomst in het ziekenhuis. Op deze manier kunnen gerichte interventies worden toegepast om angst tijdens inductie van anesthesie te voorkomen of te verminderen.

In Hoofdstuk 5 van dit proefschrift wordt de vroegtijdige identificatie onderzocht van kinderen die een hoge mate van angst zullen hebben tijdens inductie van anesthesie. Hiervoor hebben we internaliserend gedrag en situationele angst bij aankomst in het ziekenhuis onderzocht als voorspellers van angst tijdens inductie van anesthesie bij 100 kinderen (in de leeftijd van 4 tot en met 12 jaar) die een electieve operatie in dagbehandeling ondergingen. Zij waren willekeurig toegewezen aan de controlegroep van de PREVIEW studie. Internaliserend gedrag, gerapporteerd door de ouder, werd gemeten met de internaliserende schaal van de Child Behavior Checklist (CBCL). Situationele angst bij aankomst in het ziekenhuis werd beoordeeld door een onderzoeker met de modified Yale Preoperative Anxiety Scale (mYPAS). Bij de ouder werd de State Trait Anxiety Inventory for Children (STAIC) afgenomen over de situationele angst van het kind. De mYPAS en STAIC bij aankomst in het ziekenhuis bleken significante voorspellers van angst tijdens

inductie, terwijl de CBCL geen voorspeller bleek. De STAIC was de beste voorspeller en kon kinderen met een hoge mate van angst tijdens anesthesie inductie preoperatief identificeren. Het vroegtijdig identificeren van angstige kinderen is van belang, omdat interventies om angst te verminderen zo gericht kunnen worden aangeboden aan kinderen met hoge mate van angst.

Niet alleen medische behandelingen en ingrepen, maar ook medische diagnostische procedures, zoals het ondergaan van een MRI, wekken vaak angst op bij kinderen. Dit kan bijvoorbeeld worden veroorzaakt door het lawaai en de nauwe ruimte van de MRI scanner. In Hoofdstuk 6 bespreken we de impact van MRI-gerelateerde situationele angst op MRI uitkomsten. In functionele MRI onderzoeken kunnen signalen worden toegeschreven aan het gedrag dat wordt bestudeerd, terwijl ze mogelijk gedeeltelijk verband houden met situationele angst die door de MRI procedure wordt veroorzaakt. Daarnaast zijn angstige kinderen minder geneigd om deel te nemen aan MRI onderzoek, wat mogelijk leidt tot een selectiebias. Bovendien zullen angstige kinderen mogelijk meer geneigd zijn om te bewegen tijdens beeldopnames, wat resulteert in een lagere beeldkwaliteit en mogelijk in informatiebias. Om deze redenen kan situationele angst problematisch zijn voor functionele en structurele MRI onderzoeken. We hebben 1.241 zes- tot tien-jarige kinderen van de Generation R studie geïncludeerd die een oefen MRI ondergingen. Nadien ondergingen de kinderen een echte MRI (n = 1.070), tenzij ze zelf aangaven dat ze erg bang waren tijdens de oefen MRI, of als een ouder of onderzoeker dit observeerde. Internaliserende en externaliserende problemen werden beoordeeld met de CBCL, voorafgaand aan het MRI onderzoek. Situationele angst werd beoordeeld met een visueel analoge schaal. Analyses laten zien dat internaliserende en externaliserende problemen positief geassocieerd zijn met situationele angst bij kinderen tijdens de daadwerkelijke MRI, zoals gerapporteerd door kind, ouder en onderzoeker. Internaliserende problemen, externaliserende problemen en MRI-gerelateerde situationele angst, hielden verband met verminderde beeldkwaliteit. Bovendien hadden kinderen die niet deelnamen aan de daadwerkelijke MRI meer internaliserende en externaliserende problemen dan kinderen die dat wel deden. Deze resultaten benadrukken de methodologische problemen die veroorzaakt worden door MRI-gerelateerde situationele angst bij kinderen. Ook benadrukken ze het belang om in analyses te corrigeren voor situationele angst. Bovendien is het belangrijk om effectieve interventies te ontwikkelen om MRI-gerelateerde situationele angst te verminderen.

Hoofdstuk 7 omvat een algemene discussie over de vorige hoofdstukken, klinische implicaties van de bevindingen en aanbevelingen voor toekomstig onderzoek. Er is meer inzicht nodig in het onderliggende mechanisme van de postoperatieve effecten van preoperatieve VRE. Daarom moeten toekomstige VRE studies gebruik maken van meerdere postoperatieve meetmomenten, die gestandaardiseerd zijn in tijd. Bovendien is VRE mogelijk effectiever wanneer kinderen de virtuele omgeving meerdere keren en langer op voorhand kunnen verkennen. Het ontwikkelen van een smartphone VRE applicatie, die ouders en kinderen zelf kunnen downloaden, voor een draadloze VR headset kan daarom uitkomst bieden. Op deze manier kunnen kinderen thuis, gedurende een langere periode, meerdere keren worden blootgesteld. VRE zou tevens gebruikt kunnen worden om patiënten voor te bereiden op het ondergaan van een MRI. Er zijn daarom studies nodig om de effectiviteit van VRE vast te stellen als voorbereidingsmethode voor een MRI scan.

A

Appendices:

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Author affiliations

Publications

PhD portfolio

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Dankwoord

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PUBLICATIONS

Eijlers R, Legerstee JS, Dierckx B, Staals LM, Berghmans JM, van der Schroeff MP, Wijnen RWM, Utens EMWJ (2017). Development of a virtual reality exposure tool as psychological preparation for elective pediatric day care surgery: Methodological approach for a randomized controlled trial. Journal of Medical Internet Research - Research Protocols, 6 (9), e174. doi: 10.2196/resprot.7617

Eijlers R, Dierckx B, Legerstee JS, Staals LM, Utens EMWJ (2017). Voorbereiden op een operatie met virtual reality. Kinderverpleegkunde V&VN, 23 (3).

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Eijlers R, Dierckx B, Staals LM, Berghmans JM, van der Schroeff MP, Strabbing EM, Wijnen RWM, Hillegers MHJ, Legerstee JS, Utens EMWJ (2019). The effect of virtual reality exposure before elective day care surgery in reducing anxiety and pain in children: a randomized controlled trial. European Journal of Anaesthesiology, 36 (10), 728. doi: 10.1097/EJA.0000000000001059

Eijlers R, Staals LM, Legerstee JS, Berghmans JM, Strabbing EM, van der Schroeff MP, Wijnen RWM, Kind LS, Hillegers MHJ, Dierckx B, Utens EMWJ (2020). Predicting intense levels of child anxiety during anesthesia induction at hospital arrival. Journal of Clinical Psychology in Medical Settings, advance online publication.

Eijlers R, White T, Utens EMWJ, Tiemeier H, Staals LM, Berghmans JM, Wijnen RMH, Hillegers MHJ, Legerstee JS, Dierckx B (2019). Internalizing and externalizing behavior in school-aged children are related to state anxiety during magnetic resonance imaging. Submitted for publication.

PHD PORTFOLIO

Name PhD student:	Robin Eijlers
Erasmus MC department:	Child and Adolescent Psychiatry/Psychology
Research school:	NIHES
PhD period:	September 2016 – November 2019
Promotors:	Prof. dr. E.M.W.J. Utens Prof. dr. M.H.J. Hillegers
Supervisors:	Dr. B. Dierckx Dr. J.S. Legerstee

	Year	Workload (ECTS)
1. PhD training		
General academic skills		
Systematic Literature Retrieval in PubMed, Medical library Erasmus MC	2016	0.5
Basic course on Regulations and Organization for clinical investigators (eBROK®), Erasmus MC	2017	1.5
Scientific integrity, Erasmus MC	2017	0.3
CPO Patient Oriented Research: design, conduct and analysis, Erasmus MC	2017	0.3
Specific research skills		
LimeSurvey and GemsTracker, Erasmus MC	2017	0.5
Regression Analysis (ESP09), NIHES	2017	1.9
Training in scoring the mYPAS instrument (preoperative anxiety), Queen Paola Children's Hospital, Antwerp, Belgium	2017	0.5
Presentations Erasmus MC		
Pediatric Care (child life specialists)	2016	0.3
Research Meeting Pediatric Psychology	2016	0.3
Research Work Meeting Child and Adolescent Psychiatry/Psychology	2016	0.3
Pediatric Day Care Unit	2017	0.3
Anesthesiology Science Day	2017	0.3
Sophia Children's Hospital: Kick-off PREVIEW Study (demonstration)	2017	0.3
Oral and Maxillofacial surgery	2017	0.3
Studium Generale Lunch Lecture: Medical Future	2017	0.3
Colloquium Child and Adolescent Psychiatry/Psychology	2018	0.3
Sophia Research Day (plenary session)	2018	0.3
Developmental Disorders Meeting Child and Adolescent Psychiatry/ Psychology	2018	0.3
Child Anesthesiology	2018	0.3
Child and Adolescent Psychiatry/Psychology, polyclinic	2019	0.3

	Year	Workload (ECTS)
External presentations		
Dutch Association for Behavioral and Cognitive Therapy (VGCt) Autumn Congress, Veldhoven, The Netherlands	2017	1.0
Brilliant Failures in Healthcare (demonstration), Den Haag, The Netherlands	2017	1.0
Dutch Association of Anesthesiology (NVA), section Pediatric Anesthesiology, Summer Congress, Wageningen, The Netherlands	2018	1.0
European Pediatric Psychology Conference (poster), Ghent, Belgium	2018	1.0
26th IEEE Conference on Virtual Reality and 3D User Interfaces, Applied Virtual Reality for Enhanced Healthcare (workshop), Osaka, Japan	2019	1.0
12th Dutch North Sea Emergency Medicine Conference, Egmond aan Zee, The Netherlands	2019	1.0
European Pediatric Surgeons' Association Congress (poster and oral presentation), Belgrade, Serbia	2019	1.5
European Society for Pediatric Anesthesiology Congress (best abstract session), Rotterdam, The Netherlands	2019	1.0
Attended Conferences and Symposia		
Pediatric Psychology Network Conference, Utrecht, The Netherlands	2016 – 2017	0.6
Dutch Association for Behavioral and Cognitive Therapy (VGCt) Autumn Congress, Veldhoven, The Netherlands	2017	0.5
Brilliant Failures in Healthcare, Den Haag, The Netherlands	2017	0.3
Dutch Association of Anesthesiology (NVA), meeting section Pediatric Anesthesiology, Wageningen, The Netherlands	2018	0.3
European Pediatric Psychology Conference, Ghent, Belgium	2018	0.5
26th IEEE Conference on Virtual Reality and 3D User Interfaces, Osaka, Japan	2019	1.0
European Pediatric Surgeons' Association, Belgrade, Serbia	2019	1.0
Workshops, meetings, and seminars		
Research Work Meetings Child and Adolescent Psychiatry/Psychology, Erasmus MC	2016 – 2019	2.0
Research Meetings Pediatric Psychology, Erasmus MC	2016 – 2019	0.5
Clinical & Research Meetings Pediatric Psychology, Erasmus MC	2016	0.5
Science Café Child and Adolescent Psychiatry/Psychology, Erasmus MC	2016 – 2019	1.5
Erasmus Tour Sophia Researchers Board, Erasmus MC	2016	0.2
Symposium prof. dr. F.C. Verhulst, Rotterdam, the Netherlands	2017	0.2
PhD Day, Erasmus MC	2017 – 2019	0.6
Sophia Research Day, Erasmus MC	2017 – 2019	1.0
Pitch your PhD workshop, Erasmus MC	2017	0.2
Presentation skills, TULIPS for Child Health, Culemborg, the Netherlands	2017	0.2
Informed consent for children, TULIPS for Child Health, Culemborg, the Netherlands	2017	0.2

	Year	Workload (ECTS)
2. Teaching		
Supervising Master's theses and research interns		
Lesley Ringerwöle (Psychology, Erasmus University Rotterdam): *Voorspellers van de Effectiviteit van Virtual Reality Exposure als Psychologische Voorbereiding op een Operatie bij Kinderen*	2017	1.5
Betül Özkaya (Psychology, Erasmus University Rotterdam): *Virtual Reality Exposure en Preoperatieve Angst bij Kinderen en Ouders*	2017	1.5
Anastasiya Burdina	2017	0.5
Naomi Schaap (Medicine, Erasmus MC): *Relatie tussen de angstbeleving van ouder en kind voorafgaand aan een operatie*	2017 – 2018	1.5
Mirai den Dunnen (Medicine, Erasmus MC): *The Relationship between Pediatric and Parental Anxiety before Elective Surgery*	2018	1.5
Abiya Sellathurai	2018	1.0
Martina Huisman	2018 – 2019	1.0
Annemarie van der Kaaij (Psychology, Erasmus University Rotterdam): *Insights in predictors for anxiety at hospital arrival in Dutch children undergoing day care surgery using the Child Behavior Checklist (CBCL)*	2018 – 2019	1.5
Other teaching activities		
Writing a systematic review, medical students Erasmus MC	2016 – 2017	2
Practical: Social interaction, medical students Erasmus MC	2019	0.7

ECTS – European Credit Transfer and Accumulation System

1 ECTS represents 28 hours

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ABOUT THE AUTHOR

Robin Eijlers was born on January 27th, 1990 in Vlissingen, The Netherlands, as the daughter of Ronald and Anita. She grew up in Vlissingen together with her older sister Esther. In 2008, she completed her secondary education (gymnasium) at CSW Elzenlaan in Middelburg. Directly after that, she moved to Rotterdam to study Psychology at the Erasmus University Rotterdam (EUR). She specialized in Biological and Cognitive Psychology for both her bachelor's and master's program. During her studies, Robin worked as a research assistant at the Institute for Psychology at the EUR for a study on early detection of psychosocial problems in children. In 2012, she obtained her master's degree cum laude, i.e., with distinction. After graduating, she worked on several research projects at the Rotterdam Ophthalmic Institute, which is part of the Rotterdam Eye Hospital, and at MetrixLab, a global digital market research agency. In September 2016, she started her PhD at the department of Child and Adolescent Psychiatry/Psychology of the Erasmus MC – Sophia Children's Hospital in Rotterdam, which has resulted in the work described in this thesis. Her project was supervised by prof. dr. E.M.W.J. Utens, prof. dr. M.H.J. Hillegers, dr. B. Dierckx, and dr. J.S. Legerstee. Whilst completing her thesis, in October 2019, she started working part-time at PlayFit Rotterdam, a social sports organization, as both a researcher and a children's gymnastics coach. She still continues her work as a researcher at PlayFit, focusing on equal opportunities for all children to participate in sports. In August 2020, Robin started as a project leader at the EUR for the Student Wellbeing Program. Her ambition is to have an impact on mental, physical, and cognitive health of the next generation of professionals. Robin is enjoying life in Rotterdam, together with her boyfriend James. They met during their studies, just over ten years ago.