Evaluation of the Effectiveness of Virtual Reality Exposure Therapy (VRET)
in the Management of Anxiety about Dental Treatment

Evaluation of the Effectiveness of Virtual Reality Exposure Therapy (VRET) in the Management of Anxiety about Dental Treatment

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Chapter 1. General introduction

Some tortures are physical, and some are mental,
But the one that is both, Is dental – Ogden Nash

1.1 Introduction

The physical unpleasantness of dentistry has largely been conquered by developments in dentistry such as minimally invasive techniques and modern anesthetics (Öst & Skaret, 2013). However, the psychological agony manifesting itself in the form of dental anxiety is still a fairly common condition worldwide (Smith & Heaton, 2003), and effective methods to treat the extreme form of dental anxiety, i.e., dental phobia, are still in nascent stages. The core theme of this thesis is to explore the applicability of Virtual Reality Exposure Therapy (VRET) in the treatment of severe dental anxiety and dental phobia. This chapter discusses the relevant background to provide a context to the rest of this thesis. First, I describe the prevalence, etiology, maintenance and consequences of dental anxiety and dental phobia. This is followed by a summary of current treatment strategies for both conditions and their limitations. Next, I will provide a background for the need of investigating VRET for the treatment of dental phobia. Finally, I present the objectives and a brief outline of the studies that form the essential components of this thesis.

1.2 Dental anxiety, dental fear and dental phobia

Constructs like "fear", "anxiety" and "(specific) phobia" are related and represent the continuum of fear and anxious behavior (De Jongh, Oosterink, Kieffer, Hoogstraten, & Aartman, 2011). Therefore, to develop suitable strategies for the treatment of dental anxiety and dental phobia, identification and proper assessment of the fearful behavior towards dental situations is crucial.

1.2.1 Fear and anxiety

Fear as defined by ethologists is a basic emotional state of motivation triggered by a specific stimulus that causes activation of "fight or fright response" (Cannon, 1915) resulting in defensive behavior or escape (McFarland, 1987). Thus, dental "fear" is an emotional response to *specific* dental situations. Fears related to dental treatment are heterogeneous in nature, and there is evidence suggesting that these

represent a three-factor structure (van Houtem et al., 2017) consisting of: (a) fear of invasive or pain-associated dental treatment, such as undergoing extraction or root canal treatment of a tooth, dentist drilling a tooth, cutting or tearing soft tissue, undergoing surgery and insufficient anesthetic during dental treatment; (b) feeling of loss of control, such as lying in the dental chair and not knowing what's happening in the mouth, lack of explanation by dentist and feeling helpless and (c) experiencing unpleasant physical (bodily) sensations such as gagging, vomiting or fainting while undergoing dental treatment (van Houtem et al., 2017).

While dental "fear" refers to the emotional response to real or perceived imminent threat, anxiety is the anticipation of future threat" (American Psychiatric Association, 2013), and is considered to be a normal reaction to stress and a positive adaptive response that can be beneficial for alerting one to potential dangers and aiding in preparation to ward off that danger (American Psychiatric Association, 2018).

1.2.2 Types of anxiety

The construct "anxiety" encompasses two distinct types: state anxiety and trait anxiety. State anxiety refers to a transient, situation-specific emotional response towards a frightening situation that is characterized by feelings of tension and apprehension and an increased activation of the autonomic nervous system (Spielberger, 1966). Conversely, trait anxiety is the general tendency of an individual to respond to perceived threats and is a relatively stable characteristic of an individual (Spielberger, 1966). People with a high level of trait anxiety are more inclined to respond to perceived threats with a greater elevation in state anxiety than individuals with a low degree of trait anxiety (Spielberger, 1966). Thus, dental trait anxiety refers to a general tendency of an individual to experience anxiety towards a variety of dental situations and perceiving them to be threatening or dangerous.

1.2.3 Phobia

"Phobia" is a disproportionate form of anxiety (American Psychiatric Association, 2013). When the elevated level of avoidance towards dental procedures or distress from dental objects interferes an individual's normal social and occupational functioning, the condition is likely to meet the DSM-5 diagnostic criteria of specific phobia. Dental phobia can be diagnosed by undertaking a structured clinical interview as per the DSM-5 criteria (American Psychiatric Association, 2013). To this end, seven criteria must be satisfied: a) a marked and disproportionate fear within a situational or environmental context to either the presence or anticipation of (dental) objects or situations; b) an immediate anxiety response following

exposure to the phobic (dental) stimulus; c) fear that is out of proportion; d) extreme avoidance towards phobic dental stimuli; e) avoidance behavior, anxious anticipation of pain or distress that interferes with an individual's daily routine such as social activities or relationships, occupational (or academic) functioning or causes pronounced distress due to phobia; f) the duration of phobia for all ages should be at least 6 months; and g) the symptoms of phobia cannot by attributed to any other mental conditions.

Given that the terms 'dental anxiety' and 'dental fear' are used interchangeably in the literature (Asl, Shokravi, Jamali, & Shirazi, 2017; Beaton, Freeman, & Humphris, 2014), in this thesis "dental anxiety" denotes all forms of emotional apprehension in anticipation of any dental situation, whereas a pathological form of anxiety that fits the DSM diagnostic criteria of dental phobia is referred to as "dental phobia".

1.3 Tools for measurement of Dental anxiety and Dental phobia

1.3.1 Dental anxiety

Some of the most popular tools for measuring the severity of dental trait anxiety are the Dental Anxiety Scale (DAS), the Modified Dental Anxiety Scale (MDAS), the Dental Fear Scale (DFS) and the Spielberger Trait Anxiety Scale (STAI-T) (Corah, 1969; Humphris, Morrison, & Lindsay, 1995; Kleinknecht, Klepac, & Alexander, 1973; Kleinknecht, Thorndike, McGlynn, & Harkavy, 1984; Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983). The MDAS consists of five items assessing anticipatory dental anxiety, fear of dental scaling, drills and injection on a five-point Likert scale ranging from 0 ("not anxious") to 5 ("extremely anxious") (see Figure 1.1; (Beaton et al., 2014; Humphris, Crawford, Hill, Gilbert, & Freeman, 2013). The cumulative score ranges from 5-25 with greater scores suggestive of a more severe level of dental anxiety. The MDAS has proved to have high level of internal consistency and construct validity (Humphris, Freeman, Campbell, Tuutti, & D'Souza, 2000).

Another internationally widely-used measure for assessing the level of dental trait anxiety is the Dental Fear Scale (DFS). It is a 20-item questionnaire evaluating an individual's emotional, physiological reactions and avoidance towards dentistry on a 5-point scale ranging from 0 ("not at all") to 5 ("very much"). The possible cumulative score ranges from 20-100, with scores above 70 being suggestive of dental phobia (Hakeberg & Berggren, 1997). The DFS has been shown to be a sensitive, reliable and valid measure for assessing severity of dental anxiety in research (Davis, Ollendick, & Öst, 2012; Schuurs & Hoogstraten, 1993). In order to comprehensively evaluate an individual's level of dental anxiety in the clinical setting, and for research, it is recommended to use more than one measure (Schuurs & Hoogstraten, 1993).

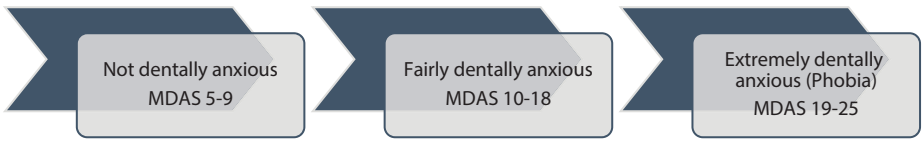

Figure 1.1 Depicting the cut-off ranges for dental anxiety and dental phobia.

Hence, in the present thesis, the severity of dental trait anxiety was indexed using both aforementioned measures (i.e., the MDAS and the DFS).

1.3.2 State anxiety

A frequent way to assess the transient anxiety response towards specific dental situations (i.e., state anxiety) used in most of the studies including the present thesis, is the use of the Visual Analogue Scale- Anxiety (VAS-A;(Luyk, Beck, & Weaver, 1988). The patient is requested to select a point (usually by putting a cross mark X) on a 0-100 mm line representing a scale ranging from totally calm and relaxed (0) to the worst fear imaginable (100) as depicted in Figure 1.2. It is considered to be a simple, sensitive, fast, reliable and valid tool for state dental anxiety assessment (Facco et al., 2011).

1.3.3 Assessing dental phobia

Although the MDAS and the DFS are both measures of dental anxiety, and are fairly easy and quick to use (Humphris et al., 1995; Newton & Edwards, 2005), these cannot be used for diagnostic purposes in terms of assessing dental phobia (King & Humphris, 2010; Oliveira, Bendo, Paiva, Vale, & Serra-Negra, 2015). As described above in section 1.1.3, a diagnosis of specific (dental) phobia needs to be established by conducting a structured clinical interview as per the DSM-5 criteria performed by a psychiatrist or psychologist.

A simpler tool that has proved to be reliable and valid for screening purposes is the "Phobia Checklist" (Oosterink, de Jongh, & Hoogstraten, 2009) which has initially been adapted from the DSM-4 criteria for specific phobia (American Psychiatric Association, 2000). The Phobia Checklist requires the patients to mark either "Yes" or "No" in response to four questions involving DSM criteria. A 'Yes' response to all four questions of this checklist makes the presence of dental phobia very likely. To this end, the Phobia Checklist has been validated against the Structured Clinical Interview for DSM-4 (First, & Gibbon., 2004) with a sensitivity of 0.95, specificity of 0.99, and an overall hit rate of 97% (Oosterink et al., 2009).

In the present thesis, recruited individuals were assessed for the possible presence of dental phobia using the Phobia Checklist criteria (Oosterink et al., 2009).

I.....I
(100mm)
Totally calm and relaxed Worst fear imaginable

Figure 1.2 Visual Analogue Scale-Anxiety (Luyk et al., 1988).

1.4 Prevalence

1.4.1 Prevalence of dental anxiety

Estimates of higher dental anxiety and dental avoidance in general population has been found to be ranging from 4-17% (Armfield, 2010; Dou et al., 2018; Eitner, Wichmann, Paulsen, & Holst, 2006; Enkling, Marwinski, & Johren, 2006; Fayad, Elbieh, Baig, & Alruwaili, 2017; Gatchel, Ingersoll, Bowman, Robertson, & Walker, 1983; Hallstrom & Halling, 1984; Halonen, Salo, Hakko, & Rasanen, 2014; Liddell & Locker, 1997; Locker & Liddell, 1991; Nicolas, Collado, Faulks, Bullier, & Hennequin, 2007; Saatchi, Abtahi, Mohammadi, Mirdamadi, & Binandeh, 2015; Sitheeque, Massoud, Yahya, & Humphris, 2015; Stouthard & Hoogstraten, 1990). However, there is considerable variability in the methods, measures and criteria used. The majority of the studies that applied measures of dental trait anxiety have used variable cut-offs to ascertain the severity of dental anxiety (Dou et al., 2018; Fayad et al., 2017; Halonen et al., 2014; Saatchi et al., 2015; Sitheeque et al., 2015). This makes it difficult to estimate through these scales the relative prevalence of individuals with either severe dental anxiety or dental phobia who require immediate attention. An agreed system to address the above concerns is the use of the established standardized DSM-criteria for diagnosing individuals with dental phobia (American Psychiatric Association, 2013).

1.4.2 Prevalence of dental phobia

Only a limited number of studies have used the valid DSM-IV specific phobia criteria for the purpose of either assessing dental phobia or estimating the prevalence of this condition within samples or population groups (Fredrikson, Annas, Fischer, & Wik, 1996; Oosterink et al., 2009; Stinson et al., 2007). Stinson and colleagues estimated that about 2.4% percent of the population fulfills the diagnostic criteria of dental phobia based upon the DSM-IV diagnostic criteria for specific phobia (Stinson et al., 2007). Research from the Netherlands suggests that around 4% of the general population (Oosterink et al., 2009) satisfies the criteria for dental phobia as indexed using the Phobia Checklist. In Sweden Fredrickson et al (1996), used a three item checklist based on DSM IV criteria for specific phobia, and reported that 2.1% and 1.6% of the population may be phobic towards dentists or injections respectively (Fredrikson et al., 1996).

1.5 Etiology and maintenance of dental anxiety and dental phobia

The acquisition of anxiety and phobia is best described by *classical conditioning theory* (Pavlov & Gantt, 1928). Within this paradigm, a previously neutral stimulus (e.g., the dentist office) can attain the ability to elicit a direct conditioned response (e.g., fear) following pairing of a neutral stimulus with an unconditioned stimulus (e.g., pain from injection). Conditioning models state that the objects and situations to which an individual is irrationally phobic resembles the previous traumatic experiences. A substantial amount of research support the acquisition of dental anxiety due to classical conditioning (De Jongh, Muris, Horst, & Duyx, 1995; Kleinknecht et al., 1973; Moore, Brodsgaard, & Birn, 1991; Öst & Hugdahl, 1985). However, classical conditioning theory faced criticism as only few individuals with anxiety and phobia reported previous conditioning experiences as origins of their phobias (Mineka & Sutton, 2006), indicating that there may be other pathways (other than classical conditioning) that led to development of anxiety and phobias. This was explained by Rachman (1977) who proposed that anxieties and phobias can be acquired and maintained via three major associative pathways in that a neutral stimulus is likely to acquire fearful qualities either directly by means of exposure to (a) a negative event or indirectly by social processes such as (b) vicarious learning or through (c) negative information (Rachman, 1977). However, critics of the Rachman's model noted that only limited individuals acquire dental anxiety and phobia via associative pathways (Mineka & Sutton, 2006). Additionally, retrospective studies supporting Rachman's model would rely on individuals' fallible memories (Merckelbach & Muris, 2001; Mineka & Sutton, 2006; Öst & Hugdahl, 1981). Hence, there could be role of other variables why many individuals following a traumatic (direct or observational) dental event do not develop phobias.

Contemporary views on development of anxiety and phobia argue that mere exposure to a negative event (as needed in classical conditioning), information or observational learning is unlikely to result in clinical phobias (Mineka & Sutton, 2006). Instead, the outcome of direct or observational conditioning may be potentiated by the negative expectancies set up by the negative information (Dadds, Davey, & Field, 2001; Mineka & Sutton, 2006). In addition, differences in individual temperamental and experiential variables (Craske, 1997; Mineka & Sutton, 2006; Muris & Merckelbach, 2001) such as genetic vulnerabilities (van Houtem et al., 2013), individual life experiences, cognitive and personality factors also differentially predispose individuals to develop and maintain dental anxiety and dental phobia (Mineka & Sutton, 2006; Mostofsky & Fortune, 2013). This explains why not all individuals develop dental anxiety or a dental phobia despite of having been exposed to negative conditioning events (direct or observational).

In sum, the etiological mechanisms and maintenance of dental anxiety and dental phobia described above highlight the complex nature of these mental health conditions. Hence, dental professionals, when assessing patients with dental anxiety and dental phobia should be aware that there are a wide array of individual differences that influence the development and maintenance of dental anxiety and dental phobia.

1.6 Consequences of dental anxiety and dental phobia

Following acquisition, individuals with dental anxiety and dental phobia develop aversive memories and negative beliefs and other cognitions about dental treatment (De Jongh et al., 1995; Skaret, Raadal, Berg, & Kvale, 1999) that lead them to avoid dentistry (White, Giblin, & Boyd, 2017). Patients' memories about their traumatic dental experiences tend to be well remembered and registered as disturbing, lasting and vivid (De Jongh, Eeden, Houtem, & Wijk, 2017; De Jongh, Fransen, Oosterink-Wubbe, & Aartman, 2006; Houtem, Wijk, & Jongh, 2015; McGaugh, 2004; McIntyre 2007; Oosterink et al., 2009; Rubin & Kozin, 1984; Shobe & Kihlstrom, 1997) and can easily be triggered when exposed to dental objects and situations. Frequent recollection of highly intrusive aversive memories and repeated confrontations with the negative dental experiences are likely to play an important role in maintenance and aggravation of symptoms of dental phobia (Houtem et al., 2015) in that reactivations of such disturbing memory could reinforce the aversive memory trace (Davey, 1989; De Jongh et al., 1995; De Quervain & Margraf, 2008). Thus, aversive memories following distressing dental experiences play a pivotal role in the maintenance of dental anxiety and dental phobia (Houtem et al., 2015).

Avoidance of dental care

Repeated activation of intrusive aversive memories is known to result in avoidance in seeking regular dental care in patients with dental anxiety and dental phobia (De Jongh, Aartman, & Brand, 2003; Houtem et al., 2015). Avoidance of dental care is possibly the most detrimental consequence of dental anxiety and dental phobia as it compromises the health and well-being of the patient (De Jongh, Aartman, & Brand, 2003). The relationship between avoidance and dental anxiety has been described by Berggren in 1984 as a "vicious cycle" (Berggren & Meynert, 1984) as shown in Figure 1.3.

Anxious dental patients who avoid regular dental care get easily entrapped in the "Vicious cycle of dental anxiety" (Berggren & Meynert, 1984; De Jongh, Schutjes, & Aartman, 2011). Repeated dental avoidance may yield more dental problems producing symptom-driven treatment patterns thereby necessitating

Figure 1.3 The vicious cycle of dental anxiety (Berggren & Meynert, 1984).

them to undergo invasive emergency dental treatment that could reinforce their anxiety and further avoidance (Armfield, Stewart, & Spencer, 2007; De Jongh, Oosterink, Kieffer, Hoogstraten, & Aartman, 2011; Oosterink et al., 2009). Also, repeated avoidance towards dental care maintains dental anxiety and dental phobia by inhibiting direct non-fearful learning; that is, avoidance would minimize direct and prolonged contact with the phobic object and hence the phobic individual might not get an opportunity to learn that the conditioned stimulus is harmless (Davis et al., 2012). An additional consequence of dental avoidance is that when patients with dental anxiety and dental phobia do visit the dentist for their appointment, their anxiety/phobia makes their treatment difficult for themselves and for their providers (Armfield & Heaton, 2013; Brahm et al., 2012). To break the avoidance cycle and negative cognitions, appropriate and timely treatment is required (Hakeberg & Wide, 2018; Shahnavaz et al., 2018; Vermaire, de Jongh, & Aartman, 2008).

1.7 Current treatment strategies for dental phobia and their limitations

Research and our prevailing experience indicate that general dentists usually refer patients with dental phobia to either specialists or psychologists (e.g. dental fear clinics) wherein they may undergo pharmacological management (e.g. sedation, general anesthesia) or receive psychotherapeutic interventions in the form of cognitive behavioral therapy (CBT) (De Jongh, Adair, & Meijerink-Anderson, 2005).

Unfortunately, there are obstacles for dental care, such as high cost (Öst & Skaret, 2013) and the relative lack or absence of learning in patients with dental phobia who undergo dental treatment under sedation or general anesthesia (De Jongh et al., 2005).

There are a wide range of methods and interventions available to target the fears and anxiety of dental patients, one of these is in vivo exposure therapy (IVET), a method from CBT that is designed to violate negative expectancies and correct underlying maladaptive thoughts and feelings (Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014). IVET involves controlled gradual presentation of the patients' feared stimuli (conditioned stimuli) in absence of aversive consequence (unconditioned stimuli; Craske et al., 2008; Dunsmoor, Niv, Daw, & Phelps, 2015). Procedurally, this is equivalent of fear extinction in which the conditioned stimulus (CS) that was previously paired with an aversive outcome (unconditioned stimulus, US) is repeatedly presented without being followed by US. Hence, the resultant learning that CS-No US (no threat) association forms the basis for exposure based therapy. In practice this means that patients with anxiety and phobia are encouraged to confront their real-life anxiety or phobia provoking situations gradually and repeatedly by cognitive behavioural therapists or by dentists trained in using IVET.

However, albeit IVET is considered to be the gold standard for treatment of dental phobia in adults (Wide Boman, Carlsson, Westin, & Hakeberg, 2013), and children (Gomes et al., 2018), not many general dentists are trained to administer IVET, and therefore may refer the patients to psychological services (CBT therapists), which are not widely available. Even if such services are available the patients are usually put on a long waiting list for treatment (Lovell & Richards, 2001). About one-third of the patients who get an opportunity to undergo IVET, express difficulty to face the actual threat due to fear of exposure (Garcia-Palacios, Hoffman, See, Tsai, & Botella, 2001; Kent, 1997; Van der Zijpp, er Horst, de Jongh, & Makkes, 1996) and as a result may not benefit from IVET.

1.8 Virtual Reality Exposure Therapy (VRET)

Considering the limitations of conventional IVET, it has been found useful to apply a technology-based therapeutic intervention that can elicit sufficient feelings of fear, be less mentally demanding in patients with dental anxiety and dental phobia. Recently, technology-based interventions that are easily accessible, tolerable, economical and that are as effective as conventional IVET are being developed (Carlbring, Andersson, Cuijpers, Riper, & Hedman-Lagerlöf, 2018). These interventions are known to reduce the in-patient clinician time (Marks, Cavanagh, & Gega, 2007) and treatment drop-outs (Short, Fuller, Norr, & Schmidt, 2017). It is

conceivable that if IVET is effective, then exposure to virtual counterparts (Botella, Fernandez-Alvarez, Guillen, Garcia-Palacios, & Banos, 2017) of IVET would also be effective as well in patients with dental phobia.

The term Virtual Reality (VR) was first coined by Jaron Lanier in 1980's (Firth, 2013). It can be defined as "an environment which is produced by a computer and seems very like a reality to the person experiencing it"[1]. In essence, VR applications facilitates new learning (Boeldt, McMahon, McFaul, & Greenleaf, 2019) by enabling the user to interact with controlled immersive three dimensional computer-generated 3-dimensional virtual world (Lindner et al., 2017) inside the head mounted device (HMD) in real time (Bouchard, Côté, & Richard, 2007). HMD comprises of two screens for each eye that are attached in front of the eyes covering the entire visual field of the patient and a head tracking device that detects the head movements (Rothbaum, Hodges, Smith, Lee, & Price, 2000). The simulator computer generates the VR environment which is then seen through the HMD that instantaneously updates the VR environment in real time as per the head movements of the patient (Rothbaum et al., 2000). A user-interface computer is used by the therapist to observe what the patient is seeing through the HMD and control the VR environment. In addition to rich visual stimuli, olfactory, auditory and tactile stimuli are presented to patient to simulate real-world interactive experiences (Lindner et al., 2018). The key aim of the immersive VR system is to perceptually replace the outside world with a VR environment so as to psychologically engage the user with a situation-specific simulated digital content (Rizzo & Shilling, 2017). VR enables objective and consistent format for documenting the sensory stimuli and enables the therapist to control the VR environment as per the needs of the patient.

VR as a mode to conduct exposure therapy was proposed two decades ago (Rothbaum et al., 1995). Recently, virtual reality exposure therapy (VRET) has evolved as the generation next treatment modality for anxiety disorders and specific phobias (Carl et al., 2018). In fact, the American Psychological Association recommends VRET as an alternative to IVET for the treatment of fear of flying (American Psychological Association, 2019). Also, the German clinical practice guidelines for anxiety disorders recommends VRET as an alternative option for treatment of Agoraphobia when IVET is not available or possible (Bandelow et al., 2014; Wechsler, Kümpers, & Mühlberger, 2019). VRET is easy to use by therapists and often more acceptable to patients compared to IVET (Carl et al., 2018). It enables individualized, gradual and controlled, immersive confrontation to the patients' phobic situations. VRET integrates real time computer graphics, body tracking devices and other sensory inputs (Maples-Keller, Yasinski, Manjin, & Rothbaum, 2017). It allows the therapist to systematically control the type, intensity, duration and repetition of exposure

1 https://www.collinsdictionary.com/dictionary/english/virtual-reality (Accessed 10/11/2018)

(Diemer, Pauli, & Mühlberger, 2015) of the patient to their phobic situation in an highly immersive and interactive computer environment within a meaningful and familiar contextual setting (Parsons & Rizzo, 2008). Results of four meta-analyses have consistently demonstrated that VRET is effective in reducing the symptoms of anxiety-related disorders (Morina, Ijntema, Meyerbroker, & Emmelkamp, 2015; Opris et al., 2012; Parsons & Rizzo, 2008; Powers & Emmelkamp, 2008). Further, there is evidence suggesting that VRET is equally effective (Carl et al., 2018) or slightly better than IVET in the treatment of specific phobias (Powers & Emmelkamp, 2008). VRET allows better patient-centered care as patients' undergo exposure treatment at their own pace under controlled conditions and enables therapist to apply strategies consistently to maximize/optimize exposure therapy (covered in Chapter 8 under section 8.4; Lindner et al., 2018). Although, VRET is known to be a powerful alternative for the treatment of specific phobias, it has not been evaluated yet as a potential therapy for dental phobia. Therefore, the purpose of the current thesis is to explore the possibility of using VRET in the treatment of dental phobia. The thesis comprises a series of six related chapters that comprehensively evaluated the applicability of VRET in a dental context.

1.9 Aim and objectives of the thesis

1.9.1.1 Aim

To determine whether VRET has the potential to reduce dental anxiety and treat phobia among a sample of patients diagnosed with dental phobia.

1.9.1.2 Objectives of the thesis

a) To evaluate and compare the efficacy of VRET versus an informational pamphlet (IP) control group in terms of anxiety reductions in patients with dental phobia and
b) To evaluate the real-time effect of VRET on the course of participant's physiological Heart Rate (HR) response on being exposure to a series of dentally related cues during therapy.

1.10 Thesis outline

In this thesis, the rest of the chapters represent the sequential research studies that were conducted to achieve the thesis objectives.

Chapter 2 reports on a systematic review that evaluated the effectiveness of technology-based interventions in the treatment of dental anxiety in children

and adults. Results from this study formed the basis of and informed the need for conducting most of the studies in this thesis.

Chapters 3 and 4, describes the initial case studies performed to explore VRET in the treatment of dental phobia. Also, the essential set-up, advantages, and limitations for using VRET in a general dental practice is described and discussed.

Chapter 5 reports on the findings of a feasibility study on ten randomized patients with dental phobia. The study evaluated the safety and efficacy of VRET compared to the informational pamphlet (IP) control condition in treatment of dental phobia using a multiple baseline study design. Safety was determined by evaluating for any personal adverse events or symptom exacerbation following intervention with both conditions. Efficacy of VRET was evaluated by comparing level of patients' state anxiety as indexed by a Visual Analogue Scale (VAS-A) and dental anxiety measured with both the Dental Anxiety Scale (MDAS) and the Dental Fear Survey (DFS; 16-times within a 14-week study period, and at six-month follow-up), and its behavioral avoidance, with that of an IP control condition. Also, patients' heart rate response during VRET, and their experience post-VRET were noted.

Chapter 6 describes the protocol of the randomized controlled trial designed to evaluate the efficacy of VRET compared to the IP control condition in the treatment of dental phobia. Also, the VRET procedural steps, methods to evaluate physiologic HR response and virtual reality (VR) experience during and after VRET are described.

Chapter 7 presents the findings of the randomized controlled trial on thirty patients with dental phobia. The effectiveness of VRET in reduction of state anxiety (as indexed by the Visual Analogue Scale (VAS) A, and dental anxiety (as measured by both the Modified Dental Anxiety Scale (MDAS) and the Dental Fear Survey (DFS) was compared to the IP control condition at baseline, pre-post intervention, 1-week, 3 months and 6-months follow-up. Also, the trial evaluated the pre-post changes in the behavioral avoidance, variations in heart rate and VR experience during and post-VRET. Further, the study determined the acceptability towards dental treatment and number of patients who had no dental phobia in both conditions at 6 months follow-up.

An important note regarding the RCT should be made. At the beginning of the trial, one of the objective was to determine the correlation between the presence, realism, cybersickness and heart rate experienced by the patients during and after VRET. Unfortunately, we could not include this objective as the correlation analysis and its interpretation was found to be too complicated. Therefore, it was not feasible to include this objective in the thesis.

Chapter 8 includes a global synthesis of the presented studies, mechanism of VRET, factors that affect the effectiveness of VRET and the strengths and limitations of included studies. The thesis is concluded with future directions for conducting VRET research in the treatment of dental phobia.

Chapters 2, 3, 4, 5, 6 and 7 have been published in international peer-reviewed journals. There are overlaps in the information provided in the publications. Hence, the abstracts of all articles are removed and the texts in articles are adjusted to enable the thesis coherent.

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Chapter 2. Are technology-based interventions effective in reducing dental anxiety in children and adults?–A systematic review*

Kumar Raghav Gujjar, Arjen van Wijk, Ratika Kumar, Ad de Jongh

2.1 Introduction

Despite improvements in modern dental technology and use of advanced pain-control techniques in contemporary dental practice, the global prevalence of dental anxiety has remained relatively stable since the last thirty years (Boyle, Newton, & Milgrom, 2010). It is estimated that 10-40% of the population in western countries suffer from dental anxiety (Halonen, Salo, Hakko, & Rasanen, 2014; Hill, Chadwick, Freeman, O'sullivan, & Murray, 2013; Humphris & King, 2011; Oosterink, De Jongh, & Hoogstraten, 2009; Singer et al., 2012; White, Giblin, & Boyd, 2017). Much higher rates are seen in some non-western countries (up until 77%) (Mohammed et al., 2014).

When apprehension towards dental situations is a *transitory affective response* that follows confrontation with specific dental situations, it is referred to as 'state anxiety'. In contrast, 'dental trait anxiety' (Corah, 1986) is the *general tendency* of an individual to experience anxiety towards dental objects and situations. For the purpose of the present review, we were interested in the latter construct, for which we will use the term 'dental anxiety' throughout this paper.

Dental anxiety typically emerges during childhood, albeit it can also occur later in life, (De Jongh, Muris, Horst, & Duyx, 1995; Oliveira, Vale, Bendo, Paiva, & Serra-Negra, 2017; Oosterink et al., 2009; Seligman, Hovey, Chacon, & Ollendick, 2017) and is known to be relatively stable across the life span of an individual (Muris, Merckelbach, van Brakel, Mayer, & van Dongen, 1998; Oosterink et al., 2009). Patients experiencing a high level of dental anxiety have been found to report higher levels of pain during dental procedures (Lin, Wu, & Yi, 2017), and are more likely to delay their dental treatment (Armfield, Stewart, & Spencer, 2007; De Jongh, Schutjes, & Aartman, 2011). Poor oral health due to untreated dental anxiety in children (Tickle et al., 2009) might compromise individuals' overall growth

* Gujjar, K. R., Van Wijk, A., Kumar, R., & De Jongh, A. (2019). Are Technology-Based Interventions Effective in Reducing Dental Anxiety in Children and Adults? A Systematic Review. *Journal of Evidence Based Dental Practice, 19*(2), 140-155. doi:https://doi.org/10.1016/j.jebdp.2019.01.009

and development and may also act as a risk factor for serious systemic disease in adulthood (Seligman et al., 2017). In children and adults, compromised oral health and poor quality of life due to avoidance of oral care is likely to worsen over time and often requires extensive and more invasive dental treatment at a later date (Armfield et al., 2007; Vermaire, De Jongh, & Aartman, 2008). Patients with dental anxiety are also difficult to manage in the dental office as they may need more time for treatment, and are often unsatisfied with their dental treatment (Quteish Taani, 2002). Furthermore, general dentists may not be trained sufficiently to manage dental patients with psychological morbidities. Considering the significant challenges associated with management of dental anxiety and related avoidance of oral care it is valuable to determine the efficacy of interventions aimed to treat dental anxiety.

Psychological interventions meant to reduce dental anxiety are either administered before or during dental procedures (Armfield & Heaton, 2013; Carter, Carter, Boschen, AlShwaimi, & George, 2014; De Jongh, Adair, & Meijerink-Anderson, 2005). These interventions focus on alleviating psychological distress (Burghardt, Koranyi, Magnucki, Strauss, & Rosendahl, 2018), perceived pain, anticipatory fear and avoidance towards dental treatment. Extant research supports Cognitive Behavioral Therapy (CBT) as the gold standard psychological therapy for the treatment of dental anxiety in both children (Gomes et al., 2018; Shahnavaz, Hedman, Grindefjord, Reuterskiold, & Dahllof, 2016) and adults (Wide Boman, Carlsson, Westin, & Hakeberg, 2013). However, owing to limited training opportunities available for general dentists for learning to administer therapeutic (cognitive behavioral) interventions, patients with dental anxiety may be referred to specialists or dental fear clinics, but these services are not widely available. In addition, there are indications that the majority of individuals with specific phobias including dental phobia, do not seek professional help (Choy, Fyer, & Lipsitz, 2007). Moreover, those who do schedule an appointment for evidence based mental health care, are not only frequently kept on long waiting lists (Lovell & Richards, 2001), the treatment they eventually receive appears not always to be evidence based (Andrews, Issakidis, Sanderson, Corry, & Lapsley, 2004). In the absence of timely and effective treatment for their dental anxiety, the majority of patients with dental anxiety or dental phobia may have no other option than to undergo dental treatment under sedation or general anesthesia. However, these pharmacological procedures do not treat the underlying dental anxiety and are associated with risks and side effects (De Jongh et al., 2005).

In recent years, several technology-based interventions for the treatment of dental anxiety in children and adults have been developed, which save time and require minimal training on the part of dentist (Hirai & Clum, 2006). These include interventions such as video modeling (Al-Namankany, Petrie, & Ashley, 2015, 2016;

Kazancioglu, Tek, Ezirganli, & Demirtas, 2015), audio distraction (Thoma et al., 2015), audio-visual distraction (Al-Khotani, Bello, & Christidis, 2016; Kaur et al., 2017; Padrino-Barrios, McCombs, Diawara, & De Leo, 2015; Prabhakar, Marwah, & Raju, 2007), video hypnosis (DiClementi, Deffenbaugh, & Jackson, 2007), progressive muscle relaxation instructional tape (Moore, Brodsgaard, Berggren, & Carlsson, 1991) and technology-based CBT delivered in a variety of formats such as Computer Assisted Relaxation Learning (CARL; Heaton, Leroux, Ruff, & Coldwell, 2013), Computerized-Cognitive Behavioral Therapy (C-CBT; Tellez et al., 2015) and psychologist guided internet-based Cognitive Behavioral Therapy (ICBT; Shahnavaz et al., 2018). From a clinical dental practice perspective, it is important to establish whether there is sufficient evidence to justify the use of technology-based interventions for the treatment of dental anxiety (Hirai & Clum, 2006). Accordingly, the purpose of the present study was to systematically review the available studies that examined the effectiveness of technology-based interventions in alleviating moderate to severe dental anxiety.

2.2 Methods

The review was registered in PROSPERO (Identifier: CRD42017064810) and reported as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Moher, Liberati, Tetzlaff, Altman, & Group, 2009). A systematic search of eligible articles in English language published before 25th July 2018 was conducted to include all the old and recent published articles in the following electronic databases: Pubmed-Medline, EMBASE, PsycINFO, CINAHL, Scopus and The Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials: CENTRAL). Only articles published in English were included given that the authors were proficient in reading and understanding English.

2.2.1 Inclusion and exclusion criteria

Randomized Controlled Trials (RCTs) evaluating children and adults with moderate to severe dental anxiety were considered eligible to be included in the review. Studies that did not include individuals reporting dental anxiety or evaluated patients' state anxiety only, were excluded.

2.2.2 Interventions

According to US National Library of Medicine's Medical Subjects Headings (MeSH), technology is the application of scientific knowledge to practical purposes in any

field and includes methods, techniques, and instrumentation. For the purpose of this review, technology-based psychological interventions that were delivered using a computer (e.g., computerized cognitive behavioral therapy, C-CBT), audio and video media, virtual reality, internet and mobile phones were considered eligible to be included. However, studies using combinations of two or more technology-based interventions such as those combining Virtual Reality Exposure Therapy (VRET) and Cognitive Behavioral Therapy or audio hypnosis and video systematic desensitization were excluded.

2.2.3 Control

The inactive control conditions comprised of no treatment, placebo, dental treatment as usual, or a waiting list control condition. Studies using active controls were excluded as the purpose was to estimate the absolute effects of the technology-based intervention compared to inactive controls (Karlsson & Bergmark, 2015).

2.2.4 Search strategy

A comprehensive search strategy of a single database is included in Table 2.1. Based on the eligibility criteria the titles and abstracts of potential studies were screened against inclusion and exclusion criteria independently by one of the reviewers (KRG) without being blinded to authors, institutions, and journal name or trial results. Ten percent of randomly selected titles and abstracts of publications identified by the search strategy were independently screened by two authors (KRG and RK). Any disagreements about inclusion of an article were planned to be resolved by consensus and by involving other co-authors (ADJ and AVW). However, because the authors showed a 100% agreement concerning the articles that should proceed to full text screening, one author (KRG) continued to screen the remaining studies (Peckham, Brabyn, Cook, Tew, & Gilbody, 2017).

The full text of the included articles were retrieved, and the articles were reviewed by KRG to check whether they fulfilled the inclusion criteria. Relevant data of the study characteristics were extracted and transferred into an Excel sheet in a pre-defined form. The data entry of study characteristics for all included studies was done by KRG. To ensure accuracy and reliability of the entered data, a second reviewer (RK) randomly cross-checked 50% of the study characteristics against the article full text for all the included studies. Missing or additional data of eligible studies were obtained by contacting the authors via email. If the authors did not respond to the email requests, missing information was recorded as 'Not reported'.

Table 2.1 Showing search strategy.

Name of the database	Search strategy
PubMed	"Dental Anxiety"[Mesh] AND (computer OR computer-based OR cyber OR cyberspace OR electronic OR "electronic mail" OR email OR e-mail OR internet OR internet-based OR net OR online OR virtual OR "virtual reality" OR web OR web-based OR web based OR "world wide web" OR www OR audio OR "audio-visual" OR video OR phone OR telephone OR "smart phone" OR "cell phone" OR "cellular phone" OR iphone OR "SMS" OR "short message service" OR "text message" OR testing OR mobile OR "mobile phone" OR ipad OR tablet OR "smart device" OR digital OR "personal digital assistant" OR pda OR cd-rom OR technology OR technologies OR technological)

2.2.5 Outcomes

2.2.5.1 Primary outcome

Effectiveness of technology-based interventions was evaluated by comparing the change from pre- to post-intervention dental anxiety scores, between the technology-based intervention and control group.

2.2.5.2 Secondary outcomes

a. Safety of using technology-based interventions was determined by evaluating whether participants experienced any side-effects during the therapy and follow-up.
b. Change in dental avoidance following the intervention was determined by recording the number of participants who scheduled a dental appointment during follow-up.

2.2.6 Reporting of included studies

The completeness of reporting in the included studies was assessed using the CONSORT (Consolidated Standards of Reporting Trials) statement guidelines. (Moher et al., 2010)

2.2.7 Quality assessment

The quality of included studies were assessed by performing a Risk of Bias analysis. ROB of included studies was evaluated by the two reviewers (KRG and RK) using the revised Cochrane ROB tool for randomized parallel group RCT's (ROB 2.0; Higgins et al., 2016). The tool was utilized to evaluate the bias in the

randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of the reported result, and overall bias. Any disagreements between the reviewers were resolved through discussions or by discussing with the third person (ADJ and AVW). We contacted study authors via email for clarification of missing information in the article when it was necessary and feasible.

2.3 Results

A summary of the stage-wise results of the literature search and review is presented in Figure 2.1. A search in the databases yielded 1312 records of studies published from 1991 until July 2018. After removing the duplicates, the titles and abstracts of 894 articles were read, leading to selection of 31 articles for full text examination. The full text of these 31 articles were retrieved and the reference lists of each were checked to detect any other relevant publications. Following in-depth reading of the text, seven articles met the inclusion criteria. Twenty-four articles were excluded for a variety of reasons as shown in Figure 2.1.

2.3.1 Study characteristics

A 100% inter-rater reliability was noted between the first and the second reviewer (KRG and RK). The included studies were carried out in the USA (Tellez et al., 2015), Europe (Al-Namankany et al., 2015, 2016; Kazancioglu et al., 2015; Thoma et al., 2015) and Asia (Gujjar, van Wijk, Sharma, & De Jongh, 2018; Kaur et al., 2017). Of the seven included studies, three studies were done among pediatric patients (Al-Namankany et al., 2015, 2016; Kaur et al., 2017). All studies were conducted at a single study site. Only four studies reported study duration, which ranged from 6-17 months (Al-Namankany et al., 2015; Gujjar et al., 2018; Kazancioglu et al., 2015; Tellez et al., 2015).

Level of dental anxiety was evaluated in five included studies using screening questionnaires such as the dental subscale of Children's Fear Survey Schedule–short form (DFSS-SF; Kaur et al., 2017), Abeer Children Dental Anxiety Scale (ACDAS; Al-Namankany et al., 2015, 2016) the Hierarchical Anxiety Scale (HAF; Thoma et al., 2015), the Modified Dental Anxiety Scale (MDAS; Gujjar et al., 2018; Tellez et al., 2015), the Dental Anxiety Scale (DAS) (Kazancioglu et al., 2015) or the Dental Fear Scale (DFS; Gujjar et al., 2018). In two studies, apart from dental anxiety, patients were also assessed for dental phobia prior to the intervention based upon diagnostic criteria of specific phobia using the ADIS-IV (Tellez et al., 2015) or the Phobia Checklist (DSM-IV) (Gujjar et al., 2018).

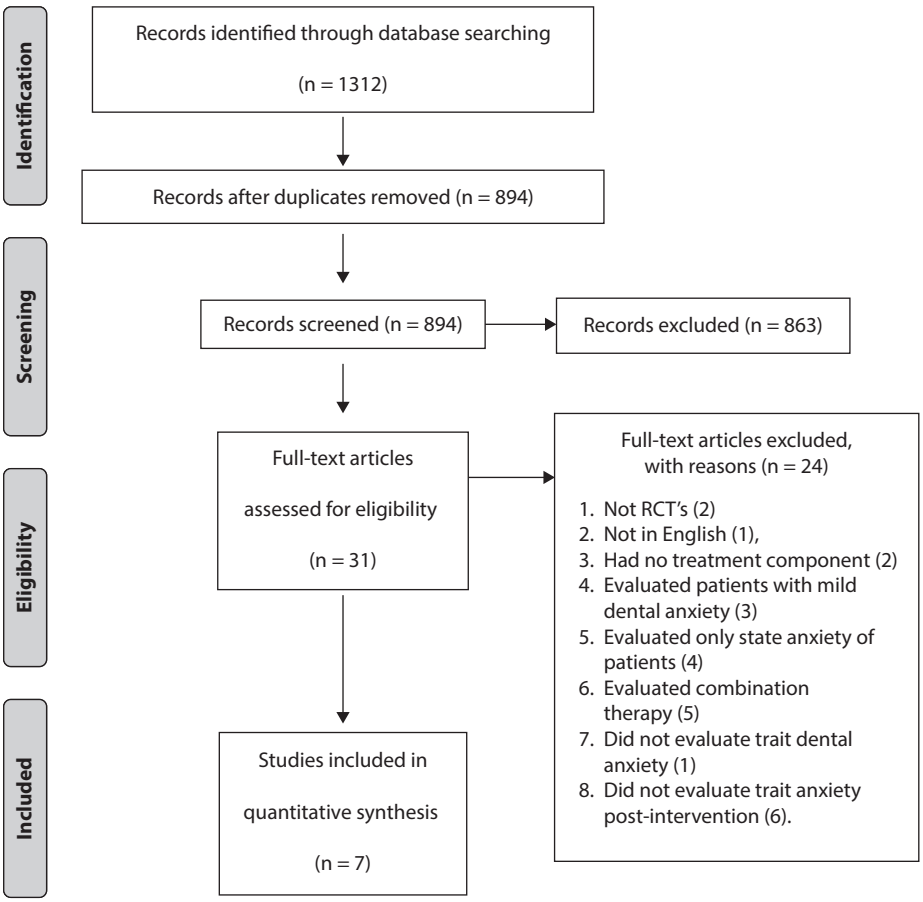

Figure 2.1 Showing flow diagram of study selection process

The number of technology-based treatment sessions varied from one to three. Four out of seven studies did not mention the duration of the intervention (Al-Namankany et al., 2015, 2016; Gujjar et al., 2018; Kaur et al., 2017). For those studies that did report duration of the intervention, duration ranged from five minutes (Kazancioglu et al., 2015) to one hour (Tellez et al., 2015). Four studies did not follow-up on the participants after the intervention. The remaining three studies reported a follow-up ranging from 1 week (Kazancioglu et al., 2015) to 6 months (Gujjar et al., 2018; Tellez et al., 2015).

All included studies compared technology-based intervention to inactive controls. Notably, we did not identify any study which compared technology-based interventions with active controls (CBT). See Table 2.2 for detailed description regarding the number of participants randomized, withdrawals after randomization, details of the intervention and control group and severity of the condition.

Table 2.2 Characteristics of included studies

Author and year	Number of randomized patients; Age range; mean age (SD); Gender	Intervention group and content	Control group and content	Withdrawals after randomization	Severity of condition
Gujjar Kumar Raghav et al. 2018	10; 18-60 years; 28.5 years (14.1); Male (4) and Female (6).	VRET involved exposure to anxiety eliciting cues such as sitting in a dental chair, an oral examination with instruments, an introduction to a syringe and exposure to the dental drill.	IP provided details about patient comfort, description of dental procedures and postoperative pain management.	None	MDAS score ≥ 15 and satisfying "Phobia Checklist" criteria of dental phobia.
Kaur, R et al. 2017	60; Two age groups: 4-6 years and 6-8 years; mean age and SD not reported; gender distribution not reported.	Audio [A] (either English or Hindi or Punjabi songs) and audio-visual [AV] short dramatic clips, video songs and cartoons.	Control (dental treatment as usual).	None	4-6 yrs. DFSS-SF (AV = 19.10, A = 19.30, C = 20.10) 6-8 yrs. DFSS-SF (AV = 16.30, A = 18.70, C = 20.90).
A. Al-Namankany et al. 2016	68; 6-12 years; mean age of Test group = 9.15 years (2.75), Control group = 9.07 years (2.47); Male (22) and Female (34).	Modelling video of a dentist making a dental filling under local anesthesia in a 9-year-old girl.	Control video oral hygiene instruction video of the same dentist and a girl in a non-clinical sitting.	Modelling video (5); Control video (7).	> 26 ACDAS.
Thoma Myriam V et al. 2015	92; 29-90 years; mean age of Experimental group-58.76 (13.52); control group 55.67 (12.36); 49 Female; 43 Male.	Experimental group-listening to relaxing music of Latin choral- 'Miserere' by Allegri (CD Gimell 454 939–2).	Control group-resting in silence.	None	HAF = 34.6 (9.85) (experimental); 31.76 (9.34) (control).
Tellez et al.2015	151; 18-70 years; 44.7 years (13.1); Female-61.6%.	Immediate treatment (IT) with C-CBT.	Wait-list (WL).	5 WL and 2 IT.	Patients with MDAS ≥ 19 or with at least 2 MDAS items ≥ 4. ADIS-IV > 4 for dental phobia.

Author and year	Number of randomized patients; Age range; mean age (SD); Gender	Intervention group and content	Control group and content	Withdrawals after rand-omization	Severity of condition
Kazancioglu, Hakki Oguz et al. 2015	333; 18-25 years; 22.63 years (8.22); Male-147; Female-153.	Group 1-basic verbal information about operative procedures and recovery; Group 2 -basic verbal information and through a movie on third molar extraction with details of operative procedures and recovery.	Control group –Verbal basic information devoid of the details of the operative procedures and recovery.	33	Mean baseline DAS score of the patient was 11.21 (SD not reported).
Al-Namankany, et al. 2015	80; 8–16 years; 12 years (SD not reported); 55.2 % of the test group males, and 44.8 % of the control group males.	Modelling video showing a dentist applying a nasal mask prior to placing a dental restoration under Inhalational Sedation for a 9-year-old girl.	Control video showing oral hygiene instruction with the same dentist and girl in non-clinical setting.	5 (modelling); 9 (control).	≥ 26 ACDAS

DFSS-SF = Dental subscale of children's fear survey schedule–short form, ACDAS = Abeer Children Dental Anxiety Scale, HAF = Hierarchical Anxiety Scale, MDAS = Modified Dental Anxiety Scale, DAS = Dental Anxiety Scale, DFS = Dental Fear Scale, VRET = Virtual Reality Exposure Therapy, IP = Informational pamphlet, C-CBT = Computerized Cognitive Behavioral Therapy.

2.3.2 Types of interventions and controls

Of the seven studies, five used technology-based interventions that were administered at the clinic, while in two studies, interventions were administered both at home and at the clinic (Al-Namankany et al., 2015, 2016). Three out of seven studies tested modelling with single video prior to dental treatment (Al-Namankany et al., 2015, 2016; Kazancioglu et al., 2015), and one study evaluated C-CBT before dental treatment (Tellez et al., 2015). C- CBT involved psycho-education, motivational interviewing and graded exposure to videos of fear eliciting stimuli (Tellez et al., 2015). One study evaluated VRET prior to dental treatment (Gujjar et al., 2018). Two studies examined interventions such as relaxation with music (Thoma et al., 2015) and distraction with songs (audio and audio-visual) (Kaur et al., 2017), that were administered before (Thoma et al., 2015) and during (Kaur et al., 2017) the dental treatment respectively.

The inactive control conditions comprised of dental treatment as usual (Kaur et al., 2017) resting in silence prior to oral hygiene treatment (Thoma et al., 2015), a wait-list (Tellez et al., 2015), a video showing a demonstration of oral hygiene instructions to a patient by a dentist in a non-clinical setting (Al-Namankany et al., 2015, 2016), the provision of basic verbal information about third molar surgery (Kazancioglu et al., 2015), and an informational pamphlet about dental anxiety (Gujjar et al., 2018). See Table 2.3 for more information about inclusion/exclusion criteria, measures, time points at which measures were recorded and findings of the included studies.

2.3.3 Outcomes

The data obtained were heterogeneous in terms of the variety of inactive control conditions, number of sessions, duration of sessions, time points reported and duration of the follow-up. Thus, only a narrative synthesis of the results can be presented.

2.3.3.1 Primary outcome

Effectiveness of technology-based interventions

Only four studies reported separate pre-post (within-group) comparisons of dental anxiety scores (Al-Namankany et al., 2015, 2016; Kazancioglu et al., 2015; Thoma et al., 2015). As shown in Table 2.3 compared to the inactive control condition, three studies showed a significantly greater pre-post reduction in dental anxiety scores after administration of a video modelling intervention. The videos in these studies showed a dentist applying the nasal mask for inhalational sedation (Al-Namankany et al., 2015), a dentist doing a dental filling under local anesthesia (Al-Namankany et

Table 2.3 Characteristics of included studies

Author and year	Inclusion criteria	Exclusion criteria	Primary measure	Secondary measure	Time points reported	Findings
Gujjar Kumar Raghav et al. 2018	Dental avoidance for > 12 months and in need of a dental filling or extraction or both with a planned maximum treatment length of 30 minutes per appointment.	Hearing or visual impairment, known mental disorders, developmental or intellectual disability and cognitive impairment, known balance disorders, epileptic patients, cardiac problems. Patients who are undergoing, or have undergone, any cognitive behavioral therapy (CBT)-based intervention for dental phobia, cannot understand English, Patients wearing glasses of greater than plus 3.5 power.	Safety by evaluating any side-effects and symptom exacerbation following therapy, VAS-A, MDAS, DFS and BAT.	HR and VRET experience (presence, realism, distress and cybersickness).	Baseline periods 5-9 weeks prior to intervention, pre-intervention, post-intervention, Follow-up every week till 14th week and at 6 months.	1. VRET patients experienced moderate presence, realism and mild cybersickness post-VRET. 2. No symptom exacerbation was reported Post-VRET. 3. VRET significantly lowered VAS-A, MDAS, DFS and behavioral avoidance scores compared to control. 4. There was no increase in average heart rate during VRET. 5. Majority of VRET patients (4 out of 5) had no dental phobia and scheduled a dental appointment compared to control.

Author and year	Inclusion criteria	Exclusion criteria	Primary measure	Secondary measure	Time points reported	Findings
Kaur, R et al. 2017	Restoration of a carious tooth without administration of local anesthesia and extraction or endodontic procedure that required administration of local anesthesia.	Children with lack of orientation and mental and physical disabilities.	Heart rate.	1. DFSS-SF. 2. Clinical anxiety rating scale and co-operative behavior rating scale.	Before, during and after 1st visit (Examination), 2nd visit (drill) and 3rd visit (Local anesthesia).	1. HR- Patients were more relaxed in the following order AV>Audio>control in both age groups 2. DFSS-SF Patients were least anxious in the following order AV>Audio>control in both age groups. 3. Clinical anxiety rating scale and co-operative behavior rating scale -Children were most cooperative and relaxed in the following order AV>Audio>control in both age groups.
A. Al-Namankany et al. 2016	Availability of DVD facilities at home, healthy children with ASA scale of class I and II; and children with a score of ≥ 26 on ACDAS.	Children not meeting the inclusion criteria; children with a learning disability; children in need of emergency dental treatment.	ACDAS	VAS, parent/ legal guardian opinion about use of modeling video.	1. ACDAS before (1st visit), after watching the video and immediately before dental treatment (2nd visit) 2. VAS during 2nd visit.	1. Statistical significance ($P < 0.05$) in ACDAS score from the first to second visit between the test and control groups for the response on question 6 on ACDAS. 2. Statistical significance ($P < 0.05$) in VAS score (Sitting in dental chair, examination with mirror, fissure sealant/ prophylaxis, Local anesthesia, tooth drilling, tooth extraction) and 98.3% favored use of video modelling.

Author and year	Inclusion criteria	Exclusion criteria	Primary measure	Secondary measure	Time points reported	Findings
Thoma, Myriam V et al.2015	Having a regular scheduled appointment, understand German language, and minimum age of 18 years.	None	STAI-S	STAI-T, HAF, VAS, Mood Multidimensional Mood State Questionnaire.	Before and after hygiene treatment.	1. State anxiety was reduced in the experimental group post intervention. 2. Experimental group showed increase in the alertness of participants. 3. Participants in the control group were calmer and had better mood. 4. Experimental and control group had no influence in the reduction of trait (STAI-T) and dental trait (HAF) anxiety.
Tellez et al. 2015	18 and 70 yrs of age, know English, have scheduled a dental treatment appointment, gave consent, high MDAS, and have oral impairment.	Unable to provide written informed consent.	MDAS	ADIS-IV, Client Satisfaction Questionnaire.	Change from one week before appointment to one month after appointment.	1. Significant decrease in MDAS scores from baseline to 1-month follow-up in the IT group compared to WL group. 2. Significant reduction in ADIS-IV ratings of fear, avoidance, and clinical severity symptoms from baseline to 1-month follow-up was noted in the IT group. 3. Fewer IT patients met criteria for dental phobia at follow-up compared to WL group. 4. Majority of IT patients (83.3%) were satisfied with treatment.

Author and year	Inclusion criteria	Exclusion criteria	Primary measure	Secondary measure	Time points reported	Findings
Kazancioglu, Hakki Oguz et al. 2015	Ages 18 to 25 years; ASA classification I or II; healthy, impacted, lower third molars; and IIIB surgical difficulty grade on the Pell-Gregory and Winter scales.	Systemic illnesses, psychiatric diseases, local infection, tobacco use, oral contraceptive and regular sedative medication use, pregnancy, and lactation, no pain before the third molar surgery, extracted for orthodontic reasons without any complaint, previously bad dental treatment history.	DAS; STAI.	Pain assessed with VAS during surgery, 1 day, 3 days and 7 days.	DAS and STAI scores measured immediately before, immediately after, and 1 week after the surgical procedure; VAS during surgery, 1 day, 3 days and 7 days.	Group 2 (movie group) had significantly lowered DAS and STAI-S scores immediately and 1 week after the surgical procedure; patients with high anxiety had higher pain scores on visual analog scale; watching a movie about third molar extraction led to increased anxiety and pain during the postoperative period.
Al-Namankany, et al. 2015	Availability of DVD facilities at home; children aged 8–16 years; healthy children with ASA class I and II; and children who were assessed to be dentally anxious based on the score of ≥ 26 on the ACDAS.	Children who did not satisfy the inclusion criteria; learning disabilities; in need of emergency dental treatment and children with previous experience with Inhalational sedation.	ACDAS	VAS	ACDAS- first visit as a baseline score prior to watching the video and on the second visit after watching the video and immediately before the start of the dental treatment; VAS-second visit during treatment.	Significant difference in the change in ACDAS score from the first to second visit between the test and control groups for Question 12 on ACDAS; In the modelling group 22.2 % showed no change in the ACDAS for the nasal mask administration before and after watching the video, whereas 77.8 % of the control group showed no change in the ACDAS; VAS- decreased anxiety scores in the modelling group.

DFSS-SF = Dental subscale of children's Sear Survey Schedule–short form, ACDAS = Abeer Children Dental Anxiety Scale , STAI-S = State version of State-Trait Anxiety Inventory , STAI-T = Trait version of State-Trait Anxiety Inventory , HAF = Hierarchical Anxiety Scale, VAS = Visual Analog Scale, MDAS = Modified Dental Anxiety Scale, ADIS-IV = Anxiety Disorders Interview Schedule, DAS = Dental Anxiety Scale, ASA = American Society of Anesthesiology, DFS = Dental Fear Scale, VRET = Virtual Reality Exposure Therapy IP = Informational pamphlet, C-CBT = Computerized Cognitive Behavioral Therapy.

al., 2016) and third molar surgery (Kazancioglu et al., 2015). There was no significant pre- to post-decrease of dental anxiety in the study which evaluated relaxation with music (Thoma et al., 2015). Three studies that compared C-CBT (Tellez et al., 2015), VRET (Gujjar et al., 2018) and audio-visual distraction with songs (Kaur et al., 2017) to the inactive control condition (between-group comparisons) showed statistical significant differences. Effect sizes of either within-group or between-group comparisons were not reported in six of the included articles (Al-Namankany et al., 2015, 2016; Kaur et al., 2017; Kazancioglu et al., 2015; Tellez et al., 2015; Thoma et al., 2015).

2.3.3.2 Secondary outcomes

a. Safety of using technology-based interventions.
Out of seven studies only three studies reported about safety (i.e., side-effects) following the interventions. More specifically, in the case of music therapy (Thoma et al., 2015), and C-CBT (Tellez et al., 2015) no side-effects were noted. Four out of five patients experienced side-effects in form of moderate cybersickness (vomiting) following VRET, albeit no symptom exacerbations were reported (Gujjar et al., 2018).

b. Only one study (VRET) evaluated avoidance of dental treatment following intervention during follow-up (Gujjar et al., 2018). The majority of the VRET patients (four out of five) reported a significant reduction of dental avoidance and underwent actual dental treatment following intervention compared to the controls.

2.3.4 Completeness of reporting of included studies

Completeness of reporting was determined in accordance with the updated CONSORT 2010 check list. Overall assessment of the methodological issues in the included studies as per the specific items of the CONSORT check list can be found in Table 2.4. Out of seven included studies, only two studies mentioned trial registration details (Gujjar et al., 2018; Tellez et al., 2015). Four out of seven studies included a CONSORT flow chart (Al-Namankany et al., 2015, 2016; Gujjar et al., 2018; Tellez et al., 2015), mentioned period of recruitment and follow-up of the trial (Al-Namankany et al., 2016; Gujjar et al., 2018; Kazancioglu et al., 2015; Tellez et al., 2015), and had a table that depicted the baseline characteristics of participants (Gujjar et al., 2018; Kazancioglu et al., 2015; Tellez et al., 2015; Thoma et al., 2015). Three studies conducted sub-group or adjusted analyses (Kaur et al., 2017; Kazancioglu et al., 2015; Tellez et al., 2015) and four studies reported missing data (Al-Namankany et al., 2015, 2016; Kazancioglu et al., 2015; Tellez et al., 2015) of which only one (Tellez et al., 2015) mentioned how missing data were handled.

Only three studies mentioned their funding sources (Gujjar et al., 2018; Tellez et al., 2015; Thoma et al., 2015).

Table 2.4 Overall table depicting the items of CONSORT 2010 check list that were evident in included studies.

Specific topic items of CONSORT 2010 check-list			Studies that included this item (n = 7)
1	Title and abstract		
	1a	Identification as a randomized trial in the title	3
	1b	Structured summary of trial design, methods, results, and conclusions	3
2	Introduction Background and objectives		
	2a	Scientific background and explanation of rationale	7
	2b	Specific objectives or hypotheses	5
3	Methods trial design		
	3a	Description of trial design including allocation ratio	2
	3b	Important changes to methods after trial commencement (eligibility criteria), with reasons	0
4	Participants		
	4a	Eligibility criteria for participants	7
	4b	Settings and locations where the data were collected	6
5	Interventions		
	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered		5
6	Outcomes		
	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	7
	6b	Any changes to trial outcomes after the trial commenced, with reasons	0
7	Sample size		
	7a	How sample size was determined	2
	7b	When applicable, explanation of any interim analyses and stopping guidelines	0
8	Randomization Sequence generation		
	8a	Method used to generate the random allocation sequence	6
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	0
9	Randomization Allocation concealment		5
10	Randomization implementation		
	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions		3
11	Blinding		
	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	4
	11b	If relevant, description of the similarity of interventions	2

Specific topic items of CONSORT 2010 check-list			Studies that included this item (n = 7)
12	Statistical methods		
	12a	Statistical methods used to compare groups for primary and secondary outcomes	7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	0
13	Results Participants flow (Diagram strongly recommended)		
	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	4
14	Recruitment		
	14a	Dates defining the periods of recruitment and follow-up	4
	14b	Why the trial ended or was stopped	0
15	Baseline data		
	A table showing baseline demographic and clinical characteristics for each group		4
16	Numbers analyzed		
	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups		7
17	Outcomes and estimation		
	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	3
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	0
18	Ancillary analyses		
	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory		3
19	All-important harms or unintended effects in each group		3
20	Discussion Limitations		
	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses		4
21	Discussion Generalizability		
	Generalizability (external validity, applicability) of the trial findings		6
22	Discussion Interpretation		
	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence		5
23	Other information Registration		
	Registration number and name of trial registry		2
24	Other information Protocol		
	Where the full trial protocol can be accessed, if available		1
25	Other information Funding		
	Sources of funding and other support (such as supply of drugs), role of funders		3

2.3.5 Quality assessment

ROB analysis

Although all seven included studies reported that the participants were assigned to conditions at random, six studies reported how randomization was carried out (Al-Namankany et al., 2015, 2016; Gujjar et al., 2018; Kazancioglu et al., 2015; Tellez et al., 2015; Thoma et al., 2015) five studies provided information as to how the allocation was concealed and how randomization was implemented (Al-Namankany et al., 2015, 2016; Gujjar et al., 2018; Kazancioglu et al., 2015; Tellez et al., 2015). Three articles contained a statement that participants and/or personnel were blinded (Al-Namankany et al., 2015, 2016; Kazancioglu et al., 2015). Selective reporting was found in two studies [that reported only a subset of the results of the ACDAS (Abeer Children Dental Anxiety Scale) questionnaire] (Al-Namankany et al., 2015, 2016). Overall bias was low in three included studies (Gujjar et al., 2018; Kazancioglu et al., 2015; Tellez et al., 2015) and in high in four (Al-Namankany et al., 2015, 2016; Kaur et al., 2017; Thoma et al., 2015). ROB ratings for each bias across studies are presented in Table 2.5.

Table 2.5 Showing Risk of Bias analysis of included studies.

Author and year	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall Bias
Gujjar Kumar Raghav. 2018 (Gujjar et al., 2018)	Low	Low	Low	Low	Low	Low
Kaur et al. 2017 (Kaur et al., 2017)	High	Some concerns	Low	Low	Low	High
Al-Namankany. 2016 (Al-Namankany et al., 2016)	Low	High	Some concerns	Low	High	High
Thoma Mariam V. 2015 (Thoma et al., 2015)	High	Some concerns	Low	Low	Low	High
Tellez. 2015 (Tellez et al., 2015)	Low	Low	Low	Low	Low	Low
Kazancioglu. 2015 (Kazancioglu et al., 2015)	Low	Low	Low	Low	Low	Low
Al Namankany. 2015 (Al-Namankany et al., 2015)	Low	High	High	Low	High	High

2.4 Discussion

As far as we are aware, this is the first systematic review that evaluated the effectiveness of technology-based interventions for the treatment of dental anxiety. The data show that the majority of the available technology-based interventions (i.e., video modelling, C-CBT, VRET and distraction with audio-visual video) are effective in reducing dental anxiety scores at post-intervention relative to both baseline and control conditions. However, not all included studies in the present review met reporting standards in accordance with the CONSORT check-list. Although poor reporting does not necessarily imply poor methodological quality, future studies should adhere to the CONSORT guidelines to establish transparency, methodological rigor and reproducibility of the research. Despite the fact that the majority of the technology-based interventions outperformed the inactive controls with respect to a significant reduction in dental anxiety scores (Al-Namankany et al., 2015, 2016; Gujjar et al., 2018; Kaur et al., 2017; Kazancioglu et al., 2015; Tellez et al., 2015), quality assessment revealed a high risk of bias in the majority of the included studies (Al-Namankany et al., 2015, 2016; Kaur et al., 2017; Thoma et al., 2015).

In the present review, all studies (n = 3) that tested video modelling against controls were found to be effective in reducing the severity of dental anxiety in samples consisting of both adults and children. Only one study evaluated C-CBT (Tellez et al., 2015) and found it to be effective in reducing dental anxiety. C-CBT administration also resulted in a larger proportion of patients no longer fulfilling the criteria of the dental phobia diagnosis at follow-up, compared to the controls. However, the results of this study should be viewed with caution because, unlike other included studies in which technology-based interventions were either administered by dentists (Gujjar et al., 2018; Kaur et al., 2017; Kazancioglu et al., 2015), self-administered by patients (Thoma et al., 2015) or a combinations of both (Al-Namankany et al., 2015, 2016), C-CBT was administered by trained psychologists (Tellez et al., 2015), which could have led to superior results. Future research could examine differences in treatment effects of delivering C-CBT by trained dental practitioners versus dental auxiliaries.

Only one study evaluated VRET and found it to be significantly more beneficial in terms of dental anxiety reduction compared to the informational pamphlet controls in patients diagnosed with dental phobia. At 6-month follow-up, 80% of the VRET patients did not meet the diagnostic criteria of dental phobia anymore, scheduled dental appointments and underwent dental treatment. However, the study sample consisted of only ten patients and four out of five of the VRET patients experienced moderate cybersickness post therapy (Gujjar et al., 2018). Clearly, the justification for its routine use in dental practice needs to be further substantiated by the results of long term clinical trials (Raghav et al., 2016). Hence, the observed

findings with the application of video modelling, C-CBT and VRET supports the extant knowledge on the efficacy of behavioral interventions in the treatment of dental anxiety (Wide Boman et al., 2013).

In the two distraction studies included in this review (Kaur et al., 2017; Thoma et al., 2015), the audio-visual distraction administered during dental treatment significantly reduced dental anxiety in children compared to audio distraction and treatment as usual controls (no intervention) (Kaur et al., 2017). Conversely, music relaxation administered prior to dental treatment yielded no dental anxiety reducing effect compared to the control (resting in silence) (Thoma et al., 2015). Likewise, no strong conclusions could be drawn from the studies on audio-visual distraction and music relaxation due to the limited number (n = 2) of studies, yet it could be assumed that the distraction with music and audio-visual interventions may be more effective for patients with mild forms of anxiety (De Jongh et al., 2005) compared to patients with severe dental anxiety. This is because distraction therapies operate on the principle of masking of fear-stimuli prior to or during dental treatment and do not facilitate learning in patients with dental anxiety (Lahmann et al., 2008). On the contrary, behavioral interventions with video modelling, C-CBT and VRET enable patients to control their own perception of stress during actual dental treatment (Wright & Kupietzky, 2014) and result in reduced pain sensitivity.

The data obtained from the included studies was heterogeneous, which did not allow pooled effect sizes to be calculated. It is recommended that future studies include widely used and one standardized measures (e.g. MDAS for adults) in order to allow for the aforesaid pooled analysis. Further testing of technology-based interventions using more robust methods is also needed, to support their use in general dental practice. To this end, effectiveness of technology-based interventions in dental anxiety reduction could be estimated more precisely by comparing these to the gold standard CBT. Comparison with CBT would allow drawing of valid conclusions on whether beneficial effects of technology-based interventions (in terms of symptom reduction, cost-effectiveness and patient satisfaction) extend beyond those of already available interventions such as CBT provided by psychologists and trained dentists.

Probably the most prominent methodological limitation observed in the majority of the included studies was the absence of independent outcome assessors (Al-Namankany et al., 2015, 2016; Kazancioglu et al., 2015; Tellez et al., 2015; Thoma et al., 2015) and behavioral avoidance tests (Al-Namankany et al., 2015, 2016; Kaur et al., 2017; Kazancioglu et al., 2015; Tellez et al., 2015; Thoma et al., 2015). With regard to the latter, inclusion of an observer rated behavioral avoidance test (BAT) before and after the intervention rather than an evaluation with a self-report measure would be invaluable in future studies to determine, and to predict the effects of treatment on patients' behavior in real dental, potentially anxiety provoking situations. Although, most

of the included studies showed reductions in dental anxiety, increased attendance at future dental appointments is the ultimate goal. No analyses were conducted to evaluate attendance rates because the follow-up periods in most studies was too brief. Likewise, only one study reported on the safety aspects of the intervention (Gujjar et al., 2018). Hence, for future research we recommend the use of reliable and valid outcome measures to assess patient safety, acceptability, satisfaction, attendance, and cost-effectiveness of technology-based interventions.

We found several studies that examined the effectiveness of combinations of technology and non-technology-based interventions. These were excluded from the present review because it is difficult to draw any inferences about the effectiveness of the constituent standalone interventions. Examining the evidence base for the effectiveness of standalone technology-based interventions first could eventually lead to more effective combination therapies tailored to the needs of specific populations.

The main limitation of the present review was the small number of studies that were found eligible to be included. Thus, the conclusions drawn must be considered tentative. Also, publication in English language was an inclusion criterion, which precluded inclusion of potentially eligible studies published in other languages.

In conclusion, within the limitations of the systematic review, the results converge to suggest that technology-based interventions are useful as adjunct to standard dental care, evidence regarding the effectiveness of these interventions in children and adult population is still scarce. Yet, emerging technology-based interventions hold promise because, potentially, these may be capable in overcoming the shortcomings of traditional treatment of dental anxiety. Further, these may have possible remote applications for treatment of dental anxiety due to their adaptability to be delivered through the internet or by self-administration (Gordon, Heimberg, Tellez, & Ismail, 2013). For instance, in resource poor settings, where dentists are not available to devote time for treatment of dental anxiety, dental auxiliaries could be trained in administering technology-based interventions for treatment of dental anxiety. Accordingly, high quality trials are needed to determine the (relative) effectiveness of emerging interventions such as smart-phone based exposure treatment (McNeil, 2018), VR enhanced video exposure therapy (Adolph, 2017), VRET (Raghav et al., 2016) and internet-based CBT (Shahnavaz et al., 2018) for treatment of dental anxiety.

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Chapter 3. Virtual reality exposure therapy for the treatment of dental phobia*

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3.1 Introduction

Research suggests that 50-60% of individuals suffer from a specific fear of dental procedures and dental related objects and situations (De Jongh, Adair, & Meijerink-Anderson, 2005). This fear can result in reduced dental visits (Armfield, Stewart, & Spencer, 2007) and poor oral health (Armfield, Slade, & Spencer, 2009). When the avoidance (Oosterink, De Jongh, & Hoogstraten, 2009), anxious anticipation (Coriat, 1946), or distress (van Wijk & Hoogstraten, 2003) in the feared situations interferes significantly with the person's normal routine, occupational functioning, social activities or relationships, or there is a marked distress about having the dental fear, the condition is termed as 'dental phobia'. Dental phobia is classified as a specific phobia within the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders-fifth edition; American Psychiatric Association, 2013).

With regard to the treatment of fears and phobias, therapeutic procedures using gradual and systematic confrontations with the fearful objects and situations, such as systematic desensitization and *in vivo* exposure, are the first line treatments (American Psychological Association, 2006; Deacon & Abramowitz, 2004; Moore, Brodsgaard, & Abrahamsen, 2002). These procedures can be applied either in imaginal (*in vitro*), or in real life (*in vivo*). Since imaginary procedures have been found to be less effective than *in vivo* exposure, the latter has generally been accepted as the treatment of choice (Emmelkamp, Bouman, & Scholing, 1992). The basic assumption of *in vivo* exposure is that a fear response gradually extinguishes when the provoking stimulus (for instance, the sound of the drill) is repeatedly presented, but is not followed by an aversive event (e.g., one involving pain) so that the person learns that such feared consequence is not likely to happen (Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014).

A large array of studies supports the efficacy of exposure therapy as the treatment of choice for specific fears and phobias, (American Psychological Association, 2006; Deacon & Abramowitz, 2004; Moore et al., 2002) including dental related fears (Gauthier, Savard, Hallé, & Dufour, 1985; Moore, Brodsgaard, Berggren, & Carlsson,

* Gujjar, K. R., Sharma, R., & De Jongh, A. (2017). Virtual reality exposure therapy for treatment of dental phobia. *Dental Update, 44*(5), 423-435. doi:10.12968/denu.2017.44.5.423

1991; Smith, Kroeger, Lyon, & Mullins, 1990; Gros & Antony, 2006). However, one major drawback of this approach that has been identified, is that individuals may be too frightened to face their fears due to anticipatory anxiety (Coriat, 1946) of getting harmed while confronting with the real situation (as in *in-vivo* exposure therapy). This may result in refusal or termination of therapy (Garcia-Palacios, Hoffman, See, Tsai, & Botella, 2001). Thus, any therapy for dental anxiety which is less mentally demanding for dental phobic patients could potentially improve their compliance and adherence to treatment.

Virtual Reality Exposure Therapy (VRET) is a relatively novel cognitive-behavioral approach which has been successfully used for treating a number of specific phobia subtypes, including fear of enclosed spaces, (Botella, Baños, Villa, Perpiñá, & García-Palacios, 2000) fear of heights, (Krijn et al., 2004) fear of flying (Muhlberger, Wiedemann, & Pauli, 2003) and spider phobia (Garcia-Palacios, Hoffman, Carlin, Furness, & Botella, 2002). VRET is carried out in a contextually-related (Parsons & Rizzo, 2008) computer-generated virtual environment, which facilitates systematic confrontations with the fear provoking stimuli.

One important advantage of VRET is that the clients face the computer generated (virtual) counterpart of their fearful stimuli in a gradual and controlled manner (McLay et al., 2012) at their own pace (Baus & Bouchard, 2014), and under the privacy of the therapist's office (North, North, & Coble, 1997). Additionally, while *in vivo* exposure is usually delivered by a trained psychologist, and requires training on the part of therapist, administration of VRET may only need knowledge of computer operation and training to run the VRET software (Raghav et al., 2016). Moreover, VRET may also be safer, less embarrassing, and cost-effective therapy compared to reproducing a real-world situation as in *in vivo* exposure (Wald, 2004). Indeed, a recent meta-analysis has suggested that VRET is equally effective, and slightly better compared to the gold standard *in vivo* exposure therapy, in the treatment of anxiety disorders (Powers & Emmelkamp, 2008).

Although, VRET exhibits a powerful means of modifying affect because of its immersive nature, the effectiveness of VRET has not been tested yet on patients suffering from dental phobia. The aim of this case report is to present the initial findings of the application of VRET on two patients with dental phobia.

3.2 Case Presentation

Two patients reported to SEGi Oral health centre, Malaysia with a history of repeated avoidance of dental treatment and self-reported dental fear for more than two years.

Patient A was a 56 year old Malay female with fear of pain and sensitivity resulting from the use of the dental drill. Her fear of dental drills had roots in a

traumatic childhood dental experience. During the clinical interview, she recounted that at the age of 12 years, she was subjected to a dental drill and fill procedure whilst she experienced severe sensitivity and pain. On reporting the pain, she was ridiculed and forced to complete the treatment by the dentist and the nurse. She reported having painful memories of "very rough handling" by her dentist and her experience of "gripping the handle of the dental chair tightly". The scolding, belittlement and embarrassment accrued from the dental team initiated intense distrust and fear towards subsequent dental treatments. She had evaded dental treatment for the past 2 years when she reported to us. At the time of her visit, she required multiple dental fillings and was extremely anxious about her dental treatment procedures.

Patient B was a 24 year old Malay female who was extremely fearful of getting pain and sensitivity from sharp dental instruments and dental drills. Similar to the previous case, her dental fear also had origins in a childhood traumatic dental experiences, starting when she was 10 years old. She described the dentist jabbing her gums many times while performing scaling which resulted in severe pain and bleeding. The dentist did not respond to her pleas to stop even after telling repeatedly that the scaler was hurting her. She was also horrified to see a significant amount of blood in her spit after the procedure. The second traumatic dental experience occurred when she was 16 years old, and visited another dentist for a tooth restoration procedure. She recollected feeling helpless during the procedure as the injection was ineffective and despite complaining about sensitivity, the dentist did not stop drilling her tooth. Her traumatic dental experiences resulted in an extreme distrust of dentists and complete avoidance of any dental treatment for 3 years. During her visit, she required several dental procedures such as scaling and dental restorations and was extremely anxious about her dental treatment.

The specific clinical criteria of the two patients included, the lack of any:

1. Hearing or visual impairments such as stereoscopy blindness or nystagmus.
2. Mental disorders such as psychosis, post-traumatic stress disorder, developmental or intellectual disability and cognitive impairment.
3. Known balance disorders such as vertigo and cybersickness.
4. Previous history of epileptic seizures.
5. History of cardiac problems.

Further, both patients had no other specific phobia and had never received any treatment for their dental anxiety in the past.

The patients were interviewed using the 'phobia checklist' (Oosterink et al., 2009) for dental phobia. Based on the history, examination and 'phobia checklist' criteria, the diagnosis 'dental phobia' was confirmed for both the patients.

3.3 Treatment

The patients were explained about the procedure of VRET in detail and informed consents were obtained from both patients. They self-rated their baseline level of state anxiety with a Visual Analogue Scale (VAS-A), and their level of dental trait anxiety with both the Modified Dental Anxiety Scale (MDAS), and the Dental Fear Survey (DFS). In addition, prior to therapy the patients underwent a behavior test to assess their ability to confront dental situations.

VRET was conducted with a simulator computer which rendered the virtual dental environment and the other (user interface) computer allowed the researcher (KR) to control and individualize stimuli presented. The simulator computer comprised of DELL XPS 8700 Desktop with NVIDIA GeForce GTX 750 TI OC 2GB GDDR5 graphic card. The simulator computer displayed 3D stereoscopic scene through the Oculus Development Kit-2 Head Mounted Device (HMD) to the patient.

The patients were asked to sit in the dental chair and were assisted in wearing the HMD by the researcher. The VR (Virtual Reality) system displayed a surrounding 3D stereoscopic scene of a simulated dental operatory with a dental chair, overhead light, and dental instruments through the HMD to the patients. To enhance immersion characteristic of the virtual environment, typical smell of a dental clinic (drops of oil of cloves on cotton wool) was introduced. Initially, the patients were made to view the simulated dental environment scene passively for two minutes to facilitate orientation. The built-in motion tracking in the HMD allowed the patients to turn their head and look around. The patients were able to see their virtual counterpart inside the HMD as they explored the virtual dental operatory by moving their head.

The researcher was able to view and control what the patients were seeing in the simulated dental environment on the user interface computer screen (e.g. virtual dentist movements). Patients were exposed to the following hierarchy of virtual scenarios:

1. Sitting on the dental chair (no tools), screen shot shown in Figure 3.1.
2. Inspection of the oral cavity using mouth mirrors, screen shot shown in Figure 3.2.
3. The introduction of an injection, screen shot shown in Figure 3.3.
4. The introduction of drills without sounds, screen shot shown in Figure 3.4.
5. The introduction of drills with sounds, screen shot shown in Figure 3.4.

Exposure to the above mentioned scenes was well-controlled.

Patients received the VRET in multiple sessions with different scenarios. They were asked to rate their current distress at the end of each exposure, using a Subjective Units of Distress (SUD) scale. Each scenario sequence was repeated a number of times until patient's distress decreased substantially before proceeding to the next scenario. The patients were encouraged to keep their mouth slightly open from

scenario 2 through 5 and were instructed to follow the directions of the researcher. They were assured that their mouth would not be touched at any point during the VRET session. The patients were allowed to progress at their own pace. If the SUDS scores of the patient during exposure with any of the VR scenario increased, the subsequent exposures were continued until the participant felt able to overcome the fearful stimuli as demonstrated by lower SUDS scores (< 3).

After the VR exposure session, the patients reported their state anxiety (VAS-A) and dental trait anxiety (MDAS and DFS) levels. They also rated their VR experience, intentions to undergo VRET in the future, and underwent a behavior test to determine the extent of the patients' ability to confront dental situations immediately after VRET. The patients were offered the opportunity to return to the SEGi oral health centre later and avail an actual dental procedure. They were not offered any incentive or discount for the dental treatment.

Patients' state anxiety level (VAS-A), and severity of dental trait anxiety (MDAS, and DFS) were assessed at baseline, immediately after VRET, after their first dental visit post VRET, and at 6 months follow-up. Also at 6 months follow-up, the phobia checklist was used to determine whether the patients fulfilled the criteria for dental phobia.

3.4 Measures

3.4.1 Subjective Units of Distress (SUD) scale

A SUD scale was used to index the intensity of subjective distress currently experienced by the patients (Wolpe, 1969). It is used by therapists as a standard measure to evaluate the progress of exposure-based therapies. Typically, the patient is asked by the therapist: "*On a scale of 0-10, where 0 is no discomfort and 10 is the worst discomfort you can experience, how much discomfort do you feel right now?*" For this case report, the researcher recorded the SUDS scores during each exposure of the VRET session. Patient was moved to the next hierarchy level of VRET only when their current anxiety level was reduced to < 3 SUD score. Patients were not aware of this criterion. Each scenario was repeated until the anxiety decreased to the desired level (< 3 or less) and only then the next scenario was introduced.

3.4.2 State anxiety

State anxiety level was determined utilizing the Visual Analogue Scale for Anxiety (VAS-A) (Luyk, Beck, & Weaver, 1988) at baseline, immediately following VRET, after their first dental visit and at 6 months post VRET. The VAS-A has been found to be a simple, sensitive, fast, reliable and valid tool to measure level of state anxiety (Facco et al., 2011).

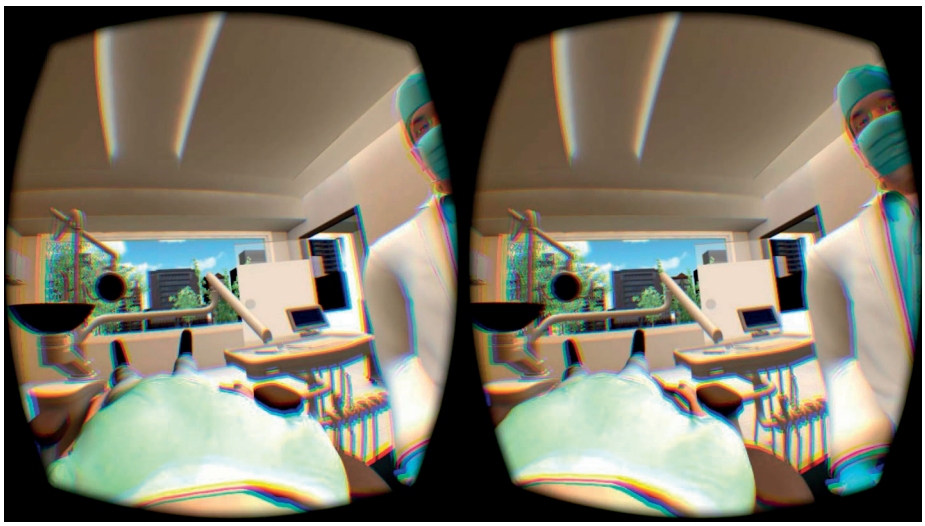


Figure 3.1 Screen shot of scenario-1 of sitting on the dental chair.

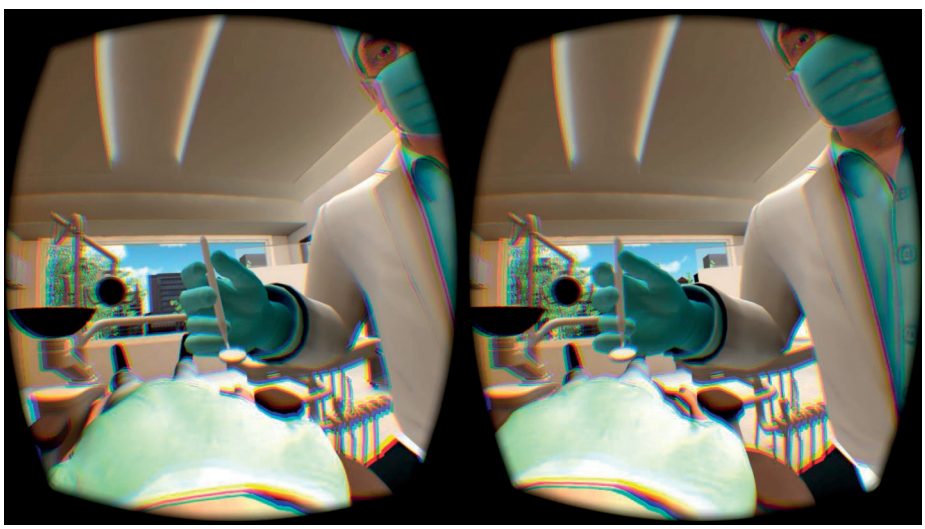


Figure 3.2 Screen shot of scenario-2 during examination of the oral cavity with mouth mirrors.

3.4.3 Dental trait anxiety

Severity of dental trait anxiety was measured using Modified Dental Anxiety Scale (MDAS) (Humphris, Morrison, & Lindsay, 1995) and Dental Fear Survey (DFS) (Kleinknecht, Klepac, & Alexander, 1973) at baseline, immediately after VRET, after their first dental visit and at 6 months post VRET. Possible MDAS

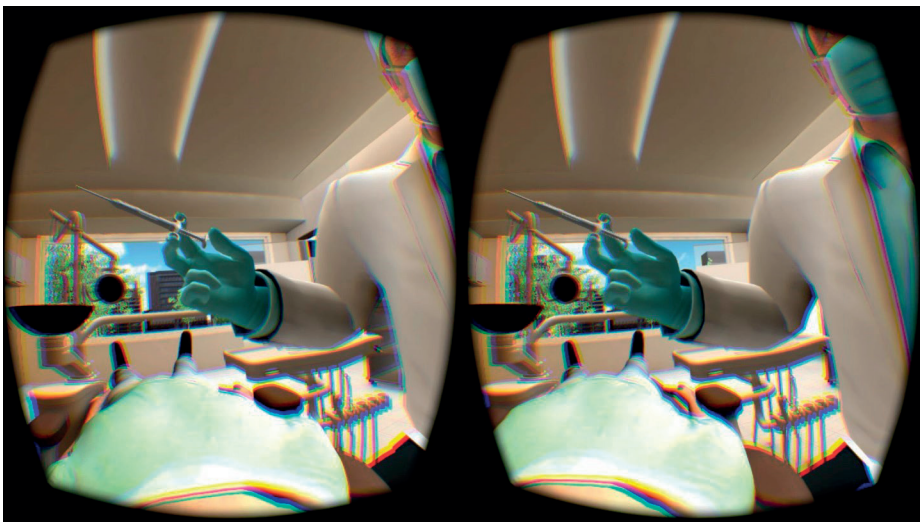


Figure 3.3 Screen shot of scenario-3 during introduction of the dental injection.

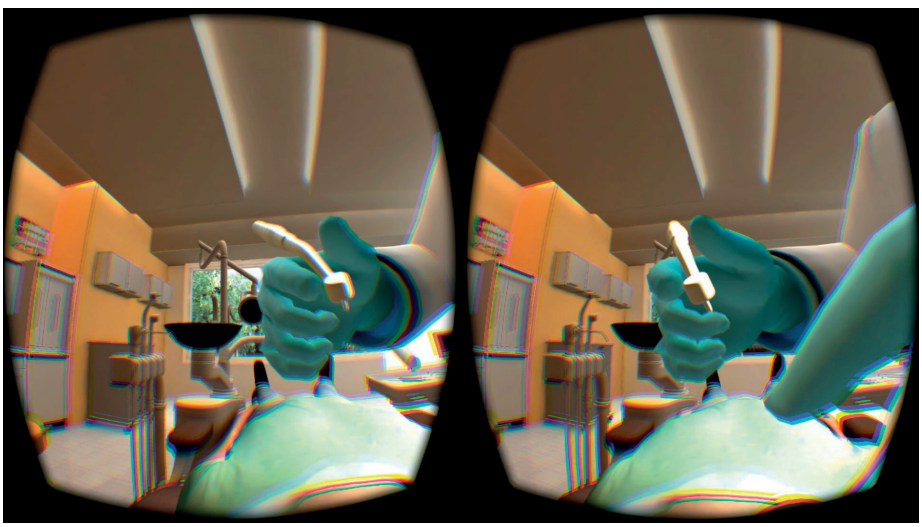


Figure 3.4 Screenshot of scenario-4 and 5 during dental drill procedure.

scores range from 5 to 25, with greater scores indicating higher level of dental trait anxiety. The MDAS has shown high levels of internal consistency and good construct validity (Humphris, Freeman, Campbell, Tuutti, & D'Souza, 2000). Possible DFS scores range from 20 to 100, with greater scores indicating higher levels of dental anxiety. The DFS has established reliability, validity and sensitivity (Davis, Ollendick, & Öst, 2012).

3.4.4 Behavior test

A Behavior test was conducted prior to, and immediately after VRET based on the self-reported measure of the patients' level of discomfort to the contrived situation (Hersen, 2006). The test was similar to the VRET scenarios, and provided a baseline behavioral assessment measure to compare the responses of the patient before and after the VRET. The test was similar to the one used by Doering et al, (Doering, Ohlmeier, De Jongh, Hofmann, & Bisping, 2013) and comprised of introducing five situations that usually occur during a dental visit (i.e., sitting in the dental chair, inspection of the oral cavity using two dental mirrors, showing the patient an approaching dental syringe, showing the patient an approaching dental drill, both with and without sound). Patients were asked by the observer to assess his/her level of anxiety on a scale of 0–10 in each situation (Doering et al., 2013) during each of the aforementioned dental situations. This behaviour test was performed at baseline and after completion of VRET.

3.4.5 VR experience

Immediately after VRET, the patients rated the level of "presence", "realism" and "severity of nausea" using 11-point verbal rating scales (VRS; Hoffman et al., 2001). Their intentions to undergo VRET in the future and to revisit the dental office for treatment were also measured using the 11-point VRS (Juster, 1966)

3.4.6 Phobia Checklist

The phobia checklist was used for the assessment of dental phobia in this case report (Oosterink et al., 2009). This specific screening tool for measuring dental phobia has been validated against the Structured Clinical Interview for DSM-IV (First & Gibbon, 2004) with a sensitivity of 0.95, specificity of 0.99, and an overall hit rate of 97% (Oosterink et al., 2009). The phobia checklist consists of four questions based on the DSM-IV-TR criteria (American Psychiatric Association, 2000) for specific phobia. The patients are told to mark either a 'YES' or 'NO' response against the following questions related to their dental anxiety:

a. The sight of the feared object or experiencing the situation evokes an excessive fear response.
b. The fear is greater than justified.
c. Avoidance or giving up things because of the fear.
d. Avoidance of the situation or object causes daily impairment

An individual is categorized as dental phobic only upon answering as 'YES' against all four questions of the phobia checklist in affirmative. In the present case report, the checklist was administered during diagnostic interview and at 6 month follow-up. At diagnostic interview, both patients responded as 'YES' against all the statements and hence were classified as dental phobic.

3.5 Results

Patient A and B received VRET in a single appointment for a duration of 25 minutes and 20 minutes respectively. Table 3.1 shows self-reported dental anxiety scores at different time points for both patients. The state anxiety (VAS-A) and dental trait anxiety (MDAS, DFS) scores showed a downward trend following VRET. The gains were maintained until follow-up of 6 months for both the patients. Table 3.2 shows reduction in behavioral test scores post-VRET. Graph-3.1 shows the number of VRET sessions that were required to reach SUDS of ≤ 3 with different VR scenarios for both the patients.

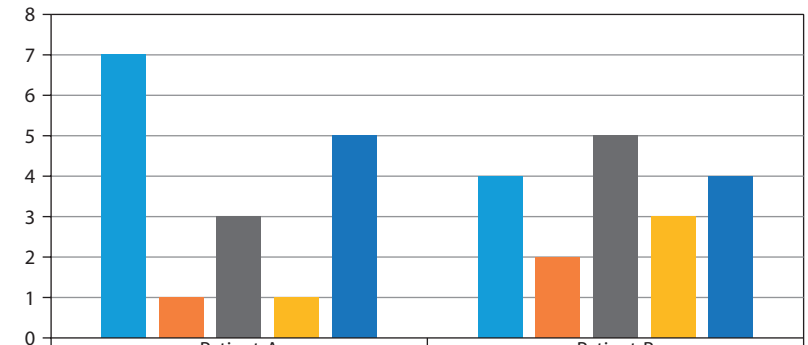
Table 3.1 Dental anxiety scores at different time points.

Measures	Patient-A				Patient-B			
	Baseline	Immediately after VRET	1st dental treatment after VRET	**6 months follow-up**	Baseline	Immediately after VRET	1st dental treatment after VRET	**6 months follow-up**
VAS-A	70	15	10	**10**	55	0	0	**0**
MDAS	21	13	8	**7**	17	7	7	**7**
DFS	71	25	34	**32**	65	35	26	**25**

Table 3.2 Pre-VRET and post-VRET scores of behavioral test.

Behavior test	Patient-A		Patient-B	
	Pre-VRET	Post-VRET	Pre-VRET	Post-VRET
Sitting on the chair	6	2	6	1
Mouth Mirror	5	3	7	1
Syringe	5	3	10	2
Drill with no sound	7	3	7	1
Drill with sound	7	3	7	2

Patients A and B rated the "presence" they felt during VRET at 10 and 8 respectively. Both rated the "realism" of the virtual world at 10. Patient A reported mild



	Patient-A	Patient-B
Sitting on Chair	7	4
Mouth mirror	1	2
Syringe	3	5
Drill without sound	1	3
Drill with sound	5	4

Graph 3.1 shows the number of VRET sessions that were required to reach SUDS of ≤ 3 with different VR scenarios for both the patients.

nausea after the VRET. When evaluated for their intentions to undergo VRET in the future, patient A indicated that there was "a good possibility", and patient B indicated this to be "very probable". Patient A indicated to be "almost sure" and patient B to be "certain" about revisiting the dental clinic again. Within 6 months after VRET, patient A underwent scaling, multiple fillings and crown placement at a private clinic, whereas patient B underwent scaling and multiple dental restorations. Upon evaluation at 6 months follow-up, both patients did not meet the criteria for dental phobia based upon the phobia checklist for dental phobia.

3.6 Discussion

To our knowledge, this case report was the first to explore the applicability of VRET in the treatment of dental phobia. VRET resulted in a notable reduction of various self-reported dental anxiety scores. The treatment gains were maintained after having undergone a real dental treatment, and at six month follow-up. Both patients enjoyed the therapy and acknowledged that it had proved very useful to them in reducing their dental anxiety. Most importantly, their tendency to avoid dental treatment disappeared, and both of them were able to undergo dental procedures successfully within 6 months after receiving VRET. Notably, both patients no longer met the criteria for dental phobia at 6 months follow-up.

Efficacious use of VRET in the treatment of dental anxiety as demonstrated in this case report is comparable to its success in the treatment of other anxiety disorders such as fear of enclosed spaces (Botella et al., 2000), fear of heights (Krijn et al., 2004), fear of flying (Muhlberger et al., 2003) and spider phobia (Garcia-Palacios et al., 2002).

There are substantial limitations that relate to case report methodology in general (Campbell, Stanley, & Gage, 1963), hence we need to be cautious in interpreting the results. The study was conducted only on two female dental phobic patients. However, both the patients responded well to VRET. The approximate duration of the VRET session ranges from 20-150 minutes based on the results of our pilot studies. From a practical point of view, one minor issue associated with the use of VR seems to be the occurrence of simulation sickness experienced by some patients. In the present case, patient A who had not reported any history of simulation sickness, developed very mild nausea following VRET. The reason could be due to prolonged VR exposure for 25 minutes. To this end, it is important to note that for VRET to be effective, the VR environment should make the patients "feel present" (Krijn, Emmelkamp, Olafsson, & Biemond, 2004; Krijn et al., 2004) in the fear provoking environment (Baus & Bouchard, 2014) just as a realistic experience enables the patients to confront their anxiety-provoking stimuli (Garcia-Palacios et al., 2001). Although this has the potential disadvantage of inducing some simulation sickness, however, the positive effects of VRET on dental anxiety in this case report could be attributed to high levels of presence and realism experienced by both the patients. There is evidence to suggest that simulation sickness can be prevented by administering VRET for less than 20 minutes or by giving breaks to the patient during the VRET sessions (Hoffman et al., 2001).

An advantage of VRET is that it is flexible to use as the exposure scenarios can be stopped, paused, restarted and repeated, whenever and, for as many times as considered necessary (Baus & Bouchard, 2014). VRET for the treatment of dental phobia may not require any special training, a basic knowledge to operate the computer and to run the VRET software may be sufficient to administer VRET. The entire exposure process may be accomplished by a dental auxiliary using a computer in the safety and privacy of the practitioner's office (Baus & Bouchard, 2014). Moreover, it can be used in situations where *in-vivo* exposure is considered risky for the patient (Wald, 2004). The results from this case report seem to be promising. However, in order to establish the efficacy of VRET in treatment of dental anxiety, these results are awaiting replication using carefully controlled trials.

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Chapter 4. Is virtual reality exposure therapy (VRET) the future treatment for anxious dental patients?*

Kumar Raghav Gujjar, Ad de Jongh

4.1 Introduction

Fear of dental treatment is very common (Hill, Chadwick, Freeman, O'sullivan, & Murray, 2013; Humphris & King, 2011; Nicolas, Collado, Faulks, Bullier, & Hennequin, 2007; Oosterink, De Jongh, & Hoogstraten, 2009). It is estimated that as many as 75% of the US adults experience dental fear ranging from mild to severe (Getka & Glass, 1992; Milgrom, Weinstein, & Getz, 1995). In the UK, 15% of adults suffer from extreme dental fear (British Dental Health Foundation, n.d.). Dental phobia, the severe form of dental fear which entails a set of diagnostic criteria as defined by DSM-5, has been found to be the most common type of phobia (about 4%) in the general population, followed by height phobia and spider phobia (Oosterink et al., 2009).

Research has consistently demonstrated that dental fears and phobias result in reduced dental visits (Armfield, Spencer, & Stewart, 2006), poor oral health (Armfield, Slade, & Spencer, 2009), and reduced quality of life (Vermaire, De Jongh, & Aartman, 2008). People who display apprehension of undergoing dental treatment often find themselves caught in a vicious cycle of avoidance. Dental fear makes people avoid dental care until they are confronted with a dental emergency requiring invasive treatment that further reinforces their fear of dental objects and situations (Armfield, Stewart, & Spencer, 2007; De Jongh, Schutjes, & Aartman, 2011).

Dental phobia and related avoidance of dental care are significant problems for both patients and the dental professional. Treatment of patients with this condition may be more time consuming as they are difficult to manage during treatment session and are likely to be dissatisfied with the treatment they receive (Quteish Taani, 2002). Adequate management of distress and fear associated with dentistry is important as it can enhance the overall treatment experience of both patient and the dentist by reducing patients' perceived pain and unpleasantness (Villemure,

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Slotnick, & Bushnell, 2003) and by enabling the dentist to work effectively and efficiently (Bare & Dundes, 2004).

4.2 Treatment of dental phobia

There is broad consensus that those experiencing dental fear and phobia benefit from Cognitive Behavioral Therapy (CBT; Deacon & Abramowitz, 2004; Moore, Brodsgaard, & Abrahamsen, 2002; Wide Boman, Carlsson, Westin, & Hakeberg, 2013) based interventions. The standard procedure advocated for management of dental phobia is in-vivo exposure therapy which involves systematic and repeated encounters of patients with situations that cause anxiety (e.g., an injection needle or the sound of the drill; Gros & Antony, 2006; Wide Boman et al., 2013). However, in-vivo exposure therapy is often difficult to administer as phobic patients are reluctant to face the threat. It has been widely reported that when patients realize that the exposure therapy entails facing the threat (in this case dental treatment), about 25% of them either refuse the therapy or terminate it (Garcia-Palacios, Hoffman, See, Tsai, & Botella, 2001). Consequently, a significant number of individuals fail to achieve clinically significant symptom relief or experience a return of fear following exposure therapy (Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014). Even delivery of appropriate therapy for dental phobia may not be feasible or affordable as psychological services for dentally anxious patients are scarce (Allen & Girdler, 2005) and treatment costs are high (Boyle, Newton, & Milgrom, 2010). Also, not all general dentists have time or the training to provide CBT. Pharmacological interventions such as intravenous sedation and general anesthesia frequently advised in cases of dental phobia do not extinguish the fear response in the long term, resulting in maintenance of avoidance of dental situations (De Jongh, Adair, & Meijerink-Anderson, 2005).

During the last decade, several technology-based interventions such as Computer- Assisted Relaxation and Learning (CARL; Heaton, Leroux, Ruff, & Coldwell, 2013), Computerized-CBT (C-CBT; Tellez et al., 2015) and Virtual Reality Exposure Therapy (VRET; Gujjar, Sharma, & De Jongh, 2017; Gujjar, van Wijk, Kumar, & De Jongh, 2019; Gujjar, van Wijk, Sharma, & De Jongh, 2017) have been developed to help alleviate patients' dental anxiety. CARL is a computer based exposure therapy which trains the patient in relaxation, distraction and enhancement of their self-efficacy. This program is designed to first run in in-vitro mode followed by an in-vivo mode. The in-vitro mode involves computer controlled, hierarchical exposure of patients to video-taped scenes of injection procedure, while the in-vivo mode involves exposing the patients to a hierarchy of real life injection procedure. C- CBT involves computerized psycho-education, motivational interviewing and fear

reduction via exposure to videos of patients' fear eliciting stimuli. However, both CARL and C-CBT have drawbacks such as not being engaging enough due to their video based formats and possible reluctance of phobic patients to face needles in real life in case of CARL's in-vivo mode (Garcia-Palacios et al., 2001). VRET does not involve making the patient face real life threats or view videos passively and could address the limitations of CARL and C-CBT. Further, VRET allows exposure to be carried out in multiple dental contexts (e.g., diagnostic instruments, syringe and dental drills), while being both less invasive and more immersive for the patients.

4.3 Virtual Reality Exposure Therapy (VRET)

According to the dictionary, virtual reality is an "artificial environment which is experienced through sensory stimuli (such as sights and sounds) provided by a computer" (Webster, 2018). Using virtual reality for treatment of phobias involves controlled exposure of the phobic patients to the virtual sights and sounds of their fear provoking stimuli. VRET integrates real-time computer graphics and body tracking devices to systematically expose patients to an immersive, interactive and highly controllable computer-generated virtual environment with rich sensory visual, olfactory and auditory cues (Maples-Keller, Yasinski, Manjin, & Rothbaum, 2017) within a contextually relevant setting (Parsons & Rizzo, 2008). From a theoretical perspective, the suggested VRET mechanism embodies the mechanism of traditional exposure therapy wherein emotional processing is facilitated by activation of the underlying fear structure through controlled confrontations with individuals' feared (i.e., conditioned) stimuli in absence of an aversive event in a therapeutic setting until extinction occurs (Maples-Keller et al., 2017). For VRET to be effective, patients should feel engaged and perceive themselves to be physically present and interacting in the virtual world. Thus, presence is assumed to be an important mediating variable between the VR media and the level of the anxiety induced (Alsina-Jurnet, Gutiérrez-Maldonado, & Rangel-Gómez, 2011).

The rich multi-sensory VRET has been found effective in the treatment of several specific phobia subtypes, including flying phobia, arachnophobia, height phobia, driving phobia and dental phobia (Botella, Fernandez-Alvarez, Guillen, Garcia-Palacios, & Banos, 2017; Gujjar et al., 2019; Gujjar, van Wijk, et al., 2017; Maples-Keller et al., 2017). In fact, results of five independent meta-analyses show that VRET is effective in reducing symptoms of anxiety-related disorders (Carl et al., 2018; Morina, Ijntema, Meyerbroker, & Emmelkamp, 2015; Opris et al., 2012; Parsons & Rizzo, 2008; Powers & Emmelkamp, 2008). Further, there is evidence suggesting that VRET is slightly, but significantly, more effective than in vivo exposure therapy in treatment of specific phobias (Powers & Emmelkamp, 2008).

The purpose of this paper is to present two unique cases and discuss the use, the potential advantages and limitations of VRET within the context of general dental practice. We have conducted pioneering research examining the potential of VRET in treatment of dental phobia. Results of our studies [(a multiple baseline feasibility study) (Gujjar, van Wijk, et al., 2017) and RCT (Gujjar et al., 2019)] show that VRET is associated with a significant reduction in both state and dental trait anxiety scores and an improvement in dental treatment acceptance, compared to the study control condition. Although VRET has shown promising results in the treatment of dental phobia in our earlier studies (Gujjar, Sharma, et al., 2017; Gujjar et al., 2019; Gujjar, van Wijk, et al., 2017), it should be noted that we only tested VRET among adults in a single session. Because multiple VRET sessions generally yield larger effect sizes (Powers & Emmelkamp, 2008), we present the first findings about the applicability of VRET in an adult patient with severe dental phobia. Furthermore, we present the results of our first case in a pediatric patient with dental phobia who underwent a single VRET session. However, as VRET is a novel technique, we first describe the VRET set-up.

4.3.1 VRET set-up

The VRET device consists of a user-interface computer, a simulator computer and a head mounted device (HMD) as shown in Figure 4.1. Simulator computer systematically exposes the patient to a virtual dental environment by displaying a 3D stereoscopic[2] scene through the HMD worn by the patient. The virtual dental environment comprises of a simulated dental operatory with a dental chair, overhead light, dental instruments and a virtual dentist. Patients see their virtual counterpart (torso and legs as seen by ourselves when sitting in a dental chair) in first person and the entire dental operatory through the HMD when they turn their heads around to look. The VRET operator (e.g. general dentist/therapist) watches and controls what the patients observe in the virtual dental environment with a user-interface computer.

Patients undergoing VRET with our current VRET device[3] receive standardized step-wise exposure to the following hierarchy of virtual dental scenarios:

1. VR1- Sitting in the dental chair and looking around the dental operatory surrounded with instruments and a virtual dentist on the right hand side.
2. VR2- Virtual dentist moves with a dental mirror towards the patients seemingly to do an oral examination.

2 Stereoscopic" refers to the process of watching two different images of an object at different angulations at the same time creating a sense of depth and solidity in the image.

3 DELL XPS 8700 Desktop with a NVIDIA GeForce GTX 750 TI OC 2GB GDDR5 graphic card and the Oculus Development Kit-2 Head Mounted Device (HMD). We used the license of commercial "DATS" (Dentist Anxiety Treatment Simulator) product developed by Virtual Simulations Inc. Interested parties may contact info@virtasim.com for further information.

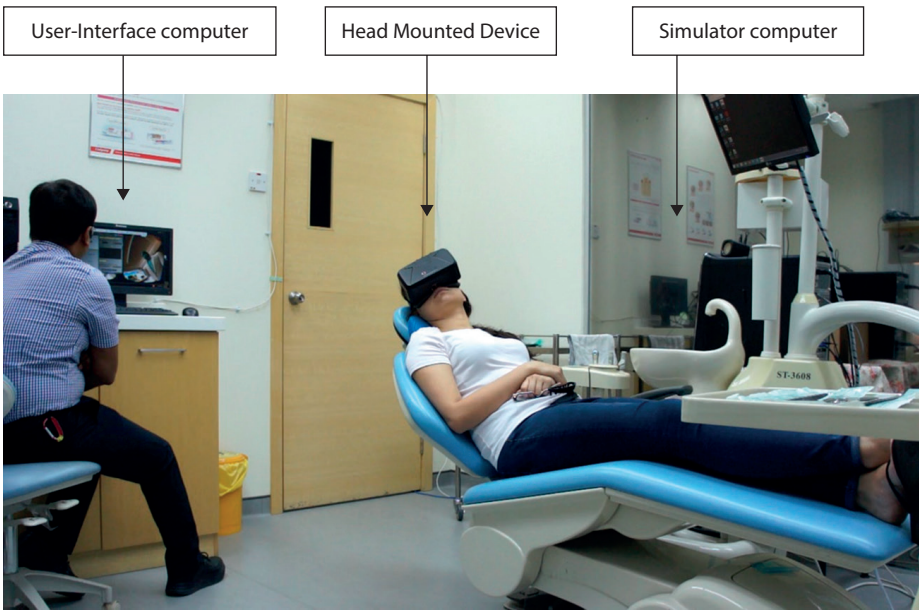

Figure 4.1 Showing the VRET device.

3. VR3- Virtual dentist carries a dental syringe towards the patient.
4. VR4- Virtual dentist carries a dental drill (with no sound) towards the patient.
5. VR5- Virtual dentist carries a dental drill (with sound) towards the patient.

Patients are encouraged to keep their mouth open from scenarios VR2-VR5. During the session, patients are requested to focus on their fear-eliciting stimuli and to describe any strange sensations or feelings. They are asked to rate their level of distress on the Subjective Unit of Distress Score (SUDS) ranging from 0 to 10 where, 0 is 'no discomfort' and 10 is 'the worst distress experienced' (Wolpe, 1969). Each scenario is repeatedly presented to the patient until a SUDS of ≤ 2 is achieved, after which the next scenario is presented. Patients undergo exposure at their own pace and the duration of VRET is flexible based on the ability of patients to confront all the VR scenarios in a single visit. For instance, if they feel overwhelmed due to fear during the first session, they were scheduled another appointment for an additional VRET session and the exposure starts again with the first scenario (VR1). Additional VRET sessions are conducted until the patients confronts all VR scenarios (VR1-VR5) in a single session. Figure 4.2 shows the pictorial representation of the VRET set-up.

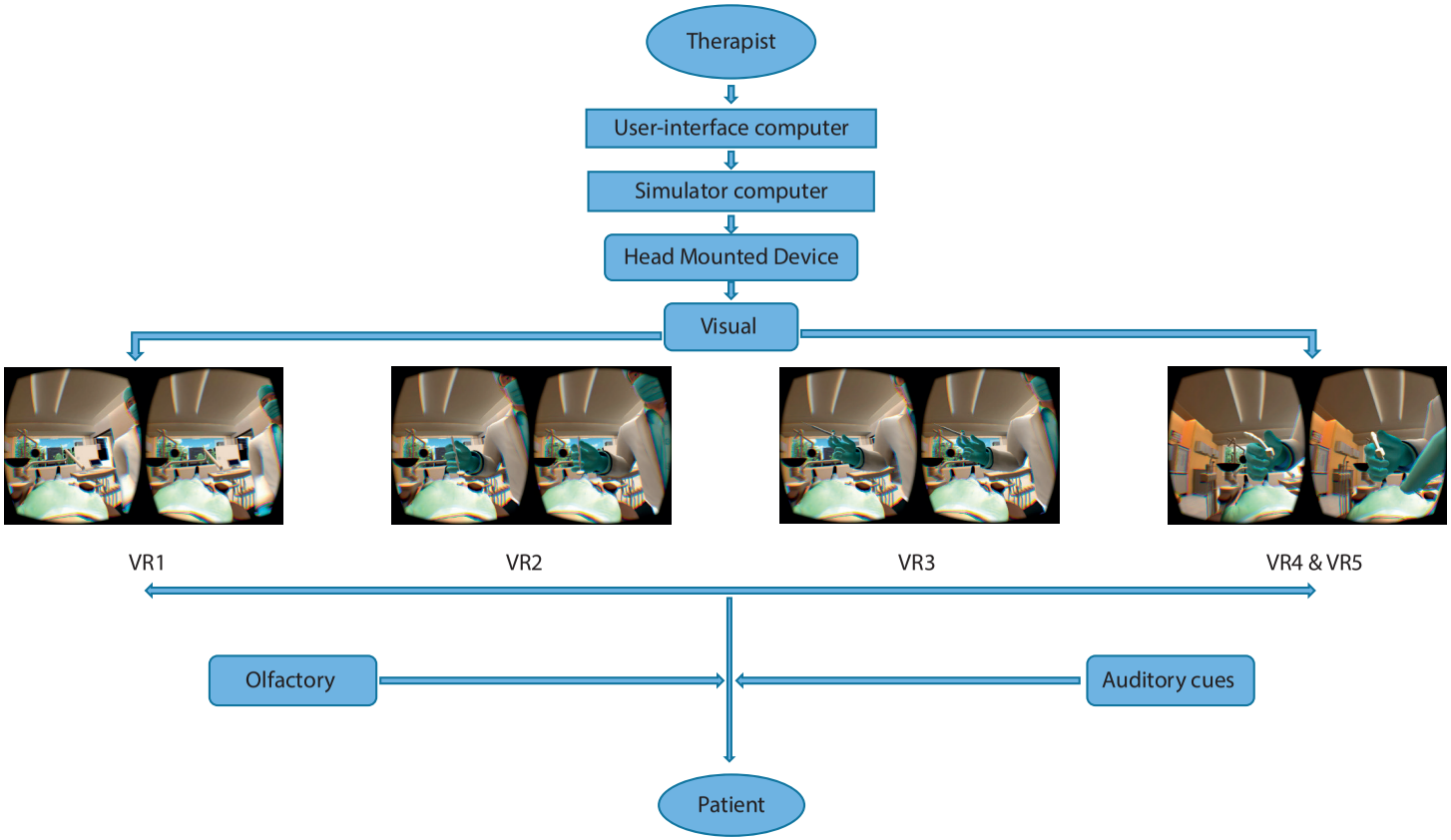

Figure 4.2 Showing the pictorial representation of VRET set-up.

4.4 Case studies

The two case studies that we describe here were conducted at SEGI Oral Health Centre, Malaysia. To examine the effectiveness of the treatment, patients first received a detailed explanation about VRET and signed an informed consent form. Their baseline state anxiety was measured using the Visual Analogue Scale (VAS-A; Luyk, Beck, & Weaver, 1988) while their dental trait anxiety scores were indexed using both the Modified Dental Anxiety Scale (MDAS; Humphris, Morrison, & Lindsay, 1995) and the Dental Fear Scale (DFS; Kleinknecht, Klepac, & Alexander, 1973). Both patients were assessed for presence of dental phobia using the 'Phobia Checklist' criteria (Oosterink et al., 2009) by KRG. This tool comprises of four questions based on the DSM-IV-TR with a sensitivity of 0.95, specificity of 0.99, and an overall hit rate of 97%. During the Phobia Checklist interview, patients are requested a 'YES' or 'NO' response to the following questions related to their dental anxiety:

1. Does the sight of the feared object or experiencing the situation evokes an excessive fear response?
2. Is the fear greater than justified?
3. Is there avoidance or giving up things because of the fear?
4. Does avoidance of the situation or object causes daily impairment?

An individual is diagnosed as dental phobic only upon answering 'YES' to all four questions of the Phobia Checklist.

Behavioral Avoidance Test (BAT; Doering, Ohlmeier, De Jongh, Hofmann, & Bisping, 2013) was performed before and after final VRET session/s. This involved standardized observation of behaviour and an interview to determine avoidance towards five different commonly encountered dental situations (i.e., sitting in the dental chair, inspection of the oral cavity using two dental mirrors, approaching dental syringe, approaching dental drill without sound and approaching dental drill with sound). After the BAT, patients' self-reported state anxiety (VAS-A) and dental trait anxiety (MDAS and DFS) was recorded. The VRET session was planned to be conducted in a single session, however, if it was deemed that the patient requires additional VRET sessions, the post-intervention state and dental trait anxiety questionnaires (VAS-A, MDAS and DFS) and BAT were administered at the end of the last VRET session. The VR experience (presence, realism and cyber sickness) of the patients were evaluated with an 11-point Verbal Rating Scale (VRS; Hoffman et al., 2001) after the final VRET session. See Table 4.1 for a detailed description of outcome measures that could be used for VRET.

Table 4.1 Description of outcome measures.

	Measure	Description
1.	**Visual analogue scale for anxiety (Luyk et al., 1988)**	VAS-A is a simple, fast and valid tool used for assessing state dental anxiety. It is recorded by asking the patients to draw a cross mark (X) on a 0-100 mm scale from totally calm (0) and relaxed to worst fear imaginable (100).
2.	**Modified Dental Anxiety Scale (Humphris et al., 1995)**	MDAS is a 5-item scale assessing anticipatory dental anxiety, fear of dental cleanings, drilling, and injections on a 5-point Likert scale. The possible scores range from 5 to 25, with greater scores indicating higher level of dental anxiety.
3.	**Dental Fear Survey (Kleinknecht et al., 1973)**	DFS is a 20-item measure to identify the patients' emotional and physiological reactions associated with dentistry, as well as avoidance of dental care. Possible scores range from 20 to 100, with greater scores indicating higher levels of dental anxiety.
4.	**Behavioural Avoidance Test (Doering et al., 2013)**	In this test, the patient is evaluated by observing the behaviour and interviewing the patient before and after intervention. The test includes 5 situational steps that occurs during a routine dental visit (e.g. sitting in the dental chair, inspection of the oral cavity using two dental mirrors, approaching dental syringe, approaching dental drill without sound and approaching dental drill with sound). The approaching steps of the patient towards their fearful stimuli (similar to VRET stimuli) is evaluated and compared before and after intervention. Also, the state anxiety of the patient is measured on a scale of 0-10 in each situation and compared before and after intervention. To measure whether the patients is able to tolerate the situation/s, the number of steps completed and the state anxiety scores is noted.
5.	**VR experience (Hoffman et al., 2001)**	[4]Presence, realism and cybersickness (severity of nausea) were measured with an 11-point verbal rating scales.

Alia[5]

Alia, a 40-year-old Pakistani female patient reported to SEGI Oral Health Centre, Malaysia with a history of repeated dental avoidance and self-reported dental fear. She reported that her first negative dental event occurred around 13 years ago, when she had to undergo root canal treatment on one of her molars. She recollected being terrified of the syringe, the dental drill and the endodontic files that were used during her appointment. She recalled that when she cried out of pain, the dentist admonished her, dismissed her fear and told her to be brave. Alia reported that after this traumatic appointment, she often visualized the distressing events resulting in

4 *0 = No presence, realism and cybersickness*
1-3 = Mild presence, realism and cybersickness
4-6 = Moderate presence, realism and cybersickness
7-9 = Strong presence, realism and cybersickness
10 = Profound presence, realism and cybersickness

5 Pseudonym. Patients' names have been changed to protect identity

her avoiding visiting the dentist for prolonged periods of time. The second negative dental experience occurred four years back when she visited another dentist for a dental extraction. This time she tried deep breathing techniques to distract herself but to no avail. She repeatedly asked the dentist to be gentle and told them that she was afraid of injections. However, the dentist did not consider her plea and she continued to feel helpless throughout the extraction procedure. When Alia reported for treatment at the Oral Health Centre, she complained about a painful lower right molar. Her baseline state and dental trait anxiety scores were high (VAS-A = 75, MDAS = 25 and DFS = 92). A number of her teeth required extractions. Upon evaluation of the 'Phobia Checklist' criteria (Oosterink et al., 2009) a diagnosis of dental phobia was confirmed. After receiving a detailed explanation about VRET, Alia signed the consent form after which she underwent three VRET sessions. The total duration of the VRET over 3 sessions was 47 minutes. During the first VRET session Alia only tolerated VR1 to VR 3 scenarios, during which she constantly gripped the arms of the dental chair and reported experiencing intrusive images from previous traumatic dental experiences, muscle stiffness and numbness in the lower jaw upon watching the syringe scenario (VR3). In the second session Alia was able to tolerate VR1 to VR3 scenarios and felt less muscle stiffness and numbness in the lower jaw with the syringe scenario (VR3) compared to the first VRET session. In the third VRET session, she successfully completed all VR (VR1-VR5) scenarios without signs of fear (e.g., gripping the handle of the dental chair) and reported no intrusive memories about her past traumatic dental experience and no muscle stiffness and numbness in the lower jaw with the syringe scenario (VR3). She experienced strong presence and realism, and no cybersickness (nausea) after completion of the VRET sessions. After the last VRET session, Alia expressed that she feels confident that in future she would be able to face all injections and dental instruments. Her VAS-A, MDAS and DFS scores decreased to 10, 8 and 25 respectively. Further, there was reduction in behavioral avoidance as seen in Table 4.2. Within 6 months, Alia scheduled her dental appointment and underwent dental treatment including scaling, extractions and multiple restorations. At 6 months follow-up, the VAS-A (20), MDAS (12) and DFS (41) scores were found to be reduced relative to the baseline and Alia had no dental phobia (according to Phobia checklist).

Claire[6]

Claire, a 10-year-old female child reported with dental fear that had started three years earlier when she underwent dental extraction of one of her lower back deciduous teeth. She reported that the procedure was very painful and that she had continuously cried throughout the procedure. The dentist who was rude to her

6 Patient name has been changed to protect identity.

did not acknowledge her pain and consequently did not take measures to manage her pain. Claire indicated that she is scared of dentists and hides at home when her parents want to take her to the dentist. When Claire first visited our dental practice, her baseline state and dental trait anxiety scores were VAS-A = 50, MDAS = 20 and DFS = 65, respectively. She required scaling and restorations on few of her teeth. A diagnosis of dental phobia was confirmed after evaluation with 'Phobia Checklist' criteria (Oosterink et al., 2009). Claire underwent a single VRET session for a duration of 23 minutes. She fidgeted, shivered and was constantly rubbing her closed hands as the exposure unfolded to higher level of anxiety provoking stimuli. A reduction in SUDS scores (≤ 2) was noted with all VR scenarios in a single session. Post-VRET her VAS-A, MDAS and DFS scores reduced to 40, 14 and 45. Also, there was improvement in her behavioral avoidance as shown in Table 4.2. Further, Claire experienced strong presence and realism, and no cybersickness (nausea) after VRET. Within 6 months, she underwent scaling and restorations of her teeth. At 6 months follow-up, lowered VAS-A (25), MDAS (11) and DFS (35) scores were maintained and Claire no longer fulfilled the diagnostic criteria of dental phobia.

Table 4.2 Pre-VRET and post-VRET scores of behavioral avoidance test.

Behavior test	Alia		Claire	
	Pre-VRET	Post-VRET	Pre-VRET	Post-VRET
Sitting on the chair	3	0	6	1
Mouth Mirror	4	0	6	2
Syringe	10	2	10	2
Drill with no sound	8	1	9	2
Drill with sound	10	1	10	2

4.5 Discussion

The cases described in this paper are the first in dental literature that have explored the applicability of VRET in an adult patient with severe dental phobia using multiple VRET sessions and the usability of VRET in a pediatric dental phobic patient. Our earlier case study (Gujjar, Sharma, et al., 2017) and feasibility study (Gujjar, van Wijk, et al., 2017) tested the effects of a single VRET session on adult patients with dental phobia. In the present report, VRET resulted in noteworthy reductions in state anxiety, dental trait anxiety and behavioral avoidance. The self-reported measures were validated by patients' behavioral changes when they scheduled their dental appointments and underwent dental treatment (Morina et al., 2015). In addition, both patients had no dental phobia at 6 months follow-up.

4.5.1 VRET's relevance for general dental practice

There are several advantages that might make VRET an enticing alternative treatment modality for dental phobia. It can be specifically tailored to apply exposure treatment more ecologically and effectively (Botella et al., 2017). In individuals who are reluctant to confront the real threat as in In-vivo exposure therapy, VRET could be used as a first step in the exposure hierarchy (Kampmann et al., 2016). It is flexible as the exposure can be easily controlled by the therapist (Maples-Keller et al., 2017; North, North, & Coble, 1997; Wilson, Foreman, & Tlauka, 1997). The sense of security and lack of embarrassment that VRET offers to the patients can enable them to freely express their thoughts and feelings which otherwise could be difficult to express explicitly upon confronting the real-life situations (Baus & Bouchard, 2014; Hartanto et al., 2014). To this end, VRET may improve the relationship between the general dentist and patient. Furthermore, the safe, protected, realistic and controlled exposure may make this therapy invaluable for use in children and in individuals with special health care needs who, due to mental and physical disabilities cannot undergo exposure in real life situations. Moreover, VRET could be cost effective as the exposure can be repeated as many times needed (Baus & Bouchard, 2014). Table 4.3 displays a number of clinical tips for the use of VRET by the general dental practitioner.

4.5.2 Limitations of VRET

Some limitations of VRET are worth noting. Firstly, the initial cost involved for the VRET set-up and the development of software may be relatively high (around 10,000 USD). However, in recent years, there appears to be a dramatic reduction in the cost of VR technology. For instance, today a wide variety of smart phones support VR and the therapy could easily be administered using inexpensive Google cardboard glasses (costing fifteen dollars or less). Also, there have been unprecedented improvements in computer technology such as inexpensive memory, low-cost faster graphic accelerator as well as better quality of VR in terms of better graphics and more realistic VR environments. Rapid development in VR has led to speculations that the number of VR users is going to increase by 400% by the end of 2018 (ThinkMobiles, 2017). Secondly, treatment providers would need additional training to run the VRET software. However, due to technological advancements current VRET software and devices are user-friendly and easy to master. Thirdly, some patients may experience cybersickness during and post-VRET (Gujjar, Sharma, et al., 2017; Gujjar, van Wijk, et al., 2017). Cybersickness could be limited to some extent by increasing the frequency of the breaks during VRET (Gujjar, van Wijk, et al., 2017) or by using medication (Gujjar, van Wijk, et al., 2017).

Table 4.3 Some clinical tips for the general dental practitioners that could be helpful while carrying out VRET.

1. VR set-up requires a spacious area to work freely.
2. The dentist need to pay attention to establishing 'rapport' and a good working alliance with the patient.
3. To enhance immersion, characteristic odor (drops of clove oil on cotton wool) of the dental operatory could be used.
4. HMD could be bulky for the patients. It would be good to use a neck pillow (with a disposable cover) so that the neck is supported adding to the comfort when the patient is seated in the dental chair with HMD.
5. The surface of HMD could be cleaned with antiseptic wipes and covered with disposable plastic covers or cling wraps between patients.
6. To familiarize the patients prior to VRET, allow the patients to watch the VR environment for two minutes.
7. Provide 10-minute breaks to prevent cybersickness.
8. Be cautious that the introduction of the stimuli is gradual and that the patient does not feel overwhelmed.
9. After the VRET session, allow the patient to remain seated for at least 15 minutes so that they get adapted to the real world.

It should be noted that there is more to being successful with behavioral based applications such as VRET than simply confronting the patient with feared scenes. In general practice, psychologists and dentists with a cognitive behavioral background should be involved to carefully screen patients for their appropriateness to undergo therapy, assess the patient to select the appropriate fear-eliciting stimuli for the treatment, titrate the exposure to the feared stimulus, monitor and provide support to the patient undergoing the procedure, among other interventions. In addition, there are non-specific factors (i.e., those associated with the relationship with the dentist/therapist) that may contribute to what is needed for a successful outcome. Therefore, it is conceivable that not all dental patients (and probably not all dentists) are appropriate candidates for the use of this type of intervention. In line with this, it could be argued that without paying attention to these issues, for instance, if the VR experience is too overwhelming, the treatment may be ineffective or even potentially harmful. However, despite these seemingly important factors it is interesting to note that there is mounting evidence showing that the effectiveness of standard VRET applications have become an effective alternative, and with regard to efficacy comparable to the results of traditional treatments for phobias (Botella et al., 2017). Yet, in certain more severe cases, dental professionals need to work collaboratively with mental health professionals in using these technologies or to assess whether individuals with, for instance, a psychiatric background and/or a history of childhood trauma may be too vulnerable to undergo VRET and need expert help. In other words, in such instances specialized forms of psychotherapy [e.g., EMDR, Eye Movement

Desensitization and Reprocessing; Doering et al., 2013) might be a more appropriate option to reduce patients' burden of phobic fear and comorbid mental health problems.

4.6 Conclusion

Multiple VRET sessions in an adult patient and a single VRET session in a pediatric patient successfully treated their dental phobia. This is in line with our previous clinical experiences with the use of VRET and results of our research that supports the safety and efficacy of VRET in treatment of dental phobia (Gujjar, Sharma, et al., 2017; Gujjar, van Wijk, et al., 2017). The use of VRET in children and other populations, including individuals with intellectual disabilities, needs to be explored further using controlled studies, however, sufficient preliminary evidence exists for general dentists to explore VRET in their dental practice.

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Chapter 5. Virtual reality exposure therapy for the treatment of dental phobia: A controlled feasibility study*

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5.1 Introduction

Research suggests that about 25% of the population suffers from a fear towards specific dental procedures, whereas about 4% fulfills the criteria for dental phobia (Oosterink, De Jongh, & Hoogstraten, 2009). Because the resultant avoidance towards dental treatment could have considerable impact on both oral and general health (Schuller, Willumsen, & Holst, 2003), timely management of dental phobia is central to improving dental attendance and quality of life.

Cognitive behavioral therapy (CBT), in the form of in vivo exposure therapy (IVET), is the treatment of choice for fearful dental patients (Gordon, Heimberg, Tellez, & Ismail, 2013) (Wide Boman, Carlsson, Westin, & Hakeberg, 2013). More recently, Virtual Reality Exposure Therapy (VRET) has gained acceptance in the treatment of a wide variety of fears and specific phobias (Botella, Baños, Villa, Perpiñá, & García-Palacios, 2000; Garcia-Palacios, Hoffman, Carlin, Furness, & Botella, 2002; Muhlberger, Wiedemann, & Pauli, 2003; Powers & Emmelkamp, 2008). This treatment involves exposure to individual's fear provoking objects and situations using a computer-generated environment in a well-controlled graded manner, until extinction occurs (Krijn, Emmelkamp, Olafsson, & Biemond, 2004; Krijn et al., 2004).

There are a number of potential advantages of VRET over IVET. Firstly, VRET is safe and acceptable as the patients face a credible, virtual counterpart of their fear-eliciting stimuli in a gradual and controlled manner (McLay et al., 2012) at their own pace (Baus & Bouchard, 2014), and under the privacy of the therapist's office (North, North, & Coble, 1997). Secondly, VRET is flexible as the therapist can adapt the exposure based on the fear hierarchy of an individual (Gregg & Tarrier, 2007). Thirdly, VRET may be a cost-effective therapy as it can be repeated a number of times as per the needs of the patient (Baus & Bouchard, 2014). However, high initial costs of the Virtual Reality (VR) equipment and software, resources for basic

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training of personnel and cybersickness are some of the potential barriers in the use of VRET (Gregg & Tarrier, 2007; Krijn et al., 2004).

Regarding the effectiveness of VRET, it has been found that this treatment approach is equally effective (Valmaggia, Latif, Kempton, & Rus-Calafell, 2016) or slightly more effective than IVET in the treatment of specific phobias. For example, a meta-analysis (Powers & Emmelkamp, 2008) indicated that VRET yielded better results than IVET in the treatment of specific phobias, including fear of flying (Rothbaum et al., 2006), acrophobia (Emmelkamp et al., 2002), social phobia (Klinger et al., 2005), and panic disorders (Botella et al., 2007). However, until now VRET has yielded only limited support as a treatment for dental phobia. Although a recent case study on two patients with dental phobia reported that VRET was effective in reducing avoidance towards dental treatment (Gujjar, Sharma, & De Jongh, 2017), controlled research is lacking.

The purpose of the present study was, therefore, to evaluate the feasibility, in terms of safety and efficacy, of applying VRET on a sample of dental phobic patients. Primary aims were to evaluate safety by determining any adverse events or symptom exacerbation after intervention with VRET and, to determine the efficacy of VRET by comparing the reduction in dental anxiety and its behavioral effects with that of an Informational pamphlet (IP), using a controlled multiple baseline study design. Secondary aims were to examine the real-time heart rate (HR) response of participants during VRET, and to evaluate patients' quality of VR experience (presence, realism and cybersickness) post VRET. The first hypothesis of the study was that no adverse events or symptom exacerbation would be reported following VRET. The second hypothesis was that the application of VRET would be associated with a lowered state anxiety, trait dental anxiety and behavioral avoidance compared to IP. We also hypothesized that the application of VRET would be associated with a significant reduction in patients' mean heart rate, and that participant's experience high level of presence and realism, with low level of cybersickness post VRET. Also, the proportion of patients meeting DSM-IV criteria for dental phobia and number of patients scheduling dental appointment would be significantly greater in the VRET condition than in the IP condition.

5.2 Method

5.2.1 Participants and design

The study protocol was approved by the ethical board of SEGi university, Malaysia (Reference: EC01/14-01). The authors abided by the ethical principles of psychologists and code of conduct as set out by the American Psychological Association while conducting this research. The present study is a pilot feasibility study for

a randomized controlled trial which is registered with International Standard Randomized Controlled Trial Number (Identifier: ISRCTN25824611). Participants were recruited from the outpatient service of the Oral Health Centre of the Faculty of Dentistry of the SEGi University in Malaysia. Patients who had not visited the dentist since the past 12 months, or reported anxiety and avoidance of dental procedures or both, were screened for the presence of dental phobia using the Modified Dental Anxiety Scale (MDAS). Patients with a MDAS score ≥ 15 (n = 56), who provided informed consent, were interviewed using the Phobia Checklist (Oosterink et al., 2009). The checklist was administered during screening and at 6 month follow-up. The inclusion and exclusion criteria, the participant recruitment process and measures used at different phases of the study are enumerated in Figure 5.1.

Ten participants (six females and four males) were eligible to participate in the present study. Out of ten participants, eight were Chinese, two were Malay and two were Indian. Eligible participants were randomized (1:1 allocation ratio) to either the VRET condition or an informational pamphlet (IP) control condition using a sealed, opaque, sequentially numbered envelopes (SNOSE) allocation concealment method (Doig & Simpson, 2005). Safety of using VRET was evaluated by determining any adverse events or symptom exacerbation after intervention. A non-concurrent multiple-baseline design (Herson & Barlow, 1976) across subjects was used to evaluate the efficacy of the interventions. This design is often employed to study behavior outcomes of ten or fewer participants (Graham, Karmarkar, & Ottenbacher, 2012). The treatment condition is initiated at different time points for different participants, which allows one to conclude that the outcomes are a result of the treatment rather than merely temporal effects (Christ, 2007). Internal validity of the data in multiple baseline study designs is assured by the evaluation of formative data collected at multiple time points (Christ, 2007). In our study, participants from both groups were randomly assigned to one of the baseline periods (5, 6, 7, 8, and 9 weeks) as shown in Table 5.1. After completing the baseline duration, the participants were administered their respective interventions. Participants 1-5 (P1-5) received VRET while, Participants 6-10 (P6-10) received IP.

The outcome measures of interest in this study were state anxiety, measured using a Visual Analogue Scale-Anxiety (VAS-A; Luyk, Beck, & Weaver, 1988), dental trait anxiety, indexed by both the Modified Dental Anxiety Scale (MDAS; Humphris, Morrison, & Lindsay, 1995) and the Dental Fear Survey (DFS; Kleinknecht, Klepac, & Alexander, 1973), and behavioral avoidance, using a behavioral avoidance test (BAT; Doering, Ohlmeier, De Jongh, Hofmann, & Bisping, 2013). The questionnaires to record state and trait dental anxiety scores were sent via email within a 14-week study period, and once again at 6-month

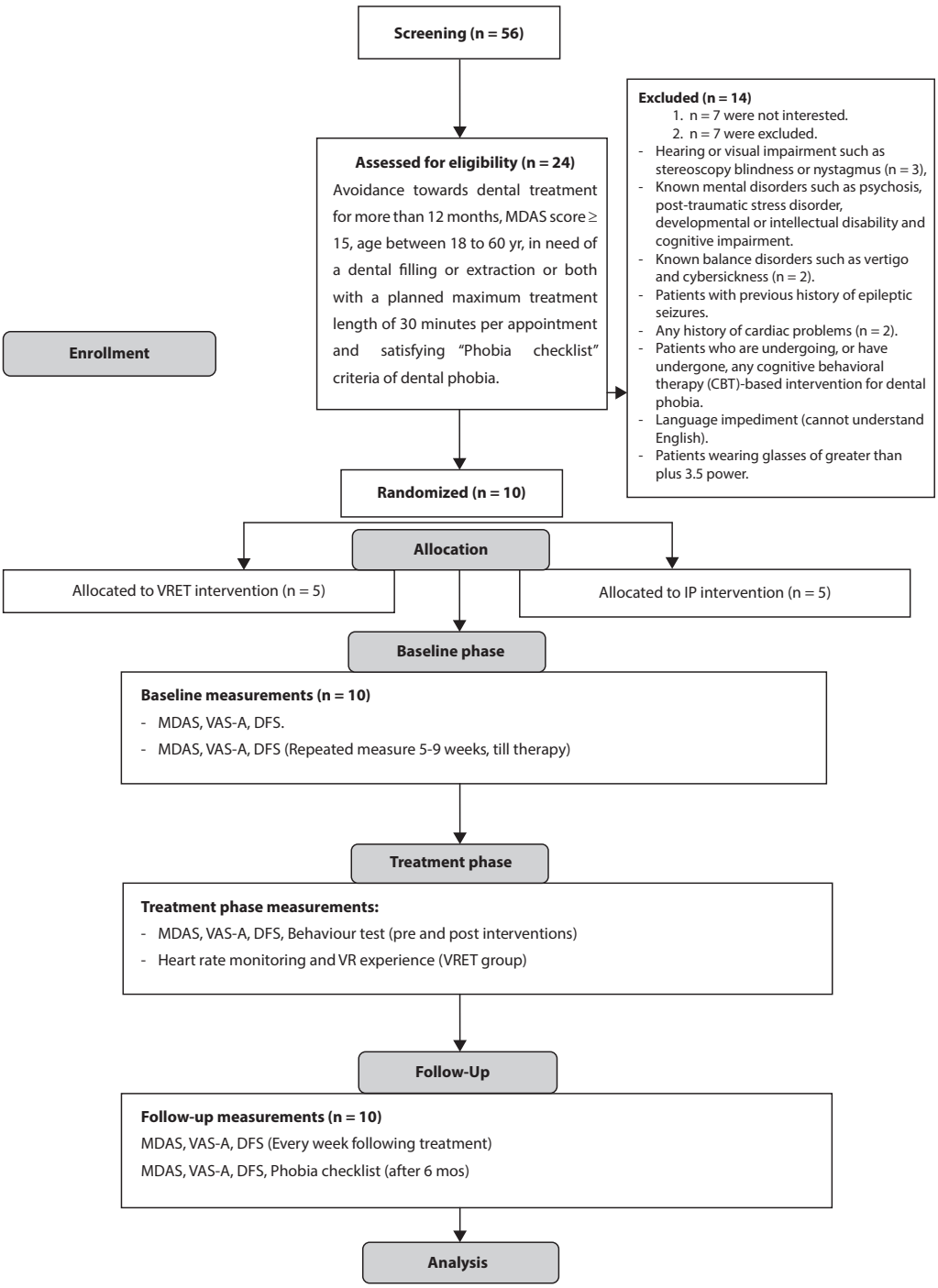

Figure 5.1 Showing overview of patient flow.

Table 5.1 Measurement planning (a) Repeated measurements in a Multiple Baseline Design and (b) Measurements at two time points.

Planning of measurements																
1[a]	B0	B1	B2	B3	B4	**Intervention 5thWk**		F6	F7	F8	F9	F10	F11	F12	F13	F14	F- 6 mos
						Pre	**Post**										
	B0	B1	B2	B3	B4	B5		**Intervention 6thWk**		F8	F9	F10	F11	F12	F13	F14	F- 6 mos
								Pre	**Post**								
	B0	B1	B2	B3	B4	B5		B6	**Intervention 7thWk**		F9	F10	F11	F12	F13	F14	F- 6 mos
									Pre	**Post**							
	B0	B1	B2	B3	B4	B5		B6	B7	**Intervention 8th Wk**		F10	F11	F12	F13	F14	F- 6 mos
										Pre	**Post**						
	B0	B1	B2	B3	B4	B5		B6	B7	B8	**Intervention 9th Wk**	F10	F11	F12	F13	F14	F- 6 mos
											Pre	**Post**						
2[b]	**Two time points**																
Baseline														Follow-up at 6 months			

B*-Baseline; 5-9 weeks,

F**-Follow-up; 5-9 weeks

[a] Each baseline phase length was randomly assigned to one participant in the VRET, and to one participant in the informational pamphlet group and assessed for VAS-A, MDAS and DFS.

[b] For all n = 10 patients: Presence of dental phobia was evaluated using phobia check list at B0 = Baseline and at 6 months' follow-up

follow-up as shown in Table 5.1. The BAT was administered twice: pre and post intervention, and the number of situations the participant was able to tolerate was noted as depicted in Table 5.2 and 5.3. Participants were asked to rate their anxiety repeatedly during the VRET session, from 0 to 10, on the Subjective Unit of Distress Scale (SUDS; Wolpe, 1969). Each situational cue was repeatedly administered until the participant reported a SUDS score ≤ 2, after which the next cue was introduced (Raghav et al., 2016). The participants were unaware of this criterion. During the VRET intervention, the participants' HR was continuously monitored. Post VRET, the participants were observed for 15 minutes' to preclude any adverse events, and were assessed for the quality of their VR experience namely presence, realism and cybersickness (Hoffman et al., 2001) measured using 11-point Numerical Rating Scales (NRS) as shown in Table 5.2, where 0 = No presence, realism or Cybersickness and 10 = Pronounced presence, realism or Cybersickness. Additionally, patients' intentions to undergo VR therapy in the future and revisiting the dental office for their dental treatment were also evaluated (Yes/No response).

Table 5.2 Description of primary and secondary outcome measures.

Primary Outcome measures		
	Measure	**Description**
1.	**Safety**	Determined by asking for any adverse events or symptom exacerbation post-VRET.
2	**Visual analogue scale for anxiety**	VAS-A is a simple, sensitive, fast, reliable and valid tool in state dental anxiety assessment (Luyk, et al., 1988). It was recorded by asking the participants to draw a cross mark (X) on a 0-100 mm scale from totally calm (0) and relaxed to worst fear imaginable (100).
3.	**Modified Dental Anxiety Scale**	MDAS is a 5-item scale assessing anticipatory dental anxiety, fear of dental cleanings, drilling, and injections on a 5-point Likert scale (Humphris, et al. 1995). The possible scores range from 5 to 25, with greater scores indicating higher level of dental anxiety. The test shows high levels of internal consistency and good construct validity (Humphris, Freeman, Campbell, Tuutti, D'Souza, 2000).
4.	**Dental Fear Survey**	The Dental Fear Survey (DFS) is a 20-item measure to identify the participants' emotional and physiological reactions associated with dentistry, as well as avoidance of dental care. Possible scores range from 20 to 100, with greater scores indicating higher levels of dental anxiety. The test has established reliability, validity and sensitivity (Davis, Ollendick, & Öst, L.-G, 2012).

	Measure	Description
	Primary Outcome measures	
5.	**Behavioural Avoidance Test**	This test was carried out before and after the intervention, by means of standardized observation of behaviour and an interview for both the intervention groups. The participant undergoes several approaching steps towards their anxious stimuli similar to the VRET scenarios and provides a baseline behavioral assessment measure to compare the responses of the patient before and after the interventions. The test contained 5 situational steps that occurred during a dental visit (e.g. sitting in the dental chair, inspection of the oral cavity using two dental mirrors, approaching dental syringe, approaching dental drill without sound and approaching dental drill with sound). Participants were asked to assess his/her level of state anxiety on a scale of 0–10 in each situation. To measure whether the patients was able to tolerate the situation/s the number of steps completed was noted. Both observation and responses to the standardized situations were recorded during the procedure (Doering, et al., 2013).
	Secondary outcome measures	
1.	**Psychophysiological parameter**	A HR wrist band was used to record the real time response of the participants during VRET. The device was integrated with the VR software and the output was recorded on exposure with cues during therapy.
2.	**VR experience after VRET**	**Presence, realism and cybersickness (severity of nausea)** were measured with an 11-point verbal rating scales*(Hoffman, et al., 2001). **Intention to use VR goggles again and to revisit the dental surgery** was measured using a yes/no response.

*0 = No presence, realism and cybersickness
1-3 = Mild presence, realism and cybersickness
4-6 = Moderate presence, realism and cybersickness
7-9 = Strong presence, realism and cybersickness
10 = Profound presence, realism and cybersickness

At 6-month follow-up all participants were reevaluated for dental phobia using the Phobia Checklist (Oosterink et al., 2009) and for any symptom exacerbation. We also determined the number of participants who scheduled a dental appointment following the intervention. All outcome measures and the temporal sequence of these assessments are shown in Tables 5.2 and 5.3 respectively.

Table 5.3 Overview of timing of outcome measures.

		Measurements						
		Primary outcome					***Secondary outcomes (only with VRET)***	
		Safety ***(only with VRET)***	*VAS -A*	*MDAS*	*DFS*	*BAT*	*Physiological response (HR) (Only with VRET)*	*VR experience (Only with VRET)*
Baseline(B0)		–	X	X	X	–	–	–
Repeated baseline measures (5-9 weeks).		–	X	X	X	–	–	–
	Pre-intervention	–	X	X	X	X	–	–
Intervention	*During intervention*	–	–	–		–	X	–
	Post-intervention	X	X	X	X	X	–	X
Repeated follow-up measures (5-9 weeks)		–	X	X	X	–	–	–
Follow-up at 6 months		X	X	X	X	–	–	–

5.2.2 Interventions

5.2.2.1 VRET group[7]

VRET was administered by KR, who was trained in administering VRET by a resource person from Virtual simulations Inc., Québec, Canada (developer of the VRET software). All VRET sessions were videotaped and the coauthors watched the videos to assure treatment integrity.

VRET participants were seated in the dental chair and assisted in wearing the head mounted device (HMD), and the heart rate (HR) wrist band. The baseline HR was recorded for ten minutes with no VRET display. After 10 minutes, the VR system and the HMD were turned 'ON' to show a three dimensional (3D) stereoscopic scene of a virtual dental operatory to the participant. The built-in motion tracker

7 VRET was conducted utilizing two networked computers of which the VR-simulator computer (Dell XPS-8700 desktop with 4th Generation Intel Core i7-4790 processor (8M Cache, up to 4.0 GHz) and ASUS NVIDIA GEFORCE GTX 750 TI OC 2GB GDDR5 graphic card) rendered the virtual environment and the other User interface-computer allowed the researcher to control and individualize the VR stimuli presented to the patient. An Oculus development kit 2 HMD (Head Mounted Display) with a resolution of 960X1080 per eye was used to immerse the participants in the VR dental environment. A Mio-link wrist band was used to record the HR of the VRET participants in real-time during therapy.

in the HMD allowed the participants to look around the virtual dental operatory by turning their head. The participants were also able to see their own virtual counterpart (participant avatar) and a virtual dentist avatar. After making the participants watch the simulated dental environment for two minutes to facilitate orientation, situational cues enacted by the dentist avatar in the VR environment were introduced in the following order:

1) Sitting passively on the dental chair (no tools).
2) Inspection of the oral cavity using mouth mirror.
3) Introduction of an injection.
4) Introduction of drill without sound
5) Introduction of drill with sound

Through scenario #2 to #5, participants were requested to keep their mouth open. All participants received the therapy in one session.

5.2.2.2 Informational Pamphlet (IP) group

Participants in the Informational Pamphlet (IP) group received a pamphlet containing information compiled from the Academy of General Dentistry fact sheet on dental anxiety (Academy of General Dentistry, 2010). It included standard information such as a description of dental procedures, and postoperative pain management, to help patients overcome their dental anxiety. Participants were seated in the same area where they completed the self-reported measures, and were given time to review the pamphlet in detail and ask the researcher questions related to their dental anxiety.

5.2.3 Analytic strategy

Analysis of primary outcome measures involved the assessment of a) Safety of using VRET by evaluating the participants for any adverse events following therapy and for any symptom exacerbation during the follow-up and b) Efficacy of VRET in comparison with IP, by performing a visual analysis for the dependent measures VAS-A, MDAS and DFS prior to, during and after interventions for measuring changes relative to the baseline phase using the method of Lane and Gast method (Lane & Gast, 2014). Also, BAT scores and steps within the treatment conditions were compared using paired samples t-tests.

Analysis of secondary outcome measures involved the evaluation of a) trend of mean scores of HR of the different VR scenarios that were graphically plotted and b) VR experience (presence, realism and cybersickness) with descriptive statistics (means and standard deviation). Additionally, the number of participants who no longer met the criteria for dental phobia after 6 months, and the number of

participants who had scheduled a dental appointment within the past 6 months, were noted. All analyses were conducted using SPSS (IBM, version 23, Chicago IL, USA).

5.3 Results

The mean age of the participants was 28.5 years (SD = 14.1). All participants completed the study except one (IP group, P-7), who did not respond to the questionnaire that was mailed to the participants after the 9^{th} week of the study.

5.3.1 Safety of VRET

No adverse events or symptom exacerbation were reported post-therapy. In addition, no participant dropped out in VRET group.

5.3.2 Analyses for state anxiety and dental trait anxiety

All the results from the visual analyses are reported in the Tables 5.4, 5.5, 5.6 and Figures 5.2, 5.3, 5.4.

The visual analysis revealed stability of both groups before the intervention (more than 80% of the data were within 25 % of the median) with all dependent measures. There were clear differences in the absolute, relative, median and mean level changes in the VAS-A, MDAS and DFS scores after interventions. Further, the majority of VRET group participants showed higher PND (Percentage of Non-Overlap Data) scores of 100% and lower POD (Percentage of Overlap Data) of 0% compared to IP group. Thus, the results of the visual analysis suggest that VRET intervention caused greater reduction of VAS-A, MDAS and DFS scores compared to the IP intervention.

We performed a post-hoc intention to treat analysis on the dependent measures and alpha was set at 5%. Evaluation of group differences in changes over time using a 2 (pre-treatment *vs* post-treatment) × 2 (VRET *vs* IP) repeated measures MANOVA (on VAS-A, MDAS and DFS simultaneously) revealed a significant main effect of time, $F(3, 6) = 6.71$, $p = 0.024$, but no significant interaction between time and group, $F(3, 6) = 3.19$, $p = 0.11$. Subsequent univariate testing showed a significant decrease in mean score for the VAS-A, $F(1, 8) = 5.91$, $p = 0.04$, the MDAS, $F(1, 8) = 24.66$, $p < 0.001$, and DFS, $F(1, 8) = 14.24$, $p = 0.005$, from pre-intervention to post-intervention. In addition, and more interestingly, a significant condition by time interaction effect was found for MDAS, $F(1, 8) = 8.61$, $p = 0.019$, and for the DFS, $F(1, 8) = 10.53$, $p = 0.012$, resulting from the fact that MDAS and DFS scores showed a

Table 5.4 Overview of visual analysis of VAS-A dependent measure.

	Within Condition Analysis		Between Conditions Analysis							
	Level		Trend:		Change in Level				Data Overlap	
	Stability Envelope									
Participants	A	B	Direction change	Stability Change	Relative Change	Absolute Change	Median Change	Mean Change	PND	POD
1	Stable	Stable	No Change	None	-0.5 decelerating	-1 Improving	-1 Improving	-1.3 Improving	30%	70%
2	Stable	Stable	Zerocelerating to Decelerating	None	-6.5 improving	-7 improving	-7 improving	-6.1 Improving	100%	0%
3	Stable	Variable	Zerocelerating to Decelerating	Stable to Variable decelerating	-3 improving	-3 improving	-3.5 improving	-4.6 Improving	100%	0%
4	Stable	Variable	Zerocelerating to Decelerating	Stable to Variable decelerating	-4 improving	-4 improving	-6 improving	-5.5 improving	100%	0%
5	Stable	Stable	Zerocelerating to Decelerating	None	-2.5 improving	-3 improving	-2 improving	-2.8 improving	100%	0%
6	Stable	Stable	No Change	None	Slight improving (0.5)	-2 improving	-1 improving	-0.8 improving	30%	70%
7	Stable	Stable	Zerocelerating to accelerating	None	-2 improving	-2 improving	-2 improving	-1.8 improving	100%	0%
8	Stable	Stable	Zerocelerating to Decelerating	None	-3.5 improving	-4 improving	-4 improving	-4.1 improving	100%	0%
9	Stable	Variable	No Change	Stable decelerating to Variable decelerating	No change	No change	-0.5 improving	-1.2 improving	42.80%	57.14%
10	Stable	Stable	Decelerating to zerocelerating	None	-1 improving	-1 improving	-1 improving	-1 improving	66.60%	33.33%

Table 5.5 Overview of visual analysis of MDAS dependent measure.

	Within Condition Analysis		Between Conditions Analysis							
	Level		Trend:		Change in Level				Data Overlap	
	Stability Envelope									
Participants	A	B	Direction change	Stability Change	Relative Change	Absolute Change	Median Change	Mean Change	PND	POD
1	Stable	Stable	accelerating to zerocelerating	None	-10 improving	-9 improving	-10 improving	-19.5 improving	100%	0%
2	Stable	Stable	zerocelerating to decelerating	None	-5 improving	-5 improving	-6 improving	-16.3 improving	100%	0%
3	Stable	Stable	zerocelerating to decelerating	None	-4.5 improving	-3 improving	-4.5 improving	-5.7 improving	100%	0%
4	Stable	Stable	decelerating to zerocelerating	None	-9 improving	-9 improving	-9 improving	-8.7 improving	100%	0%
5	Stable	Stable	zerocelerating to decelerating	None	-8.5 improving	-9 improving	-9 improving	-9.5 improving	100%	0%
6	Stable	Stable	None	None	-0.5 improving	-2 improving	-1.5 improving	-1.2 improving	10%	90%
7	Stable	Stable	None	None	No change	No change	No change	No change	0%	100%
8	Stable	Stable	None	None	-6 improving	-6 improving	-6.5 improving	-6.4 improving	100%	0%
9	Stable	Stable	accelerating to decelerating	None	-1 improving	-1 improving	-1 improving	-2 improving	42.85%	57.14%
10	Stable	Stable	None	None	-2 improving	-1 improving	No change	-0.6 improving	0%	100%

Table 5.6 Overview of visual analysis of DFS dependent measure.

	Within Condition Analysis		Between Conditions Analysis							
	Level		Trend:		Change in Level				Data Overlap	
	Stability Envelope									
Participants	A	B	Direction change	Stability Change	Relative Change	Absolute Change	Median Change	Mean Change	PND	POD
1	Stable	Stable	Zerocelerating to decelerating	No change	-35.5 improving	-37 improving	-36.5 improving	-37.7 improving	100%	0%
2	Stable	Stable	Zerocelerating to accelerating	No change	-21 improving	-25 improving	-21 improving	-20.6 improving	100%	0%
3	Stable	Stable	Zerocelerating to decelerating	No change	-20.5 improving	-21 improving	-21 improving	-19.9 improving	100%	0%
4	Stable	Stable	Accelerating to zerocelerating	No change	-30.5 improving	-27 improving	-29.5 improving	-29.5 improving	100%	0%
5	Stable	Stable	Slow decelerating to rapid decelerating	No change	-29 improving	-28 improving	-37 improving	-35.3 improving	100%	0%
6	Stable	Stable	Decelerating to accelerating	No change	-5 improving	-4 improving	-4.5 improving	-5.8 improving	80%	20%
7	Stable	Stable	No change	No change	-8 improving	-11 improving	-9.5 improving	- 9 improving	100%	0%
8	Stable	Stable	No change	No change	-21.5 improving	-28 improving	-28 improving	-26.8 improving	100%	0%
9	Stable	Stable	No change	No change	5 deteriorating	2 deteriorating	No change	-3 improving	42.85%	57.14%
10	Stable	Stable	Accelerating to decelerating	No change	-4.5 improving	-4 improving	-16.5 improving	-8.2 improving	100%	0%

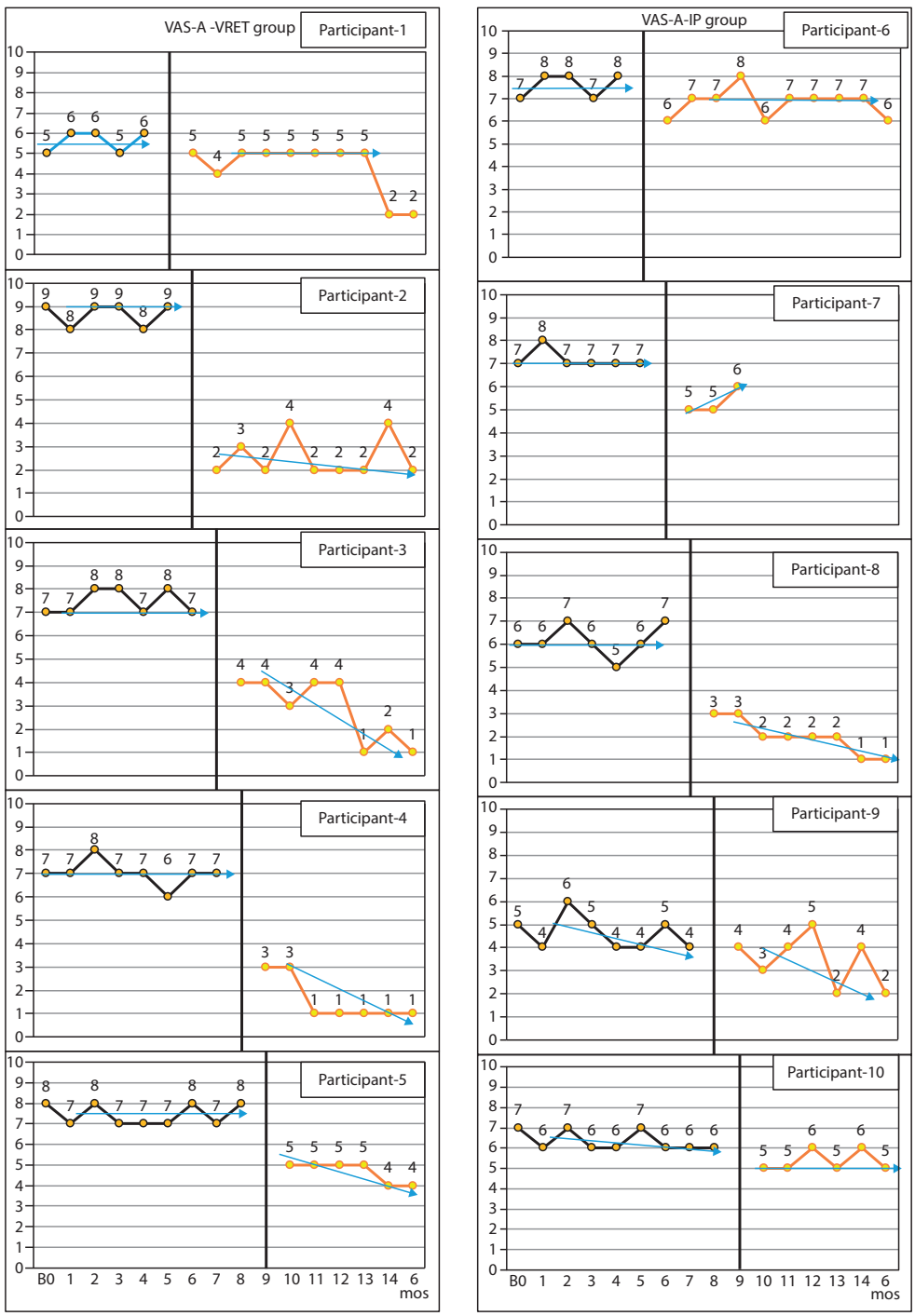

Figure 5.2 Graphical representation of VAS-A scores of all participants.

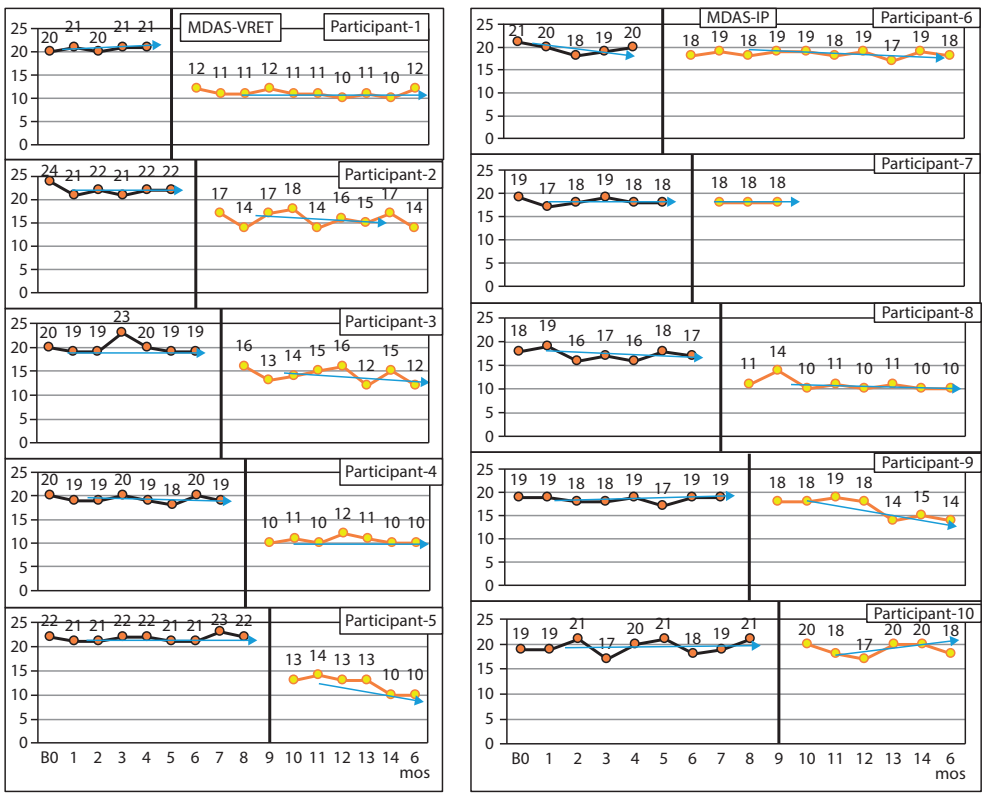

Figure 5.3 Graphical representation of MDAS scores of all participants.

stronger decrease in the VRET condition. A number of post-hoc comparisons using independent samples t-tests for mean VAS-A, MDAS and DFS scores revealed no significant differences between the groups. Yet, some of the comparisons showed quite large effect sizes in favor of the VRET group, in particular at follow-up (see Table 5.7).

5.3.3 Behavioral avoidance

A paired-t test comparing the pre- and post-intervention BAT scores, and number of steps the patient was able to tolerate, revealed statistically significant differences between pre- and post-scores with large Cohen's *d* effect sizes (4.2 and -1.4), respectively, in the VRET condition (see Table 5.7). In contrast, in the IP condition no significant differences between the means of the pre-BAT and post BAT scores, or the number of BAT steps, were found with a moderate to large Cohen's *d* effect sizes (1.0 and -0.4, respectively).

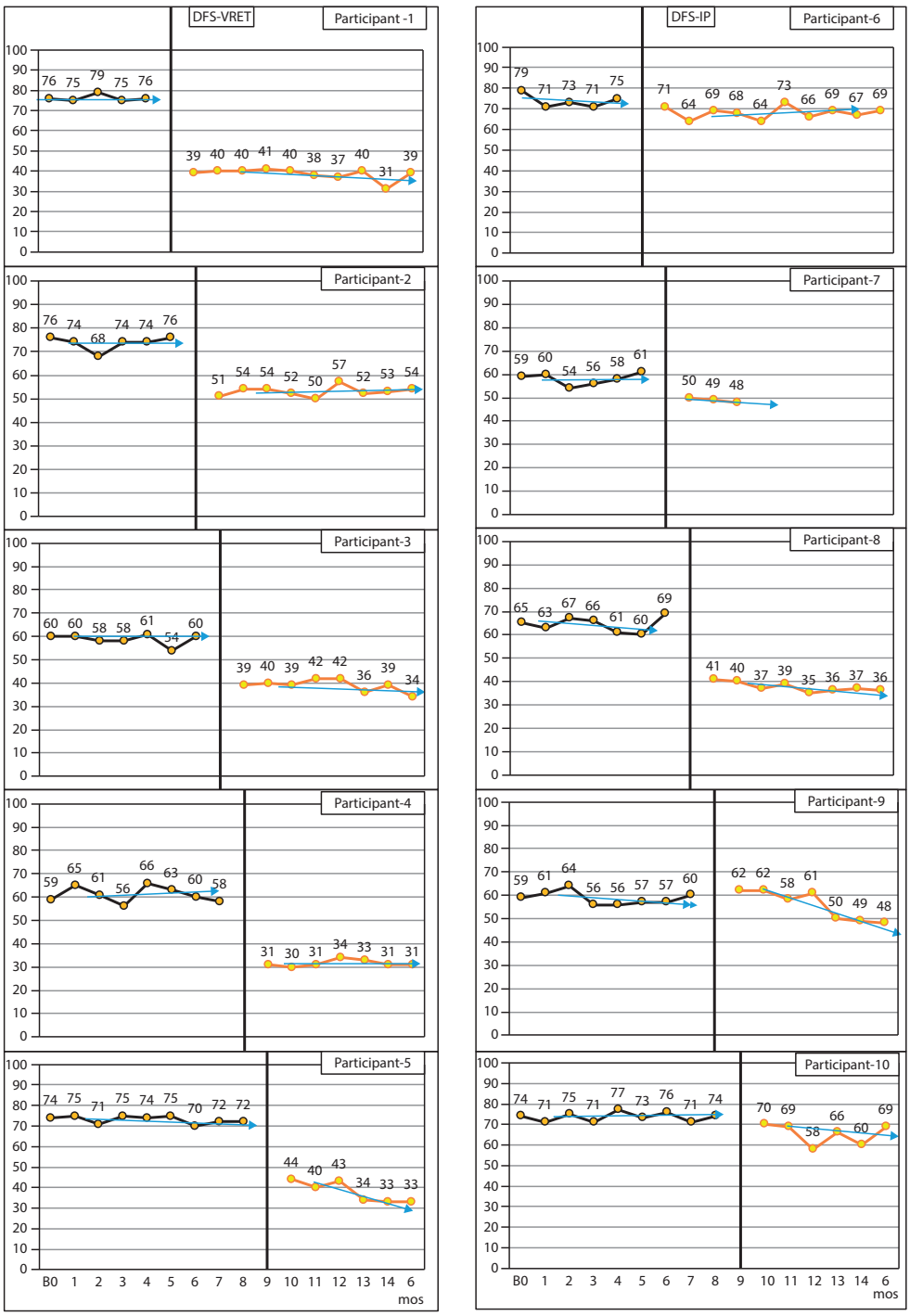

Figure 5.4 Graphical representation of DFS scores of all participants.

Table 5.7 Mean scores, standard deviations and between subgroups effect sizes for the total sample, on all variables.

Dental anxiety scores				
		VRET	**IP**	
		Mean (SD)	**Mean (SD)**	**Effect Size**
Baseline	VAS-A	7.2 (1.4)	6.4(0.8)	-0.66
	MDAS	21.2(1.7)	19.2(1.1)	-1.35
	DFS	69.0(8.7)	67.2(9.0)	-0.20
Pre-Intervention	VAS-A	7.9(1.1)	7.6(1.5)	-0.22
	MDAS	21.2(1.7)	20.4(2.0)	-0.41
	DFS	71.6(12.7)	65.2(15.0)	-0.46
Post-Intervention	VAS-A	4.2(4.2)	6.0(2.4)	0.52
	MDAS	14.2(3.1)	18.6(4.0)	1.22
	DFS	50.4(8.5)	63.3(16.4)	0.98
Follow up	VAS-A	2.0(1.2)	3.5(2.0)	0.89
	MDAS	11.6(1.6)	15.0(3.3)	1.29
	DFS	38.2(9.3)	55.5(14.1)	1.44
Behavioral Avoidance scores				
		Pre-Intervention	**Post-Intervention**	
		Mean (SD)	**Mean (SD)**	**Effect Size**
VRET	BAT	41.2 (5.5)	12.8 (7.5)	4.2*
	BAT STEPS	3.2 (0.8)	4.4 (0.5)	-1.43*
IP	BAT	36.4 (4.9)	34.4 (6.0)	1.0
	BAT STEPS	3.2 (0.4)	3.4(0.5)	-0.4

***P (< 0.05).**

VRET = Virtual Reality Exposure Therapy, IP = Informational Pamphlet, VAS-A = Visual Analogue Scale-Anxiety, MDAS = Modified Dental Anxiety Scale, DFS = Dental Fear Scale,BAT = Behavioral Avoidance Test, BAT-steps = Behavioral Avoidance Test Steps.

5.3.4 HR measurement

As shown in Figure 5.5, the average HR of all VR-participants showed an initial decline from baseline towards the idle phase. After the idle phase, with an increase in anxiety provoking stimuli, there was a slow increase in average HR relative to the idle phase in participants P-1, 3 and 5. However, a steady alleviation of heart rate (relative to baseline) was evident towards the end of VRET in P1-P4. Hence, the confrontation with the increasingly more anxiety eliciting stimuli during VRET did not cause any apparent acceleration in HR during therapy.

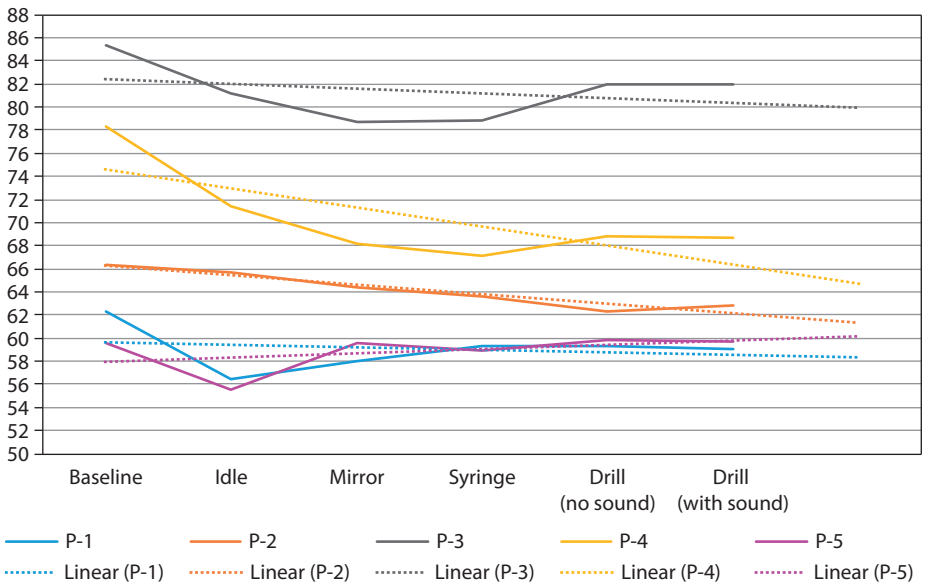

Figure 5.5 Mean heart rate of the VRET participants across different VR scenarios.

5.3.5 Virtual Reality Experience

The average presence and the realism experienced by all the participants was 5.4 (SD = 1.82) and 6.8 (SD = 1.64), respectively. All participants in the VRET condition experienced cybersickness (nausea), except patient P-2. The average cybersickness (nausea) experienced by VRET participants was 4.2 (SD = 0.50). Yet, all VRET participants expressed their intentions to undergo similar therapy in the future, and to revisit the dental surgery for treatment.

5.3.6 Presence of dental phobia

At 6-month follow-up, of the nine treatment completers, six (four from the VRET group and two from the IP group) no longer met the diagnostic criteria of dental phobia at 6-month follow-up.

5.3.7 Dental attendance

Although all VRET participants showed their interest, four out of five scheduled an appointment and underwent treatment, but none of the IP participants, scheduled an appointment for dental treatment following the intervention.

5.4 Discussion

This is the first controlled feasibility study which evaluated safety and preliminary efficacy of using VRET in dental phobic individuals. Conducting such a pilot study is important to determine any difficulties in timing of measurements and limitations of VRET prior to commissioning the randomized controlled trial. The initial results suggest that VRET is a safe, well-tolerated and acceptable treatment for dental phobia. That is, no symptom exacerbation was reported post-VRET, the confrontation with the anxiety provoking stimuli did not increase patients' heart rate during therapy, and no participant dropped out during the course of the treatment. Furthermore, our hypothesis that the application of VRET would be associated with a significant reduction in state anxiety, trait dental anxiety, and behavioral avoidance was supported by the present findings. All VRET participants expressed their intentions to undergo similar therapy in the near future and in scheduling an appointment for their dental treatment. The findings of self-reported measures were substantiated by the majority of VRET participants (four out of five) scheduling appointments and undergoing dental procedures such as scaling followed by extractions and fillings. It appeared that six months after the VRET intervention the number of participants who no longer met the criteria of dental phobia was higher in the VRET group compared to the IP group. The above inferences suggest that VRET is a safe and effective treatment alternative for dental phobia.

The significant decrease in behavioral avoidance observed in VRET participants is corroborated by the finding that more participants in the VRET group scheduled their dental appointments and visited the dentist within the 6 months' follow-up after the intervention. It could be argued that, in vivo exposure to the phobic stimuli during the BAT may have influenced the post-treatment effects by being a part of therapeutic intervention (Cochrane, Barnes-Holmes, & Barnes-Holmes, 2008), notably in VRET. However, the fact that BAT in the IP group showed no difference regarding both avoidance scores, and total BAT steps, after the intervention suggests that exposure to the BAT had only limited influence over the effect of VRET (Krijn et al., 2004). Despite the fact that the BAT scores, and number of situations the participant was able to tolerate in the IP condition did not decline significantly, the effect size found was moderate to large which may indicate a lack of power to detect a pre-post difference within this group.

We measured both subjective and objective fear response of the VRET participants to determine the feasibility for conducting a RCT. No apparent raise in HR during VRET seems to have occurred. The downward trend observed towards the end of VRET may be suggestive of psychophysiological habituation. However, the results of the HR data should be interpreted with caution as it included the average of the physiologic responses of arousal and habituation which might have occurred with each VR scenario.

Additional studies need to be conducted to determine the psychophysiological arousal by comparing the baseline physiologic HR response with the first exposure HR of each VR scenario. Also, physiological habituation may be determined by comparing the first exposure HR response to the last exposure HR response with each VR scenario.

The VR environment comprised a routine dental practice set-up with a patient avatar and a male Caucasian dentist avatar. VRET participants indicated to experience moderate presence and realism regarding this virtual environment. This might explain the reduction in anxiety within the VRET group. To this end, it is assumed that VRET facilitates emotional processing by an activation of people's underlying fear structure through controlled confrontation with the fearful stimuli without aversive outcomes (Rothbaum, Hodges, Smith, Lee, & Price, 2000), and that one learns that the fear is unfounded, thereby adjusting negative, irrational predictions (Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014). This explanation is supported by the finding that one of the participants who experienced lower VR presence during VRET showed no reduction in dental trait anxiety at the end of the study.

Despite the positive findings of our study, some limitations are worth noting. Firstly, a majority of participants who underwent VRET, experienced moderate cybersickness (nausea) post-session. This indicates how important it is to put more effort in reducing cybersickness to increase the applicability of VRET. We had provided breaks every 20 minutes in the present study. However, as the patients still experienced nausea, we decided to increase the frequency of the breaks in the planned randomized controlled trial (Raghav et al., 2016). Additionally, simulator sickness may be reduced by software improvements which reduce the lag in VR display, using galvanic vestibular stimulation, VIRMO tablets and improving the stability by including a virtual nose in the VR scene, but there is no conclusive evidence to support the use of these adjuncts. Future studies should be conducted to determine their usefulness in reducing the simulator sickness in VRET patients. Secondly, and most importantly, the study had a limited follow-up of 6 months, and a small sample size, clearly restricting the generalizability of the study results. Small 'N' study designs such as the present study, allow flexibility in recruiting participants, and are usually employed in the developmental phases of novel interventions (Folke et al., 2015; Graham et al., 2012). Thirdly, we did not measure heart rate response or cybersickness for the IP control group as our primary objective for measuring HR was to ascertain the physiological HR response occurring during the graded exposure to VRET, and not during reading of the informational pamphlet. Similarly, we believe that it was unreasonable to record and compare the HR response between the groups, given the intrinsic differences between the well-defined VRET scenarios and the indistinct educational content of the pamphlet. Lastly, the use of a Caucasian dentist avatar, given the multi-cultural Malaysian population, could be a limitation of our study. However, the face mask and the head cap worn by the dentist avatar

throughout VRET concealed his race to some extent. Moreover, as all three ethnic groups (Chinese, Indian and Malay) were included in the sample, using an avatar for one of these races could have confounded the results. A neutral Caucasian avatar could have possibly reduced this bias. The findings that participants experienced moderate presence and realism may be suggestive that the race and sex of dentist avatar did not affect the outcome. Regardless of the ethnicity, cultural and religion background of the participants, VRET seemed to be effective in reducing the trait dental anxiety on a limited sample of dental phobic patients of this population. Further research should be conducted to study the influence of VRET with similar and dissimilar combinations of race and sex of the dentist avatar with different populations in the treatment of dental phobia. The role of race, gender and language of the recruiting researcher and the therapist should also be explored in future VRET studies.

In conclusion, the preliminary results of this multiple baseline study are a first indication that it is feasible to use VRET in dental practice, and that this treatment is safe and has the potential to significantly decrease severe dental anxiety and reduce the avoidance tendency compared to IP standard of care among patients with dental phobia without symptom exacerbation. VRET allows patients to face their fear in a controlled and safe environment because the simulation can be stopped, paused, restarted as well as repeated, whenever, and for as many times as necessary (Baus & Bouchard, 2014). To this end, the virtual form of exposure used in the present study was effective and may have formed a useful bridging step between the therapists' office and real-life (Pastorino & Doyle-Portillo, 2015). Since, VRET does not require any specialized training for the general dentist, it may improve access to wider populations, and result in better overall oral health. Further research is warranted to confirm the effectiveness of VRET on a larger sample of dental phobic patients.

5.5 Funding

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Chapter 6. Efficacy of virtual reality exposure therapy for the treatment of dental phobia: A randomized controlled trial – A study protocol*

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6.1 Background

It is estimated that as many as 75 per cent of US adults experience some degree of dental anxiety, from mild to severe (Getka & Glass, 1992; Milgrom, Weinstein, & Getz, 1995) and that 50-60% of individuals suffer from a specific fear of dental procedures and dental related stimuli (De Jongh, Schutjes, & Aartman, 2011). Given that dental phobia belongs to the most common phobic conditions in our society, finding a suitable specific non-invasive strategy to reduce dental anxiety and treat dental phobia is both warranted and important.

Exposure based treatment programs are considered as the gold standard in the treatment of specific fears and phobias (American Psychological Association, 2006; Deacon & Abramowitz, 2004; Moore, Brodsgaard, & Abrahamsen, 2002), including those related to the dental treatment situation (Gauthier, Savard, Hallé, & Dufour, 1985), (Moore, Brodsgaard, Berggren, & Carlsson, 1991; Smith, Kroeger, Lyon, & Mullins, 1990). However, potential drawbacks include: (a) the difficulty for patients to mentally visualize the anxiety inducing threat as in imaginal exposure therapy (Baus & Bouchard, 2014), (b) the unwillingness of patients to face the actual threat in *in vivo* exposure therapy (IVET) resulting in refusal or termination of therapy accounting for 25% (Garcia-Palacios, Hoffman, See, Tsai, & Botella, 2001), (c) the failure to achieve clinically significant symptom relief, and return of fear, following exposure therapy (Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014), (d) the poor availability of psychological services (Allen & Girdler, 2005) and (e) the high costs (Boyle, Newton, & Milgrom, 2010) involved with this treatment.

Recently, VRET has become a viable alternative for *in vivo* exposure in the treatment of fears and specific phobias (Krijn, Emmelkamp, Olafsson, & Biemond, 2004)

* Raghav, K., Van Wijk, A. J., Abdullah, F., Islam, M. N., Bernatchez, M., & De Jongh, A. (2016). Efficacy of virtual reality exposure therapy for treatment of dental phobia: a randomized control trial. *BMC oral health, 16*(1), 25. doi:10.1186/s12903-016-0186-z

including claustrophobia (Botella, Baños, Villa, Perpiñá, & García-Palacios, 2000), acrophobia (Krijn, Emmelkamp, Biemond, et al., 2004), fear of flying (Muhlberger, Wiedemann, & Pauli, 2003), and spider phobia (Garcia-Palacios, Hoffman, Carlin, Furness, & Botella, 2002). This involves conducting exposure therapy using computer generated Virtual Reality (VR) environments by systematic confrontations of patients with their potentially fear-provoking (i.e., 'conditioned') stimuli so that habituation occurs (Krijn, Emmelkamp, Olafsson, et al., 2004; Krijn, Emmelkamp, Biemond, et al., 2004). Compared to IVET, VRET is safer because the patients faces the virtual representation of their threat more gradually in a controlled manner, and at their own pace (Baus & Bouchard, 2014). As the entire exposure process in VRET is completed under privacy of therapists' office it may elicit less fear of social embarrassment to the patients (Costa, Carvalho, & Nardi, 2010). VRET can be repeated, whenever and, for as many times (Baus & Bouchard, 2014) as necessary without incurring any additional costs. In-vivo exposure therapy requires training on the part of therapist and is usually delivered by trained psychologists. Compared to this, administration of VRET may just require a working knowledge of computer operation and basic training to operate the apparatus.

VRET is known to elicit a feeling of being "present" in the virtual environment (Krijn, Emmelkamp, Olafsson, et al., 2004; Krijn, Emmelkamp, Biemond, et al., 2004). This sense of presence is considered to be the essence for the effectiveness of VR (Laurel, 1995) and has been found to be an important mediating variable (Krijn, Emmelkamp, Olafsson, et al., 2004) between the VR media and the level of anxiety induced (Alsina-Jurnet, Gutiérrez-Maldonado, & Rangel-Gómez, 2011). Presence in VR is measured subjectively with questionnaires or objectively with physiological measures [e.g., heart rate (HR), body posture, skin conductance level; Krijn, Emmelkamp, Olafsson, et al., 2004; Krijn, Emmelkamp, Biemond, et al., 2004). VRET was found to be able to elicit physiologic responses in individuals with fear of flying phobia (measured by HR and skin-conductance) when exposed to VR flights, and these responses decreased following repeated VR exposure flights (Mühlberger, Herrmann, Wiedemann, Ellgring, & Pauli, 2001). Psycho-physiological arousal forms the basis for an effective exposure based therapy (Neudeck & Wittchen, 2012). A recent systematic review has suggested that VRET does elicit psychophysiological arousal, thereby rendering it to be a promising treatment modality for treatment of anxiety disorders (Diemer, Muhlberger, Pauli, & Zwanzger, 2014). However, the effect of VRET on HR is inconclusive because of limited well designed studies (Diemer et al., 2014). Also, there is no published research examining the role of VRET in causing psychophysiological arousal in anxious dental patients. Further, studies examining the relationship between subjective presence and physiological responses are limited (Wiederhold, Kaneda, Cabral, Lurie, & Wiederhold).

A recent meta-analysis suggests VRET to be slightly, but significantly, more effective than IVET (*in vivo* exposure therapy; Powers & Emmelkamp, 2008). Although, VRET provides a powerful means of modifying affect, because of its immersive nature, it has not been tested yet as a therapy for dentally related anxiety or dental phobia. In an effort to answer this question, we will describe use of VRET simulation software for the treatment of dental phobia and means to test its efficacy in the present protocol. The primary objective of the protocol is to describe the determination of the efficacy of VRET versus an informational pamphlet control group in terms of dental trait and state anxiety reductions at 1 week, 3 months and 6 months follow-up among a sample of patients suffering from dental phobia. The secondary objectives are to describe the determination of (a) the real-time effect of VRET on the course of participant's physiological response (HR) on exposure with a series of dentally related cues during therapy and (b) the relation between subjective (i.e., presence) and more objective (i.e., HR) measures during VRET. It is hypothesized that: (a) VRET would result in a significantly reduced level of dental trait anxiety (measured by MDAS, Modified Dental Anxiety Scale) and Dental Fear Survey (DFS) and state anxiety (indexed by VAS-A, Visual Analogue Scale-Anxiety) at 1 week, 3 months and 6 months follow-up compared to the informational pamphlet control group, (b) VRET would result in significantly higher reduced physiological arousal (i.e., HR) to dental anxious stimuli/cues relative to the baseline HR values following therapy, (c) VRET will demonstrate a positive correlation between subjective and objective measures of 'presence'.

6.2 Methods

6.2.1 Trial Design

The study will be conducted in compliance with local regulations and internationally established principles of the declaration of Helsinki (64^{th} World Medical Association General Assemble, Fortaleza, Brazil, 2013). The study and protocol were approved by the Ethics Commission of the SEGi University (Reference: EC01/14-01). This VRET study will be designed as a single blind (Biostatistician will be blinded), randomized controlled trial with two parallel arms: VRET and Informational Pamphlet (IP) groups with an allocation ratio of 1:1 as shown in Figure 6.1. Thirty participants undergo block randomization so that we have equal distribution of participants in both the groups. In order to preserve the allocation concealment, we will be using, sealed, opaque, sequentially numbered envelopes (SNOSE); (Doig & Simpson, 2005). Envelopes will be opened serially (next highest number) only after the participant details (patient unique number, date and patient signature)

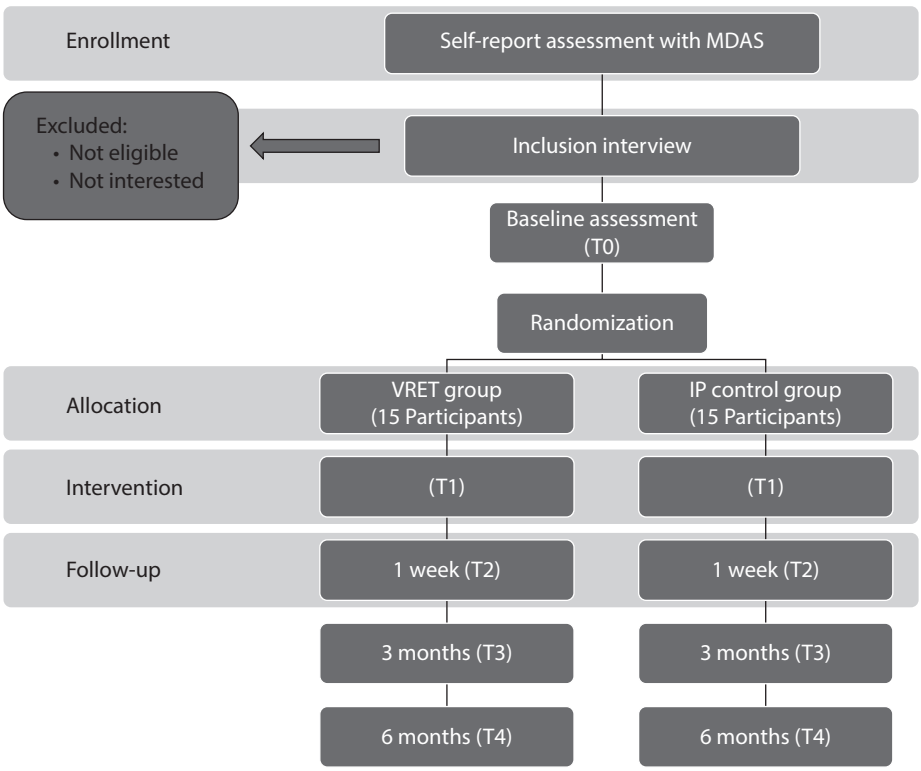

Figure 6.1 Participant Flow and timing of evaluation.

are entered on the envelope. Carbon paper inside the envelope enables transfer of details to the assignment card. Cardboard or aluminum foil inside the envelope renders the envelope impermeable to intense light (Schulz & Grimes, 2002).

The two groups are assessed at baseline (T0), before and after intervention (T1), at 1-week follow-up (T2), 3 months after treatment (T3) and 6 months after treatment (T4) on a set of variables that are linked to the various research questions. The participant flow and timing of evaluation is depicted in Figure 6.1.

6.2.2 Participants

Adult outpatients who have not visited the dentist since last 12 months or those reporting with anxiety and avoidance of dental procedures will be screened and recruited from the outpatient service of Oral Health Centre of faculty of Dentistry, SEGi University at Malaysia. The trial process starts with a short self-report assessment with a MDAS questionnaire to screen for possible dental phobia. Interested participants, who agreed to participate in our VRET Dental Phobia study, with a

MDAS score of ≥ 15, will be contacted and given an appointment by the researcher for an interview. A screening tool, the "Phobia Checklist" (Oosterink, De Jongh, & Hoogstraten, 2009) will be used for the assessment of dental phobia in this study. This measure for assessing dental phobia has previously been validated against the Structured Clinical Interview for DSM-IV with a sensitivity of 0.95, specificity of 0.99, and an overall hit rate of 97% (Oosterink, et al., 2009). The phobia checklist consists of four questions based on the DSM-IV-TR (American Psychiatric Association, 2000) criteria for specific phobia. The patients are requested to mark either a 'Yes' or 'No' response to the following questions related to their dental anxiety:

a. The sight of the feared object or experiencing the situation evokes an excessive fear response.
b. The fear is greater than justified.
c. Avoidance or giving up things because of the fear.
d. Avoidance of the situation or object causes daily impairment.

An individual is categorized as dental phobic only upon answering 'Yes' against all four questions of the phobia checklist. In the present study, the checklist will be administered during the screening interview and at 6 month follow-up.

Anticipated timeline for this study will be as follows:

1. Enrollment to Inclusion Interview: Maximum 1 week.
2. Inclusion Interview to Baseline, Randomization & Allocation: Maximum 1 week.
3. Baseline, Randomization & Allocation- Intervention: Maximum 1 week.

6.2.3 Eligibility Criteria

6.2.3.1 Inclusion Criteria

Participants should satisfy all criterion for inclusion.

- Meeting the criteria of "Phobia checklist".
- An age between 18 to 50 yr.
- Any dental phobic patient requiring the following planned dental treatment/s of *at least* 30 minutes per appointment.
    1. Restorative dental procedure which may or may not be requiring local anesthesia.
    2. Extraction procedure requiring local anesthesia.

The participants will be recruited from the out-patient department of the oral health Centre where it is mandatory for every patient to undergo a diagnostic examination. The information about treatment needs will be obtained from the findings of the diagnostic examination.

6.2.3.2 Exclusion criteria

Presence of any criteria mentioned below result in exclusion of the participant.

- Hearing or visual impairment such as stereoscopy blindness or nystagmus.
- Known mental disorders such as psychosis, post-traumatic stress disorder, developmental or intellectual disability and cognitive impairment.
- Known balance disorders such as vertigo and cybersickness.
- Patients with previous history of epileptic seizures.
- Any history of cardiac problems.
- Patients who are undergoing, or have undergone, any cognitive behavioral therapy (CBT)-based intervention for dental phobia.
- Language impediment (cannot understand English).
- Patients wearing glasses of greater than plus 3.5 power.

6.2.4 Outcome measures

Tables 6.1 and 6.2 provide an overview of the measures at various time points. Participants of both groups are evaluated using a series of measures as mentioned below. The participants of the VRET group will undergo HR monitoring in real time, assessed for subjective discomfort/distress and evaluated for VR experience at T1 during the intervention as depicted in Tables 6.1 and 6.2.

6.2.4.1 Primary Outcome measures

6.2.4.1.1 Anxiety will be determined utilizing VAS-A, MDAS and DFS survey

- **Visual analogue scale for state anxiety (**VAS-A; Luyk, Beck, & Weaver, 1988). VAS-A will be recorded by asking the participants to draw a cross mark (X) on a 0-100 mm horizontal scale with the extreme left edge of the scale indicating feeling totally calm and relaxed (0) and the extreme right edge, feeling the worst fear imaginable (100). The measured distance from the left edge of the line to the cross mark placed by the participants to the nearest millimeters provides a quantitative variable that can be used in statistical analysis. The VAS-A has been found to be a simple, sensitive, fast, reliable and valid tool to measure level of state anxiety (Facco et al., 2011).
- **Modified Dental Anxiety Scale** (Humphris, Morrison, & Lindsay, 1995). The Modified Dental Anxiety Scale (MDAS; Humphris et al., 1995) is a 5-item scale assessing dental (trait) anxiety. Respondents are asked to rate their level of anxiety across five different scenarios (e.g., anxiety response on a previous day to a prospective dental visit, when in the waiting room, when about to have tooth drilled, teeth scaled and injection to the gums) on a 5-point Likert scale ranging from "not at all anxious" to "extremely anxious", and possible scores range from 5 to 25, with greater scores indicating higher level of dental anxiety.

Table. 6.1 Showing overview of measures at different time periods.

		Measurements						
		Primary outcome			**Secondary outcomes** (Only with VRET)			
		State anxiety (VAS-A)	Trait anxiety (MDAS)	Dental Fear Survey (DFS)	Behavioral test	Physiological parameter (HR)	Subjective Unit of Distress Scale (SUDS)	VR experience
Baseline (T0)	Screening interview	X	X	X	–	–	–	–
Intervention (T1)	Preoperative interview	X	X	X	X	–	–	–
	VRET[a] session or IP[b]	–	–	–	–	X	X	X
	Postoperative interview	X	X	X	X	–	–	–
Follow-up (T2,T3)	E mail	X	X	X	–	–	–	–
Follow-up (T4)	E mail	X	X	X	–	–	–	–

Note: 'X' Indicates timing of measurement of the outcome measures.
[a]VRET: Virtual Reality Exposure Therapy.
[b]IP: Informational Pamphlet.

Table. 6.2 Showing measures during VRET session.

Measures		VRET session																										
		Baseline phase (10 min)	Training phase (2 min)	Experimental phase (sessions repeated p, q, r, s, t times until SUDS score ≤ 2)																								Immediate Post-therapy phase (10 min)
				Scenario#1 (Idle)					Scenario#2 (Mirror)					Scenario#3 (Syringe)					Scenario#4 (Drill with no sound)					Scenario#5 (Drill with sound)				
1	**Number of exposures**			1	2	3	4	p	1	2	3	4	q	1	2	3	4	r	1	2	3	4	s	1	2	3	4	t	X
2	**Subjective measure (SUDS)**			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
3	**Subjective measure (Presence)**			X	–	–	–	–	X	–	–	–	–	X	–	–	–	–	X	–	–	–	–	X	–	–	–	–	X
4	**Subjective measure (Realism)**			X	–	–	–	–	X	–	–	–	–	X	–	–	–	–	X	–	–	–	–	X	–	–	–	–	X
5	**Subjective measure (Nausea)**			X	–	–	–	–	X	–	–	–	–	X	–	–	–	–	X	–	–	–	–	X	–	–	–	–	X
7	**Objective measure (HR)**	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Note: 'X' Indicates timing of measurement of the outcome measures

The MDAS shows high levels of internal consistency and good construct validity (Humphris, Freeman, Campbell, Tuutti, & D'Souza, 2000).

– **Dental Fear Survey** (Kleinknecht, Klepac, & Alexander, 1973)**.** The Dental Fear Survey (DFS; Kleinknecht et al., 1973) is a 20-item measure used to identify emotional and physiological reactions associated with several aspects of dentistry, as well as avoidance of dental care due to anxiety. Possible scores range from 20 to 100, with greater scores indicating higher levels of dental anxiety. The DFS has established reliability, validity and sensitivity (Davis, Ollendick, & Öst, 2012).

6.2.4.1.2 Behavioral Avoidance Test

A Behavioral avoidance test will be done prior to, and immediately after, the interventions at T1 by means of standardized observation of behaviour, and an interview for both the groups. The test is similar to the VRET scenarios, and provides a baseline behavioral assessment measure to compare the responses of the patient before and after the VRET. This *in vivo* test represents an observer-rated instrument earlier used by Doering et al (Doering, Ohlmeier, De Jongh, Hofmann, & Bisping, 2013). It contains 5 situations that occur during a dental visit (e.g., sitting in the dental chair, inspection of the oral cavity using dental mirrors, approaching dental syringe, approaching dental drill without sound and approaching dental drill with sound). While the patient undergoes the dental visit it is observed whether he/she is able to tolerate the situation, and he/she is asked by the observer to assess his/her level of anxiety on a scale of 0–10 in each situation. Both observation and answers to the standardized questions are recorded during the procedure.

6.2.4.2 Secondary outcome measures

6.2.4.2.1 Psychophysiological parameter

A heart rate wrist band will be used to record the real time response to VRET at T1 during VRET session. The device will be integrated with the VR software and the output will be recorded during therapy.

6.2.4.2.2 Subjective Units of Distress (SUD) scale

The SUD scale is an eleven-point scale (Wolpe, 1969) to measure the intensity of subjective distress currently experienced by an individual. It is used by the therapist in desensitization based therapies as a standard to evaluate the progress of the therapy. Typically the patient is asked by the therapist "On a scale of 0-10 where, 0 is no discomfort and 10 is the worst, how do you feel right now". The researcher will record the SUDS scores during each VR scenario exposure of the VRET session. During the VRET session each VR exposure is repeated, until there is

habituation demonstrated by a relatively low SUD score (≤ 2), and the next scenario is introduced. The total number of VR exposures with each VR scenario that was required to achieve SUDS score of ≤ 2 will be summed up and recorded by the researcher post-therapy.

6.2.4.2.3 VR experience: will be evaluated at T1.

- **Time perception** is determined by asking the participants to calculate approximately the duration of VR immersion with therapy (Schneider, Kisby, & Flint, 2011) and the ratio of subjective and objective duration will be evaluated.
- **Presence** will be measured using an 11-point verbal rating scale (VRS) (Hoffman et al., 2001).
- **Realism** will be indexed with an 11-point (VRS) (Hoffman et al., 2001).
- **Severity of nausea ('cybersickness')** will be measured using an 11-point VRS (Hoffman et al., 2001).
- **Intention to use VR goggles** again will be indexed with a yes/no response.
- **Intention to revisit the dental surgery** will be measured with a yes/no response.

6.2.5 Procedure

After arrival at the dental office, participants will receive a detailed explanation about the study from the researcher. All participants will be asked for a written informed consent to participate in the study. The participants will be interviewed to screen for dental phobia using the "Phobia checklist" by the researcher. The interview will take 0.5 to 1.5 hours. The participants will undergo the baseline assessments (T0) which will include use of questionnaires to record the participants' characteristics such as demographic information, self-reported oral health, self-reported dental attendance and history of a bad experience with a previous dentist (Milgrom, Newton, Boyle, Heaton, & Donaldson, 2010). Completing the questionnaires will take 10-15 minutes. The interview and questionnaire are completed on the same day. Informed consent and pre-operative data will be collected in the waiting area. The participants undergo VRET at their own pace free of cost. The assessment of state and trait dental anxiety will be done utilizing the VAS-A (Luyk et al., 1988), MDAS (Humphris et al., 1995) and DFS (Kleinknecht et al., 1973). After T0, the participants will be block randomized as mentioned in Figure 6.1 into VRET intervention and informational pamphlet control groups.

6.2.6 VRET group

6.2.6.1 Description of the VRET system used

The VRET software has been developed for this study by Virtual Simulations Inc in collaboration with KR and ADJ. The hardware comprises of two networked

computers of which the VR-simulator PC (Personal Computer) renders the virtual environment and the other User interface-PC (UI-PC) allows the therapist to control and individualize stimuli presented. The VR-simulator software will generate the VR dental environment using a Dell XPS-8700 desktop with 4th Generation Intel Core i7-4790 processor (8M Cache, up to 4.0 GHz) and ASUS NVIDIA GEFORCE GTX 750 TI OC 2GB GDDR5 graphic card. The system will generate the display at a rate of 60 frames per second. To immerse the participants in the VR dental environment we will use an Oculus development kit 2 HMD (Head Mounted Display) with a resolution of 960X1080 per eye and with a 100 degree field of view (nominal).

6.2.6.2 Treatment room configuration

The waiting and VR treatment area will be shaped, using cues usually present in these areas. For VRET, a simulated dental environment will be created, with a dental chair, overhead light, and dental instruments and to enhance immersion characteristic dental clinic-related smell (drops of oil of cloves on cotton wool) will be introduced. The room temperature will be maintained at 21°C.

The treatment room where the study will be conducted will be equipped with:

1. Two networked computers and a HMD as described above.
2. Oculus positional tracking camera mounted on a tri-pod: To track the head movements in real-time.
3. Logitech C-920C webcam mounted on a tri-pod: To record the video for future validations and evaluate the participant's body response during VRET.
4. YOGA Mini Tie Clip Condenser Microphone: To record the voice of the participants during VRET, It is synchronized with the webcam.
5. MIO LINK HR wrist band: To record the real-time HR of the participants during therapy.
6. SUUNTO movestick mini: For wireless transfer of HR data from the wrist band to the simulator PC.
7. PHILIPS wireless portable speaker BT100B/37: To produce characteristic dental drill sound.

6.2.6.3 The simulated dental experience

The VRET system will be operated by the author of this study. Training will be provided by a clinical psychologist and Virtual Simulations Inc. When participants assigned for VRET visit the dental office the researcher records the unique reference number and initiates the VRET session. The Simulator PC, UI PC and video camera are turned on. Participants will be seated in a supine position comfortably in the dental chair and will be assisted in wearing the HMD (in "off" mode) and HR bracelet (left hand) by the researcher. Also, a hand held computer mouse will be given to the participants which acts as a panic button. The participants will hold

the computer mouse with their right hand and will be instructed how to activate the panic button by clicking the mouse (under their control) when the presented scenario feels unbearable to them during the VRET session. The simulator PC is connected with the UI PC. On the UI window the researcher enters the patient/subject name, connects the UI with VR simulator by entering VR Internet Protocol address and presses the start button of the log record for real time HR recording continuously during the session.

6.2.6.4 Phases of VRET session

The phases are depicted in Table 6.2.

Baseline phase

During this phase, the participants will see no display (Black screen) through the HMD (In "off" mode) for 10 minutes. Concurrently, the VR simulator software will record the HR. The purpose will be to record the resting HR as per HR wrist band manufacturer's instructions.

Training phase

The HMD is turned "on" once during the entire VRET session at this phase. In general, participants may show a higher physiological response when exposed to see something novel, this is referred to as orientation effects (Andreassi, 1995). To overcome this, the participants in this phase will first view a surrounding 3D (3 Dimensional) stereoscopic scene of simulated dental environment through the HMD and only take a passive role by watching the interactive scene for 2 minutes. The participants are encouraged to turn his head and look around the virtual dentist's office by way of the built-in motion tracking present in the HMD. Thus, the test subject will be lying on a real dentist chair while he will see its virtual counterpart inside the HMD as he looks around, turning his head. To allow the test subject to feel immersed in the virtual environment, we will include a generic 3D model of a person lying on the dentist chair such that when looking down, the subject will see what feels like his own body. The virtual environment seen by the patient will be displayed to the researcher on the computer screen and the HR will also be recorded.

Experimental phase

In this phase, participants are exposed to five different VR scenarios (Idle, Mirror, Syringe, Drill with no sound, Drill with sound). The duration of each exposure will be 35 seconds. The interactive part of the simulated dental environment will be controlled by the researcher using the tool selection option on the UI window of the computer. The researcher will be able to control the playback of the VR scenarios.

VRET is conducted using a pre-determined hierarchy as follows:

1. Scenario#1 (Idle). This shows a dental operatory with various instruments surrounding the patient's chair and a virtual dentist sitting next to the patient's right hand inside the 3D scene.
2. Scenario#2 (Mirror). This shows the virtual dentist inspecting the oral cavity by picking the dentist's mirror from the tray and approaching towards the patient's oral cavity.
3. Scenario#3 (Syringe). This shows the virtual dentist performing injection by picking the syringe from the tray and approaching towards the patient's oral cavity.
4. Scenario#4 (Drill with no sound). This shows the virtual dentist picking the drill and approaching towards the patient's oral cavity with no sound of the drill.
5. Scenario#5 (Drill with sound). This shows the virtual dentist picking the drill. The drill makes the characteristic dental drill sound when approaching towards the patient's oral cavity.

Participants will be exposed to the virtual dental scenarios in a gradual manner. To give the participants a gradual and optimal VRET, participants will be encouraged to rate their anxiety every 35 seconds following immersion with each VR scenario exposure by means of SUDS (Wolpe, 1969). The general rule applied during exposure therapy is that the exposure is continued until the subjective score of the patient is reduced to less than 50% (Richard & Lauterbach, 2011).The VRET which we are planning to use in the current experiment has only a limited set of stimuli. Accordingly, we have decided to have a safe cut off of ≤ 2 SUDS scores before moving to the next VR scenario. This criterion was earlier applied in a similar study (Krijn, Emmelkamp, Biemond, et al., 2004). The exposures with scenario 1, 2, 3, 4 and 5 are repeated p,q,r,s and t times respectively until SUDS score of ≤ 2 is achieved. For instance, when participant reaches ≤ 2 SUDS with VR scenario of sitting idle on the dental chair then the next VR scenario of inspecting the oral cavity with a dental mirror is introduced. In subsequent sessions, the intensity of VR experiences will be progressively increased from a less threatening scenario to a more threatening scenario to make the simulation more realistic while focusing on areas of particular stress. For example, if a dental phobic participant report a fear of drills, the exposure is progressively increased from Scenario-1 (less fear evoking –'Sitting in the dental chair') to Scenario-5 (more fear evoking –'Drill with sound'). To this end, situational cues that are simulated with VR scenarios are presented by the therapist in a well-controlled manner. During the simulated dental procedure participants will be asked to keep their mouth open similar to real dental experience from Scenario#2 (Examination with mirrors) through

Scenario#5 (Drill with sound) and are advised to follow the instructions of the researcher, for example 'to open their mouth really wide'. The added stimulus such as keeping the mouth open will be standardized and applied to all the participants. Participants will receive the therapy in one long session for 150 minutes with a 10-min break/s to avoid simulator sickness. If the participant's SUDS rating has not decreased to 2 with any of the VR scenarios within 30 minutes of exposure the researcher will continue with the next VR scenario. The session will be video recorded for future validations and analysis of the subject's body response during the VRET exposure.

Only verbal guidance and exposure techniques will be used on the participants during VRET. There will be no relaxation or other CBT-based interventions during therapy. Participants will be instructed to become as involved as possible and focus on their most frightening stimuli of the particular part of the virtual environment (describing the situation, any strange sensations and their feelings). This will be done to avoid dissociation from the VR experience. During the simulated treatment, real-time recording of the psychophysiological parameters (HR) will be determined to obtain more 'objective' measures of the physiological state of the participants during therapy. The HR responses obtained with different cues (Idle, Mirror, Syringe, Drill with no sound and Drill with sound) in this phase will be compared with the baseline phase (No display) to study the HR variations. The subjective measures of presence, realism and nausea (cybersickness) are recorded following the 1st exposure of each VR scenario as shown in Table 6.2.

Immediate post-therapy phase

In this phase, the HR is recorded for 10 minutes and the participants are asked to fill out a series of self-reported measures as displayed in Table 6.2 and undergo the Behavioral Avoidance Test. The total number of VR exposures with each VR scenario will be summed up and recorded by the researcher. Also, the participants fill out the questionnaire on over-all presence, realism and nausea (cybersickness). After the VRET session, participants will remain in the waiting room for 15 min before leaving. This will be done in order to make sure that are no negative side effect of VRET *a posteriori*.

One week after treatment and at intervals of 3 and 6 months, the study participants will receive questionnaires that are used to assess the participants' current dental anxiety scores and avoidance tendency (see Table 6.1) by email.

6.2.7 Informational Pamphlet control group (IP)

Participants in the IP group will be given three pages of information based on that of a dental website company, and of a fact sheet about dental anxiety from the

Academy of General Dentistry (Academy of General Dentistry, 2010). The pamphlet will contain details about the standards of care such as patient comfort, description of dental procedures and postoperative pain management. Participants will be seated in the same area where they completed the screening and are given time to review the pamphlet in detail. Also, an opportunity is given to the participants to ask the researcher information about dental phobia. The study participants will receive a total of 5 assessments, To, T1, T2, T3 and T4 similar to VRET intervention group.

Following interventions, the participants of both the groups are told that if they have any question/s about their condition, they can call a telephone helpline that facilitates patient access to information and address any questions they might have (between 08:00 to 17:00 from Monday to Friday).

6.2.8 Sample size

Since the approach of the study is novel, there is scanty comparable research available to use for a sample size calculation. We used the difference between two independent means' for sample estimation (independent-samples t-test). In a previous study (Heaton, Leroux, Ruff, & Coldwell, 2013) the response within each subject group was normally distributed with standard deviation (MDAS) 4.22. If the true difference in the experimental and control means (MDAS) is 6, we will need to study 12 experimental subjects and 12 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with probability (power) 0.9. The Type I error probability associated with this test of this null hypothesis is 0.05. Since drop-outs are unavoidable when collecting follow-up data, the sample number needs to be adjusted for the estimated drop-out rate. We are estimating a drop-out rate of 15% in this study. Adjusting the sample for 15% drop-out and 10% for VR crash results in sample of 30 participants (15 experimental and 15 control participants).

6.2.9 Data analysis

The analyses will be performed based on the Consolidated Standards of Reporting Trials (CONSORT) statement regarding e-health (Eysenbach & Group, 2011). An independent biostatistician will carry out the statistical analysis using SPSS 20.0.The recorded data will be labelled so that the biostatistician will not be able to distinguish between the two groups. All data will be analyzed using an intention-to-treat analysis. We will also conduct a per protocol analyses. Descriptive statistics will be calculated, whereas discrete variables will be summarized by frequencies or proportions. Continuous variables will be reported as means and standard

deviations or medians and range (depending on the measurement level of the variables). Data will be checked for differences at T0, T1, T2, T3 and T4 between the VRET and informational pamphlet group using independent samples t-test. Between-group changes at post treatment will be calculated by using a 2 (pre-treatment/post-treatment) × 2 (VRET/Informational pamphlet) repeated measures MANOVA. Post hoc comparisons will be applied if clarification of the main effects of the MANOVA is needed. Effect sizes between the groups will be calculated with Hedges' g. Clinical significance change analyses as described by Jacobson and Truax (Jacobson & Truax, 1991) will be conducted to determine whether the changes from pre-test to post-test are clinically significant (Jacobson & Truax, 1991). Missing data analysis will be performed and the reason for non-adherence will be registered.

The continuous monitoring of HR data will help us determine whether the physiological changes diminish following multiple exposures with each scenario (suggestive of habituation-Reliability of therapy).

To evaluate the correlation between subjective measures of VR experience (presence, realism, nausea) with objective measure of HR during each VR scenario, only the first exposure measures will be considered to eliminate the order effects as shown in Table 6.2.

Since the baseline physiology levels will vary widely between individuals, we will be determining the percentage change from baseline HR during the first exposure of each VR scenario for analyses rather than considering the absolute values. The percentage change of heart rate (%HR) will be calculated as follows:

%HR = (MeanVR – MeanBaseline)/MeanBaseline, X 100
Where,
MeanVR: Mean of HR during the VRET of 1st exposure of each VR scenario, and
Mean Baseline: Mean of HR during baseline phase of VRET session.

This will help us to compare and correlate between:

1. Self-reported subjective scores (SUDS) and Objective scores (%HR during first VR exposure of each scenario) of anxiety. Determines the validity of HR (how well do self-report scores correlate with physiological measure of HR).
2. Subjective measures of presence and the objective scores (%HR).
3. Subjective measures of presence and realism.
4. Objective scores (%HR) and subjective realism measures.
5. Objective scores (%HR) and subjective cybersickness (nausea) measures.

The association between measures will be determined using the Pearson correlation coefficient.

6.3 Discussion

The design of this randomized clinical trial offers pathways to address the efficacy of VRET in the treatment of long term trait dental anxiety. Therefore, we developed (KR, ADJ and MB) a VRET device based on exposure therapy models and will be testing the efficacy of this intervention among people with dental phobia immediately after therapy, 1 week, 3 months and 6 months post therapy, and will be comparing with the results of an informational pamphlet intervention.

In recent years VRET has become a viable treatment alternative for *in vivo* exposure therapy as evidence based treatment for specific phobias with the advantage of allowing patients to face their fears in a controlled and thus safe, environment. Patients may not feel the anticipatory fear of getting hurt as they are aware that the VRET simulation is purely virtual and that these situations can be stopped, paused, restarted as well as repeated, whenever, for as many times as deemed necessary (Baus & Bouchard, 2014). Accordingly, patients' acceptance of VRET could be relatively high.

Another important advantage of the application of VRET for dental phobia is that it may not require specialized training and the entire exposure process can be completed by a computer in the safety and privacy of the practitioner's office (Baus & Bouchard, 2014). To this end, the study is a feasibility study. If proved successful, the VRET device can be rendered by any dental auxiliaries in a general dental practice which could make it a cost-effective solution. For example, because VR technology has applications in telemedicine, in which diagnosis and treatment can be administered from a distant site (Riva & Gamberini, 2000). This may make VRET applicable in rural dental clinics, in which the therapist might not be available at long distances and the therapist views on a monitor with which the subject is interacting, and comment appropriately and therapeutically.

The strengths of our study design include randomized group allocation, use of validated standardized assessments and a long term follow-up. A limitation of the present study is the absence of IVET as gold standard control group. Yet, it is hoped that the findings of this study will provide evidence in support of the efficacy of VRET and therefore will be an important step in the treatment of dental phobia in the setting of the dental practice.

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Chapter 7. Efficacy of virtual reality exposure therapy for the treatment of dental phobia in adults: A randomized controlled trial*

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7.1 Introduction

Dental fear afflicts a significant proportion (5-15%) of the adult population, with approximately 4% satisfying the criteria for dental phobia (Hill, Chadwick, Freeman, O'Sullivan, & Murray, 2013; Humphris & King, 2011; Oosterink, De Jongh, & Hoogstraten, 2009). People with dental phobia typically avoid common dental treatment procedures and equipment such as extractions, dental drills and needles (Oosterink, De Jongh, & Aartman, 2008). Avoidance of dental treatment negatively impacts oral and general health by reducing dental attendance and uptake of dental care (Oosterink et al., 2008; Vermaire, De Jongh, & Aartman, 2008). Hence, timely and effective management of dental phobia is central to improving the oral health and quality of life of people experiencing dental phobia.

Virtual Reality Exposure Therapy (VRET) is an emerging technology that is increasingly being used for the treatment of patients suffering from specific phobia (Carl et al., 2018). During VRET patients are assisted to systematically confront their fear provoking objects and situations, within a well-controlled, computer generated virtual environment, until fear extinction occurs (Krijn, Emmelkamp, Olafsson, & Biemond, 2004). Extinction learning occurs through repeated confrontations to fear-eliciting stimuli in the absence of an aversive consequence, and can be measured by determining the initial or peak psychophysiological responses (Craske et al., 2008). For exposure therapy to be effective, it should be designed to violate core expectancies and administered until this is achieved (Craske et al., 2014). Evidence suggests that higher initial fear responses and the enhancement of fear extinction through the modulation of behavioral parameters such as multiple contexts, mass extinction, or concurrent exciters are likely to lead to improved treatment outcomes and successful VRET (Botella, Fernandez-Alvarez, Guillen, Garcia-Palacios, & Banos, 2017). Also, for VRET to be effective and engaging for

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the patients, the virtual environment should consistently elicit the feeling of being present and real during the therapy (Botella et al., 2017). Recent research suggests that the application of VRET not only is less likely to cause deterioration in symptoms following therapy compared to wait-list controls (Fernandez-Alvarez et al., 2018), but also is associated with better patient acceptance compared to the gold standard, i.e., in vivo exposure therapy (Garcia-Palacios, Hoffman, See, Tsai, & Botella, 2001).

Preliminary evidence suggests that VRET may also be beneficial to individuals suffering from dental phobia (Botella et al., 2017; Gujjar, Sharma, & Jongh, 2017; Gujjar, van Wijk, Sharma, & De Jongh, 2018). We conducted a series of experiments to study the effects of VRET that showed VRET to be both effective in reducing dental trait anxiety and avoidance tendencies in patients with dental phobia (Gujjar et al., 2017; Gujjar et al., 2018). However, these VRET studies had several limitations, including the fact that the sample sizes were small (n = 1-5), outcome variables such as physiological arousal and habituation had not precisely been measured, and temporal variations of crucial factors that might have influenced the effectiveness of VRET (i.e., presence, realism, distress, and cybersickness experienced by patients during VRET) had not been evaluated.

The purpose of the present study was to address the limitations of earlier studies and to establish the efficacy of VRET in the treatment of dental phobia. The primary outcome measures were to evaluate and compare the state and dental trait anxiety scores post-intervention, and at 1 week, 3 month and 6 month follow-up, between VRET and the Informational Pamphlet (IP) condition. The secondary outcome measures evaluated the (a) difference between pre-post behavioral avoidance between VRET and the IP condition, (b) physiological Heart Rate (HR) changes during and post-VRET, (c) temporal variations in VR experience (presence, realism, cybersickness and distress) during and post-VRET, (d) dental treatment acceptance, and (e) the number of patients who no longer met the diagnostic criteria for dental phobia following the intervention in both conditions. Several hypotheses were tested to evaluate the effects of successful VRET. Firstly, we predicted that VRET would be associated with a significant reduction in patients' state anxiety and dental trait anxiety compared to the IP condition. Secondly, that VRET would be associated with a significantly greater reduction in behavioral avoidance compared to the IP, following intervention. Thirdly, that VRET would be associated with an increase in heart rate (HR) response (physiological arousal) during VRET, and a significant decrease in HR response (physiological habituation) after VRET. Fourthly, that patients would experience strong presence and realism with no cybersickness post-VRET. Finally, we hypothesized that a significantly greater proportion of the VRET participants would improve on their dental attendance and would no longer meet the diagnostic criteria of dental phobia, compared to their IP counterparts, 6 months following the intervention.

7.2 Methods

7.2.1 Design and participants

This study was a two-arm, parallel group RCT, conducted among patients visiting the outpatient services of the Faculty of Dentistry, SEGi University, Malaysia. The trial was approved by the ethical review board of SEGi University, Malaysia (Reference: EC01/14-01) and registered in the trial registry ISRCTN (Identifier: ISRCTN25824611). Figure 7.1 shows the CONSORT flow chart for the study.

7.2.2 Screening

Adult patients visiting the university dental clinic a) who had not visited a dentist during the past 12 months or b) reported fear and avoidance towards dental procedures, were screened for the presence of dental phobia using the original MDAS (Humphris, Morrison, & Lindsay, 1995) questionnaire in English.

7.2.3 Inclusion criteria

Consenting patients with an MDAS score greater than or equal to 15 (n = 84) were assessed for dental phobia by KRG using the Phobia Checklist (Oosterink et al., 2009). Phobia Checklist is a screening instrument that has been validated against the structured clinical interview for DSM-IV with a sensitivity of 0.95, specificity of 0.99 and overall hit rate of 97% (Oosterink et al., 2009).

Eligible patients were asked whether they would be interested to participate in the study or wished to undergo their routine dental treatment at baseline (T0). Those patients who expressed interest were enlisted to participate in the trial. They required no emergency dental care nor there was any delay in their dental treatment.

7.2.4 Exclusion criteria

Patients with hearing or visual impairment such as stereoscopy blindness or nystagmus, known mental disorders such as psychosis, post-traumatic stress disorder (PTSD), developmental or intellectual disability, cognitive impairment, known balance disorders such as vertigo and cybersickness, previous history of epileptic seizures and a history of cardiac problems were excluded from participation. Also, patients who were undergoing, or had undergone, any form of cognitive behavioral therapy (CBT)-based intervention for their dental phobia, could not understand English or wore glasses of greater than plus 3.5 power were considered ineligible for the study.

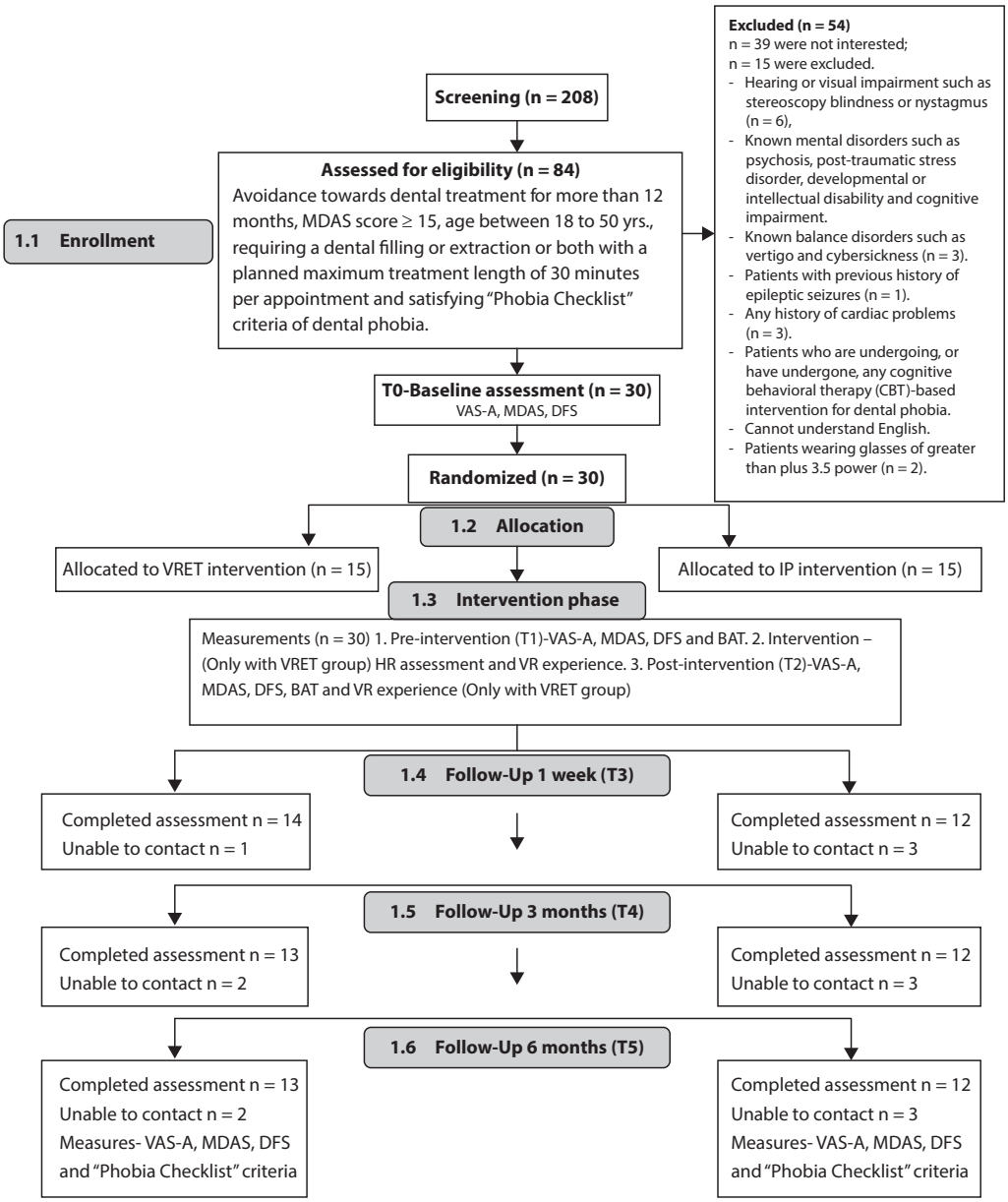

Figure 7.1 CONSORT flowchart for the study.

7.2.5 Randomization

Patients who were deemed eligible for the study, having met the diagnostic criteria of dental phobia (n = 30), were randomized (allocation ratio of 1:1) to either the VRET or the IP condition using the SNOSE (Sequentially Numbered, Opaque Sealed Envelopes) method of allocation concealment (Doig & Simpson, 2005; Schulz & Grimes, 2002) at T0. Patients and the researcher (KRG) were aware of the allocated intervention. Blinding of statistician to the condition allocation was ensured by concealment of group identifiers on the main data file and using a separate data file for analyzing the physiological data of the VRET patients. Following randomization, patients were scheduled an appointment approximately within a week to undergo either VRET or to participate in the IP condition. KRG explained the purpose of the study to the patients by stating that the study compared the use of VRET and an informational pamphlet to determine whether this would have any effect on their dental anxiety. None of the patients in either of the conditions underwent the intervention and dental treatment concomitantly. However, after the intervention patients from both conditions were encouraged to schedule an appointment with a dentist either inside or outside the university clinic. Patients underwent several evaluations at different time points during the trial on a set of variables related to the research questions. These evaluations were done at baseline (T0), before intervention (T1) and directly after intervention (T2) along with follow up evaluations at 1 week (T3), 3 months (T4) and 6 months (T5) after the intervention.

7.2.6 Procedure

Eligible patients (n = 30, 60% women) signed a consent form to participate, after receiving detailed explanation about the study from KRG. Of all the patients, 16 were of Chinese descent, five were ethnic Malay, seven were of Indian descent and two originated from the Middle-east. At baseline evaluation (T0), approximately one week prior to the intervention, patients completed a questionnaire related to their demographic information, state anxiety and dental trait anxiety.

7.2.7 Intervention

On the scheduled day, prior to the intervention (T1), patients completed self-report questionnaires on state anxiety and dental trait anxiety in the waiting area, following which they were administered either VRET or IP intervention.

7.2.7.1 VRET

VRET was conducted utilizing two network computers of which the VR-simulator computer (Dell XPS-8700 desktop with 4th Generation Intel Core i7-4790 processor (8M Cache, up to 4.0 GHz) and ASUS NVIDIA GEFORCE GTX 750 TI OC 2GB GDDR5 graphic card) rendered the virtual environment and the other user interface-computer allowed the researcher to control and individualize the VR stimuli presented to the patient. An Oculus development kit 2 HMD (Head Mounted Display) with a resolution of 960X1080 per eye was used to immerse the participants in the VR dental environment.

Patients in the VRET condition received a single session, multiple scenario VRET, while seated in a dental chair. A two minutes break was provided to the patients at every ten-minute interval to avoid cybersickness. To enhance immersion, typical dental operatory related odour was recreated by placing cotton wool soaked in clove oil around the dental chair. Patients were exposed to five different researcher-controlled VR dental scenarios, using two networked computers and a head mounted device (HMD). A HR wristband (Mio Link) was used to record the physiologic response during and following VRET. VRET intervention included the following three consecutive phases, during which the HR was monitored concurrently.

7.2.7.1.1 Baseline phase

Patients' baseline HRs were recorded with no VR display in the HMD for 10 minutes.

7.2.7.1.2 Training phase

Through the HMD, patients viewed a 3-dimensional (3D), stereoscopic, simulated dental operatory for two minutes. Patients could see their own virtual counterpart seated in a dental chair and look around the dental operatory through the HMD by moving their head.

7.2.7.1.3 Experimental phase

Patients were exposed to five different VR scenarios (VR1 to VR5), in the following predetermined hierarchy:

a. VR1. Dental operatory with dental instruments surrounding the chair and a virtual dentist sitting on the right side of the patient.
b. VR2. Virtual dentist moves towards the patient with a dental mirror in the hand, seemingly to do an oral examination.
c. VR3. Virtual dentist holds a dental syringe and moves towards the patient.
d. VR4. Virtual dentist carries a drill (without sound) towards the patient.
e. VR5. Virtual dentist carries a drill (with sound) towards the patient.

The purpose for selecting the above VR scenarios was to gradually assist the patient confront a hierarchy of common anxiety provoking stimuli in the dental setting (Oosterink et al., 2008). Each VR scenario was repeatedly presented to the patient until a change in distress score of ≤ 2 was obtained, after which the next scenario was introduced. Patients were encouraged to keep their mouth open from VR2 through VR5. Still pictures of all the VR scenarios can be found in the case study published earlier (Gujjar et al., 2017). Total duration of VRET was noted for each patient. For the study, the VRET session was planned to be conducted in a single visit. However, if patients were unable to face all the scenarios in a single visit (for example, asking to stop VRET due to excessive fear) they were scheduled for additional appointments to complete VRET and were excluded from the study.

7.2.7.1.4 Immediate post-VRET phase

Patients completed a series of self-reported measures questionnaires (Raghav et al., 2016). HR was recorded for 10 minutes following the conclusion of VRET.

7.2.7.2 Informational pamphlet

Patients in the IP condition received a pamphlet containing standard information about overcoming dental anxiety (Heaton, Leroux, Ruff, & Coldwell, 2013). They were seated in the dental chair in the dental clinic and were allowed sufficient time (up to 45 minutes) to review the pamphlet and ask questions related to their dental anxiety.

After the interventions (T2), patients from both intervention groups completed questionnaires indexing state anxiety and dental trait anxiety. Patients from VRET condition also completed VR experience questionnaire.

7.2.8 Outcome measures

7.2.8.1 Primary outcome measure

State anxiety was measured using VAS-A (Luyk, Beck, & Weaver, 1988), while dental trait anxiety was evaluated using the original validated MDAS (Humphris et al., 1995) and the DFS (Kleinknecht, Klepac, & Alexander, 1973). All questionnaires were in English. Both state anxiety and dental trait anxiety were indexed at T0, T1, T2, T3, T4 and T5.

7.2.8.2 Secondary outcome measures

7.2.8.2.1 Behavioral Avoidance Test (BAT)

BAT was performed at T1 and T2 for both VRET and IP conditions. During this test, patients were exposed to five real dental situations (steps) and asked to rate

their level of anxiety for each, on a scale of 0 to 10 (Doering, Ohlmeier, De Jongh, Hofmann, & Bisping, 2013). The dental situations included a) sitting in the dental chair, b) getting oral cavity examined using dental mirrors, c) watching an approaching dental syringe, d) watching an approaching dental drill without sound and d) watching an approaching dental drill with sound. To measure the ability of patients to tolerate the situation/s, the number of steps completed successfully were also noted (Doering et al., 2013).

7.2.8.2.2 HR response

A Miolink (*MioGlobal, U.S*) HR wrist band was used to record the HR during and after VRET. The HR wristband was programmed to record the HR in beats per minute.

7.2.8.2.3 VR experience (presence, realism, cybersickness and distress)

Presence, realism and cybersickness were measured after the first exposure with each VR scenario and at T2, using an 11-point Verbal Rating Scale (VRS) (Hoffman et al., 2001) that ranged from 0 to 10, where 10 represented the peak presence, realism or cybersickness experience.

The intensity of the current distress experienced by the patients following exposure with each VR scenario was determined using a Subjective Unit of Distress Scale (SUDS; (Wolpe, 1969). Each VR scenario was repeatedly presented to the patient until an SUDS score of ≤ 2 was obtained, after which the next higher scenario was introduced. The scores of VR experience were recorded following first exposure with each VR scenario and at post-therapy (except SUDS).

Time perception during VRET was evaluated by asking the patients to guess the approximate duration they thought they spent in the VR environment (Schneider, Kisby, & Flint, 2011).

7.2.8.2.4 Dental attendance and number of patients who no longer met the diagnostic criteria for dental phobia.

The number of patients who had scheduled dental appointment/s before, or at, T_5 was recorded by verbally asking the participants whether or not they had made a dental appointment. This self-reported dental attendance of the patients was confirmed by crosschecking their self-report against the entries in patient records in the university clinic. All patients were assessed for presence of dental phobia using the Phobia Checklist (Oosterink et al., 2009) at T0 and T_5. Detailed description and chronology of outcome measure assessment are presented in Table 7.1 (Raghav et al., 2016).

Table 7.1 Description of primary and secondary outcome measures and timing of measurement.

Primary Outcome measures			
	Measure	**Description**	**Timing**
1.	**Visual analogue scale for anxiety (VAS-A)**	VAS-A (Luyk et al., 1988) asks the patient to put a cross mark (X) on a 0-100 mm scale from totally calm (0) and relaxed to worst fear imaginable (100). This measure is regarded as a simple, sensitive, fast, reliable and valid tool in state dental anxiety assessment (Facco et al., 2011).	T0, T1, T2, T3, T4, T5
2.	**Modified Dental Anxiety Scale (MDAS)**	MDAS (Humphris et al., 1995) comprises of a 5-item scale assessing anticipatory dental anxiety, fear of dental cleanings, drilling, and injections using a 5-point Likert scale. Possible scores range from 5 to 25, with greater scores indicating a higher level of dental anxiety. The MDAS shows a high level of internal consistency and good construct validity (Humphris, Freeman, Campbell, Tuutti, & D'Souza, 2000).	T0, T1, T2, T3, T4, T5
3.	**Dental Fear Survey (DFS)**	The Dental Fear Survey (DFS; (Kleinknecht et al., 1973) comprises of a 20-item measure to identify the participants' emotional and physiological reactions associated with dentistry, as well as avoidance of dental care. The possible scores range from 20 to 100, with greater scores indicating higher levels of dental anxiety. The DFS proved to be a reliable, valid and sensitive questionnaire (Davis, Ollendick, & Öst, 2012).	T0, T1, T2, T3, T4, T5
4.	**Behavioural Avoidance Test (BAT**	The Behavioural Avoidance Test (BAT) essentially contained 5 situational steps that occur commonly during a dental visit (e.g. sitting in the dental chair, inspection of the oral cavity using two dental mirrors, approaching dental syringe, approaching dental drill without sound and approaching dental drill with sound). The BAT involves standardized observations of behaviour and an interview for both intervention groups. The patients undergo sequential steps towards their anxious stimuli comparable to the VRET scenarios and provides a baseline behavioral assessment measure to compare the responses of the patient before and after the interventions. Patients are requested to indicate their level of state anxiety on a scale of 0–10 in each situation. To measure whether the patients are able to tolerate the situation/s the number of steps completed are noted. For the purpose of this study both observation and responses to the standardized situations were recorded during the procedure (Doering et al., 2013).	T1, T2

Primary Outcome measures			
	Measure	**Description**	**Timing**
		Secondary outcome measures	
1.	**Psycho-physiological parameter**	A HR wrist band was used to continuously record the HR response of the participants during and post VRET.	During VRET and T2
2.	**VR experience after VRET**	**Presence, realism and cybersickness (severity of nausea)** were measured with an 11-point verbal rating scales (Hoffman et al., 2001)[#]. **Intention to use VR goggles again and to revisit the dental surgery** was measured using a yes/no response.	T2
3.	**Dental attendance and dental phobia evaluation.**	Dental attendance was evaluated by asking the patients the number of visits they could make within 6 months. Presence of Dental phobia was evaluated with a "Phobia Checklist"	T5

[#]0 = No presence, realism and cybersickness
1-3 = Mild presence, realism and cybersickness
4-6 = Moderate presence, realism and cybersickness
7-9 = Strong presence, realism and cybersickness
10 = Profound presence, realism and cybersickness

7.2.9 Sample size estimation

There were limited comparable studies for estimation of sample size owing to the novelty of our trial. We used the results of an independent-samples t-test between the experimental and control group of a previous study (Heaton et al., 2013) for sample size estimation with a power of 0.9. Further, we adjusted for any drop-outs at the rate of 15% and at 10% for any crash of the VR software during therapy, getting the final sample size of 30 patients (15 VRET and 15 IP; Raghav et al., 2016).

7.2.10 Data analysis

Statistical analysis was performed using SPSS (IBM, version 23, Chicago IL, USA) with alpha set at 0.05 for all analyses. An intention to treat analysis (ITT) was conducted on the data, whereby missing values of a dropped-out patient were replaced with the mean score from the other patients in the same condition.

Primary outcome measures were analyzed using a 6 (To through T5) by 2 (VRET and IP) repeated measures MANOVA, with VAS-A, MDAS and DFS as the dependent variables. Possible differences in mean dental anxiety scores between the VRET and IP condition at To, T1, T2, T3, T4 and T5 were determined using independent-samples t-tests.

The secondary outcome measures (i.e., BAT scores and steps at T1 and T2) were compared within and between the treatment conditions using paired-samples

t-tests and independent-samples t-tests respectively. In addition, Cohen's d effect sizes were calculated within and between conditions at different time points (T1-T5). The HR data obtained during and after VRET was expressed as mean HR at baseline phase, training phase, 1st and last exposure (experimental phase) of each VR scenario, and post-VRET phase. Physiological arousal (increase in HR response) was determined by comparing the mean HRs recorded at baseline, training phase and 1st exposure of each VR scenario (experimental phase) using a repeated measures ANOVA. Physiological habituation (decrease in HR response) was indexed using a paired-samples t-test to compare the mean HRs of first and last exposure within each VR scenario and the mean HR at baseline with mean HR of post-VRET phase. Repeated measures ANOVA was performed separately for presence, realism and SUDS (distress) scores across time points. Any violations of sphericity were determined using the Mauchly's test. Since the cybersickness scores showed a non-normal distribution, these data were analyzed using the Friedman's test, followed by pairwise comparisons using the Wilcoxon signed-rank test, in case of a significant finding. A χ^2 test was performed to assess the differences in the proportion of patients with no dental phobia in both conditions at T5.

7.3 Results

The results are reported according to the updated CONSORT 2010 guidelines (Moher et al., 2012).

At T0, no statistically significant differences were found between the VRET and IP conditions with respect to age, gender, state anxiety and dental trait anxiety, implying successful randomization (as shown in Table 7.2). There were four drop-outs (one from VRET and three from IP condition) at T3 and a total of five drop-outs by the end of T4 and T5 (two from VRET and three from IP condition). No significant differences were detected between the outcome measures of the drop-outs and treatment completers, albeit a significantly lower DFS score was noted amongst the drop-outs of the IP condition, compared to the VRET condition.

All VRET patients (n = 15) required a single session and were able to undergo gradual controlled exposure with the five different VR scenarios. The mean duration of VRET sessions was 40.06 minutes (SD = 20.82; range 13-96 minutes). Ratio of mean time perception of patients (M = 30.20, SD = 15.67) to actual mean duration (M = 40.07, SD = 20.82) of the VRET sessions was 0.75.

Table 7.2 Comparison of baseline demographic, state and trait anxiety scores between the Virtual Reality Exposure Therapy (VRET) and Informational Pamphlet (IP) condition.

Variables	VRET group (n = 15)	IP group (n = 15)	Test result	d#
Age	25.3(8.6)^	23 (8.9)	t (28) = 0.70; p > 0.05	–
Sex	7 male;8 female	5 male;10 female	χ^2 (1) = 0.55; p > 0.05	–
T0-VAS[8]	70.3(14.2)	68(9.8)	t (28) = 0.52; p > 0.05	0.19
T0-MDAS[9]	18.8(2.8)	18.3(2.6)	t (28) = 0.46; p > 0.05	0.19
T0-DFS[10]	64.8(5.7)	63.8(9.3)	t (28) = 0.35; p > 0.05	0.13

^Mean score, standard deviations (in parentheses); d#, effect size reported as absolute values.

7.3.1 Primary outcome measures

The results of the analysis based on ITT did not differ from the results of the analysis based on only treatment completers. Hence, only the results of the ITT analysis are presented here.

7.3.1.1 State anxiety and dental trait anxiety

In order to compare the multiple mean dental anxiety scores over time in the VRET and IP condition, a repeated measures MANOVA was conducted (see Table 7.3 for mean scores). Results showed a significant multivariate main effect of time, F (15, 14) = 4.6, p = 0.003, implying that the mean scores over time were not the same. Subsequent univariate analysis showed that the time effect was present for all dependent variables; VAS-A, F (5, 140) = 15.3, p < 0.001; MDAS, F (5, 140) = 30.2, p < 0.001; and the DFS, F (5, 140) = 23.0, p < 0.001. Next, pairwise comparisons showed a similar effect for all dependent variables. From To to T1, no significant differences in the mean anxiety scores were evident, while from T1 to T2, statistical significant reductions in mean anxiety scores were found. From T2 to T5, the mean scores were either stable or decreased only slightly.

More interestingly, a significant multivariate interaction effect between time and condition was found, F (15, 14) = 3.3, p = 0.015, implying that not all changes over time were the same for both conditions. Subsequent univariate analysis showed that the interaction effect was present for all dependent variables; VAS-A, F (5, 140) = 12.7, p < 0.001; MDAS, F (5, 140) = 18.5, p < 0.001; and DFS, F (5, 140) = 23.1, p < 0.001. Subsequent pairwise comparisons showed a similar effect for all

8 VAS-A score ranges from 0-100; greater score indicates higher state anxiety.

9 MDAS possible score ranges from 5-25; greater score indicates higher dental trait anxiety.

10 DFS possible score ranges from 20-100; greater score indicates higher dental trait anxiety.

dependent variables. For the VRET condition, the mean anxiety scores decreased significantly from T1 to T2, and were stable across the other time points, whereas the mean anxiety scores in the IP group remained stable throughout all time points. The interaction effects for the dependent variables are illustrated in Figures 7.2, 7.3 and 7.4. As can be seen in Table 7.3, following the intervention, state and dental trait anxiety scores differed significantly between the conditions at T2, T3, T4 and T5 with large effect sizes (Cohen's d > 0.8) favoring the VRET condition.

7.3.2 Secondary outcome measures

7.3.2.1 Behavioral avoidance

Paired-samples t-tests within condition revealed statistically significant differences between pre and post intervention BAT scores [t (14) = 8.09; p < 0.01] and the number of steps patients could tolerate [t (14) = -7.36, p < 0.001]. Cohen's *d* effect sizes for BAT scores and BAT steps were larger in the VRET condition (1.24 and 1.33 respectively) compared to the IP condition (0.44 and 0.48 respectively)

With respect to between condition BAT scores and steps at T2, independent-samples t-tests revealed a significantly lower mean BAT score and a significantly greater number of steps tolerated by the patients in the VRET condition compared to the IP condition (see Table 7.3)

Table 7.3 Comparison between Virtual Reality Exposure Therapy (VRET) and Informational Pamphlet (IP) condition on mean state and dental trait anxiety scores, Behavioral Avoidance Test (BAT) scores and BAT steps, at different time points.

	T1			T2			T3			T4			T5		
	VRET	IP		VRET	IP		VRET	IP		VRET	IP		VRET	IP	
	Mean (SD)	Mean (SD)	d	Mean (SD)	Mean(SD)	d	Mean(SD)	Mean(SD)	d	Mean(SD)	Mean(SD)	d	Mean(SD)	Mean(SD)	d
VAS[11]	78.0(16.6)	68.0(12.9)	0.67	33.6(30)	68.3(12.1)	1.52*	37.1(18.6)	65.8(4.5)	2.12*	32.3(19.6)	65.8(10.3)	2.14*	34.6(27.4)	64.1(8.8)	1.45*
MDAS[12]	20.0(3.4)	17.8(2.1)	0.78	12.9(4.2)	18.2(1.9)	1.63*	11.8(3.7)	17.5(1.5)	2.02*	11.2(3.3)	17.0(1.4)	2.29*	10.0(4.6)	16.4(3.1)	1.63*
DFS[13]	68.0(7.8)	64.4(12.1)	0.35	46.8(11.5)	66.2(11.3)	1.70*	41.6(12.8)	65.7(6.1)	2.40*	38.5(13.6)	63.9(6.8)	2.36*	38.0(17.3)	61.9(7.5)	1.79*
BAT[14]	38.4(4.5)	33.4(2.8)	1.33*	21.8(8.0)	32.7(2.2)	1.86*									
BAT Steps[15]	2.1(0.3)	2.2(0.4)	0.28	3.5(0.6)	2.4(0.6)	1.83*									

* $p < 0.05$; d, effect size reported as absolute values; VRET, Virtual Reality Exposure Therapy; IP, Informational Pamphlet; T1, pre-intervention; T2, post-intervention; T3, 1 week follow-up; T4, 3 months follow-up; T5, 6 months follow-up.

11 VAS-A score ranges from 0-100; greater score indicates higher state anxiety.
12 MDAS possible score ranges from 5-25; greater score indicates higher dental trait anxiety.
13 DFS possible score ranges from 20-100; greater score indicates higher dental trait anxiety.
14 BAT possible score ranges from 5-50; greater score indicates higher avoidance.
15 BAT steps possible score ranges from 1-5; greater score indicates lower avoidance.

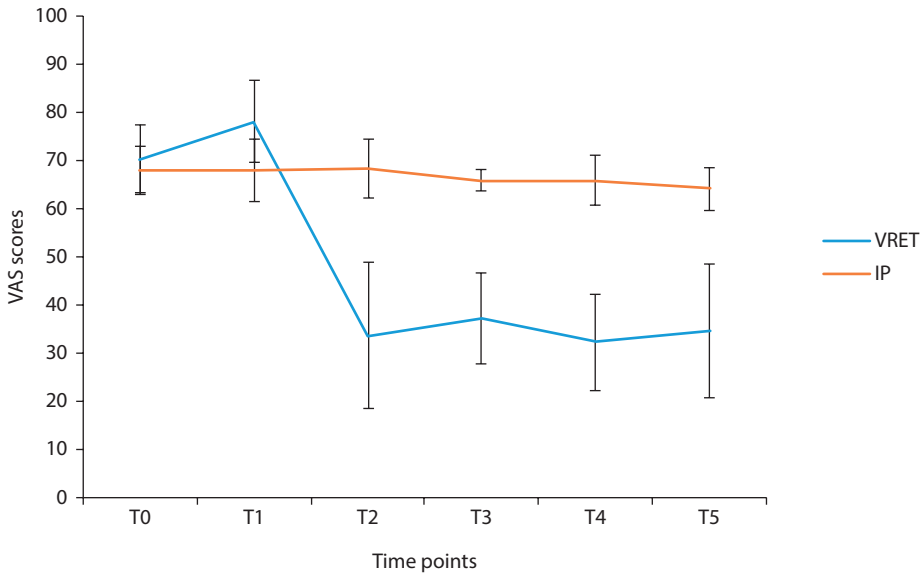

Figure 7.2 Mean VAS scores with 95% C.I. at each time point, for the VRET and IP condition separately.

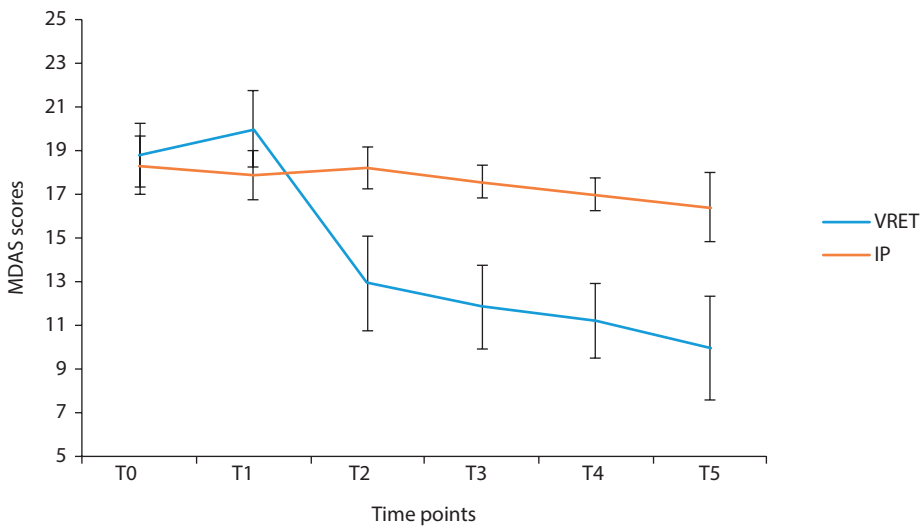

Figure 7.3 Mean MDAS scores with 95% C.I. at each time point, for the VRET and IP condition separately.

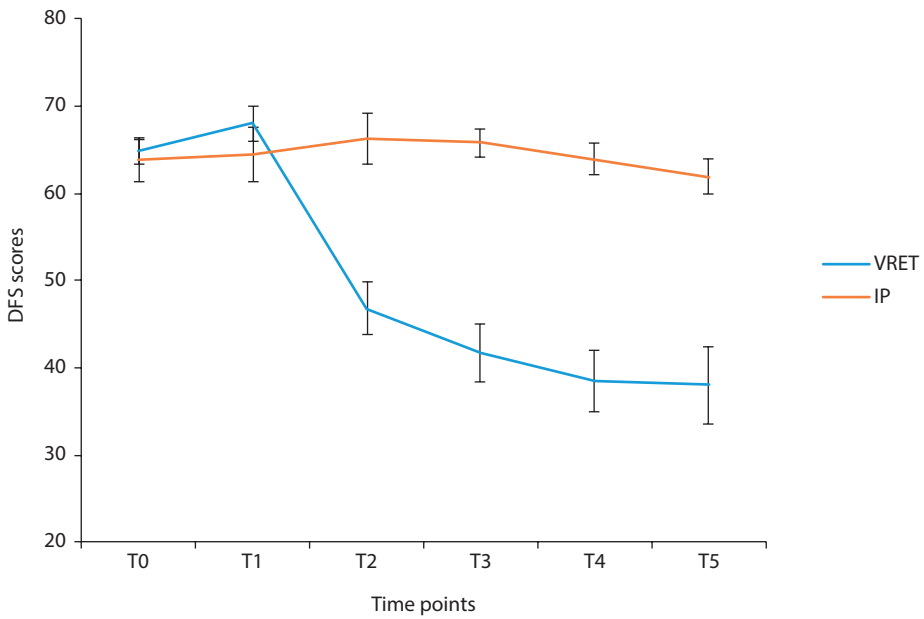

Figure 7.4 Mean DFS scores with 95% C.I. at each time point, for the VRET and IP condition separately.

7.3.2.2 Heart rate

A significant difference was found between the means of HR recorded at baseline, training phase and first exposure of each VR scenario [$F(3.3, 46.8) = 3.27$, $p < 0.05$]. A downward trend was observed for mean HRs of first exposures from scenario VR1 through VR5. Although none of the comparisons between the mean HRs of 1st and the last exposure within each VR scenario yielded a significant difference, mean post-VRET HR was significantly lower than the mean baseline HR [$t(14) = 2.25$, $p < 0.05$].

7.3.2.3 VR experience (presence, realism, cybersickness and distress)

The Mauchly's test showed no violation of sphericity regarding presence, realism and distress scores (all p's > 0.05). As seen in Table 7.4, separate comparisons for presence and realism scores at different time points of VRET (from VR1 through post-VRET) showed no significant differences, indicating that the patients experienced a consistent presence and realism throughout the VRET. However, significant differences were noted for the in-between comparisons of means of distress scores from VR1 through VR5 [$F(4, 56) = 3.98$, $p < 0.01$]. Additionally, pairwise in-between comparisons of distress scores from VR1 through VR5 revealed significant differences (all ps < 0.05) between pairs of distress scores measured at VR 1 and VR 3, VR 1 and VR 5, VR 2 and VR 3, VR 2 and VR 5, VR 3 and VR4, VR4 and VR5, implying a gradual increase in level of distress with the introduction of VR3, VR4 and VR5.

The Friedman test showed a statistically significant difference between the mean ranks of cybersickness scores measured at various time points (Table 7.4). Wilcoxon signed-rank tests showed significant differences when cybersickness scores at post-VRET were compared with the cybersickness scores at VR2, VR4 and VR5. An increase in mean cybersickness score was evident at post-VRET.

7.3.2.4 Dental attendance

A total of 16 patients, i.e., 10 (77 %) from the VRET condition, and 6 (50 %) from the IP condition [χ^2 (1) = 1.99; p > 0.05] scheduled an appointment for dental treatment and underwent actual dental treatment within 6 months following the intervention.

Table 7.4 Comparison of mean (SD) presence, realism and cybersickness scores within the Virtual Reality Exposure Therapy (VRET) condition at different time points.

	VR1		VR2		VR3		VR4		VR5		Post-VRET		
Variable	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Test result**
Presence[16]	6.80	2.59	6.93	2.01	7.26	2.28	6.20	2.85	7.80	1.93	7.33	1.71	F (5,70) = 1.62, p > 0.05[a]
Realism[16]	6.33	2.12	7.26	1.62	7.40	2.19	6.66	2.38	7.60	2.13	7.13	2.06	F (5,70) = 1.77, p > 0.05[a]
Cybersickness[16]	.66	1.63	.53	1.59	.66	1.49	.60	1.68	.46	1.80	1.66	2.43	χ^2(5) = 14.12, p < 0.05*

VR1 = Virtual Reality scenario 1, VR2 = Virtual Reality scenario 2, VR3 = Virtual Reality scenario 3, VR4 = Virtual Reality scenario 4, VR5 = Virtual Reality scenario 5, VRET = Virtual Reality Exposure Therapy; [a] Repeated Measures ANOVA, * Friedman test.

7.3.2.5 Number of patients no longer fulfilling the diagnostic criteria of dental phobia

Of the 25 treatment completers, 11 (85%) from the VRET condition, and 2 (17 %) from the IP condition [χ^2 (1) = 11.54; p < 0.001], did not fulfill the criteria of specific (i.e., dental) phobia at 6-month follow-up.

7.4 Discussion

The results of this study support our hypothesis that VRET would be associated with a significantly greater decrease in dental anxiety and behavioral avoidance compared to those who received IP as intervention. The findings of the self-reported

16 *0 = No presence, realism and cybersickness*
1-3 = Mild presence, realism and cybersickness
4-6 = Moderate presence, realism and cybersickness
7-9 = Strong presence, realism and cybersickness
10 = Profound presence, realism and cybersickness

measures are corroborated by the fact that a large proportion of VRET patients underwent actual dental treatment relative to the control condition, within six months following the intervention. Superiority of VRET over the control condition was also underlined by the finding that at 6-month follow-up, a significantly greater proportion of the treatment completers in the VRET condition than in the IP condition did not fulfill the criteria of dental phobia anymore. This suggests that the VRET as applied in the present study was efficacious in the treatment of dental phobia.

The positive effects of VRET could partly be attributed to the strong presence and realistic VR experience perceived by the patients throughout the therapy. It has been found that controlled and realistic visual, olfactory and auditory cues (Maples-Keller, Yasinski, Manjin, & Rothbaum, 2017) during VRET activate the underlying fear structure (Price, Mehta, Tone, & Anderson, 2011). Additionally, exposure optimization strategies applied in our study such as prolonged, focused and controlled confrontations with patients' feared stimuli in the absence of aversive outcome (Rothbaum, Hodges, Smith, Lee, & Price, 2000) may have resulted in a reduction of the fear response (Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014) in the patients.

Physiological habituation was evident post-VRET, implying successful exposure therapy using virtual reality (Diemer, Muhlberger, Pauli, & Zwanzger, 2014). Although HR is regarded as the most potent physiological anxiety measure in patients with specific-phobias, dissonance was observed between different measures of anxiety (Wilhelm et al., 2005). That is, while progressing to a higher anxiety provoking VR scenario/stimuli for e.g. VR3, VR4 and VR5 resulted in more distress experienced by the patients (higher SUDS score), HR (from scenario VR1 through VR5) showed a downward trend. This is consistent with Fowles' motivational theory which predicts that VRET specifically activates the behavioral inhibitory system, thereby causing a reduction in HR (Wilhelm et al., 2005). Also, the focused visual attention of the patients might have led to activation of cardiac parasympathetic activity and a reduced cardiovascular response (Wilhelm et al., 2005). In order to objectively evaluate the treatment outcomes, and to better understand the underlying mechanisms during VRET, future research could use more sensitive psychophysiological measures such as heart rate variability and skin conductance response.

Present study has several limitations that should be noted. Firstly, we could not blind the patients or the therapist to the interventions due to the apparent differences between the two interventions. However, data files containing data from different conditions were sent as separate files to the data analyst (AVW) with the patient identifiers in the data files blinded (Karanicolas, Farrokhyar, & Bhandari, 2010). Secondly, we compared VRET with a non-active IP control condition. The choice for this control was based upon the fact that informational

pamphlets are commonly used by dental practitioners due to their ease of administration. Yet, in future studies it might be useful to compare VRET with an active control such as *in vivo* exposure therapy due to greater likelihood of it providing a better estimate of the effectiveness of VRET. Thirdly, the fact that we used a sample of dental phobia patients who visited an out-patient clinic, may be considered a limitation for the generalizability of the study findings since a large number of patients with a dental phobia avoid dental offices. However, the large effect sizes that were obtained supports testing of VRET as a remote therapy in patients with dental phobia with total avoidance towards dental treatment. Fourthly, the VRET used in this study contained only five (albeit most commonly encountered) dental scenarios with all patients exposed to the same five VR scenarios. Although this was done for reasons of consistency and standardization of the intervention, it may be considered a limitation because the stimuli that trigger dental anxiety may differ for each individual (Oosterink et al., 2008). Therefore, conducting future studies in VRET using additional VR sounds and scenarios such as dental aspirator sounds, root canal and dental scaling sounds and instruments would make VRET relevant to more individuals. Fifthly, the VRET program used a caucasoid male dentist avatar, while the patient population was largely multiethnic Malaysian. Nonetheless, regardless of the sex and race of the dentist avatar, the VRET device used in the present study was able to trigger a significant fear response in patients. It would be interesting to study the effects of using VRET programs that provide option of selecting race and sex of the dentist avatar. Finally, patients experienced mild cybersickness post-VRET. However, severity of cybersickness experienced during the present study was less than what was observed during the feasibility study (Gujjar et al., 2018), possibly because more breaks were provided during the present RCT compared to the feasibility study.

7.5 Conclusion

The results of this study provide evidence to support the efficacy of VRET in the treatment of dental phobia. Also, the positive findings in relation to both subjective and objective measures support using VRET in routine dental practice.

7.6 Funding

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Chapter 8. Summary and general discussion

8.1 Introduction

In this chapter a concise overview of the conclusions drawn from individual studies, strengths and limitations of the studies that are part of this thesis that examined the effects of Virtual Reality Exposure (VRET) are presented. This is followed by a discussion about its possible mechanisms of action and the factors that are likely to influence the effectiveness of VRET. Finally the chapter concludes by discussing the impact of VRET in the dental practice, future VRET research avenues and barriers for carrying out VRET in patients with dental phobia.

The primary objective of this thesis was to compare and to evaluate the effectiveness of VRET with an information pamphlet (IP) control condition in terms of dental anxiety reduction using different samples of patients with dental phobia. The secondary objective involved evaluating the real-time physiological heart rate (HR) response of patients with dental phobia during VRET. Therefore, we conducted a series of studies with different study designs to determine the effectiveness of VRET. The next section gives an overview of the chapter-by-chapter summary of the included studies in this thesis.

8.2 Summary drawn from individual studies

8.2.1 Chapter 2

In the second chapter (Gujjar, van Wijk, Kumar, & De Jongh, 2019a), a systematic review of all published studies on technology-based interventions in the treatment of dental anxiety was conducted. The purpose was to review the extant literature regarding the effectiveness of these interventions in the treatment of moderate to severe dental anxiety. Systematic searches of the databases were carried out in two stages. The first literature search was carried out at the start of the Ph.D. study between 1969 and March 2014 which inferred that technology-based interventions in the form of VRET are unexplored in the treatment of dental phobia. This formed the basis to develop a VRET system in a dental context and to test its applicability by conducting series of related studies. The second search was conducted during the mid-Ph.D. period between 1969 to July 2018. After scrutiny, seven randomized controlled trials (RCTs) were included for review. Six studies that evaluated video modelling (n = 3), C-CBT (Computerized-based Cognitive Behavioral Therapy; n = 1), VRET (n = 1) and distraction with audio-visual (n = 1) video material showed

significant greater reductions in dental anxiety compared to inactive controls among both children and adults, suggesting that technology-based behavioral interventions work well in the treatment of dental anxiety. However, the quality of all included studies was generally poor. In addition, the majority of the studies did not evaluate the safety and avoidance of dental treatment following the intervention. This led us to evaluate the efficacy of VRET while also addressing the concerns of the previous published studies on technology-based interventions with a well-designed and high quality RCT.

8.2.2 Chapter 3

The third chapter (Gujjar, Sharma, & De Jongh, 2017) describes the preliminary findings of the first case study that evaluated the applicability of VRET. This study included two female patients aged 24 and 56 years with dental phobia. Following VRET we observed a significant reduction of behavioral avoidance and dental anxiety scores (both state anxiety and dental trait anxiety) at post-VRET and at six months follow-up. Both patients experienced strong presence and realism during VRET and acknowledged that the therapy was useful to them. Within six months, both patients scheduled their dental appointments and underwent dental treatment. Upon evaluation six months later, both patients did not fulfill the diagnostic criteria of dental phobia anymore.

8.2.3 Chapter 4

The fourth chapter of this thesis (Gujjar & De Jongh, 2019) presents the findings of the second case study that evaluated the use of VRET with an adult female patient suffering from severe dental phobia and a case with a pediatric dental phobic patient. VRET was found to be successful in reducing level of state anxiety, dental anxiety and behavioral avoidance in both patients. Further, these patients scheduled an appointment and underwent dental treatment within six months following therapy. That the treatment proved to be successful is illustrated by the fact that both patients did not meet the diagnostic criteria of dental phobia at follow-up.

8.2.4 Chapter 5

The fifth chapter (Gujjar, Wijk, Sharma, & De Jongh, 2018) discusses the results of the first feasibility study that evaluated both the safety of the use of VRET and its efficacy in the treatment of dental phobia by comparing the results of VRET with that of an informational pamphlet control (IP) condition. The study was conducted to identify shortcomings and limitations of VRET prior to commissioning the larger

randomized controlled trial and used a non-concurrent multiple baseline design among ten patients randomized to either VRET or the IP condition. VRET was found to be safe and effective in terms of a significantly greater reduction of state anxiety, dental trait anxiety and behavioral avoidance compared to the IP condition. At six month follow-up, a significantly greater proportion of VRET patients, compared to the IP patients, no longer fulfilled the diagnostic criteria of dental phobia and scheduled a dental appointment with another dentist. VRET patients experienced moderate presence and cybersickness during therapy. We found a significant reduction of HR post-VRET suggestive of physiologic habituation implying successful exposure therapy. However, precise determination of physiologic arousal and physiologic habituation were not evaluated in the feasibility study. Also, patients who underwent VRET experienced moderate cybersickness post-therapy. Hence, a RCT was planned to address the limitations of the feasibility study.

8.2.5 Chapter 6

In the sixth chapter (Raghav et al., 2016), based on the experiences obtained in Chapters 2, 3, 4 and 5, the protocol for a RCT was designed to be conducted in a study with 30 patients suffering from dental phobia. This chapter describes the design of this study that compared the efficacy of VRET against an informational pamphlet (IP) control condition in terms of reductions of state anxiety, dental trait anxiety and behavioral avoidance at one week, three month and six month follow-up. A standard, single VRET session was developed consisting of a baseline phase (no virtual reality display for ten minutes), a training phase (orientation to the virtual reality environment for two minutes), an experimental phase (exposure to the five virtual reality scenarios) and an immediate post-VRET phase for ten minutes. The frequency of breaks within the VRET session was reduced to ten minutes in order to prevent cybersickness. Temporal variations of Virtual Reality (VR) experience parameters such as presence, realism and cybersickness were planned to be determined at different time points following exposure with each VR scenario. In order to precisely measure the physiological arousal and physiological habituation, temporal changes in HR that might occur during VRET session were planned to be analyzed. Also, the number of patients who lost their dental phobia diagnosis and those who scheduled an appointment and underwent dental treatment elsewhere were planned to be evaluated at six month follow-up.

8.2.6 Chapter 7

The seventh chapter (Gujjar, van Wijk, Kumar, & De Jongh, 2019b) addresses, and discusses, the findings of the first randomized controlled study that was conducted

among 30 dental phobia patients who were randomly allocated to either VRET or an IP condition. VRET was found to be effective in terms of a significant reduction of dental anxiety scores (i.e., both state anxiety and dental trait anxiety) and behavioral avoidance compared to IP. There was evidence of physiologic habituation, i.e. a reduction of HR was noted post-VRET (relative to baseline HR). VRET patients experienced consistent strong presence and realism during therapy. However, mild cybersickness was noted in all patients post-VRET. VRET proved to be efficacious in that at six month follow-up, 85% of patients no longer fulfilled the diagnostic criteria of dental phobia compared to only 15% in the IP condition. In addition, within six months following therapy, 77% of the VRET patients scheduled their dental appointment and underwent actual dental treatment compared to 50% in the IP condition.

8.2.7 General conclusions

The findings of all included studies suggest that VRET is a safe, well-tolerated, acceptable and effective treatment for dental phobia.

8.3 Strengths and limitations

8.3.1 Strengths of this thesis

There are several strengths involving the research projects which were part of my thesis that need to be noted. Firstly, this was the first time a systematic approach to evaluate the efficacy of VRET for dental phobia was carried out. At first, two case studies were conducted to obtain preliminary evidence, whereas next a feasibility study was conducted using a multiple baseline study. Our experiences with, and the findings of, the case studies and feasibility study enabled us to design and conduct a gold standard approach of assessing the relative efficacy of both interventions using a randomized controlled trial (RCT). Secondly, the virtual environment for applying VRET was designed after consulting clinical psychologists, dentists and a software engineer in order for the VR environment to be clinically suitable, realistic and immersive. Thirdly, a multiple validated and reliable instruments was used to evaluate the various therapy outcomes (Chapter 2-7). The studies were conducted only with patients experiencing severe symptoms of dental anxiety, i.e. those fulfilling the diagnostic criteria of dental phobia using the Phobia Checklist criteria (Oosterink, de Jongh, & Hoogstraten, 2009). The use of a variety of valid and reliable self-report measures (MDAS, DFS, and the Phobia Checklist), a physiological measure

(HR) and a behavioral avoidance test (BAT) for assessing treatment outcome, made it possible to examine the external validity of the experiments (McDermott, 2011). Fourthly, the use of a BAT before and after VRET, to examine the behavioral avoidance tendency of patients who had undergone the VRET, was also important, since the objective of any treatment for phobias is to influence patients' avoidance behavior in real life situations. Taken together, the findings of the included studies in this thesis add empirical evidence to the existing scientific literature on the evidence based treatment of specific phobias.

8.3.2 Limitations of this thesis

One of the main limitations of the studies that were part of the current Ph.D. project is that none of these compared VRET with the gold standard in vivo exposure therapy (IVET). Therefore, in the future it is important to conduct studies that compare the effectiveness of VRET with that of IVET using a similar set of phobic stimuli. Secondly, the included studies had a limited follow-up of six months, which restricts conclusions regarding the empirical support for the long term effectiveness of VRET. Hence, further research is needed to validate the efficacy of VRET in the long term (Maples-Keller, Yasinski, Manjin, & Rothbaum, 2017), and to determine whether or not there is a relapse in patients with dental phobia following successful treatment using VRET. Thirdly, all studies were conducted at a single treatment center. Because we recruited the sample from a dental outpatient clinic, results from this thesis cannot be generalized to patients with extreme avoidance who do not visit the dentist at all. Therefore, to enhance the external validity and generalization of findings, future multi-site randomized controlled studies with a diverse sample are needed. While, given these considerations, on one hand the current findings may overestimate the effectiveness of VRET in the treatment of dental phobia, on the other, the large effect size obtained in the RCT (Gujjar et al., 2019b) suggests that the effects of VRET are robust. Finally, patients in all included studies underwent exposure to only a limited set (i.e., five) of dental VR scenarios (albeit most commonly encountered). Although this was done for reasons of consistency and standardization of the intervention, it may be considered a limitation because the nature and range of the stimuli that have the potential to trigger dental anxiety is much more wide and triggers may strongly vary among individuals (Oosterink, De Jongh, & Aartman, 2008). Regardless of the above limitations, the stability of treatment gains at follow-up and high acceptability of dental treatment among patients (Fernández-Álvarez, Di Lernia, & Riva, 2020) following VRET seem to make it a potentially invaluable treatment option for dental phobia.

8.4 VRET: Possible mechanisms of action

VRET is known to induce fear, emotional responses and physiological symptoms similar to in vivo exposure therapy (IVET; Riva, Bacchetta, Baruffi, & Molinari, 2002). That is, VRET involves exposure to individual's fear provoking objects and situations (conditioned stimuli) using a computer-generated environment in a well-controlled graded manner in absence of aversive consequence (unconditioned stimuli; Botella, Baños, Rosa, García-Palacios, & Quero, 2017; Craske et al., 2008; Dunsmoor, Niv, Daw, & Phelps, 2015; Lindner et al., 2017). Procedurally, this is equivalent to fear extinction in which the conditioned stimulus that was previously paired with an aversive outcome (i.e., unconditioned stimulus) is repeatedly presented without being followed by unconditioned stimulus (Rothbaum, Hodges, Smith, Lee, & Price, 2000). Hence, it is likely that the resultant new learning (*inhibitory learning*) of non-threat association between the conditioned stimulus and unconditioned stimulus forms the basis for the effectiveness of VRET.

It has been argued that the success of VRET also depends on its ability to trigger physiological responses that are similar to those induced by phobic stimuli in real-life situations (Jang et al., 2002; Nesse et al., 1985; Roth et al., 1986; Wilhelm & Roth, 1998). That is, similar to IVET, VRET should trigger heightened psychophysiological response (Craske et al., 2008) following confrontation to the phobic stimuli to be successful. However, the RCT (Chapter 7) yielded no evidence of a lack of physiological arousal in that heart rate (HR) showed a downward trend following exposure to the higher anxiety provoking VR scenarios (relative to baseline HR). This is consistent with Fowles' motivational theory (Fowles & Don 1988) which predicts that VRET specifically activates the behavioral inhibitory system, thereby causing a reduction in HR (Wilhelm et al., 2005). To objectively evaluate treatment outcome, and to better understand the physiological mechanisms (De Carvalho, Freire, & Nardi, 2010) underlying VRET, in future studies, the use of psychophysiological measures that would precisely determine the real-time physiological changes such as HR variability, skin conductance response and functional near infrared scan (fNIRS) would be enlightening. That is, recording physiological measures in real time could enable therapists/researchers (or an automated device or app) to precisely control the exposure, based upon the physiological responses of the patients which might improve treatment outcome.

Factors affecting effectiveness of VRET

As discussed in the introduction (under Section 1.7), for VRET to be effective, the exposure should be designed in such a way that it aims at violating core expectancies and should be administered until this aim is achieved (Craske et al., 2014). Therefore, the purpose of the controlled and realistic exposure to visual, olfactory and auditory

phobic cues (Maples-Keller et al., 2017) without aversive outcomes (Rothbaum, Hodges, Smith, Lee, & Price, 2000) during VRET is to activate the underlying fear structure (Price, Mehta, Tone, & Anderson, 2011). This facilitates learning in patients in that they experience that their irrational predictions are unfounded and as a result of this patients' fear subsides (Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014). For fear activation to occur, the virtual environment should be captivating for phobic patients (Maples-Keller et al., 2017) so that they interact with their feared virtual environment likewise as they would do in real life situations (Maltby, Kirsch, Mayers, & Allen, 2002). This meaningful interaction between the patient and phobic stimuli is facilitated by rich multi-sensory visual, olfactory and auditory cues (Fernández-Álvarez et al., 2020) that enable patients to perceive the situation as anxiety provoking (Lindner et al., 2017) during therapy (Maples-Keller et al., 2017), to increase the perception that the objects are real (Krijn, Emmelkamp, Biemond, et al., 2004; Krijn, Emmelkamp, Olafsson, & Biemond, 2004), and accordingly, to enhance their experience of 'being there' (Fernández-Álvarez et al., 2020). It is likely that the positive effects of VRET in this thesis were due to the strong presence and realistic VR experience (and thus greater distress) perceived by the patients consistently throughout the therapy (Chapters 3, 4, 5 and 7; Alsina-Jurnet, Gutiérrez-Maldonado, Rangel-Gómez, & María-Virgina, 2011; Ling, Nefs, Morina, Heynderickx, & Brinkman, 2014). This prolonged, focused and controlled confrontations to patients' distressing VR dental situations (Chapters 3, 4, 5 and 7) may have resulted in violation of their core expectancies and therefore led to improved treatment outcomes (Botella, Fernandez-Alvarez, Guillen, Garcia-Palacios, & Banos, 2017; Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014; Lindner et al., 2017).

Cybersickness has been considered an important barrier for successful VRET (Rebenitsch, 2015; Shiban, 2018). It refers to bodily discomfort with symptoms including a slight headache, nausea (Gregg & Tarrier, 2007; Krijn, Emmelkamp, Olafsson, et al., 2004), dizziness, disorientation and eye strain (Rebenitsch, 2015) associated with exposure to VR (Davis, Nesbitt, & Nalivaiko, 2014). The most plausible theory for the development of cybersickness is the *sensory mismatch theory* (Bos, Bles, & Groen, 2008; Davis et al., 2014; Ng, Chan, & Lau, 2019). This account is based on the premise that sensory conflict occurs when there is a difference between the sensory (visual and vestibular) information perceived by the patients in the virtual world, and the one expected by patients based on their experience in the real world (LaViola, 2000) resulting in cybersickness. However, this theory does not account for individual differences in occurrence of cybersickness (Weech, Varghese, & Barnett-Cowan, 2018), and fails to explain why sensory conflict does not cause cybersickness in all individuals (Davis et al., 2014; Davis, Nesbitt, & Nalivaiko, 2015). There is some evidence suggesting that cybersickness commonly occurs in individuals with a history of motion sickness and balance disorders (vertigo; Davis et al., 2014). While,

the underlying mechanism for cybersickness is not completely understood, there has been success in identifying other factors that impact the likelihood of users from developing cybersickness (Davis et al., 2014, 2015). For example, software and hardware factors such as use of high-end VR graphics with reduced lag in the display and sensitive motion tracking cameras that synchronously updates the user's VR view on turning their head are known to reduce cybersickness problems (Davis et al., 2014). Also, cybersickness can be prevented by increasing the level of patients' sense of control and increasing the number of breaks during VR exposure, following the manufacturers' safety warnings (Davis et al., 2014; Oculus, n.d.; Porcino, Clua, Trevisan, Vasconcelos, & Valente, 2017). Using brief exposures to VR (rather than continuous long exposures) has been found to be capable of restoring balance, hand-eye coordination, and the ability to multi-task after VR exposure (Oculus, n.d.). However, we were not able to avoid cybersickness completely in our RCT despite excluding patients with no reported history of motion sickness and vertigo, enhancing control by offering patients with a *panic button* (Levy & Radomsky, 2014), and increasing the number of breaks during VRET intervention (Gujjar et al., 2019b). Therefore, future research aimed to identify other causes of cybersickness with the purpose to reduce its occurrence, thereby increasing the potential effectiveness of VRET, is warranted. To summarise, enhanced presence, realism and distress and low cybersickness experienced by patients might have contributed to the effectiveness of VRET in the present thesis.

8.5 Impact of VRET in clinical dental practice

The successful results of VRET as demonstrated in the present thesis, support the notion that incorporating VRET in clinical dental practice is useful. There are several advantages that would make VRET an enticing treatment option for general dental practitioners and patients.

8.5.1 Benefits of VRET for dental health professionals

Firstly, VRET can be specifically tailored to conduct exposure treatments in different simulated environments effectively (Botella, Baños, et al., 2017; Fernández-Álvarez et al., 2020). Secondly, VRET provides a solution for the common perception among therapists that they have very limited control during exposure therapy and that the therapy is distressing to patients resulting in patient drop-outs (Boeldt, McMahon, McFaul, & Greenleaf, 2019). Compared to IVET, VRET is more flexible as the exposure can easily be controlled by the therapist (Lindner et al., 2017; Maples-Keller et al., 2017; Vincelli et al., 2003). Also, VRET allows dentists to precisely control

patient's exposure to their phobic stimuli enabling gradual, repeatable, engaging and individualized exposure in a safe environment. Also with VRET, the therapist is able to provide constant guidance and encouragement to the patient to confront their phobic stimuli, thereby improving the efficacy of treatment (Boeldt et al., 2019). Thirdly, in individuals who are reluctant to confront the real threat upfront (e.g., in IVET; Garcia-Palacios, Botella, Hoffman, & Fabregat, 2007), VRET could be used as a first step in the exposure hierarchy during IVET (Kampmann et al., 2016). Fourthly, upsurge in the development of economical, user friendly and fast computing software and hardware devices may encourage more therapists/general dental practitioners to use VRET in routine practice (Boeldt et al., 2019; Joda, Gallucci, Wismeijer, & Zitzmann, 2019; Riva, Wiederhold, & Gaggioli, 2016; Shiban, 2018). Finally, versatility of the VR technology could enable dental practitioners to use VR more routinely in their practice. For instance, after alleviation of dental phobia following VRET, patients may undergo VR distraction prior to or during actual dental treatment procedures (Atzori et al., 2018; La Paglia et al., 2019; Lahti, Suominen, Freeman, Lähteenoja, & Humphris, 2020; Tanja-Dijkstra et al., 2014; Tanja-Dijkstra et al., 2018) thereby further assisting the patient to keep their dental anxiety at bay. This combination of VRET and VR distraction could offer all in one solution for the treatment of dental phobia and as well adding to patient comfort and relaxation, thus becoming a useful adjunct for general dental practitioners.

8.5.2 Benefits of VRET for patients

From a patient's perspective VRET offers several benefits. Firstly, VRET allows controlled, gradual and repeated exposure to patients' phobic stimuli enabling them to learn to overcome their fears in a safe environment and minimizes distress resulting in better treatment acceptance (Boeldt et al., 2019; Fernández-Álvarez et al., 2020). Secondly, compared to IVET, the sense of security and lack of embarrassment that VRET may offer to the patients helps them to freely express their thoughts and feelings which otherwise could be difficult to express explicitly upon confronting the real-life situations (Baus & Bouchard, 2014; Hartanto et al., 2014). This could reduce chances that a patient with extreme dental fear and avoidance would abandon exposure treatment (Jang, Ku, Shin, Choi, & Kim, 2000). To this end, VRET may improve the relationship between the dentist and patient (Fernández-Álvarez et al., 2020). Finally, VRET could be cost effective because a single exposure scenario can be repeated multiple times as per the needs of the patient (Baus & Bouchard, 2014). Hence, VRET could be an important bridging-step (Pastorino & Doyle-Portillo, 2015) for patients with dental phobia before they undergo treatment in the dentist's office (Gujjar & De Jongh, 2019) and ideal for use by the general dental practitioners and dental auxiliaries.

8.6 Barriers to using VRET in real world

There are some barriers for adopting VR in general dental practice. Firstly, patients experiencing vertigo, motion sickness, epileptic seizures and those with sensory disabilities such as deafness and blindness may not be the ideal candidates for VRET. Secondly, since VRET research is still in its infancy in the field of dentistry, general dental practitioners may be reluctant (Boeldt et al., 2019; Fernández-Álvarez et al., 2020) to use it in their day to day practice until more concrete evidence is generated. This barrier could be addressed by conducting more VRET research that is relevant to dentistry and addressing the concerns of practitioners by providing them with in-depth VRET training (Boeldt et al., 2019). Offering training to therapists and general dental practitioners via accredited continuing education courses may give confidence and encourage them to practice VRET in their routine practice (Boeldt et al., 2019; Fernández-Álvarez et al., 2020). Finally, not all dental patients (and probably not all dentists) are appropriate candidates for the use of VRET and another treatment might be more appropriate for management of dental phobia. In clinical dental practice, dentists with a cognitive behavioral background, such as those specializing in the treatment of dental fear, may need to gauge the suitability of patients to undergo VRET by carefully screening them, assess the patient to select appropriate fear-eliciting stimuli for the treatment, titrate the exposure to patients' feared stimuli and monitor and provide support to the patient undergoing the procedure. In addition, non-specific factors, i.e. those factors associated with the relationship with the dentist or therapist may contribute to what is needed for a successful outcome. In line with this, it could be argued that without paying attention to these issues, for instance, if the VR experience is too overwhelming, the treatment may be ineffective or even potentially harmful. However, despite these seemingly important factors it is interesting to note that there is mounting evidence showing that the effectiveness of standard VRET applications have become an effective alternative comparable to the traditional treatments for phobias (Botella, Fernandez-Alvarez, et al., 2017). Yet, in certain more severe cases, dental professionals need to work collaboratively with mental health professionals in using these technologies or to assess whether individuals with, for instance, a psychiatric background and/or a history of childhood trauma may be too vulnerable to undergo VRET and need expert help. In other words, in such instances specialized forms of psychotherapy (e.g., EMDR therapy; Doering, Ohlmeier, de Jongh, Hofmann, & Bisping, 2013) might be a more appropriate option to reduce patients' burden of phobic fear and comorbid mental health problems.

8.7 Future research on VRET

Research on VR in dentistry so far is predominantly focused on educational teaching and motor skills training (Joda et al., 2019). The present thesis is the first of its kind to explore the successful use of VRET in treatment of dental phobia. Efficacy of VRET as demonstrated in the present thesis holds significant potential in individuals with intellectual disabilities (Rian Dutra da Cunha, 2018). The safe, realistic and controlled exposure (Lindner et al., 2017) may make this therapy specifically suitable for use in individuals with special health care needs who, due to mental and physical disabilities cannot undergo exposure in real life situations (Baus & Bouchard, 2014).

VRET could also be made available widely by making it accessible through the internet in form of online modules, and web and mobile based applications for use by both dentist and patients (as a self-help therapy; Fernández-Álvarez et al., 2020). Use of self-help VRET may be beneficial in remote regions with limited access to psychological treatments and for patients who are reluctant to visit the dentist (Cuijpers & Schuurmans, 2007). Utilization of self-help interventions may possibly allow patients to undergo treatment at their own pace at home with limited or no involvement of therapist (Oing & Prescott, 2018). Also, such automated advances in VR technology might help therapists to manage their caseloads and conserve resources (Boeldt et al., 2019; Marks, Psychiatry, Cavanagh, & Gega, 2007).

VRET may be developed as a serious game (a computer game used for therapeutic purposes), wherein the heirarchical progression system of exposure therapy could be synthesized as a generic game featured with levels, with each level as a gamified exposure task to be completed (Fernández-Álvarez et al., 2020; Lindner et al., 2017). Such gamification could be fascinating, filled with enjoyment, invoking relaxation and more engaging interventions especially for children and for individuals with special health care needs. Also, since confrontation to the phobic stimuli could be highly distressing experience for patients, gamification could possible allay the negative experience of exposure treatment.

An interesting development is the use of gaze or eye trackers in VRET. These may be used in future studies as these tracking devices involve recording the point of gaze by a camera that is integrated into the head mounted device. Eye trackers may not only be a useful diagnostic tool for dentists to assess someone's level of dental anxiety and dental phobia (Fernández-Álvarez et al., 2020), but also allow them to detect any safety behaviours such as closing of eyes by patients while confronting their phobic VR stimuli. Such detections may help the dentist to optimize exposure by encouraging the patient (when the patient looks away or closes eyes) to stop or avoid using his or her safety behavior during VRET (Lindner et al., 2017).

Although patients in all our studies underwent VRET to only five (albeit most commonly encountered) dental scenarios, conducting future VRET studies with

additional VR sounds and scenarios such as dental aspirator sounds, root canal and dental scaling sounds and instruments would make VRET relevant to more individuals. There is evidence showing that verbal interactions with avatars can influence the emotion and might improve the arousal and efficacy of VRET (Slater et al., 2006). To this end, future VRET studies exploring the role of different race and sex of the dentist avatar with or without verbal and facial cues (Qu, Brinkman, Ling, Wiggers, & Heynderickx, 2014) may lead to solutions that could enhance the effectiveness of VRET.

8.8 Conclusion

To summarize this thesis, administration of VRET in patients with dental phobia resulted in a significant reduction in dental anxiety scores and behavioral avoidance compared to informational pamphlets. In addition, a significantly greater proportion of patients in the VRET group, lost their dental phobia diagnoses, scheduled dental appointments and underwent actual dental treatment at six months follow-up. These promising results along with enhanced presence, realism, distress and lowered cybersickness experienced by patients support using VRET in a general dental practice.

This thesis is supportive of the notion that higher initial fear responses and the enhancement of fear extinction through the modulation of behavioral parameters, owing to limitless possibilities with VR technology (Lindner et al., 2017), are likely to improve treatment outcomes of VRET. There are several behavioral parameters that need to be noted (Chapter 3, 4, 5 and 7) and include a.) prolonged, focused and controlled confrontations to phobic stimuli within the virtual reality environment (Lindner et al., 2017; Maples-Keller et al., 2017), b.) deepened extinction by exposure to multiple VR scenarios or cues (Culver, Vervliet, & Craske, 2015; Fernández-Álvarez et al., 2020; Lindner et al., 2017), and c.) discouraging safety behavior by encouraging patients to open their eyes and to focus on their phobic stimuli (Craske et al., 2014; McInerney, 2019). The effectiveness of employing and manipulating these powerful parameters that potentially influence the enhancement of inhibitory learning, need to be tested further using carefully controlled VRET studies. Clearly, more research remains needed to understand mechanisms underlying behavior change in VRET and to make reliable statements and predictions about use of such therapy in children and in individuals with special health care needs with dental phobia. Also, future application of VRET as a self-therapy to treat remote patients with dental phobia needs to be explored. Hence, there is no doubt that the future applications of VR in dentistry relies on continuous progression of the information technology in coming years.

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Chapter 9. Samenvatting en algemene discussie

9.1 Samenvatting

Afhankelijk van land en culturele context heeft zo'n 2-17% van de bevolking last van angst voor de tandheelkundige behandeling, dan wel voldoen zij aan alle kenmerken van een specifieke fobie voor deze situatie. Niet zelden vermijden personen met tandartsangst, of een tandheelkundige fobie, een behandeling door een tandarts, hetgeen kan leiden tot een slechte mondgezondheid. Daarom is tijdige behandeling van deze angst van cruciaal belang om de kwaliteit van leven van deze patiënten te verbeteren.

Cognitieve gedragstherapie, in de vorm van exposure *in vivo,* wordt beschouwd als de gouden standaard wat betreft de behandeling van fobische angst voor de tandheelkundige behandeling. Exposure *in vivo* kent echter ook beperkingen, zoals een beperkte beschikbaarheid van professionele hulpverlening op het terrein van angstbehandelingen voor de tandheelkundige setting, en een relatief hoge uitval- en terugval bij patiënten die zo'n therapie ondergaan. Sinds enkele jaren is *Virtual Reality Exposure Therapy* (VRET) populair voor de behandeling van verschillende typen fobieën. Dit proefschrift bevat een reeks studies die de effectiviteit van VRET voor fobische angst voor de tandheelkundige behandeling hebben onderzocht.

In het kader van het promotietraject werd allereerst een *systematic review* (Hoofdstuk 2) uitgevoerd om de effectiviteit van op technologie gebaseerde interventies, waaronder VRET, voor de behandeling van angst voor de tandheelkundige behandeling vast te stellen. De resultaten van deze review lieten zien dat op technologie gebaseerde interventies effectief zijn, maar ook dat gedegen onderzoek naar VRET-technologie voor de behandeling van fobische angst voor de tandheelkundige behandeling ontbreekt. Deze *review* vormde de basis voor verder onderzoek naar de effectiviteit van VRET ten aanzien van de behandeling van angsten en fobieën op tandheelkundig gebied met een reeks studies, waaronder gevalsbeschrijvingen, een haalbaarheidsstudie en een gerandomiseerde, gecontroleerde effectstudie (RCT).

Na het uitvoeren van de *systematic review* werden twee zogenoemde *case studies* (Hoofdstukken 3 en 4) uitgevoerd waarmee het belang van VRET voor tandheelkundige fobieën werd onderzocht. In het eerste onderzoek (Hoofdstuk 3) ondergingen twee volwassen patiënten met een tandheelkundige fobie een enkele VRET-sessie. In de tweede studie (Hoofdstuk 4) onderging een volwassen patiënt met een ernstige tandheelkundige fobie meerdere VRET-sessies en een kind met een tandheelkundige fobie één enkele VRET-sessie. De resultaten van deze gevalsbeschrijvingen gaven

aan dat VRET tandheelkundige angst en vermijding kan verminderen. Na zes maanden follow-up hadden de patiënten geen tandheelkundige fobie meer en waren ze in staat reguliere tandheelkundige zorg te ondergaan.

Vervolgens werd een haalbaarheidsstudie uitgevoerd (Hoofdstuk 5) om de veiligheid en werkzaamheid van VRET ten aanzien van tandheelkundige fobieën te bepalen. Dit gebeurde met behulp van een gecontroleerd onderzoeksdesign. Tien patiënten met de diagnose tandheelkundige fobie werden willekeurig toegewezen aan VRET, dan wel een controleconditie bestaande uit een brochure met psycho-educatie gericht op angst voor de tandheelkundige behandeling. Alle deelnemers werden nauwlettend gemonitord waarbij de ernst van hun angst elke week, gedurende 14 weken en na zes maanden follow-up, werd geregistreerd. Na de interventie werden er geen bijwerkingen of verergering van symptomen in test- en controlegroepen gevonden. Na zes maanden follow-up bleek er sprake te zijn van een significante afname in angstscores en vermijdingsgedrag in de VRET-groep en significant meer in vergelijking met de controleconditie. Ook had de meerderheid van de VRET-patiënten (vier op de vijf) geen tandheelkundige fobie en ondergingen ze regelmatig een tandheelkundige behandeling.

Toen werd vastgesteld dat het gebruik van VRET voor de behandeling van tandheelkundige fobie haalbaar was, werd een RCT (Hoofdstuk 7) uitgevoerd waarmee de werkzaamheid van VRET werd vergeleken met de eerder genoemde brochure met psycho-educatie over angst voor de tandheelkundige behandeling. Vóór de uitvoering van de RCT werd een gedetailleerd protocol (Hoofdstuk 6) gepubliceerd. Daarin wordt beschreven dat dertig patiënten met de diagnose fobie voor de tandheelkundige behandeling willekeurig werden toegewezen aan VRET dan wel de controlegroep die de brochure had gelezen. De VRET-patiënten vertoonden een significante vermindering van angst en vermijdingstendenties in vergelijking met de controlegroep. Ze ervoeren ook een consistent sterkere aanwezigheid ('*presence*') en een sterker gevoel van realisme tijdens de therapie. Ook voldeden significant meer VRET-patiënten – in vergelijking met de controlegroep – na afloop van hun behandeling niet meer aan de diagnostische criteria van een tandheelkundige fobie (85% *versus* 17%), en ondergingen ze 6 maanden na afloop van hun behandeling significant vaker een reguliere tandheelkundige behandeling (77% *versus* 50%).

Geconcludeerd kan worden dat over het algemeen de bevindingen van alle gepubliceerde onderzoeken in dit proefschrift op convergerende wijze steun bieden aan de notie dat VRET een effectieve behandeling is voor mensen met een fobische angst voor de tandheelkundige behandeling, en dat deze methode in de reguliere tandartspraktijk kan worden gebruikt. Op die manier effenen de resultaten van dit proefschrift de weg naar verder onderzoek naar VRET-toepassingen bij personen met specifieke zorgbehoeften, zoals diegenen die last hebben van een fobische angst

voor de tandheelkundige behandeling, en naar de mogelijkheid van zelfhulp met VRET, bijvoorbeeld in het geval het lastig is een therapeut *face-to-face* te raadplegen.

9.1 Summary

High levels of dental anxiety and dental phobia afflicts 2-17% of the population. Individuals with dental anxiety or a dental phobia often avoid dentistry leading to poor oral health. Therefore, timely management of dental anxiety is central to improving the quality of life of patients with dental anxiety and dental phobia. Cognitive Behavioural Therapy in the form of in vivo exposure therapy (IVET) is considered the gold standard treatment for dental phobia. However, IVET also has some limitations such as limited availability of psychological services to provide this therapy within the dental setting and relatively high drop-out and treatment relapse rates in patients undergoing therapy. Recently, Virtual Reality Exposure Therapy (VRET) has gained popularity for treating several phobias. This thesis includes a series of related studies that evaluate the effectiveness of VRET in treatment of dental phobia.

To this end, a systematic review (Chapter 2) was conducted to determine the effectiveness of technology based interventions in treatment of dental phobia. The results of this review revealed that technology based interventions are effective but that thorough research into VRET technology for the treatment of dental phobia is lacking. This systematic review formed the basis for further research into the effectiveness of VRET in the treatment of fears and phobias related to dental treatment with a series of studies including case reports, a feasibility study and a well-designed randomised controlled trial (RCT).

After the completion of the systematic review, two case studies (Chapter 3 and 4) exploring the role of VRET in treatment of dental phobia were conducted. In the first case study (Chapter 3) both adult patients (24 and 56 years) diagnosed with dental phobia underwent a single VRET session. In the second case study (Chapter 4), an adult patient (40 years) with severe dental phobia underwent multiple VRET sessions and a paediatric patient (10 years) with dental phobia underwent a single VRET session. The results of these case studies indicated that VRET may reduce dental anxiety and behavioural avoidance. At 6 months follow-up, the study participants in both case studies had no dental phobia and underwent regular dental care.

Next, a feasibility study (Chapter 5) was conducted to determine the safety and efficacy of VRET in treatment of dental phobia, using a controlled multiple baseline study design. Ten patients diagnosed with dental phobia were randomly assigned to VRET or a control condition consisting of a brochure with psychoeducation about management of fear towards dental treatment. All participants were closely

monitored with their dental anxiety scores recorded every week for 14 weeks and at 6 months follow-up. Ten patients diagnosed with dental phobia were randomly assigned to either VRET or a control condition consisting of a psychoeducation brochure on management of fear towards dental treatment. All participants were monitored closely registering the severity of their anxiety every week, for 14 weeks and after 6 months of follow-up. Following the intervention there were no adverse events or symptom exacerbation in test and control groups. At 6 months follow-up, there was a significant reduction in the dental anxiety and behavioural avoidance scores in the VRET group compared to the controls. Also, majority of VRET patients (four out of five) had no dental phobia and underwent regular dental treatment.

Upon finding that use of VRET for treatment of dental phobia is feasible, a RCT (Chapter 7) that compared the efficacy of VRET with informational pamphlet control was conducted. A detailed protocol (Chapter 6) was published prior to conduction of RCT. Thirty patients diagnosed with dental phobia were randomly assigned to either VRET or informational pamphlet control group. VRET patients showed a significant reduction in the dental anxiety and behavioural avoidance scores compared to the controls. They also experienced consistently stronger presence and realism during therapy. Also, significantly more VRET patients – compared to the control group – no longer met the diagnostic criteria of a dental phobia (85% *versus* 17%) at the end of their treatment, and were significantly more likely to undergo 6 months post-treatment regular dental treatment (77% *versus* 50%).

Overall the findings from all published studies in this thesis show converging evidence that VRET is an effective treatment for dental phobia and can be used in routine dental practice. In this way, the results of this thesis pave the way for further research into VRET applications in persons with specific care needs, such as those who suffer from a phobic fear of dental treatment, and into the possibility of self-help with VRET, for example in case it is difficult to consult a therapist face-to-face. Given the current COVID-19 pandemic, use of smart VRET technology has become more relevant to continue treatment of patients' dental anxiety and dental phobia remotely.

List of other authors and contributions

List of co-authors

Co-authors who were involved in the publications presented in this thesis:

1. Prof. Dr. Ad de Jongh.
2. Assoc. Prof. Arjen van Wijk.
3. Dr. Ratika Kumar.
4. Prof. Md. Nurul Islam.
5. Prof. Fawzia Abdullah
6. Marc Bernatchez

Authors' contributions

Chapter 2: Are technology-based interventions effective in reducing dental anxiety in children and adults?–A Systematic Review

1. *Authors:* Kumar Raghav Gujjar, Arjen van Wijk, Ratika Kumar, Ad de Jongh
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3. *Study implementation and data collection:* Kumar Raghav Gujjar
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6. *Revision of the manuscript:* Kumar Raghav Gujjar, Ad de Jongh
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Chapter 3: Virtual reality exposure therapy for treatment of dental phobia

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Chapter 4: Is Virtual Reality Exposure Therapy (VRET) the future treatment for anxious dental patients?

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Chapter 5: Virtual reality exposure therapy for the treatment of dental phobia: A controlled feasibility study

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Chapter 6: Efficacy of virtual reality exposure therapy for treatment of dental phobia: a Randomized Control Trial – A study protocol

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Chapter 7: Efficacy of Virtual Reality Exposure Therapy for the Treatment of Dental Phobia in Adults: A Randomized Controlled Trial

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7. *Agreed to the final version of the manuscript:* Kumar Raghav Gujjar, Arjen van Wijk, Ratika Kumar, Ad de Jongh

List of publications

1 Gujjar, K. R., & De Jongh, A. (2020). Response to Use of Virtual Reality for the Management of Anxiety and Pain in Dental Treatments: Systematic Review and Meta-Analysis [Letter to the editor]. *Journal of Clinical Medicine* (*under review*). Appendix A.

2 Gujjar, K. R., & De Jongh, A. (2019). Is Virtual Reality Exposure Therapy the Future Treatment for Anxious Dental Patients? *California Dental Association Journal*, 47(8), 7. (Invited article).

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4 Gujjar, K. R., Van Wijk, A., Kumar, R., & De Jongh, A. (2019). Are Technology-Based Interventions Effective in Reducing Dental Anxiety in Children and Adults? A Systematic Review. *Journal of Evidence Based Dental Practice*, 19(2), 140-155. doi:https://doi.org/10.1016/j.jebdp.2019.01.009

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7 Raghav, K., Van Wijk, A. J., Abdullah, F., Islam, M. N., Bernatchez, M., & De Jongh, A. (2016). Efficacy of virtual reality exposure therapy for treatment of dental phobia: a randomized control trial. *BMC oral health*, 16(1), 25. doi:10.1186/s12903-016-0186-z

List of awards, conference presentations and science communication

List of awards during PhD

1. *International Association of Dental Research Giddon award 2020* for outstanding research in Behavioural Dentistry.
2. *International Association of Dental Research-ANZ Colgate Travel award* to participate at the IADR-ANZ Colgate Poster Competition 2019.
3. *Australian Government Endeavour Executive Fellowship Award in Dentistry 2018*. This is a competitive, merit-based fellowship which provides opportunities for overseas citizens and Australians to undertake study, research or professional development in Australia and overseas.

List of conference presentations during PhD

1. **Gujjar, K.R.**, Sharma, R., De Jongh, A. (2019). Is heart rate a good measure to determine the quality of Virtual Reality Experience in patients with dental phobia? Poster presentation at the IADR-ANZ 2019 conference (October 2019), Brisbane, Australia.
2. **Gujjar, K.R.**, van Wijk, A., Kumar, R., & De Jongh, A. (2019). Efficacy of virtual reality exposure therapy for the treatment of dental phobia in adults: A randomized controlled trial. Paper presented at IADR-ANZ 2018 conference (September 2018), Perth, Australia.
3. **Gujjar, K.R.**, De Jongh, A., Abdullah, F., Islam, M.N., Bernatchez, M. (2015). Use of Innovative VRET in Management of Dental Anxiety. Proceeding of FDI Bangkok conference, 65 (Suppl.2), pp.123. https://onlinelibrary.wiley.com/doi/abs/10.1111/idj.12195
4. **Gujjar, K.R.,** De Jongh, A., Abdullah, F., Islam, M.N., Bernatchez, M. 2014. Use of virtual reality technology to treat dental anxiety. Poster presented at IADR-SEADDE 2014 (August 2014) at Kuching, Sarawak, Malaysia.

List of invited talks during PhD

1. **Gujjar (2020)** Invited Speaker *"Role of Virtual Reality Exposure Therapy in Dental Anxiety reduction among patients"* at the international online webinar on 14th September 2020 conducted by SDM University, India.
2. **Gujjar (2020)** Invited Speaker *"Contemporary management strategies of the anxious pedodontic patient"* presented at Tutor Calibration Day on 1st of February 2020 at School of Dentistry, Charles Sturt University, Orange, NSW, Australia
3. **Gujjar (2019)** Invited Speaker *"Research experience of Virtual Reality Exposure Therapy on anxious dental patients"* presented at XRC (Extended Reality) Seminar on 24th October 2019.
4. **Gujjar (2019)** Invited Keynote Speaker "*Virtual Reality Exposure Therapy for Treatment of Dental Phobia*" presented at ADHOTA 2019 Conference on 18th October 2019, Sydney, Australia. http://www.adohtaconferences.com/nsw-act/speakers
5. **Gujjar (2019)** Invited speaker for poster presentation on "*Virtual Reality Exposure Therapy for treatment of dental phobia"* at Dental Health Services Victoria, Public Oral Health Innovations Conference '19 on 5th April 2019, Melbourne, Australia.
6. **Gujjar (2018)** invited speaker *"Virtual Reality approaches to reduce patient anxiety in the dental clinical setting"* on 5th October 2018 at Research Sandpit UQ School of Dentistry, Brisbane, Australia.

List of science communications during PhD

1. Invited Radio talk on 25th March 2020 by 2 BS radio Australia. Topic: Virtual Reality Exposure Therapy to treat dental phobia.
2. Magazine articles
   - ADA NSW wrote an exclusive article on *"Using Virtual Reality to Reduce Patient Fear"* in the ADA NSW Dentist April 2020 magazine (page 24). (https://indd.adobe.com/view/ca3eea13-1f14-4862-a004-ec2a7049e97f).
   - Bite magazine (Magazine for Australian dental professionals) interviewed me on my research journey of using Virtual Reality to treat dental phobia. The article was published in June 2020 which featured me on the cover page. The article can be accessed by clicking the web link below. https://issuu.com/engagemedia/docs/bite_june_2020.

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About the author

Kumar Raghav is a general dentist and a lecturer in Clinical Dentistry at the School of Dentistry and Health Sciences, Charles Sturt University, Australia. He was born in Dharwad, India and did his schooling from Shaktinagar, a rural Indian town that had limited access to dental care. Kumar's passion of working with anxious dental patients stems from his own childhood traumatic dental experiences that resulted in him developing dental anxiety. He obtained his Bachelor's in Dentistry (B.D.S) in 2002 and Master's in Paediatric Dentistry (Children's Dentistry) in 2006 from India and started working with anxious dental patients, especially children who were afraid of dentists. Kumar has worked as an academic and clinician across India, Libya, Malaysia and Australia. His interest in treating children and adults with dental phobia led him to pursue a PhD focusing on dental phobia from ACTA School of Dentistry, University of Amsterdam. His PhD investigates whether Virtual Reality Exposure Therapy could be used for treatment of dental phobia in adults. The PhD study is a self-funded project and is steered under the supervision of promotor prof. dr. A. de Jongh and co-promoter dr. A. J. van Wijk.

Appendix-A. Response to "Use of Virtual Reality for the Management of Anxiety and Pain in Dental Treatments: Systematic Review and Meta-Analysis"[17]

Kumar Raghav Gujjar, Ad de Jongh

Letter to the editor

With interest we read the systematic review and meta-analysis written by López-Valverde and colleagues (Lopez-Valverde et al., 2020). The authors gathered the existing evidence of Virtual Reality (VR) on the reduction of pain and dental anxiety during dental treatments. The authors included studies until November 2019 that compared virtual reality distractions systems with standard care situations in children and adults with dental anxiety. Based on the results of their study, the authors concluded that VR is an effective tool to reduce pain and anxiety during dental treatment.

Although this article is meant to inform dental professionals about the relative effectiveness of VR, an emerging technology-based intervention for treatment of dental anxiety (Gujjar, van Wijk, Kumar, & de Jongh, 2019), regrettably, the conclusions drawn by López-Valverde et al (Lopez-Valverde et al., 2020) are based on noteworthy methodological errors and wrong interpretations from the included articles in their study. In view of the impact this meta-analysis may have in the development of treatment guidelines and policies, we believe that it is our moral responsibility to express our thoughts about this article to the authors, the editors and the readers of this journal. To this end, we would like to highlight the following, in our opinion, problematic points.

Firstly, the authors assessed the quality of the included studies by using the modified Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines (von Elm et al., 2008) for observational studies, rather than the standard Consolidated Standards of Reporting Trials (CONSORT) guidelines(Moher et al., 2010) which are specifically meant for assessing the quality of *randomised controlled trials*. Secondly, despite the purpose of the research question was to

17 Gujjar, K. R., & De Jongh, A. (2020). Response to Use of Virtual Reality for the Management of Anxiety and Pain in Dental Treatments: Systematic Review and Meta-Analysis [Letter to the editor]. *Journal of Clinical Medicine* (*under review*).

determine the dental anxiety reduction with VR *distraction* during dental treatment it seems that the authors were not aware of the fact that Virtual Reality *exposure* therapy (VRET) is a fully different treatment with a different indication (long term rather than a short term alleviation of the fear response) with an entirely different mechanism of action (Gujjar et al., 2019). Consequently, the authors wrongly included two articles that explored the efficacy of VRET for the treatment of dental phobia (Gujjar et al., 2019; Raghav et al., 2016) rather than of VR distraction, the purpose of their study. Thirdly, a remarkable mistake was that one of the included study on VRET, was a study *protocol* (Raghav et al., 2016) and not an RCT. Fourthly, in stark contrast to authors' inclusion criteria (i.e. RCT participants undergoing VR distraction during dental treatment), the study participants in Gujjar et al's (2019) study did not undergo actual dental treatment during VRET (Gujjar et al., 2019). Fifthly, the authors boldly stated that none of the included studies blinded the outcome assessor. However, in the study conducted by Gujjar et al, the outcome assessor (statistician) was blinded (Gujjar et al., 2019). Lastly, a wide array of other flaws need to be mentioned. For example, in Table 3, the authors have swapped the MDAS scores of the test and control for Gujjar et al's study (Gujjar et al., 2019). In Figure 7, the authors wrongly interpreted the study results of Gujjar et al.'s study that used a visual analogue scale to determine the level of participants' state anxiety rather than the severity of pain (Gujjar et al., 2019). Finally, in Table 4, the authors exchanged the visual analogue scale scores of the experimental and the control group for the study of Gujjar et al. (2019).

In summary, the conclusions drawn by authors casts serious doubts as these are based on range of inconsistencies in the methods and results of their systematic review. Given these methodological problems and inconsistencies we request the editors to take their responsibility and have authors review their methods and results to prevent further dissemination of incorrect information in the scientific community.

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