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CHAPTER 1

General introduction

The overarching topic of this thesis is dental anxiety and its severe form, dental phobia. These phenotypes, and the emotions attached with these, can complicate dental treatment, not only for the patient, but also for the oral health professional. For most people it is obvious that dentally anxious and dentally phobic patients undergo treatment with feelings of inconvenience and discomfort, if treatment is not avoided at all. To treat these patients so called “special dental care clinics” were founded (Aartman et al., 1997). In such clinics not only patients with high levels of dental anxiety or dental phobia are treated, but also patients with, for example, severe gagging problems and fainting problems.

In the present dissertation, the focus is on these three patient categories (i.e., those with severe levels of dental anxiety or dental phobia, those who severely gag during dental treatment, and those with fainting problems related to dental treatment), who visit special dental care clinics. The general purpose of this dissertation is to increase the knowledge about dental anxiety, dental phobia, gagging and fainting during dental treatment. The main aim is to find an answer to the question as to whether or not these conditions are inter-related, or should be considered as separate entities. In the remainder of this chapter a description of relevant background topics is given, and an outline of the studies that are part of the dissertation. Firstly, the relevant background regarding dental anxiety and dental phobia is presented. This is followed by a summary of the literature pertaining to the alleged etiology of anxiety and anxiety disorders, including dental anxiety and dental phobia. Next, a background is provided regarding fainting and gagging related to dental treatment. Finally, a short overview is presented of heritability studies about fear and phobias, including the scarcely available literature concerning the heritability of dental fear. For all the topics mentioned above, the gaps in the literature were assessed, which have served as the basis for the studies in this thesis.

Dental fear, dental anxiety and dental phobia

Fear is a normal response to a genuine danger (American Psychiatric Association, 2013) and that is why dental fear is considered to be a normal emotional reaction to a perceived threat in the dental setting (Klingberg & Broberg, 2007). Dental anxiety is defined as a more general state of anticipatory concern related to dental treatment. Dental phobia is a severe (pathological) form of dental fear and dental anxiety, and is defined as a disproportional fear of (invasive) dental procedures (American Psychiatric Association, 2000). According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; APA 2013, pp 298) dental phobia is classified as a specific phobia, an anxiety disorder that is characterized by: a) a marked and disproportional fear within an environmental or situational context to the presence or anticipation of a specific object or situation; b) exposure to the phobic

stimulus provokes an immediate anxiety response, which may take the form of a situationally bound panic attack; c) the person recognizes that the fear is out of proportion; d) the phobic situation(s) is avoided or else is endured with intense anxiety or distress; e) the avoidance, anxious anticipation or distress in the feared situation(s) interferes significantly with the person's normal routine, occupational (or academic) functioning, or social activities or relationships, or there is marked distress about having the phobia. Furthermore, the symptoms for all ages must have a duration of at least 6 months.

Prevalence of dental anxiety and dental phobia

It is assumed that dental fear, dental anxiety and dental phobia may develop from childhood (Locker, et al., 1999; Öst, 1987) to adulthood (Oosterink et al., 2009; Locker et al., 1999). A review article analyzing the literature on dental anxiety of the past 50 years found no clear answer to the question as to whether the prevalence of dental anxiety has increased or decreased over the last decades (Smith & Heaton, 2003). Yet, it has been found that about 25%-40% of the adult population in Western societies, including The Netherlands, report moderate dental anxiety (Halonon et al., 2014; Singer et al., 2012; Oosterink et al., 2009) and 5%-18% of the population, suffers from high levels of dental anxiety, depending on the sampling methods, specific measures and cut-off points used (Hill et al., 2013; Humphris & King, 2011; Armfield, 2010; Nicolas et al.; 2007; Schuller et al., 2003; Locker, 2003; Hakeberg et al., 1992), whereas 2%-4% suffers from dental phobia (Oosterink et al., 2009; Stinson et al., 2007; Fredrikson et al., 1996).

Association of dental anxiety with socio-economic background variables

On average, women report higher levels of dental fear and anxiety than men (e.g., Humphris & King, 2011; Oosterink et al., 2009; Schuller et al., 2003; Stouthard & Hoogstraten, 1990), but women do not fulfill the screening criteria for dental phobia more frequently than men (Oosterink et al., 2009; Fredrikson et al., 1996). With respect to level of education, contradictory findings are reported in several studies. Some studies indicated that individuals with a low level of education are more likely to report a high level of dental anxiety compared to those with a higher level of education (e.g., Erten et al., 2006), but other studies failed to find such an association (Vassend, 1993; Stouthard & Hoogstraten, 1990). Furthermore, a high level of dental anxiety and dental phobia has been found to be associated with irregular dental care or avoidance of dental care (Hill et al., 2013; Armfield, 2013; Armfield et al., 2007), a deteriorating oral health (Schuller et al., 2003; Stouthard & Hoogstraten,

1990), a lower health related and generic quality of life (Vermaire et al., *in press*; Vermaire et al., 2008; Mehrstedt et al., 2007) and a negative impact on social life (Cohen et al., 2000). Thus, it is clear that high levels of anxiety or dental phobia can negatively affect peoples' wellbeing.

The etiology and maintenance of anxiety in general, dental anxiety and dental phobia

Most people are familiar with the fact that distressing events tend to be well remembered and leave behind lasting and vivid memories (e.g., McIntyre & Roozendaal, 2007; McGaugh, 2004). Enhanced memory for disturbing events can be extremely functional, because this mechanism helps us to remember threatening situations (McGaugh, 2004) and gives us guidance for future actions. However, distressing experiences may also lead to highly aversive memories, which may contribute to the development and maintenance of anxiety and related conditions (Kindt & Soeter, 2011; De Quervain et al., 2009; Pratt et al., 2004). Reactivation and retrieval of these disturbing memories can lead to a physical fear response (Cuthbert et al., 2003), such as an increased heart rate (Leutgeb et al., 2011).

Also for the development of dental anxiety and dental phobia the negative affect associated with the experience of a disturbing (dental) event appears to be an important conditioning factor which could lead to the formation of aversive memories (Humphris & King, 2011; Oosterink et al., 2009; Locker et al., 1999; Moore et al., 1991). A limitation of previous studies regarding aversive memories and dental anxiety is that the self-reported content and characteristics (disturbance, emotionality and vividness) of these memories were not examined or at least not reported. Empirical studies in other domains of anxiety disorders found that not just the content, but also the emotional characteristics of those memories are associated with symptom severity (e.g., Arntz et al., 2005; Berntsen et al., 2003). Another limitation is that we do not yet know whether, and in what way, the memories of these past disturbing events play a role in the maintenance of dental trait anxiety, and whether the characteristics of these memories are associated with current anxiety levels. Lastly, it has not investigated as yet whether individuals who are highly anxious about the dental situation, when confronted with their fear eliciting stimuli (for instance, an invasive dental treatment), store more disturbing memories of this event compared to low anxious individuals, which would not only explain the severity of individuals' fear response, but also the difficulties dentists sometimes face when trying to treat them. Although these results have been found in laboratory studies, translational research in a relevant clinical setting is lacking and greatly needed.

The heterogeneous nature of dental fear

Dental fear may not be considered as a homogeneous phenomenon, but as a collective term for fear of one or more objects and situations present in the dental setting (e.g., Oosterink et al., 2008; De Jongh et al., 1998). Oosterink identified 67 objects or situations within the dental setting that were potentially fear provoking (Oosterink et al., 2008). The question is whether this broad collection of objects or situations can be subdivided in distinct typologies that may relate to different treatment strategies. Oosterink and colleagues performed an exploratory factor analysis on the set of 67 stimuli using a sample of a 1,000 individuals. They identified a two-factor solution, with a first factor being an 'invasive treatment-related stimuli factor', and a second being a 'non-invasive-treatment related factor'. However, close inspection of the results suggests that the two factors were very general in nature, with only a modest proportion of explained variance (51.4%). In addition, a number of items showed low factor loadings and/or low communalities. This suggests that a more complex factor structure may be underlying the various situations and objects that make the dental setting fear provoking for many individuals. Building on the work of Oosterink et al. (2008), Wong and colleagues (Wong et al., 2015) conducted both an exploratory (EFA) and a confirmatory factor analyses (CFA) on 73 items, thereby covering the same 67 potentially fear-eliciting stimuli as well as six additional items. Their EFA revealed a seven-factor solution (dental check-up, perceived lack of control, clinic environment, injection, scale and drill, surgery and empathy) that explained 71.3% of the total variance. However, in this study the sample was relatively heterogeneous and the number of individuals included in the EFA and the CFA was low relative to the number of items, which potentially reduces the generalizability of the results. Therefore, replicating the analysis using a larger and heterogeneous sample is likely to provide better insight in the distinct typologies underlying the construct of dental fear. This may be important for research, for the proper assessment of varying subtypes of fears, and for the development of appropriate treatment strategies (De Jongh et al., 2011).

Fainting or dizziness during dental treatment

In the DSM-5 dental phobia is classified as a specific phobia of the Blood-Injection-Injury (B-I-I) subtype (APA, 2013), a phobia subtype that is characterized by a negative response to blood, needles, injuries and invasive medical procedures (APA, 2013). According to the DSM-IV-TR (APA, 2000) the unique characteristic of B-I-I phobia is that a part of the individuals suffering from this condition display a strong vasovagal response following exposure to a phobic stimulus, which induces feelings of dizziness and an increased likelihood of vasovagal fainting (Page, 1994; Öst et al., 1984). This response is opposite to the normal cardiac re-

sponse observed in individuals with any other specific phobia, who show only an increase in heart rate, without the subsequent feelings of dizziness or fainting (e.g., Elsesser et al., 2006). Despite the fact that certain types of dental treatment can be considered as an invasive medical treatment (for instance extractions or placing dental implants), based upon clinical experience it is doubtful whether many dental phobics suffer from such a typical vasovagal fainting response (e.g., Leutgeb et al., 2011) as was suggested by the current classification of dental phobia within DSM-IV-TR (i.e., “Specific Phobias of the Blood-Injection-Injury Type, may have detrimental effects on dental and physical health, because the individual may avoid obtaining necessary medical care”, page 446, APA, 2000). In other words, we found it of importance to investigate whether the current classification of dental phobia, as part of the B-I-I cluster, could be justified.

Gagging during dental treatment

Gagging during dental treatment has often been found to severely interfere with dental treatment and may, therefore, be considered a barrier to successfully complete dental treatment. Using a MEDLINE-PubMed search with the themes: “gag reflex dentistry”, “gag reflex dental”, “gagging dentistry” or “gagging dental” we found that since 1953 only about 200 articles were published about gagging and dentistry. This shows that gagging during dental treatment is still a relatively unexplored area of dental research. A significant part of these studies appeared to include case reports (e.g., Packer et al., 2005), articles about patient management (e.g., Sari & Sari, 2010), and small case-control studies examining differences between gaggers on non-gaggers (e.g., Akarşlan & Erten, 2010). However, basic information such as the prevalence rate of dental-treatment related gagging, and its possible socio-demographic correlates (i.e., gender, age, country of birth and level of education) of gagging in the general population proved to be greatly lacking. Also the question whether gagging during dental treatment would be associated with higher levels of dental anxiety and greater avoidance of dental care has not yet been resolved. To this end, until now only one study properly investigated dental attendance patterns in individuals with and without gagging problems showing no differences in visit frequency between gaggers and non-gaggers (Akarşlan & Yildirim Biçer, 2013). Some studies showed that individuals who suffer from an excessive gag reflex experience the dental treatment as more fearful than those without severe gagging problems (Akarşlan & Yildirim Biçer, 2013; Uziel et al., 2012; Winocur et al., 2011; Akarşlan & Erten, 2010), although other studies failed to find such a difference (Van Linden van den Heuvel et al., 2008). Yet, it is also still unknown whether the increased levels of dental anxiety reported by those who suffer from gagging could best be explained by fear of certain stimuli specifically related to gagging (e.g., intraoral stimuli; Bassi et al., 2004),

typical dental objects and situations (e.g., pain, injections or the sound of the drill; Oosterink et al., 2009), or to an underlying general vulnerability factor.

Heritability of anxiety and phobia

Besides exposure to a distressing situation, there are two other pathways through which dental fears and dental anxiety (Oosterink et al., 2009) can be acquired (i.e., vicarious exposure and transmission of information and instruction; Rachman, 1977). But, these three pathways of fear alone do not always (e.g., King et al., 1998) or completely (e.g., Oosterink et al., 2008) explain why dental fears and phobias develop. Several authors claim that, in addition to Rachman's theory of fear acquisition (Rachman, 1977), a fourth pathway exists, namely a non-associative path (Poulton & Menzies, 2002). According to the non-associative theory of fear acquisition (Poulton & Menzies, 2002) some fears and specific phobias would be the result of innate fears shared by all humans. Besides, several authors state that some adults develop specific phobias because they either have an enhanced genetic liability to fear specific situations or have a deficit in the (probably genetically given) mechanisms to dispose themselves of fear responses (e.g., habituation or desensitization; Poulton & Menzies, 2002; Mineka & Öhman, 2002). Moreover, it has been suggested that for a number of specific phobias familial factors, which are partly genetic, influence the risk of developing specific phobias (Kendler et al., 1999).

Studies that tried to quantify the variance in a population due to genetic, shared environmental (i.e., family), and unique environmental (i.e., individual specific) influences for a certain trait or disorder are twin studies. These studies are a valuable source of information about the genetic basis of complex traits (Boomsma et al., 2002) by providing heritability estimates for a specific phenotype. In general, anxiety disorders have been found to be moderately heritable (Hettema et al., 2001). A meta-analysis of data from family and twin studies of several psychiatric disorders, including phobias, explored the role of genetic and environmental factors in the etiology of these conditions (Hettema et al., 2001). Strong support was found for a familial risk (i.e., a familial component to fears and phobias) for phobic disorders. In addition, phobias were found to be moderately heritable with an estimated heritability in the range from 20%-40%, depending on the type of phobia (Hettema et al., 2001). However, in this study the specific phobias were grouped together with the other main categories of phobias (e.g., agoraphobia), making it difficult to estimate the explained variance by genetic factors for a subtype of specific phobia *per se* (Hettema et al., 2001). Until now, only one study provides information about the estimated heritability of dental anxiety in an adult population (Vassend et al., 2011). The results showed that dental anxiety is moderately heritable. Since this study was conducted among a relatively small sample

of adult twins, replicating this study in a large sample of adult twins may give us additional information about the genetic liability to develop dental anxiety.

Conclusion and outline of this thesis

The literature presented above shows that the mechanisms underlying the etiology of dental anxiety and dental phobia are not completely understood. In addition, a limited amount of literature (showing contradictory results or gaps in knowledge) is available that pertains to dental treatment related fainting and gagging. Therefore, the purpose of this thesis is to increase the currently available knowledge about dental anxiety and dental phobia, as well as dental treatment related fainting and gagging. In order to achieve more insight in the aforementioned topics six studies are presented covering these topics. Yet, two important notes should be made here regarding the content of my dissertation. The first note concerns the original goal of my Ph.D. track. At the start, one of the main goals was to examine whether a deletion variant of one candidate gene, i.e., the ADRA2B-gene encoding the alpha-2B adrenergic receptor in de amygdala (e.g., De Quervain et al., 2007), would be more prevalent among individuals with high levels of dental anxiety than among those with average levels of dental anxiety. The main reason for this was the publication of a study, showing that individuals with the deletion variant compared to individuals without this deletion variant not only had a substantial enhancement of emotional memory for positive and negative pictures, but also increased re-experiencing symptoms of posttraumatic stress disorder (De Quervain et al., 2007). Our research group was interested in solving the question as to whether individuals with high anxiety levels would show enhanced emotional memory for events underlying their dental anxiety, and also whether they would be more likely to possess the deletion variant of the ADRA2B-gene than their low anxious counterparts. However, the inclusion of a sufficient large number of individuals with high levels of dental anxiety or dental phobia to conduct proper DNA-analyses during the period of my Ph.D. program turned out to be too time consuming because of the large drop out of participants. Consequently, my thesis does not contain data about the relation between ADRA2B-gene and the presence of enhanced emotional memory for experiences that are supposed to underlie their dental anxiety. Just before finishing my thesis, a large part of the collected DNA-samples collected over a period of 6 years could finally be analyzed. Unfortunately, the majority of the samples that were analyzed appeared to not contain enough DNA to perform further DNA-analysis.

The other important note relates to the fact that during my Ph.D. program we were given the ability to start a collaboration with the Netherlands Twin Register (Boomsma et al., 2006). Our aim was to collect data regarding dental anxiety, dental phobia, fainting and

gagging during dental treatment in order to get insight in the heritability estimates of these traits. However, again collection of sufficient data to conduct proper twin analyses appeared to be very time consuming and complicated. Therefore, it was not feasible to include any data about heritability estimates of dental anxiety, dental treatment related fainting and gagging in my PhD thesis.

The six studies included in my thesis are presented in the following order:

In *Chapter 2* an overview is provided of studies conducted in the field of heritability which were aimed to (1) gain insight into the background of heritability studies of specific phobias and corresponding fears; (2) develop a better understanding of the genetic liability to develop fears and phobias; and (3) to provide clues for future research regarding the heritability of specific phobias and corresponding fears.

In *Chapter 3* the results are described of an exploratory and a confirmatory factor analysis that were carried out among a large population-based sample. These were aimed to explore 1) the conceptual structure of dental fear and 2) to develop a descriptive framework for the classification of dental fear.

The results of a study that aimed to get more insight in the development and maintenance of dental trait anxiety are presented in *Chapter 4*. In that study the presence, content and characteristics of memories of events that initiated or exacerbated dental anxiety were assessed, as well as the relationships between current levels of dental trait anxiety and some key features of these memories. The study used a semi-structured interview and included dental phobics, subthreshold dental phobics, and normal controls.

Whereas *Chapter 4* focusses on the etiology and maintenance of dental trait anxiety, *Chapter 5* focusses on dental state anxiety during dental treatment and the formation of memories of dental treatment. For the purpose of this study, a subsample of individuals investigated for the study presented in *Chapter 4* with either high or low levels of dental trait anxiety were exposed to an invasive dental treatment. Immediately after this treatment, and at two-week follow-up, the memory characteristics of both groups were assessed and compared. The possible association between dental state anxiety and characteristics of the memory was assessed and explained in the light of laboratory studies on memory formation and memory retrieval.

The aim of the study presented in *Chapter 6* was to determine the co-occurrence of dental phobia, typical dental (and B-I-I related) fears, vasovagal fainting, and avoidance of dental care in a large sample of individuals. Also the conceptual validity of dental phobia as part of the Blood-Injection-Injury (B-I-I) phobia subtype within DSM-IV-TR is discussed.

Research about dental-treatment related gagging describes large gaps in the existing knowledge on this phenomenon. Therefore, the purpose of the study presented in *Chapter 7* was to supplement the existing information about gagging during dental treatment. The

aims of the study were to derive a prevalence estimate of gagging during dental treatment in a large sample, to investigate some socio-demographic and psychological correlates of gagging, and the relationship between gagging and self-reported oral health and avoidance of dental care.

In *Chapter 8* a general discussion and summary are presented as well as practical and theoretical implications and suggestions for future studies.

This thesis is based upon four publications in peer reviewed journals and two research articles that are submitted for publication. The information in some of the publications or submissions shows overlap or is redundant. Therefore, all abstracts were removed and the text was uniformed as much as possible.

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