Anxiety disorders in children with autism spectrum disorders: A clinical and health care economic perspective
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INTRODUCTION

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A Clinical and Health Care Economic Perspective
Anxiety disorders

Anxiety is a normal and healthy response to danger or a threatening situation. When anxiety becomes excessive, persistent, and it impairs one’s functioning, one is classified as having an anxiety disorder (American Psychiatric Association [APA], 2000). Anxiety disorders are common, affecting 2% - 27% of the children at a given time during childhood or adolescence (Costello, Egger, & Angold, 2005). The Diagnostic and Statistical Manual of Mental Disorders 4th Edition – Text Revision (DSM-IV-TR; APA, 2000) distinguishes the following anxiety disorders; separation anxiety disorder, social anxiety disorder, specific phobia, generalized anxiety disorder, obsessive-compulsive disorder, panic disorder with and without agoraphobia, agoraphobia without a history of panic disorder, post-traumatic stress disorder, acute stress disorder, anxiety disorder due to a medical condition, substance-induced anxiety disorder, and anxiety disorder not otherwise specified. Note that for the new version of the DSM (DSM-5), several changes are proposed including the assignment of current DSM-IV-TR anxiety disorders to other categories (e.g., placing obsessive-compulsive disorder in the category of ‘obsessive-compulsive and related disorders’, and placing post-traumatic and acute stress disorder in the category of ‘trauma- and stressor related disorders’) (APA, 2012).

Anxiety disorders are found to be associated with a poorer quality of life (e.g., Bastiaansen, Koot, Ferdinand, & Verhulst, 2004), higher societal costs (e.g., Bodden, Dirksen, & Bögels, 2008), a lower self-competence (e.g., Chansky & Kendall, 1997; Messer & Beidel, 1994), and may negatively affect family functioning (see the reviews of Bögels & Brechman-Toussaint, 2006, and Majdandžić, De Vente, Feinberg, Aktar, & Bögels, 2012). Moreover, having an anxiety disorder in childhood or adolescence may have consequences for later problems in (young) adulthood. For example, the study conducted by Woodward and Fergusson (2001) reported that young adults who suffered from an anxiety disorder in adolescence, as compared to their peers who did not have an anxiety disorder, were at increased risk to endorse later problems. That is, they were 3.5 times more likely to have an anxiety disorder, they were twice as likely to suffer from depression, they were almost four times more likely to have illicit drug dependence, and were 2.5 times less likely to attend university.

Cognitive-behavioral therapy (CBT) is a well-studied intervention and is found effective in the treatment of anxiety disorders in children (e.g., Barret, Duffy, Dadds, & Rappee, 2001;
Bodden et al., 2008; Kendall, Brady, & Verduin, 2001). CBT consists of six essential components, namely psycho-education (e.g., providing information about anxiety and anxiety disorders), somatic management (e.g., relaxation skills training, attention tasks), cognitive restructuring (e.g., identifying maladaptive thoughts, challenging and modifying them), problem solving (e.g., how to deal/cope with anxiety), exposure (e.g., systematic, behavioral exposure to feared situations), and relapse prevention (e.g., increase generalization of learned skills) (Velting, Setzer, & Albano, 2004). Systematic reviews of the literature report that 64% - 72% of the children are free from their primary anxiety disorder after having followed CBT (Cartwright-Hatton, Roberts, Chitsabesan, Fothergill, & Harrington, 2004; In-Albon & Schneider, 2007). In addition, a meta-analytic review found that CBT for children with anxiety disorders is more effective compared to waitlist (Cohen’s $d = 0.68$), and probably also more effective compared to other treatments (defined as any treatment other than CBT; Cohen’s $d = 0.27$) (Ishikawa, Okajima, Matsuoka, & Sakano, 2007).

**Autism spectrum disorders**

Children with autism spectrum disorders (ASD) are characterized by varying degrees of impairments in three domains; (1) social interaction, (2) communication, and (3) restrictive, repetitive, and stereotyped patterns of behaviors, interests, and activities (APA, 2000). Over the last decades the definition of ASD has broadened and prevalence rates of ASD have risen from early estimates of 10 per 10,000 till 110 per 10,000 (Matson & Kozlowski, 2011). The DSM-IV-TR distinguishes several ASD subtypes of which autistic disorder, Asperger’s syndrome and pervasive developmental disorder – not otherwise specified (PDD-NOS) are the most common. Children with autistic disorder are required to have significant impairments in the social, communicative and repetitive domain, while children with Asperger’s syndrome display impairments in the social and repetitive domain, and have no significant delay with respect to their language and cognitive development. Children with PDD-NOS are characterized by (at least) impairments in the social domain and do not meet full criteria for the other ASD subtypes (APA, 2000). Of note, for the DSM-5 it is proposed to no longer make the distinction between ASD subtypes, to aggregate the symptoms of the social and communicative domain, and to require that individuals with ASD meet criteria for the social-communicative domain as well as the criteria for the repetitive domain (APA, 2012), see also Chapter 9 for more information.
Although the prevalence rate of ASD may not be as high as the prevalence rate of other disorders (such as anxiety disorders or mood disorders), from a societal point of view the costs and health care service consumption associated with ASD are of major impact (e.g., Mandell, Cao, Ittenbach, & Pinto-Martín, 2006, found that children with ASD had expenditures ten times higher compared to other children; also see the introduction of Chapter 4 for more information). Children with ASD often suffer from comorbid disorders such as anxiety disorders, depressive disorder, attention deficit hyperactivity disorder (ADHD) and behavior problems (e.g., De Bruin, Ferdinand, Meester, De Nijs, & Verheij, 2007; Simonoff et al., 2008). However, if – and how – these comorbid problems interact with the core ASD characteristics, and if – and to what extent – they interfere with the child’s daily functioning, is not yet known. The study of De Bruin and colleagues (2007) found some support for ASD severity to be associated with comorbid psychiatric disorders as parents rated children with ASD and comorbid disorders (as compared to children with ASD without comorbidity) to be more severely disturbed in domains of social contact and communication. However, the direction of this association was not examined: Are children with more severe ASD more likely to develop comorbid disorders or do comorbid disorders increase ASD severity?

**ASD and comorbid anxiety**

Despite the fact that Kanner (1943) already described the co-occurrence of rather specific fears (phobias) in children with autism, and noted that many of the core features of autism – particularly the insistence on sameness and the repertoire of routines – are anxiety driven, it was not until the last decade that research has begun to examine anxiety (disorders) in children with ASD in more detail. There are several reasons why anxiety (disorders) may be an important concomitant problem in children with ASD, and why anxiety may be more prevalent in ASD compared to other clinical groups. First, anxiety may – in part – be inherent to ASD; i.e., ‘anxiety and compulsions’ are found to be part of the broader autism phenotype (Kamp-Becker, Ghahreman, Smidt, & Remschmidt, 2009). Second, the distress that is caused by ASD may further enhance anxiety symptoms (Wood & Gadow, 2010). Third, ASD deficits in cognitive and social-emotional processing may leave the child more vulnerable to cope with triggers, and to develop anxiety (van Steensel, Bögels, Magiati, & Perrin, 2013). Finally, ASD and anxiety disorders share several symptoms, and children with ASD and children with anxiety disorders may be difficult to distinguish on several domains. That is, a study by Hartley and Sikora (2009) found that there were no significant differences between children
with ASD and children with anxiety disorders in the endorsement of stereotyped/restrictive patterns of interest, non-functional routines or rituals, stereotyped or repetitive motor mannerisms, and preoccupation with parts of objects. In addition, only a trend \( (p < .10) \) was observed for children with ASD having higher endorsements than children with anxiety disorders with respect to the failure to develop peer relationships, and lack of social/emotional reciprocity. Such overlap in symptoms may complicate the diagnostic process. In addition, a lack of validated instruments to measure anxiety in ASD makes disentangling the two disorders even more difficult. Next to the overlap in symptoms and the measurement issues, the reliability and validity of the use of self-report in ASD has been questioned (e.g., Mazefsky, Kao, & Oswald, 2011; White, Schry, & Maddox, 2012). That is, children with ASD may be less reliable reporters about their inner states due to varying difficulties with describing and understanding (their own) emotions (e.g., Begeer, Koot, Rieffe, Meerum Terwogt, & Stegge, 2008; Mazefsky et al., 2011).

Perhaps because of the above mentioned issues, prevalence rates of comorbid anxiety (disorders) in children with ASD vary enormously across studies (11% - 84%; White, Oswald, Ollendick, & Scahlill, 2009). Thus, although anxiety is found to be a common problem in children with ASD, it is less clear exactly how common comorbid anxiety disorders are, and which factors are associated with higher prevalence rates (e.g., gender, age, IQ, ASD subtype; see Chapter 1). Further, it is reported that children with ASD may experience higher levels of anxiety compared to some clinical samples (see MacNeil, Lopes, & Minnes, 2009, for a review), however, these findings have not yet been replicated, and studies comparing the rates of comorbid (anxiety) disorders in ASD samples to other clinical groups are rare. In addition, while research has demonstrated that the presence of anxiety disorders in typical developing children have consequences in terms of quality of life and societal costs (Bastiaansen et al., 2004; Bodden et al., 2008), these issues have not been examined for children with ASD and comorbid anxiety disorders specifically. There are studies that have reported that children with ASD have a lower quality of life, and have higher health care costs compared to both non-clinical as well as clinical samples (e.g., Bastiaansen et al., 2004; Kuhltan et al., 2010; Liptak, Stuart, & Auinger, 2006; Peng, Hatlestad, Klug, Kerbeshian, & Burd, 2009; see Chapter 3 and 4 for a more detailed introduction). Further, it is unknown whether comorbid anxiety disorders in children with ASD are different compared to clinically anxious children, and whether or not these anxiety disorders need to be treated different.
CBT is found to be effective to treat anxiety disorders in clinically anxious children (e.g., Barret et al., 2001; Bodden et al., 2008; Kendall et al., 2001), and a growing body of evidence is emerging about its applicability in children with ASD (e.g., Chalfant, Rapee, & Carroll, 2007; Reaven et al., 2009; Sofronoff, Attwood, & Hinton, 2005; Wood et al., 2009). There are several reasons why CBT may also be used in children with ASD; CBT is usually highly structured, goal-directed, and provides clear ‘rationales’ (e.g., how you behave depends on how you feel, and how you feel depends on what you think; anxious thoughts make you feel anxious, thus, changing anxious thoughts will make you feel less anxious). In addition, several researchers have suggested a similar information-processing style in children with ASD and children with anxiety disorders; i.e., both groups would be more focused on (threatening) details instead of the global context (e.g., Chalfant et al., 2007; Ooi et al., 2008). Children with ASD also differ on several aspects from clinically anxious children, which may affect the effectiveness of CBT. That is, the implementation of learned strategies may take longer, skills that are learned during CBT may generalize less to other settings or new (anxiety-provoking) situations, and core ASD symptoms/ASD-related difficulties may interfere with treatment effectiveness (e.g., Ozsivadjian & Knott, 2011; Reaven et al., 2009; Sofronof et al., 2005; Wood et al., 2009). Next to the question of whether CBT is effective, another question – within the constraints of resources and funding allocations – is how anxiety disorders in children with ASD are best to be treated when considering both effectiveness and costs. In other words: Is CBT the treatment of choice for children with ASD from a health care economic perspective, or are the interventions that are usually provided to children with ASD more cost-effective? Treatments that are usually given to children with ASD (further referred to as TAU) may include psycho-education, theory of mind (TOM) training, social skills training, individual, parent, or family guidance, other psychosocial interventions, as well as medication targeting (anxious) behavior. However, these treatments often do not specifically aim to treat anxiety, and it has not been investigated whether these TAU-interventions are effective for treating anxiety in ASD. A clear evidenced-based intervention for the treatment of anxiety in ASD is currently lacking (Van Rooijen & Rietveld, 2012), and although first results of studies examining the effectiveness of CBT are promising (e.g., Chalfant et al., 2007; Reaven et al., 2009; Sofronoff et al., 2005; Wood et al., 2009), the effectiveness of this treatment has rarely been compared to alternative interventions (see Chapter 6 for a more detailed introduction).
Description of the study

Data for the first chapter were gathered by reviewing the existing literature and the data of the second chapter were collected from a mental health care center in Maastricht. For the other chapters, (subsamples of) the data of families who were recruited via seven mental health care centers throughout the Netherlands were used (Chapter 3 to 9). In total, 237 children and their parent(s) participated. Initially, only children who were offered CBT to treat their anxiety disorders were asked to participate. However, in a later phase of the study, the inclusion was broadened. That is, all children with anxiety disorders who were in need of treatment were then eligible for the study; children either received CBT or treatment as usual. From this stage on cost questionnaires were collected and ADI-R’s (Autism Diagnostic Interview-Revised; Lord, Rutter, & Le Couteur, 1994) were administered (and retroactive administered for those already included in the study). In addition, a sample of typically developing children was recruited as a comparison group which consisted of 90 children, and their parents.

Outline of the dissertation

The aim of this dissertation was to examine some of the issues discussed above. Its central theme is ‘Anxiety disorders in children with and without ASD’. The dissertation is subdivided into four parts, each with its own subtheme, namely (1) Prevalence, (2) Impact, (3) Treatment, and (4) Explorations.

In the first part of this dissertation, Prevalence, two studies are described. The first is a meta-analytic review of which the aim was to give an estimate of the prevalence of anxiety disorders in children with ASD. For this chapter, 31 studies involving 2,121 children were selected (Chapter 1). In the second study, the rates of comorbid (anxiety) disorders between children with ASD and children with ADHD are compared (Chapter 2). Participants in this chapter were 80 children (40 children with ASD and 40 children with ADHD), and their parent(s).

The second part of this dissertation, Impact, also consists of two studies. In the first, it is examined whether comorbid anxiety disorders in children with ASD are similar – or different – from those of children with anxiety disorders without ASD, and whether anxiety disorders have a similar – or different – impact on quality of life (Chapter 3). The data of all (237) families were used in this chapter. In the next study, the societal costs associated with ASD
and comorbid anxiety disorders are examined, and costs between children with ASD and comorbid anxiety disorders, children with anxiety disorders, and typically developing children are compared (Chapter 4). For this study, the data of all participants that filled in the cost questionnaire were used which consisted of 73 children with ASD and comorbid anxiety disorders, 34 children with anxiety disorders, and 87 typically developing children.

In the third part of this dissertation, Treatment, two studies are described. In the first study it is examined (1) whether CBT is effective for the treatment of comorbid anxiety disorders in children with ASD, and (2) whether treatment effectiveness between children with and without ASD is different (Chapter 5). In this study, the data of all children who have received CBT for the treatment of their anxiety disorders were used; 79 children with ASD and comorbid anxiety disorders, and 95 children with anxiety disorders. In the second study of this subpart, it is examined whether CBT is cost-effective compared to TAU in the treatment of anxiety disorders for children with ASD (Chapter 6). For this study the data of 49 families were used; 24 children received CBT, and 25 children received TAU.

In the last part of this dissertation, Explorations, three studies are described and each explores a different issue that is worth further investigation. The first study examines whether early ASD symptoms (rated retrospectively) and current ASD-traits are more common in children with anxiety disorders than in a sample of typically developing children (Chapter 7). The study used the data of those children with and without anxiety disorders (without ASD) for which the ADI-R (Lord et al., 1994) was available; 42 children with anxiety disorders and 42 typically developing children recruited from the general population (controls). In the second study, the psychometric properties of an instrument designed for typically developing children to assess anxiety (SCARED-71; Bodden, Bögels, & Muris, 2009) is examined for its applicability in children with ASD (Chapter 8). Further, the psychometric properties of the SCARED-71 for children with ASD and comorbid anxiety disorders are compared to those of clinically anxious children. Data of all (237) families were used in this study. Finally, in the third study the possible implication of changing DSM-5 criteria with respect to the classification of ASD is examined (Chapter 9). The ADI-R was used to examine this issue, which was administered to the parents of 90 children with ASD and comorbid anxiety disorders.

The dissertation ends with a discussion which integrates, aggregates, critically examines and discusses the results of the aforementioned chapters. Clinical implications and recommendations for future studies are given.