Improving treatment of anxiety in children with autism spectrum disorder in clinical practice: the importance, effect and implementation of the video game *MINDLIGHT*

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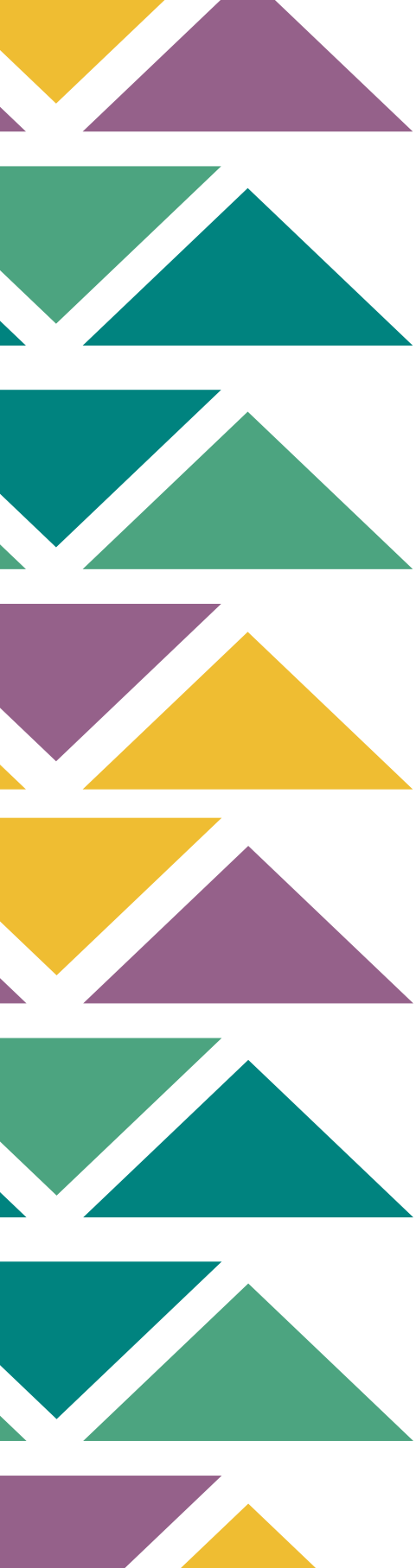


CHAPTER 1

General introduction

Anxiety in Children with Autism Spectrum Disorder

It is known that, worldwide, one in 160 children is diagnosed with an autism spectrum disorder (ASD; World Health Organization, 2018). According to the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (American Psychiatric Association, 2013), ASD is characterized by some degree of impaired social behaviour, communication and language, together with the presence of repetitive behaviour and specific interests. Until 2013, the DSM-4 (American Psychiatric Association, 2000) divided ASD into three subtypes: autistic disorder, Asperger's disorder, and pervasive developmental disorder—not otherwise specified (PDD-NOS). With the introduction of the DSM-5 (American Psychiatric Association, 2013), all diagnoses were transformed into one diagnosis, autism spectrum disorder, with differentiation based on the level of severity. In most cases, the characteristics of an ASD begin to be apparent during the first five years of life and tend to persist into adolescence and adulthood (World Health Organization, 2018).

Children with ASD often have comorbid problems, such as attention deficit hyperactivity disorder and oppositional defiant disorder (Salazar, 2015). The most prevalent comorbid problem in children with ASD is anxiety disorders (Salazar, 2015). Anxiety in children with ASD leads to a wide variety of impairments in daily life, including self-injurious behaviour, depressive symptoms, gastrointestinal problems, family stress, and problems in relationships with peers and teachers (Hallett, Lecavalier, & Sukhodolsky, 2013; Kerns et al., 2015; Mazurek et al., 2013). Moreover, comorbid disorders are associated with long-term negative consequences, including more severe disorder symptoms, less social competence, a longer mental illness course, greater functional disability, and higher service utilization later in (adult) life (Kerns et al., 2013).

The negative consequences of anxiety are often the reason behind children with ASD and their parents seeking mental help in a clinical agency, without always recognizing that these problems are related to anxiety. It is important that children and their parents receive adequate and effective anxiety assessment and treatment in mental healthcare so that the current consequences of anxiety can be decreased and the long-term consequences of anxiety prevented. Therefore, it is important to know more about the characteristics and treatment of anxiety in children with ASD.

Part 1:
Anxiety, Depression and Suicidal Ideation in Children with ASD

Prevalence and risk factors of anxiety in children with ASD

Prevalence rates of anxiety in children with ASD vary between 11 per cent and 84 per cent (White, Oswald, Ollendick, & Scahill, 2009). More specifically, it has been shown that 56 per cent of children with ASD suffer from at least subclinical levels of anxiety (Strang et al., 2012) and approximately 40 per cent of children with ASD meet the criteria of at least one anxiety disorder (Van Steensel, Bögels, & Perrin, 2011). The wide variation in prevalence rates can be explained by differences in the sample (e.g. children with ASD in a clinical setting or community samples; Kerns et al., 2016a; Kerns & Kendall, 2013) and methodology. For instance, there are differences in the sensitivity of the instruments used to assess the severity of anxiety in children with ASD (e.g. questionnaire or interview), or differences in the way anxiety is operationalized (e.g. symptoms or disorder). Finally, anxiety ratings differ between informants, with parental stress being an important predictive factor of higher parent as compared to child ratings of anxiety in children with ASD (Ooi et al., 2016).

Some of the most frequently reported anxiety disorders and symptoms seen in children with ASD are specific phobias, generalized anxiety disorder, separation anxiety disorder, obsessive compulsive disorder and social phobia (White et al., 2009). Until recently, anxiety in children with ASD received little attention in the literature because of diagnostic overshadowing (Kerns et al., 2016a). Anxiety symptoms among children with ASD were attributed to the autism spectrum disorder and therefore did not receive the scientific and clinical attention that they deserve. Nowadays, it is well established that many anxiety symptoms are related to the core symptoms of ASD but are not specific to the population of children with ASD (Kerns et al., 2016a). For example, only a subset of children with ASD show specific fears (e.g. fear of clowns, fireworks or the dark), fear of novelty and change, and social anxiety. However, children with ASD have difficulty expressing specific anxious thoughts and feelings, making it difficult to recognize anxiety in these children (Ghaziuddin, Ghaziuddin, & Greden, 2002). Avoidant behaviour, increased arousal, fearful obsessions, withdrawal behaviour and worry in these children all point to the presence of an underlying anxiety process that is not adaptive and cannot be explained merely by the presence of ASD (Ghaziuddin et al., 2002; Kerns et al., 2016a). In these cases, the severity of the anxiety should be assessed, and when criteria of a particular anxiety disorder are met, the corresponding DSM-5 classification could be ascribed.

Because of the high prevalence and severity of anxiety in children with ASD, it is important to examine the risk factors for developing anxiety in this target group. The

literature shows a lot of inconsistency in terms of risk factors, which, as mentioned, may be due to sample and methodological heterogeneity (Kerns & Kendall, 2013). Age, cognitive abilities (developmental level or IQ), gender, genetic factors, environmental family factors and chronic negative life events have been shown to be risk factors for anxiety (Kerns et al., 2016a; Van Steensel & Heeman, 2017; Vasa & Mazurek, 2015). Finally, difficulties with emotion and arousal regulation have been shown to be related to the presence of anxiety in children with ASD (Kerns et al., 2016a; Vasa & Mazurek, 2015). Because of the high inconsistency in the results of previous studies, further research is needed to obtain more information about the prevalence and risk factors of anxiety in children with ASD.

Prevalence of depression and suicidal ideation in children with ASD

In addition to their elevated anxiety, children with ASD often suffer from other comorbid problems. As in the general child population, anxiety is highly correlated with depressive symptoms in children with ASD (Vasa et al., 2013), suggesting that children with ASD and anxiety symptoms often suffer from high levels of depressive symptoms (Ung et al., 2013). Indeed, Kerns and colleagues (2015) found that children with ASD and anxiety displayed more depression and self-injury than children with ASD alone. When levels of depressive symptoms increase, children with ASD may also develop suicidal thoughts. These thoughts, also known as suicidal ideation, appear to be common in children with ASD and elevated anxiety symptoms (Hooyer & Sizoo, 2016).

It has been shown that 13 per cent of children with ASD and elevated anxiety meet the criteria of a major depressive disorder or dysthymia (Ung et al., 2013). Furthermore, 29–40 per cent of children with ASD and elevated anxiety experience suicidal ideation (Demirkaya et al., 2016; Mukaddes & Fateh, 2010). A subset of the population of children with ASD that is especially at risk of developing anxiety, depressive symptoms and suicidal ideation is children with ASD and normal cognitive functioning (De-la-Iglesia & Olivar, 2015; Mayes et al., 2011b). Because of their average or above average cognitive abilities and introspection skills, these children are more aware of their social disabilities and often experience higher social demands that they are unable to meet. In turn, this may lead to (social) anxiety symptoms, putting them more at risk of developing depressive symptoms and suicidal ideation (Brereton, Tonge, & Einfeld, 2006; De-la-Iglesia & Olivar, 2015; Hannon & Taylor, 2013; Mayes, 2011b; Sterling, Dawson, Estes, & Greenson, 2008; Storch et al., 2013). Despite the heightened vulnerability of these children to the development of anxiety and depression, there is a lack of knowledge about the specific self-reported prevalence rates of depressive symptoms and suicidal ideation in children with ASD, normal cognitive functioning and elevated anxiety. Therefore, this needs further investigation.

Aims of current thesis: Part 1

In Part 1 of the current thesis, prevalence rates and risk factors of anxiety symptoms in children with ASD were further investigated (Chapter 2). Also, the prevalence of depressive symptoms and suicidal ideation in children with ASD and elevated anxiety was examined (Chapter 3). The aim of the current thesis is to add knowledge to previous literature in multiple ways. First, the majority of previous studies focusing on anxiety and depression in children with ASD only used parent reports (e.g. Gotham et al., 2013; Mayes et al., 2013; Strang et al., 2012; Vasa et al., 2013) *or* clinical interviews *or* observations (e.g. Hardan & Sahl, 1999; Mukaddes & Fateh, 2010), whereas the studies reported in this thesis use both parent and child reports of anxiety and depressive symptoms. This is because children with ASD and normal cognitive functioning may have difficulty with the face-to-face expression of anxious and depressed thoughts (Ghaziuddin et al., 2002), but have been shown to be able to accurately report anxious and depressed thoughts in a questionnaire (Ooi et al., 2016; Ozsivadjian, Hibberd, & Hollocks, 2013), where they only have to choose the most suitable (multiple choice) answer to a specific question about anxiety or depression. Therefore, self-reports can add valuable information to existing knowledge on the prevalence of anxiety, depression and suicidal ideation in children with ASD.

Secondly, the anxiety and depression symptoms were investigated in a specific clinical Dutch sample of children with ASD, normal cognitive functioning and a high level of daily impairment. This way, there was less heterogeneity in the severity of psychiatric symptoms and cognitive functioning in the study population than in several other studies using large community samples (e.g. Gotham et al., 2013). Because of this heterogeneity, prevalence rates and risk factors that were found in these studies (e.g. Gotham et al., 2013) may not necessarily apply to a specific subset of children with ASD. Because a specific clinical Dutch sample of children with ASD was used in the present thesis, the prevalence and risk factors for anxiety and depression obtained can contribute as a reliable piece of the knowledge jigsaw on the prevalence and risk factors of anxiety and depression in the total Dutch population of children with ASD. Moreover, because a clinical sample of children with ASD that already received treatment at a mental health agency was used, results of the current thesis are directly applicable to and relevant for therapists in clinical practice.

Part 2:
Treatment of Anxiety in Children with ASD

Cognitive-behavioural therapy for children with ASD

For typically developing children with anxiety symptoms, cognitive behavioural therapy (CBT) is considered the most effective evidence-based treatment (e.g. Warwick et al., 2017). Recently, two meta-analyses (Sukhodolsky, Bloch, Panza, & Reichow, 2013; Ung, Selles, Small, & Storch, 2015) and one Cochrane review (James, James, Cowdrey, Soler, & Choke, 2013) showed that CBT has a moderate effect on anxiety in children with ASD, compared to no treatment or active control conditions. However, there was substantial heterogeneity in the effect sizes (Sukhodolsky et al., 2013; Ung et al., 2015), with some studies showing large effect sizes and other studies showing medium or small effect sizes. Moreover, it remains unclear whether adaptations to the standard treatment components of CBT (e.g. cognitive restructuring and exposure) are necessary, or if children with ASD can receive regular CBT identical to typically developing children (Johnco & Storch, 2015). Both CBT treatment protocols designed for typically developing children (e.g. Denken + Doen = Durven [Discussing + Doing = Daring], van Steensel & Bögels, 2015; BRAVE-Online, Conaughton, Donovan, & March, 2017) and CBT protocols adapted to children with ASD (e.g. the Coping Cat programme for children with anxiety and ASD, McNally Keehn, Lincoln, Brown, & Chavira, 2013; Multimodal Anxiety and Social Skills Intervention, White et al., 2010) have shown promising results. Recently, a review by Hunsche and Kerns (2019) has shown that one individual CBT programme (Denken + Doen = Durven, van Steensel & Bögels, 2015) and a group CBT programme (Behavioural Interventions for Anxiety in Children with Autism [BIACA], Woods et al., 2009) are probably efficacious for children with ASD and anxiety, indicating effectiveness when compared to a control group, but not when compared to alternate treatments (e.g. pharmacological treatment; see Chambless & Hollon, 1998). This study also shows that there are not yet any well-established (effectiveness is proved compared to alternative treatment) adapted or standard CBT programmes for children with ASD and anxiety symptoms. An ongoing RCT currently tests the efficacy of BIACA compared to standard CBT and pharmacological treatment (Sertraline) in children with ASD (Kerns et al., 2016b).

There are some important limitations to CBT for anxiety, both in general and specifically for children with ASD. Firstly, children with ASD have difficulties with abstract thinking and verbal expression of their cognitions, which are skills that children have to use in CBT sessions (Johnco & Storch, 2015). Secondly, in the treatment of children with ASD, it is important to incorporate their special interests, because this is often engaging and salient for the child and can thereby increase the effectiveness of the treatment

(Johnco & Storch, 2015). In CBT sessions, it can be difficult to adapt to these special interests because of the relatively static and verbal techniques that are mostly used. Thirdly, it has been shown that the generalization of skills learned in CBT to daily life situations is difficult for children with ASD (de Marchena, Eigsti, & Yerys, 2015; McNally Keehn et al., 2013). Finally, long waiting lists and low cost-effectiveness are limitations of CBT (as stated in Granic, Lobel, & Engels, 2013). Because of these limitations of CBT, it is important to develop new effective anxiety treatments for children with ASD.

The video game *Mindlight*

Recent studies have suggested that video games have the capability to enhance the mental health of children and adolescents by providing them with immersive and compelling social, cognitive and emotional experiences (Ferguson & Olsen, 2013; Granic et al., 2013). Studies with clinical samples have indeed shown that video games have a positive effect on mental problems among children and adolescents. For instance, Merry and colleagues (2012) found that the video game *SPARX* was effective in reducing depressive symptoms among adolescents between 12 and 19 years old. Moreover, the video game *Dojo* was shown to be effective in decreasing anxiety and externalizing the problems of children in residential care (Schuurmans, Nijhof, Engels, & Granic, 2018). For children with ASD, previous studies have shown that video games are effective in improving emotion regulation skills (e.g. *Secret Agent Society*, Beaumont, Rotolone, & Sofronoff, 2015). In all these studies, it is concluded that a video game is a potential and more engaging alternative to the usual care for adolescents in clinical settings, and that video games could be used to address some of the unmet demand for treatment.

The video game investigated in the current thesis is *Mindlight*. This applied video game was developed for the treatment of anxiety symptoms and disorders in children aged 8–16. *Mindlight* is based on several evidence-based principles of CBT (Abramowitz, Deacon, & Whiteside, 2011; Muris & Field, 2008), and uses elements of neurofeedback to teach children to regulate their anxiety levels (Hammond, 2005). The premise of the game is that Little Arthur is left by his parents on the doorstep of his grandmother's scary and dark mansion. The mansion and his grandmother turn out to be cursed. Arthur must learn to use his own inner strength to overcome his greatest fears in order to end the curse and free the mansion and his grandmother. He can accomplish this by using his '*Mindlight*', a light bubble that can shine on the dark surroundings and that can be controlled by his own inner strength. In other words, when children play *Mindlight*, they have to use their own inner strength to overcome their fears and let Arthur free the mansion and his grandmother. This inner strength is measured by a neurofeedback headset (the MindWave, NeuroSky, CA,

USA; Johnstone, Blackman, & Bruggemann, 2012a) that children put on when they are going to play *Mindlight*. This headset records electroencephalogram (EEG) using dry sensor technology, which consists of an active and reference electrode and which filters signals on delta, theta, alpha and beta waves. In *Mindlight*, the alpha and beta waves especially are used for real-time feedback. The MindWave headset has good reliability and validity (Johnstone et al., 2012a); it has been demonstrated that it can be used reliably in research with children that have a developmental disorder (e.g. ADHD; Johnstone et al., 2012b).

In *Mindlight*, the alpha and beta waves are used for neurofeedback in several ways. First of all, the recorded alpha waves reflect the degree of relaxation of the child. This feature is used in the exposure techniques (the evidence-based principle of CBT; Abramowitz et al., 2011) that are embedded in the game: when children are exposed to threatening stimuli (e.g. monsters), they have to apply relaxation techniques such as deep breathing and self-talk in order to overcome their fears and gain points. Furthermore, the recorded beta waves reflect the degree of concentration and the allocation of the player's attention. Focused concentration allows children to solve attention bias modification (ABM) puzzles in *Mindlight*. ABM is an evidence-based training protocol that has its roots in CBT; it is based on the idea that attentional biases characterized by hyper attention towards threatening stimuli play a role in the pathogenesis of childhood anxiety (Muris & Field, 2008). ABM has been shown to reliably reduce anxiety by retraining the attentional system to focus on positive stimuli (Bar-Haim, 2010). *Mindlight* uses this principle in the ABM puzzles, by rewarding children for focusing on positive aspects of the environment. More specifically, children learn to move their attention towards positive stimuli (e.g. portraits of happy faces) and shift their attention away from negative or threatening stimuli (e.g. mean faces). Recent studies have investigated the effect of *Mindlight* on elevated anxiety symptoms in school children (Schoneveld et al., 2016; Schoneveld, Lichtwarck-Aschoff, & Granic, 2017). It has been shown that *Mindlight* is equally effective to a control game and to the Dutch translation of the CBT group treatment protocol Coping Cat (Nauta & Scholing, 1998) in decreasing anxiety symptoms over time.

There are several reasons why *Mindlight* could also be effective in decreasing anxiety in children with ASD and why it has some advantages over the previously mentioned limitations of CBT. It is known that children with ASD profit more from visual prompts and structured sensory information than from verbal information (Johnco & Storch, 2015; Silver & Oaks, 2001). *Mindlight* is a computer-based intervention in which visual aids and structured sensory information are integrated to train emotion regulation skills (e.g. relaxation techniques). Moreover, in treatment of children with ASD, it is important to incorporate their special interests—for example, by using

these special interests as a metaphor (Johnco & Storch, 2015). Therapists could use the metaphors in *Mindlight* to explain therapeutic content, to reinforce treatment participation and to build a therapeutic relationship. Furthermore, children with ASD have difficulties recognizing their emotions and expressing their thoughts and feelings (White et al., 2009). *Mindlight* is an experiential game, which means that the game play makes children aware of their physical and emotional feelings and the way in which they can alter these feelings. Finally, *Mindlight* requires less intensive supervision by a therapist than CBT and can be played at home, which might shorten waiting lists and lower treatment costs (Granic et al., 2013). This way, *Mindlight* could be a suitable and effective new anxiety treatment for children with ASD and needs further investigation.

The role of externalizing behaviour

It has been reported that the interplay between anxiety and externalizing behaviour in children with ASD may complicate the treatment course (Ung et al., 2013). For example, children with ASD and externalizing behaviour might not recognize the presence of anxiety, they may have difficulty focusing on and learning from the intervention, and parents of these children might have difficulty supporting them in regulating anxiety, because these children often express their anxiety by showing disruptive behaviour (Eisenberg et al., 2009; Storch et al., 2012; Ung et al., 2014). Therefore, externalizing behaviour is an important individual factor that might have a negative impact on the decrease of anxiety symptoms during a video game intervention. It is important to investigate the potential negative impact of this behaviour on the decrease of anxiety, because it will provide us with more insight into the individual factors that determine the children for whom a video game intervention like *Mindlight* is most effective. Moreover, study outcomes can potentially contribute to the personalization of anxiety treatment in children with ASD. If externalizing behaviour turns out to have a negative impact on the decrease of anxiety, this would imply, for example, that for children with ASD and externalizing behaviour, it is important to adapt anxiety treatment to their poor impulse control and inattentive behaviour (Eisenberg et al., 2009), or to focus treatment first on externalizing behaviour in order to improve the effectiveness of the anxiety treatment.

The additive effect of CBT on *Mindlight*

Children with ASD have difficulty generalizing the skills they learn in therapy to multiple contexts in their daily lives (McNally Keehn et al., 2013; White et al., 2009). It is therefore possible that children with ASD do not automatically know how to use the coping skills they learn during *Mindlight* in scary situations encountered in daily life (McNally Keehn et al., 2013; White et al., 2009). Importantly, it has been shown that anxiety regulation skills need to be practised in multiple fearful contexts in order to maintain

treatment effects (Craske et al., 2014). Therefore, it is crucial to stimulate and support this generalization of skills in children with ASD.

Research has shown that the generalization of coping skills that are learned in therapy can be stimulated using elements of CBT (Swan, Carper, & Kendall, 2016). It is possible that the addition of CBT elements to *Mindlight* could also enhance generalization of the learned coping skills among children with ASD. In *Mindlight*, children learn how to regulate their anxiety levels in an experiential way. In CBT, reflection on this learning process could be stimulated by the therapist by exploring together with the child the anxious cognitions and feelings that were experienced during the game play. In turn, they could examine in what way the child altered these anxious cognitions (cognitive restructuring; Waters et al., 2008) during the game into effective coping thoughts (Swan et al., 2016), and how they could use these thoughts to improve their coping skills in anxious situations in daily life. Eventually, children could practise these coping skills with support from their parents in multiple daily life situations; this way, generalization of the learned skills is stimulated (Craske et al., 2014; Swan et al., 2016). Using the experiences in *Mindlight* as an input for the CBT elements, the anxiety treatment is engaging and vivid, and CBT elements could be implemented without facing the limitations of CBT for children with ASD. Instead, experiential (*Mindlight*) and explicit (CBT) learning are combined in an optimal way, which might lead to a higher total decrease of anxiety symptoms in children with ASD. To investigate the potential advantages of a combined *Mindlight* and CBT intervention, further research is necessary which investigates the additive effect of CBT on *Mindlight* in decreasing anxiety symptoms of children with ASD.

Aims of current thesis: Part 2

The aim of Part 2 of the current thesis is to investigate the effect of *Mindlight* on anxiety symptoms among children with ASD in a clinical setting (Chapter 4 + 5). Also, it was tested whether externalizing behaviour had a moderating effect on the decrease of anxiety symptoms among the participating children with ASD (Chapter 6). Moreover, it was investigated whether CBT elements had an additive effect on *Mindlight* in decreasing anxiety symptoms among children with ASD (Chapter 7). Finally, a summary and general discussion of the main findings were presented (Chapter 8). In addition, suggestions for future research and clinical implications and recommendations related to the studies were discussed.

This thesis could lead to more insight into the background and effect of an innovative treatment vehicle (*Mindlight*) that could have a potential advantage over the original CBT protocols for children with ASD in a clinical setting. Moreover, this thesis shows the possibilities and advantages of combining innovative treatment such

as *Mindlight* with existing treatments (CBT) for anxiety symptoms in children with ASD in clinical practice. This way, the current thesis has high clinical relevance and could provide mental health agencies with important input for improving anxiety treatments for children with ASD.

Overview and Research Questions of Thesis

Part 1: Anxiety, depression and suicidal ideation in children with ASD

Chapter 2: Prevalence and Risk Factors of Anxiety in a Clinical Dutch Sample of Children with an Autism Spectrum Disorder

- What are the prevalence and risk factors of anxiety in children with an autism spectrum disorder?

Chapter 3: Prevalence of Comorbid Depressive Symptoms and Suicidal Ideation in Children with an Autism Spectrum Disorder and Elevated Anxiety

- What is the prevalence of depressive symptoms and suicidal ideation of children with an autism spectrum disorder and elevated anxiety?

Part 2: Treatment of anxiety in children with ASD

Chapter 4: Study Protocol: The Effect of the Video Game *Mindlight* on Anxiety Symptoms of Children with an Autism Spectrum Disorder

Chapter 5: An RCT Testing the Effect of the Video Game *Mindlight* on Anxiety Symptoms of Children with an Autism Spectrum Disorder

- What is the effect of the video game *Mindlight* on anxiety symptoms of children with an autism spectrum disorder?

Chapter 6: The Moderating Effect of Externalizing Behaviour on the Decrease of Anxiety Symptoms During a Video Game Intervention for Children with an Autism Spectrum Disorder

- What is the moderating effect of externalizing behaviour on the decrease of anxiety symptoms during a video game intervention for children with an autism spectrum disorder?

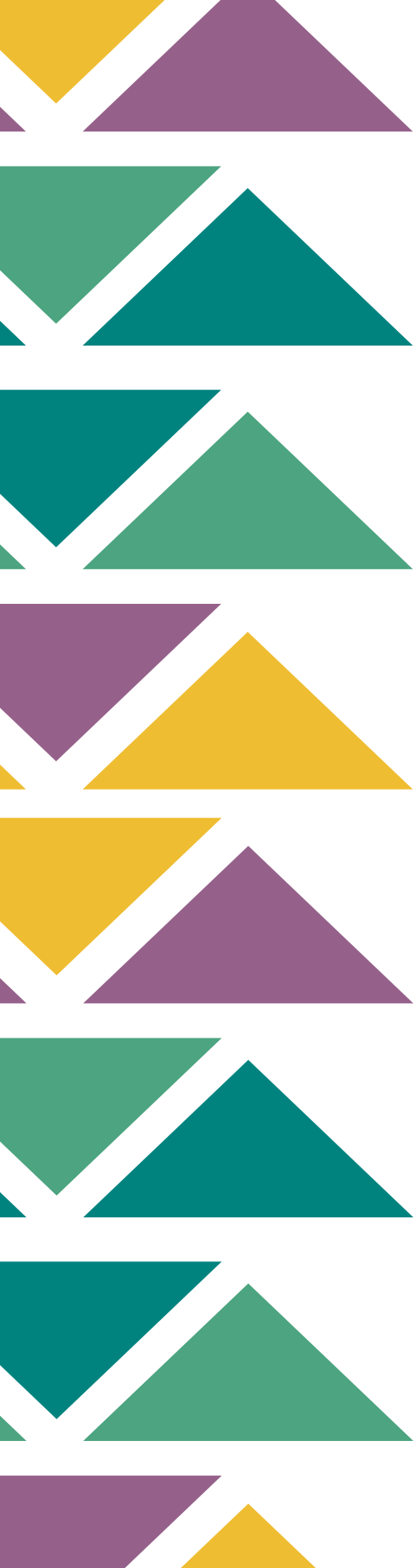
Chapter 7: A Single Case Series Design Testing the Additive Effect of CBT Elements on the Video Game *Mindlight* in Decreasing Anxiety Symptoms of Children with an Autism Spectrum Disorder

- What is the additive effect of CBT elements on the video game *Mindlight* in decreasing anxiety symptoms of children with an autism spectrum disorder?

Chapter 8: General Discussion

PART I

Anxiety, Depression and Suicidal Ideation in Children with ASD



CHAPTER 2

Prevalence and Risk Factors of Anxiety in a Clinical Dutch Sample of Children with an Autism Spectrum Disorder

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ABSTRACT

Anxiety is highly prevalent in children with an autism spectrum disorder (ASD). However, there is inconsistency in studies investigating prevalence and risk factors of anxiety in children with ASD. Therefore, the first aim of the present study was to give an overview of the prevalence of anxiety symptoms in a clinical Dutch sample of children with ASD. The second aim was to investigate age, gender, ASD subtype and IQ as potential risk factors for anxiety in this sample. In total, 172 children with ASD (8-15 years) and their parents participated in the present study. Specialized services in which children with ASD were recruited were two mental health institutes and one secondary special education school. The findings showed that more than 60% of the participating children with ASD had at least subclinical anxiety symptoms according to children. More than 80% of the children with ASD had at least subclinical anxiety symptoms according to parents. It was found that younger children and girls with ASD had more anxiety symptoms than older children and boys with ASD. Moreover, it was found that children with a higher PIQ and lower VIQ had more specific phobia symptoms. The findings suggest that in a clinical context, children with ASD have a high risk to have co-occurring anxiety symptoms, especially girls and younger children with ASD. Therefore, early prevention and treatment of anxiety in children with ASD who are most at risk is important.

INTRODUCTION

Recent studies have demonstrated that comorbid psychiatric problems are common among children with an Autism Spectrum Disorder (ASD; e.g. Salazar et al., 2015). Anxiety is one of the most prevalent comorbid psychiatric problems in children with ASD, with prevalence rates varying between 11-84% (White, Oswald, Ollendick, & Scahill, 2009). More specifically, it has been shown that 56% of the children with an ASD suffer from at least subclinical anxiety (Strang et al., 2012) and approximately 40% of the children with an ASD meet the criteria of at least one anxiety disorder (Van Steensel, Bögels, & Perrin, 2011). Some of the most frequently reported anxiety disorders and symptoms seen in children with an ASD are specific phobias, generalized anxiety disorder, separation anxiety disorder, obsessive-compulsive disorder and social phobia (White et al., 2009).

The distinct anxiety disorders show a wide variation in prevalence rates (11-84%; White et al., 2009) in the population of children with ASD. The big differences in prevalence rates are mainly due to sample and methodological heterogeneity, differences in the assessment of anxiety in children with ASD and differences in the operationalization of anxiety (Kerns & Kendall, 2013). In some studies only parent report of anxiety was used (e.g. Bradley, Summers, Wood, & Bryson, 2004), whereas in other studies a combination of parent and child (e.g. Bellini, 2004) or parent and teacher (Lecavalier, 2006) report of anxiety was used. These respondents differ in their assessment of anxiety in children with ASD. For example, there is some evidence that teachers give higher ratings of anxiety than parents (Gadow et al., 2005). Moreover, some children with ASD may have difficulties with emotional insight or accurately detecting and interpreting one's own emotions (White et al., 2009), which could lead to higher symptom ratings of parents compared to children. However, other children with ASD might be able to report on their own stress and social attributions (Meyer, Mundy, Van Hecke, & Durocher, 2006). For example, ASD children with age appropriate intellectual and verbal abilities have relatively intact emotion recognition abilities (Bauminger & Kasari, 1999). This implicates that some children with ASD may at least be comparable to parents in their report of anxiety symptom levels. Furthermore, anxiety could be conceptualized as anxiety symptoms measured by a questionnaire (Bellini, 2004), but also as anxiety disorders measured by a structured interview (de Bruin, Ferdinand, Meester, de Nijs, & Verheij, 2007). The use of interviews is associated with higher prevalence rates of total anxiety, while for social anxiety disorder the use of questionnaires is associated with higher prevalence rates (Van Steensel et al, 2011). These conceptual and methodological differences and the heterogeneity of the ASD population may lead to variation in the prevalence rates across studies.

Because anxiety causes significant impairment in children with ASD, it is important that efforts are made to improve the identification and assessment of these symptoms. The impairments caused by anxiety consist of poor daily living skills and problems in relationships with peers, teachers and family (Drahota, Wood, Sze, & van Dyke, 2011; Hallett, Lecavalier, & Sukhodolsky, 2013; Kim et al., 2000). Moreover, anxiety underlies comorbid symptoms of children with an ASD, for example oppositional and aggressive behavior (Cervantes, Matson, Tureck, & Adams, 2013) and depressive symptoms (Vasa et al., 2013). The impairments and comorbid symptoms caused by anxiety also underline the importance of effective treatment of anxiety and prevention of further escalation.

To be able to prevent further escalation of anxiety, it is important that risk factors that predict the development of anxiety are identified. In this way, children with ASD can be profiled on vulnerability for the development of anxiety. Moreover, prevention and treatment can specifically be tailored to the ASD-children with elevated risk to develop anxiety. In the literature, several potential but inconsistent risk factors for the development of anxiety in children with ASD are identified. Again, the inconsistency in risk factors is often due to conceptual and methodological differences between studies and the heterogeneity of the ASD population (Kerns & Kendall, 2013).

Age is one of the potential but inconsistent risk factors. Most studies reported that anxiety in children with ASD increases from preschool to adolescence (e.g. Davis Iii et al., 2011a; Dickerson Mayes, Calhoun, Murray, & Zahid, 2011). Potentially, the delayed cognitive and motor development in children with ASD do not permit the recognition and expression of anxiety symptoms until adolescence (Davis Iii et al., 2011a). However, there is also evidence that only clinical anxiety is higher in adolescents with ASD compared to school children with ASD, and that subclinical anxiety is higher in school children with ASD compared to adolescents with ASD (Vasa et al., 2013).

There are also mixed data regarding the differential prevalence rates of anxiety for girls and boys with ASD. Some studies showed that girls with ASD have more anxiety symptoms (Gadow et al., 2005) and other studies showed that anxiety is more prevalent in boys with ASD (Dubin, Lieberman-Betz, & Michele Lease, 2015). There are more studies showing that anxiety symptoms are equally prevalent in boys and girls with ASD (Sukhodolsky et al., 2008; Vasa et al., 2013; Worley, Matson, Sipes, & Koziowski, 2010). This could be explained by the hypothesis that the shared neurobiological dysfunctions in boys and girls with ASD have an overriding effect on psychopathology, leading to comparable anxiety levels in boys and girls with ASD (Brereton, Tonge, & Einfeld, 2006).

Moreover, several studies showed that the prevalence of anxiety varies among the different subtypes of ASD. The studies that specifically focused on comparing anxiety

levels across ASD subtypes suggest that ASD severity is associated with the level of anxiety, and that children with less severe ASD symptoms might be most comorbid with anxiety (MacNeil, Lopes, & Minnes, 2009). Specifically, children with Asperger Disorder experience more anxiety than children with PDD-NOS, and children with PDD-NOS experience more anxiety than children with Autistic Disorder (Gadow et al., 2005; Weisbrot, Gadow, Devincent, & Pomeroy, 2005; White et al., 2009). This is in line with research that showed that higher IQ or better cognitive functioning predicted more severe anxiety in children with ASD (e.g. Dubin et al., 2015; Salazar et al., 2015; Vasa et al., 2013), because children with Asperger Disorder have a higher IQ than children with PDD-NOS and Autistic Disorder (e.g. Blackshaw et al., 2001). Higher IQ and developmental level may allow children with Asperger Disorder to engage more in higher-order cognitions (e.g. worry, foresight and imagery), which are the hallmark of several anxiety disorders (Kerns & Kendall, 2013). Moreover, it is possible that children with a higher IQ are more exposed to situations (e.g. interactions with peers) that provoke social anxiety (Salazar et al., 2015). Finally, children with Asperger Disorder have better verbal capacities than children with PDD-NOS and Autistic Disorder, which supports the communication of anxiety to parents and teachers (Salazar et al., 2015).

Conversely, there is some evidence that anxiety in general is more common in children with PDD-NOS, followed by children with Autistic Disorder and Asperger Disorder (Van Steensel et al., 2011). Moreover, Dickerson Mayes and colleagues (2011) found that anxiety increased with autism severity. In line with this, some studies reported that a lower mean IQ of children with ASD is associated with higher prevalence rates of anxiety (e.g. Van Steensel et al., 2011). Because children with PDD-NOS and Autistic Disorder have more severe ASD-symptoms than children with Asperger Disorder, they may experience more ASD-related anxiety, for example anxiety for unexpected social situations (Van Steensel et al., 2011).

Furthermore, the verbal IQ (VIQ) and performance (non-verbal) IQ (PIQ) should be considered as more specific risk factors for anxiety in children with ASD. PIQ is often relatively high and VIQ relatively low in children with ASD (Chapman et al., 2011). This is consistent with the core ASD symptom of communication impairments, which may be reflected in weak verbal capacities in children with ASD. Unlike in the normal population, impairments in communication may have an inverse relationship with anxiety in children with ASD. For example, deficits in both receptive and expressive communication skills are associated with less anxiety symptoms in children with ASD (Davis Iii et al., 2012). In line with this finding, there is some evidence that ASD children with lower non-verbal and higher verbal skills show more anxiety and mood problems, which would mean that a low PIQ and high VIQ are related to more anxiety in children with ASD (Kim et al., 2000). However, other research showed that children with PDD-

NOS had higher anxiety levels as communication deficits increased (Davis Iii et al., 2011b).

It can be concluded that there is inconsistency in results of studies investigating prevalence and risk factors of anxiety in children with ASD. Therefore, the first aim of the present study was to give an overview of the prevalence of anxiety symptoms in a clinical Dutch sample of children with ASD. The second aim was to investigate the risk factors for anxiety in this sample of children with ASD. More specifically, age, gender, ASD subtype and IQ were examined as potential risk factors for anxiety in children with ASD. We expected that older children with ASD experience more anxiety than younger children with ASD and that there was no difference in anxiety between boys and girls with ASD. Also, we expected that children with Asperger Disorder experience more anxiety than children with PDD-NOS and Autistic Disorder. In line with this, we expected that ASD children with a higher (V)IQ experience more anxiety than children with a lower (V)IQ.

It is believed that the present study provides new knowledge on the field of anxiety in children with ASD, because both parent- and child-rated anxiety levels were measured and these levels were compared. In the majority of the previous studies on anxiety in children with ASD (e.g. Gotham et al., 2013; Strang et al., 2012; Vasa et al., 2013), only parent-rated anxiety levels were measured. Since children with ASD have shown to be able to accurately report their anxious cognitions (Ozsivadjian, Hibberd, & Hollocks, 2013), self-reports of anxiety can add important an valuable new knowledge about the way in which children with ASD assess their own internalizing symptoms. Moreover, there are hardly any studies that examined anxiety levels in children with ASD in Dutch children with ASD (e.g. Muris et al., 1998) and most studies included large community samples of children with ASD with all levels of impairment (e.g. Gotham et al., 2013), while in the present study a specific clinical sample children with ASD was included who had a high level of daily impairment and who received intensive treatment at a mental health institute.

MATERIAL AND METHODS

Procedures

In the present study, screening data on anxiety was obtained that was later used for the inclusion of participants in a randomized controlled trial (RCT) testing the effect of an anxiety intervention for children with an ASD (see study protocol: Wijnhoven, Creemers, Engels, & Granic, 2015). This RCT (including the screening procedure) was carried out with approval of the medical ethics committee "Commissie Mensgebonden Onderzoek (CMO) Arnhem-Nijmegen" in the Netherlands (NL50023.091.14) and in accordance

with the ethical standards of the Declaration of Helsinki as revised in 2000. Passive consent was received to use the screening data of children and parents in the present study. However, when they eventually participated in the RCT and they received an intervention (experimental or control condition), active and written informed consent was received.

Specialized services in which children with ASD were recruited were two mental health institutes and one secondary special education school. First, parents received a letter with information about the study. If parents and children were interested in participation after reading the letter, they both filled in screening questionnaires on anxiety (SCAS-C; Scholing, Nauta, & Spence, 1999a); SCAS-P; (Scholing, Nauta, & Spence, 1999b). All children and parents (with passive consent) who filled in screening questionnaires were part of the present study, regardless of their anxiety levels and eventual participation in the RCT.

Participants

In total, 172 children with an ASD (Autistic Disorder, Asperger Disorder, PDD-NOS) and their parents participated in the present study. Of the participating children, 134 were male (77.9%) and 38 were female (22.1%). Their age was between 8 to 15 years old (M = 11.25, SD = 2.02). Furthermore, 105 children were in primary school (61.0%) and 67 were in secondary school (39.0%). Of the children in primary school, 39 followed special education (37.1%). Of the children in secondary school, 38 followed special education (56.7%). Moreover, 29 children in secondary school followed vocational training (43.3%), 2 followed vocational training/high school training (3.0%), 8 followed high school training (11.9%), 15 followed high school training/pre-university training (22.4%), 6 followed pre-university training (9.0%) and 5 (7.5%) followed other secondary education. Most of the children were of Dutch origin (> 90%). Inclusion criterion was sufficient knowledge of the Dutch language. Exclusion criteria were absence of parental permission and presence of prominent suicidal ideation or other severe psychiatric problems that needed immediate treatment (e.g. severe trauma).

Instruments

Anxiety symptoms. A Dutch translation of the Spence Children's Anxiety Scale for Children (SCAS-C; Scholing et al., 1999a) was used to measure anxiety symptoms of the participating children. The SCAS consists of 44 items on a 4-point scale, ranging from 'never' to 'always'. Scores on items range from 0 to 3, with higher scores indicating more anxiety symptoms. Moreover, the scale consists of six subscales that are in line with the different anxiety disorders that are described in the Diagnostic and Statistical Manual of Mental Disorders 4th Edition – Text Revision (DSM-IV-TR; APA, 2000). However, the

obsessive compulsive subscale was not included in the present study, because in children with ASD this behavior is often not related to anxiety, but serves as a form of self-soothing behavior or as a regulation of excitement or arousal (Scahill & Challa, 2016). Moreover, in the DSM-V (APA, 2013) the Obsessive Compulsive Disorder was not defined as an anxiety disorder anymore (Van Ameringen, Patterson, & Simpson, 2014). Furthermore, the fear of physical injury subscale was defined as 'specific phobia' in the present study. This because the items of the SCAS-C/P that belong to this subscale do not only refer to fear of physical injury, but also to other specific fears like fear of heights and fear of darkness. The SCAS-C contains six positive filler items, which are not used in the calculation of the total score or subscale scores. The SCAS has a high validity and reliability (Muris et al., 1998; Spence, Barrett, & Turner, 2003). Moreover, anxiety symptoms that are measured with both the SCAS-C can be reliably clustered into the anxiety disorder categories as described in the DSM-IV (Muris et al., 2000). Cronbach's alpha was .94.

Moreover, a Dutch translation of the Spence Children's Anxiety Scale for Parents (SCAS-P; Scholing et al., 1999b) was used to measure anxiety symptoms of the participating children according to the parents. The SCAS-P consists of 38 items on a 4-point scale ranging from 0 (never) to 3 (always). The items of the SCAS-P were formulated as closely as possible to the corresponding item of the child version of the SCAS. The SCAS-P consists of the same six subscales as the child version. Also for the SCAS-P, the obsessive compulsive subscale was not included and the fear of physical injury subscale was defined as 'specific phobia' in the present study. The SCAS-P has a good reliability and validity (Nauta et al., 2004). Moreover, anxiety symptoms that are measured with both the SCAS-P can be reliably clustered into the anxiety disorder categories as described in the DSM-IV (Nauta et al., 2004). Cronbach's alpha was .90.

ASD and comorbid diagnoses. All the participating children were diagnosed with an Autism Spectrum Disorder at a mental health institute in the Netherlands. Of these children, 119 were diagnosed with the ASD-subtype PDD-NOS (69.2%), 29 were diagnosed with the ASD-subtype Asperger Disorder (16.9%) and 22 were diagnosed with the ASD-subtype Autistic Disorder (12.8%). ASD diagnoses were based on psychological and/or psychiatric assessment of the DSM-IV criteria for Autistic Disorder, Asperger's Disorder or PDD-NOS. This assessment was adapted to the diagnostic 'needs' of the individual child and for example consisted of a developmental anamnesis with parents, contact with the child's teacher, and/or standardized observation of the child with the Autism Diagnostic Observation Scale (ADOS; Bildt, Greaves-Lord, & De Jonge, 2013). Comorbid diagnoses were attention-deficit hyperactivity disorder (45.3%), (persistent) depressive disorder (7.0%), oppositional defiant disorder (3.5%), obsessive-compulsive disorder (1.7%), reactive attachment disorder (1.7%) and post-traumatic stress disorder

(1.2%). Moreover, 9.3% of the participating children had some kind of learning disability (e.g. dyslexia).

IQ. The level of cognitive functioning (IQ) was measured by an intelligence test. Of the participating children, 141 children underwent an intelligence test in their clinical trajectory at the mental health institute where they were treated. The Total IQ (TIQ) is an indicator of the overall level of cognitive functioning, and consists of a Verbal IQ (VIQ) and a Performance (non-verbal) IQ (PIQ). Only VIQ and PIQ were included as variables in the present study. This because in the present study, the mean absolute difference between VIQ and PIQ was 12.85 (*SD* = 9.04). A discrepancy of this magnitude is often considered to be statistically significant (Wechsler, 1991), with the consequence that TIQ was not a reliable indicator of the level of cognitive functioning of the participating children. Therefore, VIQ and PIQ could better be used as separate indicators of the level of verbal and non-verbal cognitive functioning. If children had a history of multiple IQ assessments, the most recent IQ measurement was included. In the present study, the mean VIQ was *M* = 104.87 and the mean PIQ was *M* = 97.85.

In total, 134 children were assessed by the third edition of the Wechsler Intelligence Scale for Children (WISC-III; Wechsler, 1991), which has shown to be a reliable and valid intelligence test for children in the age of 6 to 16 years old. Because two children were under the age of six when they had their most recent IQ assessment, they underwent an alternative intelligence test. One child was assessed by the Revisie Amsterdamse Kinderintelligentie Test (RAKIT; Bleichrodt, Drenth, Zaal, & Resing, 1987) and the other child was assessed by the third edition of the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III; Wechsler, 2002). Finally, five children were assessed by the non-verbal intelligence test Snijders-Oomen Niet verbale Intelligentietest (SON-R 2.5-7; Tellegen, Winkel, Wijnberg-Williams, & Laros, 1998).

Analysis

First, the prevalence of anxiety symptoms in the participating children with ASD was assessed. Descriptive statistics (means and standard deviations) were retrieved from child and parent-rated SCAS total anxiety and SCAS subscales of generalized anxiety, specific phobia, social phobia, separation anxiety and panic disorder/agoraphobia. To assess the prevalence of elevated anxiety symptoms, the cut-offs for subclinical anxiety scores were used. Using the Dutch norm data of the SCAS-C (Muris, Schmidt, & Merkelbach, 2000) and the Dutch-Australian norm data of the SCAS-P (Nauta et al., 2004), a subclinical score on total anxiety and all subscales was defined by a score of > *m* + 1 *sd* on the SCAS-C/P. The norms for the SCAS-P were based on the means and standard deviations for the 'normal control children' (separately for boys and girls) in the age of 6-11 (for the children of 8-11) and 12-18 (for the children of 12-15) that were

reported in the study of Nauta and colleagues (2004). The norms for the SCAS-C were based on the means and standard deviations for boys and girls in the age of 7-12 (for the children of 8-12) and 13-19 (for the children of 13-15) that were reported in the study of Muris and colleagues (2000).

Second, two series of path analyses were performed using Mplus version 7.2 (Muthén & Muthén, 1998-2012) to examine the relationship between potential risk factors and anxiety symptoms of the participating children as reported by the children (series 1) and as reported by their parents (series 2). For both series path analyses were applied with risk factors (gender, age, verbal IQ, performance IQ, ASD-subtypes) as predictors and anxiety symptoms as dependent variables. By using this type of analysis, predictors were free to correlate. The advantage of path analysis above regression analysis was that all available information of the data was used. To estimate the parameters of the path model, the Bayes estimator was applied based on Markov Chain Monte Carlo (MCMC)-estimation using diffuse (non-informative) prior probability distributions as default. The Bayesian estimation was used, because the more traditional estimation method (Maximum Likelihood) failed due to model identification issues (Zyphur & Oswald, 2015). The fit of the model was evaluated by posterior predictive checking expressed in Posterior Predictive P-values (*PPP*). *PPP*-values of .50 implied good model fit, small *PPP*-values (e.g., < .05) implied poor model fit (Muthén & Asparouhov, 2012; Zyphur & Oswald, 2015). Standardized posterior regression coefficients were reported with Bayesian *p*-values if $p < .05$.

The composition of ASD-subtypes consisted of three categories: PDD-NOS, Asperger Disorder and Autistic Disorder. Effects of the three groups on anxiety symptoms and disorders were examined using unweighted effects coding (Cohen et al., 2003). Two codes represented the three groups PDD-NOS, Asperger Disorder and Autistic Disorder; one coded 1, 0, -1 and the second 0, 1, -1. Regression weights represented the deviation of the outcome variable for each separate group from the grand mean. Only the effects of PDD-NOS and Asperger Disorder were visible in the output. To determine the effect of Autistic Disorder on anxiety symptoms and disorders, a second path analysis was conducted with a different coding system (-1, 1, 0 and -1, 0, 1) (Cohen et al., 2003).

Effects of missing data

Because 31 children did not undergo an intelligence test (18.0% of 172), logistic regression analyses were conducted in SPSS 21 (IBM Corp., 2012) to examine attrition effects for sex and age. For the analyses on the effect of risk factors on anxiety symptoms (SCAS-C/P), attrition on VIQ and PIQ was the dependent binary variable.

No differences in attrition were found for both sex (OR = 0.78, 95% CI [0.29, 2.06], $p = 0.61$) and age (OR = 1.10, 95% CI [0.91, 1.33], $p = 0.33$).

RESULTS

Prevalence of anxiety symptoms

Table 1 shows the means and standard deviations of the total and subscale SCAS scores of the parents (SCAS-P) and children (SCAS-C). Table 2 shows the counts and percentages of children with at least subclinical anxiety symptoms according to parent and child assessment. In total, 66.3% of the participating children with ASD had child-rated subclinical or clinical anxiety symptoms on the total scale and/or on at least one subscale and 81.4% of the participating children with ASD had parent-rated subclinical or clinical anxiety symptoms on the total scale and/or on at least one subscale. It showed that for all anxiety disorders, more than 30% of the participating children with ASD experienced at least subclinical anxiety symptoms according to assessments of both parents and children. The parent assessment showed that for total anxiety and panic disorder/agoraphobia, more than 50% of the participating children with ASD experienced at least subclinical anxiety symptoms.

To assess whether the difference in number of children with at least subclinical anxiety between the parent and child ratings was significant, the McNemar test for related proportions ($\chi^2(1)$) was conducted (see Table 2). The number of children with parent-rated subclinical total anxiety ($p < 0.001$), separation anxiety ($p = 0.006$), panic disorder/agoraphobia ($p < 0.001$) and generalized anxiety ($p < 0.001$) was significantly higher than the number of children with child-rated subclinical anxiety on these anxiety scales. Parent and child ratings did not significantly differ in the number of children with subclinical social phobia and specific phobia ($p > 0.05$).

Table 1

Means and Standard Deviations of the Total and Subscale Scores of Children (SCAS-C) and Parents (SCAS-P)

	Children (n = 168) *M (SD)*	Parents (n = 172) *M (SD)*
Total anxiety	29.03 (18.47)	29.07 (14.61)
Separation anxiety	4.37 (3.90)	5.18 (3.62)
Social phobia	5.76 (3.92)	6.79 (3.74)
Panic disorder/Agoraphobia	4.37 (4.55)	4.05 (3.42)
Specific phobia	4.20 (2.88)	4.63 (2.94)
Generalized anxiety	5.39 (3.65)	4.65 (2.61)

Note. N = Number; *M* = Means; *SD* = Standard Deviations.

Table 2

Counts, Percentages and $\chi^2(1)$-values of Children with At Least Subclinical Anxiety Symptoms According to Parent and Child Assessment

	Children (n = 168) *n (%)*	Parents (n = 168) *n (%)*	$\chi^2(1)$-value
Total anxiety	67 (39.9)	104 (61.9)	22.74***
Separation anxiety	60 (35.7)	80 (47.6)	7.52**
Social phobia	79 (47.0)	78 (46.4)	0.00
Panic disorder/Agoraphobia	55 (32.7)	94 (56.0)	22.22***
Specific phobia	62 (36.9)	71 (42.3)	1.42
Generalized anxiety	54 (32.1)	82 (48.8)	13.50***

Note. N = Number; *%* = Percentage.
* $p \leq .05$. ** $p \leq .01$. *** $p \leq .001$.

Risk factors for anxiety symptoms of children with ASD

For child-rated anxiety symptoms and parent-rated child anxiety symptoms path analyses were conducted using the Bayes estimator. Each of the 18 path models show a fit with *PPP*-values varying between .433 to .438, which implied a good fit (Zyphur & Oswald, 2015).

Age and gender

The path analyses results for child-rated anxiety symptoms are shown in Table 3. Girls with ASD had significantly more total anxiety symptoms than boys with ASD (β = .23,

$p < .01$). Moreover, girls with ASD had significantly more separation anxiety symptoms ($\beta = .13$, $p < .05$), social phobia symptoms ($\beta = .23$, $p < .01$), panic disorder/agoraphobia symptoms ($\beta = .30$, $p < .001$) and generalized anxiety symptoms ($\beta = .19$, $p < .01$) than boys with ASD. Gender was not a significant predictor of specific phobia symptoms.

Concerning the predictor age, younger children with ASD had significantly more child-rated total anxiety symptoms than older children with ASD ($\beta = -.14$, $p < .05$). Also, younger children with ASD had significantly more separation anxiety symptoms ($\beta = -.32$, $p < .001$) than older children with ASD. Age was not a significant predictor of social phobia symptoms, specific phobia symptoms, panic disorder/agoraphobia symptoms and generalized anxiety symptoms.

In Table 4 the path analyses results for parent-rated child anxiety symptoms are shown. Girls with ASD had significantly more total anxiety symptoms than boys with ASD ($\beta = .17$, $p = .01$). Moreover, girls with ASD had significantly more social phobia symptoms ($\beta = .21$, $p < .01$), panic disorder/agoraphobia symptoms ($\beta = .22$, $p < .01$) and generalized anxiety symptoms ($\beta = .22$, $p < .01$) than boys with ASD. Gender was not a significant predictor of separation anxiety symptoms and specific phobia symptoms.

Concerning the predictor age, younger children with ASD had significantly more parent-rated separation anxiety symptoms ($\beta = -.27$, $p < .001$) and specific phobia symptoms ($\beta = -.15$, $p < .05$) than older children with ASD. Age was not a significant predictor of total anxiety, social phobia symptoms, panic disorder/agoraphobia symptoms and generalized anxiety symptoms.

IQ

Children with a lower VIQ had significantly more child-rated specific phobia symptoms than children with a higher VIQ ($\beta = -.22$, $p < .05$) and children with a higher PIQ had significantly more specific phobia symptoms than children with a lower PIQ ($\beta = .20$, $p < .05$; see Table 3). VIQ and PIQ were not found to be significant predictors of all other child-rated subscale anxiety symptoms. According to parents, VIQ and PIQ were not significant predictors of all parent-rated total and subscale anxiety symptoms (see Table 4).

ASD subtypes

For child-rated anxiety, none of the three ASD subtypes were significant predictors of all child-rated total and subscale anxiety symptoms (see Table 3). For parent-rated anxiety, children with PDD-NOS had significantly less panic disorder/agoraphobia symptoms ($\beta = -.16$, $p < .05$) compared to the overall mean of this variable (see Table 4). Moreover, children with Asperger Disorder had significantly less social phobia symptoms ($\beta = -.20$, $p = .01$) compared to the overall mean of this variable. Children

with Autistic Disorder had significantly more total anxiety symptoms (β = .28, $p < .01$), more social phobia symptoms (β = .22, $p < .05$), more specific phobia symptoms (β = .25, $p < .05$) and more panic disorder/agoraphobia symptoms (β = .27, $p = .01$) compared to the overall means of these variables.

Table 3

Path Analyses with Age, Gender, IQ (VIQ, PIQ) and ASD-subtype (Autistic Disorder, Asperger Disorder, PDD-NOS) as Predictors and Child-rated Symptoms of Total Anxiety, Separation Anxiety, Social Phobia, Panic Disorder/Agoraphobia, Specific Phobia and Generalized Anxiety as Dependent Variables

	Total Anxiety	*Separation Anxiety*	*Social Phobia*	*Specific Phobia*	*Panic/ Agora Phobia*	*Generalized Anxiety*
	Beta	*Beta*	*Beta*	*Beta*	*Beta*	*Beta*
Gender	.23**	.13*	.23**	.10	.30***	.19**
Age	-.14*	-.32***	.06	-.08	-.10	-.05
VIQ	-.07	-.14	.02	-.22*	.01	.07
PIQ	.07	.08	.01	.20*	-.00	-.02
PDD-NOS	-.01	-.02	.06	-.10	.05	.04
AS	.07	.04	.03	.03	.10	.07
AD	-.08	-.03	-.10	.06	-.19	-.13

*Note. Beta's are standardized regression weights. AS = Asperger Disorder; AD = Autistic Disorder. * $p \leq .05$. ** $p \leq .01$. *** $p \leq .001$.*

Table 4

Path Analyses with Age, Gender, IQ (VIQ, PIQ) and ASD-subtype (Autistic Disorder, Asperger Disorder, PDD-NOS) as Predictors and Parent-rated Symptoms of Total Anxiety, Separation Anxiety, Social Phobia, Panic Disorder/Agoraphobia, Specific Phobia and Generalized Anxiety as Dependent Variables

	Total Anxiety	*Separation Anxiety*	*Social Phobia*	*Specific Phobia*	*Panic/ Agora Phobia*	*Generalized Anxiety*
	Beta	*Beta*	*Beta*	*Beta*	*Beta*	*Beta*
Gender	.17**	.06	.21**	-.01	.22**	.22**
Age	-.09	-.27***	.10	-.15*	-.03	-.06
VIQ	-.02	.01	.05	-.07	-.08	-.04
PIQ	.14	.12	.07	.14	.15	.14
PDD-NOS	-.09	-.04	.04	-.11	-.16*	-.06
AS	-.15	-.05	-.20**	-.10	-.08	-.09
AD	.28**	.10	.22*	.25*	.27**	.17

*Note. Beta's are standardized regression weights. AS = Asperger Disorder; AD = Autistic Disorder. * $p \leq .05$. ** $p \leq .01$. *** $p \leq .001$.*

DISCUSSION

The first aim of the present study was to provide an overview of the prevalence of anxiety symptoms in a clinical Dutch sample of children with ASD. The findings showed that the prevalence of both parent-rated and child-rated subclinical and clinical anxiety symptoms was high: more than 60% of the participating children with ASD had at least subclinical anxiety symptoms according to children and more than 80% of the children had at least subclinical anxiety symptoms according to parents. Parents reported higher total anxiety, separation anxiety, panic disorder/ agoraphobia and generalized anxiety than children. The results of the present study provide new knowledge on the field of anxiety in children with ASD, because child-rated anxiety levels were measured and these levels were compared with parent-rated anxiety levels, while in the majority of the previous studies on anxiety in children with ASD (e.g. Gotham et al., 2013; Strang et al., 2012; Vasa et al., 2013), only parent-rated anxiety levels were measured. Moreover, there are hardly any studies that examined anxiety levels in children with ASD in Dutch children with ASD (e.g. Muris et al., 1998) and most studies included large community samples of children with ASD with all levels of impairment (e.g. Gotham et al., 2013), while in the present study a specific clinical sample children with ASD was included who had a high level of daily impairment and who received intensive treatment at a mental health institute.

The child-rated prevalence of anxiety (66.3%) that was found in the present study was only slightly higher than the prevalence rates in the study of Strang and colleagues (2012) and Vasa and colleagues (2013). They found that respectively 56% (Strang et al., 2012), 52% (school children; Vasa et al., 2013) and 54% (adolescents; Vasa et al., 2013) of the children with ASD had at least subclinical anxiety symptoms. However, other studies found that only respectively 22% (Lecavalier, 2006) and 46% (Gotham et al., 2013) of the children with ASD had at least subclinical anxiety symptoms. Moreover, the parent-rated prevalence (81.4%) of anxiety that was found in the present study was higher than the prevalence rates that were found in all the above described studies (Gotham et al., 2013; Lecavalier, 2006; Strang et al., 2012; Vasa et al., 2013).

There are several possible explanations for the relatively high prevalence rates in the present study. The prevalence rates of anxiety may differ as a result of the differences in levels of cognitive functioning between the participants included in the studies. The participating children in the study of Gotham and colleagues (2013) had for example a mean verbal IQ of 80 and a mean non-verbal IQ of 86. The children that participated in the present study had a relatively high mean verbal and non-verbal IQ of respectively 105 and 98, and higher IQ has shown to be related to higher levels of anxiety (e.g. Dubin et al., 2015; Salazar et al., 2015).

Moreover, it is possible that the differences in prevalence rates are due to the use of different cut-offs for anxiety symptoms. Strang and colleagues (2012) for example reported prevalence rates of subclinical anxiety on basis of a borderline score on a general anxiety scale of a questionnaire, while in the present study subclinical anxiety was defined as a subclinical score on the total scale and/or on at least one subscale of the SCAS-C/P. When the prevalence rates of subclinical anxiety were only based on the total SCAS scale, 43.3% of the children had child-rated and 63.4% of the children had parent-rated subclinical anxiety symptoms in the present study. These percentages are more comparable to those that were found in other studies (Gotham et al., 2013; Strang et al., 2012; Vasa et al., 2013).

It is also possible that the difference in cultural background of the participants in the present study and previous studies could be an explanation for the differences in outcomes. Several studies showed that SCAS-based anxiety scores differ among different cultures and countries (Li, Delvecchio, Di Riso, Nie, & Lis, 2016; Essau, Sasagawa, Anastassiou-Hadjicharalambous, Guzman, & Ollendick, 2011). Since previous studies predominantly or entirely included American participants and mostly used American norm data (e.g. Gotham et al., 2013) and the present study included only Dutch participants and used Dutch norm data (SCAS-C) and Dutch-Australian norm data (SCAS-P), it is possible that the difference in origin and cultural background partly explained the difference in reported prevalence of anxiety in children with ASD.

Finally, anxiety levels may differ as a result of the differences in sample specificity. The study with lower prevalence rates of anxiety (Gotham et al., 2013) included a large community sample of children with ASD, with anxiety levels that may not have reached clinical significance in all children. The present study included a clinical Dutch sample with ASD children, who received treatment at a mental health institute because of the high daily impairment that in most cases was (partly) caused by the presence of high anxiety levels.

The higher parent ratings compared to the child ratings of anxiety could be explained by the family problems that were highly prevalent in the present study. These problems could lead to less agreement between parents and children in their report of anxiety. Parents with conflicts, stress or psychiatric symptoms may project their own problems on their children, leading to a parental overreport of anxiety symptoms (Kroes, Veerman, & De Bruyn, 2003). These discrepancies suggest that it is important to use both child and parent report in studies on children with ASD.

The second aim was to investigate the risk factors for anxiety in this sample of children with ASD. More specifically, age, gender, ASD subtype and IQ were investigated as risk factors for anxiety in children with ASD. Parent-rated total anxiety symptoms were more prevalent among younger than among older children with

ASD. This finding contradicts previous studies that have shown that anxiety increases with age in the ASD population (e.g. (Davis et al., 2011a; Dickerson et al., 2011). The findings in the present study are more in line with research in the normal population showing that most anxiety disorders decrease with age, because childhood anxiety may lead to other psychopathology in adolescence, for example depression (Seligman & Ollendick, 1998). This similarity to the findings in the normal population may be due to the relatively high cognitive levels of the participating children compared to other studies in the ASD population (e.g. Van Steensel et al., 2011), which may be related to a course of psychopathology levels over time that is also present in the normal population (Davis et al., 2011a). When examining the findings on age differences in the prevalence of separation anxiety and specific phobia symptoms in children with ASD, it can be concluded that these findings are also in line with previous research in the normal population. This research indicated early childhood as a risk period for separation anxiety and specific phobia and showed a decrease in prevalence from early childhood to mid adolescence (Breton et al., 1999; Kashani & Orvaschel, 1990).

Concerning the differential prevalence rates of anxiety for boys and girls with ASD, girls with ASD had more anxiety than boys with ASD. This finding was not in line with previous research showing that there are no gender differences in anxiety between boys and girls with ASD (e.g. Sukhodolsky et al., 2009; Vasa et al., 2013; Worley et al., 2010). However, the finding that girls with ASD are more anxious than boys with ASD is consistent with research on gender differences in anxiety in the normal population (Lewinsohn et al., 1998). Again, this may be explained by the relatively high cognitive levels of the ASD sample in the present study compared to other studies (e.g. Van Steensel et al., 2011), leading to the same neuropsychological basis of gender differences in anxiety as in the normal population (Brereton et al., 2006). Moreover, the higher prevalence of anxiety in girls in the present study could be explained by the higher acceptability of female anxiety by parents (McLean & Anderson, 2009), which may have led to underreport of clinical anxiety in boys by parents. Moreover, having ASD is related to higher stress levels (Gillott & Standen, 2007), which in turn leads to a more profound expression of personality traits in terms of coping strategies. Anxiety-related personality traits (e.g. neuroticism) are more prevalent among girls than among boys (McLean & Anderson, 2009), which suggests that girls with ASD show more anxious behavior and coping strategies than boys with ASD.

The finding that ASD children with a higher PIQ and lower VIQ had more child-rated specific phobia symptoms is inconsistent with research showing that deficits in both receptive and expressive communication skills are related to less anxiety symptoms in children with ASD (Davis et al., 2012), but is consistent with the finding that children with PDD-NOS had higher anxiety levels as communication deficits increased (Davis et al.,

2011b). There is some evidence that specific fears related to particular people, animals or situations could be reduced by verbalization of feelings (Tabibnia, Lieberman, & Craske, 2008), which may prevent the development of this kind of anxiety into a full specific phobia. ASD children with a higher PIQ and lower VIQ may have difficulty with verbalizing their feelings, explaining why they experience more symptoms of specific phobia. Other anxiety disorders may be more complex in nature, which may have led to a smaller, non-significant impact of these verbalization skills on the presence of these anxiety disorders.

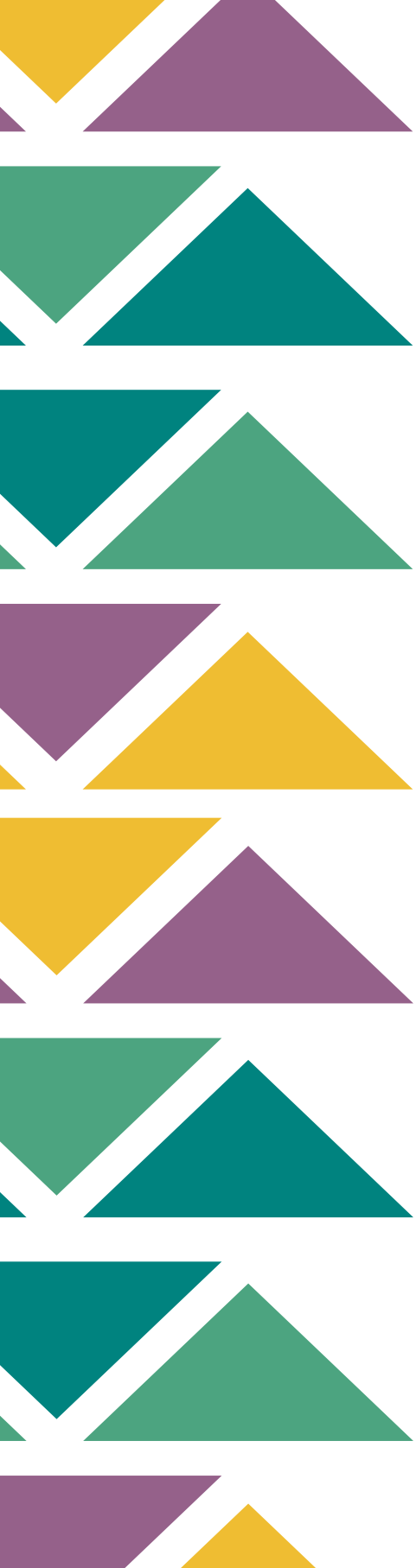
On one hand, the finding that parent-rated anxiety is more prevalent in children with Autistic Disorder than in children with Asperger Disorder and PDD-NOS contradicts some previous studies (e.g. Gadow et al., 2005; Weisbrot et al., 2005; White et al., 2009), but on the other hand this finding is more or less in line with other studies (e.g. Dickerson Mayes et al., 2011; Van Steensel et al., 2011). A possible explanation for the inconsistent findings on ASD-subtype as risk factor for anxiety is the limited validity in how ASD-subtypes are assigned in the DSM-IV, with similar core symptom presentations across subtypes (Grzadzinski, Huerta, & Lord, 2013). This limited specificity of subtypes may have led to the variation in anxiety levels in children with different ASD-subtypes between the existing studies. The low validity of the ASD-subtypes in the DSM-IV was the rationale for moving to a categorical system in the new DSM-V with a single diagnostic dimension: severity of ASD-symptoms (APA, 2013).

There are some limitations in the present study. The intelligence levels of the participating children were not always known, leading to a considerably smaller number of children that could be included in this part of the analyses. Despite the estimations of the missing values that were made in the analyses, these missing values could have lowered the reliability of the statistical results. Moreover, the questionnaires (SCAS-C/P) in the present study were not specially designed for children with ASD (White et al., 2009). Also, it is possible that the SCAS did not purely measure anxiety symptoms, but also impairments that are part of the core ASD symptoms (e.g. social withdrawal as a consequence of high arousal). As a consequence, the participating children with ASD may not have accurately reported their anxiety symptoms. In their review on the use of anxiety assessment tools in children with ASD, Grondhuis and Aman (2012) reported that the lack of psychometric characteristics for the ASD population of the SCAS may lead to an unreliable assessment of anxiety. However, they also state that the SCAS might be useful for ASD children who are higher functioning and who have moderate language and cognitive abilities (Grondhuis & Aman, 2012), which are characteristics that are applicable to the participating children in the present study. Moreover, it is possible that not only the presence of an autism spectrum disorder was related to the high level of anxiety symptoms in the present study, but also other comorbid disorders

like attention-deficit hyperactivity disorder, which has also shown to be highly related to anxiety in children (e.g. Jarrett, Wolff, Davis, Cowart, & Ollendick, 2016). Finally, the lack of a comparison group and the use of norms could possibly have biased the outcomes in the present study.

One clear message from this study is the high extent to which anxiety problems co-occur with ASD in a clinical sample of children. When children with ASD are referred to a mental health institute, they often have subclinical or clinical levels of anxiety. However, what we do not yet know is the developmental sequelae of these disorders and the impact each has on the other over time. Future research using longitudinal designs to investigate the mechanisms responsible for the development of anxiety in children with ASD seems warranted. Moreover, it is important to investigate the reliability and validity of the new ASD classifications in the DSM-V and the predictive validity of anxiety questionnaires in the population of children with ASD, because this may lead to less sample and methodological heterogeneity. These suggested future studies could eventually lead to a more extensive, more valid and more reliable explanatory framework for the development of anxiety in children with ASD.

The present study has some implications for clinical practice. The findings suggest that children with ASD have a high risk to have co-occurring anxiety symptoms. Especially girls and younger children with ASD may be at risk to develop anxiety. Therefore, early prevention of anxiety in children with ASD who are most at risk is important. On basis of the results in the present study, it seems especially important to offer an anxiety prevention program to young girls (e.g. in the age of 4-8) with ASD. Moreover, the present study showed that a considerable number of children with ASD already met the criteria of one or more anxiety disorders. Currently, anxiety is often interpreted as a part of the ASD in clinical practice, which may lead to an under-reporting and thus lack of treatment for anxiety as a separate condition ('diagnostic overshadowing'; Simonoff et al., 2008). When anxiety in children with ASD is treated, this may also lead to a decrease in impairment caused by the core ASD symptoms (White et al., 2009). Thus, attention has to be paid to the assessment of the presence of anxiety disorders when children with ASD are referred to or receive mental health care. When children with ASD meet the criteria for one or more anxiety disorders, it is important that they receive treatment for their anxiety symptoms that is adapted to their capacities and difficulties.



CHAPTER 3

Prevalence of Comorbid Depressive Symptoms and Suicidal Ideation in Children with an Autism Spectrum Disorder and Elevated Anxiety

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Wijnhoven, L. A. M. W., Niels-Kessels, H., Creemers, D. H. M., Vermulst, A. A., Otten, R., & Engels, R. C. M. E. (2019). Prevalence of comorbid depressive symptoms and suicidal ideation in children with autism spectrum disorder and elevated anxiety symptoms. *Journal of Child & Adolescent Mental Health, 31*(1), 77-84. doi:10.2989/17280583.2019.1608830.

ABSTRACT

Children with autism spectrum disorder (ASD) often have comorbid depressive symptoms and suicidal ideation. The aim of the present study was to examine levels of depressive symptoms and suicidal ideation in a sample of children with ASD, normal cognitive functioning and elevated anxiety. In total, 93 children with ASD of 8-16 years old with normal cognitive functioning and (sub)clinical anxiety symptoms participated in the present study. Both parents and children filled in questionnaires to measure the level of depressive symptoms. Moreover, children reported their level of suicidal ideation. More than 35% of the children with ASD reported clinical levels of depressive symptoms, while according to parents even more than 75% of these children showed clinical levels of depressive symptoms. Girls reported significantly higher levels of depressive symptoms than boys. Moreover, 32.2% of the children with ASD and anxiety had suicidal thoughts and 2.2% of the children showed active suicidal ideation. No gender differences were found in suicidal ideation. The findings indicated that children with ASD, normal cognitive functioning and anxiety symptoms have an increased prevalence of clinical depressive symptoms and suicidal ideation. Therefore, depressive symptoms and suicidal ideation should be assessed when working with anxious children with ASD.

INTRODUCTION

It is well-established that anxiety symptoms are highly prevalent in children with autism spectrum disorder (ASD, e.g., Wijnhoven, Creemers, Vermulst, & Granic, 2018). Moreover, similar to the general population of children, anxiety is highly correlated with depressive symptoms in children with ASD (Vasa, et al., 2013). Therefore, children with ASD and elevated anxiety often have comorbid depressive symptoms (Ung et al., 2013). Furthermore, thoughts about committing suicide, one of the co-occurring symptoms of depression, also appear to be common in children with ASD (Hooijer & Sizoo, 2016). Particularly children with ASD and normal cognitive functioning are at risk to develop elevated anxiety and comorbid depressive symptoms and suicidal ideation (De-la-Iglesia & Olivar, 2015). However, there is little knowledge about the prevalence of depressive symptoms and suicidal ideation in children with ASD, normal cognitive functioning and elevated anxiety. Therefore, the aim of the present study was to examine levels of depressive symptoms and suicidal ideation in a sample of children with ASD, normal cognitive functioning and elevated anxiety.

The reported prevalence of depressive symptoms and suicidal ideation in children with ASD is higher than in the general child population (Mayes, Calhoun, Murray, Ahuja & Smith, 2011a; Hooijer & Sizoo, 2016). However, prevalence rates strongly differ in existing studies, with rates of depressive symptoms in children with ASD varying from 1.4% (Simonoff et al., 2008) to 72% (Mayes, Calhoun, Murray, & Zahid, 2011b) and rates of suicidal ideation varying between 11% (Storch et al., 2013) and 42% (Mukaddes & Fateh, 2010). The wide variation in prevalence rates may be due to heterogeneity in the selected research population in the existing studies, with varying levels of cognitive functioning and comorbid psychiatric problems of the participating children with ASD (e.g., Mayes et al., 2011a; Mayes et al., 2011b; Brereton, Tonge, & Einfeld, 2006; Simonoff et al., 2008).

In a recent study in children with ASD and anxiety symptoms, 13% of the children met the criteria for a major depressive disorder or dysthymia (Ung et al., 2013). Also, children with ASD and high levels of anxiety showed more suicidal ideation (29-40%; Mukaddes & Fateh, 2010; Demirkaya et al., 2016) than children with ASD and lower levels of anxiety (13.8%; Mayes, Gorman, Hillwig-Garcia, & Syed, 2013). Furthermore, it was shown that children with higher cognitive functioning were more aware of the (social) disabilities that come along with their ASD than children with ASD and cognitive impairments (De-la-Iglesia & Olivar, 2015; Mayes et al., 2011b) and that they were more likely to experience higher social demands they are unable to meet (De-la-Iglesia & Olivar, 2015). This puts children with ASD and higher cognitive functioning at risk for developing (social) anxiety symptoms (De-la-Iglesia & Olivar, 2015), which in turn makes them vulnerable to develop depressive symptoms (Brereton et al., 2006; De-la-Iglesia

& Olivar, 2015; Mayes 2011b; Sterling, Dawson, Estes, & Greenson, 2008) and suicidal ideation (Hannon & Taylor, 2013; Storch et al., 2013). Previous studies showed no gender differences in depressive symptoms and suicidal ideation in children with ASD and higher cognitive functioning (Hurtig et al., 2009; Hannon & Taylor, 2013).

In sum, it can be concluded that children with ASD, normal cognitive functioning and elevated anxiety symptoms have a high risk to develop depressive symptoms and suicidal ideation (De-la-Iglesia & Olivar, 2015; Mayes et al., 2011b; Hannon & Taylor, 2013). However, research has shown that it can be difficult to diagnose depression inchildren with ASD and normal cognitive functioning, because of difficulties in verbal (face-to-face) communication about feelings (Ghaziuddin, Ghaziuddin, & Greden, 2002). Moreover, symptoms of ASD can mask some core features of depression, for example when children with ASD show 'dark' obsessions or rituals (Ghaziuddin et al., 2002; Magnuson & Constantino, 2011). As a result, depression in children with ASD may be underreported in previous studies using verbal reports of depression (e.g., a clinical interview; Ghaziuddin et al., 2002). Since children with ASD and normal cognitive functioning have shown to be able to accurately report their anxious and depressed cognitions in a questionnaire (Ozsivadjian, Hibbert, & Hollocks, 2014; De-la-Iglesia & Olivar, 2015), self-reports can add valuable and reliable information about the prevalence of depressive symptoms and suicidal ideation in children with ASD, leading to less underreport. However, little is known about the specific self-reported prevalence rates of depressive symptoms and suicidal ideation in children with ASD, normal cognitive functioning and elevated anxiety.

Therefore, the aim of the present study was to examine prevalence rates of depressive symptoms and suicidal ideation in children with ASD, normal cognitive functioning and elevated anxiety symptoms using self-reports and parent-reports. In addition, gender differences in depressive symptoms were tested. We aimed to contribute to the existing literature on depression and suicidal ideation in the population of children with ASD by investigating depressive symptoms and suicidal ideation in a specific understudied ASD-sample, and by using both self- and parent reports.

METHODS

Procedure

The study utilized data collected as part of a Randomized Controlled Trial (RCT) testing the effectiveness of an intervention tailored to decrease anxiety symptoms in children with ASD (see study protocol: Wijnhoven, Creemers, Engels, & Granic, 2015). The RCT was carried out in accordance with the ethical standards of the medical ethics committee CMO Arnhem-Nijmegen in the Netherlands (NL50023.091.14) and

the Declaration of Helsinki. Data were collected in two mental health institutes and one secondary school for special education. Children with ASD in the age of 8-15 were screened for anxiety symptoms with the Spence Children's Anxiety Scale for children (SCAS-C; Scholing, Nauta, & Spence, 1999a) and parents (SCAS-P; Scholing, Nauta, & Spence, 1999b). They were eligible for participation in the RCT when parents and/ or children reported at least subclinical levels of anxiety on the SCAS-C/P. Exclusion criterion was the presence of severe psychiatric problems that needed immediate treatment. When active informed consent was obtained from parents and children above the age of 12 for participation in the RCT, children and their parents filled in a pretest, including the SCAS-C/P and a questionnaire for depressive symptoms (Child Depression Inventory, CDI-2(:P); Kovacs, Braet, & Stikkelbroek, 2016). All children and parents that filled in a pretest were included in the present study. In total, 90 children with anxiety symptoms and 93 parents filled in the CDI-2 at pretest.

Participants

Of the sample, 71 were male (76,3%) and 22 were female (23,7 %). Participants were between 8 to 15 years old (M = 11,15 SD = 1,98). ASD diagnoses were based on assessment by a qualified psychologist or psychiatrist of the Diagnostic and Statistical Manual of Mental Disorders 4th Edition – Text Revision (DSM-IV-TR; American Psychiatric Association, 2000) criteria for Autistic Disorder (9.7%), Asperger's Disorder (18.3%) or PDD-NOS (72%). This assessment was carried out by a clinical expert who conducted a diagnostic assessment that was adapted to the diagnostic 'needs' of the individual child and for example consisted of a developmental anamnesis with parents and/or standardized observation of the child with the Autism Diagnostic Observation Scale (ADOS; Bildt, Greaves-Lord, & De Jonge, 2013). With the introduction of the DSM-5 (American Psychiatric Association, 2013), all diagnoses were transformed into the DSM-5 diagnosis Autism Spectrum Disorder. Of the participating children, 75 children underwent an intelligence test (third edition of the Wechsler Intelligence Scale for Children, WISC-III; Wechsler, 1991) at the mental health institute where they were treated. Mean total IQ was M= 102.16 (SD 18.14), indicating normal cognitive functioning. Sixty children were in primary school (64.6%), 31 were in secondary school (34.4%). Of those in primary school, 19 followed special education (31.7%) because of ASD-related impairments such as overarousal and social problems. Of the children in secondary school, 21 followed special education (67.7%). Most of the children were of Dutch origin (90,3%).

Instruments

Depressive symptoms were measured using the Dutch translation of the CDI-2 (Kovacs et al., 2016). The CDI-2 consists of 28 items measured on a 3-point scale ranging from 0 (depressive symptom is absent) to 2 (depressive symptom is always present). The child version of the Dutch CDI-2 has good psychometric qualities (Kovacs et al., 2016). The cut-off score is 14; a total score of 14 or higher means that the child has clinical levels of depressive symptoms, a strong indication for the presence of a depressive disorder (Kovacs et al., 2016). Cronbach's alpha was .84.

Depressive symptoms according to the parents were measured with the Dutch translation of the CDI-2:P (Kovacs et al., 2016). The CDI-2:P consists of 17 items measured on a 4-point scale ranging from 0 (not at all) to 3 (almost always). The parent version of the Dutch CDI-2 has good reliability, internal consistency and a good convergent validity (Kovacs et al., 2016). The divergent validity is low. The cut-off score is 16; a total score of 16 or higher means that the child has clinical depressive symptoms, a strong indication for the presence of a depressive disorder. Cronbach's alpha was .73.

Current suicidal ideation of the children was measured by item 8 of the CDI-2, with the answer options 'I do not think about killing myself' (0; no suicidal ideation), 'I think about killing myself but would not do it' (1; suicidal thoughts but no intention for suicidal behavior) and 'I want to kill myself' (2; suicidal thoughts and risk of suicidal behavior).

Analyses

First, the prevalence of depressive symptoms and current suicidal ideation was assessed using descriptive statistics. Second, T-tests for independent groups in SPSS 21 (IBM Corp., 2012) were used to test differences (significance threshold $p \leq .05$) between boys and girls in parent-rated and child-rated depressive symptoms (total score on CDI-2 and CDI-2:P). A parametric t-test was used to compare the level of depressive symptoms, because this was measured on a continuous scale (total CDI-score). Fisher's Exact Test was used to test the difference between the number of boys and girls that had a child-rated and parent-rated CDI-2-score above the cut-off. McNemar test for related proportions ($\chi^2(1)$) was used to test the difference between the number of children and parents with a CDI-2-score above the cut-off. Finally, the Fisher's Exact Test was conducted to test the difference between boys and girls in score 1 (suicidal thoughts but no intention for suicidal behavior) and 2 (suicidal thoughts and risk of suicidal behavior) on item 8 of the CDI-2 about current suicidal ideation. Non-parametric tests were used for these comparisons of two proportions (number of boys/girls and parents/children), because a parametric t-test is not suitable for statistically comparing two proportions.

RESULTS

Depressive symptoms

Table 1 shows the descriptives of the total CDI-2-scores for parents (CDI-2:P), children (CDI-2) and for boys and girls separately. Table 2 shows the counts and percentages of children with clinical depressive symptoms according to parent- and child-report. Girls with ASD and anxiety showed significantly more child-rated depressive symptoms than boys (see Table 1). However, crosstabs analysis showed that there is no significant difference between boys and girls in the percentage of children with clinical child-rated depressive symptoms (CDI-score $\geq$ 14; see Table 2). Parents reported no significant difference between boys and girls in depressive symptoms (see Table 1) and in percentage of children with clinical parent-rated depressive symptoms (CDI-score $\geq$ 16, see Table 2). There was a significant difference between child-report and parent-report in percentage of children who had clinical levels of depressive symptoms (χ^2 *(1)* = 29.64, $p < .001$). The number of children with clinical parent-rated depressive symptoms was significantly higher than the number of children with clinical child-rated depressive symptoms.

Table 1

Means, Standard Deviations and T-values for Child-rated Depressive Symptoms (CDI-2) and Parent-rated Depressive Symptoms (CDI-2:P)

	Total			Boys			Girls			
	n	*M*	*(SD)*	*n*	*M*	*(SD)*	*n*	*M*	*(SD)*	*t*-value (df)
CDI-2 Total	90	12.23	(6.84)	69	11.13	(5.74)	21	15.86	(8.84)	-2.3 (88)*
CDI-2:P Total	93	19.42	(5.73)	71	18.92	(5.57)	22	21.05	(6.06)	-1.54 (91)

Note. n = number; *M* = mean; *SD* = standard deviation.
$^{*}p \leq .05$. $^{**}p \leq .01$. $^{***}p \leq .001$.

Table 2

Counts, Percentages and P-values (Fisher's Exact Test) of Children with Clinical Depressive Symptoms according to Child (CDI-2) and Parent (CDI-2:P) Assessment

	Total		Boys		Girls		
	n	Frequency (%)	*n*	Frequency (%)	*n*	Frequency (%)	*p*-value
Score CDI-2 ≥14	90	32 (35.6%)	69	21 (30.4%)	21	11 (52.3%)	.075
Score CDI-2:P ≥16	93	70 (75.3%)	71	52 (73.2%)	22	18 (81.8%)	.574

Note: n = number; *%* = percentage.
$^{*}p \leq .05$. $^{**}p \leq .01$. $^{***}p \leq .001$.

Suicidal ideation

Table 3 shows the counts and percentages of the participating children on current suicidal ideation. In total, 32.2% of the children thought about killing themselves, but would not do it and 2.2% had active suicidal intentions. There was no significant difference between the percentage boys and girls in the prevalence of current suicidal ideation (t = -1.47, p > .05). However, concerning the prevalence of active suicidal ideation, it is remarkable that the total of 2.2% of the children with active suicidal intentions were all boys.

Table 3

Counts and Percentages for the Score on Item 8 About Suicidal Ideation in the Child-rated CDI-2 (Score 0= "I do not think about killing myself", Score 1= "I think about killing myself, but would not do it", Score 2 = " I want to kill myself")

	Total (n = 90) *n (%)*		Boys (n = 69) *n (%)*		Girls (n = 21) *n (%)*	
CDI-2 item 8 score 0	59	(65.5%)	48	(69.6%)	13	(61.9%)
CDI-2 item 8 score 1	29	(32.2%)	21	(30.4%)	8	(38.1%)
CDI-2 item 8 score 2	2	(2.2%)	2	(2.9%)	0	(0%)

Note: n = number; *%* = percentage; *M* = mean; *SD* = standard deviation.

DISCUSSION

The aim of the present study was to provide insight into the prevalence rates of depressive symptoms and suicidal ideation in children with ASD, normal cognitive functioning and elevated anxiety. Findings showed that more than 35% of the children with ASD reported clinical levels of depressive symptoms, while according to parents even more than 75% of these children showed clinical levels of depressive symptoms. This indicates that the prevalence of depressive symptoms in the participating children was high, especially considering the fact that a relatively young population of children with ASD was included in the present study. Girls reported significantly higher levels of depressive symptoms than boys. Moreover, findings showed that 32.2% of the children with ASD had suicidal thoughts and 2.2% of the children showed active suicidal ideation. No gender differences were found in suicidal ideation.

The elevated levels of depressive symptoms that were found in the present study were also found in the study of Ung and colleagues (2013). However, prevalence rates of depressive symptoms were much higher than in several other studies with samples of children with ASD and without anxiety symptoms (e.g., Lopata et al., 2010; Strang

et al., 2012; Kim et al., 2000). The findings in the current study indicated that similar to the normal population of children (Brady & Kendall, 1992), anxiety and depression are highly correlated in children with ASD and normal cognitive functioning. This finding underlines the importance of clinical awareness for depressive symptoms in anxious children with ASD and normal cognitive functioning.

The higher percentage of clinical parent-rated than child-rated depressive symptoms could be explained by family problems that were highly prevalent in the present study. It has been shown that parents with marital conflicts, stress or psychiatric problems might project their own problems on their children, leading to a parental overreport of depressive symptoms (Kroes, Veerman, & De Bruyn, 2003). Alternatively, it is possible that children underreported their depressive feelings. As earlier stated, it has been shown that children with ASD and normal cognitive functioning are capable of reporting their anxious and depressed cognitions in a questionnaire (Ozsivadjian, Hibbert, & Hollocks, 2014; De-la-Iglesia & Olivar, 2015). However, the norms of the CDI-2 have not been tested in a sample with children with ASD (Kovacs, 2016). It is possible that children with ASD are only sufficiently capable of reporting their depressive symptoms in a questionnaire that has been validated in a specific ASD-sample. These hypotheses suggest that it is important to use both child and parent reports in studies on children with ASD.

In contrast to Hurtig and colleagues (2009), our study showed higher levels of depressive symptoms in girls compared to boys. This might be explained by the fact that the present study population consisted mostly of children (mean age 11), while the Hurtig-study used an adolescent sample (mean age 13). It is known that ASD in girls with average to high cognitive levels is diagnosed relatively late in life as compared to boys with high cognitive levels (Van Wijngaarden-Cremers et al., 2014). This might lead to more stressful life events in girls in childhood, because their symptoms of ASD are not yet recognized and treated. In turn, this may lead to a higher risk in girls than in boys for depressive feelings in childhood.

The level of suicidal ideation in the participating children with ASD was comparable with some studies (Demirkaya et al., 2016; Mukaddes & Fateh, 2010), but higher than in other studies (Storch et al., 2013, Mayes et al., 2013). The studies that included samples with relatively high percentages of comorbid anxiety symptoms (Mukaddes & Fateh, 2010; Demirkaya et al., 2016) found rates of suicidal ideation (respectively 54% and 44%) that were comparable to the ones found here. This might imply that a higher comorbidity of depression and anxiety symptoms increases the prevalence of suicidal ideation in children with ASD.

The absence of gender differences in suicidal ideation could be explained by the knowledge that suicidal statements might be made by some children with ASD when

they are overwhelmed by distress and incapable of regulating and coping with these feelings effectively (Brereton et al., 2006; Gillott, Furniss & Walter, 2001; Wood & Gadow, 2010). Because the emotional and communication problems are part of the core ASD symptoms in both boys and girls, the potential coping style of reacting with suicidal statements to stressful and overwhelming situations might also be equal for boys and girls with ASD.

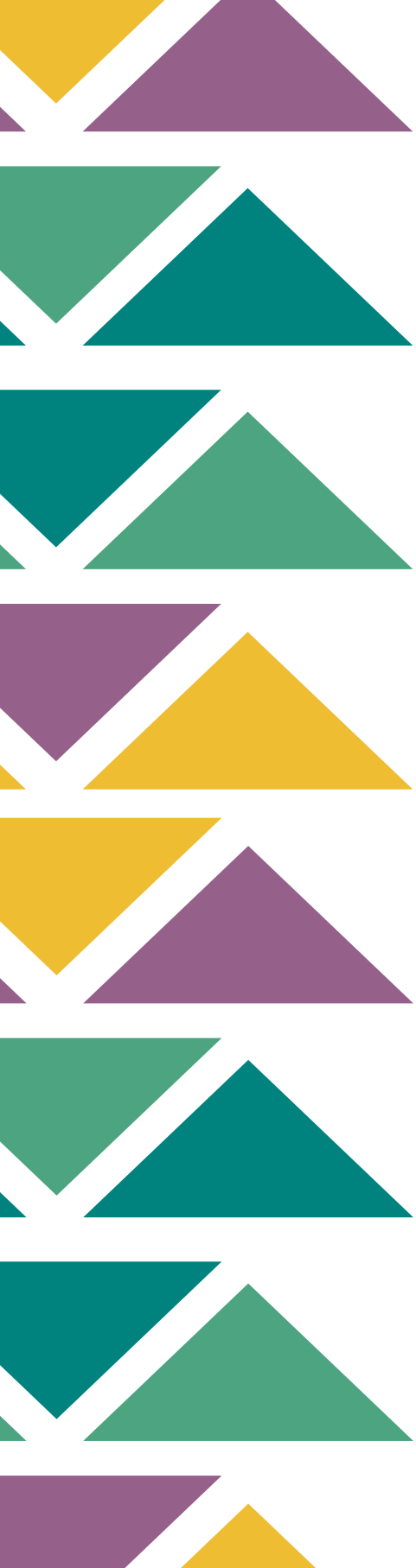
There are some limitations in the present study. First, as stated before, it is unclear whether the CDI-2 is suitable for children with ASD, as the psychometric norms of the CDI-2 have not been tested in children with ASD (Kovacs et al., 2016). Second, suicidal ideation was measured with only one item and only assessed current suicidal ideation, which might have led to an underestimation of this concept. Using a questionnaire with more items about suicidality would lead to more detailed and reliable information. The third limitation is the lack of a comparison group of anxious children without ASD or non-anxious children with ASD, leading to limits in making causal statements about either condition with respect to depressive symptoms. Future research should focus on more extensive examination of suicidal ideation in children with ASD, which can lead to more insight in the specific characteristics of suicidal ideation in this population and give input for better recognition and treatment.

Implications

Studies using a multi-informant approach to assess the high prevalence of comorbid depressive symptoms and suicidal ideation in children with ASD, normal cognitive functioning and elevated anxiety in a clinical sample are very rare. Our study is one of the first to show that these children have a high prevalence of co-occurring clinical levels of depressive symptoms and suicidal ideation. In turn, comorbid depression and anxiety symptoms have shown to exacerbate ASD-symptoms like social functioning deficits, stereotypic and externalizing behavior (Matson & Nebel-Schwalm, 2007). Therefore, assessment of both depressive symptoms and suicidal ideation needs clinical attention when children with ASD, normal cognitive functioning and anxiety are referred to mental health care or when anxiety is recognized in these children during treatment. When children with ASD meet the criteria of a depressive disorder and when they report suicidal ideation, it is of significant importance that they receive a depression treatment that is adapted to their capacities and impairments.

PART 2

Treatment of Anxiety in Children with ASD



CHAPTER 4

Study Protocol: The Effect of the Video Game *Mindlight* on Anxiety Symptoms of Children with an Autism Spectrum Disorder

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Wijnhoven, L. A. M. W., Creemers, D. H. M., Engels, R. C. M. E., Granic, I. (2015). The effect of the video game '*Mindlight*' on anxiety symptoms of children with an Autism Spectrum Disorder: study protocol for a randomized controlled trial. *BMC Psychiatry, 15:* 138.

ABSTRACT

In the clinical setting, a large proportion of children with an autism spectrum disorder (ASD) experience anxiety symptoms. Because anxiety is an important cause of impairment for children with an ASD, it is necessary that effective anxiety interventions are implemented for these children. Recently, a serious game called *Mindlight* has been developed that is focused on decreasing anxiety in children. This approach is based on recent research suggesting that video games might be suitable as an intervention vehicle to enhance mental health in children. In the present study it will be investigated whether *Mindlight* is effective in decreasing (sub)clinical anxiety symptoms in children who are diagnosed with an ASD. The present study involves a randomized controlled trial (RCT) with two conditions (experimental versus control), in which it is investigated whether *Mindlight* is effective in decreasing (sub)clinical anxiety symptoms in children with an ASD. For this study, children of 8-16 years old with a diagnosis of an ASD and (sub)clinical anxiety symptoms will be randomly assigned to the experimental (N = 60) or the control (N = 60) condition. Children in the experimental condition will play *Mindlight* for one hour per week, for six consecutive weeks. Children in the control condition will play the puzzle game *Triple Town*, also for one hour per week and for six consecutive weeks. All children will complete assessments at baseline, post-intervention and 3-months follow-up. Furthermore, parents and teachers will also complete assessments at the same time points. The primary outcome will be child report of anxiety symptoms. Secondary outcomes will be parent report of child anxiety, child/parent report of depressive symptoms, and parent/teacher report of social functioning and behavior problems. This paper aims to describe a study that will examine the effect of the serious game *Mindlight* on (sub)clinical anxiety symptoms of children with an ASD in the age of 8-16 years old. It is expected that children in the experimental condition will show lower levels of anxiety symptoms at 3-months follow-up, compared to children in the control condition. If *Mindlight* turns out to be effective, it could be an important contribution to the already existing interventions for anxiety in children with an ASD. *Mindlight* could then be implemented as an evidence-based treatment for anxiety symptoms in children with an ASD in mental health institutes and special education schools.

BACKGROUND

In the clinical setting, a large proportion of children with an autism spectrum disorder (ASD) experience anxiety symptoms. Between 11% and 84% of all children with an ASD experience some degree of impairing anxiety (White, Oswald, Ollendick, & Scahill, 2009). More specifically, 21% of the children with an ASD suffer from subclinical anxiety (Strang et al., 2012) and approximately 40% of the children with an ASD meet the criteria of at least one anxiety disorder (Van Steensel, Bögels, & Perrin, 2011). Some of the most frequently reported anxiety disorders and symptoms seen in children with an ASD are simple phobias, generalized anxiety disorder, separation anxiety disorder, obsessive-compulsive disorder and social phobia (White et al., 2009).

Moreover, anxiety is an underlying cause of several symptoms of ASD. For example, anxiety underlies or affects the stereotype and rigid behavior (Rodgers, Glod, Connolly, & McConachie, 2012) and the problems in social functioning (Chang, Quan, & Wood, 2012) that children with an ASD often show. Anxiety also underlies comorbid symptoms of children with an ASD, for example oppositional and aggressive behavior (Cervantes, Matson, Tureck, & Adams, 2013) and depressive symptoms (Vasa et al., 2013). Furthermore, anxiety in children with an ASD has a negative impact on adaptive functioning, daily living skills and relationships with peers, teachers and family (Drahota, Wood, Sze, & Van Dyke, 2011; Hallett et al., 2013; Kim, Szatmari, Bryson, Streiner, & Wilson, 2000). Therefore, it is important that anxiety in children with an ASD is treated and prevented from further escalation.

Recognition of anxiety symptoms in children with an ASD is not new. In the original description of children with an ASD, Kanner (1943) stated that a number of these children had "substantial anxiety problems". Yet, the evaluation and treatment of anxiety in children with an ASD has only recently received empirical attention (White et al., 2009). Many studies showed the effectiveness of adapted versions of cognitive behavioral therapy (CBT; e.g. McNally Keehn, Lincoln, Brown, & Chavira, 2013) or new interventions especially developed for children with an ASD (e.g. White et al., 2013), reasoning that the traditional form of CBT is not suitable for children with an ASD. On the other hand, a recent study of Van Steensel and Bögels (Van Steensel & Bögels, 2015) has shown that CBT is effective in reducing anxiety symptoms in children with an ASD, and that CBT is as effective for children with an ASD as for children without an ASD.

However, there are some important limitations to CBT for anxiety, both in general and specifically for children with an ASD. First, CBT largely consists of teaching children to become conscious of their negative thoughts, to evaluate these thoughts, and eventually to challenge them and formulate thoughts that are more accurate. These sessions have a face-to-face, verbal and cognitively complex character.

Because children with an ASD have a cognitive and social impairment, they have difficulties with learning skills in these CBT-sessions and as a result they are often not intrinsically motivated for CBT (Silver & Oaks, 2001). Therefore, a greater focus on visual aids and structured sensory information is an important requirement in anxiety treatment for children with an ASD (Silver & Oaks, 2001; Chalfant, Rapee, & Carroll, 2007). Second, there is a large gap between the knowledge that children gain in CBT and the implementation and practice of this knowledge in daily life. Especially for children with ASD, frequent practice and exposure opportunities are important in anxiety interventions (White et al., 2009). However, the exercises in CBT that do exist are mostly de-contextualized and do not fully represent the situations in which children experience their anxiety. A third limitation of CBT is limited access to care and long waiting lists to care that is accessible (Granic, Lobel, & Engels, 2014). Finally, the low cost effectiveness is a limitation of CBT, which many mental health institutions experience as a barrier to treatment delivery. Therefore, it is important that new anxiety interventions are developed that can provide a solution for the above mentioned limitations.

Recently, it has been shown that video games have the potential to enhance mental health and well-being in children and adolescents (Ferguson & Olson, 2013). For example, Merry et al. (2012) found that the video game 'SPARX' was effective in reducing depressive symptoms among adolescents in the age between 12-19 years old. They concluded that it was a potential alternative to usual care for adolescents with depressive symptoms in primary care settings and that it could be used to address some of the unmet demands for treatment. More recently, the serious game *Mindlight* (Playnice Institute) has been developed for the treatment of anxiety disorders in children. A recent study has tested the effect of *Mindlight* on anxiety symptoms in school children (Schoneveld et al., 2016). This study showed that both the anxiety of the children who played *Mindlight* as the anxiety of the children who played the control game significantly decreased over time. However, no studies to date have investigated the effect of a serious game on anxiety symptoms of children with an ASD.

Mindlight has the aim to tackle anxiety in children by using several treatment mechanisms. First of all, it uses exposure techniques, one of the most empirically-validated treatment components of CBT for anxious individuals (Abramowitz, Deacon, & Whiteside, 2011). During exposure, individuals are gradually exposed to the threatening cues. In this way, they are getting habituated to these cues and eventually they are getting more comfortable and less anxious when being exposed to them. Moreover, *Mindlight* uses neurofeedback mechanisms, which is effective in decreasing anxiety symptoms of children (Hammond, 2005). These mechanisms are focused on regulating arousal levels associated with anxiety through relaxation and concentration. Finally,

attention bias modification is incorporated in *Mindlight*, which is a therapy mechanism in which children learn to (a) disattend to threatening cues and shifting attention away from those cues and to (b) focus on positive aspects of the environment in the service of relevant goals (Muris & Field, 2008).

It is hypothesized that *Mindlight* has the potential to serve as an effective new intervention for children with ASD and comorbid (sub)clinical anxiety symptoms, and that it can overcome the limitations of CBT. First, it is known that children with ASD often feel a close affinity for technology and games, which means that the participating children are probably intrinsically motivated to play a game like *Mindlight* in therapy (Khandaker, 2009). Moreover, it has been reported that computer based training could be an effective tool in treatment for children with ASD, due to its visual and structured character (Silver & Oaks, 2001). *Mindlight* uses visual aids and structured sensory information to a great extent, both for creating a 'scary' exposure environment and for teaching important treatment concepts. Furthermore, *Mindlight* includes frequent practice and exposure opportunities. Because *Mindlight* can be played repeatedly, with the difficulty level increasing as children become better players, there is a great deal of practice and exposure involved in playing this game. As a result, the gap between knowledge and behavior may be substantially decreased and effective cognitive and emotional coping skills can be automatized and possibly generalized with practice. Finally, therapy skills can be practiced at home, which means that children have an easier access to mental health care. In this way, the waiting lists can become shorter and the therapy costs can be decreased when implementing a game like *Mindlight* as therapy tool.

In the present study, the primary aim is to investigate whether *Mindlight* is effective in reducing (sub)clinical anxiety symptoms in children with an ASD. The secondary aim is to examine whether *Mindlight* is effective in reducing parent report of child anxiety, and the anxiety-related depressive symptoms, social functioning and behavior problems of the participating children. To investigate these aims, a multi method symptom assessment is used, including parent, teacher and child reports (White et al., 2009). If *Mindlight* turns out to be effective for anxious children with an ASD, it could be considered as a new therapeutic intervention next to the already existing approaches for anxiety in children with an ASD.

METHODS

The study design will be reported in line with the CONSORT 2010 Statement for reporting parallel group randomized trials (Schulz, Altman, Moher, & Group, 2010). The medical ethics committee CMO Arnhem-Nijmegen in the Netherlands has given

approval for the conduction of this study (NL50023.091.14). Moreover, the study is registered in the Dutch Trial Register for RCT's (NTR5069).

Design

The present study involves a randomized controlled trial (RCT) with two conditions (experimental versus control), in which it is investigated whether the new video game *Mindlight* is effective in treating (sub)clinical anxiety symptoms in children with an ASD. For this study, children in the age of 8-16 years old with a diagnosis of an ASD according to the Diagnostic and Statistical Manual of Mental Disorders 4th Edition – Text Revision (DSM-IV-TR; American Psychiatric Association, 2000) will be screened for anxiety symptoms. The children with (sub)clinical anxiety symptoms will be selected and approached for participation.

After the selection and recruitment, children will be randomly assigned to the experimental or control condition. At baseline (T0), children, parents and teachers will fill in questionnaires. Moreover, parents will undergo a semi-structured interview (ADIS-P; Siebelink & Treffers, 2001) to determine whether their child meets the criteria of one or more anxiety disorders. At post-intervention (T1) and at 3-months follow-up (T2), children, parents and teachers will fill in questionnaires again to evaluate the effect of *Mindlight*. At 3-months follow-up, parents will undergo the semi-structured interview again to test whether *Mindlight* also had an effect on the present anxiety disorder(s) in the participating children. Figure 1 shows a schematic overview of the design in the present study.

Participants' eligibility

Children with an ASD (DSM-IV-TR: Autistic disorder, Asperger disorder, PDD-NOS; (American Psychiatric Association, 2000) in the age between 8 to 16 years old will be assessed for eligibility by a screening. This screening consists of filling in an anxiety questionnaire by both children (SCAS-C; Scholing, Nauta, & Spence, 1999a) and parents (SCAS-P; Scholing, Nauta, & Spence, 1999b). When children have at least subclinical levels of anxiety, they are eligible for participation in the study. Moreover, they have to have sufficient knowledge of the Dutch language. Exclusion criteria are absence of parental permission and presence of prominent suicidal ideation or other severe psychiatric problems that need immediate treatment (e.g. severe trauma's).

Procedure

Contexts of recruitment are mental health institutes (e.g. GGZ Oost Brabant) and special education schools in the Netherlands. First, parents will receive a letter with information about the screening and the study. Moreover, children and parents will

be asked to fill in the SCAS-C/P (Scholing et al., 1999a/b). When children have at least subclinical levels of anxiety and meet the other inclusion criteria, children and parents will be approached to participate in the study. If children and parents agree with participation, active written informed consent of the parents and the children who are above the age of 12 will be obtained.

After obtaining active written informed consent, children will be randomly allocated to the experimental or control condition. Children in the experimental condition will play *Mindlight* individually for one hour per week during 6 consecutive weeks at the recruitment location. Moreover, children may receive treatment as usual (TAU) parallel with *Mindlight*. TAU will mainly be offered by mental health institutes and might for example consist of psycho-education on ASD, play/drama therapy, parent guidance and/or medication. These types of TAU will be monitored and reported during the course of the study, and will be tested as potential confounders in the analyses. Children in the control condition will play the computer game *Triple Town* individually for one hour per week during 6 consecutive weeks at the recruitment location. Again, children may receive TAU parallel with the game. Moreover, they will have the opportunity to play *Mindlight* after the 3-months follow-up if this game turns out to be effective.

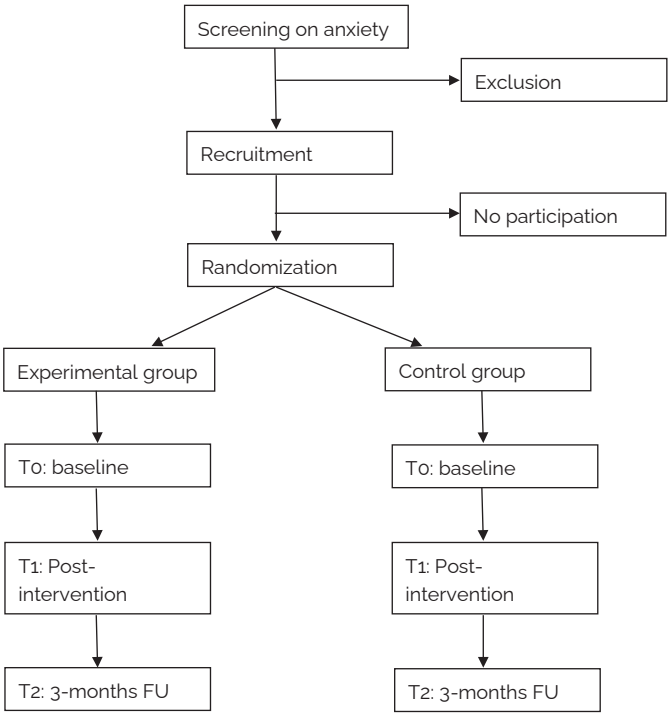


Figure 1. Flow diagram of recruitment, randomization and assessments. FU = Follow-up.

Sample size

A priori power analysis was performed in G*Power 3.1 (Faul, Erdfelder, Lang, & Buchner, 2007) to calculate the sample size that is required in the present study. It is expected that *Mindlight* is significantly more effective in reducing anxiety symptoms of the participating children than *Triple Town*. Previous studies on the effect of already existing modified versions of CBT on anxiety among children with an ASD reported moderate to large effect sizes on anxiety symptoms (e.g. Danial & Wood, 2013; McNally Keehn et al., 2013; Reaven, Blakeley-Smith, Culhane-Shelburne, & Hepburn, 2012). It is assumed that the implementation of *Mindlight* in clinical practice is worth consideration, when the effect of *Mindlight* is at least equal to the effect of the present anxiety treatments for children with an ASD. Therefore, the power calculation is conducted with a moderate expected effect size (f = .25) of condition (experimental or control condition) at 3-months follow-up. Moreover, it was expected that the Type I error was .05 and that the Type II error was .20 (power is .80). When computing these assumptions, it was calculated that a sample of 86 participants would be satisfactory in the present study. Eventually, the sample size was increased by 40% to compensate for loss to follow-up (estimated at 20%) and possible loss of power due to potential clustering of data in case of group formation (estimated at 20%), resulting in 120 participants (60 in experimental condition and 60 in control condition).

Intervention

The intervention that will be investigated is called *Mindlight*. This is a video game aimed at children of 8 - 16 years old and is based on principles of cognitive-behavioural therapy (CBT) and neurofeedback, which are evidence-based interventions for anxiety-disordered children and adults. Briefly, the premise of the game is that Little Arthur is left on the doorstep of a scary mansion by his parents. Arthur must learn to use his own inner strength to overcome his greatest fears so the shadows in the house can hold no power over him. He can accomplish this by using his *Mindlight*, a light bubble that can shine on the surroundings and that can be controlled by his own inner strength. This 'inner strength' will be measured by a neurofeedback headset (the 'MindWave'; Neurosky USA; Johnstone, Blackman, & Bruggemann, 2012a), which children will put on when they are going to play *Mindlight*. This headset records EEG using dry sensor technology, which consists of an active and reference electrode. The signals that are measured will be filtered on Delta, Theta, Alpha and Beta waves. In *Mindlight*, especially the Alpha and Beta waves will be used for real time feedback. Research has shown that the Mindwave headset has good reliability and validity (Johnstone et al., 2012a), and that it can be used in research with children who have a developmental disorder (e.g. ADHD; Johnstone et al., 2012b).

In *Mindlight*, the Alpha and Beta waves will be used in several ways. First of all, the recorded Alpha waves reflect the degree of relaxation of the child. This feature is used in the exposure techniques (CBT) that are embedded in the game (see also Figure 2): when the child sees threatening stimuli (e.g. monsters) several times during the game and learns to maintain calm when facing them, the child eventually gets habituated to them and can gain points more easily.

Furthermore, the recorded Beta waves reflect the degree of concentration and the allocation of attention of the player. Focused concentration allows the player to solve attention bias modification (ABM) puzzles. ABM is a training protocol that has its roots in CBT and that is based on the idea that distorted cognitions, particularly attentional biases characterized by hyper attention towards potential threats, play a role in the pathogenesis of childhood anxiety (Hammond, 2005). ABM has been shown to reliably reduce anxiety by retraining the attentional system to focus on positive stimuli (Bar-Haim, 2010). *Mindlight* uses this principle in the ABM-puzzles, by rewarding children for focusing on positive aspects of the environment (measured by the neurofeedback device). More specifically, they learn to move towards, and quickly respond to, positive stimuli (e.g., portraits of happy faces) and disattend to, or shift attention away from, negative stimuli (e.g., mean faces, threatening animals).

To minimize the chance of finding placebo-effects of *Mindlight*, children in the control condition will also receive a computer game. In this way, the amount of attention that children in the experimental condition and children in the control condition receive is equal, and the effects that may be found can uniquely be ascribed to the game itself. The computer game that the children in the control condition are going to play is called '*Triple Town*'. In this puzzle game, the player has to build a city. The bigger the city you build, the more points you can receive. To accomplish this, you have to combine elements (e.g. trees and houses) in a strategic way. Moreover, you have to block bears that try to hinder you in building the city. In this way, the child learns to think strategically in order to overcome challenges. Moreover, children learn to keep a goal and to persevere in order to reach this goal. However, the game is not specifically focused at reducing anxiety levels, which makes '*Triple Town*' a suitable game for the control condition.

The gaming sessions will be led by qualified therapists, or by master students who are supervised by qualified therapists. In session 1, the therapist starts with psycho-education on anxiety. After that, the anxiety of the child will be discussed, the therapist will explain the game and eventually the therapist will clarify that this game is focused on decreasing the anxiety of the child. Then, the child will play the game for approximately 40 minutes. After playing the game, the therapist will ask the following standardized questions: 1) How did the gaming go today? 2) What did you

find difficult/What did you find easy? 3) What did you learn in the game? 4) Could you apply and practice the skills you have learned in scary or difficult situations in daily life? In session 2-6, the therapist will start the session with discussing the previous week and the skills the child has practiced at home. When the child mentions that he has practiced the skills in a scary or difficult situation, this will be reinforced by the therapist. In this way, the therapist does not add explicit therapeutic elements to the gaming sessions, but children do get stimulated to think about their anxiety and the way they can apply and practice the skills they have learned in the game in daily life.

Figure 2. Relaxation mechanic *Mindlight*: remain calm to enlighten environment.

Study outcome measures

Table 1 shows an overview of the different time points, the questionnaires that were filled in on each time point and the informants that were involved.

Table 1

Overview of assessments

	Screening	T0	T1	T2
Child				
Anxiety (SCAS-C)	χ	χ	χ	χ
Depression (CDI 2)		χ	χ	χ
Therapeutic expectancies (PETS)		χ		
Parent*				
Anxiety (SCAS-P)	χ	χ	χ	χ
Anxiety disorders (ADIS-P)		χ		χ
Depression (CDI 2:P)		χ	χ	χ
Social functioning (VISK)		χ	χ	χ
Behavior problems (SDQ)		χ	χ	χ
Therapeutic expectancies (PETS)		χ		
Teacher				
Social functioning (VISK)		χ	χ	χ
Behavior problems (SDQ)		χ	χ	χ

Note. *The primary caregiver of the child will fill in the questionnaires. The ADIS-P will be conducted with both parents (if possible).

Screening measures

To test their eligibility, children will be screened on anxiety symptoms using the SCAS-C for child report and the SCAS-P for parent report (Scholing et al., 1999a/b). Children are eligible for participation when the child and/or the parent report the presence of subclinical child anxiety. Moreover, demographical questions (e.g. sex, age, educational level) will be asked to both children and parents. Finally, some questions about the child's gaming behavior (e.g. 'How many hours per week do you game?') will be asked.

Primary outcome measure

Anxiety symptoms will be measured with the Dutch translation of the Spence Children's Anxiety Scale (SCAS; Scholing et al., 1999a). The SCAS consists of 44 items (e.g. 'I am afraid when I have to sleep alone', 'I worry about things') on a 4-point scale, ranging from 'never' to 'always'. Scores on items ranged from 0 to 3, with higher scores indicating more anxiety symptoms. Moreover, the scale consists of six subscales that are in line with the different anxiety disorders that are described in the DSM-IV: panic/agora

phobia, separation anxiety, social phobia, generalized anxiety, obsessive compulsive anxiety and anxiety for physical injury. The SCAS has a high validity and reliability (Muris, Schmidt, & Merckelbach, 2000; Spence, Barrett, & Turner, 2003).

Secondary outcome measures

Anxiety of the child according to the parents will be measured with the Dutch translation of the Spence Child Anxiety Scale for Parents (SCAS-P; Scholing et al., 1999b). The SCAS-P consists of 38 items on a 4-point scale ranging from 0 (never) to 3 (always). The items of the SCAS-P were formulated as closely as possible to the corresponding item of the child version of the SCAS. Only items referring to an internal state (e.g. item 4: 'I feel afraid') were rephrased into observable behaviour for parents (e.g. 'My child complains of feeling afraid'). The SCAS-P consists of the same six subscales as the child version. The SCAS-P has a good reliability and validity (Nauta et al., 2004).

The presence of anxiety disorders according to the parents will be assessed with the Dutch translation of the Anxiety Disorders Interview Schedule for DSM-IV, Parent version (ADIS-P; Siebelink & Treffers, 2001). This is a semi-structured diagnostic parent interview that can be used to diagnose anxiety disorders in children of 7-17 years old. The interview will be administered by a qualified therapist or by a master student under supervision of a qualified therapist. In this study, the presence of the following DSM-IV anxiety disorders will be examined: separation anxiety disorder, social phobia, specific phobia, panic disorder, agora phobia and generalised anxiety disorder. The interview consists of standardized questions, with 'yes', 'no' and 'different' as possible answers. At the end of the interview, the interviewer has to give his/her clinical judgement about the severity of every disorder. On basis of this judgement, the interviewer will make a definitive decision about the presence (yes/no) of the different anxiety disorders. The ADIS-P has a strong reliability and validity (Siebelink & Treffers, 2001).

Depressive symptoms will be measured using the Dutch translation of the Child Depression Inventory 2 (CDI 2; Timbremont, Braet, & Roelofs, 2008). The CDI 2 consists of 28 items measured on a 3-point scale ranging from 0 (depressive symptom is absent) to 2 (depressive symptom is always present) (e.g., 'I don't feel alone' = 0, 'I often feel alone' = 1, 'I always feel alone' = 2; 'Sometimes I'm sad' = 0, 'I'm often sad' = 1, 'I'm always sad' = 2). The children have to choose the answer that is most in accordance with their own thoughts and feelings. The validity and reliability of the Dutch CDI 2(:P) is still being investigated, but it already has been shown that the original (American) version of the CDI 2(:P) (Kovacs, 2011) has a good reliability, internal consistency and convergent validity (Bae, 2012).

Depression according to the parents will be measured with the Dutch translation of the Child Depression Inventory 2 for parents (CDI 2:P; Timbremont et al., 2008) will

be used to measure parental assessment of depressive symptoms of their child. The CDI 2:P consists of 17 items measured on a 4-point scale ranging from 0 (not at all), 1 (some of the time), 2 (often), or 3 (most of the time) (e.g. 'My child looks sad'; 'My child seems lonely'). The parent has to assess to which extent the items are in accordance with their child's thoughts and feelings.

Social functioning according to the parents and teacher will be measured with the 'Vragenlijst voor Inventarisatie van Sociaal gedrag van Kinderen' (VISK), a Dutch translation of the Children's Social Behaviour Questionnaire (CSBQ; Luteijn, Jackson, Volkmar, & Minderaa, 1998). The VISK consists of 49 items measured on a 3-point scale (0 = not applicable, 1 = sometimes applicable, 2 = often applicable). The items are divided over six problem scales: being not well tailored to social situations; limited tendency to engage in social interactions; orientation problems in time, space and place; not understanding social information; stereotype behavior; and anxiety for and resistance against changes. Hartman and colleagues (2007) reported that the VISK has a good validity and reliability.

Internalizing and externalizing behaviour problems according to the parents and teacher will be measured with the Dutch translation of the Strengths and Difficulties Questionnaire (SDQ; Van Widenfelt, Goedhart, Treffers, & Goodman, 2003). The SDQ consists of 25 items, measured on a 3-point scale (0 = not true, 1 = a little bit true, 2 = certainly true). Moreover, an impact supplement can be completed, by which the impact of the behavior problems on daily functioning of the child and its family can be assessed. The items of the SDQ are divided over the following scales: emotional problems, behavior problems, hyperactivity/ attention problems, problems with peers and social behavior. There are separate forms for parents and teachers. The SDQ has a sufficient reliability and validity (Goedhart, Treffers, & Van Widenfelt, 2003).

Treatment expectancies according to child and parents will be measured using the Dutch translation of the Parent Expectancies for Therapy Scale (PETS; Kazdin & Holland, 1991). The PETS has a parent and child version, and each version consists of seven items measured on a 6-point scale ranging from 1 (I totally disagree) to 6 (I totally agree). The items of the PETS are divided over the following subscales: credibility, child improvement and parent involvement. The PETS has a good validity and reliability (Nock & Kazdin, 2001).

Data analysis/statistical analysis

Following the intention-to-treat principle (Gillings & Koch, 1991), all children randomized to a condition will be included in the analyses to test the study objectives. Multiple imputations will be used for missing observations at post-intervention and 3-month

follow-up. Reporting of the results of the study will be in accordance with the CONSORT 2010 Statement (Schulz et al., 2010).

To investigate the differences in the development of anxiety symptoms between children in the experimental condition and children in the control condition, a 3 (within-subjects: pre, post, follow-up) by 2 (condition: experimental vs. control) ANOVA (repeated measures) will be conducted, with anxiety symptoms (child report) as the dependent variable. The direct effect of *Mindlight* on parent report of child anxiety, parent/child report of depressive symptoms, and parent/teacher report of social functioning and behavior problems will be investigated in the same way. Furthermore, remission rates of the anxiety disorders that were diagnosed at baseline (with ADIS-P) will be calculated at 3-months follow-up, and Chi-square (χ^2) tests will be conducted to compare remission rates between the experimental and control group. In the above mentioned analysis plan it is assumed that the children will play the game individually and that therefore the data will not be clustered. However, in case of clustered data due to the formation of groups in which several children play the game in the same room, the analyses will be conducted in MPLUS 6.11 (Muthén & Muthén, 1998-2007).

Finally, possible baseline differences between the two conditions in demographic variables (e.g. age, sex, educational level), anxiety symptoms, gaming behaviour and treatment expectancies will be checked. Moreover, possible differences in TAU between the experimental and control condition will be checked at all time points. Variables that show different distributions between the two groups will be entered as confounders in all models testing the effectiveness of the intervention.

DISCUSSION

The present study protocol gives an overview of a study design for a randomized controlled trial testing the effect of the serious game *Mindlight* in decreasing anxiety symptoms of children with an ASD. The primary aim is to investigate whether *Mindlight* is effective in reducing (sub)clinical anxiety symptoms of children with an ASD in the age of 8-16 years old. The secondary aims are to investigate whether *Mindlight* is effective in reducing parent report of child anxiety and the anxiety-related problems in social functioning, depressive symptoms and behavior problems of children with an ASD. It is expected that *Mindlight* is effective in reducing anxiety symptoms of the children in the experimental condition, compared to the children in the control condition that play *Triple Town*. Furthermore, it is expected that *Mindlight* is more effective than *Triple Town* in reducing parent report of child anxiety, parent/child report of depressive symptoms and parent/teacher report of social functioning and behavior problems.

Strengths and limitations

The present study design has a few strengths and limitations. A strength is that it is the first study investigating the effect of a serious game in a clinical context with children who are diagnosed with an ASD and who have comorbid (sub)clinical anxiety symptoms, which could lead to a new way of treating anxiety in children with an ASD. An additional strength is that children with an ASD often feel a close affinity for technology and games (Khandaker, 2009; Silver & Oaks, 2001) and that the participating children are probably intrinsically motivated to play a game like *Mindlight* in therapy. Furthermore, *Mindlight* includes frequent practice, exposure opportunities, visual aids and structured sensory information, which all stimulate the automatization and the generalization of skills to daily life in the participating children. Another strength is that this study may lead to the implementation of *Mindlight* in mental health institutes, which may result in an easier access to mental health care, shorter waiting lists and lower therapy costs. Finally, this study has multiple outcome measures, which makes it possible to investigate other direct effects of *Mindlight* on anxiety-related symptoms (e.g. depressive symptoms) of the participating children.

A limitation of the present study design is that the children in the control condition might have played *Triple Town* already before the start of the study. This may have a positive (e.g. more practice) or negative (e.g. boredom) influence on the effect of the game. Moreover, only short-term effects (3-months follow-up) of *Mindlight* will be investigated. In this way, no conclusions can be drawn about the long-term effects of *Mindlight* on anxiety symptoms of the participating children. Finally, there are no standardized protocols for offering and implementing a video game in a clinical therapy session. This implies that the best form of implementation still needs to be discovered and improved by experience.

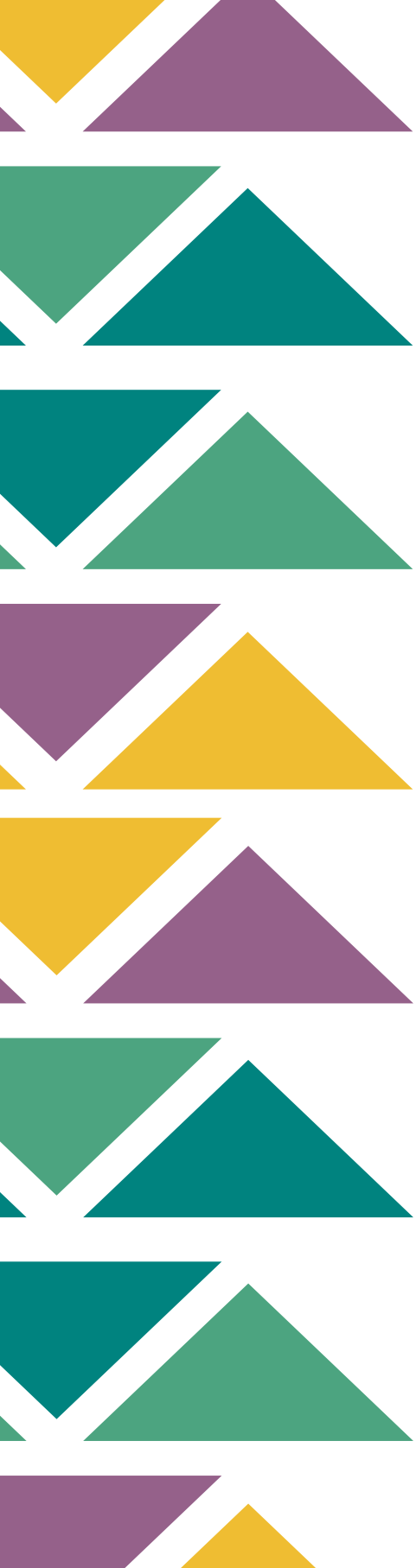
Implications for practice

Anxiety symptoms are highly common in children with an ASD. Still, treatment on anxiety in children with an ASD only recently has received some empirical attention. This may be caused by the fact that anxiety is often underdiagnosed in children with an ASD (White et al., 2009). In this way, anxiety treatment for children with an ASD is not common and the development of evidence-based anxiety treatments has not been focused upon until recently. By developing and investigating new anxiety treatments for children with an ASD, these may be more frequently offered in mental health institutes in the future. Moreover, if *Mindlight* turns out to be effective for anxious children with an ASD, it could be considered as a good and suitable therapeutic alternative to the already existing interventions for anxiety in children with an ASD. *Mindlight* could then

be implemented as an evidence-based treatment for children with an ASD in mental health institutes and special education schools.

Conclusion

This paper aimed to describe a study that will investigate the effect of the serious game *Mindlight* on (sub)clinical anxiety symptoms of children with an autism spectrum disorder in the age of 8-16 years old. It is expected that children in the experimental condition will show lower levels of anxiety symptoms at 3-months follow-up, compared to children in the control condition. If *Mindlight* turns out to be effective, this could provide a significant contribution to the evidence-based treatment of anxiety in children with an ASD.



CHAPTER 5

Effects of the Video Game '*Mindlight*' on Anxiety of Children with an Autism Spectrum Disorder: A Randomized Controlled Trial

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ABSTRACT

In the clinical setting, a large proportion of children with an autism spectrum disorder (ASD) experience impairing anxiety symptoms. Recently, an applied videogame called *Mindlight* has been developed that focuses on decreasing anxiety in children. The present study involved a randomized controlled trial (RCT) investigating the effect of *Mindlight* on (sub)clinical anxiety symptoms in children with an ASD. In total, 109 children of 8-16 years old with an ASD and (sub)clinical anxiety symptoms were randomly assigned to the experimental (N=53) or the control (N=56) condition. Children in the experimental condition played *Mindlight,* children in the control condition played a commercial game (*Triple Town*) for one hour per week, for six consecutive weeks. All children and parents completed assessments at baseline, post-intervention and 3-months follow-up. Results showed no differences in decrease of child-rated anxiety symptoms between both conditions. However, the decrease of parent-rated anxiety symptoms was significantly larger in the experimental condition. Mechanisms of change associated with treatment outcomes were not investigated in the present study. Therefore, it remains unclear which specific or non-specific factors contributed to the decrease in anxiety symptoms in both conditions. The present study provided some preliminary evidence that video games are a promising new intervention vehicle for children with an ASD and anxiety, at least according to parents. However, further research on working mechanisms is needed, in order to specify to what extent and for which children with ASD *Mindlight* could be an effective anxiety treatment.

INTRODUCTION

Anxiety is a common comorbid mental health problem among children with an autism spectrum disorder (ASD). Recently we showed that 66.3% of the children with an ASD experienced at least subclinical anxiety and that 81.4% of the parents reported that their child experienced at least subclinical anxiety (Wijnhoven, Creemers, Vermulst, & Granic, 2018). The most common anxiety disorders and symptoms observed in children with an ASD are simple phobias, generalized anxiety disorder, separation anxiety disorder, obsessive-compulsive disorder and social phobia (White, Oswald, Ollendick, & Scahill, 2009). Anxiety in children with an ASD is a primary cause of impairment in daily life (Hallett et al., 2013) and is associated with a higher risk for other comorbid problems such as depressive symptoms (Vasa et al., 2013; Kerns et al., 2016a) and oppositional and aggressive behavior (Cervantes, Matson, Tureck, & Adams, 2013). In terms of these children's quality of life, it thus seems important to develop effective treatments focused on reducing anxiety in children with an ASD.

Cognitive behavioral therapy (CBT) is the most effective evidence based therapy to treat anxiety (e.g.,Warwick et al., 2017). Regarding ASD, two meta-analyses (Sukhodolsky, Bloch, Panza, & Reichow, 2013; Ung, Selles, Small, & Storch, 2015) and one Cochrane review (James, James, Cowdrey, Soler, & Choke, 2013) have shown moderate to large effects of CBT. However, there was large heterogeneity in the outcomes and effect sizes of the included studies (Sukhodolsky et al., 2013; Ung et al., 2015). Moreover, there are some important challenges in providing CBT for anxious children with an ASD, as they have difficulties with verbal expression and abstract thinking (Johnco & Storch, 2015). Furthermore, in treatment of children with ASD it is important to incorporate special interests as a stimulation or metaphor (e.g., a specific character in a movie), because this is engaging and salient for the child and can thereby increase treatment effectiveness (Johnco & Storch, 2015). However, adapting to these special interests in CBT sessions may be difficult. Finally, research showed that children with ASD have difficulties with generalizing skills they learned in traditional CBT to multiple contexts in daily life (de Marchena, Eigsti, & Yerys, 2015; McNallyKeehn et al., 2013).

Video games have been shown to have the potential to enhance mental health and well-being in children (Ferguson & Olson, 2013; Granic, Lobel, & Engels, 2013). Recently, the applied video game *Mindlight* was developed to tackle anxiety in children of 8 to 16 years old by using three treatment mechanisms. First, during the evidence-based CBT-element exposure (Abramowitz, Deacon, & Whiteside, 2011), children are exposed to threatening cues while applying relaxation techniques (e.g., deep breathing, self-talk). This way, they learn to regulate their anxiety while facing threatening cues. Second, *Mindlight* uses neurofeedback to help train children to regulate arousal levels

associated with anxiety through relaxation and concentration (Hammond, 2005). Finally, attention bias modification aims at teaching children to ignore threatening cues and focus on positive or neutral features in the environment (Muris & Field, 2008). Several studies have tested the effect of *Mindlight* on school children with elevated anxiety symptoms (Schoneveld et al., 2016; Schoneveld, Lichtwarck-Aschoff, & Granic, 2018; Tsui, 2016). The most recent study showed that *Mindlight* was as effective as the CBT group treatment protocol Coping Cat (Nauta & Scholing, 1998), with improvements maintained at 6-month follow-up (Schoneveld et al., 2018). The within-group effect sizes of both *Mindlight* and Coping Cat were small to medium at post-test, and medium to large at 3- and 6-month follow-ups.

Up to now, the effect of *Mindlight* has not yet been investigated in anxious children with an ASD. There are several reasons why *Mindlight* could be effective in reducing anxiety in this target group and why it could have advantages over CBT. *Mindlight* is a computer based intervention that uses visual aids and structured sensory information to train emotion regulation skills (e.g., relaxation). Previous studies already showed that video games are for example effective in improving emotion regulation skills in children with ASD (e.g. Secret Agent Society; Beaumont, Rotolone, & Sofronoff, 2015). Moreover, therapists could use the metaphors in *Mindlight* to explain therapeutic content, to reinforce treatment participation and to build a therapeutic relationship (Johnco & Storch, 2015). Finally, *Mindlight* is an experiential game, meaning that it makes children aware of their physical and emotional feelings and the way in which they could alter these feelings. In turn, these experiences should make it easier to practice and generalize the skills they have learned in the game in daily life. For these reasons, *Mindlight* may serve as a suitable and effective treatment for anxiety in children with ASD.

Design and Hypotheses

This randomized controlled trial (RCT) evaluated the effectiveness of *Mindlight* in reducing anxiety symptoms of children with ASD. To control for placebo-effects of *Mindlight*, children in the control condition received a commercial puzzle game (*Triple Town*) without therapeutic elements. It was expected that children who played *Mindlight*, relative to *Triple Town*, would show reduced anxiety levels immediately after the intervention and at 3-months follow-up. Secondarily, it was expected that more children would recover from anxiety disorders at 3-months follow-up after playing *Mindlight,* than after playing *Triple Town*.

MATERIAL AND METHODS

Participants

In total, 109 children with a diagnosis of an ASD were included in the analyses (77.1% male). ASD diagnoses were based on psychological and/or psychiatric assessment of the Diagnostic and Statistical Manual of Mental Disorders 4th Edition – Text Revision (DSM-IV-TR; American Psychiatric Association, 2000) criteria for Autistic Disorder, Asperger's Disorder or Pervasive Developmental Disorder – Not Otherwise Specified (PDD-NOS). This assessment was conducted by a clinical expert who conducted a diagnostic assessment that was adapted to the diagnostic 'needs' of the individual child and for example consisted of a developmental anamnesis with parents and/or standardized observation of the child with the Autism Diagnostic Observation Scale (ADOS; Bildt, Greaves-Lord, & De Jonge, 2013). In total, 78 children (71.6%) were diagnosed with PDD-NOS, 20 children with Asperger's Disorder (18.3%) and 11 children Autistic Disorder (10.1%). When the DSM-5 was introduced (American Psychiatric Association, 2013), all diagnoses were transformed into the DSM-5 diagnosis Autism Spectrum Disorder. Furthermore, all participating children had at least subclinical anxiety symptoms, based on a screening with the Spence Children's Anxiety Scale for children and parents (SCAS-C/P; Scholing, Nauta, & Spence, 1999a/b). Mean anxiety score of the participating children at screening (T0) was subclinical for both child- (Subclinical score: 30.98 - 43.85, Muris, Schmidt, & Merkelbach, 2000; mean SCAS-score: 33.22) and parent-report (Subclinical score: 23.9 - 33.6, Nauta et al., 2004; mean SCAS-score: 32.33). Table 1 shows the number and percentage of diagnosed comorbid psychiatric disorders in the participating children.

Mean age was 11.10 (*SD* = 2.07, range 8-16). Seventy children were in primary school and 39 were in secondary school. Of those in primary school, 23 followed special education. Of those in secondary school, 24 followed special education. Most children were of Dutch origin (96.2%). Mean total IQ was 102.26 (*SD* = 17.18).

Table 1

Number and Percentage of Children Diagnosed with a Psychiatric Disorder at the Time of Inclusion

Psychiatric diagnosis	*N* (%)
Anxiety Disorder	19 (17.4)
Attention-Deficit Hyperactivity Disorder	45 (41.3)
(Persistent) Depressive Disorder	10 (9.2)
Oppositional Defiant Disorder	3 (2.8)
Obsessive-Compulsive Disorder	1 (0.9)
Reactive Attachment Disorder	3 (2.8)
Tic Disorder	4 (3.7)
Post-Traumatic Stress Disorder	1 (0.9)
Learning Disability (e.g. Dyslexia)	8 (7.3)

Procedure

A medical ethics committee approved the current study (NL50023.091.14). All procedures were in accordance with the 1964 Helsinki declaration. The RCT was registered in the Trial Register (NTR5069). Children were recruited through a residential setting and a special education school. All children with ASD between 8-16 years old and their parents received an information letter and were screened for anxiety symptoms with the SCAS-C/P (Scholing et al., 1999a/b). In the residential institute, the child's mentor, as daily caregiver, filled in the questionnaires. Subclinical anxiety symptoms were defined as mean + 1SD on the total score and/or one or more subscales (OCD subscale excluded) of the SCAS-C and/or SCAS-P (Muris, Schmidt, & Merkelbach, 2000; Nauta et al., 2004). Overall, 197 children and their parents (or caregivers) were screened, of which 127 children (64,5%) and 155 parents (78,7%) reported at least subclinical anxiety symptoms. Children were eligible when parents and/or children reported at least subclinical levels of anxiety and when they had sufficient knowledge of the Dutch language. Exclusion criteria were absence of parental permission and presence of prominent suicidal ideation or other severe psychiatric problems that needed immediate treatment (e.g., severe trauma). When children and parents agreed to participate, active written informed consent of the parents and the children who were above the age of 12 was obtained.

In total, 122 children and their parents agreed to participate and gave active written informed consent. Families were randomly assigned to the experimental (n = 59) and control condition (n = 63). Randomization was performed by an independent researcher

and was carried out separately for each location of the different institutes (n = 6), using a computerized random number generator. Randomization was stratified by gender and age (8-11 and 12-15 years old). After inclusion of participants in the residential institute, it was decided that this small subsample (n = 13) would be left out of the final analyses, because of the strong differences between the characteristics of this subsample compared to the rest of the participants. These differences include a higher mean age (M = 14.06) and stronger contamination between the children in both conditions because of the residential nature of the setting. Moreover, they differed in behavior and impairment from the other children by showing more severe conduct problems. The remaining 109 children (n = 53 experimental group; n = 56 control group) were all included in the statistical analyses (see Figure 1).

Children in the experimental condition played *Mindlight* and children in the control condition played the commercial computer game '*Triple Town*'. All children played their game individually in sessions of one hour per week during 6 consecutive weeks at the recruitment location. Moreover, all children received treatment as usual (TAU) parallel with *Mindlight* or *Triple Town*. TAU did not focus on anxiety symptoms and therapists were instructed to not focus on anxiety symptoms in TAU. Table 2 shows an overview of the percentages of five different types of TAU that were received by children in the experimental and control condition. A Fisher's Exact Test showed that the number of children that received a specific type of TAU did not significantly differ between both conditions at T1, T2 and T3 (all $p > .05$).

The screening was defined as T0 and the SCAS-C/P score of the participating children at T0 was used as baseline score. At pre-intervention (T1), children and parents filled in questionnaires. Moreover, parents underwent a semi-structured interview (ADIS-P; Siebelink & Treffers, 2001) to determine whether their child met the criteria of one or more anxiety disorders. The average time between T0 and T1 was 6 weeks (1.5 months). At post-intervention (T2) and at 3-months follow-up (T3), children and parents filled in questionnaires again to evaluate the effect of *Mindlight*. A second interview was conducted at 3-months follow-up to examine whether *Mindlight* also had an effect on the present anxiety disorder(s).

Table 2

Percentages of Different Types of Treatment as Usual (TAU) that Children in the Experimental and Control Condition Received at T1 (Pre-Intervention), T2 (Post-Intervention) and T3 (3-Months Follow-up)

	T1 (pre-intervention)		T2 (post-intervention)		T3 (3-months FU)	
	Experimental	Control	Experimental	Control	Experimental	Control
Psycho-education	9.4	14.3	7.5	8.9	11.3	14.3
Parent guidance	39.6	41.1	22.6	26.8	24.5	28.6
Play/drama therapy	9.4	3.6	7.5	3.6	7.5	1.8
CBT	0.0	1.9	0.0	1.9	0.0	0.0
Medication	32.1	42.9	26.4	33.9	26.4	32.1

Note. CBT = Cognitive Behavioral Therapy.

Primary outcome measure

Table 8 in Appendix A shows an overview of the different time points, all questionnaires, and informants.

Child-rated Anxiety Symptoms. The Spence Children's Anxiety Scale (SCAS; Scholing et al., 1999a) was used to measure child-rated anxiety symptoms. The SCAS consists of 44 items (e.g., 'I am afraid when I have to sleep alone', 'I worry about things') on a 4-point scale, ranging from 'never' (0) to 'always' (3). The scale consists of six subscales as described in the DSM-IV: panic/agora phobia, separation anxiety, social phobia, generalized anxiety, obsessive compulsive anxiety and anxiety for physical injury. The SCAS has good psychometric properties (Muris, Schmidt, & Merckelbach, 2000; Spence, Barrett, & Turner, 2003) (Cronbach's alpha .86 to .94).

Secondary outcome measures

Parent-rated Anxiety Symptoms. The Dutch translation of the Spence Child Anxiety Scale for Parents (SCAS-P; Scholing et al., 1999b) was used to measure parent-rated anxiety symptoms. The items of the SCAS-P correspond with the items of the child version of the SCAS, but does not contain filler items. Items referring to an internal state (e.g., item 4: 'I feel afraid') were rephrased into observable behaviour for parents (e.g., 'My child complains of feeling afraid'). The SCAS-P has also good psychometric properties (Nauta et al., 2004). Cronbach's alpha ranged from .77 to .90.

Anxiety disorders. The Anxiety Disorders Interview Schedule for DSM-IV, Parent version (ADIS-P; Siebelink & Treffers, 2001) was used to assess whether participating children met the criteria of several DSM-IV anxiety disorders at T1 and T3. This way, remission rates could be calculated at T3. In this study, the presence of separation anxiety disorder, social phobia, specific phobia, panic disorder, agoraphobia and

generalised anxiety disorder were assessed. The interview was administered by a qualified therapist or by a master student under supervision of a qualified therapist. The ADIS-P has strong reliability and validity (Siebelink & Treffers, 2001). Students received training and weekly supervision by a qualified therapist on the administration and severity ratings of the ADIS.

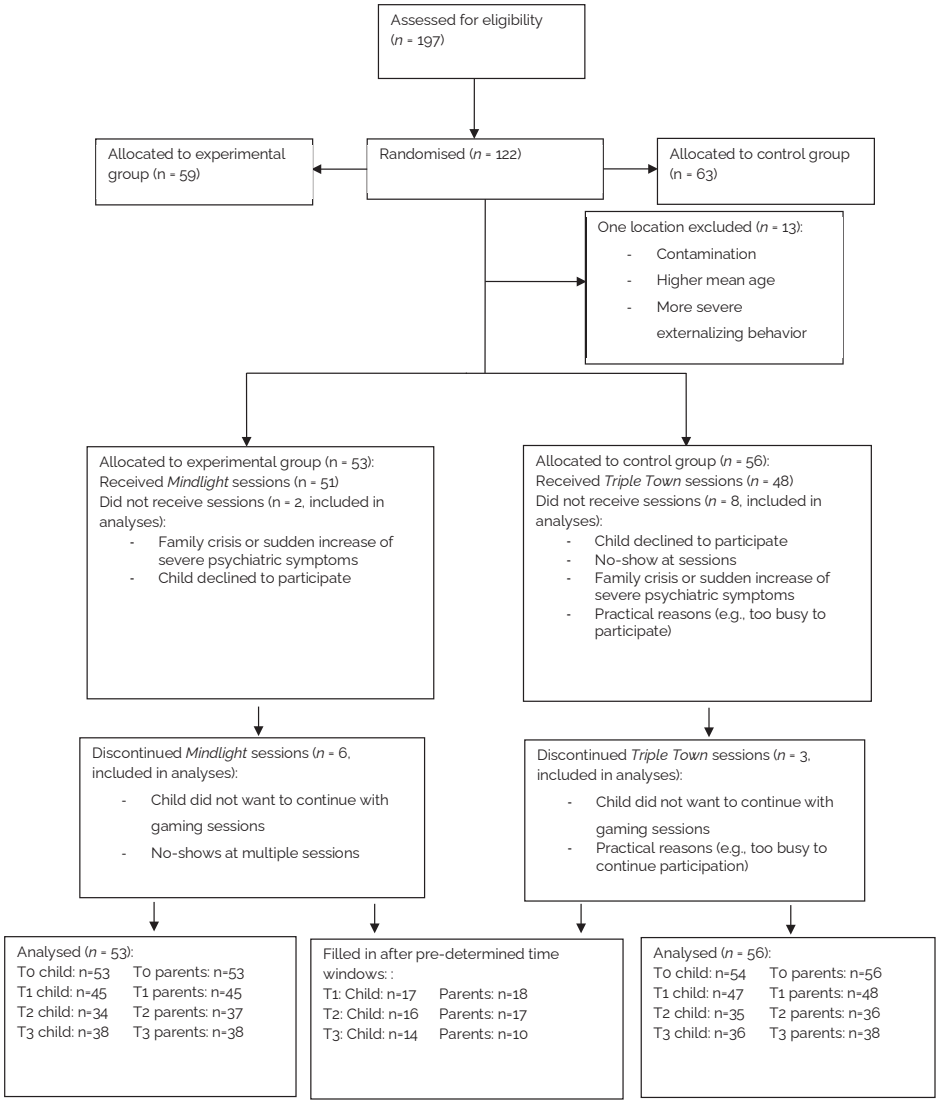


Figure 1. Participant flow from baseline through follow-up.

Treatment expectancies. The Parent Expectancies for Therapy Scale (PETS; Kazdin & Holland, 1991) was used to measure treatment expectancies. The PETS has a parent and child version, each consisting of seven items (e.g., 'I think this treatment is suitable for my/my child's complaints') measured on a 6-point scale ranging from 1 (I totally disagree) to 6 (I totally agree). The PETS has a high validity and reliability (Nock & Kazdin, 2001). Cronbach's alpha was .87 for the child-report and .79 for the parent-report.

Other secondary outcomes. Information about the other secondary outcomes can be found in Appendix A.

Intervention

Mindlight is a video game aimed at children of 8 - 16 years old and is based on principles of cognitive-behavioural therapy (CBT) and neurofeedback. Briefly, the premise of the game is that Little Arthur is left on the doorstep of a scary mansion by his parents. Arthur must learn to use his own inner strength to overcome his greatest fears so the shadows in the house can hold no power over him. He can accomplish this by using his *Mindlight*, a light bubble that can shine on the surroundings and that can be controlled by his own inner strength. This 'inner strength' was measured by a neurofeedback headset (the 'MindWave'; Neurosky USA; Johnstone, Blackman, & Bruggemann, 2012a), which children put on when they played *Mindlight*.

To minimize the chance of finding placebo-effects of *Mindlight*, children in the control condition received the computer game '*Triple Town*'. In this puzzle game, the player has to build a city. The bigger the city you build, the more points you can receive. *Triple Town* is a commercial game that did not have the aim to reduce anxiety levels of the participating children.

An Independent samples T-test showed that there was no significant difference in treatment adherence between the experimental and control condition ($p > .05$). More information about *Mindlight, Triple Town*, the protocol for the game sessions and treatment adherence can be found in Appendix B.

Analyses

The intended type of analyses that was described in the study protocol (Wijnhoven et al., 2015) was ANOVA repeated measures. Power analysis in G*Power 3.1 (Faul, Erdfelder, Lang, & Buchner, 2007) for this analysis showed that a sample of 120 participants would be necessary to find a moderate effect size (f=.25) with a power of .80, while compensating for potential loss to follow-up and clustering of data with a 40% increase in sample size. However, Latent Growth Curve Modeling (LGCM: Muthén & Muthén, 1998-2015) was chosen over ANOVA repeated measures, as LGCM provides more

information on individual change in anxiety symptoms over time. A Monte Carlo study conducted in M-plus (Muthén & Muthén, 2002) ensured the LGCM analyses were also adequately powered with the intended sample size of 120. Because the final sample was N = 109, the power decreased to .77.

First, descriptive statistics were computed with T-tests for independent groups for the different anxiety measures for boys and girls, and both conditions separately. LGCM was used to examine changes in anxiety symptoms over time. Full Information Maximum Likelihood (FIML) (Enders, 2010, p. 14; Johnson & Young, 2011) was used for handling missing values. This estimator requires that the missing data are at least 'missing at random'. With Little's MCAR test in SPSS 21 (IBM Corp., 2012), it was supported that this was the case for all primary and secondary variables. The Root Mean Square of Approximation (RMSEA; critical value ≤.08; Steiger, 1990), the Comparative Fit Index (CFI; critical value >.95; Marsh, 2004) and the chi-square (*df*) were used as model fit indices. The small samples of 53 (experimental group) and 56 (control group) and the missing data at T2 and T3 may have led to poor small sample performance of global fit criteria. The maximum likelihood chi-square statistic and RMSEA are fit measures less suited for small samples (n < 200; Taasoobshirazu & Wang, 2016; Chen, Curran, Bollen, Kirby & Paxton, 2008). However, Coffman and Millsap (2006) reported that despite a poor global fit, a model may provide a good approximation of the actual individual growth curve. Moreover, McNeish and Harring (2016) have developed a correction procedure for chi-squares in small samples with missing values based on the Bartlett correction (Bartlett, 1950). Applying this procedure led to more acceptable values (see Results).

Second, to decide which covariates to include in the final analyses, the potential effect of gender, age, medication use, treatment as usual (number of different types of TAU), intervention location, treatment expectancies, total IQ, ethnicity, parental marital status was first tested. First, all covariates were tested one by one as predictors of the intercept i and the slope s of the growth model for children and for parents. Significant covariates (gender for parents and children and treatment expectancies for children) were included in the latent growth curve analyses (growth models and testing differences in growth parameters between both conditions). The final step was to test differences in growth parameters between the two conditions using chi-square differences tests, controlling for gender (parents and children) and treatment expectancies (children).

Finally, remission rates were investigated by examining the number of children meeting the criteria of ADIS-P separation anxiety disorder, social phobia, specific phobia, panic disorder, agoraphobia and generalized anxiety disorder (Siebelink & Treffers, 2001) at T1 and T3. Moreover, we tested whether remission rates for all anxiety

disorders differed between the two conditions using binary logistic regression analyses in SPSS 21 (IBM Corp., 2012).

RESULTS

Pre-Intervention Differences

Demographic analyses indicated no variability in ethnicity (96% of the children were of Dutch origin). No significant differences were found between both conditions in age (t (107) = -1.08, p = .28), TIQ (t (86) = -1.14, p = .26), gender (χ^2 (1) = .71, p = .40), education of the child (χ^2 (3) = .51, p = .92) and parental marital status (χ^2 (4) = 4.51, p = .34). Therefore, no covariates were used to control for these background variables.

Descriptive statistics

Table 3 shows the descriptive statistics for the parent- and child-rated SCAS total scores at T0 and T1 for boys and girls. At T0 and T1, girls had significantly more child-rated anxiety symptoms than boys. For parent-rated anxiety, no significant differences were found in anxiety symptoms between girls and boys at T0 and T1.

Table 4 shows the means, standard deviations, and t-values for the parent- and child-rated SCAS total scores. Test results for randomly allocated groups at T0 were also reported in Table 4. At T1 and T2, no significant differences were found in parent- and child-rated anxiety symptoms between both conditions. At T3, children in the experimental condition had significantly less parent-rated anxiety symptoms than children in the control condition.

Furthermore, Table 5 shows the mean decrease and within-group effect sizes (Cohen's D) for both conditions. For the experimental condition, effect sizes were large for child-rated anxiety and large to very large for parent-rated anxiety. For the control condition, effect sizes were medium to large for child-rated anxiety and medium to large for parent-rated anxiety. For child-rated and parent-rated anxiety at T0-T2, the between-group effect-size was very small. For child-rated anxiety at T0-T3, the between-group effect-size was very small. For parent-rated anxiety at T0-T3, the between-group effect-size was medium.

Table 3

Means, Standard Deviations and t-values for Child-rated Anxiety (SCAS-C) and Parent-rated Anxiety (SCAS-P) at T0 and T1 for Boys and Girls

	Boys *n* = 84 *M (SD)*	Girls *n* = 25 *M (SD)*	*t*-value (df)
SCAS-C T0	30.91 (15.22)	40.44 (21.16)	-2.09 (32)*
SCAS-P T0	31.77 (13.12)	36.92 (10.40)	-1.80 (107)
SCAS-C T1	29.73 (13.49)	40.05 (21.01)	-2.17 (27)*
SCAS-P T1	29.35 (9.98)	32.77 (11.25)	-1.36 (91)

Note 1. *n* = number; *M* = mean; *SD* = standard deviation.
Note 2. For SCAS-C T0 and T1, df's are corrected for unequal variances.
* $p \leq .05$. ** $p \leq .01$. *** $p \leq .001$.

Table 4

Means, Standard Deviations and t-values for Child-rated Anxiety (SCAS-C) and Parent-rated Anxiety (SCAS-P) at T0, T1, T2 and T3 for the Experimental and Control Condition

	Experimental *n* = 53 *M (SD)*	Control *n* = 56 *M (SD)*	*t*-value (df)	*p*-value
SCAS-C T0	32.77 (15.32)	33.50 (18.94)	0.22 (105)	.83
SCAS-P T0	32.42 (11.49)	33.46 (13.81)	0.43 (107)	.76
SCAS-C T1	31.31 (14.93)	33.04 (17.28)	0.51 (90)	.61
SCAS-P T1	29.27 (10.12)	31.00 (10.57)	0.81 (91)	.42
SCAS-C T2	21.82 (10.62)	23.37 (12.06)	0.57 (67)	.57
SCAS-P T2	23.54 (10.37)	24.08 (8.91)	0.24 (71)	.81
SCAS-C T3	21.66 (11.68)	21.61 (11.66)	-0.02 (72)	.99
SCAS-P T3	20.08 (7.18)	23.92 (9.34)	2.01 (74)*	.05

Note. *n* = number; *M* = mean; *SD* = standard deviation.
* $p \leq .05$. ** $p \leq .01$. *** $p \leq .001$.

Table 5

Mean Decrease and Within-Group Effect Sizes (Cohen's D) for Child-rated Anxiety (SCAS-C) and Parent-rated Anxiety (SCAS-P) at T0-T2 and T0-T3 for the Experimental and Control Condition

	Experimental *n* = 53 *Diff*	Cohen's D	Control *n* = 56 *Diff*	Cohen's D	Between-group Cohen's D
SCAS-C T0-T2	10.95	.84	10.13	.76	.16
SCAS-P T0-T2	8.88	.90	9.38	.76	.11
SCAS-C T0-T3	11.11	.90	11.89	.81	.14
SCAS-P T0-T3	12.34	1.39	9.54	.70	.51

Note. *n* = number; *Diff* = difference.

Latent growth curve modeling analyzing child-rated anxiety symptoms[1]

It was tested whether a linear or quadratic function described the relationship between time and individual anxiety scores in the most optimal way. A linear model, with intercept *i* (initial level of anxiety) and slope *s* (degree of change of anxiety over time) fitted best to the data ($\chi^2(12)=45.64$, $p<.001$, CFI=.829 and RMSEA=.160). For the experimental condition, mean intercept was 32.53 and mean slope was -1.84 ($p<.001$). For the control condition, mean intercept was 33.43 and mean slope was -2.09 ($p<.001$). The course of child-rated anxiety symptoms is shown in Figure 2.

The intercept (*i*) and slope (*s*) were then regressed on gender and treatment expectancies. In the experimental condition, gender showed a significant effect on *i* (B=9.53, $p=.027$) and *s* (B=-1.92, $p=.002$), and in the control condition treatment expectancies showed a significant effect on *s* (B=-.13, $p=.005$). This means that girls in the experimental condition showed higher initial levels of child-rated anxiety and a greater decrease in child-rated anxiety symptoms than boys. Moreover, children in the control condition with higher treatment expectancies had a significantly greater decrease in child-rated anxiety symptoms.

The final step was testing differences in the growth parameters between both conditions while controlling for gender and treatment expectancies. The results are shown in Table 6. Constraints on *i* or *i* and *s* led to non-significant increases in chi-square indicating no significant difference between both conditions in the decrease of child-rated anxiety symptoms.

1 Latent growth curve analyses were also conducted for the total sample of *n*=122. The results of these additional analyses were comparable to the results described in the present study. For child-reported anxiety, constraints on *i* or *i* and *s* led to non-significant increases in chi-square, indicating no significant difference between the experimental and control condition. For parent-reported anxiety, constraining *i* and *s* to be equal in both conditions led to a significant increase in chi-square of 3.954 ($p=.047$), indicating that the decrease of parent-rated anxiety was significantly higher in the experimental condition compared to the control condition.

Table 6

Test Results of Differences in Growth Parameters for Child-rated (SCAS-C) and Parent-rated (SCAS-P) Anxiety Symptoms between Experimental and Control Condition

	χ^2	*df*	*p*	RMSEA	CFI	$\Delta\chi^2(1)$	*p*
Children							
baseline model	47.704	20	.000	.113	.866		
i constrained	48.151	21	.000	.109	.869	.447	.504
i + *s* constrained	49.569	22	.000	.107	.867	1.418	.234
Parents							
baseline model	30.303	16	<.001	.091	.920		
i constrained	30.497	17	<.001	.085	.924	.194	.660
i + *s* constrained	36.696	18	<.001	.098	.895	6.199	.013

Note: RMSEA = Root Mean Square of Approximation; CFI = Comparative Fit Index.

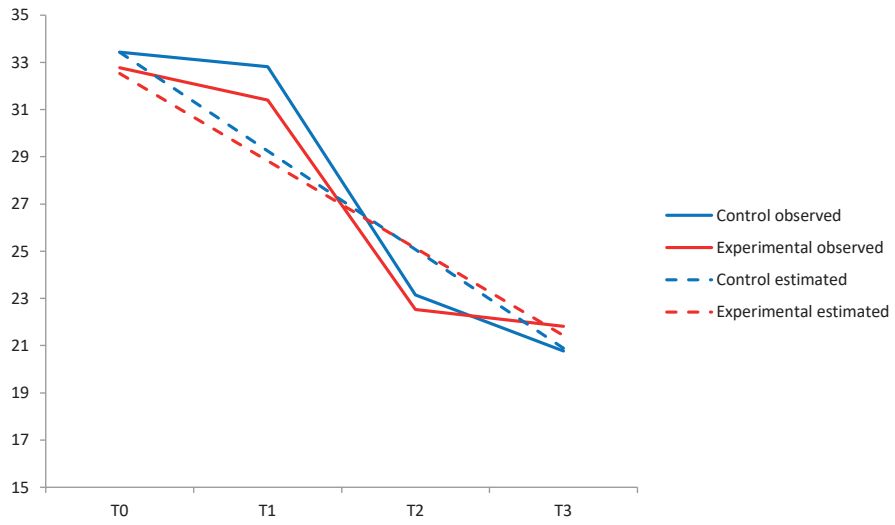


Figure 2. Observed and estimated values for child-rated anxiety symptoms (SCAS-C), illustrating the interaction between time (T0-T3) and condition (experimental/control).

Latent growth curve modeling analyzing parent-rated anxiety symptoms[1]

A linear model showed a best fit to the data ($\chi^2(12)=26.34$, $p<.001$, CFI=.919, RMSEA=.105). For the experimental condition, mean intercept was 32.38 and mean slope was -1.98 ($p<.001$). For the control condition, mean intercept was 33.39 and mean slope was -1.56 ($p<.001$). The course of parent-rated anxiety symptoms in both conditions over time is shown in Figure 3.

The intercept (*i*) and slope (*s*) were then regressed on gender. In the experimental condition, gender did not have a significant effect on *i* and *s* (*p*>.05) and in the control condition gender showed a significant effect on *s* (B=-1.50, *p*=.041). This means that girls in the control condition showed a significantly higher decrease of parent-rated anxiety symptoms than boys.

The final step was testing differences in the growth parameters between both conditions with the model of the second step as baseline model, which means that there was controlled for gender. The results are shown in Table 6. Constraining *i* to be equal in both conditions led to a non-significant increase in chi-square of .19 (*p*>.05). Constraining *i* and *s* to be equal in both conditions led to a significant increase in chi-square of 6.20 (*p*=.013), indicating that the decrease of parent-rated anxiety symptoms was significantly higher in the experimental condition compared to the control condition.

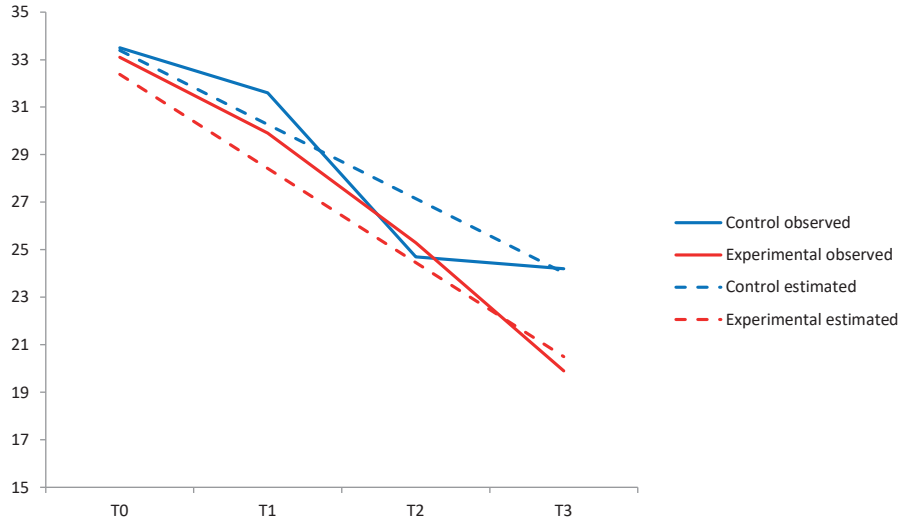


Figure 3. Observed and estimated values for parent-rated anxiety symptoms (SCAS-P), illustrating the interaction between time (T0-T3) and condition (experimental/control).

Remission rates

Table 7 shows remission rates based on the ADIS-P (Siebelink & Treffers, 2001) in the experimental and control condition. Remission rates did not significantly differ between both conditions (*p*>.05). For panic disorder and agoraphobia sample sizes were too small to analyze.

Table 7

Number of Children with ADIS-P Anxiety Disorder at T1, Remission Rates at T3 and Odds Ratios on Subscales Separation Anxiety Disorder, Social Phobia, Specific Phobia, Panic Disorder, Agoraphobia and Generalized Anxiety Disorder in Experimental and Control Condition

	Experimental		Control		OR [95% CI]
	n (%) with disorder at T1	*n* (%) with disorder at T3	*n* (%) with disorder at T1	*n* (%) with disorder at T3	
Separation Anxiety	13 (11.9)	4 (3.7)	12 (11.0)	6 (5.5)	2.25 [0.44, 11.52]
Social Phobia	26 (23.9)	17 (15.6)	31 (28.4)	20 (18.3)	0.96 [0.32, 2.87]
Specific Phobia	31 (28.4)	29 (26.6)	39 (35.8)	34 (31.2)	0.47 [0.09, 2.60]
Panic Disorder	1 (0.9)	0 (0.0)	3 (2.8)	0 (0.0)	-
Agoraphobia	1 (0.9)	0 (0.0)	1 (0.9)	0 (0.0)	-
Generalized Anxiety	22 (20.2)	13 (11.9)	26 (23.9)	20 (18.3)	2.31 [0.66, 8.03]
Any Anxiety Disorder	53 (100)	16 (30.2)	54 (96.4)	20 (37.0)	1.20 [0.51, 2.85]

Note. *n* = number; *%* = percentage; OR = Odds Ratio; CI = Confidence Interval; Any Anxiety Disorder = *n* (%) of children without any remitted anxiety disorder.

DISCUSSION

This study tested the effectiveness of video game *Mindlight* on anxiety symptoms and disorders in children with an ASD. Unexpectedly, there were no differences in the decrease of anxiety between the experimental and control condition according to children. Secondary outcomes showed that children who played *Mindlight* had greater improvements in parent-rated anxiety symptoms than *Triple Town* at 3-months follow-up. The medium effect size was in line with previous studies examining the effect of CBT (Sukhodolsky et al., 2013; Ung et al., 2015) on anxiety of children with ASD. No differences between *Mindlight* and *Triple Town* were found regarding remission rates, depressive symptoms, problematic social functioning and internalizing and externalizing behavior problems.

The course of child- and parent-rated anxiety symptoms and anxiety remission rates showed that anxiety in both conditions decreased to anxiety symptoms beneath (or equal to) the subclinical level at 3 months follow-up (SCAS-C T3 mean experimental: 21.66 < 30.98, control: 21.61 < 30.98; SCAS-P T3 mean experimental: 20.08 < 23.9, control: 23.92 = 23.9). It is possible that these similar effects in decrease of anxiety symptoms and disorders in both conditions could be explained by the overall positive effect of games on mental health of children (Ferguson & Olson, 2013; Granic, Lobel, & Engels, 2013). In both games children could have projected their anxious feelings on

elements in the game and the game play could have been used to cope with these anxious feelings, for example by relaxation (Ferguson & Olson, 2013). This would also be in line with previous studies showing that video games are effective in improving emotion regulation skills in children with ASD (e.g. Secret Agent Society; Beaumont, Rotolone, & Sofronoff, 2015). Furthermore, it is possible that not only the games had a within-subjects effect on anxiety symptoms of the participating children, but also TAU activities like medication, parent guidance or psycho-education. Furthermore, the therapeutic attention and alliance could have been a non-specific factor that partly explained the decrease of anxiety symptoms and disorders in both conditions (Crawford, Frank, Palitz, Davis, & Kendall, 2017).

The course of anxiety symptoms was similar for child-report and parent-report (see Figure 1), however results showed that only *Mindlight* had a significant effect on parent-rated anxiety symptoms. A potential explanation may be the focus of the story in *Mindlight* on "home-based" anxiety symptoms (e.g., darkness and monsters). Potentially, *Mindlight* did have a larger effect on these home-based anxiety symptoms than *Triple Town*, because of the stronger exposure to the home-based threatening cues in the game. This effect may be more visible for parents, as parents see their children at home every day. Children might also have experienced this effect on their home-based anxiety symptoms, but they still might have experienced some anxiety in other contexts because of their difficulty with generalization of skills they learned (de Marchena, Eigsti, & Yerys, 2015). The anxiety in other contexts (e.g., at school) might have been less visible for parents. Indeed, Craske and colleagues (2014) stated that anxiety regulation skills need to be practiced in multiple fearful contexts in order to remain effective. Moreover, possibly parents were more conscious of therapeutic elements in *Mindlight* (or absence of such elements in *Triple Town*) by the stories of their child about the game, in turn leading to increasing expectations of *Mindlight* during the course of the sessions.

Girls showed higher initial levels and a stronger decrease of anxiety symptoms than boys in the experimental condition. This could be explained by more intact pretend play skills in girls with an ASD as compared to boys (Knickmeyer, Wheelwright, & Baron-Cohen, 2008), ultimately leading to a greater projection of anxious feelings of girls on *Mindlight*. This way, girls may have benefitted more from the learnt coping skills and be better able to generalize learnt skills to daily life situations.

There are several strengths to the present study. First, this is the first study testing the impact of an applied game for anxiety in a sample of children with ASD. Moreover, the study was properly powered and used a rigorous RCT design, in particular for a clinical context. Previous studies investigated CBT treatment protocols that were often adapted to make them more suitable for children with an ASD (e.g., White et al.,

2010), but using an applied game as an intervention vehicle is a new way of creating an engaging treatment that suits the interests and abilities of children with an ASD. Third, the multi-method and multi-informant approach is a strength of the present study. Finally, the use of an active control condition in which children played a non-therapeutic game is also an advantage, providing us the opportunity to control for potential placebo or attention-specific effects of *Mindlight*.

There are also limitations to be discussed. There was drop-out and some assessments were completed too late. However, this is common in research conducted in a clinical context with multi-problem families. Another limitation pertains to the weak original model fits, which may be caused by the sample size (e.g., Taasoobshirazu & Wang, 2016). However, model fits were corrected, leading to more acceptable values (McNeish and Harring, 2016). Moreover, it remains unclear what mechanisms of change contributed to the decrease in anxiety symptoms. It is for example possible that not only the evidence-based elements of *Mindlight* did have had an effect on the anxiety symptoms of the participating children, but also non-specific factors such as wearing a neurofeedback headset during the game. Furthermore, the questionnaires (SCAS-C) in the present study were not specially designed for children with ASD (White et al., 2009). Despite the literature stating that children with high cognitive capacities are able to accurately report their thoughts and feelings (Ozsivadjian, Hibbert, & Hollocks, 2014; De-la-Iglesia & Olivar, 2015), it is possible that the participating children suffered from alexithymia (reduced ability to identify emotions; Bird & Cook, 2013) to some extent, which may have affected the reliability of the measures. Also, the interference of the research team in the content of TAU and the possible direct and indirect effect of specific content of TAU on anxiety are limitations of the present study. Finally, a limitation is that the ADIS-P was only used to measure remission rates of anxiety disorders and not as an indicator of (decrease in) anxiety severity.

Future research should focus on further confirming the efficacy of *Mindlight*, investigating its longitudinal effects and investigating its acceptability in a clinical sample. Moreover, it is important to examine potential moderators (e.g., psychiatric comorbidity). Finally, it should be studied how the generalizability could be further increased.

Conclusions

The present study provided some preliminary evidence that video games are a promising new intervention vehicle for children with an ASD and anxiety, at least according to parents. However, it remains unclear which specific or non-specific factors contributed to the decrease in anxiety symptoms in both conditions. Therefore, further research on working mechanisms is needed.

APPENDIX A

Other secondary outcomes

Child- and parent-rated depressive symptoms of children and parents were measured with the Dutch translation of the Child Depression Inventory 2 (CDI-2(:P); Kovacs et al., 2016). Parent-rated problematic social functioning was measured with the 'Vragenlijst voor Inventarisatie van Sociaal gedrag van Kinderen' (VISK), a Dutch translation of the Children's Social Behaviour Questionnaire (CSBQ; Luteijn, Jackson, Volkmar, & Minderaa, 1998). Parent-rated Internalizing and externalizing behaviour problems were measured with the Dutch translation of the Strengths and Difficulties Questionnaire (SDQ; Van Widenfelt, Goedhart, Treffers, & Goodman, 2003). All questionnaires have a good reliability and validity (Goedhart, Treffers, & Widenfelt, 2003; Hartman et al., 2007; Kovacs et al., 2016). Table 8 shows an overview of the different time points, all questionnaires, and informants.

Table 8

Overview of Assessments

	Screening (T0)	Pre-intervention (T1)	Post-intervention (T2)	3-months follow-up (T3)
Child				
Anxiety (SCAS-C)	X	X	X	X
Therapeutic expectancies (PETS)		X		
Depressive symptoms (CDI-2)		X	X	X
Parent				
Anxiety (SCAS-P)	X	X	X	X
Anxiety disorders (ADIS-P)		X		X
Therapeutic expectancies (PETS)		X		
Depressive symptoms (CDI-2:P)		X	X	X
Problematic social functioning (VISK)		X	X	X
Internalizing and externalizing behavior problems (SDQ)		X	X	X

Results of other secondary outcomes

Latent growth curve analyses on other secondary outcomes (depressive symptoms, problematic social functioning and internalizing and externalizing behavior problems) showed no significant differences between both conditions (see Table 9-12).

Table 9

Test Results of Differences in Growth Parameters for Child-rated Depressive Symptoms (CDI-2) between Experimental and Control Condition

	χ^2	*df*	*p*	RMSEA	CFI	$\Delta\chi^2(1)$	*p*
baseline model	15.60	6	.016	.121	.905		
i constrained	16.88	7	.018	.114	.902	1.28	.258
i + *s* constrained	16.89	8	.031	.101	.912	.01	.920

Note: RMSEA = Root Mean Square of Approximation; CFI = Comparative Fit Index.

Table 10

Test Results of Differences in Growth Parameters for Parent-rated Depressive Symptoms (CDI-2:P) between Experimental and Control Condition

	χ^2	*df*	*p*	RMSEA	CFI	$\Delta\chi^2(1)$	*p*
baseline model	10.22	4	.037	.120	.942		
i constrained	10.64	5	.059	.102	.948	.40	.527
i + *s* constrained	11.65	6	.070	.093	.948	1.01	.315

Note: RMSEA = Root Mean Square of Approximation; CFI = Comparative Fit Index.

Table 11

Test Results of Differences in Growth Parameters for Parent-rated Problematic Social Functioning (VISK) between Experimental and Control Condition

	χ^2	*df*	*p*	RMSEA	CFI	$\Delta\chi^2(1)$	*p*
baseline model	5.51	4	.239	.059	.987		
i constrained	6.32	5	.276	.049	.989	.81	.368
i + *s* constrained	6.79	6	.341	.035	.993	.47	.493

Note: RMSEA = Root Mean Square of Approximation; CFI = Comparative Fit Index.

Table 12

Test Results of Differences in Growth Parameters for Parent-rated Internalizing and Externalizing Behavior Problems (SDQ) between Experimental and Control Condition

	χ^2	*df*	*p*	RMSEA	CFI	$\Delta\chi^2(1)$	*p*
baseline model	5.65	4	.227	.062	.981		
i constrained	7.91	5	.161	.073	.967	2.26	.133
i + *s* constrained	8.40	6	.210	.061	.972	.49	.484

Note: RMSEA = Root Mean Square of Approximation; CFI = Comparative Fit Index.

APPENDIX B

Intervention

Mindlight is a video game aimed at children of 8 - 16 years old and is based on principles of cognitive-behavioural therapy (CBT) and neurofeedback, which are evidence-based interventions for anxiety-disordered children and adults. Briefly, the premise of the game is that Little Arthur is left on the doorstep of a scary mansion by his parents. Arthur must learn to use his own inner strength to overcome his greatest fears so the shadows in the house can hold no power over him. He can accomplish this by using his *Mindlight*, a light bubble that can shine on the surroundings and that can be controlled by his own inner strength. This 'inner strength' was measured by a neurofeedback headset (the 'MindWave'; Neurosky USA; Johnstone, Blackman, & Bruggemann, 2012a), which children put on when they played *Mindlight*. This headset recorded EEG using dry sensor technology, which consists of an active and reference electrode. The signals that were measured were filtered on Delta, Theta, Alpha and Beta waves. In *Mindlight*, especially the Alpha and Beta waves were used for real time feedback. Research has shown that the Mindwave headset has good reliability and validity (Johnstone et al., 2012a), and that it can be used in research with children who have a developmental disorder (e.g. ADHD; Johnstone et al., 2012b).

In *Mindlight*, the Alpha and Beta waves were used in several ways. First of all, the recorded Alpha waves reflected the degree of relaxation of the child. This feature was used in the exposure techniques (CBT) that are embedded in the game (see also Figure 2): when the child saw threatening stimuli (e.g. monsters) several times during the game and learned to maintain calm when facing them, the child eventually got habituated to them and could gain points more easily.

Furthermore, the recorded Beta waves reflected the degree of concentration and the allocation of attention of the player. Focused concentration allowed the player to solve attention bias modification (ABM) puzzles. ABM is a training protocol that has its roots in CBT and that is based on the idea that distorted cognitions, particularly attentional biases characterized by hyper attention towards potential threats, play a role in the pathogenesis of childhood anxiety (Hammond, 2005). ABM has been shown to reliably reduce anxiety by retraining the attentional system to focus on positive stimuli (Bar-Haim, 2010). *Mindlight* used this principle in the ABM-puzzles, by rewarding children for focusing on positive aspects of the environment (measured by the neurofeedback device). More specifically, they learned to move towards, and quickly respond to, positive stimuli (e.g., portraits of happy faces) and disattend to, or shift attention away from, negative stimuli (e.g., mean faces, threatening animals).

To minimize the chance of finding placebo-effects of *Mindlight*, children in the control condition also received a computer game. In this way, the amount of attention

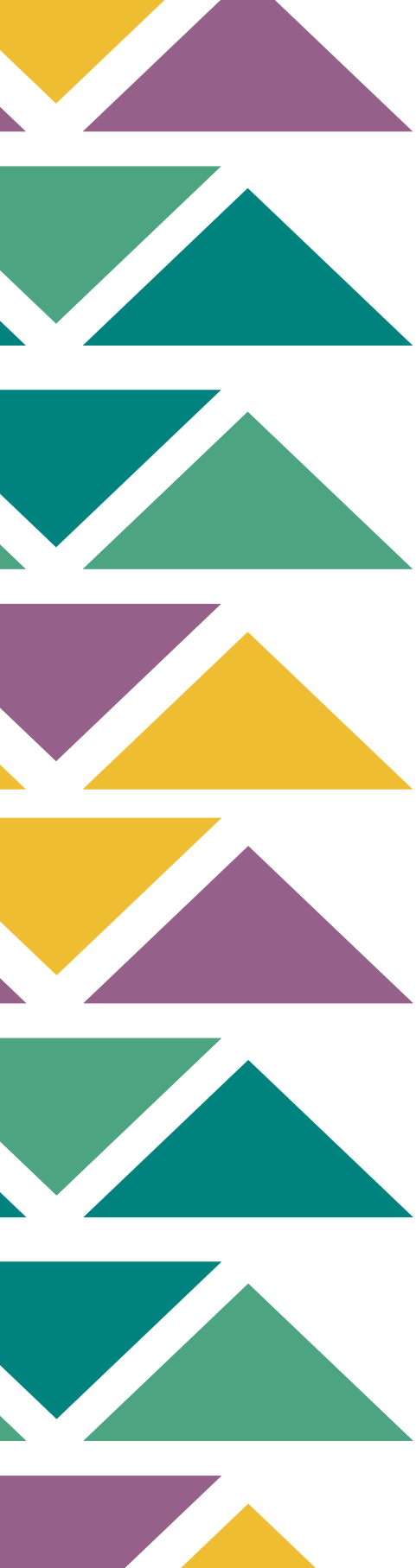
that children in the experimental condition and children in the control condition received was equal, and the parent-rated effects that were found could uniquely be ascribed to the game itself. The computer game that the children in the control condition played is called '*Triple Town*'. In this puzzle game, the player has to build a city. The bigger the city you build, the more points you can receive. To accomplish this, you have to combine elements (e.g. trees and houses) in a strategical way. Moreover, you have to block bears that try to hinder you in building the city. By playing this control game, children learned to think strategically in order to overcome challenges. Moreover, children learned to keep a goal and to persevere in order to reach this goal. However, the game was not specifically focused at reducing anxiety levels, which made '*Triple Town*' a suitable game for the control condition.

Table 13 shows the percentages of treatment adherence in the experimental and control condition. An Independent samples T-test showed that there was no significant difference in treatment adherence between the experimental and control condition ($p > .05$). The protocol for the gaming sessions was equal for the experimental and control condition. The gaming sessions were led by qualified therapists, or by master students who were supervised by qualified therapists. In session 1, the therapist started with psycho-education on anxiety. After that, the anxiety of the child was discussed, the therapist explained the game and eventually the therapist clarified that this game was focused on decreasing the anxiety of the child. Then, the child played the game for approximately 40 minutes. After playing the game, the therapist asked the following standardized questions: 1) How did the gaming go today? 2) What did you find difficult/ What did you find easy? 3) What did you learn in the game? 4) Could you apply and practice the skills you have learned in scary or difficult situations in daily life? In session 2-6, the therapist started the session with discussing the previous week and the skills the child had practiced at home. When the child mentioned that he had practiced the skills in a scary or difficult situation, this was reinforced by the therapist. In this way, the therapist did not add explicit therapeutic elements to the gaming sessions, but children did get stimulated to think about their anxiety and the way they could apply and practice the skills they had learned in the game in daily life.

Table 13

Percentages of Treatment Adherence in theExperimental and Control Condition

	Experimental %	Control %
0 sessions	3.8	14.3
1 session	3.8	1.8
2 sessions	3.8	0.0
3 sessions	0.0	1.8
4 sessions	3.8	1.8
5 sessions	11.3	0.0
6 sessions	73.6	80.4



CHAPTER 6

The moderating effect of externalizing behavior on the decrease of anxiety symptoms during a video game intervention for children with an Autism Spectrum Disorder

Authors:
Wijnhoven, L. A. M. W., Creemers, D. H. M., Engels, R. C. M. E., & Otten, R. (2019).

ABSTRACT

One of the most prevalent internalizing problems among children with an autism spectrum disorder (ASD) is anxiety. Moreover, it has been shown that anxiety is highly correlated to the presence of externalizing problems in children with ASD. In a recent Randomized Controlled Trial (RCT), the effect of the video game '*Mindlight*' on anxiety symptoms of children with an ASD was tested (Wijnhoven et al., submitted). Externalizing behavior is one of the possible factors that might have had a negative impact on the decrease of anxiety symptoms in children with ASD during the investigated video games. The aim of the present study was therefore to investigate the moderating effect of externalizing behavior on the decrease of anxiety symptoms during a video game intervention for children with an ASD. In total, 109 children of 8-16 years old with a diagnosis of an ASD and their parents participated in the present study. Parents filled in questionnaires to measure the level of anxiety symptoms at screening, pretest, posttest and 3-months follow-up. Moreover, parents filled in a questionnaire to measure the level of externalizing behavior at pretest. Results showed that externalizing behavior did not have an impact on the course of anxiety symptoms during a video game intervention for children with ASD. This implicates that this type of intervention does not have to be adapted to children with ASD and comorbid externalizing behavior and that video games might be a suitable intervention vehicle for these children, because it increases their motivation and engagement and in this way its effectiveness.

INTRODUCTION

Children with an Autism Spectrum Disorder (ASD) often have multiple comorbid psychiatric disorders (Joshi et al., 2010), including both internalizing and externalizing disorders (Vaillancourt et al., 2017). It has been found that 13% of the children with an ASD show a dual high-risk trajectory from childhood through adolescence with the stable presence of both internalizing and externalizing problems (Vaillancourt et al., 2017). One of the most prevalent internalizing problems among children with an ASD is anxiety, with 66.3% of the children experiencing at least child-rated subclinical anxiety and parent-rated prevalence of (sub)clinical anxiety even exceeding 80% (Wijnhoven, Creemers, Vermulst, & Granic, 2018). It has been shown that anxiety is highly correlated to the presence of externalizing problems in children with an ASD. For example, Farrugia and Hudson (2006) found that anxiety was associated with the presence of disruptive behavior in children with an ASD. Moreover, Ung and colleagues (2013) found that the percentage of comorbid externalizing diagnoses in children with an ASD and anxiety was high, with 34.26% of the children having a comorbid ADHD diagnosis and 29.63% of the children having a comorbid Oppositional defiant disorder diagnosis.

The correlation between anxiety and externalizing behavior in children with an ASD might be explained by their difficulty with emotion regulation (Samson et al., 2015). Because of their problematic emotion regulation, both feelings of anxiety and anger are often canalized in a dysfunctional way. For example, it has been shown that elevated levels of anxiety might lead to intense feelings of distress in children with an ASD. In turn, children with an ASD have difficulty with regulating these feelings of distress and show problematic behavior problems like irritability, temper outbursts, aggression and/or self-injurious behaviors to lower their distress (Samson, 2015). Moreover, it has been reported that externalizing behavior is used by children with an ASD to avoid or to escape from a fearful situation (Storch et al., 2012; Ung et al., 2013). In this way, externalizing behavior in children with an ASD might have a coping function. This combination of feelings of anxiety and externalizing behavior in children with an ASD is associated with high functional impairment in daily life and family interference (Storch et al., 2012).

In a recent Randomized Controlled Trial (RCT), the effect of the video game '*Mindlight*' on anxiety symptoms of children with an ASD was tested (Wijnhoven et al., submitted). In that study, it was shown that *Mindlight* was effective in decreasing parent-rated anxiety symptoms, but not in decreasing child-rated anxiety symptoms of children with an ASD. Moreover, children who played *Mindlight*, but also children who played the control game *Triple Town* showed a decrease in anxiety symptoms. It is however unclear which type of children with an ASD benefited most from the video

games that were studied and which individual factors played a role in the decrease of anxiety symptoms during both games. Externalizing behavior is one of the possible factors that might have had an influence on the decrease of anxiety symptoms in children with ASD during the investigated video games.

It has been reported that the interplay between anxiety and externalizing behavior in children with an ASD may complicate the course of treatment (Ung et al., 2013). For example, children with an ASD and externalizing behavior may refuse to participate in game sessions that focus on anxiety symptoms when they do not recognize the presence of anxiety and therefore the need for intervention (Ung et al., 2013). Moreover, it is possible that the combination of ASD and externalizing behavior has a negative impact on parents' ability to cope with daily situations in which disruptive behavior and anxiety are highly intertwined, because they do not recognize the underlying anxiety and only try to decrease the disruptive behavior (Storch et al., 2012). In turn, this may lead to a less effective parental support of the learned coping skills that children should use when they are anxious in daily situations. Finally, children with externalizing behavior may have difficulties with focusing on and learning from the intervention (video game) presented to them, because of poor impulse control and inattentive behavior (Eisenberg et al., 2009). Indeed, Antshel and colleagues (2011) showed that a social skills training was effective in increasing social skills in children with an ASD, but failed to improve social skills of children with an ASD and comorbid ADHD.

The aim of the present study was therefore to investigate the moderating effect of externalizing behavior on the decrease of anxiety symptoms during a video game intervention (*Mindlight* and *Triple Town*) for children with an ASD. It was expected that externalizing behavior would have a negative impact on the course of anxiety symptoms during the video game intervention. In other words, it was expected that children with more externalizing behavior showed a lower decrease in anxiety symptoms during the game sessions than children with less externalizing behavior. This would implicate that for children with an ASD, anxiety symptoms and comorbid externalizing behavior it is important to adapt anxiety treatment to their poor impulse control and inattentive behavior, or to first focus treatment on their externalizing behavior in order to improve effectiveness of the anxiety treatment.

METHOD

Procedure

The study was part of a Randomized Controlled Trial testing the effectiveness of video game ('*Mindlight*') tailored to decrease anxiety symptoms in children with an ASD (Wijnhoven et al., submitted; Dutch Trial Register NTR5069). The study was

carried out in accordance with the ethical standards of the medical ethics committee CMO Arnhem-Nijmegen in the Netherlands (NL50023.091.14) and the Declaration of Helsinki. Data were collected in two mental health institutes and one secondary school for special education. Children were eligible when parents and/or children had at least subclinical levels of anxiety SCAS-C; Scholing, Nauta, & Spence, 1999a, and SCAS-P; Scholing, Nauta, & Spence, 1999b) at screening (T0). Exclusion criterion was the presence of severe psychiatric problems that need immediate treatment. When active informed consent was obtained from parents and children above the age of 12 and when children eventually participated in the RCT, children and their parents filled in a pretest (T1), posttest (T2) and 3-months follow-up (T3), which included the SCAS-C (Scholing et al., 1999a) and SCAS-P (Scholing et al., 1999b) to measure anxiety symptoms over time. The questionnaires for parents also included a questionnaire for internalizing and externalizing behavior (SDQ; Van Widenfelt, Goedhart, Treffers, & Goodman, 2003). In total, 109 children participated in the RCT and the parents of these children filled in the SDQ at pretest (T1), posttest (T2) and 3-months follow-up (T3). In the present study, the score on externalizing behavior at pretest (T1) was used to test the moderating effect of externalizing behavior on the decrease of anxiety symptoms.

Participants

In total, 109 children of 8-16 years old with a diagnosis of an ASD and their parents participated in the RCT (Wijnhoven et al., submitted). Of the participating children, 84 were male (77.1%) and 25 were female (22.9%). Their age was between 8 and 16 years old (M = 11.10, SD = 2.07). Their mean SDQ-score on externalizing behavior at T1 was M = 9.09 (SD = 3.21), indicating a subclinical level of externalizing behavior (see Instruments). ASD diagnoses were based on psychological and/or psychiatric assessment of the Diagnostic and Statistical Manual of Mental Disorders 4th Edition – Text Revision (DSM-IV-TR; American Psychiatric Association, 2000) criteria for Autistic Disorder, Asperger's Disorder or PDD-NOS. This assessment was carried out by a clinical expert who conducted a diagnostic assessment that for example consisted of a developmental anamnesis with parents and/or standardized observation of the child with the Autism Diagnostic Observation Scale (ADOS; (Bildt, Greaves-Lord, & De Jonge, 2013). In total, 78 children (71.6%) had the diagnosis PDD-NOS, 20 children Asperger's Disorder (18.3%) and 11 children Autistic Disorder (10.1%). With the introduction of the DSM-5 (American Psychiatric Association, 2013), all diagnoses were transformed into the DSM-5 diagnosis Autism Spectrum Disorder. Moreover, some children had comorbid externalizing disorders and were diagnosed with ADHD (41.3%) or oppositional defiant disorder (2.8%).

Instruments

Parent-rated anxiety symptoms. Parent-rated anxiety symptoms were measured with the Dutch translation of the Spence Child Anxiety Scale for Parents (SCAS-P; Scholing, Nauta, & Spence, 1999b). The SCAS-P consists of 38 items on a 4-point scale ranging from 0 (never) to 3 (always). The items of the SCAS-P were formulated as closely as possible to the corresponding item of the child version of the SCAS. Only items referring to an internal state (e.g. item 4: 'I feel afraid') were rephrased into observable behaviour for parents (e.g. 'My child complains of feeling afraid'). Research showed that the SCAS-P has a good reliability and validity (Nauta et al., 2004). Cronbach's alpha ranged from .77 to .90 across assessment waves.

Parent-rated externalizing behaviour. Parent-rated externalizing behaviour was measured with the Dutch translation of the Strengths and Difficulties Questionnaire (SDQ; Van Widenfelt, Goedhart, Treffers, & Goodman, 2003). The SDQ consists of 25 items, measured on a 3-point scale (0 = not true, 1 = a little bit true, 2 = certainly true). The items of the SDQ are divided over the following subscales: emotional problems, behavior problems, hyperactivity-attention problems, problems with peers and social behavior. Based on the findings in the study of Goodman, Lamping and Ploubidis (2010), the combination of the subscales behavior problems and hyperactivity-attention problems (10 items) was used to measure externalizing behavior (with total score range of 0-20). The study of Maurice-Stam and colleagues (2018) showed that the clinical cut-off score on the SDQ for externalizing behavior in Dutch children of 6-11 years old was 10. Research has shown that the SDQ has a sufficient reliability and validity (Goedhart, Treffers, & Widenfelt, 2003). Cronbach's alpha ranged from .61 to .71 across assessment waves.

Intervention

In the RCT (Wijnhoven et al., submitted), 59 children received *Mindlight* (experimental condition) and 63 children received *Triple Town* (control condition). The premise of *Mindlight* is that Little Arthur is left on the doorstep of the scary mansion of his grandmother by his parents. Arthur must learn to use his own inner strength to overcome his greatest fears so the shadows in the house can hold no power over him. He can accomplish this by using his *Mindlight*, a light that shines on the surroundings and that can be controlled by his own inner strength. This 'inner strength' refers to the degree of relaxation and concentration of the child during the exposure to threatening cues and was measured by a neurofeedback headset (the 'MindWave'; Neurosky USA; Johnstone, Blackman, & Bruggemann, 2012), which children put on when they played *Mindlight*.

To control for placebo-effects of *Mindlight* when investigating its effectiveness, children in the control condition received a commercial puzzle game (*Triple Town*) without therapeutic elements. In this puzzle game, children had to build a city. The bigger the city they built, the more points they received. Children had to think strategically in order to overcome challenges and they had to persevere in order to reach their goal.

Because the gaming sessions in both the experimental and control condition took place in mental health agencies, they were supervised by qualified therapists, or by master students who were supervised by qualified therapists. Moreover, the therapists followed the same session protocol in the experimental and control condition. More information about *Mindlight* and the protocol for the game sessions can be found in the study protocol paper (Wijnhoven, Creemers, Engels, & Granic, 2015).

Analyses

Latent Growth Curve Modeling (LGCM) using the statistical package Mplus version 7.2 (Muthén & Muthén, 1998-2015) was applied to examine whether externalizing behavior had a moderating effect on the decrease of anxiety symptoms of the participating children. The first three steps of the LGCM were equal to the analyses that were conducted in the RCT (Wijnhoven et al., submitted). A fourth step was added to investigate the effect of externalizing behavior on the course of anxiety symptoms.

First, it was tested whether a linear or quadratic function described the relationship between time and individual anxiety scores in the most optimal way, with four time points at T0=0, T1=1.5, T2=3 and T3=6, corresponding with the number of months after screening (T0). To deal with missing values (externalizing behavior at T1: N = 16; anxiety symptoms at T0-T3: see Wijnhoven et al., submitted), we used Full Information Maximum Likelihood (FIML) estimator (Enders, 2010, p. 14; Johnson & Young, 2011). The Root Mean Square of Approximation (RMSEA; critical value ≤.08; Steiger, 1990), the Comparative Fit Index (CFI; critical value >.95; Marsh, Hau, & Wen, 2004) and the chi-square (*df*) were used as model fit indices. The small sample correction of McNeish and Harring (2016) was used to correct the chi-squares, which has shown to lead to more acceptable values in small samples with missing values. In the second step, the covariate gender was added to the model. In the third step, it was tested whether the intercept and slope were different for the control (*Triple Town*) and experimental (*Mindlight*) condition. In a fourth and final step, it was tested whether the intercept and slope of the experimental and control condition could be predicted by externalizing behavior.

RESULTS

First, the latent growth curve of anxiety was developed. A linear model showed a best fit to the data ($\chi^2(12)=26.34$, $p<.001$, CFI=.919 and RMSEA=.105). For the experimental condition, mean intercept was 32.38 and mean slope was -1.98 ($p<.001$). For the control condition, mean intercept was 33.39 and mean slope was -1.56 ($p<.001$).

The intercept (*i*) and slope (*s*) were then regressed on the covariate gender. This model showed a fit of $\chi^2(16)=30.30$, $p<.001$, CFI=.920 and RMSEA=.091. In the experimental condition, gender did not have a significant effect on *i* and *s* (p>.05) and in the control condition gender showed a significant effect on *s* (B=-1.50, $p=.041$).

The third step was testing differences in the growth parameters between the experimental and control condition. Constraining *i* to be equal in both conditions led to a non-significant increase in chi-square of .19 ($p>.05$). Constraining *i* and *s* to be equal in both conditions led to a significant increase in chi-square of 6.20 ($p=.013$). This means that the decrease of parent-rated anxiety symptoms was significantly higher in the experimental condition compared to the control condition.

The fourth and final step was testing whether externalizing behavior had an effect on the course of anxiety symptoms in the experimental and control condition. Therefore, *i* and *s* were regressed on gender and externalizing behavior. Model fit was $\chi^2(22)=37.78$, $p<.001$, CFI=.911 and RMSEA=.081. Both in the experimental and control condition, externalizing behavior did not have a significant effect on *i* and *s* (p>.05). This means that externalizing behavior did not have a significant effect on the decrease of anxiety symptoms in both the experimental and control condition.[2]

DISCUSSION

The aim of the present study was to test the moderating effect of externalizing behavior on the decrease of anxiety symptoms during a video game intervention (*Mindlight* and *Triple Town*) for children with an ASD. Contrary to the expectations, externalizing behavior did not have an impact on the course of anxiety symptoms during a video game intervention for children with ASD.

The findings in the present study are in contrast with the findings in the study of Antshel and colleagues (2011), who found that children with ASD and comorbid ADHD failed to improve during a social skills group intervention treatment. An explanation for this difference could be that individual game interventions are more suitable and

2 When the effect of externalizing behavior on the decrease of anxiety in the total group was investigated, equal results were found: there was no significant effect of externalizing behavior on the intercept nor the slope of anxiety symptoms (resp. B = -0.052, $p = 0.289$; B = -0.004, $p = 0.929$).

therefore more effective for children with ASD and externalizing behavior than group interventions, as in the study of Antshel and colleagues (2011).

First of all, children may have more influence on the course of individual game sessions than on the course of a group intervention. Greater autonomy in gameplay has been found to relate to more self-esteem, positive mood and motivation in game players (Ryan, Rigby, & Przybylski, 2006). *Mindlight* and *Triple Town* sessions in the RCT had a standardized beginning and ending, but the course of the game play itself could be fully determined by the child, whereas in group sessions, the course of the session often is standardized (e.g., by a protocol). It is possible that this greater autonomy led to a greater persistent, optimistic motivational style in the participating children than a group therapy environment (Granic, Lobel, & Engels, 2013; Ryan et al., 2006). In turn, this may have led to less externalizing behavior and a greater focus and engagement during the game sessions than during the social skills group intervention. In this way, externalizing behavior might not have had a negative impact on the decrease of anxiety symptoms during the video game interventions.

Moreover, children might receive more therapeutic attention in individual game sessions than in a group intervention. It has already been shown that therapeutic attention and alliance are non-specific factors that partly explain the decrease of mental health problems during treatment (Crawford, Frank, Palitz, Davis, & Kendall, 2017). In the *Mindlight* and *Triple Town* sessions, children played the game on their own without extensive interference or supervision of a therapist. However, if the child needed help or attention, the therapist was able to directly offer the help the child needed at that moment. In group sessions, children may have to wait before they receive help or attention from the therapist. For children with high externalizing behavior, the possibility of direct therapeutic attention might especially be important, because of impulsive and inattentive behavior (e.g., interrupting the session protocol and lack of ability to wait for help) and low regulation of behavior and emotions (e.g., becoming angry during an exercise) that is often present in these children (Eisenberg et al., 2009; Eisenberg et al., 2001). The presence of a therapist who can offer help and attention when needed, might therefore be more suitable and effective for children with ASD and externalizing behavior.

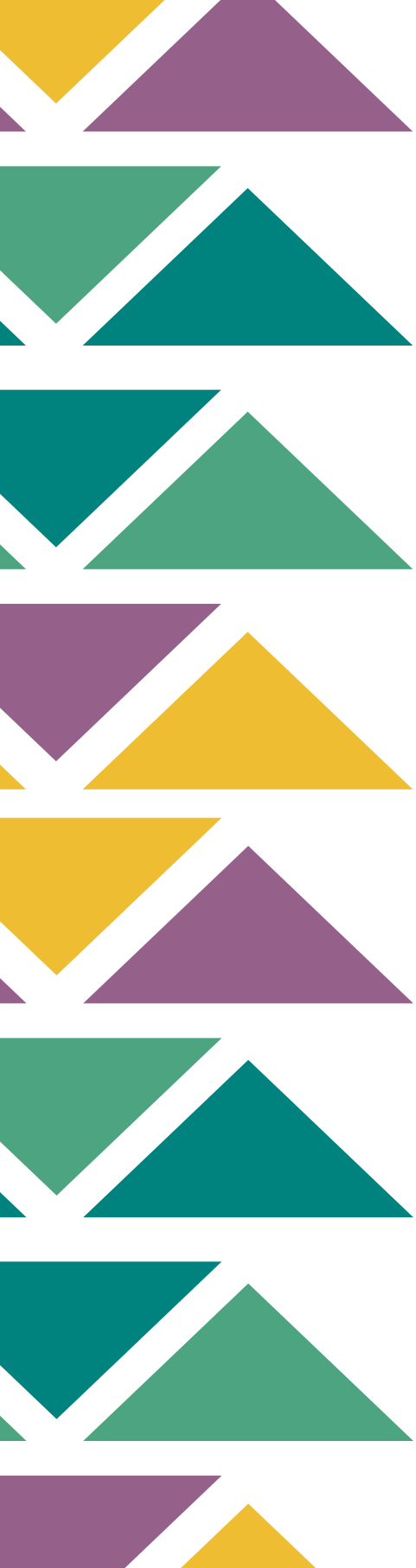
Another explanation for the difference in outcomes between the study of Antshel and colleagues (2011) and the present study is that in the study of Antshel and colleagues (2011), the children with externalizing behavior were all diagnosed with ADHD. In the present study, a continuous measure of externalizing behavior was used. Moreover, only part of the children in the sample was diagnosed with ADHD (41.3%) and the mean SDQ-score on externalizing behavior did not exceed the clinical cut-off (M = 9.09; clinical cut-off = 10). It is possible that therefore the children in our sample had

milder externalizing problems than the children in the sample of the study of Antshel and colleagues (2011), leading to a smaller negative impact of externalizing behavior on the decrease of anxiety symptoms during the intervention.

The present study has some limitations. First, it is possible that parents filled in the items on externalizing behavior on basis of the behavior of their child at that moment. It is possible that the child was acting out at the moment the parent filled in the questionnaire, but that this child typically did not show externalizing behavior. This might especially be the case for children that did not have a comorbid diagnosis of ADHD or ODD. In this way, it is possible that the outcomes on the measure of externalizing behavior in the present study did not fully represent the behavior of the child during the game sessions. Second, only parent-ratings of externalizing behavior were used in the present study. A multi-informant approach of parent-ratings, therapist-ratings and teacher-ratings would have led to a more reliable and representative measure of externalizing behavior in the present study.

Future research should further investigate the individual factors that determine which type of children with ASD benefit most from video game interventions like *Mindlight*. In this way, therapists can better determine for which type of children with ASD video games are most suitable and effective.

This study has a few implications for clinical practice. The findings in the present study indicate that externalizing behavior in children with ASD did not have a negative impact on the effect of a video game intervention on anxiety symptoms. This implicates that this type of intervention does not have to be adapted to children with ASD and comorbid externalizing behavior and that video games might be a suitable intervention vehicle for these children, because it increases their motivation and engagement and in this way its effectiveness. Therefore, it is important to further improve and investigate this way of treating mental health problems in children with ASD.



CHAPTER 7

A Single Case Series Design Testing the Additive Effect of CBT Elements on the Video Game *Mindlight* in Decreasing Anxiety Symptoms of Children with an Autism Spectrum Disorder

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ABSTRACT

The applied video game *Mindlight* was developed for treatment of anxiety symptoms and disorders in children. A recent randomized controlled trial (RCT) investigated the effect of *Mindlight* on anxiety in children with autism spectrum disorder (ASD) and showed that *Mindlight* was more effective than a control game in decreasing parent-rated anxiety symptoms, but not in decreasing child-rated anxiety symptoms. Based on experiences during the RCT, it was hypothesized that adding elements of cognitive behavioral therapy (CBT) could further enhance the effect of *Mindlight*. Therefore, the aim of the present study was to examine the additive effect of CBT elements on *Mindlight* in decreasing anxiety symptoms of children with ASD in a clinical setting. Moreover, it was tested whether perceived coping skills of children showed a higher increase during CBT compared to *Mindlight*. To study this, a non-concurrent multiple baseline design with 8 children with ASD in the age of 8-12 was used. Results showed that CBT did not have the hypothesized additive effect on *Mindlight* in decreasing anxiety of children with ASD. Instead, multiple participants already experienced a decrease in anxiety symptoms during the *Mindlight* sessions. Yet, several participants did experience a stabilization in anxiety symptoms at a low level during the CBT sessions in combination with an increase in coping skills. For now, it can be concluded that *Mindlight* in combination with CBT might be a potential effective treatment for some children with ASD and anxiety that clinicians could consider to use in daily practice in the future.

INTRODUCTION

Video games have the potential to enhance mental health and well-being in children and adolescents (Granic, Lobel, & Engels, 2014; Ferguson & Olson, 2013). The applied video game *Mindlight* was developed for treatment of anxiety symptoms and disorders in children. Recent studies have shown that *Mindlight* was equally effective as a control game, as well as to the Dutch translation of the CBT group treatment protocol Coping Cat (Nauta & Scholing, 1998) in decreasing anxiety symptoms over time (Schoneveld et al., 2016; Schoneveld, Lichtwarck-Aschoff, & Granic, 2018). A more recent randomized controlled trial (RCT; Wijnhoven et al., submitted) tested whether *Mindlight* was effective in decreasing anxiety symptoms in children with autism spectrum disorder (ASD) in a clinical setting. This study showed that *Mindlight* was more effective than a control game in decreasing parent-rated anxiety symptoms. Yet, the intervention was not more effective than a control game in decreasing child-rated anxiety symptoms. Based on experiences during the RCT, it was hypothesized that adding elements of cognitive behavioral therapy (CBT) could further enhance the effect of *Mindlight*. Therefore, the aim of the present - non-concurrent multiple baseline - study was to examine the additive effect of CBT elements on *Mindlight* in decreasing anxiety symptoms of children with ASD in a clinical setting.

Mindlight aims to tackle anxiety in children by using exposure to threatening cues (Abramowitz, Deacon, & Whiteside, 2011; Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014), neurofeedback to help train children to regulate arousal levels associated with anxiety (Hammond, 2005) and attention bias modification (Muris & Field, 2008; see study protocol for more information about *Mindlight*: Wijnhoven, Creemers, Engels, & Granic, 2015). There are several reasons why *Mindlight* could be effective in decreasing anxiety in children with ASD. It is known that children with ASD profit more from visual prompts and structured sensory information than from verbal information (Johnco & Storch, 2015; Silver & Oaks, 2001). *Mindlight* is a computer based intervention that uses visual aids and structured sensory information to train emotion regulation skills (e.g., relaxation). Moreover, in the treatment of children with ASD it is important to translate their special interests in metaphors (Johnco & Storch, 2015). Therapists could use the metaphors in *Mindlight* (e.g., the main character 'Arty') to explain therapeutic content, to reinforce treatment participation and to build a therapeutic relationship. Finally, children with ASD have difficulties with recognizing and expressing their thoughts and feelings (White, Oswald, Ollendick, & Scahill, 2009). *Mindlight* is an experiential game, which means that it makes children aware of their physical and emotional feelings and the way in which they could alter these feelings.

Despite the effective and suitable treatment elements in *Mindlight*, it is still unclear how to design therapy sessions in clinical practice in order to maximize the effect of

the game intervention on anxiety symptoms of children with ASD. In the RCT that was performed to test the effect of *Mindlight* on anxiety symptoms of children with ASD (Wijnhoven et al., submitted), therapists supervised the *Mindlight* sessions of the children without offering therapeutic elements. Results of that study showed that child-rated anxiety symptoms decreased during the game sessions, but increased again between post-intervention and the 3-months follow-up. An explanation for this increase might be that children with ASD do not automatically know how to use the coping skills they learned during the game in scary situations they encounter in daily life. Research indeed showed that children with ASD have difficulties with generalizing skills they learned in therapy to multiple contexts in daily life (White et al., 2009; McNallyKeehn et al., 2013). Craske and colleagues (2014) suggested that anxiety regulation skills need to be practiced in multiple fearful contexts in order to generalize and remain effective. This indicated that children who played *Mindlight* need to practice the skills they learned in multiple daily life situations (e.g., at school and during social activities) in order to generalize the learned coping skills and to maintain long-lasting effects.

Ceranoglu (2010) reported that video games in therapy could support the therapist in building a therapeutic relationship, evaluating a child's cognitive processing style, and elaborating and clarifying internal conflicts of the child. These are potential positive effects of video games on therapist-child interactions and coping skills of children *during* the therapy sessions. However, little is known about how to establish optimal generalization of the coping skills children learned in the video game to daily life situations. Swan, Carper and Kendall (2016) stated that coping skills are adaptive ways of processing and reacting to internal and external stressors that could be learned in therapy, but that these skills would also need to be applied and practiced in daily life. Moreover, the authors argued that the generalization of coping skills to daily life could be maximized by the therapist by providing elements of cognitive behavioral therapy (CBT) that focus on altering cognitive biases and dysfunctional behavior. These elements could be used to increase the reinforcement of desired behavior, stimulating practice in multiple anxiety-provoking situations and to increase the use of reminders of learned skills (e.g., 'coping thoughts'; Swan et al., 2016).

These insights could also be used to maximize the generalization of the learned coping skills in *Mindlight* to daily life. It is argued that CBT elements could be used by the therapist to explore together with the child in what way they could practice coping skills they learned in daily life (e.g., at school) by using the experiences during the gameplay. Fernando and colleagues (2015) showed that using a combination of video game sessions and therapist-guided CBT improved therapy effects and enhanced treatment adherence in adolescents with bulimia nervosa when compared with

treatment as usual. It was expected that the addition of CBT elements to the *Mindlight* sessions would maximize therapeutic effects on anxiety symptoms of children with ASD.

Theoretical background *Mindlight*-CBT sessions

Cognitive biases form an important underlying mechanism of anxiety symptoms in children (Waters, Wharton, Zimmer-Gembeck, & Craske, 2008). These biases comprise an increased attention to threatening cues and a fearful interpretation of these cues, which elicits feelings of anxiety in children. Research has shown that these biases are also present in anxious children with ASD (Luxford, Hadwin, & Kovshoff, 2017). When these biases continue to exist, threatening cues maintain the capacity to prompt anxiety in children over time and may even lead to increasing avoidance of those threatening cues (Waters et al., 2008). Therefore, it is important to target both the attention bias and interpretation bias in treatment of anxiety symptoms in children.

In the game *Mindlight*, children are exposed to threatening cues (e.g., monsters) and they experience how they can regulate their anxiety during exposure by neurofeedback (Hammond, 2005). Moreover, attention bias modification puzzles are aimed at letting children experience how to shift attention towards positive stimuli and shift attention away from negative and threatening stimuli (Muris & Field, 2008). It has been shown that it is important to specifically (and not implicitly) target attentional processes for threat-biases in anxiety treatment for children in order to change these biases (Waters et al., 2008; Waters et al., 2018), which makes the attention bias modification puzzles an important element in *Mindlight*. Altogether, *Mindlight* is an experiential way of learning how to cope with anxious thoughts and feelings, in which children do not actively need to reflect on this learning process. However, reflection on this learning process could result in generating effective 'coping thoughts' that might improve the generalization of the coping skills that children with ASD learned in *Mindlight* to daily life (Swan et al., 2016).

In the CBT-sessions, reflection is introduced by the therapist by exploring the interpretation biases of the child during the gameplay. This can be realized by helping the child in expressing the experienced anxious cognitions and feelings during the play of *Mindlight*. Also, therapist and child could discuss in which way the child decreased or altered these anxious cognitions during the game. By using the experiences during *Mindlight*, this reflection process could be made easier, more vivid and more engaging for the child than in 'normal' CBT-sessions, which has shown to be important in children with ASD (Johnco & Storch, 2015). In turn, they could examine in which daily situations they also experienced these anxious cognitions and how they could use the skills they learnt in the game in these specific situations to alter the anxious cognitions

(cognitive restructuring; Waters et al., 2008) into the earlier described 'coping thoughts' (e.g., 'When I breath calmly in and out, I can do this'). In their homework (exposure) exercises, children could practice the skills they learnt in scary situations at school, at home and at social activities, which in turn could improve their overall coping skills in multiple scary situations in daily life (Craske et al., 2014; Swan et al., 2016). Moreover, parents are involved in the CBT-sessions to transfer the control from the therapist to the parents, and to stimulate parents to support their children in practicing learned coping skills at home (Swan et al., 2016), which has shown to be especially important in CBT for children with ASD (Storch et al., 2013). By adding CBT elements to the *Mindlight* sessions, attention biases and interpretation biases are targeted. Eventually, this could lead to a better generalization of coping skills to daily life and to a higher total decrease of anxiety symptoms in children with ASD.

Design and hypotheses

The aim of this study was to examine the potential additive effect of evidence-based CBT elements (cognitive restructuring and exposure to multiple daily situations) on *Mindlight* in decreasing child-rated anxiety symptoms of children with ASD in a clinical setting. Moreover, it was tested whether perceived coping skills of children showed a higher increase during CBT compared to *Mindlight*. To study this, a non-concurrent multiple baseline design was used (see Onghena & Edgington, 2005; Smith, 2012). Because daily assessments were administered, the course of the anxiety symptoms could be investigated in a more elaborate way. Moreover, coping skills were assessed, resulting in a more extensive analysis of the potential working mechanisms of *Mindlight* and CBT. It was expected that CBT elements would increase the effect of *Mindlight* on child-rated anxiety symptoms of children with ASD. Moreover, it was expected that perceived coping skills of children showed a higher increase during CBT compared to *Mindlight* exclusively.

MATERIALS AND METHODS

Procedure

A medical ethics committee approved the current study (NL50023.091.14) and all procedures were in accordance with the 1964 Helsinki declaration. In the concurrent multiple baseline design that was used (Onghena & Edgington, 2005; Smith, 2012; see Figure 1), participating children were randomly assigned to four different lengths (A-D) of baseline periods (Baseline phase; M). These baseline periods consisted of playing *Mindlight* in weekly sessions of one hour. After the *Mindlight* sessions (Baseline phase; M), participants received two weekly CBT sessions of one hour (Treatment phase; T).

By offering *Mindlight* in the baseline phase and CBT sessions in the treatment phase, the additive effect of CBT elements on *Mindlight* could be investigated. By randomly determining the start of the CBT sessions, it was possible to statistically control for external factors such as therapeutic attention, repeated testing and maturation.

In the present study, *N*=8 children with ASD in the age of 8-12 years old participated. Context of recruitment was a mental health institute (GGZ Oost Brabant) in the Netherlands. To determine eligibility, parents and children filled in a screening (T0) on anxiety symptoms (SCAS-C for children; Scholing, Nauta, & Spence, 1999a; SCAS-P for parents; Scholing, Nauta, & Spence, 1999b). If children had at least subclinical anxiety symptoms, they were approached for participation. When children and parents agreed to participate, active written informed consent of the parents was obtained. Participating children were randomly assigned to a baseline period of 4-7 weekly *Mindlight* sessions (see Figure 1: A=4, B=5, C=6, D=7 *Mindlight* sessions). In total, two children were randomly assigned to each baseline length. Children and parents rated the child's anxiety level on a scale of 0-10 on a daily basis during 10 weeks (70 days) after the first baseline assessment, which took place one week before the start of *Mindlight*. Primary and secondary outcomes were assessed before the start of *Mindlight* (T1; see Figure 1), after the last *Mindlight* session (T2), after the last CBT session (T3) and at 3-months follow-up (T4). Moreover, parents underwent a semi-structured interview (ADIS-P; Siebelink & Treffers, 2001) at T1 and at T4 to determine the remission rates of the anxiety disorders that are described in the Diagnostic and Statistical Manual of Mental Disorders 4th Edition – Text Revision (DSM-IV-TR; American Psychiatric Association, 2000).

	A	B	C	D	
0					T1
7	M	M	M	M	
14	M	M	M	M	
21	M	M	M	M	
28	M	M	M	M	T2 A
35	T	M	M	M	T2 B
42	T	T	M	M	T2 C; T3 A
49		T	T	M	T2 D; T3 B
56			T	T	T3 C
63				T	T3 D
70					

Figure 1. Overview of daily measurements (0-70) and the time points for the start of *Mindlight* (M), CBT (T) and T1-T3 in all four baselines (A=4, B=5, C=6, D=7 *Mindlight* sessions).

Participants

In total, 8 children (7 boys and 1 girl) of 8-12 years old with a diagnosis of an ASD participated in the present study. ASD diagnoses were based on psychological and/or psychiatric assessment of the DSM-IV (American Psychiatric Association, 2000) criteria for Autistic Disorder, Asperger's Disorder or PDD-NOS. This assessment was carried out by a clinical expert who conducted a diagnostic assessment that was adapted to the diagnostic 'needs' of the individual child and for example consisted of a developmental anamnesis with parents and/or standardized observation of the child with the Autism Diagnostic Observation Scale (ADOS; Bildt, Greaves-Lord, & De Jonge, 2013). The other inclusion criterion was the presence of at least subclinical anxiety symptoms, defined by mean + 1 SD on the total score and/or one or more subscales (OCD subscale excluded) of the SCAS-C and/or SCAS-P (Muris, Schmidt, & Merkelbach, 2000; Nauta et al., 2004). Exclusion criteria were absence of parental permission and presence of prominent suicidal ideation or other severe psychiatric problems that need immediate treatment (e.g., severe trauma). Moreover, children with ASD who already received treatment for their anxiety symptoms were excluded. Receiving treatment for other ASD-related symptoms was not an exclusion criterion. All participants (and/or their parents) received psychological and/or pharmaceutical treatment for other ASD-related symptoms. All participating children were in primary school, with two children following special education. The total IQ of all children was > 85. All children were of Dutch origin.

Participant 1 (4-Week Baseline)

Participant 1 is an 8-year old boy that was included in the present study because of clinical levels of social phobia and specific phobia symptoms and subclinical levels of generalized anxiety symptoms. He had a fear of making mistakes in school assignments and was afraid of unprepared and unpredictable school situations. He was often afraid of being bullied by classmates and had a fear of failure in interactions with other children. At home he worried a lot about the above described subjects. Because of these worries and fears, he wanted to stay with his parents and he showed resistance to go to school multiple days per week. Finally, he was afraid of various types of birds, dolls and heights.

Participant 2 (4-Week Baseline)

Participant 2 is a 12-year old boy that was included in the present study because of clinical levels of specific phobia and subclinical levels of separation anxiety, panic disorder/agoraphobia and generalized anxiety symptoms. He was afraid of thunder/lightening, injections, airplanes/flying and firework. Moreover, he was afraid of

becoming sick and getting a severe illness. Furthermore, he was afraid of sleeping alone and being home alone. Finally, he was afraid of going to crowded places and he worried a lot about the health of his family and himself and severe events that took place in the world, like war and terroristic attacks.

Participant 3 (5-Week Baseline)

Participant 3 was a boy of 8 years old that was included in the study because of clinical levels of specific phobia and generalized anxiety symptoms and subclinical levels of separation anxiety. He was afraid of choking in water and did not dare to swim underwater for a longer period of time. Moreover, he worried a lot about how his friends would think about him and about his school achievements. Finally, he was afraid to be home alone and to be away from home for a night.

Participant 4 (5-Week Baseline)

Participant 4 is a 10-year old boy that entered the study with clinical levels of social phobia, specific phobia and generalized anxiety symptoms. He showed a resistance to go to school because of his anxious feelings. He was afraid that he would do shameful things in interactions with other children and he was afraid of making mistakes in his school assignments. He worried a lot about his achievements at school and about his interactions with other children. He also complained about having 'strange thoughts' about scary persons when he went to bed. Moreover, he had specific fears for bees/ insects, thunder/lightning, blood, loud noises and throwing up.

Participant 5 (6-Week Baseline)

Participant 5 was a 10-year old girl that was included in the present study because of clinical levels of social phobia and specific phobia symptoms and subclinical levels of separation anxiety and generalized anxiety symptoms. She was afraid of making mistakes in school assignments and of asking for help in school situations. She worried about her achievements at school. Finally, she had specific fears for loud noises and darkness.

Participant 6 (6-Week Baseline)

Participant 6 was a boy of 10 years old that was included in the present study because of social phobia symptoms on a clinical level that were reported by both himself and by his parents. He had a strong fear of failure at school and in interactions with other children. His biggest fear was to make mistakes in social situations. Participant 6 did not suffer from other types of anxiety symptoms.

Participant 7 (7-Week Baseline)

Participant 7 was a 8-year old boy that was included in this study because of clinical levels of social phobia symptoms, specific phobia symptoms and generalized anxiety symptoms. Moreover, he had subclinical levels of panic disorder. He was afraid of making mistakes in school assignments and in social situations with adults and other children. He worried about how other children would think about him and was afraid that he would do shameful things in front of other people. His anxiety was expressed in panic symptoms, like trembling or feeling dizzy. Finally, he was afraid of loud noises.

Participant 8 (7-Week Baseline)

Participant 8 was a 11-year old boy that was included in the study because of clinical levels of social phobia and specific phobia symptoms and subclinical levels of agoraphobia symptoms. He was afraid of making mistakes in school assignments and worried about the transition to secondary school. He also had difficulties with starting a conversation with others and was afraid of unpredictable and unprepared social situations. Moreover, he often was afraid of going to crowded places, like a shopping mall or a cinema. Finally, he had a specific fear for darkness.

Instruments

Primary outcome measure

Child-rated Anxiety Symptoms. The Dutch translation of the Spence Children's Anxiety Scale (SCAS; Scholing et al., 1999a) was used to measure child-rated anxiety symptoms. The SCAS consists of 44 items (e.g., 'I am afraid when I have to sleep alone', 'I worry about things') on a 4-point scale, ranging from 'never' to 'always'. Scores on items ranged from 0 to 3, with higher scores indicating more anxiety symptoms. Moreover, the SCAS contains 6 positive filler items that are not included in the calculation of the total score. The scale consists of six subscales that correspond with the different anxiety disorders that are described in the DSM-IV: panic/agora phobia, separation anxiety, social phobia, generalized anxiety, obsessive compulsive anxiety and anxiety for physical injury. The SCAS has good validity and reliability (Muris, Schmidt, & Merckelbach, 2000; Spence, Barrett, & Turner, 2003).

Moreover, anxiety symptoms were assessed with daily questions that children had to answer via the e-mental health platform of the mental health agency where they were recruited. At the end of every day, they had to rate their anxiety ('How anxious/nervous did you feel today?') and their happiness ('How happy did you feel today?') during that day on a scale from 0 to 10, with a higher score indicating respectively more anxiety or happiness. Moreover, the daily questionnaire contained five filler items

about the time spent on daily activities of the child (e.g. 'How many hours did you play with other children today?').

Secondary outcome measures

Parent-rated Anxiety Symptoms[3]. The Dutch translation of the Spence Child Anxiety Scale for Parents (SCAS-P; Scholing et al., 1999b) was used to measure parent-rated anxiety symptoms. The SCAS-P consists of 38 items on a 4-point scale ranging from 0 (never) to 3 (always). The items and subscales of the SCAS-P correspond with the items of the child version of the SCAS. Only items referring to an internal state (e.g., item 4: 'I feel afraid') were rephrased into observable behaviour for parents (e.g., 'My child complains of feeling afraid'). Moreover, the SCAS-P does not contain positive filler items like the child version. The SCAS-P consists of the same six subscales as the child version. The SCAS-P has good reliability and validity (Nauta et al., 2004).

Furthermore, parents also had to answer daily questions on the anxiety symptoms of their child via the e-mental health platform of the mental health agency where they were recruited. At the end of every day, they had to rate the anxiety ('How anxious/nervous did your child feel today?') and happiness ('How happy did your child feel today?') of their child during that day on a scale from 0 to 10, with a higher score indicating respectively more anxiety or happiness.

Anxiety disorders. The Dutch translation of the Anxiety Disorders Interview Schedule for DSM-IV, Parent version (ADIS-P; Siebelink & Treffers, 2001) was used to assess the presence of anxiety disorders in the participating children. This is a semi-structured diagnostic interview focusing on parents that can be used to diagnose anxiety disorders in children of 7-17 years old. The interview consists of standardized questions, with 'yes', 'no' and 'different' as possible answers. On basis of the answers, the interviewer has to give his/her clinical judgement about the severity of every disorder. At the end of the interview and on basis of the clinical judgements, the interviewer makes a definitive decision about the presence (yes/no) of the different anxiety disorders. In this study, the presence of the following DSM-IV anxiety disorders was assessed: separation anxiety disorder, social phobia, specific phobia, panic disorder, agoraphobia and generalised anxiety disorder. The interview was administered by a qualified therapist or by a master student under supervision of a qualified therapist. The ADIS-P has good psychometric properties (Siebelink & Treffers, 2001).

Coping skills. The Dutch translation (CSLK; de Boo & Wicherts, 2009) of the Coping Strategies Checklist for Children (CCSC-R1; Ayers & Sandler, 1999) was used to assess the self-reported coping skills of the participating children. The CSLK consisted of 54

3 Parent-rated results were presented in the Appendix.

items (e.g. 'When I have problems or difficulties.....I listen to music; I do not think about it') on a 4-point scale, ranging from 'hardly ever' to 'almost always'. The CSLK consisted of five subscales with a further division of several subscales: Problem focused coping (Cognitive decision making, Direct problem solving, Seeking Understanding), Positive cognitive reframing (Positivity, Control, Optimism), Distraction strategies (Distracting actions, Physical release of Emotions), Avoidance Strategies (Avoidant actions, Repression, Wishful thinking) and Support Seeking Strategies (Support for actions, Support for feelings). Scores on items ranged from 1 to 4, with higher scores indicating that the corresponding coping strategy is more present in a child. The CSLK has shown to be a valid and reliable questionnaire (de Boo & Wicherts, 2009).

Treatment protocol *Mindlight*-CBT sessions

Because the intervention took place in a mental health agency, it was conducted by qualified psychologists, or by master students who were supervised by qualified psychologists. First, children played *Mindlight* (M; see Figure 1) for one hour per week during the baseline period at the recruitment location. In the *Mindlight* sessions, the therapist gave an introduction (e.g., instructions) and conclusion (e.g. discussion learning points). During the game, the therapist stayed in the same room as the children, but could only be approached for questions or help. This session protocol was identical to the protocol that was used in the RCT (Wijnhoven et al., 2015). After the last *Mindlight* session, children received two CBT-sessions (T). In the first CBT-session, the therapist and child discussed anxious thoughts and feelings that were experienced during the game. Moreover, they discussed how the child reduced his/her anxious thoughts and feelings during the game. After that, the therapist guided the child in making the translation from the strategies that were used by the child to reduce anxiety during the game into ways in which the child could use these skills (e.g., exposure, cognitive restructuring and relaxation) in anxious situations in daily life. Finally, the therapist and child together created a homework exercise in which the child should practice the skills that were learned in the game in one or more anxious situations in daily life (e.g. at school or at home). In the second CBT-session, the therapist and child discussed how the homework exercise went and what the child learned from the exercise. Moreover, they examined how the child could continue with practicing the learned skills in anxious situations in daily life after the end of the CBT-sessions. Parents were invited to join the two CBT-sessions during the last 15 minutes in order to stimulate and help the child with creating homework exercises and to think about ways in which they could support their child in executing the homework exercises.

Sample size

In a study aimed on power in single case series designs (e.g., multiple baseline design), in which the power of designs with different numbers of participants (3-7) and assessments were compared, it was found that a number of data points (assessments) of 40 and higher resulted in sufficient statistical power, regardless of the number of included participants (Heyvaert et al., 2017). In the current study, eight participants were included and data were collected in 70 daily assessments per participant, resulting in sufficient statistical power.

Statistical analysis

Randomization tests (Bulté & Onghena, 2008) were conducted with the SCRT package (Edgington & Onghena, 2007) that was integrated in a web-app ('Shiny app'; De Tamal, Michiels, Vlaeyen, & Onghena, 2017) to analyze the difference in decrease of the daily measured anxiety symptoms between the baseline phase (*Mindlight*; M; see Figure 1) and treatment phase (CBT; T) over all eight participants. Because randomization tests do not rely on a random sampling assumption, they can provide a better alternative than parametric statistical tests for analyzing data from single-case (series) designs. This way, the additive effect of CBT on *Mindlight* in decreasing anxiety symptoms of children with ASD could be tested in a reliable way.

To analyze individual differences in decrease of anxiety symptoms, the course of the daily measured anxiety symptoms (see Figure 2-9) was visually analyzed for every participant, with phase X (7 days before start of *Mindlight*), phase M (*Mindlight*/Baseline phase) and phase T (CBT/Treatment phase). The dots indicate the exact anxiety level on a particular day (0-10), the dotted lines indicate least squares regression trends over the different phases (X, M and T). So, visual analyses could show whether anxiety symptoms decreased in a meaningful way in the different phases and could therefore provide insight into the extent to which change could be attributed to *Mindlight* and CBT (Lane & Gast, 2014). Moreover, to investigate whether anxiety symptoms measured by the SCAS-C significantly decreased over time (T0-T4), the Reliable Change Index (RCI; Jacobson & Truax, 1991) was calculated for each participant. The RCI was calculated by dividing the difference in total scores on the SCAS-C (T0-T4) by the standard deviation (SD) of the total scale of the SCAS-C as reported in the study of Muris and colleagues (2000). An RCI > 1.96 on a level of $\alpha = .05$ (two-sided test) indicated a significant change over time (Jacobson & Truax, 1991). Moreover, the RCI's were calculated for the differences in SCAS-C scores between T1 (pre-test) and T2 (post-*Mindlight*), between T2 and T3 (post-CBT) and between T3 and T4 (3-months follow-up), to investigate for each participant whether the decrease of anxiety symptoms took place in specific phases of the study. Also, the RCI's were calculated for the difference

in CSLK subscale scores between T0-T4, T1-T2, T2-T3 and T3-T4 for each participant, to investigate whether coping skills changed over the total course and in specific phases of the study. Finally, the remission rates of the anxiety disorders in the ADIS-P (Siebelink & Treffers, 2001) were described for each participant.

RESULTS

Statistical outcomes

The Randomization tests were conducted to investigate whether the decrease of the daily measured anxiety symptoms in the CBT phase (T) was significantly different from the decrease of the daily measured anxiety symptoms in the *Mindlight* phase (M) over all eight participants. Results of the Randomization tests showed that there was no significant difference between the decrease in anxiety symptoms in the CBT phase (T) and the *Mindlight* phase (M). In other words, results showed that CBT elements had no significant additive effect on decreasing anxiety symptoms next to *Mindlight* ($p > .05$).

Summary of clinical outcomes

Table 1 shows the differences and RCI's in SCAS scores (total scale) over the course of the study (screening through 3-months follow-up), between pre-test and post-*Mindlight*, between post-*Mindlight* and post-CBT and between post-CBT and 3-months follow-up for every participant. Results showed that participant 1 and 2 experienced a significant decrease in anxiety symptoms over the total course of the study. Moreover, participant 5 showed a significant decrease in anxiety symptoms between the end of *Mindlight* and the end of CBT. All other participants did not show any significant decrease.

According to the ADIS-P that was administered at pre-test and at 3-months follow-up, participant 1, 3, 7 and 8 remitted from several or all specific phobias, participant 3 remitted from generalized anxiety disorder and participants 6 and 8 remitted from social phobia at 3-months follow-up.

Finally, the results of the CSLK showed that participant 1, 3 and 5 showed a significant decrease in avoidance during one or more phases of the study. Moreover, participant 2, 4 and 8 showed a significant increase in positive coping skills such as direct problem solving, cognitive restructuring and seeking distraction during one or more phases of the study. Participant 5 and 7 both showed a significant increase and decrease in positive coping skills during the course of the study, which did not lead to eventual improvements at 3-months follow-up. Finally, participant 6 showed a significant decrease in positive coping skills during the course of the study.

Table 1

Differences and RCI's for SCAS Scores Between T0-T4 (Screening-3 months FU), T1-T2 (Pre-test-Post – Mindlight), T2-3 (Post-Mindlight – Post-CBT) and T3-4 (Post-CBT – 3 months FU) for Every Participant

	pp1		pp2		pp3		pp4		pp5		pp6		pp7		pp8	
	Diff	RCI	Diff	RCI	Diff	RCI	Diff	RCI	Diff	RCI	Diff	RCI	Diff	RCI	Diff	RCI
T0-T4	12	2.15	20	3.58	0	.00	4	.72	2	.36	5	.90	7	1.25	9	1.61
T1-T2	5	.90	1	.18	4	.72	3	.54	-4	-.73	-2	-.36	0	.00	7	1.25
T2-T3	-3	-.54	6	1.08	8	1.43	3	.54	14	2.54	1	.18	4	.72	3	.54
T3-T4	5	.90	6	1.08	-6	-1.08	6	1.08	-4	-.73	-4	-.72	-3	-.54	0	.00

Note. RCI > 1.96 indicates a clinically significant decrease. Diff = Difference.

Individual outcomes

Participant 1

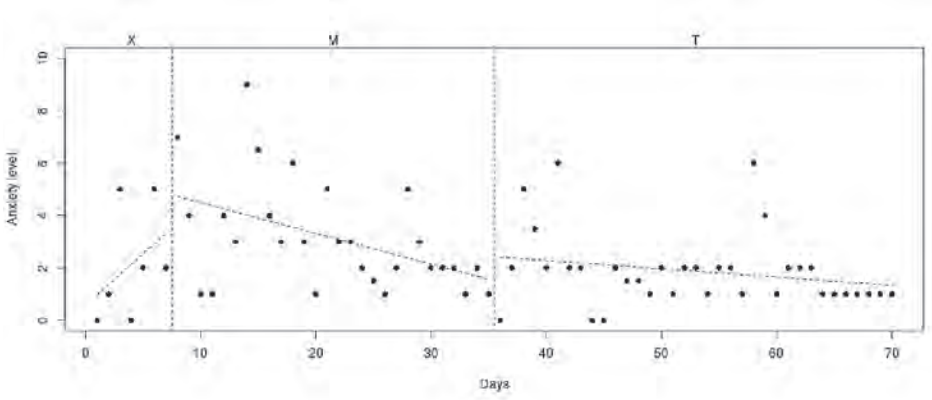


Figure 2. Course of daily measured anxiety level (0-10) over 70 days for participant 1.

The course of daily measured anxiety symptoms of participant 1 is shown in Figure 2. Visual analysis showed that daily measured anxiety symptoms increased in the week before *Mindlight* (phase X) and that the anxiety symptoms showed a clinically relevant decrease (from mean score 5 to mean score 2) during the *Mindlight* sessions (phase M). The anxiety symptoms of participant 1 slightly decreased during the CBT sessions (phase T) and showed a stabilization at a low level from week 50. The results of the SCAS-C showed a significant decrease in anxiety symptoms from screening through 3-months follow-up (RCI: 2.15 > 1.96; see Table 1). The ADIS-P that was administered with the parents of participant 1 showed the same diagnoses at 3-months follow-up as at pretest (social phobia and specific phobia), but the number of specific phobias decreased from three (doctors/dentist, birds, dressed up people) to only one (doctors/

dentist). The results of the CSLK showed that seeking support for actions (RCI: 3.10 > 1.96) and avoidance (RCI: 2.00 > 1.96) significantly decreased from pretest to 3-months follow-up. Participant 1 may have learned to cope with anxious situations on his own, leading to less support seeking actions. However, results of the CSLK also showed that positive coping skills such as seeking distraction (RCI: 3.03 > 1.96), seeking support for his feelings (RCI: 2.42 > 1.96) and cognitive restructuring (RCI: 3.11 > 1.96) significantly decreased from post-CBT to 3-months follow-up.

Participant 2

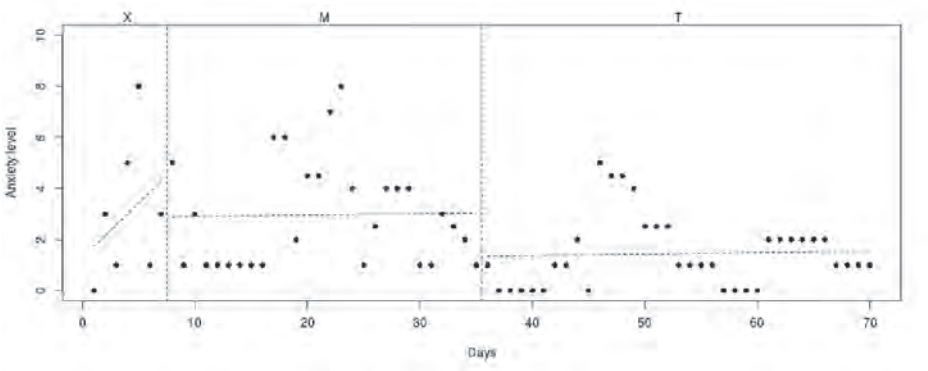


Figure 3. Course of daily measured anxiety level (0-10) over 70 days for participant 2.

The course of daily measured anxiety symptoms of participant 2 is shown in Figure 3. Visual analysis showed that daily measured anxiety symptoms increased in the week before *Mindlight* (phase X) and that the anxiety symptoms did not decrease during the *Mindlight* sessions (phase M). During the CBT-sessions (phase T), the anxiety symptoms did not decrease but showed a lower and more stable level than during the *Mindlight* sessions (from mean score of 3 to mean score of 1.5). The results of the SCAS-C showed a significant decrease in anxiety symptoms from screening through 3-months follow-up (RCI: 3.58 > 1.96; see Table 1). The ADIS-P that was administered with the parents of participant 2 showed no difference in diagnoses between pretest and 3-months follow-up. The results of the CSLK showed that cognitive restructuring (RCI: -2.11 > -1.96) and control (RCI: -2.24 > -1.96) increased from pretest to 3-months follow-up. Also, optimism significantly increased from post-*Mindlight* to post-CBT (RCI: -1.99 > -1.96), but significantly decreased from post-CBT to 3-months follow-up (RCI: 1.99 > 1.96). Positive thoughts significantly decreased from post-*Mindlight* to post-CBT (RCI: 1.96), but highly increased from post-CBT to 3-months follow-up (RCI: -3.19 > -1.96). Finally, wishful thinking significantly increased from post-CBT to 3-months follow-up

(RCI: -2.35 > -1.96). Overall, coping skills of participant 2 increased to a great extent during the course of the study.

Participant 3

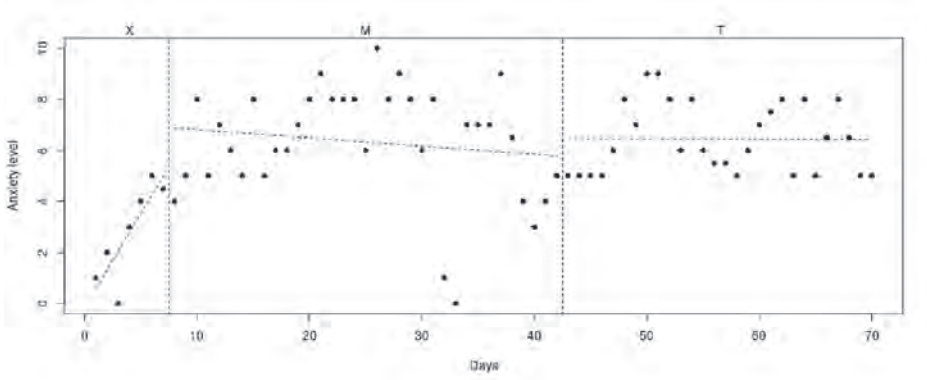


Figure 4. Course of daily measured anxiety level (0-10) over 70 days for participant 3.

The course of daily measured anxiety symptoms of participant 3 is shown in Figure 4. Visual analysis showed that daily measured anxiety symptoms increased in the week before *Mindlight* (phase X) and continued to be at a high level (mean score of 6/6.5) during the *Mindlight* (phase M) and CBT sessions (phase T). The results of the SCAS-C showed that there was no significant decrease of anxiety symptoms from screening through 3-months follow-up (see Table 1). In contrast, results of the ADIS-P showed that participant 3 met the criteria of generalized anxiety disorder and specific phobia at pretest, but did not meet the criteria of any anxiety disorders at 3-months follow-up. Results of the CSLK showed that avoidance in general (RCI: 3.34 > 1.96), repression (RCI: 3.24 > 1.96) and avoidant actions (RCI: 2.71 > 1.96) significantly decreased from pretest to post-*Mindlight*. Moreover, avoidance in general (RCI: 2.91 > 1.96) and avoidant actions (RCI: 3.16 > 1.96) also significantly decreased from pretest to 3-months follow-up.

Participant 4

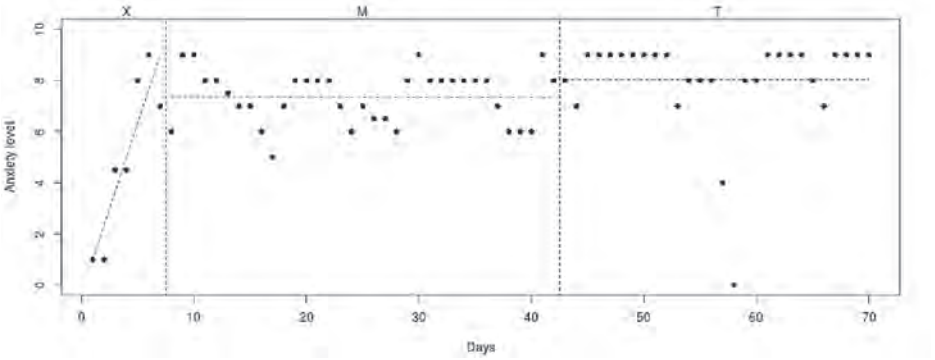


Figure 5. Course of daily measured anxiety level (0-10) over 70 days for participant 4.

The course of daily measured anxiety symptoms of participant 4 is shown in Figure 5. Visual analysis showed that daily measured anxiety symptoms increased in the week before *Mindlight* (phase X) and continued to be at a high level (mean score of 7/8) during the *Mindlight* (phase M) and CBT sessions (phase T). The results of the SCAS-C showed that there was no significant decrease of anxiety symptoms from screening through 3-months follow-up (see Table 1). Results of the ADIS-P showed that there was no difference in diagnoses of anxiety disorders between pretest and 3-months follow-up. In contrast with these results, outcomes of the CSLK showed that seeking support for his feelings (RCI T1-T2: -5.43 > -1.96; RCI T1-T4: -6.04 > -1.96) and actions (RCI T1-T2: -4.14 > -1.96; RCI T1-T4: -3.10 > -1.96) significantly increased from pretest to post-*Mindlight* and from pretest to 3-months follow-up. Moreover, direct problem solving significantly increased from pretest to post-*Mindlight* (RCI: -2.79 > -1.96).

Participant 5

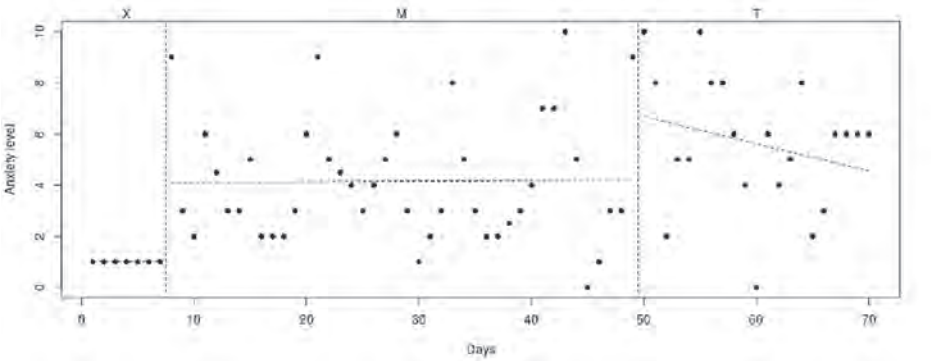


Figure 6. Course of daily measured anxiety level (0-10) over 70 days for participant 5.

The course of daily measured anxiety symptoms of participant 5 is shown in Figure 6. Visual analysis showed that daily measured anxiety symptoms increased from the week before *Mindlight* (phase X) through the end of the *Mindlight* sessions (phase M) and that the anxiety symptoms showed a slight decrease after the start of the CBT sessions (phase T), but did not end at a satisfying low level at the end of the CBT sessions (mean score of 4.5). The results of the SCAS-C showed no significant decrease in anxiety symptoms from screening through 3-months follow-up, but a significant decrease in anxiety symptoms between the end of *Mindlight* and the end of CBT, which is in line with the course of the daily measured anxiety symptoms (RCI: 2.54 > 1.96; see Table 1). The ADIS-P that was administered with the parents of participant 5 showed no difference in diagnoses between pretest and 3-months follow-up. Results of the CSLK showed that avoidance in general significantly decreased from post-*Mindlight* to post-CBT (RCI: 2.91 > 1.96). However, several positive coping skills (e.g. RCI cognitive restructuring: 3.71 > 1.96, RCI direct problem solving: 3.88 > 1.96, RCI seeking support: 2.89 > 1.96) also significantly decreased from post-*Mindlight* to post-CBT. Eventually, these positive coping skills significantly increased again from post-CBT to 3-months follow-up to the same level as at the end of the *Mindlight* sessions (RCI cognitive restructuring: -4.04 > -1.96, RCI direct problem solving: -4.86 > -1.96, RCI seeking support: -2.49 > -1.96).

Participant 6

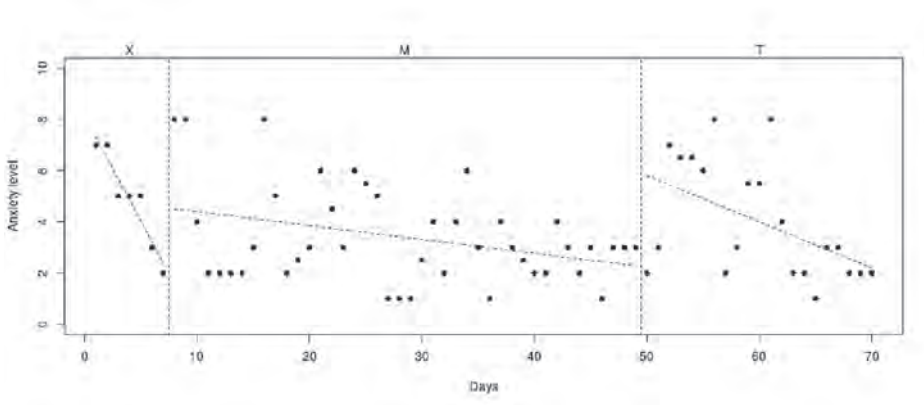


Figure 7. Course of daily measured anxiety level (0-10) over 70 days for participant 6.

The course of daily measured anxiety symptoms of participant 6 is shown in Figure 7. Visual analysis showed that daily measured anxiety symptoms were high at the start of all phases (X, M and T) and decreased during all phases. Anxiety levels were low at

the end of the CBT sessions (mean score of 2), but were not stabilized. The results of the SCAS-C showed no significant decrease in anxiety symptoms from screening through 3-months follow-up (see Table 1). Results of the ADIS-P showed that participant 6 met the criteria of social phobia at pretest, but not at 3-months follow-up. Results of the CSLK showed that direct problem solving (RCI: 2.60 > 1.96) and analyzing the problem (RCI: 2.19 > 1.96) significantly decreased from pretest to 3-months follow-up.

Participant 7

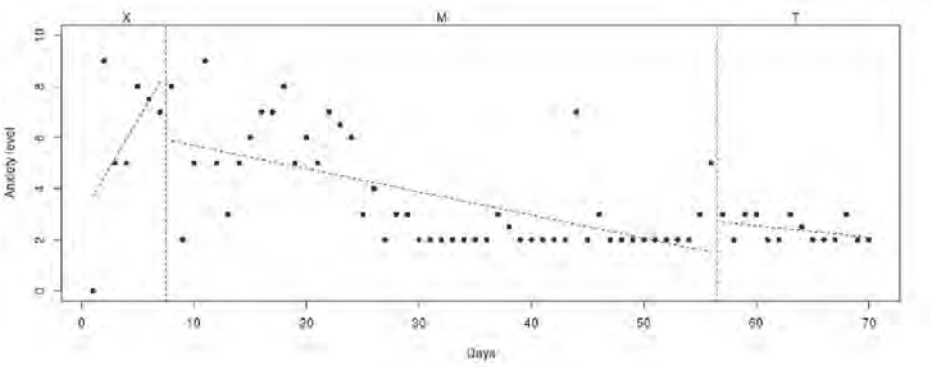


Figure 8. Course of daily measured anxiety level (0-10) over 70 days for participant 7.

The course of daily measured anxiety symptoms of participant 7 is shown in Figure 8. Visual analysis showed that daily measured anxiety symptoms increased during the week before *Mindlight* (phase X) and that anxiety symptoms decreased from the start of *Mindlight* through the end of the CBT sessions (from mean score of 6 to mean score of 2). During the CBT sessions, anxiety symptoms stabilized at a low level. The results of the SCAS-C showed no significant decrease in anxiety symptoms from screening through 3-months follow-up (see Table 1). The ADIS-P that was administered showed that participant 6 met the criteria of social phobia, specific phobia and generalized anxiety disorder at pretest, but did only meet the criteria of social phobia at 3-months follow-up. Results of the CSLK showed that several positive coping skills significantly increased from post-*Mindlight* to post-CBT (e.g. RCI direct problem solving: -3.57 > -1.96, RCI cognitive restructuring: -3.08 > -1.96, RCI seeking support: -2.04 > -1.96), but significantly decreased again from post-CBT to 3-months follow-up (RCI direct problem solving: 3.22 > 1.96, RCI cognitive restructuring: 3.71 > 1.96, RCI seeking support: 4.12 > 1.96).

Participant 8

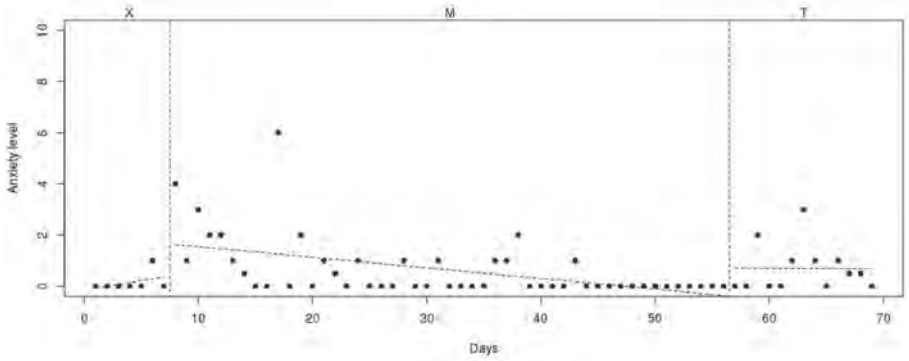


Figure 9. Course of daily measured anxiety level (0-10) over 70 days for participant 8.

The course of daily measured anxiety symptoms of participant 8 is shown in Figure 9. Visual analysis showed that daily measured anxiety symptoms were at a stable low level during all phases (X, M and T). During the *Mindlight* sessions, anxiety symptoms slightly decreased from a mean score of 2 to a mean score of 0. The results of the SCAS-C showed no significant decrease in anxiety symptoms from screening through 3-months follow-up (see Table 1). The ADIS-P that was administered showed that participant 8 met the criteria of social phobia and specific phobia at pretest, but did not meet the criteria of any anxiety disorder at 3-months follow-up. Results of the CSLK showed that seeking support in general (RCI: -2.98 > -1.96) seeking support for his feelings (RCI: -2.82 > -1.96) increased from pretest to 3-months follow-up.

DISCUSSION

The aim of this study was to examine the potential additive effect of CBT on *Mindlight* in decreasing child-rated anxiety symptoms of children with ASD in a clinical setting. CBT did not have the hypothesized additive effect on *Mindlight* in decreasing anxiety of children with ASD, which was illustrated by the randomization tests and visual analyses. Moreover, analysis of the SCAS scores at T2-T3 showed that participant 5 was the only participant to show a clinically significant decrease in anxiety symptoms during the CBT sessions.

When examining the daily measured anxiety symptoms in Figure 2-9 more in detail, it can be seen that five participants (participant 1, 2, 6, 7 and 8) already showed a decrease in anxiety symptoms during the *Mindlight* sessions, which is in line with Schoneveld and colleagues (2016, 2018) and Wijnhoven and colleagues (submitted). Moreover, three of these participants (1, 2 and 7) showed a pattern of stabilization of

anxiety symptoms at a low level during and after the CBT-sessions. Analysis of the SCAS scores indicated that two of these participants (1 and 2) experienced a clinically significant decrease in anxiety symptoms over the course of the study, and that four of these participants (1, 6, 7 and 8) remitted from one of more anxiety disorders at 3-months follow-up. This indicates that five participants seem to have benefited from the *Mindlight* sessions and that the CBT-sessions had a stabilizing effect on anxiety symptoms in three of these five participants. For two participants, this was supported by the clinically significant decrease in anxiety symptoms over time and for four participants the remission rates at 3-months follow-up supported this conclusion.

However, for three participants (3, 4 and 5) visual analysis showed that neither *Mindlight* nor CBT had a decreasing effect on their anxiety symptoms. This finding was partly supported by both the analysis of the SCAS scores and the remission rates at 3-months follow-up. Participant 5 did show a clinically significant decrease in anxiety symptoms during the CBT-sessions, but the anxiety level at the end of the CBT-sessions was still high, indicating that this decrease was not clinically satisfying. In addition, participant 3 remitted from generalized anxiety disorder and specific phobia at 3-months follow-up, while visual analysis of the daily measured anxiety symptoms did not show improvements in his anxiety level and the RCI of the SCAS scores at T3-T4 even showed an increase in anxiety symptoms. This could be explained by the difference in outcomes of anxiety assessment with a questionnaire (SCAS-C) and an interview (ADIS-P), which has been shown to lead to different anxiety ratings (Van Steensel, Bögels, & Perrin, 2011).

Moreover, it was expected that perceived coping skills of children showed a higher increase during CBT compared to *Mindlight*. Four out of five participants who experienced a decrease in anxiety symptoms during one or more phases of the study (participant 1, 2, 7 and 8) also showed an increase in coping skills between pretest and 3-months follow-up or between post-*Mindlight* and post-CBT. For participant 2 and 8, positive coping skills increased until the 3-months follow-up, indicating that coping skills might have generalized to daily life situations. Participant 1 and 7 showed a decrease in positive coping skills from the end of the CBT-sessions to 3-months follow-up, meaning that the generalization of coping skills did not endure for these participants. Moreover, participant 6 showed a decrease in the coping skills direct problem solving and analyzing the problem over time. This participant experienced social phobia and fear of failure, which might require coping skills like the ability to apply relaxation techniques or task concentration in fearful social situations (e.g. Bögels, 2006), which were not measured. Finally, the participants (3, 4 and 5) who did not experience a decrease in anxiety over time showed only small improvements in their coping skills. On basis of these results, it can be concluded that it is likely that in

four participants the CBT-sessions have contributed to an increase in coping skills and in turn to a stabilization in anxiety symptoms at a low level, and that in two of these participants the learned coping skills were also generalized to daily life situations (in line with Craske et al., 2014; Swan et al., 2016).

The difference in outcomes between participants could be explained by several possible factors. When comparing the SCAS scores at T0 and T1, it can be seen that those children who showed a decrease in anxiety already showed a decrease in anxiety symptoms (except for participant 8) between screening and pretest, and that the children that did not show a decrease in anxiety symptoms showed an increase in anxiety symptoms between screening and pretest. It is possible that the waiting time between screening and pretest had an anticipation effect on the anxiety symptoms of the improvers (Ahola et al., 2017), which means that anticipation of treatment may have prepared the participants for the intervention by activating therapeutic processes such as increasing awareness of their anxiety symptoms (Arrindell, 2001), installation of hope (Dowling & Rickwood, 2015) and increasing expectations of treatment effect (Thiruchselvam et al., 2019). Furthermore, it is remarkable that participant 1 and 2 showed the highest overall improvements on anxiety symptoms, anxiety disorders and coping skills, because these children received the smallest amount of *Mindlight* sessions (4 sessions). This is in line with the study of Stice and colleagues (2009), showing that a shorter program duration was associated with a better treatment outcome. Especially for children with ASD this might be true, considering the effort and energy that it costs for these children to engage in a large number of therapy sessions because of their social and cognitive difficulties (Johnco & Storch, 2015). For these children, it might be more important to invest in practicing coping skills in multiple daily life situations (as suggested by Craske et al., 2014) than to follow a long treatment protocol. Finally, the overall lack of a stable decrease in anxiety symptoms over time might be due to the presence of multiple psychiatric diagnoses (e.g., ASD and ADHD) in most of the participating children.

This study has a few limitations. First, because some children already showed a decrease in anxiety symptoms during the *Mindlight* sessions (baseline), it is statistically more difficult to find a significant additive effect of CBT on *Mindlight* compared to studies in which the baseline period did consist of a waiting time (e.g. Spuij, van Londen-Huiberts, & Boelen, 2013). However, the results of the visual analyses and the clinical outcomes provided a more in-depth and balanced view of the results by showing the individual trajectories. Second, despite the use and comparison of multiple methods, the visual analysis of data is a qualitative analysis method and in this way rather subjective.

Overall, it could be concluded that CBT did not have a significant additive effect on *Mindlight* in decreasing anxiety symptoms of children with ASD. Instead, multiple participants already experienced a decrease in anxiety symptoms during the *Mindlight* sessions, which is in line with the decreasing anxiety symptoms in previous studies on *Mindlight* (Schoneveld et al., 2016, 2018; Wijnhoven et al., submitted). Yet, several participants did experience a stabilization in anxiety symptoms at a low level during the CBT sessions in combination with an increase in coping skills. These children might have practiced the skills they learned during *Mindlight* and CBT in multiple situations in daily life, which may have led to an improvement of their overall coping skills and in turn to a decrease in anxiety symptoms (Craske et al., 2014; Swan et al., 2016). Children who did not show a decrease in anxiety symptoms may not have been able to improve their coping skills, for example because of a lack of practice in daily life situations. Alternatively, the combination of *Mindlight* and CBT may not be fulfilling treatment expectations and needs for these children, leading to a lack of decrease in anxiety symptoms.

The study has some clinical implications. It showed that for some children with ASD, treatment consisting of only *Mindlight* might be sufficient to decrease their anxiety symptoms, while for other children the addition of CBT may be useful. There are also children with ASD that do not benefit from *Mindlight* and CBT at all and need other types of treatment. This confirms the well-known fact that the population of children with ASD is heterogeneous, both in its clinical presentations and its treatment needs. It requires sufficient clinical expertise to be able to obtain that information that is necessary to obtain the optimal adjustment to the child's needs and ultimately a personalized treatment. Future research should provide better insight into the individual factors that could predict which type of children with ASD benefit from which kind of treatment. For now, it can be concluded that *Mindlight* in combination with CBT might be a potential effective treatment for some children with ASD and anxiety that clinicians could consider to use in daily practice in the future.

APPENDIX

In this Appendix, graphs (Figure 10-17) of the parent-rated daily measured anxiety level of the participating children are presented and discussed. For most part, results of the parent-rated daily measured anxiety level resemble the results of the child-rated daily measured anxiety level (Figure 2-9). Results of Randomization tests showed that there was no significant difference between the decrease in parent-rated anxiety symptoms in the CBT phase (T) and the *Mindlight* phase (M). In line with the results of the child-rated anxiety symptoms, CBT had no significant additive effect on parent-rated anxiety symptoms next to *Mindlight* ($p > .05$).

When examining the individual outcomes, it can be seen that the course of the parent-rated anxiety level over 70 days largely resembles the course of the child-rated anxiety level. Like in the child-rated results, participant 1, 2, 6 and 7 showed a decrease in anxiety symptoms over time. This decrease was more supported by the RCI's of the parent-rated SCAS scores (see Table 2) than the RCI's of the child-rated SCAS scores (see Table 1). As can be seen in Table 2, results for participant 1, 2, 6 and 7 showed a clinically significant decrease of parent-rated anxiety symptoms (measured with SCAS) between screening and 3-months follow-up, while for child-rated anxiety symptoms this was only the case for participant 1 and 2. Only participant 8 showed no decrease in anxiety over time, but in the child-rated results it can be seen that the decrease for participant 8 was also small due to the low starting level of anxiety.

For participant 1 and 2, a difference was found in the timing of the decrease of anxiety symptoms. For the parent-rated anxiety symptoms of participant 1, a higher decrease was found in the CBT phase (T), while for the child-rated anxiety symptoms a higher decrease was found in the *Mindlight* phase (M). For participant 2, the *Mindlight* phase showed a higher decrease of parent-rated anxiety symptoms compared to the child-rated anxiety symptoms. Surprisingly, RCI's of the parent rated SCAS scores showed a clinically significant decrease in anxiety symptoms between T2 (post-*Mindlight*) and T3 (post-CBT) and not between T1 (pre-test) and T2 (post-*Mindlight*), which would have been in line with the high decrease of parent-rated daily measured anxiety symptoms.

However, for participant 2 the daily measured anxiety symptoms were continued to be measured during three weeks after T3 (post-CBT assessment), which showed that the high decrease during the *Mindlight* sessions and the first week of the CBT-sessions did not persist after the last CBT session, but showed a slightly unstable pattern. The RCI's of participant 2 also showed a negative RCI between T3 (post-CBT) and T4 (3-months follow-up), indicating an increase in anxiety symptoms. Possibly, the slightly unstable pattern after the last CBT session was the beginning of an increase in

anxiety symptoms till 3-months follow-up. Finally, for participant 3 and 5 parents rated the level of anxiety symptoms lower than children over the whole course of the study.

Table 2

Differences and RCI's for Parent-rated SCAS Scores Between To-T4 (Screening-3 months FU), T1-T2 (Pre-test-Post – Mindlight), T2-3 (Post-Mindlight – Post-CBT) and T3-4 (Post-CBT – 3 months FU) for Every Participant

	pp1		pp2		pp3		pp4		pp5		pp6		pp7		pp8	
	Diff	RCI	Diff	RCI	Diff	RCI	Diff	RCI	Diff	RCI	Diff	RCI	Diff	RCI	Diff	RCI
To-T4	14	2.57	8	2.05	-3	-.55	8	1.47	3	.71	14	2.57	19	3.49	7	1.29
T1-T2	4	.74	-5	-1.18	7	1.29	3	.55	-4	-.95	-6	-1.10	9	1.65	-1	-.18
T2-T3	6	1.10	9	2.13	2	.37	1	.18	-2	-.47	9	1.65	0	.00	1	.18
T3-T4	-2	-.37	-15	-3.55	-7	-1.29	6	1.10	5	1.18	-1	-.18	0	.00	7	1.29

Note. RCI > 1.96 indicates a clinically significant decrease. Diff = Difference.

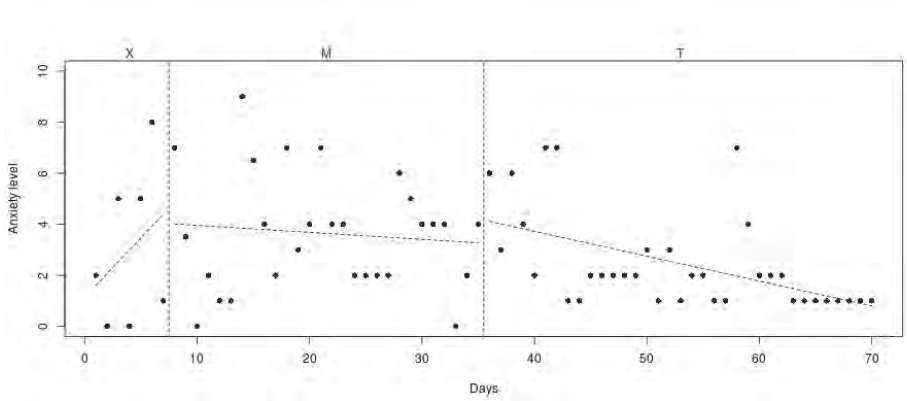


Figure 10. Course of parent-rated anxiety level (0-10) over 70 days for participant 1.

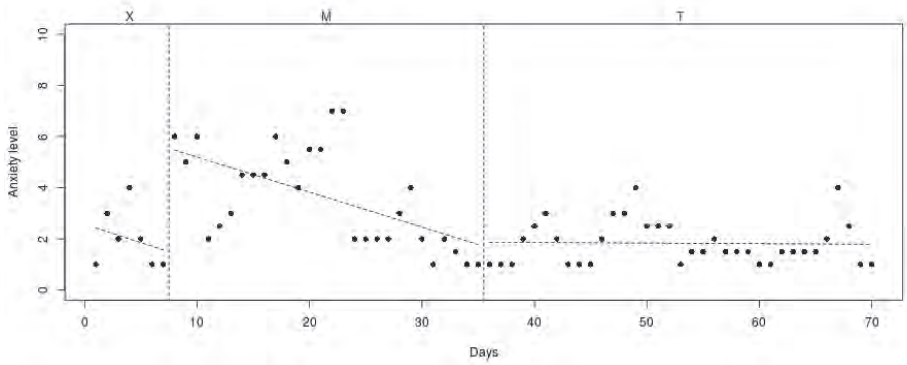


Figure 11. Course of parent-rated anxiety level (0-10) over 70 days for participant 2.

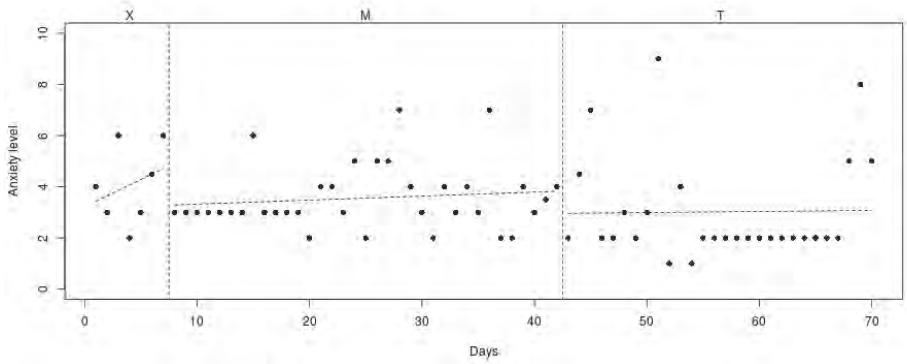


Figure 12. Course of parent-rated anxiety level (0-10) over 70 days for participant 3.

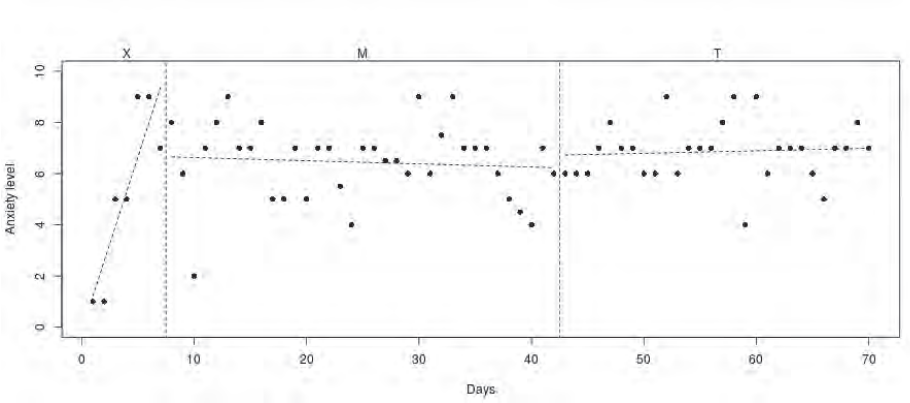


Figure 13. Course of parent-rated anxiety level (0-10) over 70 days for participant 4.

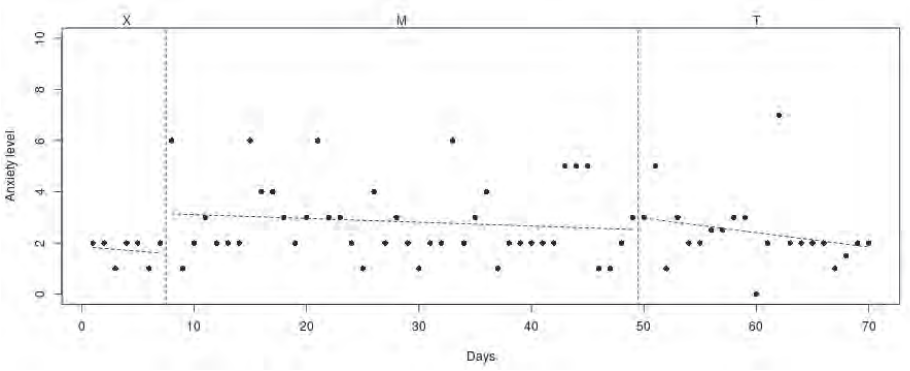


Figure 14. Course of parent-rated anxiety level (0-10) over 70 days for participant 5.

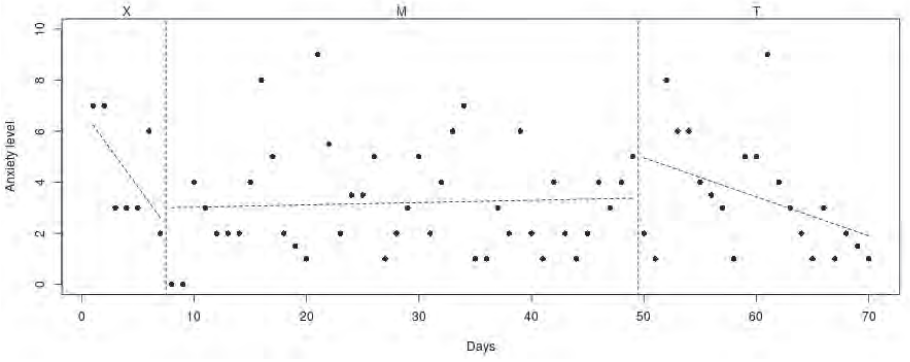


Figure 15. Course of parent-rated anxiety level (0-10) over 70 days for participant 6.

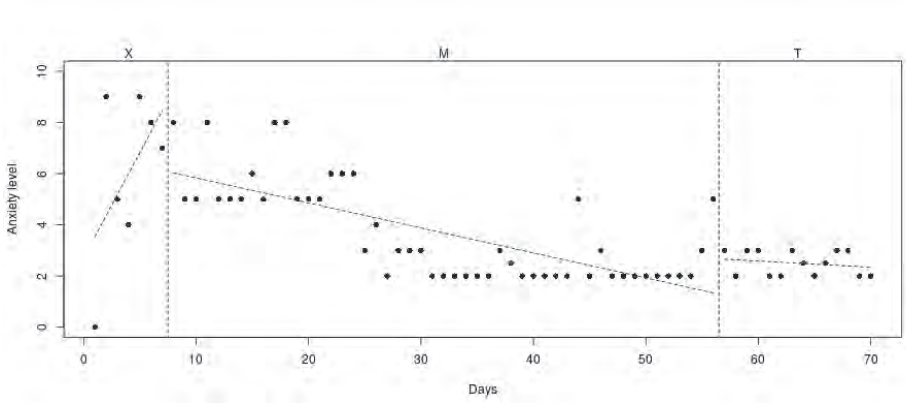


Figure 16. Course of parent-rated anxiety level (0-10) over 70 days for participant 7.

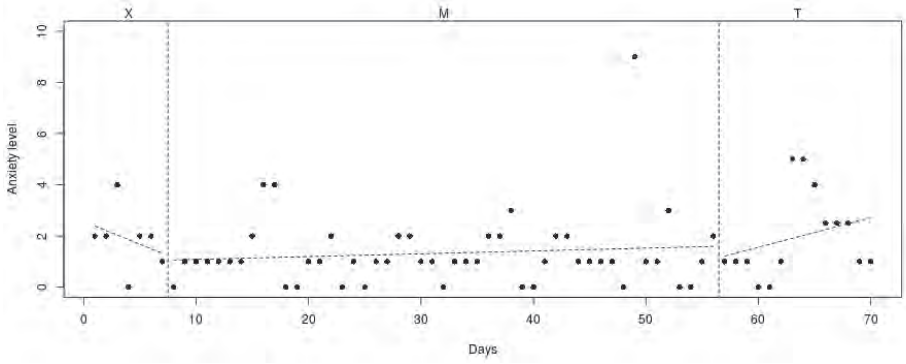
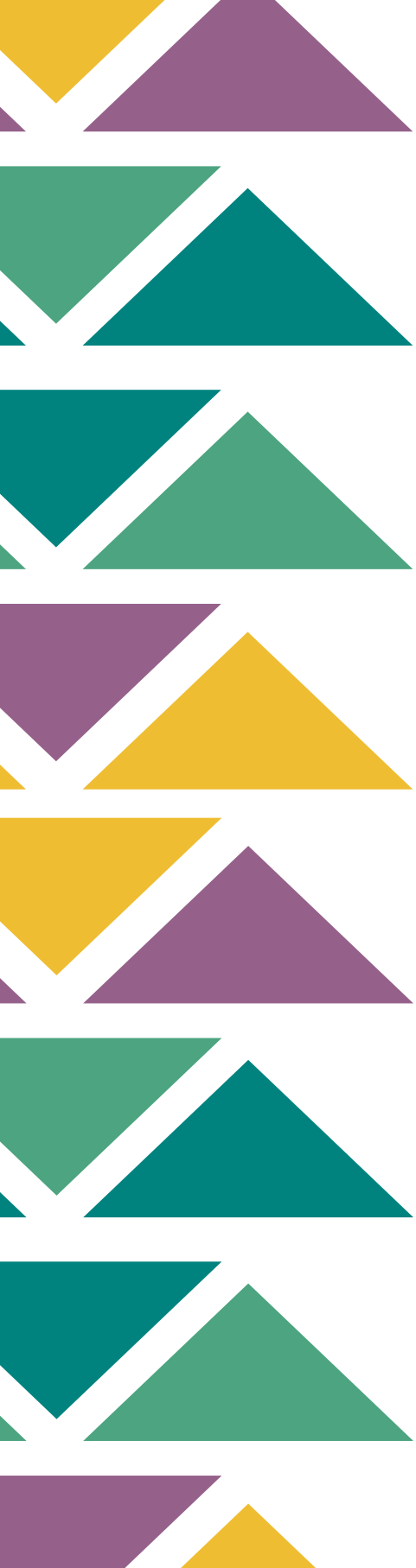


Figure 17. Course of parent-rated anxiety level (0-10) over 70 days for participant 8.



CHAPTER 8

General Discussion

Study Aims

The main goal of the current thesis was to improve the treatment of anxiety in children with autism spectrum disorder in clinical practice by testing the effect and feasibility of an innovative treatment tool: the applied video game *Mindlight*, which was specifically developed to target children's anxiety pathology.

The first aim was to point to the relevance of this study by showing the prevalence and risk factors of anxiety symptoms in children with autism spectrum disorder (ASD). Moreover, the prevalence of comorbid depressive symptoms and suicidal ideation in children with ASD and elevated anxiety was explored.

The second aim was to test the effectiveness of *Mindlight* on anxiety symptoms of children with ASD in a clinical setting. In addition, it was tested whether externalizing behaviour had a moderating effect on any change in anxiety symptoms among the participating children. Finally, it was tested whether elements of cognitive behavioural therapy (CBT) had an additive effect on *Mindlight* in decreasing anxiety symptoms among children with ASD.

In this chapter, the main findings are summarized and discussed in the light of existing knowledge in research and clinical practice. Finally, suggestions for future research and clinical implications and recommendations are provided.

SUMMARY OF MAIN FINDINGS

Part 1: Anxiety in Children with an ASD

In the first part of this thesis, the relevance of improving the assessment and treatment of anxiety in children with ASD was shown by examining the prevalence and risk factors of anxiety in a clinical Dutch sample of children with ASD (Chapter 2). Prevalence and risk factors of child- and parent-rated anxiety symptoms were investigated in 172 children aged 8–15 with ASD. The specialized institutions in which children with ASD were recruited were two mental healthcare institutes and a secondary special education school. Children and their parents filled in self-report questionnaires on anxiety symptoms. Findings showed that more than 60 per cent of the participating children with ASD had at least subclinical child-rated anxiety symptoms, while more than 80 per cent of the children with ASD had at least subclinical parent-rated anxiety symptoms. It was found that younger children and girls with ASD were more likely to suffer from anxiety symptoms than older children and boys with ASD. Moreover, it was shown that children with a higher performance (non-verbal) IQ (PIQ) and a lower verbal IQ (VIQ) were more at risk for specific phobia symptoms. These findings suggest that, in a clinical context, children with ASD show a high prevalence of co-occurring anxiety symptoms, especially girls and younger children with ASD.

Moreover, the need to strengthen and accelerate the assessment and treatment of anxiety in children with ASD was further emphasized by the high comorbidity of depressive symptoms and suicidal ideation in children with ASD and anxiety (Chapter 3). The prevalence of depressive symptoms and suicidal ideation was investigated in a small sample of 93 children aged 8–16 with ASD with normal cognitive functioning and (sub)clinical anxiety symptoms. Both parents and children filled in questionnaires to assess the level of depressive symptoms. Moreover, children reported their level of suicidal ideation. More than 35 per cent of the children with ASD showed clinical levels of child-rated depressive symptoms and more than 75 per cent of the children had clinical levels of parent-rated depressive symptoms. Girls reported significantly higher levels of depressive symptoms than boys. Moreover, 32.2 per cent of the children with ASD and anxiety had suicidal thoughts, and 2.2 per cent of the children showed active suicidal ideation (suicidal thoughts and risk of suicidal behaviour). No gender differences were found regarding suicidal ideation. Findings indicated that children with ASD, normal cognitive functioning and anxiety symptoms are likely to show high co-morbid depressive symptoms and suicidal ideation.

Part 2: Treatment of Anxiety in Children with an ASD

In the second part of the thesis, the study protocol of the randomized controlled trial (RCT) for the effectiveness study on *Mindlight* was presented, describing the background, hypotheses, design, procedure, intervention (*Mindlight*), outcome measurements and analysis method (Chapter 4). In total, 122 children aged 8–16 with ASD and (sub)clinical anxiety symptoms were randomly assigned to the experimental (N=59) or the control (N=63) condition. A small subsample (n = 13) was omitted from the final analyses because of the strong differences between the characteristics of this subsample compared to the rest of the participants. The remaining 109 children (n = 53 experimental group; n = 56 control group) were included in the statistical analyses.

Children in the experimental condition played *Mindlight* and children in the control condition played a commercial game (*Triple Town*). They all played for one hour per week for six consecutive weeks. All children and parents completed assessments at baseline, post-intervention and at three-months follow-up. Findings (presented in Chapter 5) revealed no difference in the decrease in child-rated anxiety symptoms between the two conditions; however, the decrease in parent-rated anxiety symptoms was significantly larger in the experimental condition than in the control condition. Furthermore, it seems that externalizing behaviour did not impact the course of anxiety symptoms during the game sessions. These results provide some preliminary evidence that video games are a promising new intervention vehicle for children with ASD and anxiety symptoms, at least according to parents.

In a final step, the additive effect of CBT elements to the video game *Mindlight* in decreasing anxiety symptoms of children with ASD was tested (Chapter 6). A non-concurrent multiple baseline design was used, in which eight children aged 8–12 with ASD received *Mindlight* in the baseline phase and CBT elements in the intervention phase. Results showed that CBT did not seem to have a significant additive effect on *Mindlight* in terms of decreasing anxiety symptoms among children with ASD. Instead, multiple participants had already experienced a decrease in anxiety symptoms during the *Mindlight* sessions, which is in line with the pattern of decreasing anxiety symptoms across the course of treatment in previous studies on *Mindlight* (Schoneveld et al., 2016, 2018; Wijnhoven et al., submitted). However, several participants did experience a stabilization in anxiety symptoms at a low level during the CBT sessions, in combination with an increase in coping skills.

REFLECTIONS ON MAIN FINDINGS

Heterogeneity of the ASD Population

Children with ASD and anxiety form a heterogeneous population, with different clinical expressions and severity rates of ASD, and varying levels and presentations of anxiety. Because of the complex interplay between these factors, children with ASD and anxiety also have varying needs in terms of treatment.

The current thesis has shown that, in the clinical context, children with ASD often suffer from high levels of anxiety that need effective and timely treatment. However, children with ASD present anxiety symptoms in multiple ways, which has implications for the choice of treatment. Therefore, it is important to start with a thorough description and interpretation of the anxiety symptoms of a child with ASD. This may help a clinician decide whether or not to diagnose a comorbid anxiety disorder. According to Kerns and colleagues (2016), four steps need to be taken to facilitate a reliable description and interpretation of the anxiety symptoms, based on which a clinician can decide whether or not to diagnose an anxiety disorder in a child with ASD. First, it is important to determine whether anxiety symptoms are to be expected given the developmental level of the child. Second, the level of impairment that anxiety causes over and above the impairment that is caused by the ASD alone should be taken into account. Third, anticipatory fears, worries and avoidance that are part of an anxiety disorder need to be distinguished from the typical emotion regulation and sensory difficulties of children with ASD. The fourth and final step is to determine whether anxiety triggers symptoms over and above what can be expected from the core symptoms of ASD (Kerns et al., 2016).

To illustrate the consequences of these steps for the decision as to the most suitable anxiety treatment for an individual child with ASD, two examples are given. The first example is a child with a high level of social functioning with severe and specific social worries about being rejected by others, which negatively affects daily functioning. The anxiety symptoms cannot be explained by the developmental level of the child, cause significant impairment, consist of specific anticipatory worries, and cannot be fully explained by the presence of core ASD symptoms. Therefore, the comorbid diagnosis of social anxiety disorder might be justified. When this child also shows a sufficient capacity of verbal expression of his negative thoughts and anxious feelings, treatment that is also used for typically developing children with social anxiety might be effective, such as CBT (Warwick et al., 2017).

On the other hand, a child with ASD and a low level of social functioning can often experience confusion in social interactions, which might, in turn, lead to a certain degree of social anxiety. Part of the confusion in social interactions can be explained by difficulties interpreting and verbally expressing thoughts and feelings, which may lead to an overall negative feeling of 'not fitting in' with the peer group. Moreover, because of difficulties in verbally expressing thoughts and feelings, anxiety might be shown in another way. Other ways of showing anxiety among children with ASD are, for example, challenging behaviour, avoidance/withdrawal, hyperactivity, sensory behaviour (e.g. nail-biting, humming or shouting), and somatic complaints (Ozsivadjian, Knott, & Magiati, 2012). In the type of children with ASD described above, anxiety can be explained by the developmental level of the child (impaired social development). Moreover, anxiety in this type of children with ASD does not cause impairment entirely on its own, does not consist of specific anticipatory worries, and can be explained by the presence of a core ASD symptom (low level of social functioning). A comorbid diagnosis of social anxiety disorder might therefore not be justified. Because of the difficulties in interpreting and verbally expressing thoughts and feelings, the child in this example might not benefit from 'classic' CBT treatment, but (s)he may benefit from alternative ways of treatment, such as more experiential treatments (e.g. emotion-regulation training) or behavioural treatment (e.g. training behaviour with a reward system).

Nevertheless, in mental health agencies, children with ASD are often still treated with standard CBT protocols that have proved to be effective for children with ASD (e.g. Denken + Doen = Durven [Discussing + Doing = Daring], van Steensel & Bögels, 2015), or with an adaptation to a standard CBT protocol, such as the Coping Cat programme for children with anxiety and ASD (McNally Keehn, Lincoln, Brown, & Chavira, 2013) or multimodal anxiety and social skills intervention (White et al., 2010). The above described difference in treatment needs shows that offering only (adapted) CBT might

not fulfil the needs of the whole range of children with ASD and anxiety. Consequently, it can be concluded that it may be necessary to design alternative innovative evidence-based treatments (e.g., *Mindlight*) for anxiety in children with ASD.

Possible Working Mechanisms

The RCT in this thesis showed that, according to parents, *Mindlight* was more effective in decreasing anxiety symptoms than the control game *Triple Town*. The outcomes of the child-rated anxiety symptoms showed that *Mindlight* did not differ in effectiveness compared to *Triple Town* and that children who played *Mindlight* and *Triple Town* both experienced a decrease in anxiety symptoms. Because the mechanisms of change associated with treatment outcomes are not investigated in this thesis, it remains unclear which therapeutic, non-specific and individual factors contributed to the decrease in anxiety symptoms in both children who played *Mindlight* and those who played *Triple Town*. Therapeutic factors are evidence-based elements in the game intended to decrease anxiety (e.g. exposure). These factors are only present in *Mindlight*, because *Triple Town* is a commercial video game and is not specifically focused on reducing anxiety levels. Nevertheless, *Triple Town* could have had non-intentional therapeutic effects (e.g. through relaxation). Non-specific factors are other factors besides the therapeutic elements that can affect the decrease in anxiety (e.g. therapeutic attention). Individual factors are person-specific factors that can have an impact on the extent to which *Mindlight* is effective in decreasing anxiety in a specific child (e.g. presence of comorbid symptoms). In the following sections, the possible therapeutic, non-specific and individual factors that may explain the findings in the RCT on the effect of *Mindlight* in decreasing anxiety symptoms of children with ASD will be described.

Therapeutic factors

First of all, it should be mentioned that the decrease in anxiety in both the children who played *Mindlight* and those who played *Triple Town* could be explained by the overall positive effect of games on the mental health of children (Ferguson & Olson, 2013; Granic, Lobel, & Engels, 2013), regardless of therapeutic elements in the game. In both *Mindlight* and *Triple Town*, children may have projected their anxious feelings on elements in the game and the game play may have been used to cope with these anxious feelings. Both games could have reduced anxiety levels through relaxation, for example, which is an important motivation for children to play games (Ferguson & Olson, 2013) and which might have been a working mechanism in both video games. When looking specifically at *Mindlight*, the hypothesized (evidence-based) therapeutic working elements are exposure (Abramowitz, Deacon, & Whiteside,

2011), neurofeedback focused on relaxation and concentration (Hammond, 2005), and attention bias modification (Muris & Field, 2008). Because of the combination of experiential and cognitive-behavioural treatment elements, there is a high likelihood of fulfilling the treatment needs of a broad range of children with ASD. Moreover, for children, the improvement of coping skills to deal with anxiety during exposure is important and increases treatment effects (Hedtke, Kendall, & Tiwari, 2009). For children with ASD, this may be even more important, as it is more challenging for them to regulate their negative thoughts and feelings during exposure through cognitive restructuring (Moree & Davis, 2010). Yet, research has shown that therapists prefer cognitive restructuring and rarely endorse exposure techniques in anxiety treatment because of their negative beliefs about exposure and the resilience of children during the exposure (Whiteside, Deacon, Benito, & Stewart, 2016). In *Mindlight*, this barrier was overcome, as exposure is integrated into the game and the improvement of coping skills is targeted by using neurofeedback. Hence, *Mindlight* could be a valuable treatment tool for therapists to use as a basis to stimulate exposure and to improve coping skills during exposure. For example, when a child with ASD playing *Mindlight* does not know how to regulate his or her emotions during exposure, the neurofeedback elements will possibly teach the child in an experiential way how to reduce anxiety to an acceptable level by relaxation and concentration. Moreover, with the attention bias modification elements, the child receives more behaviouristic training in moving their attention towards positive or neutral stimuli and moving attention away from negative or threatening stimuli.

Of course, the above described therapeutic working elements are still hypothetical, as only the parent results showed some support for the effect of these therapeutic factors. Moreover, these therapeutic working elements have not yet been tested statistically. Nevertheless, it can be stated that the interplay between multiple therapeutic mechanisms is an advantage of *Mindlight* that could be used by the therapist as a basis to stimulate a reduction in anxiety symptoms of children with ASD. In the single-case series study investigating the additive effect of CBT elements on *Mindlight*, it has been shown that it could be useful for some children to add CBT sessions to *Mindlight*, wherein therapists could further support the generalization of the learned coping skills in daily life situations.

Non-specific factors

It has been suggested that non-specific factors also have an important role to play in explaining the effect of a treatment (e.g. Arrindell, 2001). Firstly, during the game sessions, therapeutic attention and alliance were potential non-specific factors that partly explained the decrease in child- and parent-rated anxiety symptoms and

disorders in both the *Mindlight* and *Triple Town* condition of the RCT (Crawford, Frank, Palitz, Davis, & Kendall, 2017). Secondly, a potential non-specific factor that might have played a role in the effect of *Mindlight* is autonomy. In the self-determination theory, perceived autonomy can increase the willingness to complete a certain task (Ryan, Rigby, & Przybylski, 2006). It has been shown that the level of perceived autonomy is high when playing a video game in general (Ryan et al., 2006). It is assumed that children also experienced a high level of autonomy when playing *Mindlight*, because they made their own choices about how to walk through the game and when and how to expose themselves to anxious stimuli.

Thirdly, engagement and the feeling of competence might have been high during the gameplay of *Mindlight*, because *Mindlight* is a fun game to play and children can achieve goals at their own level. In turn, this perceived autonomy, engagement and feeling of competence may have led to an increased intrinsic motivation to play *Mindlight* (Ryan et al., 2006). Intrinsic motivation, in turn, has a positive impact on self-esteem and mood (Ryan et al., 2006), which may have led to a decrease in anxiety symptoms among the participating children. The presence of autonomy and engagement are also an important advantage over CBT, wherein these factors are often not sufficiently experienced by children (Granic et al., 2013).

In the *Triple Town* condition in the RCT, intrinsic motivation may also have played a role in the decrease of child- and parent-rated anxiety symptoms. However, the finding that *Mindlight* was more effective in decreasing parent-rated anxiety than *Triple Town* might be partly due to lower autonomy, engagement and feeling of competence in children who played *Triple Town*. Children who played *Mindlight* might have been more enthusiastic about the game sessions to parents, because this game may be more challenging and enjoyable than *Triple Town*. Children might also have experienced autonomy to a certain degree during the gameplay of *Triple Town*, but to a lower extent than in *Mindlight* because of the more fixed game structure in *Triple Town*. Contrary to the children themselves, parents might have recognized the greater intrinsic motivation of children who played *Mindlight* resulting from the greater presence of perceived autonomy, engagement and feeling of competence, which might have played a role in the difference in the parent-rated effect (and the absence of this difference in the child-rated effect) of *Mindlight* and *Triple Town*.

Fourthly, the context in which the level of anxiety symptoms has been assessed by parents and children may be a non-specific factor that might have played a role in the outcomes of the RCT. *Mindlight* may have had a larger effect on 'home-based' anxiety symptoms (e.g., darkness and monsters) than *Triple Town*, because of the stronger exposure to the home-based threatening cues in the game. This effect may be more visible for parents, as parents see their children at home every day. Children might also

have experienced this effect on their home-based anxiety symptoms, but they still might have experienced some anxiety in other contexts because of their difficulty with generalization of skills they learned (de Marchena, Eigsti, & Yerys, 2015). The anxiety in other contexts (e.g., at school) might have been less visible for parents, leading to a significant effect of *Mindlight* on parent-rated anxiety and an absence of this effect on child-rated anxiety. Finally, parents were possibly more conscious of therapeutic elements in *Mindlight* (or the absence of such elements in *Triple Town*) through their child's stories about the game, in turn leading to increasing expectations of *Mindlight* during the course of the sessions, which might have led to a larger effect of *Mindlight* on parent-rated anxiety symptoms compared to *Triple Town* (e.g. Thiruchselvam et al., 2019).

Taken the above described non-specific factors altogether, it can be concluded that both *Mindlight* and *Triple Town* may have contained non-specific factors that had a decreasing effect on anxiety symptoms of the participating children, but that they may have been more present in *Mindlight* than in *Triple Town* and that they may have been more visible for parents than for children. This may have played a role in the larger effect of *Mindlight* on parent-rated anxiety (and the absence of this effect on child-rated anxiety) compared to *Triple Town*.

Individual factors

Next to therapeutic and non-specific factors, individual factors may also have played a role in the effect of *Mindlight*. In the following paragraphs, individual factors will be presented that may have played a role in the current findings on the effect of *Mindlight* on anxiety symptoms in children with ASD.

Firstly, in the RCT, girls showed higher initial levels of anxiety and a greater decrease in anxiety during *Mindlight* than boys. This could be explained by more intact pretend play skills in girls with ASD as compared to boys (Knickmeyer, Wheelwright, & Baron-Cohen, 2008). Children with ASD have difficulty with pretend play, but it has been shown that the pretend play skills of girls are better and more intact than the pretend play skills of boys. These better pretend play skills may indicate a greater capacity for girls to identify themselves with Arty in *Mindlight* and project their anxious feelings onto him. In turn, Arty might have become an individual representing their own process of improving coping skills and reducing anxiety, which might have led to a greater decrease in anxiety symptoms in girls than in boys.

Secondly, the ability to learn coping skills during *Mindlight* and the motivation to practise the learned coping skills in daily life situations might be a factor that played a role in the potential effect of *Mindlight*. When children are able to learn the coping skills of relaxation and concentration by neurofeedback during *Mindlight*, when they

know how to practise these skills in daily life situations, and when they are motivated to do so, there is a reasonable chance that their anxiety symptoms will decrease after completing the *Mindlight* sessions (e.g. Hedtke et al., 2009). Therefore, these children may have been the improvers in the RCT that is presented in this thesis. There may also be children that experienced difficulties learning coping skills during the game, possibly resulting in less capacity and motivation to practise these skills in daily life situations. For example, in children with high arousal and anxiety levels throughout the course of the game sessions in the RCT, anxiety may have caused too much impairment during the gameplay to profit from the training of coping skills in an optimal way. Moreover, the barrier to practising these skills in daily life situations may have been too high. For these children, the addition of CBT elements with more therapeutic guidance in the exposure exercises in daily life would have been necessary to overcome these barriers. Of course, all this is quite speculative and further research should reveal whether the ability to learn coping skills is indeed a factor that plays a role in the effect of *Mindlight*.

Thirdly, the extent to which parents support the use of their child's learned coping skills in different daily life situations may be an important individual factor affecting the impact of *Mindlight*. It has been shown that it is important that, after completing the therapy sessions, a smooth transfer from therapist to parent takes place so that parents support their children in practising the learned coping skills at home (Swan et al., 2016). In the RCT, some parents might have supported the child's use of relaxation or concentration strategies (learned coping skills in *Mindlight*) in daily life situations. This, in turn, may have led to a better generalization of skills in daily life situations and a greater decrease in anxiety symptoms among these children. However, the sample also consisted of multiple multi-problem families—for example, parents with psychiatric problems. For these parents, it might have been more difficult to stimulate their child to use the learned coping skills in daily life situations, thereby leading to less generalization of learned skills and a smaller decrease in anxiety symptoms.

Fourthly, the present thesis has shown that the prevalence of depressive symptoms and suicidal ideation in children with ASD and anxiety is high. The presence of comorbid depressive symptoms in individuals with an anxiety disorder is predictive of a poor treatment outcome (Van Balkom et al., 2008). When examining the difference in the effect of *Mindlight* on anxiety in children with ASD and high depressive symptoms (score on Child Depression Inventory [CDI] ≥ 14), we observed (for child-report significantly) higher levels of anxiety at three-months follow-up (mean score on Spence Children's Anxiety Scale [SCAS-C] T3: 27.17; mean SCAS for parents [SCAS-P] score T3: 23.00) than in children with ASD and low depressive symptoms (CDI-score < 14; mean SCAS-C score T3: 18.07; mean SCAS-P score T3: 19.55). When examining results in more detail,

we see that children with higher depressive symptoms show a similar decrease in anxiety to children with lower depressive symptoms. This may be due to the fact that, for child-report especially, children with higher depressive symptoms showed higher starting levels of anxiety (mean SCAS-C score T0: 43.78; mean SCAS-P score T0: 33.14) than children with low depressive symptoms (mean SCAS-C score T0: 28.60; mean SCAS-P score T0: 32.57). This may indicate that *Mindlight* had an effect on the anxiety symptoms of children with ASD and depressive symptoms, but that the anxiety symptoms of these children were still at a relatively high level at three-months follow-up. These higher anxiety levels at screening and three-months follow-up in children with high depressive symptoms can be explained by the high bidirectional negative interplay between anxiety and depression (Lavigne, Hopkins, Gouze, & Bryant, 2015). This implies that it is relevant that some of these children receive treatment for both anxiety and depression. Moreover, the presence and severity of suicidal ideation needs to be assessed, and when a child with ASD suffers from active suicidal ideation, this needs immediate treatment before treating anxiety and other depressive symptoms.

Heterogeneity and Effect of Treatment

Taken together, these reflections on the heterogeneity of the ASD population and the possible working mechanisms of *Mindlight* lead to a few conclusions about the effect of anxiety treatment for children with ASD. The heterogeneity of the ASD population and the therapeutic, non-specific and individual working mechanisms interact with each other in a complex way, leading to challenges finding one anxiety treatment that is effective for all children with ASD. Johnco and Storch (2015) state that CBT is effective in children with ASD, but that in past CBT trials, only children with ASD, high social functioning and high verbal capacity were included. It is unknown whether CBT is also suitable for and effective in children with ASD and low social functioning and low verbal capacity. The authors state that it is important in future research to focus on which forms and elements of evidence-based treatment are most effective for which type of children with ASD. For example, a child with ASD and anxiety, a low level of social functioning, limited verbal capacity and a high motivation for a game intervention might benefit from a non-verbal treatment like *Mindlight*, but might also need the support of his parents to practise the learned coping skills in daily social situations. Indeed, it has been shown that children with ASD and poorer functional and daily living skills need more parental involvement in treatment (Reaven, 2011). The addition of CBT elements may not be suitable for this child, because these elements are more verbal and therefore more difficult for this specific child. A child with ASD and anxiety, a low level of social functioning, high verbal capacity and a high motivation for a game intervention may benefit from *Mindlight*, but may also benefit from the addition of CBT

elements. This may be the case because the child has high verbal capacity and could therefore profit more from the cognitive restructuring elements in the CBT sessions (Johnco & Storch, 2015). Moreover, because of the limited social skills, this child could use extra therapeutic support in the generalization of the learned coping skills to daily social situations. Furthermore, a child with ASD and anxiety, a moderate level of social functioning, high verbal capacity and a low motivation for a game intervention should not be treated with *Mindlight*, but might benefit more from a 'standard' CBT protocol for anxiety treatment with minor adaptations if necessary.

Finally, a child with ASD, anxiety, depressive symptoms and suicidal ideation might need treatment that is effective in decreasing both anxiety and depression. Recently it has been found that mindfulness-based interventions could be effective in reducing both anxiety and depression in individuals with ASD (Spek, van Ham, & Nyklíček, 2013; White et al., 2018). Improved emotion regulation and increased emotional awareness are well-established treatment mechanisms in mindfulness-based interventions, which may very well be suitable mechanisms for individuals with ASD who have difficulty with the high-level cognitive strategies that are part of CBT (White et al., 2018). So far, these mindfulness-based interventions have only been investigated in adolescents and adults with ASD. Nevertheless, these interventions may also be effective in decreasing anxiety and depression in children with ASD. When active suicidal ideation has a prominent role in the depressive symptoms of a child with ASD, it is important to focus treatment on this specific problem first. CBT for suicide prevention (CBT-SP; Stanley et al., 2009) and the Attempted Suicide Short Intervention Programme (ASSIP; Gysin-Maillart, Schwab, Soravia, Megert, & Michel, 2016) provide two examples of interventions that have found to be effective in preventing future suicidal behaviour in typically developing individuals. Further research is needed to examine the effectiveness of these suicide prevention programmes in children and adolescents with ASD.

These hypothetical cases show that it is not possible to implement a single anxiety treatment that is effective for all children with ASD. Still, with the development of *Mindlight*, an important contribution was made to existing anxiety treatment programmes for children with ASD. This, in turn, may add to a greater availability and choice of evidence-based anxiety treatments that can serve a broader range of children with ASD and anxiety.

LIMITATIONS

There are several limitations that warrant caution in the interpretation of the results in the current thesis. First, the questionnaires in the present thesis (e.g. SCAS-C/P;

Scholing, Nauta, & Spence, 1999a, 1999b) were not specifically designed for children with ASD. Despite knowledge that the psychometric properties of these measures seem acceptable for children with ASD (see review by Lecavalier et al., 2014), this could have had a negative impact on the reliability of the measures in three ways. Firstly, there is a lack of appropriate cut-offs for children with ASD in these measures (Van Steensel & Heeman, 2017). As a result, it is unknown when a score on a measure can be defined as subclinical or clinical, and whether this is comparable to the population of typically developing children. Secondly, despite the literature stating that children with high cognitive capacities are able to report their thoughts and feelings accurately (De-la-Iglesia & Olivar, 2015; Ozsivadjian, Hibbert, & Hollocks, 2014), it is possible that participating children suffered from alexithymia (reduced ability to identify emotions; Bird & Cook, 2013) to some extent when interpreting questions on emotional states and that this affected the reliability of the measures. Thirdly, the existing anxiety measures do not take into account the possible overlap between ASD and anxiety (Van Steensel et al., 2017).

Moreover, the lack of an additional control condition that did not receive any treatment is a limitation. In the RCT, the children in the control condition that received *Triple Town* showed a decrease in child-rated anxiety symptoms equal to the children in the experimental group that received *Mindlight*. It is unknown whether non-specific factors (e.g. therapeutic attention; Crawford et al., 2017) played a role in the decrease of anxiety symptoms in both groups, or whether *Mindlight* and *Triple Town* were both effective in decreasing anxiety symptoms in children with ASD. Had a control group without any treatment (e.g. a waiting list control group) been included, better insight would have been obtained as to the causes of the decrease in anxiety symptoms. If the children in this second control group also showed a decrease in anxiety symptoms, then it would have been likely that non-specific factors played a role in the decrease; however, if these children did not show a decrease in anxiety symptoms, we could have concluded that both games were effective in decreasing child-rated anxiety symptoms.

Furthermore, there was a relatively high percentage of children and parents in the RCT that filled in the questionnaires outside the timeframe that was set. This might have had an impact on the reliability of the results in the RCT, because the results also include measurements of anxiety symptoms at time points that deviate from the original time points (e.g. pre-tests that were filled in after session 1). Yet, this is common in research conducted in a clinical context with multi-problem families. Therefore, the results may be a realistic representation of treatment and research processes in clinical practice.

Finally, the lack of outcomes on the mechanisms of change is a profound limitation of the present thesis. Specifically, it remains unclear what elements of the games

contributed to the decrease in anxiety symptoms. It is possible that it was not only the evidence-based elements of *Mindlight* (exposure and attention bias modification) that affected anxiety symptoms among the participating children, but also the positive associations with the neurofeedback headset that children wore during the game. Moreover, as described before, non-specific and individual factors may have had an impact on the decrease in anxiety symptoms.

SUGGESTIONS FOR FUTURE RESEARCH

Based on the findings presented in the current thesis, several suggestions can be made for further research. Firstly, it is important to investigate further the short- and long-term effects of *Mindlight* in children with ASD, as the results in the present study are rather inconsistent. Secondly, the specific working mechanisms of *Mindlight* for children with ASD and anxiety need to be investigated so that we obtain insight into which elements of *Mindlight* (exposure, neurofeedback, attention bias modification, or any other) are responsible for the decrease of anxiety in children with ASD. Furthermore, the possible non-specific and individual factors described earlier that have an impact on the decrease of anxiety symptoms during treatment with *Mindlight* need to be further investigated. Single case (series) designs are highly suitable, for example, to test working mechanisms and non-specific or individual factors in a heterogeneous population like the ASD population, because these designs can give better insight into complex individual processes of change than group-based research designs like RCTs (Smith, 2012). This way, the ecological and clinical validity of research findings could be increased. In turn, clinicians could better determine in future clinical practice the type of children with ASD for whom *Mindlight* might be an effective anxiety intervention and the type of children with ASD for whom another anxiety intervention might be more suitable and effective.

Also, it is important to investigate the deliverability and cost-effectiveness of *Mindlight*. When studies on deliverability and cost-effectiveness are combined, more insight could be obtained as to the most cost-effective form of implementation. For example, it could be examined whether *Mindlight* is more (cost-)effective (e.g. larger decrease in anxiety, shorter treatment duration and lower costs per session) as a preventive intervention for anxiety in children with ASD in schools or through general practitioners, or whether *Mindlight* is more (cost-)effective as a treatment of anxiety symptoms in children with ASD through mental health agencies. Also, if treatment of anxiety symptoms in children with ASD through mental health agencies turns out to be most (cost-)effective, strategies should be explored that lead to the optimal

implementation of *Mindlight* in mental healthcare. For instance, *Mindlight* may become part of digital agencies providing digital mental help (e.g. Digitale Poli, 2019a/b).

The findings in the current thesis also lead to suggestions for the development of new digital interventions (e.g. video games) for children with ASD. Because of the high heterogeneity, the high comorbidity of psychiatric problems and the different treatment needs of children with ASD, it is important to develop new digital interventions that take into account all these factors. One idea would be to develop an online platform with multiple video games with varying therapeutic aims tailored to a broad range of children with ASD—for example, video games aimed at decreasing anxiety, depression, suicidal ideation and social problems. Also, for each game, suggestions for face-to-face add-ons could be made, such as CBT elements or sessions for parents. If such a digital platform becomes accessible to children with ASD and their therapists, they could compose a personalized treatment together by selecting the video games and add-ons that are suitable for that particular child and are aimed at decreasing the psychiatric and social problems of the child. The results of further research on the working mechanisms of *Mindlight* could give direction as to the specific evidence-based treatment elements that should be integrated into the games. Moreover, further research on individual factors should indicate which children need additive treatment elements such as face-to-face CBT sessions or parental support. In turn, future research should be focused on investigating the effect of these new and personalized digital interventions.

CLINICAL IMPLICATIONS AND RECOMMENDATIONS

This thesis gives rise to several clinical implications and recommendations. Based on the findings in these studies, the heterogeneity of the ASD population and the possible working mechanisms of *Mindlight*, it is concluded that therapy for children with ASD and anxiety should be more personalized. Clinicians should decide on the kind of anxiety treatment that is most suitable and effective for a particular child with ASD based on 1) the severity and presentation of ASD and anxiety and the degree of overlap between the ASD and anxiety (Kerns et al., 2016); 2) the motivation for different treatments (e.g. high motivation for *Mindlight* increases treatment effects; Ryan et al., 2006); and 3) individual factors, including the possibility of parental involvement and the presence of comorbid depressive symptoms and suicidal ideation (Swan et al., 2016; Van Balkom et al., 2008).

Mindlight has proved to be a digital treatment method that has the potential to become a promising addition to the existing treatment curriculum in mental health agencies. As stated before, further research on therapeutic, non-specific and

individual factors as possible working mechanisms is important. Moreover, on the basis of the findings in the current thesis, new digital interventions (e.g. video games) could be developed and investigated. However, it is also important to think about the implementation of a digital intervention such as *Mindlight* in mental health agencies or even in school contexts. This is because it has already been shown that digital tools are a growing part of the treatment curriculum in mental health agencies, especially in adult patient groups. There are only a few guidelines to the implementation of such digital tools. It is important to think about and investigate how existing and future digital tools such as *Mindlight* could be implemented in mental healthcare in the most optimal and effective way. In the following paragraph, suggestions for the implementation of digital tools (in general and specifically for *Mindlight*) are presented.

Implementation and sustainability of digital tools

Firstly, it is important to note that many digital tools nowadays are developed in and for mental healthcare. However, often it remains unknown to mental health professionals how to access these tools, which tools are available and which tools are best to implement in clinical practice, which in turn may lead to a lacking acceptance and use of digital tools in mental healthcare (Hennemann, Beutel, & Zwerenz, 2017). There are several initiatives that bring together researchers, therapists, programmers and digital health developers, and that gather all the digital tools and interventions in mental healthcare. One example is Open Digital Health (2019), a website that aims to connect all the above described disciplines and create a platform for all the digital tools that are available in healthcare. Platforms like these make digital tools more accessible for therapists in mental healthcare, which may lower the barrier to use them in clinical practice.

Secondly, for most digital tools, there are no treatment protocols that provide guidance on how to offer the interventions to children in clinical practice. Important questions in this matter include: What is the role of the therapist during the sessions? To what extent will parents be involved in the use of the tool? How and to what extent should generalization to daily life be stimulated? The answers to these questions can result in guidelines or protocols for the use of digital tools in clinical practice (e.g., see Wentzel, van der Vaart, Bohlmeijer, & van Gemert-Pijnen, 2016).

Moreover, it is important to train clinicians in how to implement these tools in treatment. Many clinicians are not (yet) accustomed to the use of digital tools in treatments. The formulation of clear and practical guidelines or protocols can lower the barrier to the use of digital tools, but it is also important that clinicians receive training from a digital healthcare expert who can demonstrate how to use the digital tools and who can stimulate clinicians to use these in their clinical practice (Wykes &

Brown, 2016). This way, the barrier to the use of digital tools in mental healthcare can be further lowered.

Furthermore, it is important to prepare the healthcare environment to offer digital tools (Wykes & Brown, 2016). Mental healthcare agencies are generally not yet adapted to the practical implementation requirements that come with the development of digital tools for mental healthcare. For example, laptops need to be available that are suitable for the installation of video games or other digital treatments. Moreover, help desk services need to be available to guide clinicians when they have questions about the practical use of a digital intervention or service.

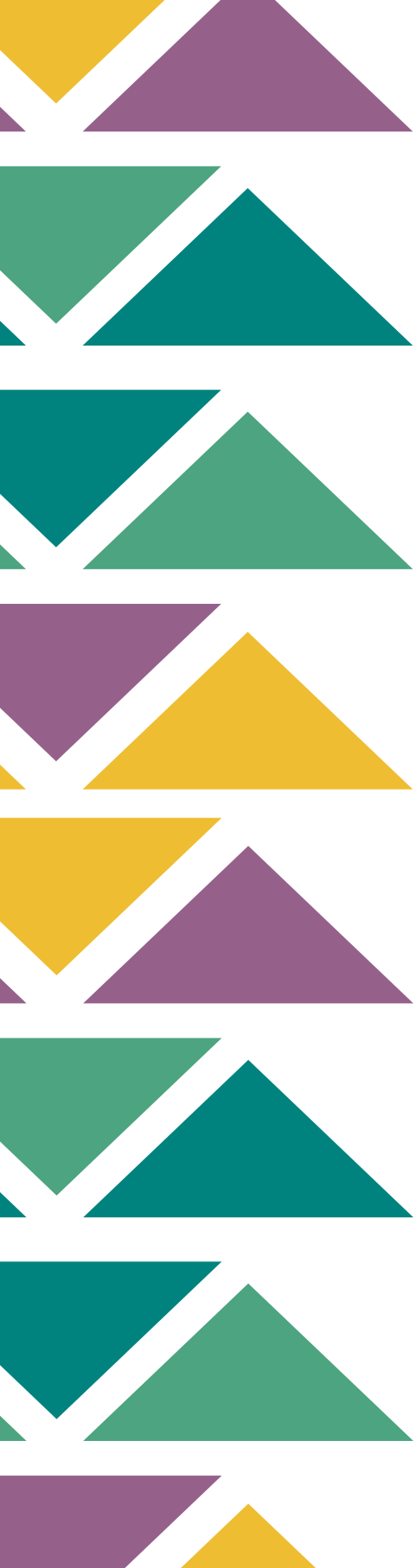
Finally, to put the above described actions into practice, it is important to design a framework on how to finance and facilitate the development, improvements, maintenance and implementation of digital tools in mental healthcare, as this is currently a substantial barrier for uptake and upscaling (Hadjistavropoulos, Nugent, Dirkse, & Pugh, 2017). In the Netherlands, there are several funding options for the implementation of digital tools in mental healthcare agencies. For example, the government has some options to request funding for the development and implementation of digital tools in healthcare (see Zorg voor innoveren, 2019a/b). Some mental health agencies are not fully aware of these opportunities, or they do not know how to use the funding in an optimal way for implementation purposes. These mental health agencies need to put more energy into facilitating and financing the implementation of digital tools in order to prevent the lack of use or misuse of digital tools and to be on top of digital developments in mental healthcare.

Concerning specific suggestions for implementation of *Mindlight*, it is important to notice that further research is first needed to investigate the short- and long-term effects and working mechanisms of *Mindlight*. When making suggestions for implementation based on the current results of the RCT, it could be stated that the control game *Triple Town* might be equally suitable as *Mindlight* to implement in clinical practice. After all, both children in the *Mindlight* and *Triple Town* condition showed a substantial decrease in anxiety symptoms over time. However, *Mindlight* gives rise to more options for further research, development and implementation. Even though *Mindlight* and *Triple Town* showed similar effects when it comes to child-report, parent-report showed better outcomes for *Mindlight t*han for *Triple Town*. Moreover, as described before, *Mindlight* was developed with the aim to decrease anxiety symptoms by therapeutic elements (exposure, neurofeedback, attention bias modification), while *Triple Town* is a commercial video game that is developed without therapeutic aims. This means that the therapeutic elements in *Mindlight* could be further investigated and developed to increase the effectiveness of *Mindlight*, while this is not possible for *Triple Town*. Moreover, the therapeutic elements in *Mindlight* offer therapists more

concrete guidelines to supervise the child in practicing the learned skills in daily life. Finally, other treatments (e.g., CBT) could be more easily combined or integrated with the therapeutic elements in *Mindlight*, which leads to more implementation options of *Mindlight* in mental health agencies. Therefore, future efforts should focus on further investigating, developing and implementing *Mindlight*, or its next versions, in clinical practice.

CLOSING STATEMENT

The population of children with ASD and anxiety is heterogeneous in both its clinical presentation and its treatment needs. The video game *Mindlight* has been shown to be a promising new intervention vehicle for children with ASD and anxiety, with the potential to contribute to existing anxiety treatments in mental healthcare for children with ASD. Moreover, the implementation of *Mindlight* might lead to a greater choice of evidence-based anxiety treatments that can serve a broader range of children with ASD and anxiety. However, the RCT only showed significant effects of *Mindlight* on parent-rated anxiety (and not on child-rated anxiety) and the single-case series study showed that *Mindlight* (with or without CBT-elements) is not an effective anxiety intervention for all children with ASD. Future research needs to elucidate which individual factors determine the type of children with ASD for whom *Mindlight* is effective and the type of children with ASD for whom another anxiety treatment may be more suitable and effective. In this way, therapeutic, non-specific and individual factors can be taken into account when clinicians make a decision about which treatment is most suitable and effective for a child with ASD and anxiety. Optimal adjustment to the child's needs will eventually lead to an effective personalized treatment. Also, new digital interventions (e.g. video games) should be developed wherein personalization is integrated into the intervention itself. In the near future, it is important that the development, funding and implementation of digital tools such as *Mindlight* receive more attention in mental healthcare. Mental health agencies need to be stimulated to facilitate and finance the development and implementation of digital tools such as *Mindlight* further in order to prevent the lack of use or misuse of digital tools and to be on top of digital developments in mental healthcare.



APPENDIX

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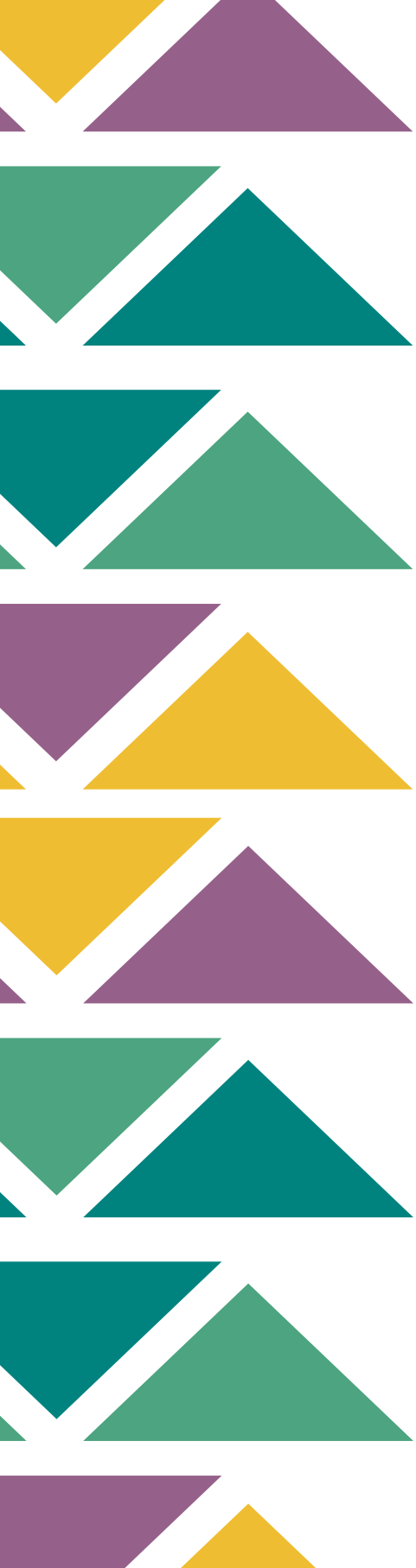


APPENDIX

Nederlandse Samenvatting

NEDERLANDSE SAMENVATTING

Het is bekend dat er wereldwijd 1 op 160 kinderen gediagnosticeerd is met een autismespectrumstoornis (ASS). Volgens de 'Diagnostic and Statistical Manual of Mental Disorders 5th Edition' (DSM-5) wordt ASS gekarakteriseerd door een bepaalde mate van beperkingen in sociaal gedrag, communicatie en taal, samen met de aanwezigheid van repetitief gedrag en specifieke interesses. Het meest voorkomende comorbide probleem bij kinderen met ASS is angststoornissen. Angst in kinderen met ASS leidt tot beperkingen in het dagelijks leven, zoals depressieve symptomen en problemen in relatie met leeftijdsgenoten, leerkrachten en ouders. De negatieve consequenties van angst zijn vaak de reden voor kinderen met ASS en hun ouders om hulp te gaan zoeken, zonder te weten dat deze consequenties gerelateerd zijn aan angst. Daarom is het belangrijk dat er goede onderkenning en behandeling van angstklachten bij kinderen met ASS komt in de geestelijke gezondheidszorg. Het eerste doel van het huidige proefschrift was dan ook om inzicht te geven in de prevalentie en risicofactoren van angst bij kinderen met ASS. Daarnaast was het doel om de werkzaamheid van een innovatieve behandeling voor angst, de video game '*Mindlight*', te onderzoeken bij kinderen met ASS en angstklachten.

Deel 1: Prevalentie en risicofactoren van angst bij kinderen met ASS

In het eerste gedeelte van dit proefschrift wordt de relevantie van het verbeteren van de onderkenning en behandeling van angst bij kinderen met ASS aangetoond door de prevalentie en risicofactoren van angstklachten bij Nederlandse kinderen met ASS in een klinische setting te onderzoeken (Hoofdstuk 2). Prevalentie en risicofactoren van angstklachten gerapporteerd door kinderen en ouders werden onderzocht in 172 kinderen met ASS in de leeftijd van 8-15 jaar. Gespecialiseerde instellingen waar kinderen met ASS werden geworven waren twee instellingen voor geestelijke gezondheidszorg en een school voor speciaal voortgezet onderwijs. Kinderen en hun ouders vulden een zelfrapportage vragenlijst in over angstklachten. Resultaten van de kind rapportage lieten zien dat meer dan 60 procent van de deelnemende kinderen met ASS ten minste subklinische angstklachten had, terwijl resultaten van de ouderrapportage lieten zien dat meer dan 80 procent van de kinderen met ASS ten minste subklinische angstsymptomen had. Daarnaast werd gevonden dat jongere kinderen en meisjes met ASS meer angstklachten lieten zien dan oudere kinderen en jongens met ASS. Ook werd aangetoond dat kinderen met een hoger performaal (visuo-motorisch) IQ (PIQ) en een lager verbaal IQ (VIQ) meer risico hadden om symptomen van specifieke fobie te hebben. Deze bevindingen laten zien dat kinderen met ASS in een klinische setting een hoge prevalentie van comorbide angstklachten hebben, met name meisjes en jonge kinderen met ASS.

Daarnaast werd de noodzaak om de onderkenning en behandeling van angst bij kinderen met ASS verder te verbeteren, benadrukt door de hoge comorbiditeit van depressieve symptomen en suïcidale ideatie in kinderen met ASS en angst (Hoofdstuk 3). De prevalentie van depressieve symptomen en suïcidale ideatie werd onderzocht in een kleine steekproef van 93 kinderen met ASS in de leeftijd van 8-16 met een normaal cognitief niveau en (sub)klinische angstklachten. Zowel ouders als kinderen vulden vragenlijsten in om de mate van depressieve symptomen te beoordelen. Verder rapporteerden kinderen hun mate van suïcidale ideatie. Uit de kind rapportage bleek dat meer dan 35 procent van de kinderen met ASS een klinisch niveau van depressieve symptomen liet zien en uit de ouderrapportage bleek dat meer dan 75 procent van de kinderen met ASS een klinisch niveau van depressieve symptomen liet zien. Meisjes rapporteerden een significant hogere mate van depressieve klachten dan jongens. Daarnaast rapporteerde 32.2 procent van de kinderen met ASS suïcidale gedachten en 2.2 procent van de kinderen rapporteerde actieve suïcidale ideatie (suïcidale gedachten en risico op suïcidaal gedrag). Er werden geen gender verschillen gevonden in suïcidale ideatie. Deze bevindingen toonden aan dat kinderen met ASS, een normaal cognitief niveau en angstklachten een risico hebben om een hoge mate van comorbide depressieve symptomen en suïcidale ideatie te laten zien.

Deel 2: Behandeling van angst in kinderen met ASS

Mindlight

In het tweede gedeelte van het huidige proefschrift wordt het effect van de video game *Mindlight* beschreven. *Mindlight* gaat over de jongen Artie, die door zijn ouders wordt afgezet bij het huis van zijn oma. Het huis en zijn oma zijn echter vervloekt, hetgeen Artie ontdekt doordat oma eruit ziet als een monster en doordat het huis donker is en vol met monsters en enge objecten zit. Deze enge spelomgeving wordt ondersteund met onheilspellende muziek en wekt de belangrijkste vroegkinderlijke angsten op, zoals angst voor het donker, scheiding van ouders, alleen zijn en monsters. Artie moet zijn eigen innerlijke kracht gebruiken om zijn angst te verminderen, zodat hij de vloek kan doorbreken en ervoor kan zorgen dat oma en het huis weer de oude worden. Hij kan dit bewerkstelligen door zijn '*Mindlight*' te gebruiken, een lichtbron op zijn pet die op de omgeving kan schijnen en die gecontroleerd kan worden door zijn eigen innerlijke kracht. Zijn 'innerlijke kracht' wordt gemeten door een neurofeedback headset (de 'Mindwave'), welke kinderen opzetten wanneer ze *Mindlight* gaan spelen. Deze headset meet EEG door middel van een actieve elektrode en een referentie elektrode. De signalen die gemeten worden, worden uiteindelijk gefilterd op Delta, Theta, Alpha en Beta golven. In *Mindlight* worden voornamelijk de Alpha en Beta golven gebruikt voor neurofeedback.

Effect van *Mindlight*

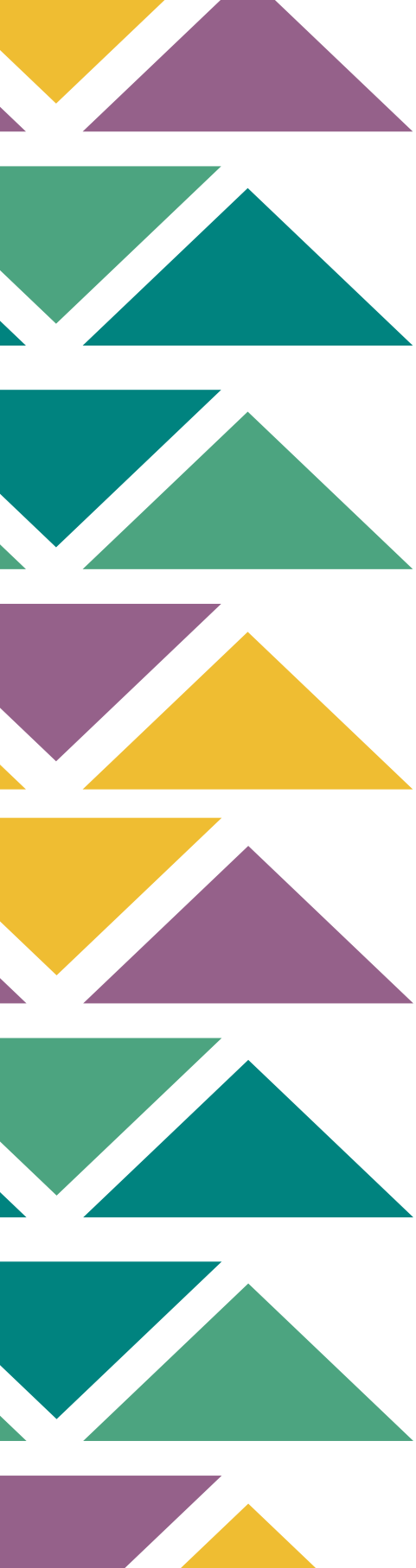
In Hoofdstuk 4 van het huidige proefschrift werd het studie protocol van de randomized controlled trial (RCT) voor de effectiviteitsstudie naar *Mindlight* gepresenteerd. Hierin werd de achtergrond, hypotheses, design, procedure, interventie (*Mindlight*), uitkomst maten en analyse methoden beschreven. In het totaal werden 122 kinderen met ASS en (sub)klinische angstklachten in de leeftijd van 8-16 jaar gerandomiseerd over de experimentele (N=59) of de controle (N=63) conditie. Een klein deel van de steekproef (n = 13) werd uit de uiteindelijke analyses weggelaten vanwege sterke verschillen tussen de karakteristieken van dit deel van de steekproef vergeleken met de rest van de participanten. De overgebleven 109 kinderen (n = 53 experimentele conditie; n = 56 controle conditie) werden geïncludeerd in de statistische analyses.

Kinderen in de experimentele conditie speelden *Mindlight* en kinderen in de controle conditie speelden een commerciële game (*Triple Town*). Ze speelden allemaal een uur per week gedurende zes opeenvolgende weken. Alle kinderen en ouders vulden vragenlijsten in bij baseline, nameting en drie maanden follow-up. De resultaten (gepresenteerd in Hoofdstuk 5) van de kind rapportage lieten zien dat er geen verschil was in de afname van angstklachten tussen de twee condities. Echter, de resultaten van de ouderrapportage lieten zien dat de afname van angstklachten in de experimentele conditie significant groter was dan in de controle conditie. Verder werd gevonden dat externaliserend gedrag geen invloed leek te hebben op het verloop van de angstklachten gedurende de game sessies. Deze resultaten zijn een voorzichtig bewijs dat video games een veelbelovend nieuw interventie medium zijn voor kinderen met ASS en angstklachten, in ieder geval volgens ouders.

In Hoofdstuk 6 werd het toegevoegde effect van elementen van cognitieve gedragstherapie (CGT) op de video game *Mindlight* in het verminderen van angstklachten bij kinderen met ASS onderzocht. Een non-concurrent multiple baseline design werd hiervoor gebruikt, waarin acht kinderen met ASS in de leeftijd van 8-12 jaar *Mindlight* speelden in de baseline fase en twee CGT sessies kregen in de interventie fase. Resultaten lieten zien dat CGT geen toegevoegd effect leek te hebben op *Mindlight* in het verminderen van angstklachten bij kinderen met ASS. In plaats daarvan werd gezien dat meerdere participanten al een afname in angstklachten ervaarden gedurende de *Mindlight* sessies, hetgeen in lijn is met het patroon van afname in angstklachten tijdens de behandeling in eerdere studies naar het effect van *Mindlight*. Echter, meerdere participanten ervaarden een stabilisatie in de afgenomen angstklachten gedurende de CGT sessies, in combinatie met een toename in coping vaardigheden.

Conclusie

De populatie van kinderen met ASS en angstklachten is heterogeen in zowel de klinische presentatie als in behoeften voor behandeling. De video game *Mindlight* is een veelbelovende nieuwe behandeling voor kinderen met ASS en angst, met de potentie om bij te dragen aan bestaande angstbehandelingen in de geestelijke gezondheidszorg voor kinderen met ASS. Verder kan de implementatie van *Mindlight* leiden tot een grotere keuze van evidence-based angstbehandelingen die een grotere range van kinderen met ASS en angst kan dienen. Echter, de RCT liet alleen significante effecten zien van *Mindlight* op angst gerapporteerd door ouders (en niet door kinderen) en de single-case studie liet zien dat *Mindlight* (met of zonder CGT-elementen) geen effectieve angstbehandeling is voor alle kinderen met ASS. Toekomstig onderzoek zal moeten ophelderen welke individuele factoren bepalen welk type kinderen met ASS gebaat is bij *Mindlight* en voor welk type kinderen een andere angstbehandeling geschikter en effectiever is. Op deze manier wordt er rekening gehouden met therapeutische, non-specifieke en individuele factoren wanneer therapeuten een beslissing maken over de behandeling die het meest geschikt en effectief is voor kinderen met ASS en angst. Een optimale aanpassing aan de behoeften van het kind zal uiteindelijk leiden tot een effectieve gepersonaliseerde behandeling. Ook zullen nieuwe digitale interventies (bijv. video games) ontwikkeld worden waarin personalisatie geïntegreerd wordt in de interventie zelf. In de nabije toekomst is het belangrijk dat de ontwikkeling, financiering en implementatie van digitale tools zoals *Mindlight* meer aandacht ontvangen in de geestelijke gezondheidszorg. Instellingen voor geestelijke gezondheidszorg moeten meer gestimuleerd worden om de ontwikkeling en implementatie van digitale tools zoals *Mindlight* verder te faciliteren en financieren om het gebrek aan gebruik of misbruik van digitale tools te voorkomen en om de digitale ontwikkelingen in de geestelijke gezondheidszorg op de voet te volgen.



APPENDIX

Dankwoord

DANKWOORD

Op de laatste dag voor mijn zwangerschapsverlof kon ik eindelijk zeggen: Het is af!!! Het was een bijzonder traject, door zowel als 'buitenpromovenda' te werken als de GZ-opleiding te doen. Na al dat harde werk breekt nu het moment aan om eens terug te blikken op dit traject en de mensen te bedanken die hieraan bijgedragen hebben.

Daan, bij jou is het allemaal begonnen. In 2010 ben ik als onderdeel van de Research Master mijn scriptie gaan schrijven op jouw PhD-project, en al snel bleek dat het veel meer was dan alleen een scriptie schrijven: we hebben met veel enhousiasme samengewerkt aan het 'Op Volle Kracht' project en dit bleek zo succesvol, dat we daarna onze samenwerking hebben voortgezet in mijn PhD-project. Jij hebt mij altijd geinspireerd om het onderste uit de kan te halen en aangemoedigd om klinisch en wetenschappelijk werk te (blijven) combineren, ook al gaat dit soms met hobbels gepaard door druk vanuit beide disciplines. ;) Bedankt voor alle ontwikkelkansen die je mij hebt gegeven binnen GGZ Oost Brabant!

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en zijn we goede vriendinnen geworden. Wat ben ik dankbaar dat je nog steeds in mijn leven bent en dat we elkaar nog steeds regelmatig zien! Dankjewel voor al je support en gezelligheid!

Ad, wat had ik zonder jouw statistische kennis gemoeten! Je hebt altijd veel tijd voor mij vrij gemaakt om samen bij jou thuis achter de computer orde te scheppen in de chaotische klinische data en hier passende analyses op los te laten. En dan kreeg ik ook nog wel eens een lift naar station Oss, omdat je het zielig vond als ik moest lopen. Wat een service! **Patrick,** toen ik begon met single case onderzoek had ik geen idee hoe ik hieraan moest beginnen. Door de vele skype meetings met jou werd ik wegwijs in deze wereld. Jij legde me met alle rust uit hoe ik te werk moest gaan. Bedankt daarvoor! **Ramon,** vanaf het begin toonde jij interesse in mijn PhD-project en wilde jij je inzetten om het project ook bij de Bascule uit te rollen. Zonder jouw inzet was het niet gelukt om zoveel kinderen bij de Bascule in mijn onderzoek te includeren, bedankt!

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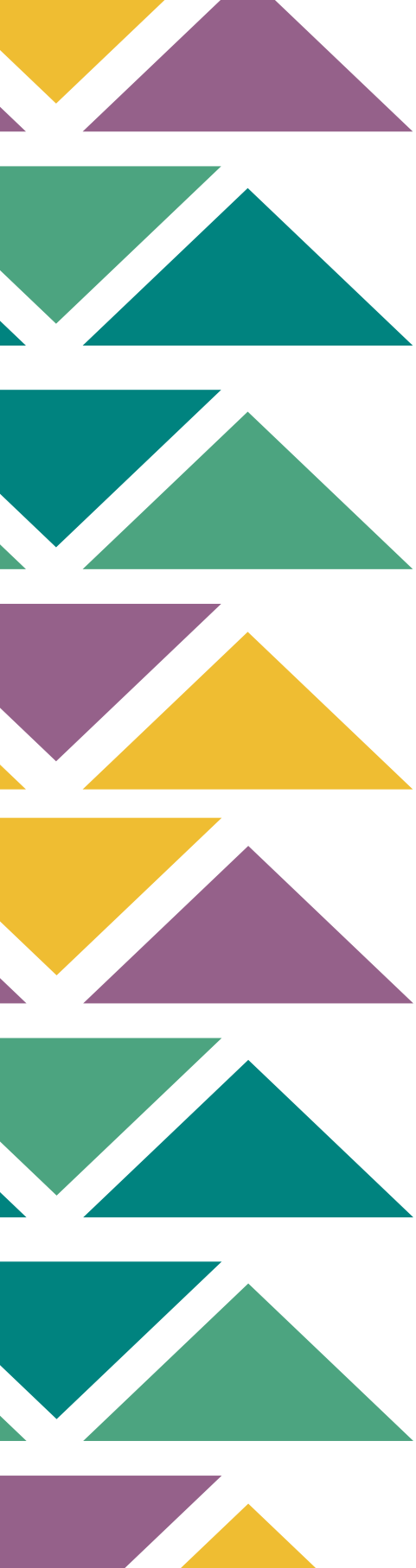
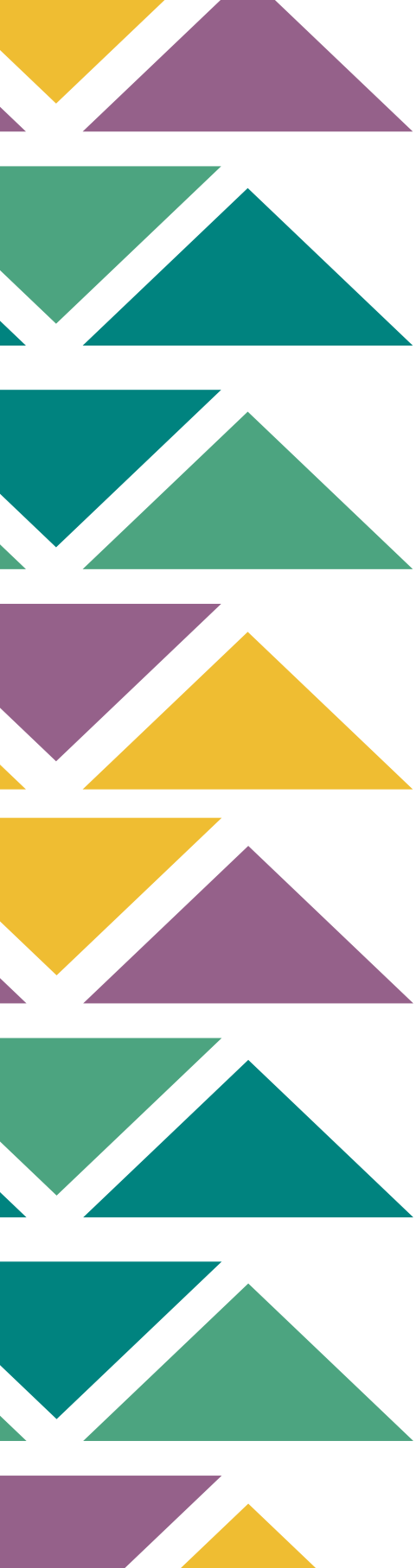


APPENDIX

Curriculum Vitae

CURRICULUM VITAE

Lieke Wijnhoven was born April 26th 1989 in Hout-Blerick (Venlo), the Netherlands. She completed her secondary education at Blariacum College in Blerick. In 2007, she started her Bachelor Pedagogical Sciences at Radboud University Nijmegen. During her Bachelor, she discovered that she had the desire to develop herself as a 'scientist-practitioner'. She started with the Research Master Behavioural Science, and after finishing this Master she completed the Master Pedagogical Sciences. She did her clinical internship at the mental health institute GGZ Oost Brabant in Oss. After finishing these two Masters, she started with combining clinical work as a therapist at GGZ Oost Brabant and research at the Radboud University. In 2014, she started with a PhD on the prevalence and treatment (with the video game '*Mindlight*') of anxiety symptoms in children with an autism spectrum disorder. Besides, she continued working as a clinician at GGZ Oost Brabant. Because she also kept the desire to develop herself as a clinician, she started with a post-master health-care psychology training program (Opleiding tot Gezondheidszorgpsycholoog) in 2017, which she completed in March 2019. After finishing both the post-master training program and her PhD, she started working as a 'Gezondheidszorgpsycholoog' (at the department 'Internalizing disorders') and senior researcher at GGZ Oost Brabant. From October 1st 2020, she started working as a scientist-practitioner at mental health institute Karakter in Nijmegen.



APPENDIX

Publications

PUBLICATIONS

Publications included in the current thesis

Wijnhoven, L. A. M. W., Creemers, D. H. M., Vermulst, A., Lindauer, R. J. L., Otten, R., Engels, R. C. M. E., Granic., I. (2020). Effects of the Video Game '*Mindlight*' on Anxiety of Children with an Autism Spectrum Disorder: A Randomized Controlled Trial. *Journal of Behavior Therapy and Experimental Psychiatry, 68,* 101548.

Wijnhoven, L. A. M. W., Niels-Kessels, H., Creemers, D. H. M., Vermulst, A. A., Otten, R., & Engels, R. C. M. E. (2019). Prevalence of comorbid depressive symptoms and suicidal ideation in children with autism spectrum disorder and elevated anxiety symptoms. *Journal of Child & Adolescent Mental Health, 31*(1), 77-84. doi:10.2989/17280583.2019.1608830

Wijnhoven, L. A. M. W., Creemers, D. H. M., Vermulst, A. A., & Granic, I. (2018). Prevalence and Risk Factors of Anxiety in a Clinical Dutch Sample of Children with an Autism Spectrum Disorder. *Frontiers in Psychiatry, 9*(50). doi:10.3389/fpsyt.2018.00050

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Manuscripts submitted for publication

Wijnhoven, L. A. M.W., Engels, R. C. M. E., Onghena, P., Otten, R., & Creemers, D. H. M. (2019). The additive effect of CBT elements on the video game '*Mindlight*' in decreasing anxiety symptoms of children with Autism Spectrum Disorder. Manuscript submitted for publication.

Other publications

Creemers, D. H. M., Wijnhoven, L. A. M. W., Stikkelbroek, Y. A. J., & Buitelaar, J. K. (2015). Depressie en suïcide. In K. Nijhof & R. C. M. E. Engels (Eds.), *Meisjes in zorg: Signalering, preventie en behandeling* (pp. 241-272). Amsterdam: Uitgeverij SWP.

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Wijnhoven, L. A. M. W., Creemers, D. H. M., Vermulst, A. A., Scholte, R. H. J., & Engels, R. C. M. E. (2013). Randomized controlled trial testing the effectiveness of a depression prevention program ('Op Volle Kracht') among adolescent girls with elevated depressive symptoms. *Journal of Abnormal Child Psychology,* 1-12.

Wijnhoven, L. A. M. W., Creemers, D. H. M., Vermulst, A. A., Scholte, R. H. J., & Engels, R. C. M. E. (2013). De effectiviteit van een depressie preventie programma ('Op Volle Kracht') bij adolescente meisjes met verhoogde depressieve symptomen. *Tijdschrift Voor Gezondheidswetenschappen*, *91*(7), 405-413.

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