Looking for mediators: cognition, perceived control and coping in the treatment of anxiety-disordered children
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Citation for published version (APA):
Chapter 1
General introduction
Anxiety disorders are very common in children and adolescents (hereafter children), with a six-month prevalence rate of 9.7% in the Netherlands in 13- to 18-year old adolescents (Verhulst, Van der Ende, Ferdinand, & Kasius, 1997) and a one-year incidence of 2.9% (Roberts, Roberts, & Chan, 2009). Anxiety disorders in children are often chronic and recurring (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003) and associated with significant impairment in academic, social and family functioning (Langley, Bergman, McCracken, & Piacentini, 2004). Moreover, these disorders impose a huge burden on emotional, social and economic costs (Bodden, Dirksen, & Bögels, 2008).

Although Cognitive Behavioral Therapy (CBT) has been found to be efficacious in the treatment of childhood anxiety disorders (Reynolds, Wilson, Austin, & Hooper, 2012; Silverman, Pina, & Viswesvaran, 2008), remission rates are generally between 54% and 74% (Cartwright-Hatton, Roberts, Chitsabesan, Fothergill, & Harrington, 2004; James, Soler, & Weatherall, 2009). This is more than the 28% to 35% remission rate in a waitlist or inactive control condition (Cartwright-Hatton et al., 2004; James et al., 2009), but still means that three to four out of ten children remain considerably or even clinically anxious after a standard treatment with CBT. Therefore, there is an urgent need to improve the efficacy of CBT.

In order to improve treatment efficacy and efficiency we can examine how CBT works (through research into mediators or mechanisms of change), which specific components are effective (through dismantling research) or for whom the treatment does and for whom it doesn't work (examination of moderators). This dissertation focuses on the first strategy: identifying mediators of CBT for anxiety disordered children. Although we can confidently claim that CBT is effective for most children, we still do not know why it is effective. Although it is assumed that specific elements of CBT (e.g. cognitive restructuring, exposure, problem solving strategies) bring about the desired change in anxiety symptoms, there is a surprising lack of research regarding the mechanisms involved in bringing about this change (Prins & Ollendick, 2003; Weersing & Weiss, 2002). Most studies focus on treatment efficacy, but only a small portion of researchers seek to understand why treatment works. To our knowledge, only five studies specifically examined mediators in the treatment of childhood anxiety disorders. Treadwell and Kendall (1996), and Kendall and Treadwell (2007) found that a decrease in negative self-statements and an increase of the ratio of positive and negative self-statements mediated treatment outcome in clinically anxious children. Alfano et al. (2009) showed that a decrease in loneliness mediated change in social anxiety in children with social phobia. Lau, Chan, Li, and Au (2010) found that a decrease in negative thoughts and an increase in coping strategies mediated treatment effects. Finally, Maric, Heyne, MacKinnon, Van Widenfelt, and Westenberg (2012) showed that post-treatment increase in school attendance and a decrease of fear were mediated by increased self-efficacy. However, only one of these studies (Maric , Heyne et al., 2012) used a longitudinal design and none incorporated in-treatment assessments. In-treatment assessments are important if one wants to examine treatment mediators, as we explain later in this introduction.
It is not only not clear which mediators play a role in the treatment of childhood anxiety, but we also need to improve the measurement of putative mediators. In addition to the use of reliable and valid questionnaires that are applicable to children, we need to develop instruments that can be used repeatedly over the course of treatment to monitor individual treatment progress in more detail. Further, to circumvent certain disadvantages associated with self-report (e.g. reliance on introspective abilities; influence of social desirability) and to measure more automatic aspects of the potential mediators, indirect measures should be developed. Repeated and indirect assessments in children are barely developed. Therefore, the main purpose of this dissertation is two-fold:

1. To improve the measurement of putative mediators in children by developing two types of instruments which are currently underrepresented in this age group: an indirect measure and a measure to repeatedly assess anxiety symptoms and severity.
2. To examine putative mediators of the treatment of childhood anxiety disorders (separation anxiety disorder, specific phobia, generalized anxiety disorder, social phobia or panic disorder with or without agoraphobia) in 8- to 18-year old children. More specifically, to examine whether a change in the amount of negative and positive thoughts, perceived control and several coping strategies precedes a reduction of anxiety symptoms.

Mediators in the Treatment of Anxiety in Children

Statistical Analysis of Mediators

We use the terms "mediator" to specify factors that may be essential in the treatment of anxiety disorders. A mediator is described as an intermediate variable in the causal sequence between an independent variable and a dependent variable (MacKinnon, 2008, p. 8). A related term is "moderator" which is described as a variable that "affects the direction and/or strength of the relation between an independent or predictor variable and a dependent or criterion variable" (Baron & Kenny, 1986, p. 1174). Essentially, a mediator refers to how or through which mechanism treatment works and a moderator refers to for whom or under what conditions treatment works. In this dissertation we will focus on mediating variables.

The most widely used guidelines to study mediation, also known as the "causal steps approach", were developed by Baron & Kenny (1986). These guidelines include the following conditions that should be met: 1) the independent variable (e.g. treatment) predicts the dependent variable (e.g. anxiety symptoms); 2) the independent variable predicts the mediating variable; 3) after controlling for the effect of the independent variable, the mediator predicts the dependent variable; and 4) the effect of the independent variable on the dependent variable is reduced or eliminated after accounting for the indirect pathway through the mediator. However, it has been demonstrated that the causal steps approach has low power in many situations, especially due to the requirement of step 1 (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002). Mediation
can still be present, even in the absence of a direct relation between treatment and outcome. Therefore, there have been several modifications to the Baron and Kenny approach.

Kraemer, Wilson, Fairburn, and Agras (2002) presented an adaptation of the causal steps approach specifically for randomized controlled clinical trials, also known as the “MacArthur approach.” The main difference between the MacArthur approach and the causal steps approach is the emphasis of temporal relations: the mediator should change after a change in the independent variable (or after the start of treatment) and before a change in the outcome variable. Therefore, the mediator and outcome variables should be measured repeatedly during the course of treatment and not at pre- and post-treatment only (Kraemer et al., 2002; Weersing & Weisz, 2002). Further, the mediator should be correlated with treatment condition and have a main or interactive effect on the outcome variable (Kraemer et al., 2002). A temporal or longitudinal design with repeated assessments can help to make the distinction whether the mediator is a causal variable (and therefore can be considered as a mechanism of change) or a covariate of change. As Laurenceau, Hayes, & Feldman (2007, p. 685) describe it: “…all mechanisms of change are mediators, but not all mediators will turn out to be mechanisms of change.” Cross-sectional designs are not fit to determine whether a mediator is a true mechanism of change, due to the lack of temporal precedence.

A longitudinal design is also preferred for several other reasons (MacKinnon, 2008, p. 194; Selig & Preacher, 2009). First, causal relationships need time to unfold and thus cross-sectional studies might overlook an effect. Second, longitudinal data allow for the examination of temporal precedence of different variables. The magnitude of this effect might be different for different time intervals. Third, both changes within and between individuals can be investigated. Fourth, with a longitudinal design one can control for previous levels of the variables. Recently, sophisticated statistical analyses have been developed to study mediators in longitudinal designs, including autoregressive models, latent growth curve models and latent difference score models (MacKinnon, 2008, pp. 201-217).

Note that both the causal steps approach and the MacArthur approach rely on the comparison of a treatment condition and a control condition. However, sometimes it is not feasible or ethical to include a control or waitlist condition, especially when the efficacy of the treatment under investigation has already been demonstrated repeatedly or when (anxiety) problems are so severe that immediate treatment is required (Doss & Atkins, 2006). In the case of a single condition design, it is more difficult to demonstrate that the changes during and after treatment are accountable to the treatment (components) and not to other factors (i.e. passage of time). In this case it is especially important to measure changes in the outcome and the putative mediator repeatedly over time during treatment (Maric, Wiers, & Prins, 2012).

Apart from the requirement of a temporal relationship between mediator and outcome, there are more requirements that should be met before concluding that a specific variable is a mediator or even a (causal) mechanism of change. Kazdin and Nock (2003) described six other requirements: 1) there should be a strong association between the intervention and mediator...
and between the mediator and therapeutic change; 2) the associations should be specific, i.e. not associated with other constructs or "non-mediators"; 3) there should be a gradient in which more of the mediator is associated with greater change in the outcome; 4) an experiment should show that manipulation of the proposed mediator is associated with a change in the outcome variable; 5) results should be consistent and replicated across studies; and 6) the proposed mediator should be plausible and coherent with theory. Maric, Wiers, and Prins and colleagues (2012) further recommend the investigation of reciprocal and sequential mediation.

As mentioned above, there are many requirements that should be met to demonstrate that a specific construct is a mediator. It is very complicated to examine all, or most, of the requirements in one study. This dissertation focuses especially on temporal precedence and possible reciprocal effects between several putative mediators and treatment outcome.

Putative Mediators in the Treatment of Childhood Anxiety Disorders

There are several theories which describe the etiological processes that lead to the development of anxiety disorders (Weems & Stickle, 2005), including biological (e.g. genetics, inhibited temperament, psychophysiology), behavioral (e.g. respondent, operant and vicarious learning), cognitive (e.g. information processing, cognitive content, perceived control) and interpersonal (e.g. attachment, parenting style, life events) models. These theories guided the development of treatment programs, for example by including cognitive restructuring to change dysfunctional thoughts or by involving parents in the treatment to account for the interpersonal component. However, as has been said before, we do not know through which mediators the treatment components bring about the desired change. In this dissertation the focus will be on three putative mediators that fall under the scope of the cognitive perspective, including negative and positive thoughts, perceived control and coping.

Negative and positive thoughts. Cognitive and information processing models assume that biases in cognition (dysfunctional cognitive schemata, negative thoughts and cognitive errors) and information processing (attention, interpretation, recall) play a central role in the development and maintenance of anxiety disorders (Beck, 2005; Beck & Clark, 1997; Kendall, 1985). Dysfunctional threat schemata are considered to be danger laden, stable and focused on future events. Anxious persons tend to overestimate the likelihood and severity of threat situations and underestimate their coping abilities (Beck, 2005).

It is assumed that a change in cognitive schemata and thoughts is essential to reduce anxiety symptoms. More specifically, the "Power of Nonnegative Thinking" hypothesis assumes that improvement during treatment is associated with a reduction of negative thoughts rather than an increase of positive thoughts (Kendall & Chansky, 1991). However, the empirical support for this claim has been mixed. In general, negative thoughts are associated with greater levels of anxiety in clinically anxious children (Kendall & Chansky, 1991; Schniering & Rapee, 2002) and normal children (Muris, Merckelbach, Mayer, & Snieder, 1998). Further, treatment efficacy studies have demonstrated that the amount and content of negative thoughts changed after
CBT (Silverman et al., 1999) and that the amount of negative thoughts can predict treatment outcome (Muris, Mayer, den Adel, Roos, & Van Wamelen, 2009).

The role of positive thoughts in anxiety is less straightforward. In some studies, psychopathology is associated with less positive thoughts (Calvete & Cardenoso, 2002; Ronan & Kendall, 1997) but in other studies this relationship has not been found (Treadwell & Kendall, 1996; Prins & Hanewald, 199; Kendall & Treadwell, 2007). Rather than examining negative and positive thoughts separately, Schwartz and Garamoni examined the ratio of positive to negative thoughts in their States of Mind Model (Schwartz, 1997; Schwartz & Garamoni, 1989). In the SOM model, an optimal ratio of positive to negative thoughts is associated with psychological health. The SOM model has been studied in children and it has been found that a lower SOM ratio is associated with more internalizing or anxiety problems (Calvete & Cardenoso, 2002; Calvete & Cardenoso, 2005; Daleiden, Kendall & Treadwell, 2007; Vasey, & Williams, 1996; Prins & Hanewald, 1997; Ronan & Kendall, 1997; Kendall & Treadwell, 2007). Further, higher SOM ratios have been reported after CBT for childhood anxiety (Kendall & Treadwell, 2007; Treadwell & Kendall, 1996).

Although an association has been found between negative thoughts, positive thoughts and SOM ratios with childhood anxiety, it remains unclear whether a change in the amount and content of thoughts is a mediator in the treatment of anxiety disorders. An indication for a mediating role of negative thoughts has been demonstrated in cross-sectional design studies by Lau et al. (2010), Treadwell and Kendall (1996) and Kendall and Treadwell (2007), but not yet in a longitudinal design. In this dissertation, we will examine the role of both negative and positive thoughts in anxiety disorders and whether they are mediators of the treatment effect in anxiety disorders.

Perceived control. Anxiety is not only defined by the interpretation of a situation as threatening, but also by the extent to which a child feels in control over its fear or the feared situation. According to Chorpita & Barlow (1998), a perceived lack of control over threatening situations is central to the development of anxiety disorders. Chorpita and Barlow (1998, p. 5) define control as "the ability to personally influence events and outcomes in one's environment." Chorpita and Barlow describe a model in which early experiences with a lack of control can lead to an increased tendency to perceive events as not within one's control, which in turn can lead to the experience of negative emotion and chronic anxiety. They propose an interaction between children's inhibited temperament, parental anxiety, parental rearing style and the development of a lack of perceived control. Parents with an anxiety disorder and/or an inhibited child more often display an overprotective and overcontrolling rearing style. As a result, the child acquires less experience with mild threatening situations. Finally, the child is more likely to have an avoidant coping style and not to feel in control over anxiety related situations. The role of perceived control as a mediator between parental rearing style and anxiety has been examined in different studies and was confirmed several times (e.g. Ballash, Pemble, Usui, Buckley, &
Perceived control is not directly targeted in treatment. However, it is reasonable to assume that improved coping and problem solving skills can enhance perceived control (“I know what I can do when I am scared”) which subsequently decreases anxiety. On the other hand, increased perceived control could be a consequence of mastery experiences in successful exposure exercises and follow on decreased anxiety. Research shows that clinically anxious children have lower levels of perceived control than non-referred children (Weems, Silverman, Rapee, & Pina, 2003). Further, a reduction of anxiety symptoms after treatment is associated with an increase in self-reported perceived control (Muris et al., 2009). However, to our knowledge, perceived control has never been formally evaluated as a potential mediator of CBT.

Coping. Anxious persons not only tend to report more negative thoughts and less perceived control, but may also have less adaptive coping abilities. The difference between perceived control and coping is that the first is the perception of one’s ability to cope with a specific, anxiety-related situation and that the latter refers to different ways of actually dealing with stressful situations. Coping has many different definitions and even more dimensions: over 400 ways of coping have been identified (Skinner, Edge, Altman, & Sherwood, 2003). We adopt the definition of Compas and colleagues (Compas, Connor-Smith, Saltzman, Thomsen, & Wadsworth, 2001) who view coping as just one aspect of a broader set of processes that are used in the response to stress. They define coping as “conscious volitional efforts to regulate emotion, cognition, behavior, physiology, and the environment in response to stressful events or circumstances” (Compas et al., 2001, p. 89).

It is surprising how little consensus there is regarding the conceptualization or measurement of ways of coping. Many coping researchers have tried to construct lower and higher order categories of coping strategies using techniques like confirmatory or exploratory factor analysis. The three most common distinctions are problem- vs. emotion-focused coping, approach vs. avoidance, and cognitive vs. behavioral coping (Skinner et al., 2003). However, both Compas and colleagues (2001) and Skinner and colleagues (2003) argue against the use of these two-dimensional categories and recommend the use of broader and hierarchical systems. Skinner and colleagues conclude that there are five core categories of coping: problem solving, support seeking, avoidance, distraction and positive cognitive restructuring.

Although it is very difficult to aggregate research findings regarding coping due to the lack of consensus about core coping categories, Compas and colleagues (2001) examined and evaluated over 60 studies regarding coping with stress during childhood. They concluded that in general, problem-focused coping is associated with better adjustment and increased coping efficacy, but that avoidant coping is associated with psychological problems and decreased coping efficacy. It is assumed that a change from passive to active emotion regulation strategies is essential for the effect of treatment. However, the mediating role of coping strategies in treatment is not clear. In one study, coping appeared to be a mediating variable in the treatment of child anxiety.
(Lau et al., 2010). However, this study did not incorporate an in-treatment assessment and this precluded strong conclusions about temporal precedence.

Assessment of Mediators

Repeated Assessment
As noted before, repeated assessment in a longitudinal design is necessary to be able to examine putative mediators in more detail. However, treatment monitoring is also important at a more individual level, referred to as “patient-oriented research” (Howard, Lueger, Maling, & Martinovich, 1993). Ongoing assessment can give information about the progress of treatment and guide decisions about the focus of treatment (Kazdin, 2005). Ongoing assessment may take place during a baseline period, each session, every other session or after a specific treatment component. Lambert and colleagues (e.g. Lambert et al., 2003) have shown that giving feedback to therapists about an individual’s treatment progress can improve treatment outcome in adults. Further, it has been found that an early positive response predicts final outcome (e.g. Wilson, 1999).

Kazdin (2005) describes several requirements for assessing changes over the course of treatment. Obviously, measures should show reliability and validity, but should also be a) acceptable to both patient and therapist; b) brief and user friendly; c) individualized to the patient’s problems and goals; d) suited for repeated use over the course of therapy; e) applicable across treatments and diverse problems; and f) have levels of degree of change. As Kazdin noted, very few measures are available that meet all of these criteria.

In general, for childhood anxiety disorders there is currently no brief, individualized and sensitive measure to evaluate treatment progress and outcome. For Obsessive Compulsive Disorder however, such an instrument is available: the Children’s Yale-Brown Obsessive Compulsive Scale (CY-BOCS; Scahill et al., 1997). We used the CY-BOCS as a reference point to develop the Anxiety Severity Interview for Children and Adolescents (ASICA, see chapter 4). The main features of the ASICA are that it a) is relatively brief; b) is client-focused and assesses an individual’s specific problems; c) can be used repeatedly over time; d) is administered by the therapist; and e) assesses three core components of the anxiety response (anxious feelings, avoidant behavior, anxious thoughts; Lang, 1968).

Direct and Indirect Assessment
Traditionally, most researchers use direct measurement instruments (e.g. questionnaires or interviews) to examine the construct of interest. However, direct measures can be inaccurate or incomplete as persons may have limited introspective abilities, may answer questions in a socially desirable way or when the processes they are questioned about occur outside conscious awareness. These disadvantages of direct measures are especially relevant in children. In the
past 15 years, over 20 alternative measurement procedures have been developed to indirectly measure constructs such as attitudes and self-concepts or attentional bias and inhibition (Nosek, Hawkins, & Frazier, 2011). These measures generally use response latencies to infer mental content. The distinction between direct (or explicit, controlled, or strategic) instruments and indirect (or implicit, uncontrolled, or automatic) instruments is that the latter assess attitudes or self-concepts without requiring awareness of what is being assessed. Indirect measures are not "more true" than direct measures, but assess constructs that are distinct, however related to self-report assessment. Direct measures (questionnaires) are thought to mainly predict controlled behavior and indirect measures (reaction time tasks) are more useful to predict automatic or uncontrolled behavior (Greenwald, Poehlman, Uhlmann, & Banaji, 2009). Therefore, next to direct measures, indirect measures might be valuable to predict relapse after treatment. Moreover, in the future, indirect measures could possibly be used as a new treatment modality to indirectly retrain specific (cognitive) biases.

The development and use of indirect measures in children is still scarce. Within the scope of the studies included in this dissertation we developed several indirect measures. In this dissertation we describe the development and use of an indirect measure of perceived control, the Perceived Control Implicit Association Procedure (IAP). The question was whether perceived control was a mediator of treatment effect in anxious youth and whether this could be established with both a direct and indirect measure.

The Present Study

The studies which are described in this dissertation are part of a large multi-center study conducted by two centers for child and adolescent psychiatry: the Departments of Child and Adolescent Psychiatry of the Academic Medical Center (AMC) / de Bascule in Amsterdam and Accare in Groningen, in cooperation with the Department of Developmental Psychology of the University of Amsterdam, the Department of Clinical Psychology of the University of Groningen and the Department of Psychiatry of the University Medical Centre in Groningen. The aim of the multi-center study was to examine (the assessment of) mediators of treatment effect for anxiety disorders (this dissertation) and obsessive compulsive disorder (dissertation in progress by Lidewij Wolters). As part of this multi-center study, the behavioral inhibition system in child and adolescent anxiety was examined, with newly developed computer tasks (see dissertation by Leentje Vervoort, 2010). Finally, several moderating variables were examined, including biological and neuropsychological factors (cortisol, executive functions) and interpersonal factors (parental psychopathology, parental rearing style, therapeutic alliance). These moderation data are currently being analyzed.
The Present Dissertation

This dissertation has two major themes: the assessment of putative mediators (Chapter 2, 3, and 4), and the examination of several putative mediators of treatment change (Chapter 5, 6, and 7). The following five research questions were examined:

1. Is the Perceived Control Implicit Association Procedure (IAP) a valid and reliable measure to indirectly assess perceived control in children?
2. Is the Anxiety Severity Interview for Children and Adolescents (ASICA) a valid and reliable measure to repeatedly assess anxiety severity during treatment?
3. Can we reliably and validly assess both negative and positive thoughts with the Children's Automatic Thoughts Questionnaire – Negative/Positive (CATS-N/P)?
4. What is the role of both negative and positive thoughts and their ratio in childhood anxiety disorders?
5. Are negative and positive thoughts, perceived control and coping strategies mediators of the treatment effect for anxiety disorders?

In Chapter 2 we describe the development of the Perceived Control IAP. This reaction time based computer task measures perceived control in an indirect way. The indirect assessment of perceived control (with the IAP) was compared to a direct measure of perceived control, the Anxiety Control Questionnaire for Children (ACQ-C), in 33 non-selected children. The IAP is further evaluated in Chapter 3 by comparing 136 anxiety disordered children with a non-selected group of 31 children. Moreover, we used a second control group of 38 non-selected children to validate the pictorial stimuli that were used in the IAP. In Chapter 4 we describe the development and clinical applicability of the ASICA. The ASICA is a short, semi-structured and clinician rated interview that can be used by the therapist to repeatedly monitor anxiety severity during treatment. The ASICA incorporates three main components of anxiety: anxious feelings, avoidance, and anxious thoughts. The psychometric properties of the ASICA were examined in 139 anxiety disordered children and 40 non-anxious children. Chapter 5 describes the development and psychometric properties of the Children's Automatic Thoughts Scale-Negative/Positive (CATS-N/P) in 554 non-selected children. The CATS (Schniering & Rapee, 2002) was originally designed to assess negative self-statements in children and adolescents. We extended the CATS with ten items concerning positive thoughts. The CATS-N/P thus enables the simultaneous examination of negative and positive thoughts in children. In Chapter 6 we use the CATS-N/P to examine the role of negative and positive thoughts in anxiety disorders by comparing 139 anxiety-disordered children and 293 non-anxious children. In Chapter 7 we investigate whether changes in negative and positive thoughts, perceived control over anxious situations, and five coping strategies are active mediators of CBT for anxiety disordered children and adolescents. One-hundred and forty-five children with a primary anxiety disorder were included and treated with twelve sessions of CBT. We employed a longitudinal design
and a state-of-the-art statistical analysis to examine temporal relationships between a change in putative mediators and a change in anxiety. Finally, in Chapter 8 the conclusions of the described studies are reviewed and discussed. We describe strengths and limitations, reflect on the clinical implications of the results and suggest recommendations for future studies.