Journal of Affective Disorders 196 (2016) 190–199

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Stress reactivity predicts symptom improvement in children with anxiety disorders

Gwendolyn C. Dieleman [a,*], Anja C. Huizink [c], Joke H.M. Tulen [b], Elisabeth M.W.J. Utens [a], Henning Tiemeier [a,b]

[a] Department of Child and Adolescent Psychiatry/Psychology, Erasmus Medical Center Rotterdam/Sophia Children's Hospital, Rotterdam, The Netherlands
[b] Department of Psychiatry, Erasmus Medical Center Rotterdam, Rotterdam, The Netherlands
[c] Department of Developmental Psychology, Faculty of Psychology and Education, VU University, Amsterdam, The Netherlands

ARTICLE INFO

Article history:
Received 7 July 2015
Received in revised form
30 November 2015
Accepted 6 February 2016
Available online 9 February 2016

Keywords:
Anxiety disorders
Treatment outcome
Autonomic nervous system
Cortisol
Cognitive behavioral therapy
Depressive symptoms

ABSTRACT

Background: We examined the longitudinal associations of autonomic nervous system (ANS) and hypothalamic-pituitary-adrenal (HPA) axis rest and reactivity measures with anxiety and depressive symptoms at one-year follow-up in children with anxiety disorders.
Methods: In a clinical sample of 152 children with a primary DSM-IV anxiety disorder, aged 8 to 12 years, anxiety and depressive symptoms were assessed with the Multidimensional Anxiety Scale for Children and the Children's Depression Inventory at pre-treatment baseline and one year later, after treatment with cognitive behavioral therapy. At baseline, children participated in a 70 min stress task. Salivary cortisol was measured directly prior to and 20 min post stress task. Skin conductance level (SCL), heart rate and high frequency heart rate variability (HRV) were continuously measured during rest and the stress task. To investigate if rest or reactivity measures predicted anxiety and depressive symptoms at one year follow-up, linear regression analyses were conducted for rest and reactivity measures of SCL, heart rate, HRV and cortisol separately.
Results: Higher SCL reactivity predicted less decrease of anxiety symptoms at one-year follow-up. Cortisol reactivity showed a weak association with depressive symptoms at one-year follow-up: lower cortisol reactivity predicted less decrease in depressive symptoms.
Limitations: Only self-reported anxiety and depressive symptoms were used. However, all predictors were objective biological measures, hence there is no risk of shared method variance bias.
Conclusions: These findings suggest that pre-treatment HPA and ANS responsiveness to stress are predictive biomarkers for a lack of symptom improvement in children with a clinical anxiety disorder.

1. Introduction

Anxiety disorders are among the most prevalent types of psychiatric disorders experienced by children and adolescents (Bittner et al., 2007; Verhulst et al., 1997), with separation anxiety disorder, specific phobia, social phobia, and generalized anxiety disorder being the most frequent childhood anxiety disorders (Beesdo-Baum and Knappe, 2012). Childhood anxiety has been associated with a range of negative outcomes, including academic underachievement, drug dependency, and an increased risk for developing other psychiatric disorders (Bittner et al., 2007; Woodward and Fergusson, 2001).

Cognitive behavioral therapy (CBT) is the treatment of choice for children with an anxiety disorder, with a remission rate of 59% following treatment (James et al., 2013). A 7–19 year follow-up study of the long-term outcomes of treated childhood anxiety disorders showed that patients with a poorer response to CBT, had higher rates of panic disorder, substance abuse and dependency in adulthood than the successfully treated controls (Benjamin et al., 2013). It is, therefore, important to identify predictors of symptom improvement in treated children with an anxiety disorder.

Several studies tried to gain insight into clinical predictors of treatment outcome in children with anxiety disorders. Some studies reported that higher anxiety severity predicts a less favorable outcome (Compton et al., 2014; Hudson et al., 2013; Last et al., 1998; Liber et al., 2010). A few studies showed that children with comorbid mood disorders are more likely to retain their primary anxiety disorder following treatment (Hudson et al., 2013; Liber et al., 2010). Various studies examined the role of parental characteristics as predictors of treatment outcome in children, but an inconsistent pattern of findings resulted (Compton et al., 2014;

* Correspondence to: Gwendolyn Dieleman, Erasmus Medical Center Rotterdam/Sophia Children's Hospital, Department of Child & Adolescent Psychiatry/Psychology, Wytemaweg 12, 3015 CN Rotterdam, The Netherlands.
E-mail address: g.dieleman@erasmusmc.nl (G.C. Dieleman).

http://dx.doi.org/10.1016/j.jad.2016.02.022
0165-0327/

Hudson et al., 2013; Legerstee et al., 2008). Because clinical characteristics are weak or inconsistent indicators of response to CBT, there is an increasing interest in identifying biomarkers to predict differential treatment response (Lester and Eley, 2013).

Physiological stress response systems have been implicated as possible important biological state markers for childhood anxiety. It can be hypothesized that children with an anxiety disorder function under conditions of persistent stress, with an excessive and prolonged stress system activation (Dieleman et al., 2015). Alterations in the autonomic nervous system (ANS) have been associated with anxiety disorders in children; children with an anxiety disorder show a pattern of heightened activity of the sympathetic nervous system (Dieleman et al., 2015; Kossowsky et al., 2012; Schmitz et al., 2011) and diminished parasympathetic control (Dieleman et al., 2015; Schmitz et al., 2011), although some studies failed to show this difference (Kossowsky et al., 2012; Kristensen et al., 2014). Another major physiological stress response system is the hypothalamic-pituitary-adrenal (HPA) axis. Glucocorticoids can act both to augment and suppress autonomic mediated changes. Cross-sectional studies related HPA axis functioning to childhood anxiety disorders, but provided inconsistent findings (Dieleman et al., 2015; Dietrich et al., 2013; Feder et al., 2004; Forbes et al., 2006; Krämer et al., 2012). This may reflect the variable methods of sampling, resting state versus stress paradigms, differences in age, developmental status, and diagnostic status of the study populations. Furthermore, differences in functioning of the HPA axis could depend on the chronicity or the severity of the disorder (Dieleman et al., 2015; Pervanidou, 2008).

Despite the evidence of altered pre-treatment HPA axis and autonomic functioning in anxiety-disordered children, studies that have assessed stress physiology as a predictor of therapy outcome in childhood anxiety disorders are lacking. This study aims to investigate the longitudinal association of stress physiology at pre-treatment baseline with anxiety and depressive symptoms at one year follow-up in a clinical sample of anxiety disordered children treated with CBT. We hypothesize that anxiety-disordered children with a stronger autonomic stress response, i.e. heightened activity of the sympathetic and diminished activity of the parasympathetic nervous system, show persistence of anxiety symptoms one year later. Also, we explore the longitudinal association between cortisol levels and anxiety symptoms at one-year follow-up, but formulate no specific hypothesis, given the inconsistent results of previous studies. Furthermore, since comorbid depressive symptoms have been associated with a less favorable treatment outcome in children with anxiety disorders (Hudson et al., 2013; Liber et al., 2010) and in previous work we observed that cortisol reactivity was specifically associated with depressive symptoms (Dieleman et al., 2010), we will also explore the longitudinal association of stress physiology with depressive symptoms.

2. Methods

2.1. Participants

This study included 152 children, aged 8–12 years, referred to the outpatient clinic of the Department of Child and Adolescent Psychiatry of Erasmus Medical Center in Rotterdam or the University Medical Center in Leiden, The Netherlands. These hospitals serve as secondary or tertiary referral centers of South-West Netherlands. Children had a primary diagnosis of separation anxiety disorder (n=57), generalized anxiety disorder (n=47), social phobia (n=29) or specific phobia (n=19). All children were diagnosed with the Anxiety Disorders Interview Schedule for DSM-IV (Silverman, 1996).

Exclusion criteria were: IQ < 85, poor command of the Dutch language, serious somatic disease, autism spectrum disorder, selective mutism, psychotic disorders, pharmacotherapy that could interfere with HPA axis or ANS functioning.

Methylphenidate treatment in children with comorbid attention deficit hyperactivity disorder was discontinued the day before physiological measurements (n=7), because methylphenidate treatment can increase heart rate and blood pressure (Ballard et al., 1976). Children on medication for an anxiety disorder were withdrawn from medication, if possible, or otherwise excluded. For children with comorbid attention deficit hyperactivity disorder, the dosage of medication was kept constant during the study as a constant dosage of medication for attention deficit hyperactivity disorder was considered unlikely to confound treatment effects. The Committees for Medical Ethics of Erasmus Medical Center and Leiden University Medical Center approved the study.

2.2. Procedure

Parents and participants signed informed consent before participation. Parents and children completed psychological questionnaires and a diagnostic interview before the physiological tests at the pre-treatment baseline and at one-year follow-up.

Physiological assessments took place in the hospital between 12.00 h and 18.30 h, because variation of cortisol levels is least in the afternoon (Wust et al., 2000). After an acclimatization period of 45 min, the session began with a resting period of 10 min. Subsequently, a mental arithmetic task and, after another resting period of 10 min, a social competence interview were administered. Saliva collection took place after resting period 1 (cortisol during rest) and 20 min after the social competence interview (cortisol following stress), because cortisol levels typically peak 20–30 min after stress. Fig. 1 presents the temporal sequence of measures. Parents were asked to report general physical condition, dietary pattern and medication use of their child. For more information on medication use, see Appendix 1.

2.3. Measures

The *Anxiety Disorders Interview Schedule for Children DSM-IV* (*ADIS-C*) is a semi-structured interview to assess DSM-IV anxiety disorders in 7- to 17-year-olds (Silverman et al., 2001). A trained psychologist conducted the interview with the child and parents separately at pre-treatment, post-treatment and one-year follow-up. To obtain a diagnosis, both a count of DSM-IV symptom criteria, as well as the level of impairment according to the parent, child, and interviewer, were taken into account. The parent and the child were asked to indicate on a 9-point scale (i.e., 0–8) to what extent the symptoms interfered with the child's daily life. Subsequently, the interviewer gave an interference rating (Clinician Severity Rating (CSR)), on the same 9-point scale, for the child and parent interview, separately. If the CSR was 4 or higher, a diagnosis was assigned. The anxiety disorder with the highest CSR was regarded as the primary anxiety disorder. Interviewers who administered the ADIS-C at follow-up were blind to pre-treatment diagnoses, disease trajectory, and physiological measures.

The *Multidimensional Anxiety Scale for Children* (*MASC*) is a 39-item self-report questionnaire (March et al., 1997), administered at pre-treatment, post-treatment and one-year follow-up, assessing anxiety symptoms during the last two weeks in children and adolescents. Items are scored from 0 to 3 (0=never true, 1=rarely true, 2=sometimes true, 3=often true). The internal consistency (.93) and one-month test-retest reliabilities (.81) of the Dutch translation are good (Liber et al., 2008).

The *Children's Depression Inventory* (*CDI*) is an age-appropriate 27-item self-report questionnaire (Kovacs, 1992), administered at