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Aroused at Home: Basic Autonomic Regulation during Orthostatic and Physical Activation is Altered in Children with Social Anxiety Disorder

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Abstract Previous research has documented altered autonomic nervous system (ANS) reactivity to laboratory-based social stress tasks in children with social anxiety disorder (SAD). It is unclear, however, whether these alterations are caused by the unfamiliar and possibly threatening lab environment or whether they generalize to other, more representative contexts. Sympathetic and parasympathetic autonomic functioning was assessed in the home (minimizing environmental threat) during a supine baseline phase and two physical activation phases (orthostatic stress, stair stepping) in children (9–13 years) with SAD ($n = 27$) and healthy control children ($n = 27$). Relative to controls, children with SAD showed tonic autonomic hyperarousal as indicated by higher heart rate and electrodermal activity during the supine baseline phase. Further, there was evidence for stronger cardiac and vascular sympathetic reactivity (T-wave amplitude, pulse wave transit time) to moderate physical activation in children with SAD. Higher autonomic arousal during rest was related to measures of trait social anxiety and general psychopathology. Groups did not differ on parasympathetic parameters. Our results extend previous laboratory findings and provide the first evidence for alterations in children with SAD during basal autonomic regulation and in the absence of explicit social evaluative threat. They may further help to clarify conflicting study results from previous laboratory studies. The findings underline the importance of psychophysiological assessment using different environments and tasks to elucidate the physiological bases of SAD.

Keywords Ambulatory assessment · Social anxiety disorder · Children · Autonomic nervous system · Psychopathology

Social anxiety disorder (SAD) is one of the most frequent mental disorders in children and youth (Kashdan and Herbert 2001). It is characterized by a persistent fear of humiliation and rejection by others and can impair the lives of affected children via fewer friendships, less academic success, and the development of comorbid disorders (Rao et al. 2007). Despite its high clinical relevance, research is just beginning to characterize the early stages of this disorder as well as its underlying psychopathology (Ollendick and Benoit 2012; Ollendick and Hirshfeld-Becker 2002; Rapee and Spence 2004). Bodily arousal is an important component of both models of SAD and more general physiological models of autonomic functioning in anxiety (e.g., Beauchaine 2001; Clark and Wells 1995). Even cognitive models of social anxiety propose that affected individuals show heightened physiological reactivity (e.g. elevated heart rate) in reaction to social evaluative stress (i.e., Clark and Wells 1995). Physiological theories, by contrast, propose that anxious individuals are not characterized by

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higher autonomic reactivity but rather by chronically elevated autonomic arousal during rest and *lower* autonomic reactivity to feared situations, leading to restricted autonomic flexibility in anxious individuals (e.g., Friedman 2007; Porges 2007; Thayer and Lane 2000).

Immediate physiological reactivity during physical, mental, and emotional stress such as anxiety is regulated by the autonomic nervous system (ANS), consisting of the sympathetic (SNS) and parasympathetic (PNS) branches. The ANS allows for fast and flexible reactions to stressful situations, such as fight-or-flight responses, by increasing SNS activation and/or decreasing PNS activation. Subsequent relaxation in turn is mediated by decreased SNS and/or increased PNS activity (Berntson et al. 1994). Typical indicators of ANS activity include heart rate (HR), finger pulse, skin conductance level (SCL), and respiratory sinus arrhythmia (RSA; e.g., Blechert and Wilhelm 2014; Kreibig 2010).

Autonomic Reactivity and Flexibility in Children with SAD

Previous studies on autonomic functioning in children and adolescents with SAD have shown inconsistent findings. Anderson and Hope (2009), for example, found no differences in physiological reactivity to a speech and conversation task between youths with SAD and controls, in line with similar findings by others (Miers et al. 2011). Alkozei et al. (2015) also found no differences in HR and parasympathetic measures in two laboratory tasks but negative correlations between autonomic response and state anxiety. However, other studies have reported elevated reactivity in socially anxious children (e.g., Matthews et al. 1986; Schmidt et al. 1999) such as increased finger pulse rates during a read-aloud task in children with SAD compared to overanxious children (Beidel 1991). Furthermore, two recent studies (Schmitz et al. 2011, 2013) documented higher SNS activity during baseline and blunted autonomic stress task responding in children with SAD and a subclinical sample, which we interpreted as an indication of restricted autonomic flexibility.

According to approaches emphasizing the adaptive role of autonomic flexibility (e.g., Thayer and Lane 2000), a high autonomic response to a stressor is not necessary equated with stress, anxiety, or psychopathology, but could indicate functional autonomic flexibility, when return to baseline activity is achieved quickly. Thus, high flexibility may provide the autonomic basis for responsive (strong response), energy efficient (swift recovery) and adaptive coping with emotional and physical stressors (Beauchaine 2001; Porges 2007; Porges et al. 1996; Thayer and Brosschot 2005; Thayer and Lane 2000). Importantly, these swift autonomic adjustments are thought to be mediated primarily by the parasympathetic nervus vagus, assessed via respiratory sinus arrhythmia (RSA). The importance of autonomic flexibility in the development of clinical anxiety has been documented by several studies (e.g., Bakker et al. 2009; Greaves-Lord et al. 2010; Monk et al. 2001; Yeragani et al. 2001). Greaves-Lord et al. (2010), for example, found that reduced autonomic flexibility (i.e., low RSA) predicted the development of anxiety symptoms in 10 to 12 year old girls 2 years after first assessment. In fact, in a recent review of 28 studies on psychophysiological differences in childhood social anxiety (Siess et al. 2014), it was concluded that autonomic reactivity alterations in SAD samples most likely emerge under two conditions: during and before intensive laboratory social stressors and when using broad assessment of both SNS and PNS parameters, capturing even subtle and mild alterations in the ANS.

A hitherto unsolved problem and likely source of these inconsistent findings is the potential context sensitivity of group differences. Stress tasks and resulting demands varied widely between studies and socially anxious children are likely to be particularly sensitive to such effects: A higher contextual threat may amplify not only stress responses but also baseline values (via anticipation effects) that may impose ceiling effects on reactivity. Thus the aim of the current study was to examine whether alterations in baseline activity and/or stress reactivity in SAD children generalizes to contexts beyond laboratory based social stress testing (c.f., Wilhelm and Grossman 2010). Reactivity to the lab environment can be expected to be particularly high in SAD children who fear interaction with strangers or authorities, contaminating 'adaptation baselines' due to excessive anticipatory anxiety, and making the interpretation of baseline patterns difficult (Schmitz et al. 2011; Wilhelm and Grossman 2010). Thus, a measurement phase preferably unaffected by anticipatory anxiety would clarify laboratory-based reactivity findings and help determine potential basic differences in autonomic functioning in SAD. Shedding light on this question would not only be important to understand the extent of autonomic alterations in children with SAD but could also provide important information to increase understanding of SAD pathology. That is, chronic alterations of ANS functioning may underlie other psychopathological mechanisms such as interoception, behavioral avoidance and even biased attention (Howells et al. 2012).

Altered Autonomic Regulation in SAD in the Absence of Stress

Studies with mixed anxiety disorder groups have repeatedly reported patterns of abnormal autonomic regulation even in the *absence* of anxiety provoking situations (e.g., Coupland et al. 2003; Dieleman et al. 2015). Even in early childhood, inhibited children show dysregulation of HR and skin conductance when presented with a non-anxiety provoking tone task

(Scarpa et al. 1997). Recently, Dieleman et al. (2015) compared cortisol and autonomic profiles of children with various anxiety disorders and controls at rest and during a mental stress task. At rest (but during anticipation of a mental stress task), anxious children showed lower basal HPA-axis responding and high autonomic arousal as indexed by lower high frequency heart rate variability, and higher basal and reactive skin conductance levels. However, there are no comparable studies investigating autonomic profiles of children with SAD in the absence of anxiety provoking stimuli.

An investigation of the nature and scope of basal alterations of psychophysiological functioning in childhood SAD needs to address three problems: (1) finding adequate task protocols, (2) dealing with anticipatory anxiety and (3) dealing with contextual variables. Additionally, a study of basal psychophysiology has to address confounding factors such as physical fitness as well as comorbid symptoms and internalizing symptoms. Regarding the first two problems, one standard test of basal autonomic functioning that does not impose any explicit emotional demands is orthostatic stress (Perlmuter et al. 2012). This involves a change in body posture from supine to standing, and has previously been used to measure characteristics of relatively pure physiological arousal in children with mixed anxiety disorders or subclinical fears (e.g., Greaves-Lord et al. 2010; Kristensen et al. 2014; Mezzacappa et al. 1997; Sharma et al. 2011). In addition to orthostatic stress, controlled physical activation can further clarify autonomic functioning, e.g., using treadmills (e.g., Leicht and Allen 2008). Some studies of physical tasks have reported baseline differences between anxious and non-anxious groups in ANS activity before physically activating tasks (Piccirillo et al. 1997; Sharma et al. 2011) as well as higher reactivity in anxious youth (e.g., Mezzacappa et al. 1997), while others have failed to find physiological differences between anxious and non-anxious groups (e.g., Kristensen et al. 2014). No such research in children with diagnosed SAD, however, has been conducted. Regarding anticipatory anxiety, a familiar setting at home can be expected to minimize basal and anticipatory anxiety (e.g., Wilhelm and Grossman 2010), alongside clear knowledge of what to expect in the current session.

The Current Study

Thus, the aim of the current study was to investigate basal autonomic functioning during rest and in reactivity to mild to moderate physical activity in children with SAD and matched healthy controls (HC). The home environment was chosen to ensure a familiar context for the tasks, without psycho-social stress and including physical activation. Particular care was taken to minimize (and assess) anticipatory anxiety prior to the study session by measuring subjective anxiety and salivary cortisol, a reliable marker for social-emotional stress (e.g., Dickerson and Kemeny 2004). The following hypotheses were tested: First, we expected higher tonic autonomic arousal as indicated by higher sympathetic and lower parasympathetic activity during rest in children with SAD compared to HC children (Beauchaine 2001; Schmitz et al. 2011; Kagan et al. 1988). Second, we anticipated more restricted autonomic flexibility as indicated by a blunted autonomic responding to orthostatic and physical stress (lower sympathetic and parasympathetic reactivity) in children with SAD in comparison to HC children (Leicht and Allen 2008; Schmitz et al. 2011). Third, we expected that potential alterations in autonomic functioning would be correlated with the degree of social anxiety in the overall sample (Schmitz et al. 2013).

Method

Participants

Children were recruited through advertisements in schools, treatment facilities and local newspapers as part of a larger research project funded by the German Research Foundation (DFG; TU 78/5-2). Interested families of both SAD and HC children ($n = 188$) were screened and gave informed consent. Those eligible ($n = 99$) were invited to a diagnostic session in which a structured clinical interview was administered (see procedure).

Inclusion criteria for the SAD group were: SAD as primary diagnosis; HC group: no lifetime diagnosis of mental disorder. Participants in the SAD group were included if they had secondary diagnoses as SAD is often accompanied by comorbid disorders (Lydiard 2001). Exclusion criteria for the SAD group included SAD not as a primary but as a secondary diagnosis, any medical treatments or conditions that could affect the physiological systems studied here (e.g., cardiac dysrhythmia, asthma), or medicated attention deficit disorder. After the interview and, thus, the validation of the diagnosis, the final sample consisted of 57 children aged 8–13 years ($n_{SAD} = 30$, $n_{HC} = 27$). In the SAD group, 15 children had one or more comorbid diagnoses (generalized anxiety disorder: $n = 5$, specific phobia: $n = 4$, separation anxiety disorder: $n = 3$, attention deficit disorder: $n = 2$, dysthymia: $n = 1$, oppositional disorder: $n = 1$, enuresis: $n = 1$).[1] Participants' characteristics are found in Table 1.

For participation, children and parents received 10€ in vouchers and 20€ in cash, respectively. Further, children in the clinical group were offered participation in group therapy. The study was approved by the local ethics committee.

[1] Children with and without comorbid disorders did not differ on any outcome measure, Fs < 1.67, ps > .203. Therefore, all children with SAD were included in one group.

Table 1 Participant Characteristics

	Social anxiety disorder *M (SD)*	Healthy controls *M (SD)*	Statistics
n	27	27	
Age (in years)	10.9 (1.32)	11.1 (1.44)	$t(52) = 0.59$, n.s.
% female	63.0	70.4	$\chi^2(1) = 0.33$, n.s.
% elementary school	29.6	18.5	$\chi^2(4) = 3.69$, n.s.
SASC-R	47.9 (13.9)	28.5 (9.69)	$t(52) = -5.93$***
CBCL-INT (T-values)	69.1 (7.24)	43.7 (6.91)	$t(53) = -13.26$***
CBCL-EXT (T-values)	53.5 (10.62)	46.0 (8.24)	$t(53) = -2.91$**
BMI-SDS	0.25 (0.93)	0.16 (0.88)	$t(55) = -0.60$, n.s.
Physical fitness (h/week)	6.17 (2.77)	8.11 (4.41)	$t(55) = 1.97$, n.s.

BMI-SDS body mass index-standard deviation scores; *CBCL-EXT* Child Behavior Checklist – Externalizing Symptoms; *CBCL-INT* Child Behavior Checklist – Internalizing Symptoms; *SASC-R* Social anxiety scale for children – revised

n.s. $p > 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$

Psychometric Measures

The Social Anxiety Scale for Children – Revised (La Greca and Stone 1993)

This questionnaire measures self-reported social anxiety symptoms in children (18 items, e.g. "I get nervous when I talk to new kids") with total scores ranging from 18 to 90. Children respond to each item using a 5-point Likert-type scale ranging from *1* (not at all) to *5* (all the time). The SASC-R has satisfactory test-retest reliability (.67) and internal consistency (.76). The internal consistency of the SASC-R in the current sample was excellent (child report: $\alpha = .95$).

Child Behavior Checklist[2] *(Achenbach and Edelbrock 1991)*

This questionnaire allows parents to report on a variety of internalizing and externalizing symptoms. The 120 items include behavioral and emotional characteristics as well as somatic well-being. Parents respond to each item using a 3-point scale ranging from *0* (not true) to *2* (very true or often true). 118 items are included to assess 8 problem scales as well as 2 superior scales (internalizing vs. externalizing). Internal consistency in the current sample was excellent (internalizing: $\alpha = .936$, externalizing: $\alpha = .875$).

Psychophysiological Measures

Electrodermal and cardiovascular measures including Heart Rate (HR) were assessed at 400 Hz using the Varioport-II system (Becker Meditec, Karlsruhe, Germany). Data inspection and artifact corrections were conducted offline using ANSLAB (Blechert et al. 2016). Since autonomic functioning can be influenced by participants' physical fitness (Nagai and Moritani 2004), parents reported on physical activity in hours per week and children's' BMI was included in statistical analyses as a potential covariate (see below).

Autonomic response to environmental events is produced through an organ specific, mostly antagonistic action of the sympathetic and parasympathetic branch of the ANS (Berntson et al. 1994). Thus, a comprehensive assessment of such responses requires measurement of various organ systems (e.g. heart, skin) and branches (PNS, SNS). Thus, following previous studies (e.g. Schmitz et al. 2011), we chose the following measures: Skin conductance level as a measure mainly indexing the SNS, HR as an indicator of joint SNS/PNS action, and RSA as a relatively pure index of PNS activity in the heart.

Sympathetic/Parasympathetic Measures: Heart Rate (HR)

As the heart is innervated by both the sympathetic and the parasympathetic branches of the ANS (Berntson et al. 1994), HR is regarded as an indicator for both systems. From the ECG lead II, the interval in milliseconds between successive R-waves (interbeat interval, IBI) was calculated. For presentation of results, IBI was converted to HR, while IBI values were used in all statistical analyses (Quigley and Berntson 1996). As artefactual R-spikes in the ECG are likely to bias estimates of HR variability parameters, they were standardized by manual interpolation and deletion (Berntson et al. 1990).

Sympathetic Measures (SNS)

Sympathetic fibers innervate autonomic effector organs such as the heart, blood vessels and sweat glands. Hence, when

[2] A more recent version was published in German in 2014. However, since data collection started before this point, the earlier version was used here.

comprehensively assessing sympathetic influences on the ANS, the broad assessment of various organic domains is necessary. To broadly capture sympathetic influences, the following parameters were chosen (c.f. Schmitz et al. 2013). Two electrodes for the assessment of electrodermal activity, reflecting electrodermal sympathetic activity (EDA; Boucsein 2011), were placed on the middle phalanx of the middle and ring fingers of the left hand using 11-mm inner diameter Ag/AgCl electrodes filled with isotonic electrode paste (TD-245, Med Associates, Inc., St. Albans, Vermont). As a parameter of EDA, skin conductance level (SCL) was used. For cardiac sympathetic activity (e.g., Kline et al. 1998) t-wave amplitude (TWA) was calculated in reference to the isoelectric ECG baseline, measured by chest ECG. Finally, to capture sympathetic influences on the vascular system, pulse wave transit time (PTT, as time between steepest upstroke and ECG R-wave) and pulse wave amplitude were assessed (PA, as peak minus trough, measured on the index finger of the left hand).

Parasympathetic Measures (PNS) and Respiration

Respiratory sinus arrhythmia (RSA) was used as a measure of the parasympathetic nervus vagus, thus PNS activity. RSA was quantified as lnHF power using fast Fourier transform as the summed spectral density function within the frequency band associated with respiration (0.13–0.50 Hz; Wilhelm et al. 2004). Since changes in RSA can be influenced by respiration independently of a change in parasympathetic activity (Wilhelm et al. 2004), respiration was measured as a control variable using respiration belts around the thorax and abdomen, and calibrated (300 ml) in both supine and standing posture to assess both respiration rate (RR) and tidal volume (V_T). Additionally, a paced breathing protocol (at a frequency of 13 breaths/min; Wilhelm et al. 2004, see Fig. 1), implemented in standing and supine posture (2 min each) allowed for RSA assessment under standardized breathing conditions.

Procedure

In an initial session at the university, the diagnostic procedure was conducted by two interviewers trained in the administration of the Kinder-DIPS (Schneider et al. 2009), a modified[3] and extended version of the Anxiety Disorders Interview Schedule for children (ADIS-C; Silverman and Nelles 1988). To reach a diagnosis on DSM-IV criteria, both the parent and child are interviewed separately, with both reports contributing to the diagnosis. Additionally, all diagnoses were supervised by a licensed clinical psychologist. At the conclusion of the diagnostic session, parents and children reported on psychopathological symptoms and sociodemographic variables (including physical fitness).

To minimize environmental threat, the actual testing session took place at the children's homes with mothers present at all times. To minimize context variability, mothers were instructed not to talk or interact with their child during the testing period (c.f., Kossowsky et al. 2012; Wilhelm et al. 2003). Furthermore, all children were familiar with the experimenter from the earlier diagnostic session (see above). Subjective and endocrine measures were assessed to check stress and anxiety levels (see below).

The first assessment phase comprised measurement in supine position: the child lay on a mat on the floor for 5 min (*Baseline*) while the experimenter left the room. The experimenter's return marked the beginning of the second assessment phase, asking the child to stand up at their own pace (Mezzacappa et al. 1997), and to remain standing still for 4 min (*Orthostatic Stress*), during which time the experimenter left the room again. As a control measure, children then completed the paced breathing protocol (see Psychophysiological Measures). Accelerometry was continuously assessed to ensure compliance. After 4 min, the experimenter returned and instructed the child to step up and down a 10 cm high stair for 4 min at 80 footsteps/minute indicated by a metronome (*Stepping*). Children rated their state anxiety on a paper-based visual analogue scale from 0 (*not at all*) to 10 (*extreme*) after each phase (Schmitz et al. 2012).

Stress and Anxiety Levels

Ratings of state anxiety after orthostatic stress and stepping were used as a control measure for subjective stress (Schmitz et al. 2012). Further, next to the autonomic nervous system (ANS), the hypothalamus-pituary-adrenal (HPA) system has been extensively studied in the context of social anxiety and social evaluative threat (e.g., Krämer et al. 2012). In stressful situations, the hypothalamic production of corticotropin-releasing hormone (CRF) increases which in turn stimulates the pituary release of adrenocorticotropin hormone (ACTH). Finally, cortisol is secreted into the bloodstream by the adrenal cortex (Axelrod and Reisine 1984). Cortisol levels can be accessed easily by assessment of saliva, and thus is a non-invasive index of HPA-axis activity. Since cortisol has a 10 to 15 min delay in reactivity to stress, the baseline measurement in our study served as a control parameter to check to potential group differences in anticipatory anxiety and stress preceding the testing session (Hinrichsen and Clark 2003).

[3] In contrast to the ADIS-C, the Kinder-DIPS uses a completely parallel version in both child and parent. While the ADIS-C relies on parental information concerning, for example, ADHD, the Kinder-DIPS also takes the child's report into consideration.

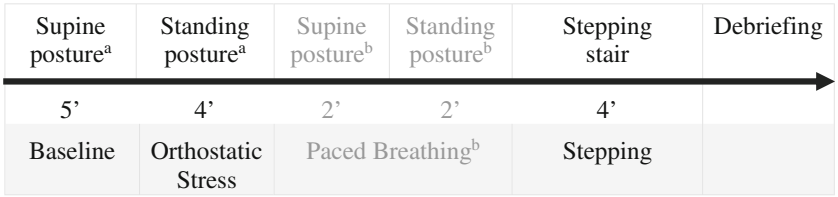

Fig. 1 Procedure and analysis segments. [a]Experimenter not present. [b]Control measure for respiratory effects; therefore only included in respiration analysis

Statistical Analyses

After raw data inspection and artifact correction, all psychophysiological measures were averaged across 1-minute-intervals and subsequently into phase[4] (4–5 min, depending on phase type). Three children with SAD were excluded due to technical difficulties. The normal distribution of all dependent variables was checked, using Kolmogorov-Smirnov-Z tests. Where normality was violated, nonparametric tests were applied, which was only the case for state anxiety.

For HR (capturing both SNS and PNS influences; Berntson et al. 1994), a 2 (Group) × 3 (Phase: Baseline, Orthostatic Stress, Stepping) ANOVA with repeated measures on Phase was calculated.[5] To avoid spurious findings through multiple testing and to reduce alpha inflation, multiple SNS measures were submitted to an overall 2 (Group) × 3 (Phase: Baseline, Orthostatic Stress, Stepping) MANOVA including TWA, PTT, PA, and SCL, with Phase as a repeated measure. In the case of a significant MANOVA, separate follow-up ANOVAs for each SNS parameter were run. To assess significant Group X Phase interactions, post-hoc t-tests compared reactivity (differential scores) on significant SNS parameters.

To control for potential respiratory confounds of RSA (Wilhelm et al. 2004) additional analyses were run. First, changes in respiration rate and tidal volume during the entire session in both groups were analyzed. Second, respiration values during paced breathing, providing a phase of stable respiration rate, were compared. Thus, for respiration, a 2(Group: SAD, HC) × 3(Phase: Baseline, Orthostatic Stress, Stepping) MANOVA including RR and V_T with repeated measures on Phase was conducted. For RSA (resembling mainly PNS activation), a 2 (Group) × 3(Phase: Baseline, Orthostatic Stress, Stepping) ANOVA with repeated measures on Phase was conducted. For the sake of brevity, effects of Phase are only reported when interacting with Group.

Furthermore, since preliminary analyses revealed autonomic differences between groups, hierarchical regression analyses were used to decompose the various possible sources of such differences using z-standardized (Cohen et al. 2003) trait variables in the overall sample. First, demographic (age, Kudielka et al. 2004), anthropometric (BMI) and physical fitness (Nagai and Moritani 2004) were added to exclude low level differences in body composition and physiological confounds of autonomic functioning. Next, general levels of psychopathology were considered. Within the latter we distinguished between general psychopathology (CBCL internalizing and externalizing symptoms; Boyce et al. 2001) and social anxiety (SASC).

Results

Participant Characteristics

As shown in Table 1, the groups were comparable on age, gender, education, and physical characteristics (BMI, physical activity).[6] As expected, children with SAD reported higher trait social anxiety.

Stress and Anxiety Levels

There were no significant differences between SAD and HC children regarding state anxiety at any point during the ambulatory session, Kolmogorov-Smirnov-Z < .936, $p > .323$, or cortisol at the beginning of the ambulatory session, $t(51) = -0.75$, $p = .456$.

Heart Rate[7]

A 2(Group: SAD, HC) × 3(Phase: Baseline, Orthostatic Stress, Stepping) mixed ANOVA revealed a main effect of Group, $F(1,51) = 6.01$, $p = 0.018$, $\eta_p^2 = .105$, but no Group x Phase interaction effect, $F < .952$, $p > .404$, Fig. 2, pointing to an elevated HR throughout the procedure in the SAD group when compared to HC children.

To further investigate relations between demographic/psychometric characteristics and tonically elevated HR scores

[4] Outliers (z-values of ≥ ± 3) were excluded in the respective statistical analyses (HR (1 SAD), SNS (2 HC, 1 SAD), PNS (4 HC, 3 SAD), RESP (1 HC, 2 SAD)).

[5] In line with previous research (Kudielka et al. 2004; Schmitz et al. 2013), BMI, gender and age were examined as covariates on all measures. Since they did not interact with Group, they were omitted ($ps > .151$) in further analysis.

[6] BMI, gender and age were examined as possible covariates on all measures (Kudielka et al. 2004). Since they did not interact with Group in any analysis ($ps > .151$), they were omitted for the sake of clarity.

[7] Significant main effects of Phase were found throughout analyses on all measures (HR; SNS; PNS) but as such are only relevant as a manipulation check for reactivity to the tasks ($p < .05$) and therefore have been left out in further presentation of results.

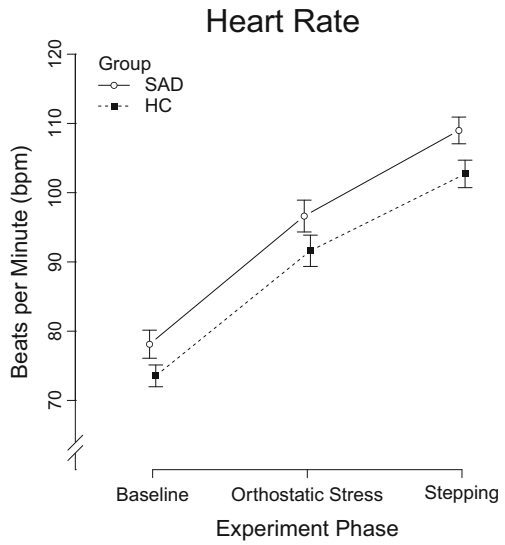

Fig. 2 Heart rate measured in bpm in children with SAD and HC children during all experimental phases (baseline (supine position), reactivity to orthostatic stress, reactivity to stepping)

in children with SAD in comparison with HC, hierarchical multiple regression regressed grand average IBI (averaged across all phases) using the aforementioned approach. The total model accounted for 15.8 % of the variance, $F(6,39) = 2.41$, $p = 0.045$. Only social anxiety (SASC-R) significantly predicted HR,[8] $p = 0.016$ (see Table 2). Thus, higher tonic HR during the session was primarily predicted by higher trait social anxiety, while other confounds or symptom clusters did not reach significance.

Sympathetic Activity

A 2(Group: SAD, HC) × 3(Phase: Baseline, Orthostatic Stress, Stepping) MANOVA including the parameters TWA, PA, PTT, SCL as dependent variables showed a significant effect of Group, Wilk's $\lambda = .813$, $F(4,46) = 2.65$, $p = 0.045$, $\eta_p^2 = .187$, and an interaction effect involving Group x Phase, Wilk's $\lambda = .818$, $F(8,190) = 2.51$, $p = 0.013$, $\eta_p^2 = 0.095$. Follow-up 2(Group: SAD, HC) × 3(Phase: Baseline, Orthostatic Stress, Stepping) ANOVAs on each of the sympathetic measures showed a significant main effect of Group on SCL values, $F(1,49) = 6.78$, $p = 0.012$, $\eta_p^2 = .122$, suggesting elevated SCL activation during the ambulatory session in children with SAD (see Fig. 3a). All other Group effects on other SNS measures were non-significant, $Fs < 2.25$, $ps > .139$.

Regarding TWA and PTT, significant Group X Phase Interactions were found for TWA, $F(1.62,79.45) = 5.74$, $p = 0.008$, $\eta_p^2 = .105$, and PTT, $F(2,97.99) = 3.33$, $p = 0.040$, $\eta_p^2 = 0.064$. All other interactions did not reach significance, $Fs < 1.55$, $ps > .221$. Post-hoc t-tests showed no group difference for TWA during Baseline, $t(49) = 0.00$, $p > .99$, $d = -0.00$.

[8] Negative values are caused by use of IBI in analysis.

Table 2 Regression of heart rate across all phases on trait variables (R^2 relates to the overall model including all blocks)

			Heart rate[a] ($R^2 = .158$*)	
	ΔR^2, p		b	p
Block 1	0.03, .757	Age	0.09	.592
		Physical fitness	0.08	.612
		BMI	-.14	.405
Block 2	.12, 0.066	CBCL-INT	-.43	0.058
		CBCL-EXT	0.07	.746
Block 3	.12, 0.016	SASC-R	-.50	0.016

BMI Body Mass Index; *CBCL-INT* Child Behavior Checklist – Internalizing Symptoms; *CBCL-EXT* Child Behavior Checklist – Externalizing Symptoms; *SASC-R* Social anxiety scale for children – revised

[a] Analyzed using IBI values

*$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$

However, group differences reached trend-level significance for difference scores (activation – baseline) during Orthostatic Stress, $t(49) = 1.98$, $p = 0.053$, $d = 0.56$, and reached significance during Stepping, $t(49) = 2.91$, $p = 0.005$, $d = 0.82$, showing hyper-reactivity in the SAD group. For PTT, groups did not differ during baseline, $t(49) = 0.56$, $p = .577$, $d = 0.16$, while group differences emerged for difference scores (activation – baseline) during Orthostatic Stress, $t(49) = 2.35$, $p = 0.023$, $d = 0.66$, and Stepping, $t(49) = 2.91$, $p = 0.042$, $d = 0.59$. Thus, children with SAD showed heightened reactivity on both TWA and PTT (see Fig. 3b, c).

To decompose the above identified group differences, we ran a similar hierarchical regression analysis as above. Baseline SCL as well as TWA and PTT (differential scores: activation – baseline) for reactivity effects in two phases (Orthostatic Stress, Stepping) were regressed on demographic and psychometric sample characteristics (see Table 3).

The overall model for skin conductance level explained 12.6 % of the variance but only reached trend level significance, $F(6,40) = 2.10$, $p = 0.075$. Only the step including CBCL internalizing and externalizing symptoms reached significance, $p = 0.039$ (see Table 3). For TWA, no regression model reached significance ($ps > .103$)

Parasympathetic Activation[9]

To assess possible respiratory differences between groups (which might confound RSA as a measure of parasympathetic activation), we calculated a 2(Group: SAD, HC) × 3(Phase: Baseline, Orthostatic Stress, Stepping) MANOVA for RR and V_T. This showed no significant main or interaction effects

[9] Results for parasympathetic activity remained unchanged when alternatively calculating complex demodulation or transfer function RSA as parasympathetic indices (see Grossman and Taylor 2007).

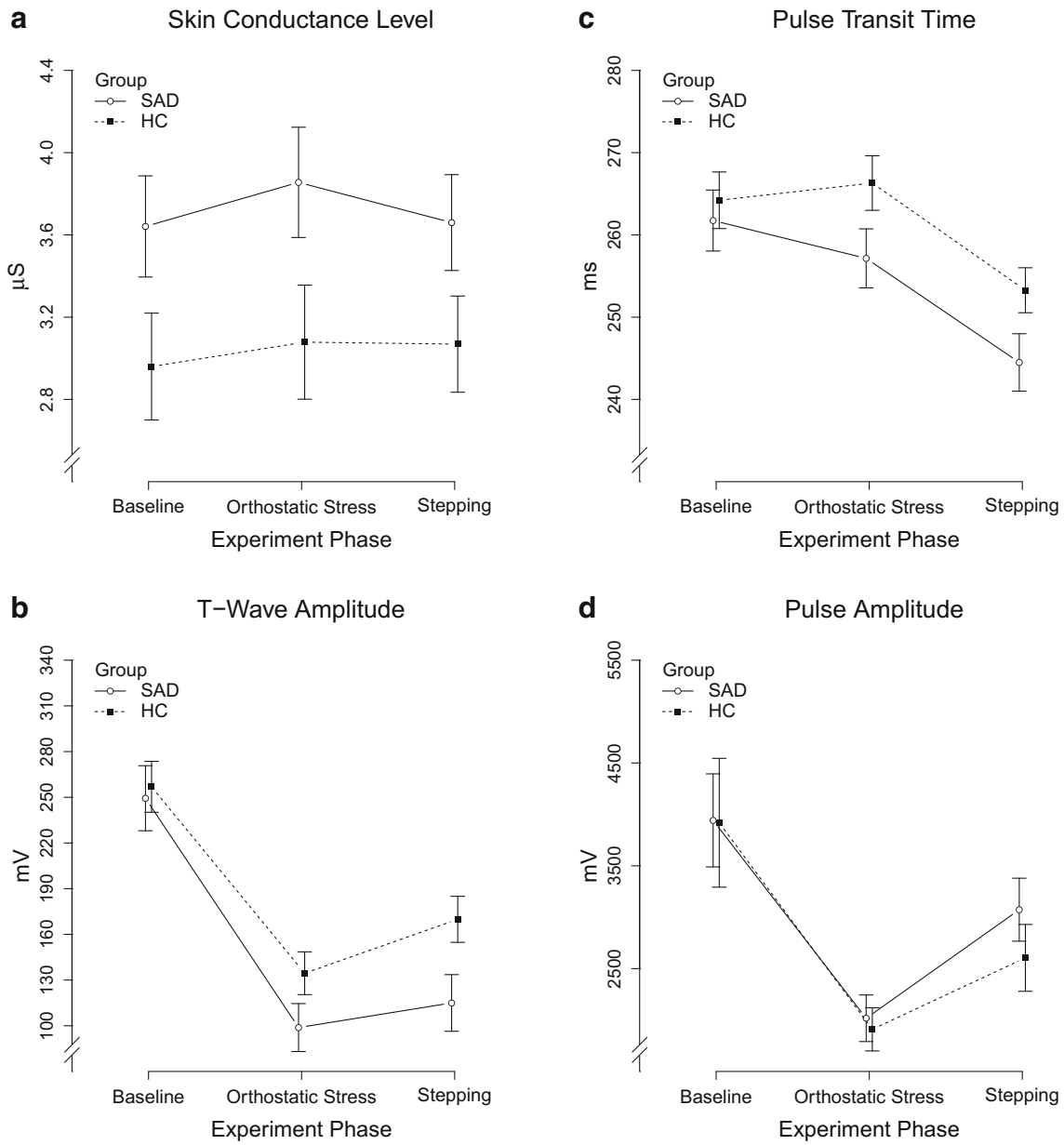

Fig. 3 Sympathetic arousal in children with SAD and HC children during all experimental phases (baseline (supine position), reactivity to orthostatic stress, reactivity to stepping

involving Group, Fs < 0.91, ps > .645 and F < 0.34, p > .853, respectively. Similar MANOVA analyses for the RR and V_T during Paced Breathing also showed no significant effects involving Group, Fs < 1.12, ps > .295. Last, despite comparable respiratory variables, the 2 × 3 ANOVA of RSA showed no significant group effect, $F(1,45) = 0.04$, $p = .836$, $\eta_p^2 = 0.001$, or interaction effect, $F(2,44) = 0.77$, $p = .470$, $\eta_p^2 = 0.034$ (see Fig. 4).

Discussion

The aim of the current study was to examine autonomic functioning in children with SAD in an ambulatory setting using a non-anxiety evoking, though physically taxing task. Based on previous laboratory findings of tonic hyperarousal at rest and restricted autonomic flexibility during social stress in SAD children, we expected affected children to show (1) higher tonic autonomic arousal as indicated by higher sympathetic and lower parasympathetic activity during rest in comparison to HC children (Beauchaine 2001; Schmitz et al. 2011; Kagan et al. 1988) as well as (2) restricted autonomic flexibility as indicated by blunted autonomic responding to orthostatic and physical stress (lower sympathetic and parasympathetic reactivity) in children with SAD in comparison to HC children (Leicht and Allen 2008; Schmitz et al. 2011). Third, we expected that potential alterations in autonomic functioning were

Table 3 Regression trait variables and tonic activation skin conductance level (R^2 relates to the overall model including all blocks)

			Skin conductance level ($R^2 = .126^{\dagger}$)	
	ΔR^2, p		b	p
Block 1	0.09, .234	Age	-.30	0.057
		Physical fitness	-.16	.303
		BMI	0.06	.717
Block 2	.13, 0.038	CBCL-INT	.30	.143
		CBCL-EXT	.12	.526
Block 3	0.01, .427	SASC-R	.16	.427

BMI Body Mass Index; *CBCL-INT* Child Behavior Checklist – Internalizing Symptoms; *CBCL-EXT* Child Behavior Checklist – Externalizing Symptoms; *SASC-R* Social anxiety scale for children – revised

† $p \leq .1$; $^{*}p \leq 0.05$; $^{**}p \leq 0.01$; $^{***}p \leq 0.001$

specifically related to social anxiety in the sample (Schmitz et al. 2013) as opposed to differences in general psychopathology or physical characteristics. The results were as follows: In line with our first hypothesis, children with SAD showed signs of tonic autonomic hyperarousal as indicated by higher HR and SCL throughout the procedure. However, contrary to our second hypothesis we found no evidence for blunted reactivity to orthostatic and stepping tasks, but rather stronger sympathetic reactivity on PTT and TWA to both tasks in SAD children. Partially confirming hypothesis three, social anxiety predicted HR, while general psychopathology predicted EDA, an indicator of SNS arousal. No group differences on parasympathetic parameters were found.

Chronic Hyperarousal in Children with SAD

To our knowledge this is the first study investigating basal autonomic functioning in childhood SAD in the absence of social-evaluative stress and minimizing environmental and anticipatory anxiety. In line with our hypothesis, even under these conditions, SNS hyperarousal was found in children with SAD. This extends previous laboratory findings (Krämer et al. 2012; Mesa et al. 2014; Schmitz et al. 2011), showing that autonomic hyperarousal at rest may not merely be an effect of the laboratory setting, but a chronic autonomic pattern that generalizes to non-threatening situations. While regression analysis showed that severity of trait social anxiety predicted elevated HR at baseline, elevated tonic activation has also been reported in studies of children with mixed anxiety disorders and inhibited temperament (Kagan et al. 1988; Monk et al. 2001; Yeragani et al. 2001) and the CBCL-internalizing predictor approached significance in our sample. Therefore it is conceivable that autonomic dysregulation at rest is a phenomenon that is more broadly related to the development of internalizing psychopathological symptoms, including social anxiety. This would further be in line with our regression results, showing that EDA arousal, as an index for SNS activity, was related to internalizing and externalizing symptoms in the sample. Thus, both social anxiety and psychopathology in general may accompany higher chronic organismic stress as indexed by higher autonomic arousal even under non-anxiety provoking conditions.

In addition, our results showed a positive correlation between social anxiety and autonomic arousal as measured by HR in the overall sample: Altered basal autonomic arousal might be the result of chronic and severe anxiety symptoms in response to major or minor social stressors, contributing to a constant emotional 'load' in affected children. The concept of "allostatic load" (McEwen and Stellar 1993) describes how an inability to adapt to repeated stressors leads to long term changes within homeostatic regulation resulting in altered, often elevated, baselines (~set points of homeostatic systems). High sensitivity to any environmental signs of threat, resultant anxiety responses and tonic autonomic changes might explain why other studies in children, youth and adults with SAD have repeatedly observed elevated baseline values on autonomic variables (Gerlach et al. 2004, 2001). This corresponds with Dieleman et al.'s (2015) suggestion that the autonomic arousal

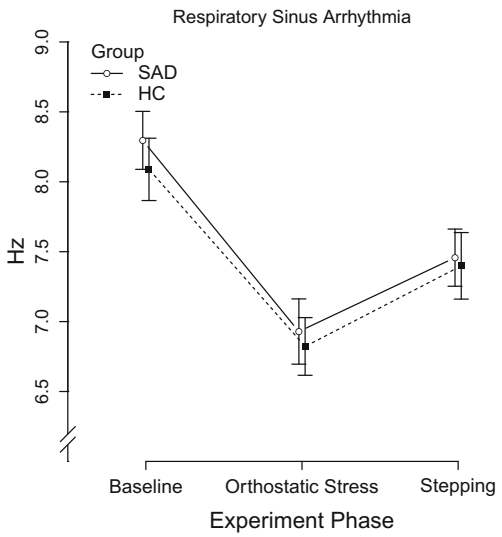

Fig. 4 Parasympathetic arousal in children with SAD and HC children during all experimental phases (baseline (supine position), reactivity to orthostatic stress, reactivity to stepping)

profiles of mixed-anxiety disordered children resemble those of individuals under chronic stress. Hence, if children with high social fears regularly experience distress in their daily lives and suffer from constant fear of negative evaluation by peers, teachers and adults, this allostatic load may lead to long-term changes in homeostatic regulation cycles, resulting in chronic sympathetic hyperarousal (Kagan et al. 1988).

Hyperreactivity in Children with SAD

Contrary to our second hypothesis, our results pointed to higher SNS reactivity during moderate physiological activation in children with SAD. In both reactivity phases, children with SAD displayed higher cardiac SNS reactivity (PTT, TWA). This resembles the recent findings of Dielemans and collegues (2015) of higher sympathetic reactivity to a non-anxiety provoking task in their mixed anxiety-disorder group compared to healthy controls. Kagan et al. (1988), who found similar reactivity to an unfamiliar situation or person in children with behavioral inhibition (a risk factor for anxiety disorders), attributed this heightened sympathetic reactivity to a lower threshold for limbic-hypothalamic arousal to unexpected changes in the environment (Kagan et al. 1988).

We found no group differences in tonic RSA or RSA reactivity. This similarity between groups in PNS activation in a non-stressful environment is partly consistent with the findings of an earlier study (Kristensen et al. 2014), who did not find dysregulation of SNS and PNS activity in response to physiological activation in anxious children. Thus, diminished parasympathetic inhibition at rest and blunted parasympathetic responding in anxious children might be restricted to *emotional* stressors. This would be in line with Beauchaines' (2001) suggestion that vagal regulation is linked to attentional and emotional processing and pertinent individual differences *under stress*. As the present task was not emotionally challenging, no vagal dysregulation was found in our SAD sample.

The finding of elevated sympathetic reactivity seems at odds with laboratory findings of *blunted* autonomic responding to social stress in children with SAD, subclinical samples and adults with SAD (Pujol et al. 2013; Schmitz et al. 2011, 2013). Blunted responding to social stress based on elevated baseline values has been reported in lab based studies. It is possible that the same population operated in a different autonomic mode in a less threatening environment at home. According to the concept of autonomic space (Berntson et al. 1991, 1994), PNS and SNS can interact in various ways that include several non-reciprocal, coupled (e.g., reciprocal: activation of one branch causes deactivation of the other branch) and also uncoupled modes (activation or deactivation of either branch is independent of the other branch). Most importantly, physiological ceiling or floor effects of an effector organ are dependent on the mode in which the ANS operates. Here it seems that particularly the SNS system was hyperactive, with no clear signature on the PNS.

However, a different explanation for a lack of blunted autonomic responding in our sample stems from motivational theories (Wright 1996). These postulate that allocation of energy depends on task difficulty and success importance, leading to less energy investment in situations which are perceived as either too easy or unsolvable (cf., Schmitz et al. 2013). If a social situation is intensified by negative social evaluation, children form the perception that the situation exceeds personal resources, and is thus unsolvable. Therefore, in the face of social-evaluative stress, a down-regulation takes place in opposition to challenging but solvable situations.

Limitations and Implications

The following limitations may apply. Even though stress was minimized as much as possible (familiar experimenter, assessment in the family home, subjective and endocrine manipulation check) and groups did not differ on subjective and HPA indices (i.e., cortisol), an emotional response to the testing procedure cannot be excluded entirely. Despite clear instructions, differential expectations might have been triggered: In a study by Wyller et al. (2014), expectations of participants with chronic fatigue syndrome about the upcoming procedure potentiated autonomic cardiovascular modulation in orthostatic challenge. Yet, reactivity to assessment is almost impossible to avoid and the extension of research to more naturalistic settings is widely recommended (Pfaltz et al. 2009; Schmitz et al. 2011; Wilhelm and Grossman 2010). Ambulatory research in children has been mainly limited to diary research (e.g., Mor et al. 2010) or ecological momentary assessment (e.g., Tan et al. 2012). While compliance is also crucial to these assessment methods, physiological assessment relies on even more compliance as movement artefacts can change data significantly. However, we strived to achieve compliance by carefully instructing the child, collecting accelometry data, and keeping the assessment phases short. Consequently, future studies may want to examine autonomic functioning using long-term ambulatory assessment methods over periods of several days, capturing both autonomic activity to daily social stress and during resting conditions including sleep phases (e.g., Pfaltz et al. 2009). Another limitation relates to possible subclinical fears in our control participants. While children of the control group did not meet diagnostic criteria for any mental lifetime diagnosis and had low psychometric levels of general psychopathology as indicated by CBCL scores, we cannot rule out the possibility that elevated subclinical fears were present in the control group. Thus, future studies should include an additional dimensional assessment of anxiety levels when comparing control and clinical groups to one another.

From a clinical perspective, the findings of autonomic hyperarousal in children with SAD may be of particular interest.

A basal state of elevated psychophysiological arousal in many or most situations can provide a basis for further symptom clusters. Elevated bodily arousal – if perceived by the individual – can lead to an inward focus of attention – with all the known adverse effects this causes (Clark and Wells 1995). Furthermore, elevated arousal might enhance anticipatory anxiety and lead to avoidance behavior, with both of these symptoms assumed to trigger a vicious circle of maintaining factors for social anxiety (Clark and Wells 1995). Through interoceptive networks, cognitive symptom clusters such as attentional biases might also be altered (Howells et al. 2012).

The finding of autonomic hyperarousal in children with SAD could increase understanding of the physiological basis of other psychopathological processes such as attentional biases or distorted cognitive processing (e.g., Stopa and Clark 2000). It may further underline the need for possible additional specific interventions targeting bodily arousal as suggested by Friedman (2007), who reported that relaxation techniques or biofeedback leads to lower tonic physiological arousal. Additionally, physiological measures could be added to standard treatment. Middleton and Ashby (1995), for example, found successful cognitive therapy in panic disorder to be accompanied by increased vagal tone and heart rate variability. However, further research – especially in children – is necessary to clarify whether conventional exposure therapy already targets these specific bodily processes.

Further, more research using larger samples could provide more power to strengthen the current null findings for the PNS, while samples with other anxiety disorders could broaden the range of findings. Also, to shed light on the specificity of setting, studies could focus on anticipatory anxiety as well as disorder-specific tasks in a natural setting or non-anxiety evoking tasks in the laboratory. That is, a direct comparison of laboratory and ambulatory data using anxiety- and non-anxiety-evoking tasks is recommended. More continuous ambulatory assessment of physiological parameters (24 h) would further allow inferences about changes in daily life.

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Compliance with Ethical Standards

Competing Interests The authors declare that they have no competing interests.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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