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Heart rate variability and salivary cortisol in very preterm children during school age

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ABSTRACT

The autonomic nervous system (ANS) plays a major role in the human stress response and reflects physical and psychological adaptability to a changing environment. Long-term exposure to early life stressors may alter the function of the ANS. The present study examines differences in the ANS between children born very preterm and full-term as well as the association between the ANS and the hypothalamic-pituitary-adrenal (HPA) axis, the other main branch of the human stress system.

Fifty-four healthy children born very preterm (< 32nd gestational week) and 67 full-term children aged 7–12 years provided data for the present study. Polysomnography (PSG) assessments were obtained during a night at the children's home in lying position at rest (wake) and during different sleep stages (stage 2 sleep, slow wave sleep, rapid-eye-movement sleep). Autonomic function was assessed by use of heart rate variability, specifically low frequency power (LF), high frequency power (HF), total spectral power (Tot Pow), and the LF/HF ratio. HPA axis activity was measured using salivary cortisol the next morning at awakening, 10, 20, and 30 min later.

Children born very preterm had lower LF/HF ratio during wake and stage 2 sleep compared to full-term children. Moreover, higher LF, Tot Pow, and LF/HF ratio during wake, stage 2 sleep, and REM sleep were related to more post-awakening cortisol secretion.

The present study provides evidence on long-term ANS alterations after very preterm birth. Moreover, findings suggest a relation between the ANS and the HPA axis and therefore support the notion of mutual feedback between the two human stress systems.

1. Introduction

The sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal (HPA) axis are the two main branches involved in the human stress response. During acute stress, the autonomic nervous system (ANS), consisting of the SNS and the parasympathetic nervous system (PNS), induces immediate rapid bodily changes through modulation of noradrenergic and cholinergic neuronal communication and the quick release of adrenaline via the sympatho-adrenal medullary system (SAM; Charmandari et al., 2005; Stratakis and Chrousos, 1995). The SNS is involved in the so-called 'fight or flight' response – the immediate reaction to a stressor, while the complementary PNS regulates 'rest and digest' processes. In addition to stress response modulation, the ANS is involved in the regulation of various physiological functions, such as the heart rate. Autonomic function can be measured by electrocardiography (ECG) and the assessment of heart rate variability (HRV; Shaffer et al., 2014). HRV describes the change in beat-to-beat intervals over time and can be separated into different frequency domain bands, with low frequency power (LF: 0.04–0.15 Hz) reflecting a combination of sympathetic and parasympathetic nervous system activity, high frequency power (HF: 0.15–0.4 Hz) predominantly reflecting parasympathetic activity, total spectral power (Tot Pow: 0.0033–0.40 Hz) reflecting the global ANS activity, and the LF/HF ratio reflecting sympathovagal balance (Stein and Pu, 2012;

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Task Force, 1996). These frequency-domain HRV indices are assumed to be trait-like markers of autonomic function (Montano et al., 2009) and a change towards increased LF/HF ratio or decreased HF reflecting a dominance of sympathetic over parasympathetic activity has been shown to be associated with poor physical and mental health (Acharya et al., 2006; Friedman, 2007). However, also overly increased HRV may be non-optimal since it may reflect non-efficient physiological functioning and energy utilization (Shaffer et al., 2014). The role of the balance between sympathetic behavioral activation and parasympathetic inhibition for behavioral and emotional regulation is object of theoretical models including the polyvagal and the neurovisceral model (Porges, 1995, 2007; Thayer et al., 2009). In their core, both models propose that fine-tuning of the parasympathetic system is important for psychosocial adjustment to a changing environment.

The ANS matures during gestation and the first months after birth (David et al., 2007; Sahni et al., 2000) and stress during these sensitive phases may lead to long–term programming of the ANS (Fyfe et al., 2014). One major stress factor during this phase that occurs in around 10% of all children worldwide is preterm birth (Blencowe et al., 2013). In particular, children born very preterm are endowed with immature organs and are exposed to several illness-related adversities and invasive treatments (Lemola et al., 2015; Roberts and Dalziel, 2006). Later in their lives, very preterm children are more likely to suffer from physical disorders and psychological disturbances, such as depression, burnout, and anxiety disorders (Aarnoudse-Moens et al., 2009; Aylward, 2005; Lemola et al., 2015), which, in turn, may be associated with alterations in autonomic function (Kanthak et al., 2017; Licht et al., 2008; van Gestel and Steier, 2011). Compared to their peers born at term, infants born preterm show decreased HRV right after birth and at theoretical term (Landrot et al., 2007; Patural et al., 2008). These changes in HRV indicate a reduced regulatory capacity, so that infants born preterm may have more difficulty in adaptively responding to environmental stressors (Shaffer et al., 2014). Regarding the question how preterm birth affects ANS development at a later age up to 7 years, the evidence is more mixed. Specifically, studies reporting that preterm children either exhibited higher LF/HF ratio (Fyfe et al., 2015), lower LF (Yiallourou et al., 2013), or lower HF (Fyfe et al., 2015; Yiallourou et al., 2013), or failed to reveal differences in frequency domains at all (Fyfe et al., 2015; Landrot et al., 2007; Yiallourou et al., 2013). In addition, a recent study by Rakow et al. (2013) including nine-year old children showed rather global HRV reductions, characterized by lower very low frequency power (VLF), LF, HF, Tot Pow, and a trend towards a lower LF/HF ratio, in children born very preterm and small for gestational age (SGA) full-terms. The above–mentioned inconsistent findings regarding HRV differences between children born preterm and full-term might be due to differences in the age ranges studied as well as differences in the measurement setting, which might introduce variance to the findings. Specifically, studies with infants measured HRV during sleep (Fyfe et al., 2015; Yiallourou et al., 2013), while studies including older children conducted ECGs over a 24 h period (Landrot et al., 2007; Rakow et al., 2013).

The second arm of the human stress system, the HPA axis, reacts more slowly by regulating the secretion of glucocorticoids, including cortisol (Clements, 2013) and is supposed to play a major role in chronic stress (Miller et al., 2007). The HPA axis can be measured through salivary cortisol assessments. Cortisol secretion increases across the first 30–45 min after morning awakening, a phenomenon termed the cortisol awakening response (CAR; Clow et al., 2004; Stalder et al., 2016). There is evidence that an increased CAR is associated with stress and a reduced CAR with fatigue, burnout, and exhaustion, despite considerable heterogeneity in findings (Chida and Steptoe, 2009). As both the HRV and the HPA axis are proposed to be trait-like characteristics that play a major role for emotional adaptability and regulation (Porges, 1995, 2007; Thayer and Lane, 2000; Chida and Steptoe, 2009), it is an important question how these two systems are interrelated. An earlier study by Stalder et al. (2011) on the relationship between HRV and the CAR found that lower global HRV was related to an elevated CAR in young adults. Interestingly, these CAR-HRV associations were consistently found for HRV assessments taken in a laboratory setting and over the pre- and post-awakening periods as well as for measures of overall HRV, LF, and HF (Stalder et al., 2011). There are only few studies, which have examined the relation between ANS and HPA axis activity in children. One study by Michels et al. (2013), including children aged 5–10 years, reported higher LF and LF/HF ratio during 10 min in supine position in a quiet room in the afternoon to be associated with a larger CAR. However, another study by Rotenberg and McGrath (2016) found no such associations in children and adolescents aged 8–18 years conducting 24 h ECGs.

A first aim of the present study was thus to examine potential differences in HRV between school-age children born very preterm and those born full-term by measuring HRV during a wake episode in a lying position at rest before sleep onset and during sleep. There are two advantages of measuring HRV separately in the evening before sleep as well as during night sleep within different sleep stages. First, this involves a more standardized measurement situation across participants compared to 24 h ambulatory assessments, since HRV is assessed during the same circadian phase and sleep stages, which may reduce the acute impact of daily experience on HRV measurement. Second, this strategy allows us to determine whether differences between very preterm and full-term children are consistent across these different psychophysiological states. Following Rakow et al. (2013), we examined HRV parameters in children born very preterm and full-term. In addition to prior studies (Landrot et al., 2007; Rakow et al., 2013), we measured HRV parameters in a lying position at rest before sleep onset and during separate sleep stages (stage 2 sleep, slow wave sleep [SWS], and rapid eye movement [REM] sleep). A second aim was to test the association between the ANS (measured through HRV) and HPA axis activity (measured as the post-awakening cortisol secretion in the morning after HRV assessment). Thereby, we address the apparent gap in research regarding the association between HRV and HPA axis activity in school-aged children.

2. Methods

2.1. Study population and procedure

The data for the present study comes from the second wave (May 2013–September 2014) of the Basel Study of Preterm Children (BSPC). Recruitment procedures have been described elsewhere in detail (see Perkinson-Gloor et al. (2015), and Lemola et al. (2015), for reports on the first study wave and Urfer-Maurer et al. (2017) and Maurer et al. (2016) for reports on the second study wave, including results regarding HPA axis activity in children born very preterm). In total, 54 (44.6%) healthy very preterm children (< 32 weeks of gestation; age: M = 9.62 years, SD = 1.36; range: 7.33–12.33 years) and 67 (55.4%) age and sex matched full-term children (age: M = 9.66 years, SD = 1.51; range: 7.5–12.92 years; see Table 1) are included in the present report as they had one night of in-home electroencephalography (EEG) and readable electrocardiogram (ECG) data. Children born very preterm were recruited from an initial cohort of 260 prematurely born children treated at the University Children's Hospital Basel (Switzerland). Full-term children were recruited from official birth notification. For each participant, parents gave written informed consent and assent was obtained from the child. Ethical approval was obtained from the Ethics Committee of Basel (Basel, Switzerland, 122/11) and the study was performed in accordance with the ethical standards laid down in the Declaration of Helsinki.

2.2. Variables

2.2.1. HRV assessment and analysis

Using Compumedics Somté PSG during a single night at the