Journal of Psychiatric Research 60 (2015) 141-147



Contents lists available at ScienceDirect

# Journal of Psychiatric Research

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

## The role of sleep and the hypothalamic-pituitary-adrenal axis for behavioral and emotional problems in very preterm children during middle childhood





Nadine Perkinson-Gloor<sup>a</sup>, Priska Hagmann-von Arx<sup>a</sup>, Serge Brand<sup>b, c</sup>, Edith Holsboer-Trachsler<sup>b</sup>, Alexander Grob<sup>a</sup>, Peter Weber<sup>d</sup>, Sakari Lemola<sup>a, \*</sup>

<sup>a</sup> Department of Psychology, University of Basel, Missionsstrasse 62, 4055 Basel, Switzerland

<sup>b</sup> Center for Affective, Stress and Sleep Disorders, Psychiatric Clinics of the University of Basel, Wilhelm Klein-Strasse 27, 4027 Basel, Switzerland

<sup>c</sup> Department of Sport, Exercise and Health, Division of Sport Science, Faculty of Medicine, University of Basel, Birsstrasse 320 B, 4052 Basel, Switzerland

<sup>d</sup> Division of Neuropediatrics and Developmental Medicine, University Children's Hospital Basel, Spitalstrasse 33, 4056 Basel, Switzerland

#### A R T I C L E I N F O

Article history: Received 3 July 2014 Received in revised form 17 September 2014 Accepted 7 October 2014

Keywords: Preterm birth Sleep Polysomnography Hypothalamic-pituitary-adrenocortical activity Behavioral problems Emotional problems

### ABSTRACT

Very preterm children are at higher risk to develop behavioral and emotional problems, poor sleep, and altered hypothalamic-pituitary-adrenocortical activity (HPAA). However, knowledge on objective sleep and HPAA as well as their role for the development of behavioral and emotional problems in very preterm children is limited. Fifty-eight very preterm children (<32nd gestational week) and 55 full-term children aged 6-10 years underwent one night of in-home polysomnographic sleep assessment. HPAA was assessed with four saliva samples in the morning (morning cortisol secretion) and four saliva samples in the evening (evening cortisol secretion). Parents completed the Strengths and Difficulties Ouestionnaire (SDO) to assess children's behavioral and emotional problems and a subscale of the Children's Sleep Habits Questionnaire to assess sleep disordered breathing. Very preterm children showed more behavioral and emotional problems (SDQ total behavioral/emotional difficulties, emotional symptoms), poorer sleep (more nocturnal awakenings, more stage 2 sleep, less slow wave sleep), and faster decreasing evening cortisol secretion compared to full-term children. Across the whole sample, more stage 2 sleep and/or less slow wave sleep were associated with more SDQ total behavioral/ emotional difficulties, hyperactivity-inattention, and peer problems. Lower morning cortisol secretion and lower evening cortisol secretion were associated with more conduct problems. In very preterm children, increased SDO total behavioral/emotional difficulties was partially explained by less restorative sleep including more stage 2 sleep and less slow wave sleep. This result points to the importance of restorative sleep for the behavioral and emotional development of very preterm children during middle childhood.

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## 1. Introduction

Pre- and perinatal adversities shape the development of health problems throughout the life-span, including mental health disturbance (Barker et al., 2002). The present study aims at shedding light on possible pathways through which very preterm birth

sionsstrasse 62, CH- 4055 Basel, Switzerland. Tel.: +41 61 267 06 38.

E-mail address: sakari.lemola@unibas.ch (S. Lemola).

(<32nd gestational week) – a major perinatal adversity involving medical complications and invasive and often painful treatment procedures, which occurs in around 1% of all births in the western world (Beck et al., 2010) – may impact on mental health during childhood, namely by altering (a) sleep patterns and (b) hypothal-amic–pituitary–adrenocortical activity (HPAA).

Generally healthy very preterm born children are at higher risk for lower mental health including psychosocial impairments such as more behavioral problems (e.g. attention problems) and emotional problems (e.g. emotional symptoms such as anxiety and depression) (Aarnoudse-Moens et al., 2009; Bhutta et al., 2002) with an up to three times increased prevalence of mood disorders during childhood and adolescence (Burnett et al., 2011). One reason for decreased psychosocial adjustment of formerly preterm

Abbreviations: AUC, area-under-the-concentration-time-curve; EEG, electroencephalography; HPAA, Hypothalamic-pituitary-adrenocortical activity; PSG, Polysomnography; REM sleep, rapid eye movement sleep; SDB, sleep-disordered breathing; SDQ, Strengths and Difficulties Questionnaire; SWS, slow wave sleep. \* Corresponding author. Department of Psychology, University of Basel, Mis-

children includes persistent alterations in sleep regulation (Rosen et al., 2003; Lemola, in press). Particularly, sleep disordered breathing (SDB) is more prevalent in formerly very preterm children (Rosen et al., 2003).

Generally, adequate sleep is an important determinant of psychosocial adjustment in childhood. School-age children (i.e., between 6 and 11 years) have a high sleep need of around 9-11 h per night (Iglowstein et al., 2003), while sleep disturbances are common with a prevalence of around 30% (Fricke-Oerkermann et al., 2007). Importantly, a large body of evidence shows that children with disturbed sleep are at higher risk for behavioral and emotional problems (for a meta-analysis see Astill et al., 2012). Experimental studies further indicate that already modest changes in sleep duration have a causal impact on children's behavioral problems (Gruber et al., 2012). However, studies measuring sleep objectively in non-clinical samples are scarce. Particularly, research conducted in an ecological setting, i.e., at the children's home, measuring sleep objectively applying sleep-electroencephalography (EEG) to examine the relationship between sleep architecture and children's behavior problems are rare. One study applying in-home sleep-EEG in 58 healthy preschoolers showed that increased stage 2 sleep and decreased slow wave sleep (SWS, or deep sleep) were associated with more behavioral and emotional problems (Hatzinger et al., 2013). Similarly, in-home polysomnography (PSG) studies in adolescents reported that more light sleep (sleep stages 1 and 2) and less SWS was associated with subclinical depressive symptoms (Brand et al., 2010), and lower scores on personality traits associated with resilience such as mental toughness (Brand et al., 2014). Taken together, these studies applying in-home PSG in healthy children and adolescents indicate that less restorative sleep (i.e., more light sleep, less SWS) is related to poor psychosocial adjustment. In particular decreased SWS, which is considered to be the most restorative sleep stage (Borbély and Achermann, 1999), has been suggested to involve decreased energy levels for the next day and therefore increased vulnerability for psychological difficulties.

A second possible reason for decreased psychosocial adjustment of preterm children include persistent alterations of the HPAA, which may be caused by painful treatment procedures, separation from parents, and treatment with artificial glucocorticoids during the perinatal phase (Karemaker et al., 2008; Kaseva et al., 2014; Lemola, in press). A large body of evidence shows that alterations in the HPAA in childhood and adolescence are related to psychosocial impairments. Generally, a hypoactive HPAA is associated with more behavioral problems, while a hyperactive HPAA is associated with more emotional problems (Hartman et al., 2013). Research on the HPAA in preterm children is scarce, but two studies lend support to the notion that preterm children show an altered HPAA. One study with 18 preterm children aged 8-14 found a trend towards a decreased cortisol response to psychosocial stress, but an increase of morning cortisol secretion (Buske-Kirschbaum et al., 2007). Similarly, Kaseva et al. (2014) found a blunted cortisol response to psychosocial stress in young adults born preterm with very low birth weight.

Taken together, there is evidence that very preterm children are at higher risk for psychosocial impairments, poor sleep and an altered HPAA. However, there are important gaps in research. First, studies examining objectively assessed sleep using PSG in very preterm children are missing. Second, studies on the relationship between sleep architecture as assessed with in-home sleep-EEG and psychosocial adjustment are rare. Third, studies on HPAA in very preterm children during middle childhood are rare, too, and missing altogether for associations between HPAA and psychosocial adjustment. Finally and most importantly, to date no study has tested whether alterations in sleep and/or HPAA are possible mediators of the effect of preterm birth on psychosocial adjustment. The main goal of the present study was therefore to shed light on possible underlying mechanism in the association between very preterm birth and psychosocial adjustment by examining the role of sleep and HPAA. The following hypotheses were proposed. First, we hypothesized to find more behavioral and emotional problems, poorer sleep (i.e., shorter sleep duration, lower sleep efficiency, more nocturnal awakenings, more light sleep (stage 1 and/or stage 2 sleep), less SWS, more SDB) and an altered HPAA in very preterm compared to full-term children. Second, we hypothesized that poorer sleep is associated with more behavioral and emotional problems and that HPAA is negatively associated with behavioral problems and positively associated with emotional problems. Third, we hypothesized that less favorable sleep-EEG and/or altered HPAA characteristics in very preterm children account for differences in behavioral and emotional problems between very preterm and full-term children.

### 2. Methods

#### 2.1. Study population

Fifty-eight healthy very preterm children (<32nd gestational week; age: M = 8.2 years, SD = 1.3; range: 6.0-10.9) and 55 full-term children (age: M = 8.3, SD = 1.3; range: 6.3-10.6) were recruited for the present study.

Fig. 1 describes the inclusion procedure of very preterm children, who were recruited from an initial cohort of 217 prematurely born children treated at the University Children's Hospital Basel (Switzerland). Participating preterm children did not differ from non-participants with regard to birth weight (1302 g vs. 1284 g, F(1,216) = .09; P = .76), gestational age (29.7 weeks vs. 29.7 weeks,



Fig. 1. Scope diagram describing the inclusion procedure of very preterm children.

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