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Fetal sleep organization: A biological precursor of self-regulation in childhood and adolescence?

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ABSTRACT

Fetal sleep states emerge during the third trimester of pregnancy and involve multiple interconnected neuronal networks. We examined whether fetal sleep characteristics predict child and adolescent self-regulation in a non-clinical sample (study group, $n = 25$; reference group, $n = 48$). Combined recordings of three sleep variables (fetal heart rate, body movements and rapid eye movements) were made for 2 h at 36–38 weeks' gestation. Fetuses showing synchronous change of sleep variables (i.e. within 3 min) at transition from quiet into active sleep reached a higher level of effortful control, both at 8–9 and 14–15 years, than fetuses not making synchronous transitions and compared with the reference group. Results are discussed from a Developmental Origins of Behavior, Health and Disease (DOBHaD) point of view. It is concluded that studying sleep ontogeny offers the possibility to gain insight into brain maturational processes and/or environmental adaptive processes that may have long term behavioral developmental consequences.

1. Introduction

Research in the laboratory and clinical settings has increased the knowledge of sleep medicine (Cardinali and Pandi-Perumal, 2006). Recent literature also reveals a renewed interest in sleep–wake cycles, their precursors and biological correlates (Saper et al., 2001, 2010). From different angles sleep is a topic of interest for biological psychology, e.g. for studies of the autonomic nervous system (Lehtonen and Martin, 2004), of learning and memory (Milner et al., 2006; Fogel and Smith, 2011), and when considering its developmental origins. Several reviews focus on the ontogeny of sleep in the fetus and the preterm and full term infant, documenting how, due to developmental plasticity, sleep plays a critical role in early brain development, arousal regulation, attention, and cognition (Mirmiran et al., 2003; Peirano et al., 2003; Graven and Browne, 2008; Scher, 2008; Mulder et al., 2011).

According to Scher (2008), the study of sleep ontogeny can document patterns of brain maturation. Physiological maturity or dysmaturity of the fetus and newborn may be the neurophysiologic expression of typical and altered developmental neural plasticity, respectively, and predict later outcome. In one study, sleep measures of both the healthy preterm infant (assessed at term equivalent age) and the healthy full-term newborn were predictive of performance on the Bayley scales of mental development at 12 and 24 months (Scher et al., 1996). In another study, in high-risk premature infants born at gestational ages from 27 to 29 weeks onwards, the degree of sleep state control after birth was associated with postnatal neurodevelopmental status at term equivalent age (Holditch-Davis and Edwards, 1998). These examples indicate that both in the absence and presence of major illness and stress, later behavioral developmental outcome is predicted by fetal and neonatal sleep state measures. These measures of brain maturation may reflect adaptation to conditions of the prenatal environment. The predictive value of these measures for behavioral developmental outcome in later life has remained unexplored due to lacking long-term follow-up studies. Therefore, in our study we examine, in a non-clinical sample, whether differences in sleep state organization in the near term fetus, may account for differences in child and adolescent self-regulation.

This study is relevant in the light of the developmental origins of health and disease (DOHaD) concept (Barker, 1998; Gluckman and Hanson, 2004; Seckl and Holmes, 2007), and the concept of

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developmental origins of behavior, health and disease (DOBHaD) in particular. The latter explicitly integrates brain–behavior relationships. The processes studied encompass variations in both typical and atypical developmental and maturational patterns (Raikkönen et al., 2011; Van den Bergh, 2011a,b,c), which are seen as adaptation to the environment resulting from gene-environment interaction (Gottlieb, 1997). They may predict behavioral development, brain–behavior relationships and health or disease expressed later in human life (Scher, 2008; Gluckman et al., 2010; Van den Bergh, 1990, 1992, 2011c).

Fetal behavioral states, also called sleep states, emerge during the third trimester of pregnancy and involve multiple interconnected neuronal networks. Functional (re)organization of sleep cycling likely occurs around 28–30 weeks postmenstrual age (PMA), 36 weeks PMA, and 48 weeks PMA (i.e. 2 months after birth) (Visser et al., 1987; Nijhuis et al., 1999; Scher, 2008). From 36 weeks' gestation onward, the low-risk fetus exhibits two states of sleep and two states of wakefulness. Each state is defined by a specific combination of three state variables: fetal heart rate pattern (HRP A through HRP D), absence or presence of fetal generalized body movements (GM) and absence or presence of rapid eye movements (REM) (Nijhuis et al., 1982; Mulder et al., 1987). Fetuses normally pass through sleep cycles of non-REM (quiet) sleep and REM (active) sleep, which last about 70–90 min (Visser et al., 1992). The time spent in wakefulness is usually less than 10%. Typical fetal sleep states show concordant (uninterrupted) association between the state parameters for prolonged time, and simultaneous (synchronized) change of state parameters ($\leq$3 min) at their beginning and end (transitions). The degree of sleep state stability and the duration of transitions into and out of a particular state are considered measures of neurophysiological development, integrity and maturity (Visser et al., 1992; Mulder et al., 1998).

Theories of self-regulation presume that human beings, from prenatal life or birth onward, display individual differences in behavioral reactivity and regulation that have implications for subsequent development and adaptation (Kopp, 1982, 2003; Calkins and Fox, 2002; Posner and Rothbart, 2000; Gunnar et al., 2009; Pruessner et al., 2010). Reactivity is understood as the arousability of physiological and behavioral systems, while self-regulation refers to neural and behavioral processes which function to modulate this reactivity. Individual differences in reactivity and regulation are thought to be constitutionally based and influenced over time by the continuous interaction between genetic factors, maturation, and experience (Rothbart and Derryberry, 1981; Rothbart and Bates, 1998; Rothbart et al., 2001; Van den Bergh, 2011c). As the child grows older, initial reactive forms of regulation are supplemented by an increasing capacity for volitional or effortful control (Derryberry and Rothbart, 1997). Much of the self-regulation development results from increasing volitional control over attentional processes and enhanced inhibitory control over motor behavior (Calkins and Fox, 2002). Starting in childhood and continuing throughout adolescence, executive functions such as attentional focusing, maintenance and shift of focusing, and inhibitory control become integrated in complex emotional and behavioral regulatory processes. These processes, in turn, are involved in planning and goal setting, responsible decision making, emotional and motivational changes, and interpersonal relationships (Rothbart and Bates, 1998; Nelson et al., 2002).

In sum, presently there is no empirical work on individual differences in typical fetal brain maturation processes, such as expressed in sleep organization, in relation to their long-term consequences for self-regulation. Therefore, the aim of this prospective longitudinal study is to examine which measures of sleep organization in the normal near-term fetus are predictors – and hence precursors – of measures of self-regulation obtained from the same individuals when 8–9 and 14–15 years of age.

2. Materials and methods

2.1. Participants

The present study is part of a long-term prospective project that was approved by the Institutional Review Board of the Katholieke Universiteit Leuven, Belgium. At the beginning of the project, 86 healthy pregnant women were enrolled at 12–22 weeks of gestation (all participants gave their informed consent). They fulfilled the following criteria: singleton pregnancy, nulliparity, clean medical history and low obstetrical risk, Dutch-speaking, Caucasian, 18–30 years old, and no use of medication or drugs. All pregnancies were dated using the last menstrual period and/or an ultrasonographic examination before 14 weeks. Socio-demographic and obstetrical data were collected by interview and medical chart review. Our sample consisted mainly of married women (94%). The course of pregnancy remained unremarkable for all women and hospital delivery between 36 and 41 weeks of gestation was uneventful. All infants were born at term, except for four infants, two in the reference group and two in the study group (see below), who were born between 36.0 and 37.0 weeks' gestation (late preterm infants). All infants were appropriate-for-dates (birth weight above the 10th percentile) and born in good condition (5-min Apgar scores 9 or 10); no postnatal medical complications occurred, including seizures, head trauma or central nervous system infections (Van den Bergh and Marcoen, 2004; Van den Bergh et al., 2005, 2006; Mennes et al., 2006, 2009).

Thirteen out of the 86 initially included mother–fetus pairs were lost to follow-up in the current investigation. Our study group comprised 25 women who participated both in a fetal behavioral observation session at the end of pregnancy and in the follow-up study on their offspring. The reference group consisted of 48 mothers and their children/adolescents who did participate in the follow-up study but not in the fetal observation study. For the follow-up study reported here, the mothers completed a temperament questionnaire when their children were 8–9 years (n = 62) and 14–15 years (n = 65) old (see below).

2.2. Fetal assessment protocol and measures of fetal behavioral state organization

Simultaneous recordings of fetal heart rate (FHR), fetal generalized body movements (GM), and fetal rapid eye movements (REM) were made for 2 h continuously at 36–38 weeks' gestation. The fetal recordings were performed with the mother resting in a semi-recumbent position in a quiet room at University Hospital Gasthuisberg in Leuven, Belgium. Recording took place between 2 and 6 pm, starting at least 1.5 h after lunch to control for potential diurnal influences and effects of maternal food intake (Mulder et al., 2010).

FHR was monitored with a cardiotocograph by means of Doppler ultrasound and recorded at a paper speed of 3 cm/min (Hewlett Packard 8040A, Böblingen, Germany).

The FHR tracings were judged visually and divided into episodes of heart rate pattern (HRP) A, B, C or D (see below) by an independent experienced researcher as previously described (Nijhuis et al., 1982; Mulder et al., 1987).

Fetal generalized body and eye movements were identified by two observers each using a linear-array real-time ultrasound scanner. The images of both devices were videotaped and the tapes were marked at the beginning and end of recording for synchronization with each other and with the FHR tracing. The presence of GM and REM was marked on-line with hand-held pushbuttons by the observer who held the first and second transducer, respectively. Fetal REM were recorded as event, but for each GM the button was pressed as long as the movement was observed. GM were defined as all fetal trunk movements, including startles. After synchronization, all information on occurrence and duration of fetal movements and HRPs was stored in a personal computer for off-line analysis (Van den Bergh, 1989).

The presence of each of four distinct behavioral states (S1F-S4F) was identified according to predefined criteria using a well-established procedure (Nijhuis et al., 1982; Mulder et al., 2011). The temporal association between HRP, GM, and REM was determined from presence-absence profiles drawn up for each state variable separately using the 3-min moving window technique (Nijhuis et al., 1982; Mulder et al., 1987). Episodes of state 1F (S1F; quiet or non-REM sleep) are defined by a stable heart rate with a small oscillation bandwidth (HRP A) and absence of general and eye movements. During state 2F (S2F; active or REM sleep), general and eye movements are present and heart rate has a wide oscillation bandwidth between the frequent accelerations (HRP B). During state 3F (S3F; quiet awake), general movements are absent and eye movements present; the heart rate pattern is stable and without accelerations (HRP C). Characteristic for state 4F (S4F) episodes (active awake) are frequent vigorous general movements in the presence of eye movements, and an unstable heart rate pattern with large accelerations (HRP D).

An episode for which none of the specified combinations was applicable was classified as 'no-state identified' (NoS) when bounded at either side by the same state, or as transition when bounded by two different states. The incidences of states 1F-4F and NoS were expressed as percentage of recording time. For each recording, the number and duration of all state transitions were determined. For the transitions from state 1F into state 2F and vice versa, distinction was made between synchronized transitions, defined by duration of $\leq$3 min, and non-synchronized transitions (duration > 3 min). The duration of transitions from state 1F into state 2F and vice versa were analysed separately, because it cannot be assumed that transitions in either direction express the same degree of functional integrity and maturity of the