The vital importance of SLEEP-FEED cycling in neurodevelopment.

Dr Nils Bergman
Cape Town, South Africa

www.skintoskincontact.com

The vital importance of SLEEP-FEED cycling in neurodevelopment.

"Neurons that fire together wire together while those which don't, won't"  
Hebb/Carla Shatz

"SENSORY STIMULUS

synapse store chemical signal

chemical signal stronger

THRESHOLD \rightarrow EXEMPT from elimination (synapse stabilised)

PATHWAY

(Rima Shore 1997)
fetal REM sleep (or active sleep) seems to be particularly important to the developing organism...

...spontaneous synchronous firing

Marks et al. 1995

"Neurons that fire together wire together while those which don't, won't."
Hebb/Carla Shatz

Peirano 2003

RELATIVE BRAIN ACTIVITY

RELATIVE BRAIN ACTIVITY

NEW SYNAPSE FORMATION

METABOLIC ACTIVITY

peaks 3 years

0 10 20 30 40w Birth 1y 3y 13y Puberty 50y 80y

MAXIMAL OCCURRENCE

MAXIMAL OCCURRENCE

Synapses

Dendrification: peak 2m & 6m

Peirano 2003

Panksepp 1998
Siegel 2005

Non-REM #
Sleep cycle ~ 50 – 60 minutes

ACQUISITION

REM
NR1
NR2
NR3
SWS

ACQUISITION
poly-sensory input
short-term memory
stored cortex
Awake and REM

Neocortex
consciousness
short term memory

CONSOLIDATION

REM
NR1
NR2
NR3
SWS

CONSOLIDATION
over stores information
"SNR" strong signals
amygdala / hippocampus
REM stage 4

Neocortex
consciousness
short term memory

GPS

HIPPOCAMPUS
Memory Function and spatial code

Amygdala
Emotional Processing Unit

Amodio 2006

Stanley Graven 2006
"Neurons that fire together wire together while those which don’t won’t."
Hebb/Carla Shatz
In adult: sleep cycles are blocked; hormones swing

SWS makes fact and episode (declarative) memory
REM sleep makes emotional memory
Also skills
CORTISOL protects from negative embedding in REM

Memory consolidation during sleep: Interactive effects of sleep stages and HPA regulation

Joseph 2014
Getting rhythm: how do babies do it?

Infant: sleep cycles begin to block on diurnal rhythms
START at 3 months
Can be “adult-like” at 6 months.
Infant sleep cycling and synchronicity with maternal sleep ensure development.

Infant sleep cycling → critical for brain development,
BUT is also determined by brain requirements:
TEMPERAMENT
PERSONALITY
OREXIN METABOLISM
“MORE SLEEP → MORE WIRING”

In ADULT: sleep blocking (two phases)
In child: will appear on its own → 3 - 12 m
ONE SIZE DOES NOT FIT ALL:

Equally *normal* at 6 months to sleep 2 hours as 6 hours

In child: will appear on its own → 3 – 12 m

Orexin activates brain, motivation, but accumulates "sleep pressure", and a flip-flop switch controls the diurnal circadian rhythm.

Separated d4 – d14 (3h morning, 3h afternoon) → examined as adults

Orexin increased

HYPERAROUSAL/INSOMNIA
CRH increased → increase CORTISOL → disrupted circadian rhythm.

REM NR1 NR2 NR3 SWS

ACQUISITION
poly-sensory input
short-term memory
stored memory

CONsolidation:
transfer information
SNR: strong signals
hypo-cerebellum
NREM stage 4

MEMORY FORMATION
7 waves: returns into brain context
organized REM

SMELL

sleep cycling regulated by MOTHER’S SMELL!!

SMELL → BRAIN WIRING

Fig. 4: Schematic representation of the interaction between sensory receptors and CNS functions within the framework of the sleep-wake cycle. Nutrients with proven effects on sensory receptors and cortical processing are included (PUPA, polysynaptic interneurons, Zn, etc; PIE, precortex).

Peirano 2003
**SMELL**

*modulates state organisation*  
elicits emotional behaviours  
activates pre-feeding actions  
anticipatory digestive physiology  
regulates pace of ingestive behaviour

*Schaal 2004*

---

**DOUCET**

The secretion of Areolar (Montgomery’s) Glands from Lactating Women Elicits Selective, Unconditional Responses in Neonates

“...breast chemosignals activate oral activity on the nipple that releases a cascade of behavioral, neural, neuroendocrine and endocrine processes in the newborn and the mother.”

*Doucet 2009*

---

The secretion of Areolar (Montgomery’s) Glands

“In early ontogeny the sleeping brain may thus remain sentient of an organism’s odor environment.”

*Doucet 2009*

---

Fewer AG → delayed grasp
Fewer AG →
Slower latch
Fewer AG →
Weaker suck
Fewer AG →
More weight loss day 3 of life
Fewer AG →
Delayed onset of lactation

In the “scentless breast”
condition, all infants were exposed to the mother’s breast
fully covered with a perfectly
transparent and airtight plastic
film (polypropylene). (the habitual visual scene of the breast devoid of corresponding odors )

(1) “Breast” group (fully uncovered mother’s breast);
(2) “Nipple” group (all remaining parts covered with plastic film);
(3) “Areola” group (remainder of the breast and nipple covered);
(4) “Milk” group (milk smeared on plastic covered breast).

Related experiments indicate, however, that the chemical cues that attract rat pups to the nipples are not produced in that region. Rather, initial nipple orientation is elicited by the odor of amniotic fluid and saliva that the mother spreads on her ventrum while grooming herself during parturition [7].

Premies fed through non-oral pathways LACK
sucking-breathing-swallowing coordination
integration of chemosensation-food intake
cephalic phase of digestive processes; → therefore display:
“poorer and more unstable sucking performance than their orally fed peers”
**Brain Wiring to Smell**

- REM
- NR1
- NR2
- NR3
- SWS

**Acquisition**
- multisensory input
- transfer information

**Consolidation**
- short-term memory
- stored cortex

**Memory Formation**
- “SNR” strong signals
- amygdala / hippocampus

**Transfer Information**
- to neocortex

**P Waves**

Stanley Graven 2006

Awake and REM

NREM stage 4

REM

**Neural Protection**

1. Messages are collected in cortex
2. In SWS sleep, moved to emotional brain (amygdala)
3. In REM sleep, fire to front of brain (approach/avoid)
4. End of sleep cycle - circuit completed

**Skin-to-Skin Can Improve the Integrity of Sleep**

**Neural Protection**

- Neural circuits that process basic information are wired earlier than those that process more complex information.
- Higher circuits build on lower circuits, and skill development at higher levels is more difficult if lower level circuits are not wired properly.

Slide by: Jack P. Shonkoff, M.D.

**Brain Architecture and Skills are Built in a Hierarchical “Bottom-Up” Sequence**

1995 as a strategy of neuroprotection. SSC appears to accelerate EEG-sleep state organization and maturation as a non-pharmacologic neuroprotective intervention when compared with two non-SSC cohorts. The prolonged benefits of these non-pharmacologic interventions are maintained over time. However, the specific mechanisms underlying these benefits remain unclear.

Slide by: Jack P. Shonkoff, M.D.
Rich-club organization of the newborn human brain

Combining diffusion magnetic resonance imaging and network analysis in the adult human brain has identified a set of highly connected cortical hubs that form a “rich club”—a high-capacity, high-activity backbone thought to enable efficient network communication. Rich club architecture appears to be a persistent feature of the mature mammalian brain, but it is not known when this structure emerges. In the human brain, this connectivity structure is already evident at birth. This rich club organization of the newborn brain is, therefore, a new domain for research and potentially a new diagnostic tool for clinicians. These results provide new insights into the development of the brain and its relationship with behavior and function.

Stigler 2011 Structural and functional magnetic resonance imaging of autism spectrum disorders

Assaf 2010 Abnormal functional connectivity of default mode sub-networks in autism spectrum disorder patients

Tractography

From National Geographic Magazine April 2014

The human connectome is the result of an elaborate development.
BRAIN WIRING

PATHWAYS → CIRCUITS → NETWORKS

CONNECTOME

networks make the "lights go on"

Reflections for practice

Smell and skin-to-skin

Sleep organization should guide care

CIRCADIAN RHYTHM

SCN
Suprachiasmatic nucleus,
Pineal gland, melatonin

Quality sleep cycling makes new circuits

Neurodevelopment and ALL memory is based in space/place!
CIRCADIAN RHYTHM

Master clock, sets other clocks ‘zeitgeber’

Human clock genes.

Rhythmic variations in physiological and behavioural processes are mediated by both endogenous and exogenous factors. Endogenous factors include self-sustaining biological pacemakers or clocks which in the absence of strong external influences ... Piggins HD 2002. Ann Med. 34(5):394-400.

CIRCADIAN RHYTHM

Master clock, sets other clocks ‘zeitgeber’

CIRCADIAN RHYTHM

ABSENT IN NEONATES


Ultradian and circadian rhythms

Ultradian: Repeated during (single circadian) 24 hour period

Hypothalamic local clocks communicate and coordinate

Pleasurable feeding - and sleeping -

The 'zeitgeber' is not light, it is feeding.

Note rhythmicity of fetal stomach → 40–50 minutes

Hunger & Satiety rhythms regulate all metabolic processes

Sleep & Awake rhythms regulate all neurological processes
The emergence of adrenocortical circadian function in newborns and infants and its relationship to sleep, feeding and maternal adrenocortical activity

Gottfried Spangler

Sleeping, feeding and maternal-infant interaction rhythms are established much earlier.

External Cues and Clock Outputs

The predominant external cue (zeitgeber) of the SCN clock is light. Clocks in peripheral tissues such as the liver also can be entrained by food.

Outputs of both the SCN and peripheral clocks impact behavioral and metabolic responses such as eating, sleep, circadian rhythms.

http://www.cell.com/fulltext/S0092-8674(08)01067-2
Central Pacemaker and Peripheral Clocks

The master pacemaker encoding the mammalian clock resides within the SCN, although clock genes are also expressed in other regions of the brain and in most peripheral tissue. Emerging evidence suggests that peripheral tissue clocks are synchronized through humoral, nutrient, and autonomic wiring and that the cell-autonomous function of the clock is important in pathways involved in fuel storage and consumption.

Joseph 2014

Getting rhythm: how do babies do it?

CORTISOL day-night rhythm
MELATONIN H3f3b gene detected
TEMPERATURE day-night rhythm

Birth ~ /~ 8w 9w 10w 11w
dates averaged “between 6 and 18 weeks”

BRAIN WIRING

REM NR1 NR2 NR3 SWS
ACQUISITION
CONSOLIDATION
MEMORY FORMATION

SLEEP CYCLE IS ONE HOUR

Stanley Graven 2006

Sleeping, feeding and maternal-infant interaction rhythms are established much earlier.

Gottfried Spangler

The emergence of adrenocortical circadian function in newborns and infants and its relationship to sleep, feeding and maternal adrenocortical activity
Sleeping, feeding and maternal-infant interaction rhythms are established much earlier.

**CIRCADIAN CORTISOL**

<table>
<thead>
<tr>
<th>Newborn</th>
<th>5 months</th>
<th>7 months</th>
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</thead>
<tbody>
<tr>
<td>none</td>
<td>some</td>
<td>most</td>
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</table>

Infant: sleep cycles begin to block on diurnal rhythms

Mother-infant synchrony

... at 12 weeks (circadian)

START at 3 months

Can be “adult-like” at 6 months.

In child: will appear on its own 3–12 m

Equally *normal* at 6 months to sleep 2 hours as 6 hours

ONE SIZE DOES NOT FIT ALL:

Pleasurable feeding – and sleeping – a physiological rhythm for premature infants.

one hour sleep-wake cycles

feed cycles

EVIDENCE FOR FEEDING FREQUENCY???

Edmond 2006
Cup feeding versus bottle feeding: Cup feeding higher breastfeeding greater stability

No RCT’s …

Because no one did the study.

No RCT’s …

Insufficient evidence

Assumption: 3kg baby, requiring 160 ml/kg/day daily requirement = 480ml

Standard CARE: 3-hourly schedule

KEY QUESTION:
WHAT IS THE STOMACH VOLUME OF THE NEONATE ??
**EVIDENCE:** (NBn 111009)

<table>
<thead>
<tr>
<th>Author</th>
<th>Capacity</th>
<th>Note:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sase</td>
<td>10-15 ml</td>
<td>Live, term fetus</td>
</tr>
<tr>
<td>Goldstein</td>
<td>10-15 ml</td>
<td>Live, term fetus</td>
</tr>
<tr>
<td>Widstrom</td>
<td>10 mls</td>
<td>Live, newborn</td>
</tr>
<tr>
<td>Zangen</td>
<td>20 mls</td>
<td>Live, (pressure)</td>
</tr>
<tr>
<td>Naveed</td>
<td>20 mls</td>
<td>Autopsy (SB)</td>
</tr>
<tr>
<td></td>
<td>20 mls</td>
<td>Autopsy (ENND)</td>
</tr>
<tr>
<td>Kernessuk</td>
<td>15 mls</td>
<td>Autopsy (in situ)</td>
</tr>
<tr>
<td>Scammon</td>
<td>30-35 ml</td>
<td>Autopsy (water</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pressure)</td>
</tr>
</tbody>
</table>

**PROPOSAL:**

The **CAPACITY** of a week old baby’s stomach is approx **20 ml**.

**WHAT IS THE STOMACH VOLUME OF THE PREMATURE ??**

**Assume low resilience**

**Assume proportionality**

Figure 3. Mean ± 2 SD of the longitudinal (open circles), the transverse (solid circles), and the anteroposterior (open squares) diameters of the stomach against the gestational age, demonstrating linear relationships.

**The CAPACITY of a low birthweight prem from 20ml / 3000g**

\[ = 0.007 \times BWt \text{ (g)} \]

1kg x 0.007 = 7mls

2kg x 0.007 = 14mls

**PROPOSAL:**

The **CAPACITY** of a neonate’s stomach is approx **20 ml**.

(7ml /kg)
Assumption: 3kg baby, requiring 160 ml/kg/day
daily requirement = 480ml

MOTHER
NATURE:
1 hourly schedule

A single MER (milk ejection reflex) is 20 ml
Regardless of breast size, mammary gland tissue fairly constant

Chymosin makes the milk into "cheese" halfway between liquid and solid stomach empties in 60 minutes...

Chymosin makes the milk into "cheese" halfway between liquid and solid stomach empties in 60 minutes...

METABOLIC ADAPTATION

SSC started in the first 20 minutes after birth

Blood glucose (1 hr) 3.17 2.56
Base excess drop 3.4 1.8
(Christenson 1992)

Blood sugar may fall ...
after 90 minutes

"There is a reason behind everything in nature" Aristotle

Would nature allow this?
MAMMALIAN FEEDING FREQUENCY AND MILK PROTEIN FAT CONTENT

CACHE - e.g. deer
- high 16 g/l
- Time interval between feeds 12 hours

NEST - e.g. cat
- high 8 g/l
- Time interval between feeds 4 hours

FOLLOW - e.g. zebra
- high 4 g/l
- Time interval between feeds 1-2 hours

CARRY - e.g. baboon
- high 2 g/l
- Time interval between feeds 1 hour

FOLLOW - e.g. goat
- high 2 g/l
- Time interval between feeds 1 hour

HUMAN
- High 1 g/l
- Time interval between feeds 12 hours
**ALLOSTASIS**

ANY STRESS: Psychological, Neurological, Endocrine, Immune

- STRESS → RESPONSE
- \( \downarrow \text{RESISTANCE} / \text{SENSITIVITY} \) → ALLOSTATIC \( \downarrow \) ALLOSTATIC LOAD → ALLOSTATIC OVERLOAD

- HEALTH \( \rightarrow \) VULNERABILITY
- WELL-BEING \( \rightarrow \) SUSCEPTIBILITY \( \rightarrow \) MORBIDITY \( \rightarrow \) MORTALITY

**RESILIENCE:** capacity to maintain healthy emotional functioning in the aftermath of stressful experiences

**ALLOSTASIS & ALLOSTATIC LOAD**

-elevated activity - sustained over time, or severe → changes the "set points" for homeostasis (e.g., increasing blood pressure, change in cholesterol level)

-elevated activity of mediators, with return to baseline and no impact on health.
ALLOSTASIS

ANY STRESS: Psychological
Neurological
Endocrine
Immune

STRESS → RESPONSE
+ RESISTANCE / SENSITIVITY +/−
ALLOSTATIC STATE
ALLOSTATIC LOAD
ALLOSTATIC OVERLOAD

PERCEPTIONS
“NEUROCEPTION”

RESISTANCE / SENSITIVITY

PERCEPTIONS

THE POINT AT WHICH CHRONIC LOAD RESULTS IN ACTUAL DISEASE OR ABNORMAL CONDITIONS.

2ND KNOCK

RESILIENCE
“capacity to maintain healthy emotional functioning in the aftermath of stressful experiences”

RESILIENCE: WELL-BEING → SUSCEPTIBILITY → MORBIDITY → MORTALITY

WELL-BEING

SUSCEPTIBILITY

MORBIDITY

MORTALITY

HEALTH

DISEASE

BARKER ‘thrifty phenotype’

“Fetal programming hypothesis”

Developmental Origins of Health and Disease
DOHaD

Epigenetic processes operate in the human fetus, and beyond.

DOHAD

Developmental Origins of Health and Adult Disease

FIG. 6. The epigenotype model of developmental origins of disease. Environmental factors acting in early life have consequences that become manifest as an altered disease risk in later life. The period of life in which external factors can influence biology extends from...
Weight gain 1st week: predicts OBESITY at 30 years

Importance → Programming - early life chronic disease

Stomach anatomy and physiology
Large volume feeds stretched stomach: doubled absorptive capacity as adult

Stomach anatomy and physiology

AMYLIN peptide

Kairamkonda 2008
In VLBW infants, continuous feeding seems to be better than intermittent feeding with regard to gastrointestinal tolerance and growth.

(J Pediatr 2005;147:43-9)

"Feed intolerance" ... ... or VOLUME intolerance?

2 - 3 hourly feeds are not physiological ... ... not pleasurable

In VLBW infants, continuous feeding seems to be better than intermittent feeding with regard to gastrointestinal tolerance and growth.

(J Pediatr 2005;147:43-9)

no rhythmicity ... how physiological is this???
how physiological is this???

http://slideplayer.com/slide/11085241/

Continuous enteral feeding impairs gallbladder emptying in infants
Giora-Jacubovitch, FRCS, Nigel J. Shaw, MRCP, and Agostino Piro, FRCS

... it can be inferred that the continuous feeding modality, enteral or parenteral, may play a role in inducing stasis in the extrahepatic biliary tree.

“Ontogeny of gastric emptying patterns in the human fetus”

Sase 2005

Note rhythmicity of fetal stomach
12 - 15 ml volumes at term.

Pleasurable feeding - and sleeping - a physiological rhythm for premature infants.

Sleep cycling \( \rightarrow \) 50 - 70 minutes

"JAKOB"

Feeding time (EBM) - pacifier provided
Mother does the feeding

1006h Feeding starts
17ml \( \sim \) 2 hrly feed
Gastric overfilling syndrome?

**Excessive volumes**
- reflux, aspiration, colic

**Excessive time interval**
- hypoglycaemia

**Adaptations**
- diabetic diathesis, obesity

Proposed Management →
Consolidation of dyadic lifestyle leads to emotional and social competence.

WHAT IT MEANS TO FEED AN INFANT IN THE NICU:
What is successful feeding?

WHAT IT MEANS TO FEED AN INFANT IN THE NICU:
What is successful feeding?

WHAT IT MEANS TO FEED AN INFANT IN THE NICU:
What is successful feeding?

WHAT IT MEANS TO FEED AN INFANT IN THE NICU:
What is successful feeding?

“Small and frequent feeds, according to the sleep cycle”
WHAT IT MEANS TO FEED AN INFANT IN THE NICU:
What is successful feeding?

"Dynamic systems theory approach" Big picture

SUMMARY!!

SKIN-TO-SKIN (Regulation)

FEEDING (Stomach)

SLEEP (Brain)

LOVE! ("mind")

Psalm 22 v 9
“I learnt trust on my mother’s breasts”

Neural circuitry of bonding

Psalm 22 v 9
“I learnt trust on my mother’s breasts”

"trust" (baṭaḥ) to hie for refuge; figuratively to trust, be bold (confident, secure, sure), (make to hope, make to trust.)

"breast" (shād) the breast of a woman or animal (as bulging) - breast, pap, teat.

Psalm 22 v 9
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In humans, oxytocin increases gaze to the eye region of human faces and enhances interpersonal trust and the ability to infer the emotions of others from facial cues.