

How the early-life environment affects the development of our stress system

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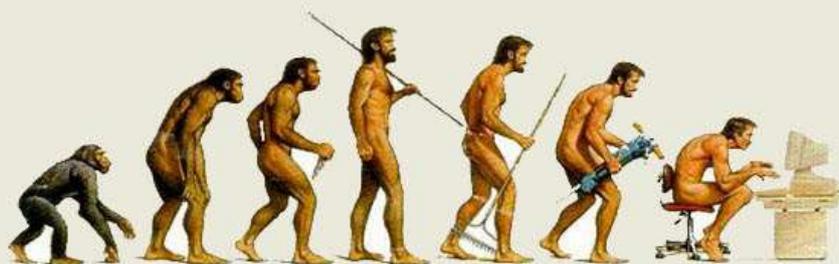
Stress Research Program

The vision is to generate evidenced based knowledge about stress in children and their families in order to reduce children's stress levels and stress related consequences

- Aim: To reduce acute stress, fear and pain during hospital visits and medical procedures
- Aim: To reduce long-term stress related to disability, disease, hospital stay, and special needs
- Aim: To prevent stress through early interventions

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Stress is not something new, but...



...our challenges are new

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Stress is not dangerous



Edvard Munch

It's necessary for survival...

4

...and sometimes a very good friend

*“If you think you aren’t in a hurry, when you are,
then you will walk slowly.
But if you know you are in a hurry and get stressed,
it’s much better because then you run”*

- Holding a public speak
- Performance, competition
- Reduce inflammation
- Lung maturation
- Stabilizes blood pressure and homeostasis

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Long-term stress is the foe

Stress related consequences:

- Sleep problems
- Cognitive problems; difficult to focus, concentrate, remember, and learn new things
- Behavioral problems; aggression, irrational behavior
- Gastro-intestinal problems
- Affected immunology
- Cardiovascular diseases
- Metabolic syndrome
 - Diabetes type 2
 - Obesity
 - High blood pressure

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- Insecure attachment and longstanding stress in the family are two major reasons for poor mental health during childhood.
- Children learn from parents/carers how to express feelings and emotions and how to handle and cope with stressful situations.
- Attachment as well as the stress system develop during early childhood in relation to the environment

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The stress system starts to develop before birth



- Yearly 15 mil babies in the world are born preterm (<37 weeks).
- 8.6% of babies born in Australia.

WHO 2012, 2018, AIHW 2016

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The life starts in a stressful environment



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Painful and stressful procedures

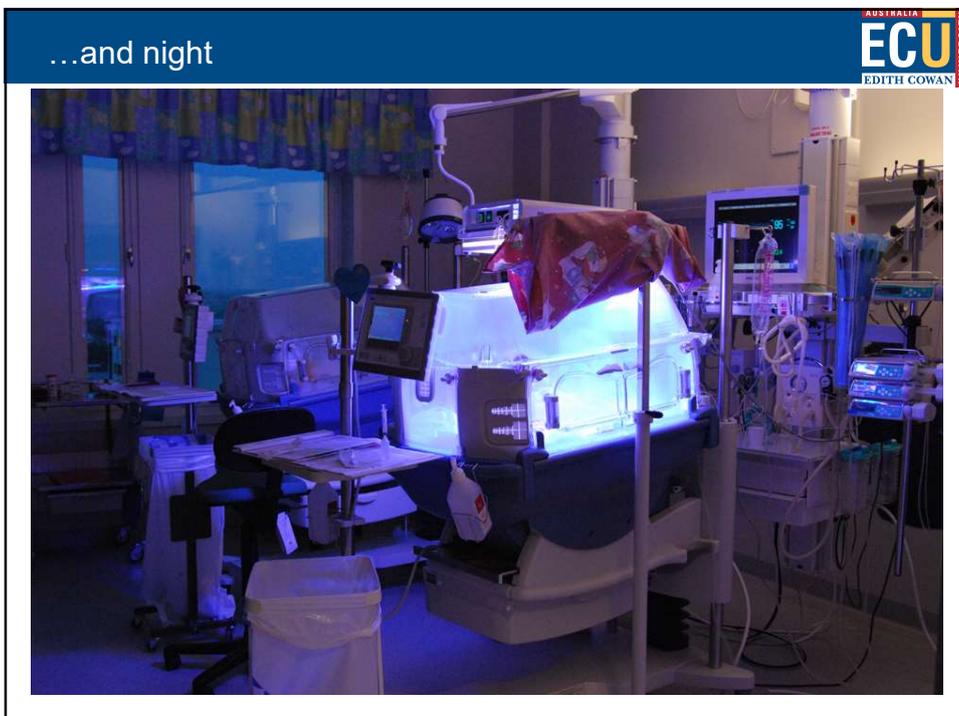
- Exposed to 7-17 invasive and potentially painful procedures a day
- 20% never receive any kind of pain relief
- On top of this, non-invasive procedures such as nappy changes; feeding; repositioning; weighing...

Carbajal et al 2015, Cruz et al 2016

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The staff take care of the babies



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... and the babies might be without support



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Premature infants in the NICU

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graph LR; A[Infants born preterm] --> B[Stressors: Intensive care Separation]; B --> C[Outcomes: Increased risk of cognitive and behavioural problems];
```

(van Baar et al Pediatrics 2009, de Jong et al Semin Fetal Neonatal Med 2012, Serenius et al JAMA 2013, Månsson & Stjernqvist Acta Paed 2014, de Jong et al Arch Dis Child 2015)

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“Man cannot live by milk alone”

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Frida Kahlo

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Present but emotionally unavailable



- Tired
- Self-absorbed
- Distressed
- Depressed

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Present but emotionally unavailable



Mothers of preterm infants

- Experience high stress and anxiety
- Have more posttraumatic stress symptoms and increased risk of posttraumatic stress disorder (PTSD)
- Higher risk of postpartum depression
- Higher risk of unsuccessful bonding

(Roque et al *JOGNN* 2017, de Paula Eduardo et al *J Affect Dis* 2019)

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Parent–infant interaction

- Ainsworth’s sensitivity scale
- Maternal Sensitivity and Responsivity Scales-R
- Emotional Availability



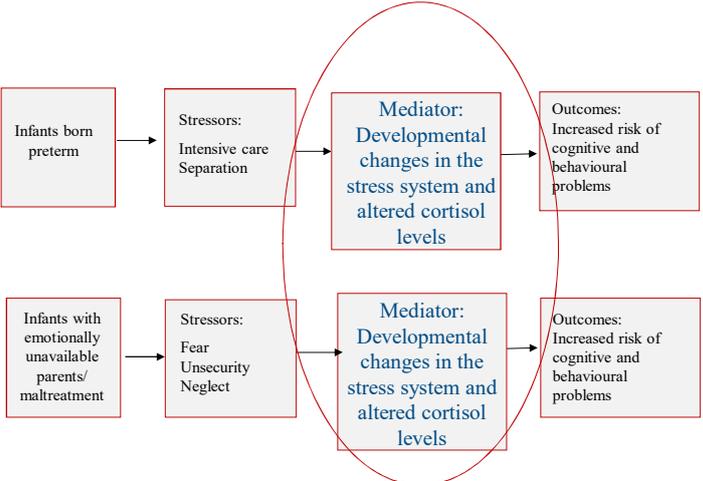

Still face procedure by Edward Tronick

Ainsworth et al 1974, Cenciotti et al. 2004, Biringen et al., 1998; Biringen, 2008.

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What do these infants have in common?



```

graph LR
    A[Infants born preterm] --> B[Stressors: Intensive care Separation]
    B --> C[Mediator: Developmental changes in the stress system and altered cortisol levels]
    C --> D[Outcomes: Increased risk of cognitive and behavioural problems]
    
    E[Infants with emotionally unavailable parents/maltreatment] --> F[Stressors: Fear Unsecurity Neglect]
    F --> G[Mediator: Developmental changes in the stress system and altered cortisol levels]
    G --> H[Outcomes: Increased risk of cognitive and behavioural problems]
    
    C --- I(( ))
    G --- I
    I --- J(( ))
    D --- J
    H --- J
            
```

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The concept of stress

1. Stressor – the challenge
2. Stress reaction
3. Stress response

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1. Stressors in childhood (not ranked)

- Being abandoned, being left alone
- Physical and psychological abuse, neglect
- Pain
- Socio-economic problems within the family

- Fear
- Bullying
- Loosing control
- Too high demands (from self or others)
- To be assessed
- Time (school, home work, family, friends, social networks, leisure activities)

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2. Stress reaction

- Fight
- Flight
- Freeze
- Tend and befriend
- Play dead



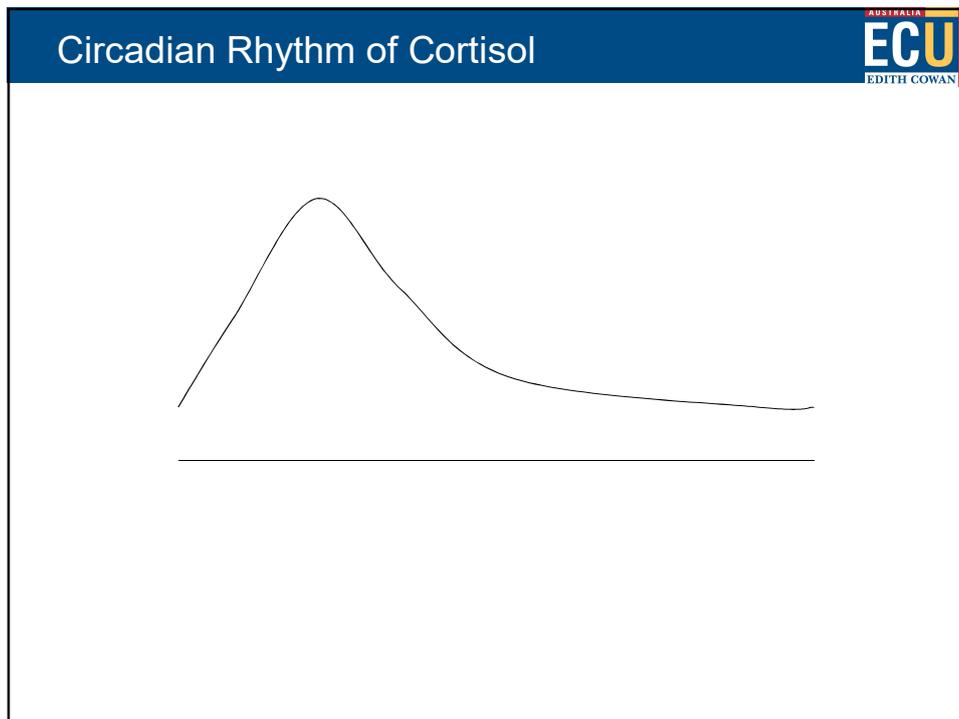
Pablo Picasso

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3. The stress response

- Increased heart rate
- Increased blood pressure
- Fast, shallow respiration
- Energy mobilization; rapid energy release of glucose and fatty acids
- Redirected blood circulation
- Affected blood coagulation
- Release of stress hormones: adrenaline, noradrenaline and cortisol

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Cortisol circadian rhythm development

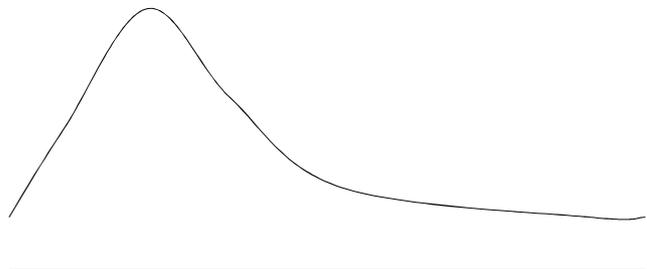
- >14,000 saliva samples
- Full-term healthy infants: 1 month post birth.
- Infants born preterm: 1 month corrected age if cared for in Family-Centred Care units.
- Infants in psychosocial high-risk families: 1-2 months albeit with higher variability than healthy full-term infants during the first year

Ivars et al 2015, 2016, Mörelius et al 2017

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Cortisol can be calculated

- Cortisol reactivity
- Co-regulation between parent and infant
- Morning/evening quotient
- Cortisol Awakening Response, CAR



The graph illustrates the Cortisol Awakening Response (CAR). It shows a single curve that begins at a low level on the left, rises to a peak, and then gradually declines back towards the baseline on the right. The x-axis represents time, and the y-axis represents cortisol levels.

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Saliva sampling from preterm baby



The photograph shows a close-up of a preterm baby's face. A hand is holding a small, white, stick-like swab near the baby's mouth, demonstrating the process of saliva sampling. The baby is lying in a hospital bed, and the background is slightly blurred.

Mörelus et al 2004, 2006

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Cortisol affects the whole body

Ögon: pupillerna vidgas
 Saliv: salivutsöndringen minskar
 Hjärta: hjärtat slår fortare och kraftigare
 Magen: blodgenomströmningen minskar och matsmältningen går långsammare
 Blodkärl: blodtrycket höjs, blodgenomströmningen i hjärna, hjärta och muskler ökar
 Lungorna: andningen blir snäll och ylig
 Muskler: musklerna blir spända
 Tarmarna: temperaturregleringen blir långsam
 Hud: blodkärlen dras samman, man svettas

FIGUR 2.1 Vid stress påverkas alla organsystem i kroppen.
 Illustration: Jeanette Engqvist.

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High levels of cortisol is toxic for the brain

Decrease

- Learning
- Memory
- Concentration
- Planning
- Decision making

Increase

- Anxiety
- Aggression

prefrontal cortex

amygdala

hippocampus

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Cortisol hinders neurons to connect and communicate and cause atrophy of neurons

Labels in diagram: Nervcell, Nervimpuls, Kapsel med signalsubstans, Synaps, Receptorer, Cellen reagerar, Nervcell.

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High stress during a period of rapid brain development affect apoptosis

Fig. 3. Neurons which fire together wire together, neurons which don't won't (35). (Figure by S Söderlind.)

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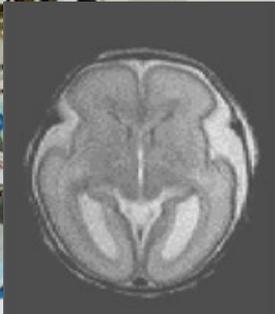
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High stress during a period of rapid brain development is not an optimal combination

Week 40



Week 25

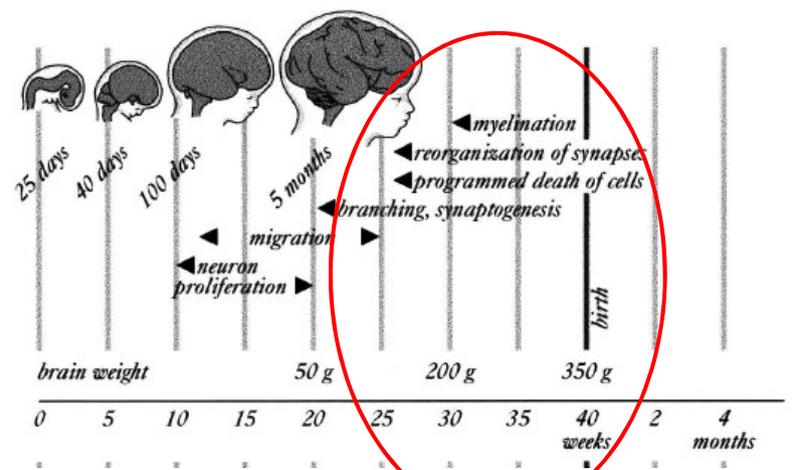


Neonatal Research Group
Hammersmith Hospital, London

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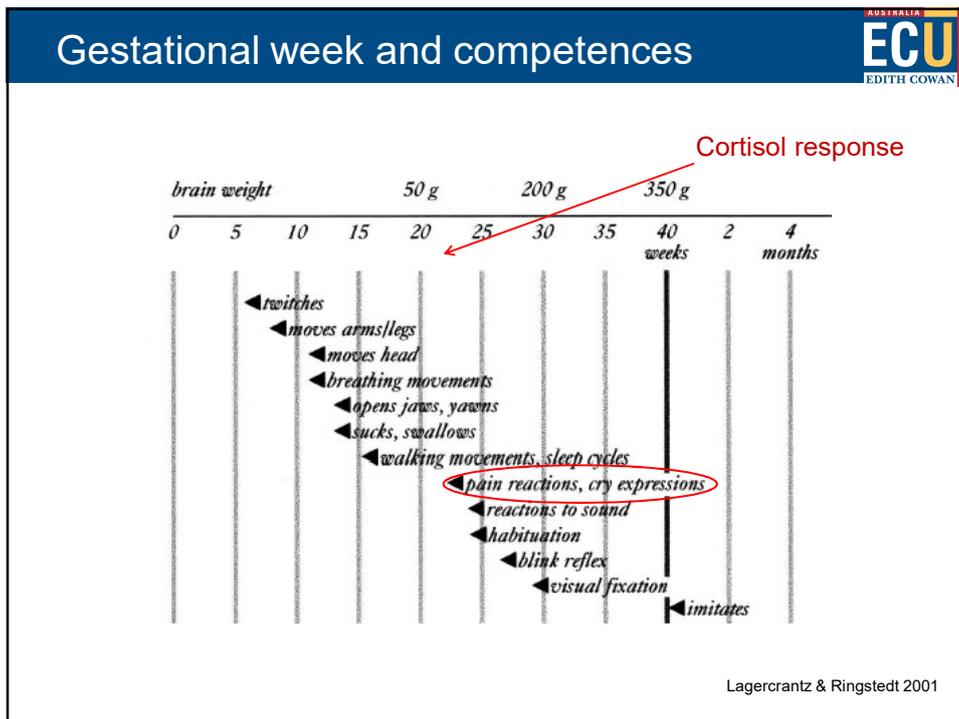
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Gestational week and brain development



Lagercrantz & Ringstedt 2001

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What do we know about cortisol in infants?

Saliva cortisol reference values for full-term infants age 0-12 months

Age	Morning values: 07:30-09:30				Noon values: 10:00-12:00				Evening values: 19:30-21:30			
	Median	Q1-Q3	Mean	SD	Median	Q1-Q3	Mean	SD	Median	Q1-Q3	Mean	SD
0	5.1	2.8-8.2	10.2	21.0	5.0	3.7-8.6	8.5	11.8	3.4	2.1-5.7	7.5	15.3
1	5.8	3.7-9.8	8.3	8.3	4.8	2.8-6.8	6.6	7.5	2.8	1.9-4.8	5.1	6.9
2	6.1	3.9-9.8	8.0	7.4	5.2	3.4-7.3	6.3	5.8	2.7	1.7-4.9	4.4	5.9
3	7.5	4.2-11.9	13.8	38.0	5.9	4.1-8.5	9.1	17.1	3.3	1.9-5.9	9.2	22.5
4	8.0	5.7-13.5	12.6	18.2	6.2	3.7-9.0	8.5	15.0	2.5	1.5-4.4	6.8	17.9
5	8.3	5.0-13.8	16.9	35.5	5.9	3.5-8.6	16.6	43.3	3.1	1.3-6.2	12.9	32.0
6	8.9	6.2-14.9	24.6	63.8	5.4	3.9-8.8	20.3	77.1	2.3	1.3-5.0	19.4	81.4
7	7.7	5.0-14.6	26.5	78.9	5.1	3.6-8.1	21.5	71.0	2.3	1.4-4.2	10.9	35.1
8	8.4	5.6-14.2	33.0	95.4	5.9	3.5-10.6	22.9	77.9	2.2	1.4-4.3	20.3	80.6
9	8.9	6.0-14.8	21.9	49.4	5.6	3.6-9.9	19.4	77.6	2.3	1.2-5.2	9.8	28.5
10	10.0	6.1-14.2	21.3	43.6	5.4	3.7-8.9	14.4	34.3	2.4	1.3-5.6	10.7	28.7
11	10.5	6.9-17.1	23.9	60.7	5.3	3.4-9.7	11.9	22.1	2.1	1.2-5.6	13.4	40.6
12	10.9	5.9-14.4	22.9	54.4	5.2	3.1-8.6	14.4	35.4	2.0	1.1-4.2	11.6	33.9

Monthly median (quartile 1-quartile 3) and mean (standard deviation) salivary cortisol levels [nmol/L] at three different sampling times: morning (07:30-09:30), noon (10:00-12:00) and evening (19:30-21:30).

doi:10.1371/journal.pone.0129502.t007

Ivars, Nelson, Theodorsson, Mörelius. *PLoSOne* 2015

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What do we know about cortisol in infants?



Saliva cortisol reference values for preterm infants age -3 -12 months

Age Month	Morning values: 07:30–09:30					Noon values: 10:00–12:00					Evening values: 19:30–21:30				
	Median	Q1-Q3	Min-Max	Mean	SD	Median	Q1-Q3	Min-Max	Mean	SD	Median	Q1-Q3	Min-Max	Mean	SD
-3	10.0	6.2–16.7	2.3–19.7	11.1	6.7	11.3	7.1–14.8	2.0–32.7	12.5	9.6	17.1	5.0–31.5	4.9–56.8	21.5	19.5
-2	7.8	3.4–16.0	1.2–15.2	17.8	27.8	6.0	3.5–13.1	1.3–19.7	14.1	30.3	6.2	4.2–12.2	0.8–77.8	12.1	16.8
-1	4.2	2.9–5.4	1.2–23.7	4.8	3.6	3.8	2.8–5.5	1.0–32.1	5.2	5.4	3.8	2.2–5.5	0.6–28.8	4.6	4.3
0	4.2	2.7–7.1	1.2–17.5	5.4	3.8	4.1	2.6–6.1	1.6–24.3	5.5	4.5	3.6	2.6–5.4	1.0–29.5	5.1	5.1
1	5.0	3.4–7.6	1.6–78.7	7.6	11.0	4.0	3.0–6.5	1.6–34.9	5.8	5.3	2.9	2.2–4.2	1.1–100	5.7	14.3
2	6.9	3.9–10.1	1.3–153 [#]	10.6 [#]	22.1 [#]	4.6	3.2–7.6	1.0–191	10.2	27.7	2.9	1.7–4.8	0.4–352	14.5	53.5
3	8.2	5.3–12.5	1.9–125	13.1	19.3	5.9	3.3–12.0	1.2–178	14.0	28.7	3.8	1.8–7.4	0.7–145	10.0	23.4
4	8.7	5.5–12.3	1.6–126	14.8	24.5	6.9	5.0–8.7	1.4–516	29.0	102	3.5	1.8–5.5	0.6–249	16.7	49.9
5	9.8	5.5–17.6	2.8–651 [#]	37.0 [#]	105 [#]	6.1	4.5–10.5	1.8–747 [#]	36.9 [#]	128 [#]	3.1	2.3–7.6	1.0–225 [#]	15.5 [#]	44.4 [#]
6	9.9	5.6–15.4	3.4–23.9 [#]	10.8 [#]	5.7 [#]	5.1	4.2–6.8	1.6–16.9 [#]	5.7 [#]	2.8 [#]	2.8	1.6–4.1	0.9–405 [#]	12.1 [#]	58.6 [#]
7	9.8	6.5–14.7	1.9–390 [#]	29.9 [#]	72.4 [#]	5.3	3.2–9.2	2.0–366 [#]	18.3 [#]	56.3 [#]	2.2	1.6–8.4	0.8–476 [#]	22.2 [#]	75.5 [#]
8	8.5	6.6–15.8	2.3–487	40.2	93.2	5.9	4.5–10.1	1.5–815 [#]	32.8 [#]	122 [#]	2.7	1.7–7.8	0.6–204 [#]	17.4 [#]	43.1 [#]
9	11.3	7.0–16.7	1.5–362 [#]	39.3 [#]	90 [#]	4.8	3.4–7.8	0.9–494 [#]	34.6 [#]	103 [#]	2.6	1.3–6.0	0.6–328	27.9	72.8
10	11.5	7.1–14.6	1.6–206	23.6	38.9	5.0	2.9–9.0	1.1–150 [#]	14.9 [#]	31.2 [#]	3.6	1.7–8.8	0.9–813	37.7	134
11	9.9	6.3–16.6	2.1–530	28.6	81.0	4.9	2.9–10.7	1.9–209	17.6	39.0	2.4	1.3–4.4	0.2–311	22.6	60.3
12	9.9	6.3–14.1	1.0–68.2	14.3	15.0	4.5	3.1–9.0	0.6–103	12.2	20.8	2.9	1.5–6.7	0.6–141	11.5	28.5

Monthly median (quartile 1 – quartile 3), min-max values, and mean (standard deviation) salivary cortisol levels [nmol/L] at three different sampling times: morning (07:30–09:30), noon (10:00–12:00) and evening (19:30–21:30). Corrected Age in months: minus three to twelve, (month: -3 = gestational week 28, -2 = gestational week 32, -1 = gestational week 36 and 0 = gestational week 40).

[#] = without one outlier > 1000 nmol/L

[#]# = without two outliers > 1000 nmol/L

<https://doi.org/10.1371/journal.pone.0182685.t005>

Ivars, Nelson, Theodorsson, Mörelus. *PLoSOne* 2017

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What do we know about cortisol in infants?



Cortisol reactivity

- Preterm babies are capable of responding to stressors with increased cortisol.
- Painful procedures without pain-relief increase the cortisol levels.
- The more painful procedures in the neonatal unit the higher cortisol levels.
- First time experiences increase the cortisol levels.

However,

- Infants of mothers with low interactive behaviour, continue to increase in cortisol during nappy change.

Gunnar et al 1992, Grunau et al 2007, Ivars et al 2012, Mörelus et al 2006, 2007, 2012, 2016

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What do we know about cortisol in infants?



Morning/evening quotient

- Infants born preterm have higher baseline cortisol levels than full-term healthy infants during the first weeks of life.
- Infants have less difference between morning and evening levels if mothers have social problems vs psychiatric problems.
- Infants have less difference between morning and evening levels if mothers are smokers.
- Preterm infants have higher evening levels across the first year as compared to full-term infants (*in manuscript*).

Mörelus et al 2006, 2012, 2017, Ivars et al 2015, 2017.

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What do we know about cortisol in infants?



Co-regulation

- Sharing the same environment facilitates a cortisol co-regulation in the mother–infant dyad as well as between twins.
- There is a co-regulation in preterm infants' and mothers' cortisol if practicing Family-Centered Care compared to when the parents need to sleep at home.

Mörelus et al 2012, 2017

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What can we do to prevent stress in newborns and support a healthy development of the stress system?

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➤ **Individualized developmental support**

Preterm infants have lower cortisol levels 1 hour (=recovery) after a stressful eye screening procedure if receiving developmental support compared to standard care.



(Kleberg, Mörelius et al 2008)

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➤ Less procedures and pain relief

The combination of oral sweet solutions/breastmilk and pacifier dampen infants' salivary cortisol in response to painful procedures.



(Mörelus et al 2006, 2009, 2016)

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➤ Involve, guide and support parents in the care

- Keeping the family together in the Neonatal Intensive Care Unit decreases stress and feelings of isolation and improves sleep for parents.
- Parents staying around the clock reduce the hospital stay with 5.3 days.
- Assessment of parents' mental health.
- Support programs.

(Ortenstrand et al 2010, Edell-Gustafsson et al 2014)

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➤ Skin-to-skin contact



- Intermittent skin-to-skin contact lower mothers' cortisol levels if repeated
- Continuous skin-to-skin contact (24/7) dampens the preterm infants' stress reactivity.
- There is a co-regulation in preterm infants' and mothers' cortisol if practicing skin-to-skin contact 24/7, compared to standard care.
- Fathers report less spouse relationship problems if practicing skin-to-skin contact.

(Möreljus et al 2005, 2015, Sahlen-Helmer et al 2020)

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EACI - EARly Collaborative Intervention



A model to guide parents of preterm infants how to read, interpret and respond to their preterm infant's immature and vague cues in the NICU.

In manuscript

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Summary

- Short term stress is our friend.
- Long term stress is our foe.
- Long-standing, high levels of cortisol is toxic for the newborn brain.
- Early life environment affects the development of the stress system and children's coping skills.
- Premature birth, emotionally unavailable parents/carers, pain and fear have a negative impact on the development of the stress system.
- Parental closeness, a sense of security, emotional availability and emotional nourishment support the development of a healthy stress system.

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Conclusion

Today's health care need to support early interventions that protect the infants' brain development in order to grow up in good mental health with fewer stress related consequences.



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*“ feels great really, because I have a son. . .
at first when I wake up I can feel tired,
but at the same time I hear him and then
I feel really happy.” (P6)*

(Edell-Gustafsson, Angelhoff, Mörelius 2014)

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