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Horizon 2020

Excellent Science

Call: ERC-2020-ADG

(Call for proposal for ERC Advanced Grant)

Topic: ERC-2020-ADG

Type of action: ERC-ADG

(Advanced Grant)

Proposal number: 101020309

Proposal acronym: SaveBrain

Deadline Id: ERC-2020-ADG

Table of contents

How to fill in the forms

The administrative forms must be filled in for each proposal using the templates available in the submission system. Some data fields in the administrative forms are pre-filled based on the steps in the submission wizard.

1 - General information

Topic	ERC-2020-ADG	Type of Action	ERC-ADG
Call Identifier	ERC-2020-ADG	Deadline Id	ERC-2020-ADG

Acronym	SaveBrain
Proposal title	Emotional environment modulation to optimize the brain development in preterm infants

Note that for technical reasons, the following characters are not accepted in the Proposal Title and will be removed: < > " &

Duration in months	*60*
Primary ERC Review Panel*	LS7 - Applied Medical Technologies, Diagnostics, Therapies and Pu
Secondary ERC Review Panel	(if applicable)
ERC Keyword 1*	LS7_10 Health services, health care research, medical ethics

Please select, if applicable, the ERC keyword(s) that best characterise the subject of your proposal in order of priority.

ERC Keyword 2	*Not applicable*
ERC Keyword 3	*Not applicable*
ERC Keyword 4	*Not applicable*
Free keywords	*Very preterm; Neonatal Intensive Care Unit; Intervention studies; Brain development; MRI; fNIRS; Separation; Parent-infant interactions; Sensory environment; Infant-directed speech; Acoustic environment; Quality of care*

*Abstract**

Preterm infants are hospitalized during a critical phase of brain development. There is a need to understand the environmental factors influencing the abnormal structural and functional brain development and delayed brain growth seen in preterm infants despite modern medical care. SaveBrain introduces a novel paradigm of the emotional environment as an essential brain protective factor in preterm infants and studies how the emotional environment affects brain outcomes in preterm infants.

SaveBrain implements an intervention, the Close Collaboration with Parents training, in two hospitals and measures the emotional environment and brain outcomes in cohorts of preterm infants recruited before and after the intervention. Based on strong preliminary data, the intervention can be expected to improve the emotional environment of preterm infants by increasing parental involvement in infant care. Recording the emotional environment will include measuring emotional auditory exposures of the infant, types of parent-infant closeness, parental wellbeing and breastfeeding. The brain outcomes will be assessed using magnetic resonance imaging (MRI) for brain volumes, gyration and white matter maturity, functional MRI for brain network connectivity and dual Near InfraRed Spectroscopy (fNIRS) for parent-infant synchrony of social brain activity, along with a clinical assessment of the quality of interaction.

SaveBrain can create ground-breaking changes in neonatal care by providing evidence of the role of the emotional environment in the brain development of preterm infants. The consequences of abnormal brain development will be alleviated in a large group of infants; 6 to 12% of all children are born preterm. Therefore, the impact of better brain development will extend from the individuals and their families to the societal level, reducing the expenses resulting from developmental problems and improving the productivity of the individuals born preterm.

Remaining characters 27

In order to best review your application, do you agree that the above non-confidential proposal title and abstract can be used, without disclosing your identity, when contacting potential reviewers?* (●) Yes ( ) No

Declarations

In case of a Synergy grant application 'Principal Investigator' means 'corresponding Principal Investigator on behalf of all Principal Investigators', and 'Host Institution' means 'corresponding Host Institution'.

1) The Principal Investigator declares to have the written consent of all participants on their involvement and on the content of this proposal, as well as of any researcher mentioned in the proposal as participating in the project (either as other PI, team member or collaborator). The ERCEA may request the applicants to provide the written consent of all participants at any time during the evaluation process.*	☒
2) The Principal Investigator declares that the information contained in this proposal is correct and complete.	☒
3) The Principal Investigator declares that all parts of this proposal comply with ethical principles (including the highest standards of research integrity as set out, for instance, in the European Code of Conduct for Research Integrity and including, in particular, avoiding fabrication, falsification, plagiarism or other research misconduct).	☒

4) The Principal Investigator hereby declares that *(please select one of the three options below)*:

-- in case of multiple participants in the proposal, the Host Institution has carried out the self-check of the financial capacity of the organisation on http://ec.europa.eu/research/participants/docs/h2020-funding-guide/grants/applying-for-funding/register-an-organisation/financial-capacity-check_en.htm or to be covered by a financial viability check in an EU project for the last closed financial year.Where the result was “weak” or “insufficient”, the Host Institution confirms being aware of the measures that may be imposed in accordance with the H2020 Grants Manual (Chapter on Financial capacity check).	○
- in case of multiple participants in the proposal, the Host Institution is exempt from the financial capacity check being a public body including international organisations, higher or secondary education establishment or a legal entity, whose viability is guaranteed by a Member State or associated country, as defined in the H2020 Grants Manual (Chapter on Financial capacity check).	○
- in case of a sole participant in the proposal, the applicant is exempt from the financial capacity check.	◉
5) The Principal Investigator hereby declares that each applicant has confirmed to have the financial and operational capacity to carry out the proposed action. Where the proposal is to be retained for EU funding, each beneficiary applicant will be required to present a formal declaration in this respect.	☒

The Principal Investigator is only responsible for the correctness of the information relating to his/her own organisation. Each applicant remains responsible for the correctness of the information related to him and declared above. Where the proposal to be retained for EU funding, the Host Institution and each beneficiary applicant will be required to present a formal declaration in this respect.

Note:

For **multi-beneficiary applications**, the coordinator vouches for its own organization and that all other participants confirmed their participation and compliance with conditions set out in the call. If the proposal is retained for funding, each participant will be required to submit a formal declaration of honour confirming this.

False statements or incorrect information may lead to administrative sanctions under the Financial Regulation 2018/1046.

Personal data will be collected, used and processed in accordance with Regulation 2018/1725 and the **Funding & Tenders Portal privacy statement**.

Please be however aware that, to protect EU financial interests, your data may be transferred to other EU institutions and bodies and be registered in the EDES database. Data in the EDES database is also subject to Regulation 2018/1725 and the EDES privacy statement.

2 - Participants & contacts

#	Participant Legal Name	Country	Action
1	TURUN YLIOPISTO	Finland	

2 - Administrative data of participating organisations

Host Institution

PIC	***Legal name***
999903064	*TURUN YLIOPISTO*

Short name: UNIVERSITY OF TURKU

Address

Street YLIOPISTONMAKI

Town Turku

Postcode 20014

Country Finland

Webpage www.utu.fi

Specific Legal Statuses

Legal person .....yes

Public body .....yes

Non-profit .....yes

International organisation .....no

International organisation of European interest .....no

Secondary or Higher education establishment .....yes

Research organisation .....yes

Industry (private for profit).....no

Enterprise Data

Based on the below details from the Beneficiary Registry the organisation is not an SME (small- and medium-sized enterprise) for the call.

SME self-declared status.....02/01/1979 - no

SME self-assessment ..... unknown

SME validation sme..... unknown

Department(s) carrying out the proposed work

Department 1

Department name: Department of Clinical Medicine ☐ not applicable

☒ Same as proposing organisation's address

Street: YLIOPISTONMAKI

Town: Turku

Postcode: 20014

Country: Finland

Principal Investigator

The following information of the Principal Investigator is used to personalise the communications to applicants and the evaluation reports. Please make sure that your personal information is accurate and please inform the ERC in case your e-mail address changes by using the call specific e-mail address:

For Advanced Grant Applicants: ERC-2020-AdG-applicants@ec.europa.eu

The name and e-mail of contact persons including the Principal Investigator, Host Institution contact are read-only in the administrative form, only additional details can be edited here. To give access rights and contact details of contact persons, please save and close this form, then go back to Step 4 of the submission wizard and save the changes.

ORCID	0000-0001-8925-2594
Researcher ID	*The maximum length of the identifier is 11 characters (ZZZ-9999-2010) and the minimum length is 9 characters (A-1001-2010).*
Other ID	*Please enter the type of ID here* / *Please enter the identifier number here*
Last Name*	Lehtonen
First Name(s)*	Liisa
Last Name at Birth	Lehtonen
Gender*	○ Male ◉ Female
Title	Prof.
Country of residence*	Finland
Nationality*	Finland
Country of Birth*	Finland
Date of Birth* (DD/MM/YYYY)	14/12/1962
Place of Birth*	Oulu

Contact address

Current organisation name	University of Turku & Turku University Hospital
Current Department/Faculty/Institute/ Laboratory name	Department of Clinical Medicine & Department of Paediatrics and Adolescent Medicine

☒ Same as organisation address

Street	YLIOPISTONMAKI		
Postcode/Cedex	20014	Town*	Turku
Phone	+358 23130253	Country*	Finland
Phone2 / Mobile	+358 408318322		
E-mail*	lianle@utu.fi		

Qualifications

Earliest award (PhD, Doctorate) Date of award (DD/MM/YYYY) 09/11/1994

Contact address of the Host Institution and contact person

The name and e-mail of Host Institution contact persons are read-only in the administrative form, only additional details can be edited here. To give access rights and contact details of Host Institution, please save and close this form, then go back to Step 4 of the submission wizard and save the changes. Please note that the submission is blocked without a contact person and e-mail address for the Host Institution.

Organisation Legal Name **TURUN YLIOPISTO**

First name* **Tutkimus** Last name* **Palvelut**

E-Mail* **tutkimuspalvelut@utu.fi**

Position in org. *Research services*

Department *Name of the department/institute carrying out the work.* ☐ Same as organisation

☒ Same as organisation address

Street YLIOPISTONMAKI

Town Turku Postcode 20014

Country Finland

Phone +358 505813578 Phone2/Mobile +xxx xxxxxxxxx

Other contact persons

First Name	***Last Name***	***E-mail***	***Phone***
Suvi	Lähteenmäki	sutujo@utu.fi	*+358415350794*

3 - Budget

Beneficiary Short Name	Direct costs														A. Total Direct Costs	B. Indirect Costs	C1. Subcontracting Costs	C2. Costs of in kind contributions not used on the beneficiary's premises	Total Estimated Eligible Costs	Requested EU contribution
	Personnel						Other direct costs							A.3 Internally invoiced goods and services						
	PI	Senior Staff	Postdocs	Students	Other Personnel costs	A.1. Total direct costs for personnel	Travel	Equipment - including major equipment	Other goods and services				A.2. Total Other Direct Costs							
									Consum-ables incl. fieldwork and animal costs	Publications (incl. Open Access fees) and dissemination	Other additional direct costs	Total other goods and services								
University Of Turku	307488	112726	257659	242540	0	920413.00	48000	197400	99590	15000	28000	142590.00	387990.00	0	1308403.00	327100.75	0	862807	2498310.75	2498310.75
Total	307488	112726	257659	242540	0	920413.00	48000	197400	99590	15000	28000	142590.00	387990.00	0	1308403.00	327100.75	0	862807	2498310.75	2498310.75

Section C. Resources (Maximum 8000 characters allowed)

PI and the Team
The research area of the PI, Professor Liisa Lehtonen, has focused on infant behaviour since 1990, starting with studies on the causes and consequences of excessive crying in infancy. Her postdoctoral studies at McGill University, Montreal, expanded her knowledge of infant behaviour and stress. Since her clinical specialty in neonatology (in 1995), she has focused her research on the brain protective care of preterm infants. First, she studied the relationship between sleep states and oxygenation in ventilated preterm infants in Case Western Reserve University, Cleveland, Ohio in 1997–2000. After returning to Finland in 2000, she started a large study, extending from pregnancy to adolescence, aimed at identifying risk factors and protective factors affecting brain development and the long-term behavioural and developmental outcomes of preterm infants. The findings suggested that maternal involvement is a protective factor for later child outcomes, which led her to develop and study family centred care. Development work and rigorous research on the effects of the Close Collaboration with Parents training programme has been her main focus during the last 10 years.
She developed the training programme together with two psychologists: Sari Ahlqvist-Björkroth and Zack Boukydis (deceased in 2015). The team, including Dr Ahlqvist-Björkroth, Professor Anna Axelin and the PI, along with a group of trained mentor nurses, has implemented the training in 14 hospitals. Professor Axelin has been the main collaborator in the research team evaluating the effects of the training; the PI and Professor Axelin have been the supervisors of two PhD students studying the effectiveness of the Close Collaboration with Parents training.

With Professor Axelin, the PI led a European survey about parental presence in neonatal units in 2013, and they have recently completed the 2nd International Closeness Survey in 23 centres (www.utu.fi/scene). The main outcomes being studied in the research project are parental depression and breastfeeding; the results are currently under analysis. Professor Rasa Tamelienė, MD, PhD, Head of the Department of Neonatology, Lithuanian University of Health Sciences, the Republic of Lithuania, and Dr Kris de Coen, Associate Head of the Department of Neonatology, Ghent University Hospital, Belgium, have participated in the 2nd International Closeness Survey. Their performance in data collection has been excellent, and they are both highly motivated to participate in the proposed research project.
All collaborators taking part in the proposed research project have extensive experience in their respective fields, and most of them have established their collaboration with the PI:
The analyses of the MRI data will be done in the University of Turku in collaboration with Professor Riitta Parkkola, a neuroradiologist. She has been responsible for the interpretation of MRI and fMRI data in the PIPARI Study led by the PI since 2000 (www.utu.fi/pipari). Auditory environment analyses will be performed in collaboration with Dr. Okko Räsänen from Tampere University, Finland, who is an expert in speech technology and the analysis of day-long child-centred audio recordings. The clinical assessment of parent-infant interaction by PCERA requires a trained team and reliability testing of the coders. Dr Sari Ahlqvist-Björkroth, PhD, is a certified trainer of the coders for PCERA.

Other direct costs consist of salaries and and per diems of the intervention team and sound analysis staff. Also, the scientific advisory board meeting costs are included.
The Intervention team consists of the PI, a psychologist from University of Turku, local nurses, research coordinators and assistants in both target hospitals and a trained team of mentor nurses from Turku University Hospital. A post-doc specialised in sound analysis from Tampere University will conduct the sound analyses.

Scientific Advisory Board
The scientific advisory board includes experts
1) Emeritus Professor Uwe Ewald, MD, from Uppsala University, Sweden; Clinical Neonatology
2) Professor Gianluca Esposito, Psychology Program, School of Social Sciences, Nanyang Technological University, Singapore, Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Department of Psychology and Cognitive Science, University of Trento, Italy; Infant Psychology, especially fNIRS technique
3) Jukka Leppänen, PhD, Senior Lecturer, Department of Psychology, University of Jyväskylä, Finland; Developmental Psychology
4) Dr Bernd Pape, Vaasa School of Economics, Finland; Statistical analyses.
The scientific board will schedule meetings at least once yearly, and additional meetings will be scheduled as needed.

Remaining characters 3236

4 - Ethics

1. HUMAN EMBRYOS/FOETUSES		Page
Does your research involve Human Embryonic Stem Cells (hESCs)?	○ Yes ◉ No	
Does your research involve the use of human embryos?	○ Yes ◉ No	
Does your research involve the use of human foetal tissues / cells?	○ Yes ◉ No	
2. HUMANS		**Page**
Does your research involve human participants?	◉ Yes ○ No	A2-1
Are they volunteers for social or human sciences research?	◉ Yes ○ No	A2-1
Are they persons unable to give informed consent?	◉ Yes ○ No	A2-1
Are they vulnerable individuals or groups?	◉ Yes ○ No	A2-2
Are they children/minors?	◉ Yes ○ No	A2-2
Are they patients?	◉ Yes ○ No	A2-3
Are they healthy volunteers for medical studies?	○ Yes ◉ No	
Does your research involve physical interventions on the study participants?	○ Yes ◉ No	
3. HUMAN CELLS / TISSUES		**Page**
Does your research involve human cells or tissues (other than from Human Embryos/ Foetuses, i.e. section 1)?	○ Yes ◉ No	
4. PERSONAL DATA		**Page**
Does your research involve personal data collection and/or processing?	◉ Yes ○ No	A2-3
Does it involve the collection and/or processing of sensitive personal data (e.g: health, sexual lifestyle, ethnicity, political opinion, religious or philosophical conviction)?	◉ Yes ○ No	A2-4
Does it involve processing of genetic information?	○ Yes ◉ No	
Does it involve tracking or observation of participants?	◉ Yes ○ No	A2-4
Does your research involve further processing of previously collected personal data (secondary use)?	○ Yes ◉ No	
5. ANIMALS		**Page**
Does your research involve animals?	○ Yes ◉ No	

6. THIRD COUNTRIES		Page
In case non-EU countries are involved, do the research related activities undertaken in these countries raise potential ethics issues?	○ Yes ◉ No	
Do you plan to use local resources (e.g. animal and/or human tissue samples, genetic material, live animals, human remains, materials of historical value, endangered fauna or flora samples, etc.)?	○ Yes ◉ No	
Do you plan to import any material - including personal data - from non-EU countries into the EU?	○ Yes ◉ No	
Do you plan to export any material - including personal data - from the EU to non-EU countries?	○ Yes ◉ No	
In case your research involves low and/or lower middle income countries, are any benefits-sharing actions planned?	○ Yes ◉ No	
Could the situation in the country put the individuals taking part in the research at risk?	○ Yes ◉ No	
7. ENVIRONMENT & HEALTH and SAFETY		Page
Does your research involve the use of elements that may cause harm to the environment, to animals or plants?	○ Yes ◉ No	
Does your research deal with endangered fauna and/or flora and/or protected areas?	○ Yes ◉ No	
Does your research involve the use of elements that may cause harm to humans, including research staff?	○ Yes ◉ No	
8. DUAL USE		Page
Does your research involve dual-use items in the sense of Regulation 428/2009, or other items for which an authorisation is required?	○ Yes ◉ No	
9. EXCLUSIVE FOCUS ON CIVIL APPLICATIONS		Page
Could your research raise concerns regarding the exclusive focus on civil applications?	○ Yes ◉ No	
10. MISUSE		Page
Does your research have the potential for misuse of research results?	○ Yes ◉ No	
11. OTHER ETHICS ISSUES		Page
Are there any other ethics issues that should be taken into consideration? Please specify	○ Yes ◉ No	

I confirm that I have taken into account all ethics issues described above and that, if any ethics issues apply, I will complete the ethics self-assessment and attach the required documents. [x]

How to Complete your Ethics Self-Assessment

5 - Call specific questions

Please indicate your percentage of working time in an EU Member State or Associated Country over the period of the grant: Please note that you are expected to spend a minimum of 50% of your total working time in an EU Member State or Associated Country.	100
Please indicate the % of working time the PI dedicates to the project over the period of the grant. Please note that the PI is expected to dedicate a minimum of working time to the project (30% for AdG, 40% for CoG and 50% for StG). The personnel cost for the PI provided in section “3-Budget” cannot be higher than the percentage indicated here. This information will be provided to the experts at Step 2 together with the section “3-Budget”.	40
I acknowledge that I am aware of the eligibility requirements for applying for this ERC call as specified in the ERC Annual Work Programme, and certify that, to the best of my knowledge my application is in compliance with all these requirements. I understand that my proposal may be declared ineligible at any point during the evaluation or granting process if it is found not to be compliant with these eligibility criteria.*	☒
Data-Related Questions and Data Protection (Consent to any question below is entirely voluntary. A positive or negative answer will not affect the evaluation of your project proposal in any form and will not be communicated to the evaluators of your project.)	
For communication purposes only, the ERC asks for your permission to publish, in whatever form and medium, your name, the proposal title, the proposal acronym, the panel, and host institution, should your proposal be retained for funding.	◉ Yes ○ No
Some national and regional public research funding authorities run schemes to fund ERC applicants that score highly in the ERC's evaluation but which can not be funded by the ERC due to its limited budget. In case your proposal could not be selected for funding by the ERC do you consent to allow the ERC to disclose the results of your evaluation (score and ranking range) together with your name, non-confidential proposal title and abstract, proposal acronym, host institution and your contact details to such authorities? This consent is entirely voluntary and refusal to give it will in no way affect the evaluation of your proposal.	◉ Yes ○ No
The ERC is sometimes contacted for lists of ERC funded researchers by institutions that are awarding prizes to excellent researchers. Do you consent to allow the ERC to disclose your name, non-confidential proposal title and abstract, proposal acronym, host institution and your contact details to such institutions? This consent is entirely voluntary and refusal to give it will in no way affect the evaluation of your proposal.	◉ Yes ○ No
The European Research Council Executive Agency (ERCEA) occasionally contacts Principal Investigators of funded proposals for various purposes such as communication campaigns, pitching events, presentation of their project's evolution or outcomes to the public, invitations to represent the ERC in national and international forums, studies etc. Should your proposal be funded, do you consent to the ERCEA staff contacting you for such purposes?	◉ Yes ○ No
For purposes related to monitoring, study and evaluating implementation of ERC actions, the ERC may need that submitted proposals and their respective evaluation data be processed by external parties. Any processing will be conducted in compliance with the requirements of Regulation (EU) 2018/1725.	
Have you previously submitted a proposal to the ERC? If known, please specify your most recent ERC application details.	○ Yes ◉ No

Excluded Reviewers

You can provide up to three names of persons that should not act as an evaluator in the evaluation of the proposal for potential competitive reasons.

First Name	
Last Name	
Institution	
Town	
Country	
Webpage	

Extended Open Research Data Pilot in Horizon 2020

If selected, all applicants will by default participate in the Pilot on Open Research Data in Horizon 2020[1] , which aims to improve and maximise access to and re-use of research data generated by actions.

However, participation in the Pilot is flexible in the sense that it does not mean that all research data needs to be open. After the action has started, participants will formulate a Data Management Plan (DMP), which should address the relevant aspects of making data FAIR - findable, accessible, interoperable and re-usable, including what data the project will generate, whether and how it will be made accessible for verification and re-use, and how it will be curated and preserved. Through this DMP projects can define certain datasets to remain closed according to the principle "as open as possible, as closed as necessary". A Data Management Plan does **not** have to be submitted at the proposal stage.

Furthermore, applicants also have the possibility to opt out of this Pilot completely at any stage (before or after the grant signature), thereby freeing themselves retroactively from the associated obligations.

Please note that participation in this Pilot does not constitute part of the evaluation process. Proposals will not be penalised for opting out.

We wish to opt out of the Pilot on Open Research Data in Horizon 2020.	○ Yes	◉ No

[1] *According to article 43.2 of Regulation (EU) No 1290/2013 of the European Parliament and of the Council, of 11 December 2013, laying down the rules for participation and dissemination in "Horizon 2020 - the Framework Programme for Research and Innovation (2014-2020)" and repealing Regulation (EC) No 1906/2006.*

ERC Advanced Grant 2020

Research proposal [Part B1]

Proposal Full Title: Emotional environment modulation to optimize the brain development in preterm infants

Acronym: SaveBrain

- Liisa Lehtonen (PI)
- University of Turku, Turku, Finland
- 60 months

Preterm infants are hospitalized during a critical phase of brain development. There is a need to understand the environmental factors influencing the abnormal structural and functional brain development and delayed brain growth seen in preterm infants despite modern medical care. **SaveBrain** introduces a novel paradigm of the emotional environment as an essential brain protective factor in preterm infants and **studies how the emotional environment affects brain outcomes in preterm infants.**

SaveBrain implements an intervention, the Close Collaboration with Parents training, in two hospitals and measures the emotional environment and brain outcomes in cohorts of preterm infants recruited before and after the intervention. Based on strong preliminary data, the intervention can be expected to improve the emotional environment of preterm infants by increasing parental involvement in infant care. Recording the emotional environment will include measuring emotional auditory exposures of the infant, types of parent-infant closeness, parental wellbeing and breastfeeding. The brain outcomes will be assessed using magnetic resonance imaging (**MRI**) for brain volumes, gyration and white matter maturity, functional **MRI** for brain network connectivity and dual Near InfraRed Spectroscopy (**fNIRS**) for parent-infant synchrony of social brain activity, along with a clinical assessment of the quality of interaction.

SaveBrain can create ground-breaking changes in neonatal care by providing evidence of the role of the emotional environment in the brain development of preterm infants. The consequences of abnormal brain development will be alleviated in a large group of infants; 6 to 12% of all children are born preterm. Therefore, the impact of better brain development will extend from the individuals and their families to the societal level, reducing the expenses resulting from developmental problems and improving the productivity of the individuals born preterm.

Section a: Extended Synopsis of the scientific proposal

Preterm birth is a risk for the developing brain of the infant. The **SaveBrain** project stems from the need to understand the environmental factors for the abnormal structural and functional brain development and delayed brain growth seen in preterm infants despite modern medical care. Current neonatal research and care emphasizes the nutritional and physiological needs of preterm infants, in addition to prevention of major structural complications of prematurity. Very little attention is paid to their emotional needs, even though the life-long bond between the parent and the newborn should be created soon after birth.

SaveBrain can create ground-breaking changes by introducing a novel paradigm of emotional environment as an essential brain protective factor in preterm infants, and the information provided will change the priorities in neonatal care. Evidence of the role of the emotional environment in the brain development of preterm infants will ensure that this area of care will get the same emphasis as the physiological stability and nutritional needs of preterm infants receive today. The consequences of abnormal brain development will be alleviated in a large group of infants; 6 to 12% of all children are born preterm. Therefore, the impact of better brain development will extend from the individuals and their families to the societal level, reducing the costs of care required due to developmental problems and improving the productivity of the individuals born preterm.

SaveBrain studies how the emotional environment affects the brain outcomes in preterm infants during a critical time period of brain growth and development.

The parent-infant bonding process is based on hormonal and physiological mechanisms (1–3) and **multisensory, reciprocal experiences during parent-infant closeness and interactions** (4–5). Both human and animal studies have shown that seeing, hearing and smelling the baby will activate the subcortical regions and increase the volume of grey matter in the parent brain, as summarized by Feldman R et al (6); less is known about the effects on the brain of the infant. The activity of one sensory system can affect the development of another, e.g. tactile stimuli can increase visual function (7) and visual stimuli can affect auditory function (8), which highlights the holistic way that environmental experiences influence infant development. The first sensory system to emerge is tactile (9). The vital importance of tactile contact for infants was shown by the historical experiment demonstrating that rhesus monkey infants preferred a soft, clothed surrogate without food over a wire surrogate with food. The infant monkeys only stayed playful and curious in the presence of the clothed surrogate (10). Primate studies, along with studies of hospitalized and institutionalized infants have proven the **crucial importance of affective interactions; the lack of such interactions leads to long-lasting consequences in emotional-behavioral development,** summarized by van der Horst and van der Veer (11) and Sullivan (3). Since then, research has shown that **deprivation from parent-infant closeness affects the structural development of the brain**. Care in institutions results in adverse brain effects compared to foster care or adoption (12-22); low birth weight infants are especially sensitive to separation (23). The separation of preterm infants into private hospital rooms alters the development of their brain gyration in the language processing area of the temporal lobe (24). These studies are relevant in current neonatal care, as the intensive care environment in hospitals is radically different from that experienced by healthy full-term infants, who spend most of their waking hours in the company of others. Hospitalized preterm infants have been reported to spend 80% of their time alone without any human contact (25). A European survey showed remarkable variation in parents' presence between hospitals, starting from 2.6 hours per day (unpublished data). An international survey showed that only 13.3% of 331 neonatal units provided parents with the facilities needed to stay with their infant throughout a 24-hour day (26). The loneliness of preterm infants deprives them from tactile, olfactory, gustatory, kinesthetic, auditory and visual contact with their parents. Instead, they are frequently exposed to harmful sensory experiences, such as high-decibel noises (27); bright lights, (28), and painful skin punctures (29).

Hospital facilities that allow parents to stay with their preterm infants improve survival, decrease infections, shorten the hospital stay (26, 30) and improve developmental outcomes of the preterm infants (31). In spite of these observations, there is no knowledge **about the way the emotional exposures influence the preterm infants' brain structure and function** and what the critical time windows are.

The present project introduces a novel paradigm of an **emotional environment as an essential brain protective factor in preterm infants. Emotional environment** is defined as multisensory environmental exposures provided in reciprocal interactions with parents, combined with a lack of unphysiological stimuli. In **SaveBrain**, these exposures will be measured by documenting the parents' presence; parent-infant skin-to-

skin contact; infant-directed speech with expression of positive affect; parents' participation in alleviating infant pain; breastfeeding; the parents' physiological and psychological wellbeing; and stronger parenting experiences. Harmful exposures to be documented are painful procedures and noise. The approach in **SaveBrain** differs profoundly from earlier studies by providing the sensory exposures as a part of emotional parent-infant interactions. In earlier studies, the effects of sensory exposures have been studied separately or in clusters, most commonly studied exposures are tactile stimuli (32, 33). Parents can provide more child-centred and warmer care compared to changing staff members; such qualities of care have been shown to promote child growth and cognitive development (23). Parent-infant skin-to-skin care provides reciprocal olfactory and auditory stimuli, visual contact, and more kinesthetic stimuli than care in an incubator; parents' presence will enable their active role in caregiving, in alleviating infant pain, and in talking to the infant. Skin-to-skin tactile stimuli can counteract the painful tactile stimuli produced by medical care (34) and the harmful consequences of painful procedures (35). The parents' improved wellbeing is likely to affect the emotional environment of the infant; preterm infants synchronize their stress level indicator cortisol to the caregiver´s level when receiving skin to skin care (36-37). Therefore, we will measure the wellbeing of parents as one factor of the emotional environment of the infant. Nobody has shown, so far, that parent wellbeing during hospitalization is associated with better infant brain outcomes in early infancy.

SaveBrain will implement an educational intervention for neonatal staff that is an innovation of the PI and her collaborators. This intervention, the Close Collaboration with Parents training, is one of the few interventions that acknowledge and support the parents' unique role already during neonatal care. By training the whole staff, all infants will be exposed to care that is more inclusive of all parents from birth, irrespective of the medical condition of the infant. The intervention provides the staff with better skills for supporting parenting and working in partnership with the parents. So far, the intervention has been shown to improve family-centred care in neonatal intensive care units (38). The parents' psychological wellbeing was supported better as they were listened to more often, and they reported better emotional support after the intervention. Consistently, nurses reported improved skills in providing emotional support and listening (manuscript). The intervention increased the parents' presence by 37% and parent-infant skin-to-skin contact by 51% in nine hospitals (manuscript) and decreased prolonged maternal depressive symptoms (39).

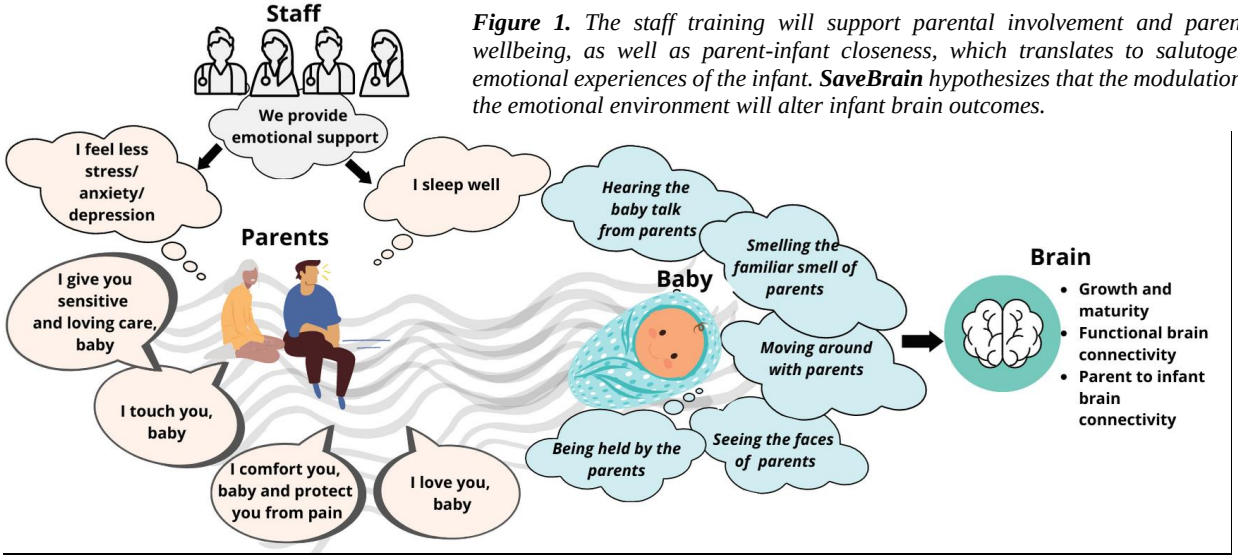

Figure 1. *The staff training will support parental involvement and parental wellbeing, as well as parent-infant closeness, which translates to salutogenic emotional experiences of the infant.* ***SaveBrain*** *hypothesizes that the modulation of the emotional environment will alter infant brain outcomes.*

Central Question of the Research Project

The central question of this research project is how emotional environment affects the structural and functional brain development of hospitalised preterm infants. **SaveBrain** hypothesises that the intervention improves brain outcomes and that the effect is mediated by an improved emotional environment. The **SaveBrain** hypotheses are that preterm infants in the post-intervention group, as compared to the pre-intervention group, will have better brain growth, more mature gyration and white matter tracts, and stronger functional connectivity at term age. Furthermore, they will have better parent-infant synchrony of the social brain activity and more optimal parent-infant interaction at four months after term age. The study will also analyse which elements of the emotional environment change and when, and which elements are more resistant to change.

Research Design: A hospital-based, multicenter, before and after the intervention study

SaveBrain compares two cohorts of preterm infants: The first cohort will be recruited before the intervention, over a time period of six months (Control), and the second cohort after the intervention (Intervention). The emotional environment during hospital care and brain outcomes will be measured for both cohorts. Preterm infants born at 22 to 32 gestational weeks will be recruited in the Kaunas, Lithuania and Ghent, Belgium. The estimated number of such infants during a 6-months period will be 78 in Kaunas and 73 in Ghent, based on 5-year statistics. The duration of the exposure to the emotional environment in the hospital might vary between 4 and 18 weeks before discharge home or to another hospital. Timeline is shown in *Figure 2.*

Intervention: The intervention, the Close Collaboration with Parents training, developed in Turku University Hospital, Finland, will be implemented in the target hospitals. The training is targeted at the staff; a minimum of 75% of the staff members will be trained within an 18-month time period. The training includes theory, exercises, practical training and reflection. The theory is learned and the exercises started using an e-learning tool that is currently being piloted in English language. The training will continue with practical training and reflections in clinical situations with a trained mentor.

Outcomes: SaveBrain measures infant brain outcomes at term age (40 gestational weeks) and social brain activity and functions at 4 months after term age. The mediating factor resulting in better brain outcomes will be the emotional environment of the unit, which will be measured and expected to become more salutogenic as a result of the intervention.

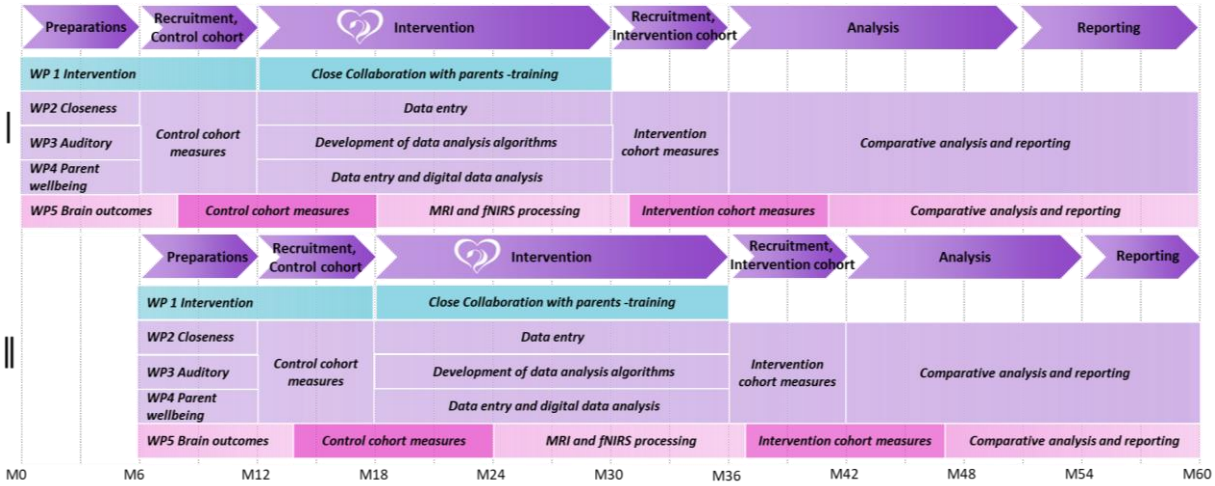

Figure 2. SaveBrain *lasts for a total of 60 months, divided into 5 Workpackages (WP) to study the emotional environment and the infant brain outcomes in Control and Intervention cohorts collected in two hospitals***.**

SaveBrain is divided into **five WorkPackages (WPs)**, including appropriate collaborators. WP1 implements and documents the implementation of the intervention. The emotional environment is divided into WP2, which looks at parent-infant closeness and interaction, WP3, which focuses on the auditory environment, specifically positive emotions in infant-directed speech, and WP4, where the parents' wellbeing is studied. WP5 consists of the infant brain outcomes at term age and at four months after term age.

Intervention (WP1) will consist of the Close Collaboration with Parents training for the neonatal staff of the target hospitals, carried out by the experienced trainer team from Turku University Hospital. Automated user data will be extracted from the e-learning tool to confirm fidelity to the training.

Emotional environment (**WP2-4)** will be measured in both Control and Intervention cohorts. As the parent-infant emotional closeness can be supported in different ways in the different phases of the care of a preterm infant, the measurement periods are divided into five different time windows, from the delivery room and to transition to home: I. Initial stabilization in the delivery room; II. Admission to the neonatal intensive care unit; III Intensive care period; IV. Convalescent care period; V. Transition to home. All parent measures include separate measures for mothers and fathers/partners.

WP2 (Closeness) will focus on **parent-infant closeness,** documenting parent-infant visual contact and skin-to-skin contact, the parents' presence in the infant's hospital room, breastfeeding and parent involvement in infant pain management. Medical chart documentation, a Closeness Diary (40), interviews and the AeroScout Real-Time Locating System, a tag carried by parents and connected to hospital wifi (https://www.stanleyhealthcare.com/aeroscout-rtls), will be used to collect data throughout the hospital stay. **WP3 (Auditory)** will measure the developmentally supportive exposures (speech with positive affect) and

harmful exposures (noise), using a 16-hour recording by LENA recorder (41-42) allowing analysis of the auditory environment of the infant. Although the adult word count has been shown to support language development in preterm infants (43), there is no research about the significance of emotional quality and infant-directed speech in preterm infants. Therefore, **SaveBrain** will utilize automatic emotion classification (44-45) on adult speech in infant-caregiver verbal interactions. To identify infant-directed speech, we will utilize existing state-of-the-art algorithms as a starting point, then adapting the classifiers to our bedside audio data using domain adaptation and active learning techniques. As a result, we can quantify the relative amount of positive speech to each infant in the NICU. Our hypothesis is that the exposure to infant-directed speech with positive emotional valence will increase and the exposure to noise will decrease after the intervention, affecting infant brain development positively.

WP4 (Parent wellbeing and parenting) will measure the parents' physiological stress levels, quality of sleep and level of activity using commercially available, valid sensor and algorithm developed by Firstbeat (www.firstbeat.fi) specialized in heart rate variability monitoring and analysis technologies. The algorithm provides information on sleep duration and latency, sleep stages, and overall sleep score as well as autonomic nervous system balance, indicating stress and recovery (46-50). Well-validated and widely used questionnaires (51-58) will be filled in by both parents to measure stress, anxiety, depressive symptoms, attachment, and parenting efficacy and confidence twice during hospital stay and at 4 months after term.

WP5 (Brain outcomes) will measure the effects of the emotional environment on infant brain development. The measurements consist of magnetic resonance imaging (**MRI**), Near InfraRed Spectroscopy (**fNIRS**), face recognition and clinical assessments of the parent-infant relationship and infant neurobehavior. The most novel method is dual fNIRS, which is an emerging method in the research of infant development (59). fNIRS measures relative concentrations of oxygenated and deoxygenated hemoglobin in the brain tissue, indicating cerebral activation and deactivation. Dual fNIRS will be recorded simultaneously from the parent and the infant to study the synchrony of their brain activities during a free play situation. The situation will be videorecorded and repeated with both the mother and the father. Measurement detectors will be attached in a cap, forming 24 channels used to locate the brain activation. The area of interest is the orbitofrontal cortex, shown to be related to the unique mother-infant relationship (60). Three-month-old infants have shown more activation of the orbitofrontal cortex in response to infant-directed speech by females as compared to adult-directed speech (61). As fNIRS has a shallow penetrance into the brain, MRI and fMRI will be used to provide precise data on the deep brain structures and networks. All of these measurements require a significant amount of financial and human resources and, therefore, are not accessible without appropriate funding.

A brain MRI scan will be performed at term age (40 weeks of gestation) using 3Tesla MRI equipment available both in Kaunas and Ghent. The analyses of brain volumes and gyration patterns will be done using voxel-based morphometry (**VBM**) and tensor-based morphometry (**TBM**), which are both artificial intelligence-based analysis methods (62); the microstructure of the white matter tracts will be analysed using diffusion tensor imaging (**DTI**) based on Tract Based Spatial Statistics (63); and brain connectivity will be analysed using dynamic fluctuations of the resting state activity during functional MRI (**fMRI**) (64).

Parent-Child Early Relational Assessment (**PCERA)** will be used to assess the quality of the parent-infant relationship at 4 months after term age. The items to be scored include parent and child positive emotions during the interaction and the regulation of emotions. The psychometric properties of PCERA are good and well documented (65-67). The interaction will be also analysed a computer-vision based solution **FaceReader** by Noldus Information Technology. The performance of FaceReader has been shown to be reliable in adults (68); we will evaluate the performance in young infants. This study will provide an opportunity to study the paternal and maternal brain separately after the long hospitalization of the infant, which may have affected them differently. **The NICU Network Neurobehavioral Scale** (69) will be utilized to assess infant neurobehavior. It has been able to show that the neurobehavioral performance of preterm infants relates to the parents' presence (70), to the level of infant-centred care in the unit (71), and to the design of the unit (30).

Statistical analysis

The brain outcomes will be compared between Control and Intervention cohorts, adjusted for covariates. This study has potentially 151 preterm infants in both cohorts. Assuming 20% refusal rate and further drop-out rate of 15%, the number of infants with successful brain outcome measures may reduce to 100 per cohort. The number of infants needed to reach 0.80 power and to detect a relative mean difference of 8% at significance level $p<0.05$ is 88 per group for regional brain volumes. The total score for the emotional environment will be created using the mean of z-scores of the individual elements in WP2-4. The salutogenic items are given a positive score and harmful items a negative score. The Cronbach alphas will be calculated for internal

consistency, and only elements with sufficient internal validity will be included. The total score and its elements will be compared between the cohorts adjusted for covariates. Secondary analyses will be done within gestational age categories as well as for different time windows to identify patient groups and time periods during their care which are susceptible or resistant to change in the emotional environment. The total score of the emotional environment during the hospital stay will be correlated to the quality of social brain functions as assessed by fNIRS, PCERA and face recognition. All tests will be performed using linear mixed models with family as a random factor.

Risks and ethical considerations

The proposed project will take place in neonatal intensive care units and involve a vulnerable patient group and their parents. High sensitivity and flexibility are needed to carry out this study. However, the PI is experienced in clinical research in the context of preterm infant care. Many of the risks of the study are related to the limitations set by the clinical context that can only be controlled in a limited degree (*Table 1*). The burden for the parents will be minimized by preferring automized data collection tools. Tools such as the wellbeing measurement devices that parents are asked to carry are commonly used by adults. A team of experienced research assistants will help the parents with the diaries and questionnaires, and they will ensure clinical referral if the questionnaires/imaging reveal a situation requiring an acute clinical intervention. The brain outcome measures are safe and will be performed without any medication. MRI is recommended as a part of the routine follow-up of very preterm infants (72).

Table 1. *Potential risks and the planned solutions.*

Risk	Solution
Intervention is not carried out as planned	Fidelity measures. More efforts can be invested if not implemented as planned.
not enough few patients; exposure to improved environment too short	Large target hospitals; care until discharge (Kaunas). If recruitment is slow, the recruitment period can be extended.
Data collection is not carried out as planned	Target hospitals with excellent performance in data collection in the International Closeness Survey (www.utu.fi/scene); a realistic amount of measures per family.
New algorithm used to recognize infant directed speech is not valid	An established LENA method will be used with valid adult word counts and measure of noise.
Dual fNIRS does not catch brain activities with sufficient granularity	A clinical assessment of the parent-infant relationship as a back-up
The improvement in the emotional environment is not large enough	Preliminary data showed room for improvement: low skin-to-skin contact in Kaunas, low presence and skin-to-skin contact in Ghent.
No group differences in the brain outcomes	The hypothesis is proved wrong and other alternatives for optimizing the brain outcomes of preterm infants have to be studied in the future

Concluding remarks

One in ten infants are born preterm. They are born with an immature brain that undergoes critical development during their hospital stay. When developing the care, optimal brain outcomes should be the central driver. **SaveBrain** will provide novel knowledge about the role of the emotional environment in optimizing the brain development of preterm infants. This knowledge has the potential to change the paradigm of neonatal care from a technical/medical approach to a more human approach. The impact of improved long-term developmental outcomes will extend from the individuals and their families to the societal level, reducing the costs of care required due to developmental problems and improving the productivity of the individuals born preterm. **SaveBrain** will provide data on new methodologies to study the connectivity of brain networks and the synergy of the social brain activation in the parent-infant dyad during early infancy in the context of a heightened risk for brain injuries. Combining novel methods with more traditional measures, the project will provide data on the feasibility, validity and reliability of the new tools. The machine learning algorithms will be used to create new tools for obtaining information about the emotional auditory environment.

SaveBrain will provide novel information on the elements and time windows of the emotional environment of neonatal care that are susceptible to change and can be modified to become more salutogenic. We will also learn which elements or time windows are resistant to change; future studies are, then, needed to tackle the change-resistant elements, as it is also essential to know who should receive additional support and when.

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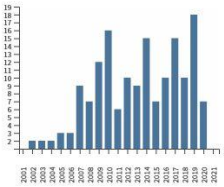
73. Ibrahim J, Mir I, Chalak L: Brain imaging in preterm infants <32 weeks gestation: a clinical review and algorithm for the use of cranial ultrasound and qualitative brain MRI. Ped Res 2018 Dec;84(6):799-806.

Section b: Curriculum vitae (max. 2 pages)

PERSONAL INFORMATION



Lehtonen, Liisa, MD, Professor
ORCID identifier: https://orcid.org/0000-0001-8925-2594
Nationality: Finnish
Date of birth: December 14, 1962
Research profile: https://research.utu.fi/converis/portal/Person/838271?auxfun=&lang=en_GB

Professor Lehtonen has over 193 publications in English (171 original research articles, 11 reviews, 4 chapters in text books, 7 editorials and commentaries) and has presented in international conferences in the USA, Canada, Australia, Japan and Europe. Her h-index is 37 by **Web of Science Core Collection** and 39 by **Scopus** (Date of search: 14.8.2020). She was nominated as an Honorary Member of the American Pediatric Society in 2015.

EDUCATION

2014 Full Professor of Pediatrics, University of Turku, Finland

2002 Docent in Neonatology, University of Turku, Finland

1997 Educational Commission for Foreign Medical Graduates Certificate, USA

1996 Board Certified Neonatologist, Department of Clinical Medicine, Faculty of Medicine, University of Turku, Finland

1994 PhD in Medicine, Department of Clinical Medicine, Faculty of Medicine, University of Turku, Finland

1993 Board Certified Pediatrician, Finland and extended to Sweden by Socialstyrelse in 2010

1987 Fully Certified Medical Doctor, Finland

1986 Medical Doctor, Faculty of Medicine, University of Oulu, Finland

CURRENT POSITIONS

Director of the Division of Neonatology, Since 2001-currently
Turku University Hospital, Department of Pediatrics and Adolescent Medicine, Finland

Professor of Pediatrics, Since 2013-currently
Department of Clinical Medicine, Faculty of Medicine, University of Turku, Finland

PREVIOUS POSITIONS

04/2011-10/2011 Senior neonatologist, *Uppsala University Hospital*, **Sweden**

09/2000-09/2001 Attending Neonatologist Turku University Hospital, Department of Pediatrics and Adolescent Medicine, Finland

07/1997-06/2000 Fellow in Neonatology, Rainbow Babies and Children's Hospital, Case Western Reserve University, Cleveland, Ohio, **USA**

07/1996-06/1997 Research Fellow, Department of Developmental Pediatrics, The McGill University-Montréal Children's Hospital Research Institute, Montréal, **Canada**

01/1994-06/1996 Fellow in Neonatology, including 25 months clinical service and 5 months research

02/1990-12/1993 Resident in Pediatrics, including 33 months clinical service and 14 months research *Turku University Hospital, Department of Pediatrics and Adolescent Medicine*, **Finland**

08/1987-02/1990 Resident in Anesthesiology, Pediatrics and Obstetrics and Gynecology, *Kainuu Central Hospital, Kajaani*, **Finland**

06/1987-07/1987 Visitor, Booth Hall Children's Hospital, Manchester, **England**

AWARDS

Honorary Member of American Pediatric Society 2015-; Docent of the Year of the Universities in Turku University Hospital 2008; Accomplishment in the research of premature babies by the Association of the Parents of Premature Babies (Kevyt r.y.) 2011; Award from Turunmaan Duodecim-seura 2012

The Close Collaboration with Parents Training program, Award for High Quality from Finnish Medical Association Oct 20, 2015; The NICU at Turku University Hospital: Center of Excellence at the Hospital District of Southwest Finland in 2017, 2018 and 2019

SUPERVISION OF POSTGRADUATE STUDENTS

12 PhD graduates. *All of them have pursued academic careers; 2 of them have tenure track professorships.* Kirjavainen, J. (2004); Latva, R. (2009); Reiman, M. (2009); Korja, R. (2009); Rautava, L. (2010); Korvenranta, E. (2010); Luoto, R. (2010); Axelin, A. (2010); Maunu, J (2010); Ekblad, M (2013); Setänen S. (2016); Raiskila S. (2018)

Currently 5 PhD students*:* Kjell Helenius, MD (the thesis submitted in the Faculty); Minna Sucksdorff, MD (all 4 publications ready); Mirka Toivonen RN, BA (all 4 publications ready); Anette Aija, MD; Anniina Väliaho, BA (Psych); Katarzyna Piatek, MD

Supervisory panel for PhD students: Arimatias Raitio, University of Turku; Kaisamari Kostilainen, Helsinki University; Johanna Rellman, Tampere University

REVIEWING ACTIVITIES

PhD Examination Opponent (7): Marianne Nordhov, Tromsø University, Norway (2011); Ioanna Milidou, Århus University, Denmark (2015); Marika Sipola-Leppänen, Oulu University, Finland (2015); Emilija Wilson, Karolinska Institutet, Sweden (2017); Elin Wahl Blakstad, Oslo University, Norway (2019); Laura Puhakka, Helsinki University, Finland (2019); Trond Nordheim, Oslo University, Norway (2020)

Reviewer of PhD theses (8): Pauliina Hiltunen, MD, Oulu University, (2003); Minna Hällström, MD, Tampere University, (2005); Satu Långström, MD, Helsinki University, (2007); Emmi Sarvikivi, MD, Helsinki University, (2008); Riikka Turunen, MD, Helsinki University, (2009); Linus Olson, PhD, (2013) Karolinska Institutet; Kaisa Kivistö, MD, Helsinki University, (2015); Elina Kyösti, MD, Oulu University, (2019)

Expert Evaluator of promotions for Professor positions (5): Full Professor at Helsinki University, Finland (2017); Associate Professorships at Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, United States (2019) and in The Hebrew University of Jerusalem, Israel (2020), Reader position, at Imperial College, London, United Kingdom (2019); Full Professorship at McGill University, Canada (2020).

Expert Evaluator of promotions for Docent (Adjunct Professorship) position (4)*:* Marjo Metsäranta, MD, Helsinki University, (2011); Ulla Sankilampi, MD, Kuopio University, (2012); Helena Valta, MD, Helsinki University, (2017); Sonja Strang-Karlsson, Helsinki University, (2017)

SOCIETIES AND EXPERT POSITIONS

Nordic Neonatal Meeting, Advisory Board Member 2003- currently; Consulting expert for the National Supervisory Authority for Welfare and Health (VALVIRA) 2004- currently; Acta Paediatrica, Associate Editor 2010- currently; Functional Planning Group of Obstetric and Neonatal Section in new Women's and Children's Hospital in Turku, Leader (2012); Steering Committee of the Specialist Training Programs at the University of Turku, Faculty of Medicine, Member 2013-, Chairperson 2019-; Member of the Coordinating Committee of Medical Specialist Training at the Ministry of Social Affairs and Health 2017-; National Committee of Medical Specialist Training Member 2013-, Chairperson 2020-.

RESEACRH AND LEADERSHIP TRAINING

Professor Lehtonen did her post-doc research training with Professor Ronald G. Barr at McGill University in Montreal, Canada, in 1996-97 and with Professor Richard Martin and Professor Avroy Fanaroff at Case Western Reserve University in Cleveland, Ohio in 1997-2000.

Professor Lehtonen has got formal leadership training in 2005-2006 (VARSA II, 30 credits) organized by the Hospital District of Southwest Finland.

Professor Lehtonen got training in pedagogy in 2017 (Leading for Change course) organized by Karolinska Institution in Stockholm, Sweden, in regarding pedagogy in specialist training in medical specialities.

Appendix: All on-going grants and submitted grants applications of the PI (Funding ID)

Mandatory information (not counted towards page limits)

On-going Grants (Please indicate "No funding" when applicable):

Project Title	Funding source	Amount (Euros)	Period	Role of the PI	Relation to current ERC proposal[2]
Developmental and Functional outcomes of very preterm Infants (PIPARI)	Signe & Ane Gyllenberg foundation	5,000	2019-2020	My roles as the PI include study design, supervision of graduate and post-graduate students and postdoctoral researchers, analysis and reporting of the results and budget responsibility..	Longterm follow of the developmental and behavioural outcomes of very preterm infants with serial imaging (ultrasound, MRI at term age and fMRI at 13 years) and assessment of mother-infant relationship forms a basis for the knowhow for the planned brain outcomes in **SaveBrain**.
Developmental and Functional outcomes of very preterm Infants (PIPARI)	G.E. Sundell foundation	60,000	2019-2020		
Developmental and Functional outcomes of very preterm Infants (PIPARI); fMRI in preterm infants	Pediatric Research Foundation, Finland	30,000	2019-2020	My roles as the PI include study design, supervision, reporting. The applicant is my collaborator, Professor Riitta Parkkola, Neuroradiology.	
Center of excellence, the Neonatal Intensive Care Unit at Turku University Hospital	The Hospital District of Southwest Finland	50,000	2019-2020	As the director of the unit, I am responsible for evidence-based quality improvement & measuring the performance outcomes of the unit. I have the budget responsibility (>11 ME).	Both academic and clinical performances of the Neonatal Intensive Care Unit at Turku University Hospital are exemplary. The development done within the field of family centred care deserves dissemination to international health care markets.
Center of excellence, the Neonatal Intensive Care Unit at Turku University Hospital	The Hospital District of Southwest Finland	30,000	2020-2021		
Electrical activity of the diaphragm signal as a method to study breathing patterns and apnea in preterm infants.	Maquet Critical Care AB	44,850	2020-2021	My roles as the PI include study design, supervision, reporting.	NAVA ventilation is a baby-friendly ventilation technique being one part of salutogenic environment for very preterm infants. It fits well with the ethos of family centred care.

[2] Describe clearly any scientific overlap between your ERC application and the current research grant or any grant application.

Family Centred Care in Neonatology	The Hospital District of Southwest Finland	21,250	2020	My role as the PI includes innovation and development of tools to implement family centred care and research on the effects on infant, parent, staff and societal perspectives.	The **SaveBrain** intervention, the Close Collaboration with Parents training program, is developed and evaluated with these and earlier research grants.
Family Centred Care in Neonatology	The Hospital District of Southwest Finland	21,250	2021		
Family Centred Care in Neonatology	The Hospital District of Southwest Finland	21,250	2022		

Grant applications (Please indicate "No funding" when applicable):

Project Title	Funding source	Amount (Euros)	Period	Role of the PI	Relation to current ERC proposal[2]
The Effect of Close Collaboration with Parents training and Single Family Room design on the Length of Stay in Hospital	Pediatric Foundation (in Finland)	161,089.00	2021-2023	My role as the PI includes study design, supervision of the PhD student and postdoctoral student involved in the study, analysis and reporting of the results and budget responsibility.	This project utilises national register data to evaluate the effects of the Close Collaboration with Parents training program and Single Family Room units on the length of hospital stay and, thereby, the economical effects on the society.

Section c: Ten years track-record (max. 2 pages)[3]

RESEARCH INTERESTS AND EXPERTISE

I have authored 182 scientific articles in English including 11 review articles; 124 of them during the last ten years (List of publications). **Web of Science Core Collection** finds 180 documents and gives h-index 37, without self-citations 34; **Scopus** finds 189 documents and gives h-index 39, without self-citations 35 (Date of search: 14.8.2020). I have supervised 12 PhD students; 8 of them since 2010. Five PhD students are currently under supervision; 3 of them close to their public defence.

My research has focused on infant behavior since my PhD studies at University of Turku followed by postdoctoral studies at the McGill University, Montreal in 1996-1997 and Fellowship in Rainbow Babies and Children's Hospital at the Case Western Reserve University, Cleveland, Ohio in 1997-2000. When returning to Finland in 2000, I started a large, still ongoing multidisciplinary research project in the University of Turku (www.utu.fi/pipari) to identify medical risk factors and protective factors for brain development and long-term outcomes of preterm infants. The PIPARI Study project has produced 69 publications and 11 PhD theses; currently 8 PhD theses are ongoing. Research findings from my studies have shown that good child development is associated with parents' involvement and parents' psychological wellbeing. These findings have motivated me to develop, together with two psychologists, a program to integrate parents in the neonatal care. In order to achieve this goal, we developed the Close Collaboration with Parents training program and studied its effectiveness in a rigorous scientific way in a team including psychologist Sari Ahlqvist-Björkroth, PhD, Professor Zack Boukydis, PhD (deceased in 2015) and Professor Anna Axelin, RN, PhD. We have implemented and studied the training in 14 hospitals so far. I am also a member of the Steering group of SCENE Network (Separation and Closeness Experiences in the Neonatal Environment, www.utu.fi/scene) including most European countries. With the SCENE Group, I have led together with Professor Axelin, two European surveys about parents' presence in neonatal units (www.utu.fi/scene).

I led a national study, the PERFECT Preterm Study in 2004-2010, showing the benefits of centralizing preterm births to level III hospitals. The findings were recently repeated in the preterm infant population in England and published in BMJ in a collaboration with Dr Chris Gale, MD, and Professor Neena Modi, MD, from the Imperial College, London. I represent Finland in iNeo Research group (since 2015-) led by Professor Prakesh Shah at Mount Sinai Hospital in Toronto, Canada. iNeo Research group is an international collaboration comparing care strategies and outcomes using population-based register data on very preterm infants. I was the main author in a recently published paper (J Pediatrics) about the impact of family rooms on infant outcomes in seven countries.

EXAMPLES OF LEADERSHIP AND WIDER IMPACT

I am Professor in Pediatrics at the University of Turku, Finland and the Director of the Division of Neonatology at Turku University Hospital in Turku, Finland. Within the hospital position, I have contributed significantly to the building of the new Women's and Children's Hospital in Turku, Finland by acquiring substantial experience from international examples, including working for seven months at Uppsala University Hospital which function with family room design. I led the functional planning group for Obstetrics and Newborn Care at the Turku University Hospital. The building is now being constructed based on those plans. My research area links strongly to the design issues of newborn care. I have contributed to a major textbook in neonatology by writing a chapter Optimization of NICU Design (authors Lehtonen L and White R. In Fanaroff & Martin's Neonatal-Perinatal Medicine. Diseases of the Fetus and Newborn. 11th Edition. Elsevier Saunders. Eds Martin RJ, Fanaroff AA, Walsh MC. Pages 577-593.)

My teaching responsibilities in the University focus on medical specialist training. I have been in leading positions both at the University of Turku as well as at the Ministry of Social Affairs and Health, Finland, related to the process of remodeling the training of medical specialists in Finland, within all 50 medical specialties. The main goals have been to unify the training programs nationally (learning goal were unified in July 2020) and to transition from time-based to competency-based training.

MAJOR CONTRIBUTION TO THE EARLY CAREERS OF EXCELLENT RESEARCHERS

My major contributions to the early careers of excellent researchers include mentoring for Associate Professor Anna Axelin in Nursing Sciences, Associate Professor Riikka Korja in Developmental Psychology and Dr Emmi Helle (née Korvenranta) in Pediatrics, who has a 4-year funding from the Finnish Academy of Science. Of all 12 PhD graduates I have supervised, five have done postdoctoral research abroad: three in the USA, one

in Sydney, Australia, and one in Uppsala, Sweden. In addition, one did part of his PhD project in Toronto, Canada and in London, England. I value international collaboration as an essential part of top research.

TEN REPRESENTATIVE PUBLICATIONS

My key articles are listed below reflecting my contribution on the organization of neonatal care between hospitals and developing family centred care and related hospital facilities.

1. **Lehtonen L**, Lee SK, Kusuda S, Lui K, Norman M, Bassler D, Håkansson S, Vento M, Darlow BA, Adams M, Puglia M, Isayama T, Noguchi A, Morisaki N, Helenius K, Reichman B, Shah PS; International Network for Evaluating Outcomes of Neonates (iNeo). Family Rooms in Neonatal Intensive Care Units and Neonatal Outcomes: An International Survey and Linked Cohort Study. J Pediatr. 2020:S0022-3476(20)30710-1. doi: 10.1016/j.jpeds.2020.06.009. Online ahead of print
2. Ahlqvist-Björkroth S, Axelin A, Korja R, **Lehtonen L**. An educational intervention for NICU staff decreased maternal postpartum depression. Pediatr Res. 2019;85(7):982-986.
3. Helenius K, Longford N, **Lehtonen L**, Modi N, Gale C; Neonatal Data Analysis Unit and the United Kingdom Neonatal Collaborative. Association of early postnatal transfer and birth outside a tertiary hospital with mortality and severe brain injury in extremely preterm infants: observational cohort study with propensity score matching. BMJ 2019;367:l5678.
4. Aija A, Toome L, Axelin A, Raiskila S, **Lehtonen L**. Parents' presence and participation in medical rounds in 11 European neonatal units. Early Hum Dev. 2019;130:10-16.
5. Raiskila S, Axelin A, Toome L, Caballero S, Montirosso R, Normann,E, Hallberg B, Ewald U, **Lehtonen L.** Parents' presence and parent–infant closeness in 11 NICUs in six European countries varies between and within countries. Acta Paediatr. 2017 Jun;106(6):878-888
6. Raiskila S, Axelin A, Rapeli S, Vasko I & **Lehtonen L**. Trends in care practices reflecting parental involvement in neonatal care. Early Hum Dev 2014;30:863-867.
7. Soukka H, Grönroos L, Leppäsalo J, **Lehtonen L**. The effects of skin-to-skin care on the diaphragmatic electrical activity in preterm infants. Early Hum Dev. 2014;90(9):531-4.
8. Korja R, Huhtala M, Maunu J, Rautava P, Haataja L, Lapinleimu H, **Lehtonen L** and the PIPARI Study Group: Preterm infant's early crying associated with child's behavioral problems and parents' stress. Pediatrics 2014; 133(2): e339-345.
9. Axelin A, Ahlqvist-Björkroth S, Kauppila W, Boukydis Z, **Lehtonen L**: Nurses' perspective on the Close Collaboration with Parents Training Program in the NICU. MCN Am J Matern Child Nurs 2014;39(4):260-8.
10. Korvenranta E, Linna M, Rautava L, Andersson S, Gissler M, Hallman M, Häkkinen U, Leipälä J, Peltola M, Tammela O and **Lehtonen L** for PERFECT Preterm Infant Study Group. Hospital costs and quality of life during the 4 years after very preterm birth. Arch Pediatr Adolesc Med 2010;164:657-663.

INVITED PRESENTATIONS

Before the Covid-19 pandemic, have given several invited talks each year, in 15 countries in 2016-2020. The most notable of the during the last 5 years are two talks at the **Graven's Conference in Florida, USA** (2020); two talks at the **55th Annual Congress of Japan Society of Perinatal and Neonatal Medicine** (2019) accompanied by a talk at Nagano Children's Hospital in Japan; two talks at the Israeli Neonatal Conference in Tel-Aviv (2019) accompanied by two other talks in Tel-Aviv and Jerusalem in Israel; **Joint European Neonatal Societies Conference in Maastricht, the Netherlands (2019) and in Venice, Italy (2017)**; Swedish Neonatal Quality Register, Stockholm, Sweden (2019); **the Australian and New Zealand Neonatal Network Meeting CPI2018, Sydney, Australia** (2018); Family Integrated Care Conference in Leeds, England (2019) and in Sydney, Australia (2018); 99nicu conference in Copenhagen (2019), Denmark, and in Vienna, Austria (2018); Neonatal Conference in Poznan, Poland (2019 and 2016), Cleveland Clinics, Ohio, USA (2018); La Fe Children's Hospital, Valencia, Spain (2018), the VIII Neonatology Conference in Kosice Slovakia (2018); European Perinatal Conference, St Petersburg, Russia (2018), the Queen Charlotte's Hospital at the Imperial College in London (2018); Residency Training in Changing Healthscape in Stockholm (2018); SCENE Symposium (I was also an organizer) in Budapest, Hungary (2019), in Lecco Italy (2018), in Ghent, Belgium (2017), and in Falun, Sweden (2016); the Neonatal Society of Latvia (2017), Gyllenberg Foundation Symposium in Helsinki, Finland (2016); Nordic Neonatal Meeting (I was also an organizer) in Århus, Denmark (2016), Maternal-Infant Nutrition and Nurture Conference, Falun, Sweden (2016); The European Workship on Neonatology, Santorini, Greece (2016).

ERC Advanced Grant 2020

Part B2

Title: Emotional environment modulation to optimize brain development in preterm infants

Acronym: SaveBrain

Section a. State-of-the-art and objectives

Preterm infants are hospitalized during the critical phase of brain development. The **SaveBrain** project stems from the need to understand the environmental factors underlying the abnormal structural and functional brain development and delayed brain growth seen in preterm infants despite modern medical care. Current neonatal research and care emphasizes the nutritional and physiological needs of preterm infants, in addition to prevention of major structural complications of prematurity. Very little attention is paid to their emotional needs, even though the life-long bond between the parent and the newborn should be created soon after birth.

SaveBrain introduces a novel paradigm of the **emotional environment as an essential brain protective factor** in preterm infants and **studies how the emotional environment affects the brain outcomes in preterm infants. SaveBrain** has the potential to provide knowledge which will change the current priorities in neonatal care. By providing evidence of the role of the emotional environment in the brain development of preterm infants, it will help this area of care to receive the same attention as the physiological stability and nutritional needs of preterm infants are given today. The consequences of abnormal brain development will be alleviated in a large group of infants; 6 to 12% of all children are born preterm. Therefore, the impact of better brain development will extend from the individuals and their families to the societal level by reducing the costs of care required due to developmental problems and by improving the productivity of the individuals born preterm.

SaveBrain studies the effects of the emotional environment on the brain outcomes in preterm infants during the critical time period of their brain growth and development in neonatal intensive care.

The parent-infant bonding process is based on hormonal and physiological mechanisms (1-3) and **multisensory, reciprocal experiences during parent-infant closeness and interactions** (4-5). Both human and animal studies have shown that seeing, hearing, touching and smelling the baby will activate the subcortical regions and increase the volume of the grey matter in the subcortical areas in both parents, as summarized by Ruth Feldman (6); less is known about the effects on the brain of the infant. The developmental effects of sensory experiences cross the borders of senses: for instance, tactile stimuli can increase visual function (7) and visual stimuli can affect auditory function (8), which emphasizes the holistic way that environmental experiences affect infant development. The vital importance of tactile contact for infants was shown by the historical experiment by Dr Harry Harlow (9) which demonstrated that rhesus monkey infants preferred a soft, clothed surrogate without food over a wire surrogate with food. The infant monkeys stayed playful and curious only in the presence of the clothed surrogate. Primate studies, together with historical studies of hospitalized and institutionalized infants, have proven the **crucial importance of affective interactions; the lack of such interactions leads to long-lasting consequences on emotional-behavioral development**, summarized by van der Horst and van der Veer (10) and Sullivan (3). Since then, research has shown that being **deprived of parent-infant closeness affects the structural brain development**. Care in institutions results in adverse brain effects compared to foster care or adoption (11-20); low birth weight infants are especially sensitive to separation (20). The separation of preterm infants into private hospital rooms alters the development of their brain gyration in the language processing area of the temporal lobe (22). These studies are relevant in current neonatal care, as the intensive care environment in hospitals is a radically different

emotional environment compared to the circumstances of healthy full-term infants, who spend most of their waking hours in the company of others. It is reported from an American hospital that hospitalized preterm infants spend 80% of their time alone without any human contact (23). A European survey showed a large variation in parents' presence between hospitals, starting from 2.6 hours per day (unpublished data). In a large international survey, only 13.3% of 331 neonatal units provided parents with the facilities needed to stay with their infant throughout a 24-hour day (24). The loneliness of preterm infants deprives them from tactile, kinesthetic, olfactory, gustatory, auditory and visual contact with their parents. Instead, hospitalized preterm infants are exposed to unphysiological sensory experiences that could never occur in the physiological in utero environment, such as high-decibel noises, often sudden alarms (25), bright lights (26), the taste and smell of feeding/intubation tubes, painful procedures such as frequent skin punctures (27) and removal of tapes and electrodes and unpleasant airway suctioning.

Hospital facilities that allow parents to stay with their preterm infants are beneficial for short-term outcomes (better survival, better growth, fewer infections, fewer hospital care days) (24, 28), as well as the long-term social-behavioral and cognitive development of the preterm infants (29). In spite of these observations, there is no knowledge **about the way emotional exposure influences the preterm infants' brain structure and function** or what the critical time windows are.

The present project introduces a novel paradigm of an **emotional environment as an essential brain protective factor in preterm infants. Emotional environment** is defined as multisensory environmental exposures provided in reciprocal interactions with parents, combined with a lack of unphysiological stimuli. In **SaveBrain**, these exposures will be measured by documenting the parents' presence; parent-infant skin-to-skin contact; infant-directed speech with expression of positive affect; parents' participation in alleviating infant pain; breastfeeding; the parents' physiological and psychological wellbeing; and stronger parenting experiences. Harmful exposures to be documented are painful procedures and noise.

The emotional experiences are mediated to the preterm infant through the sensory channels, which emerge in the following order: tactile - olfactory/gustatory - vestibular - auditory - visual (30). In earlier studies, the effects of sensory exposures have been studied separately or in clusters, most commonly studied exposures are tactile stimuli (31). Noise reduction has been performed even with silicone earplugs, excluding also developmentally supportive auditory stimuli (32). The approach in **SaveBrain** differs profoundly from earlier studies by providing the sensory exposures as a part of reciprocal, emotional parent-infant interactions. This paradigm is supported by the findings from a foster care vs orphanage care study showing that the emotional components of care, such as sensitivity with child-centred responses, as well as positive attitude towards the child in the form of acceptance, respect, and warmth, were independent determinates of catch-up growth. This then associated with higher cognitive scores at 42 months of age (33). Furthermore, the PI with her student and collaborators showed that the lack of the mother's daily visits in the neonatal unit was a stronger predictor for clinically significant behavioural problems of preterm infants at school age than any medical factors (34). More recent studies have shown that preterm infants got higher scores in cognitive and language tests if their mothers had been actively involved during their hospital care (35) and if the breastmilk volumes were higher (29). One potential mechanism for better language development is the exposure to adults' words, which stimulates the development of language processing (36). Another plausible pathway to better developmental outcomes is via better parent-infant bonding and parent wellbeing. The postpartum period is a sensitive period for both mothers and fathers to develop a loving bond to their infant, strongly regulated by oxytocin hormone and its effects in the limbic network of the brain, the centre for reward and emotionality (6). The smell of the infant and parenting experiences have been shown to elicit structural and functional neurobiological changes in the subcortical brain areas, including the medial preoptic area of the hypothalamus, the hippocampus, amygdala and dopamine reward circuit and their cortical connections (37). Skin-to-skin contact will increase parents' oxytocin levels (38). Depriving parents of physical closeness and early parenting experiences will endanger the long-term development of parenting, including parent orientation to their infant, ability to sensitively understand the infant's needs and social signals and to plan long-term parenting goals. Therefore, early intervention in the hospital can potentially have a carry-on effect, via parenting modification, on the long-term development of the child.

SaveBrain will implement an educational intervention for neonatal staff, developed and studied by the PI and her collaborators. This intervention, the Close Collaboration with Parents training, has been shown to improve family centred care in neonatal units, thereby potentially improving the emotional environment through several mechanisms. It is one of the few interventions that acknowledge and support the parents' unique role already

during the neonatal care. By training the entire staff, all infants will be exposed to care that is more inclusive of all parents from the birth, irrespective of the medical condition of the infant. The intervention provides the staff with better skills for supporting parenting and working in partnership with the parents. So far, the PI and her collaborators have shown that both parents and staff report improved family cantered care after the intervention compared to the situation before the intervention in neonatal intensive care units (39). The parents' psychological wellbeing was better supported, as they were listened to more, and they reported better emotional support after the intervention. Consistently, nurses reported improved skills in providing emotional support and listening (manuscript submitted). The intervention increased the parents' presence by 37% and parent-infant skin-to-skin contact by 51% in nine hospitals (manuscript submitted) and decreased maternal depressive symptoms (40).

Skin-to-skin contact will provide positive tactile stimuli, counteracting painful tactile stimuli produced by medical care (41) and the harmful consequences of painful procedures (42). Skin-to-skin care also provides reciprocal olfactory and auditory stimuli, visual contact, and more vestibular-proprioceptive stimuli than care in an incubator. A meta-analysis of 124 studies showed that skin-to-skin care improved head growth (43), but no one has shown how it affects the total or regional brain volumes.

The parents' presence will enable their active role in caregiving and in alleviating infant pain. These activities are likely to include infant-directed parent talk and parent responses to infants' cues and reactions, making the interaction more child-centred and warmer than interaction provided by changing staff members. The involvement of mothers has been shown to decrease the amount of painful procedures (28).

SaveBrain assumes that the parents' wellbeing can be improved in a way that affects the emotional environment of the infant. This assumption is based on research finding that the Close Collaboration with Parents training decreased maternal depressive symptoms still six months after the due date (40). Preterm infants have been shown to synchronize their stress level indicator, cortisol, to the caregiver´s level when having been prolonged time periods skin-to-skin with the parent (44-45). Parent stress and depression are known risk factors for child psychopathology (46-47). Therefore, we will measure the wellbeing of parents as one factor influencing the emotional environment of the infant. No one has shown, so far, that parent wellbeing during hospitalization is associated with better infant brain outcomes in early infancy.

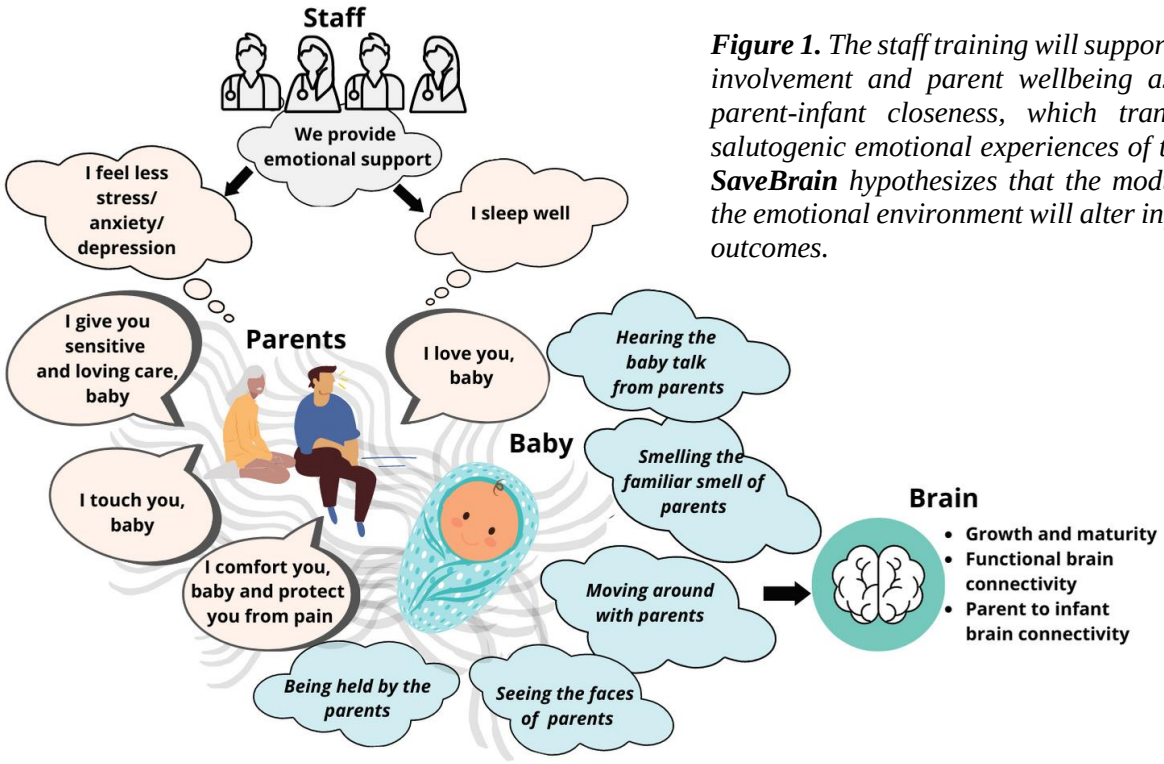


Figure 1. *The staff training will support parental involvement and parent wellbeing as well as parent-infant closeness, which translates to salutogenic emotional experiences of the infant.* ***SaveBrain*** *hypothesizes that the modulation of the emotional environment will alter infant brain outcomes.*

Central Question of the Research Project

The central question of this research project is how emotional environment affects the structural and functional brain development of hospitalized preterm infants. SaveBrain hypothesizes that the intervention improves brain outcomes and that the effect is mediated by an improved emotional environment. The SaveBrain hypotheses are that preterm infants in the post-intervention cohort, as compared to the pre-intervention cohort, will have better brain growth, more mature gyration and white matter tracts, and stronger functional connectivity at term age. Furthermore, they will have better parent-infant synchrony of the social brain activity and more optimal parent-infant interaction at four months after term age. The study will also analyse which elements of the emotional environment change and when, and which elements are more resistant to change. SaveBrain hypothesizes that the brain effects are mediated by an improved emotional environment. The study will also analyse which dimensions of the emotional environment change and when, and which dimensions are more resistant to change.

The specific hypotheses are that the Control and Intervention cohorts will differ in:

1) Total brain volumes, volumes of the medial temporal structures and volumes of the deep brain regions including areas central to parenting and emotionality: the thalami, hippocampus, amygdala, and hypothalamus

2) Gyration patterns, including temporal lobe asymmetry

3) Maturity of the pathways in the white matter, including the corpus callosum and the major motor pathways

4) Functional connectivity, especially in the thalamo-cortical pathways and the limbic pathways

5) Neurobehavioral performance

6) The quality of parent-infant interaction

7) Parent-infant synchrony in the brain activation of the orbitofrontal cortex in an interaction situation.

8) Total amount of exposures forming the emotional environment

Section b. Methodology

1) Research Design: A hospital-based, multicenter, before and after the intervention study

SaveBrain compares two cohorts of preterm infants: The first cohort will be recruited before the intervention, over a time period of six months (Control), and the second cohort after the intervention (Intervention). The emotional environment during hospital care and brain outcomes will be measured for both cohorts. Preterm infants born at 22 to 32 gestational weeks will be recruited in the Kaunas, Lithuania and Ghent, Belgium. The estimated number of such infants during a 6-months period will be 78 in Kaunas and 73 in Ghent, based on 5-year statistics. The duration of the exposure to the emotional environment in the hospital might vary between 4 and 18 weeks before discharge home or to another hospital.

2) Intervention

The educational intervention, the Close Collaboration with Parents training, developed in Turku University Hospital, Finland, will be implemented both in the Hospital of the Lithuanian University of Health Sciences Kaunas Clinics, in Lithuania, and in Ghent, Belgium, to increase the parents' involvement in the unit. The training is targeted to the staff; a minimum of 75% of the staff members will be trained within an 18-month time period. The training includes theory, exercises, practical training and reflection. The theory is studied and the exercises started independently using an e-learning tool, which is already developed and currently being piloted in English. The training will continue with practical training in clinical situations with a trained mentor, followed by reflection with the mentor.

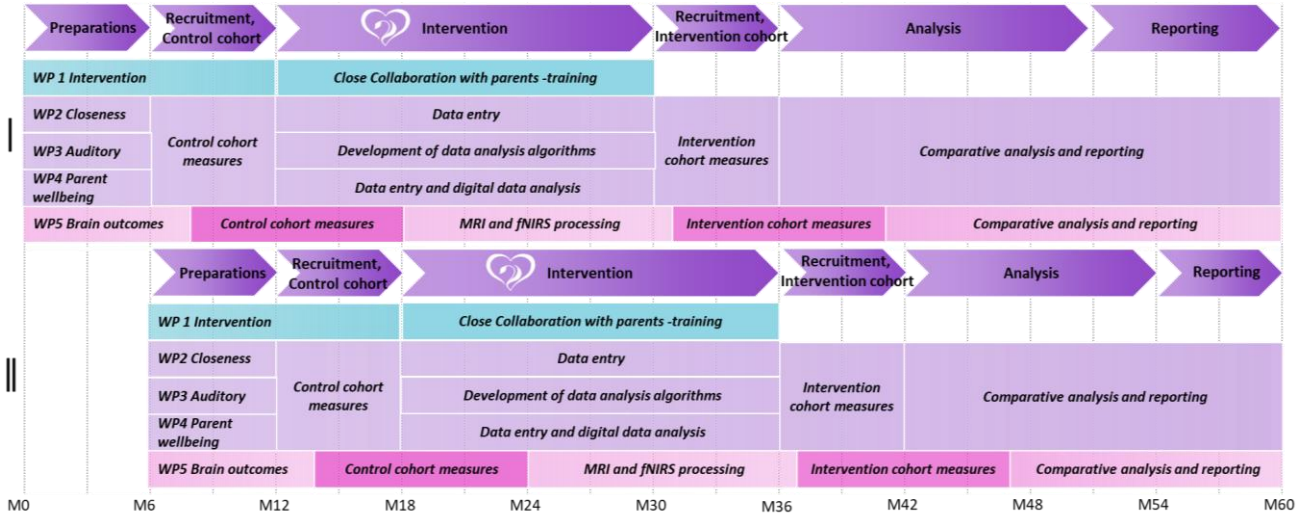
3) Outcomes

The **SaveBrain** outcome measures include infant brain volumes, structures and function at term age (40 gestational weeks) and social brain functions, measured at 4 months after term age (Table 1). The mediating factor resulting in better brain outcomes is the emotional environment of the unit, which will be measured and expected to become more salutogenic as a result of the intervention.

4) Timeline

Research project preparations, including acquiring ethical permission and study permission in the target hospitals in Kaunas, Lithuania, and Ghent, Belgium, will begin after the funding decision has been made. From the beginning of the funding period, the study will last for a total of 60 months, divided into overlapping tasks shown in *Figure 2*. Measurement preparations in the unit (6 months), pre-intervention measurements in the unit (6 months), pre-intervention child outcomes (8 months), the Close Collaboration with Parents intervention (18 months), post-intervention measurements in the unit (6 months), post-intervention child outcomes (8 months), analysis of data (16 months) and reporting of the results (8 months).

Figure 2. *The timeline to study the emotional environment and the developing brain in the* ***SaveBrain*** *project and its WorkPackages in two hospitals.*



SaveBrain WorkPackages and the outcome measures

The **SaveBrain** measures are divided into five **WorkPackages** (**WPs**), including appropriate collaborators. WP1 implements and documents the implementation of the intervention in two hospitals. The emotional environment is divided into WP2, which looks at parent-infant closeness and interaction, WP3, which focuses on the auditory environment, specifically positive emotions in infant-directed speech, and WP4, where the parents' wellbeing is studied. WP5 consists of the infant brain outcomes at term age and four months after term age.

The **intervention (WP1)** will consist of the 18-month-long training program for the neonatal staff of the target hospitals in Kaunas, Lithuania, and Ghent, Belgium. The training will be carried out by our experienced trainer team from Turku University Hospital, who have previously provided the training in 14 hospitals. Automated user data will be extracted from the e-learning tool to confirm fidelity to the training.

The **emotional environment (WP2-4)** will be measured before and after the intervention to document the change. As the parent-infant emotional closeness can be supported in different ways in the different phases of the care of a preterm infant, the measurement periods are divided into five different time windows, starting from the delivery room and ending with the transition to home: I. Initial stabilization in the delivery room (usually less than 30 minutes); II. Admission to the neonatal intensive care unit (the first two hours); III Intensive care period (days to weeks); IV. Convalescent care period, 'feeder and grower' (weeks); V. Transition to home (last week in the hospital). *Figure 3*. All parent measures include separate measures for mothers and fathers/partners. The methods are explained in *Table 1*.

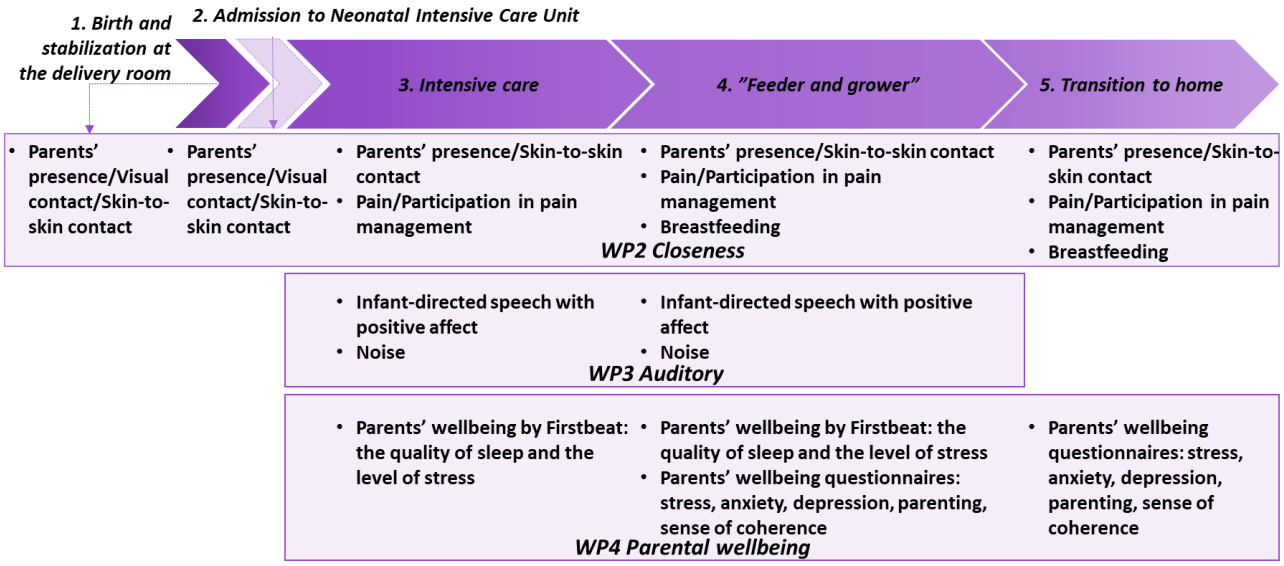
WP2 (Closeness) will focus on **parent-infant closeness,** documenting parent-to-infant visual contact, parent-infant skin-to-skin contact, parents' presence in the infant's hospital room, breastfeeding, and parent involvement in infant pain management.

WP3 (Auditory) will measure the exposure to infant-directed speech with emotionally positive valence and exposure to noise using day-long bedside audio recordings captured with a LENA recorder (48-49), allowing analysis of the complete auditory environment that an infant is exposed to. The software included in LENA enables automatic speech detection and speaker categorization (infant vocalizations or speech by male adults, female adults, and other children). Although the adult word count has been shown to support language

development in preterm infants, there is no research about the effects of emotional quality and infant-directed speech in preterm infants. Beyond linguistic input, **SaveBrain** will utilize automatic emotion classification (50-51) on adult speech segments to measure the amount of positive, neutral and negative affect in infant-caregiver verbal interactions. The emotion classification will be conducted according to arousal (low/high) and valence (negative/positive) continuums. To identify infant-directed speech segments, we will utilize existing state-of-the-art algorithms as a starting point. We will further develop and adapt the classifiers using day-long hospital bedside audio data collected prior to this study and during this study. To this end, domain adaptation and active learning techniques will be utilized. As a result, we will be able to quantify the relative amount of positive speech to each infant in the NICU. Our hypothesis is that the exposure to infant-directed speech with positive emotional valence will increase and the exposure to noise will decrease after the intervention, affecting infant brain development positively.

Parent wellbeing and parenting (WP4) will measure the parents' stress, physical activity, sleep and depression during the infant's hospital care, as well as attachment, parenting competences, and sense of coherence at transition to home by using physiological data and questionnaires. Physiological data on beat-by-beat heart rate and heart rate variability (HRV), respiratory rate and body movements will be collected using commercially available, valid sensors and algorithms developed by Firstbeat (www.firstbeat.fi), a provider of physiological analytics for sports and wellbeing, specialized in heart rate variability monitoring and analysis technologies. The algorithm uses age, height, weight, and gender as background information and provides information on sleep duration, sleep latency, sleep stage identification, and overall sleep score (based on sleep duration, HRV-based stress and recovery information, sleep stages, and movement-based restlessness factors). HRV data can be used to estimate autonomic nervous system balance, indicating stress and recovery (52-56). A movement detector provides information about physical activity intensity and duration. A 72-hour recording using a sensor on the chest, along with a sleep diary, will be collected from parents every third week during the hospital stay of the infant. Well-validated and widely used questionnaires (*Table 1*) about stress, depressive symptoms, mental well-being, parenting, attachment, and sense of coherence will be filled in by both parents when the infant is at 32 gestational weeks and before discharge to home. In addition, parent anxiety, depression and self-efficacy will be measured again at 4 months after term age.

Figure 3. *The measuring of the emotional environment during different time windows of preterm infant care*



Brain outcomes (WP5) will measure how the emotional environment affects the infant´s brain development during a developmentally critical time period. The measurements consist of magnetic resonance imaging (**MRI**), **functional MRI**, dyadic functional Near InfraRed Spectroscopy (**fNIRS**), **clinical assessment** and **automated face recognition** of parent-infant interaction and infant neurobehavior. The most novel method used is dual fNIRS, which is an emerging method in the research of infant development (57). fNIRS measures relative concentrations of oxygenated and deoxygenated hemoglobin in the brain tissue, indicating cerebral activation and deactivation. Simultaneous recording of the parent and the child allows research on social interactions and social synchrony (58). The downside of fNIRS is its shallow penetrance into the brain. Therefore, MRI and fMRI will be used to complement this method by providing precise data on the deep brain structures and networks.

1) **MRI at term age** (40 weeks of gestation)

MRI will be performed during sleep, after feeding. The scan will be performed using 3Tesla MRI equipment available in both Kaunas and Ghent. A brain MRI can be performed without sedation at a 97% success rate at term age, as shown in the PIPARI study. The imaging will include voxel based morphometry (**VBM**) and tensor based morphometry (**TBM**) (59), which are both artificial intelligence-based analysis methods, to analyse the brain volumes and gyration patterns; diffusion tensor imaging (**DTI**) to analyse the microstructure of the white matter tracts based on Tract Based Spatial Statistics (60); and functional MRI (**fMRI**) to study brain connectivity using dynamic fluctuations of the resting state activity (61).

2) fNIRS during interaction at 4 months after term age

fNIRS will be recorded simultaneously from the parent and the infant to study the synchrony of their brain activities during a free play situation. The situation will be videorecorded and repeated with both the mother and the father. Measurement detectors will be implanted in a cap, forming 24 channels used to locate the brain activation. The area of interest is the orbitofrontal cortex, shown to be related to the unique mother-infant relationship (58). Three-month-old infants have shown more activation of the orbitofrontal cortex in response to infant-directed speech by females as compared to adult-directed speech (62).

3) **PCERA and computer-vision based face recognition at 4 months after term age**

The videorecorded mother-infant and father-infant interactions – the same ones used for fNIRS – will be assessed using the Parent-Child Early Relational Assessment (**PCERA)** for the quality of the mother-infant and father-infant relationships and automated **face recognition** for emotions and eye contacts. The baby will be placed in a babysitter, and the parent will be placed face-to-face with the baby during the parent-infant free play situation. PCERA will provide information on the quality of interaction for the parent and the infant separately, as well as for the dyad. The items to be scored include parent and child positive emotions during the interaction and the regulation of emotions. The psychometric properties of PCERA are good and well documented (63-65).

The interaction will be also analysed for facial emotions utilizing **FaceReader** by Noldus Information Technology which is a computer-vision based solution for measuring people's facial emotions. The performance of FaceReader has been shown to be reliable in adults (66), but in young infants it is still under research (Baby FaceReader). We test how the facial emotions of the infant can be classified according to degree (low/high) and valence (negative/positive) using computer-vision and how this data relates to PCERA and fNIRS. In addition, Noldus's **The Observer XT** will be used to quantify the number of parent-infant eye contacts.

In addition to the main study question about the effects of the emotional environment on the quality of social brain functions, **SaveBrain** can also study how the interaction behaviour of the parent (PCERA) affect infant social brain activation (fNIRS), thereby exploring potential mediating mechanisms for the effects. In addition, this study will provide an opportunity to study the paternal and maternal brain separately after the long hospitalization of the infant, which may have affected them differently.

4) The NICU Network Neurobehavioral Scale (NNNS)

NNNS (67) will be utilized to assess infant neurobehavior. It has been shown that the neurobehavioral performance of preterm infants is related to the parents' presence (68), to the level of infant-centred care in the unit (69), and to the design of the unit (28).

Table 1. *The* ***SaveBrain*** *WorkPackages used to develop and measure the emotional environment of a neonatal unit and to measure its impact on the infant brain outcomes.*

WP1 **Intervention**	**WP1 (Intervention)** will carry out the 18-month-long training program for the neonatal staff of the target hospital. The training will be carried out by an experienced trainer team (70). **Method:** Automated user data will be extracted from the e-learning tool to confirm the fidelity to the training program.
WP2 **Closeness**	**WP2 (Closeness)** will focus on **parent-infant closeness,** documenting parent-to-infant visual contact, parent-infant skin-to-skin contact, the parents' presence in the infant's hospital room, breastfeeding, and parent involvement in infant pain management. **Phase I-II** Early parent-infant visual contact* **Method:** Medical chart documentation and the parents' interviews after recruitment.
	Phase I-III The first skin-to-skin contact** with mother and father **Method:** Medical chart documentation and the parents' interviews after recruitment.
	Phase III-IV Duration of parent-infant skin-to-skin contact **Method:** Closeness Diary for skin-to-skin contact, kept by the parents throughout the hospital care period after recruitment (71).
	Phase III-IV The parents' presence: the timing of the first visit and total duration **Method:** The parents' first visit in the patient room, from medical documentation and interviews after recruitment. The parents' presence in the patient room documented by the AeroScout Real-Time Locating System, a tag carried by parents and connected to hospital wifi. https://www.stanleyhealthcare.com/aeroscout-rtls, throughout the hospital stay after recruitment.
	Phase IV-V Beginning of breastfeeding*** **Method:** Medical chart documentation and the parents' interviews at discharge
	Phase III-IV Parent involvement in pain management and the number of painful procedures **Method:** Medical chart documentation and the parents' interviews at discharge
WP3 **Auditory**	**Phase III-V** Infant exposure to infant-directed speech with positive emotions and infant exposure to noise **Method:** A 16-hour recording by a LENA recorder with automatic speech detection and speaker categorization when the infant is at 32 gestational weeks and during the last week in hospital. A machine learning algorithm will be developed and used to detect infant-directed speech and perform speech emotion classification.
WP4 **Parent wellbeing**	**Phase III-V** The parents' physiological stress levels **Method:** Firstbeat Bodyguard 2 to capture 72-hour physiological data every third week; an algorithm to analyse the level of stress based on beat-to-beat heart rate variability.
	Phase III-V The parents' quality of sleep and level of activity **Method:** Firstbeat Bodyguard 2 to capture 72-hour physiological data every third week; an algorithm to analyse the duration and quality of sleep and the duration and level of physical activity (minutes per day, light/moderate/vigorous).
	Phase IV-V The parents' stress, anxiety and depression; questionnaire **Method:** The PSS:NICU questionnaire (72) and the 12-item Perceived Stress Scale (73), the Generalized Anxiety Disorder questionnaire (GAD-7) (74), the Edinburgh Postnatal Depression Scale (EPDS) (75) and Sense of Coherence SOC-9 (76) for both parents when their infant is at 32 gestational weeks and one day prior to discharge home.

	Phase IV-V Parenting and Sense of Coherence; Questionnaires **Method:** The Maternal Postnatal Attachment Scale (MPAS) and the Paternal Postnatal Attachment Scale (PPAS) (77), Tool to Measure Parenting Self Efficacy (78) and the Karitane Family Outcomes Tool (79) for both parents when their infant is at 32 gestational weeks and one day prior to discharge home.
WP5 **Brain outcomes**	Total and regional brain volumes and gyration **at term age** (40 weeks of gestation) **Method:** MRI, Voxel Based Morphometry and Tensor Based Morphometry analysis algorithms.
	Microstructure of white matter tracts **at term age Measure:** MRI, Diffusion Tensor Imaging using Tract Based Spatial Statistics to measure the maturity of the white matter tracts connecting limbic and paralimbic brain regions.
	Functional brain connectivity **at term age** **Method:** fMRI, dynamic fluctuations of the resting state activity focusing on the functional connectivity between thalami and bilateral somatosensory cortex, and between limbic and paralimbic brain regions.
	Interpersonal social brain activity **at 4 months** after term age **Method:** Dual parent-infant functional Near InfraRed Spectroscopy to study parent-infant brain synchrony during a videorecorded free play interaction.
	Interpersonal social brain functions **at 4 months** after term age **Method:** PCERA and Noldus Baby FaceReader and ObserverXT from the videorecorded free play interaction to assess the mother-infant and father-infant relationships, focusing on the expression of emotions and the quality of interaction, as well as the facial expression of emotions and eye contacts.
	Neurobehavioral performance of the infant **at 4 months** after term **Method:** The NICU Network Neurobehavioral Scale.

*The first parent-to-infant visual contact is defined as infant's age in minutes when the parent saw (at least) the face of the infant; the duration of the parent's presence with visual contact to the infant during initial stabilization in the delivery room and during admission a. between the mother and the infant b. between the father/partner and the infant

**Mother-infant and father-infant skin-to-skin contact is defined as the baby lying on the chest of the parent with a diaper and a cap, no other clothes on

***Breastfeeding: beginning (gestational age, weeks); frequency (times per day, when); continuation until discharge (what proportion of total milk at discharge)

**** Parent involvement in pain management in medical care procedures such as heel sticks and suctioning; beginning and frequency (the age of the infant in days, times per day) a. for the mother b. for the father/partner

Statistical analysis

Relevant background data will be collected regarding the study patients and their families to include appropriate confounders in the analyses. Basic background factors (such as gestational age) will be collected from all eligible infants and their families to perform a dropout analysis for potential selection biases. The brain outcomes of the study participants will be compared between Intervention cohort and Control cohort, adjusted for covariates (e.g. gestational age, birth weight z-score, sex, major neonatal morbidities such as intraventricular haemorrhage, sepsis, necrotizing enterocolitis).

This study has potentially 151 preterm infants in both cohorts. Assuming 20% refusal to participate, we will have 120 infants in both cohorts. Further drop-outs may reduce the number of infants with successful brain outcome measures to 100 in both cohorts. The number of infants needed to reach 0.80 power and to detect a relative mean difference of 8% at significance level $p<0.05$ is 88 per group for regional brain volumes. Earlier studies have shown e.g. a reduction in regional brain volumes in those exposed to high vs low amount of skin

breaking procedures in a group of 155 very preterm infants (81). Statistically and developmentally significant differences have been demonstrated in the formation of sulci in the temporal lobe of the brain by comparing 23 and 20 very preterm infants without brain pathology and cared for in different room types (22).

The **SaveBrain** sample is larger than those demonstrating changes in the white matter microstructure using DTI tract-based spatial statistics such as the group differences between care-in-an-institution vs foster care groups analysing (26 and 23 individuals) (21); early deprivation vs controls (36 cases and 16 controls (20); high vs low amount of painful procedures during early neonatal period (a total of 155 very preterm infants) (80). We have earlier shown statistically significant differences in the white matter microstructure between very preterm infants who were either normally grown very preterm infants (n=27) or small for gestational age (n=9) (81). We hypothesise that emotional environment in neonatal unit has an effect size comparable to early separation, painful procedures or antenatal growth failure.

The analysis of resting state activity in the fMRI has been able to show differences when comparing 33 very preterm infants subjected to painful procedures to 13 very preterm infants without invasive procedures (82). The functional connectivity had clinical developmental correlates at two years of age.

fNIRS will measure changes of oxygenated and deoxygenated from the baseline during free play interaction. The mean change in the area of interest is compared between the cohorts. In earlier studies using fNIRS, small numbers of patients have been studied. An experimental study found differences between interaction situations (stressful vs non-stressful) in a group of seven 7-9-month-old infants (83). The technique is, however, new and demanding and 10 infants were studied to get 7 successful recordings. Another study was carried out with 5-month-old (n=43) and 7-month-old (n=48) infants (84). Typical to this measure is a fairly large proportion of technically not successful recordings. **SaveBrain** has a large enough sample to get a sufficient number of technically acceptable recordings.

Caregiving behavior has been shown to associate with the quality of parent-infant interaction in a group of 30 very preterm infants measured by PCERA when the infants were at 6 months of corrected age (85). The **SaveBrain** sample size can be regarded sufficient to demonstrate group differences by PCERA. Baby FaceReader will be explored as a future tool in research of emotions of 4-month-old infants; no preliminary data is available.

To achieve a holistic, broad picture of the emotional environment, the total score for the emotional environment will be created using the mean of z-scores of the individual elements in WP2, WP3, and WP4 (*Table 1*). The salutogenic items (e.g. skin-to-skin contact) are given a positive score and harmful items (painful procedures or noise) a negative score. Cronbach alphas will be calculated for internal consistency, and only elements with sufficient internal validity will be included. Then, this total score and its elements will be compared between the cohorts to test how the educational intervention for the staff improves the emotional environment for preterm infants. Secondary analyses will be performed within the gestational age categories and for different time windows in order to identify patient groups as well as time periods during their care that are susceptible or resistant to change in the emotional environment.

All tests will be performed using linear mixed models with family as a random factor.

Risks and the planned solutions

The proposed project will take place in neonatal intensive care units and involve a vulnerable patient group of preterm infants and their parents. High sensitivity and flexibility are needed to carry out this study. Many of the risks of the study are related to the limitations set by the clinical context that can only be controlled in a limited degree. However, the PI is experienced in clinical research in the context of preterm infant care (*Table 2*).

Table 2. *Potential risks and the planned solutions.*

Risk	Solution
Intervention is not carried out as planned	Fidelity measures. More effort can be invested if the intervention is initially not implemented as planned.
Not enough patients; exposure to improved environment too short	A large target hospital (Kaunas, Lithuania or Ghent, Belgium); care until discharge (Kaunas). If recruitment is slow, the recruitment period can be extended.
Data collection is not carried out as planned	A target hospital with excellent data collection performance in earlier studies (International Closeness Survey in Kaunas and Ghent); a realistic amount of measures per family.
New algorithm used to recognize infant directed speech is not valid or reliable	An established LENA method will be used with valid adult word counts.
Dual fNIRS of parent-infant dyad is not precise	A clinical assessment of parent-infant relationship will be used as a back-up
The improvement in the emotional environment is not large enough	Preliminary data collection showed room for improvement: low skin-to-skin contact in Kaunas, low presence and skin-to-skin contact in Ghent.
No group differences in the brain outcomes	The hypothesis is proved wrong and other alternatives for protecting the brains of preterm infants have to be studied in the future

Ethical considerations

The parents of preterm infants are in a stressful situation, so automated data collection and non-invasive data collection are preferred to minimize the burden for the parents. Tools such as the wellbeing measurement devices (Firstbeat) that parents are asked to carry are commonly used by adults. A team of experienced research assistants will help the parents with the diaries and questionnaires, and they will ensure clinical referral if the questionnaires/imaging reveal a situation requiring an acute clinical intervention. The brain outcome measures are non-invasive and non-ionizing and will be performed without any medication. MRI is recommended as a part of the routine follow-up for the most immature preterm infants (86). The more detailed Ethical Self Assessment is attached (Annex 2).

Conclusion

One in ten infants are born preterm. They are born with an immature brain that undergoes critical development during their hospital stay. When developing the care and care environment, the central driver should be optimal brain outcomes. **SaveBrain** will provide novel knowledge about the role of the emotional environment in optimizing the brain development of preterm infants. This knowledge has the potential to change the paradigm of neonatal care from a technical/medical approach to a more human approach. A paradigm shift in neonatal care is urgently needed to improve the quality of life of infants and their parents during hospital care and to optimize the long-term developmental outcomes of the children. The effects of the paradigm shift will extend from the individuals and their families to the societal level by reducing the costs of care resulting from developmental problems and by improving the productivity of the individuals born preterm.

Using a combination of novel methods and more traditional measures, the project will provide data on the feasibility, validity and reliability of the new tools that can be used to research this vulnerable group of infants.

New machine learning algorithms will provide novel, exciting tools for obtaining information about the emotional auditory environment. Resting state brain activity using functional MRI will provide new information on brain connectivity during early infancy in a group of infants with a heightened risk of brain injuries, and the information will be linked to the emotional environment. The fNIRS information describing the synergy of social brain activation in the parent-infant dyad can be related to the emotional experiences in the neonatal unit as well as to the brain imaging information and parental interaction behaviour, and it also provides insights into the similarities and differences between the maternal and paternal brains after a long hospital stay.

SaveBrain will provide novel information on various elements forming the emotional environment of neonatal care that are susceptible to change and can be modified to become more salutogenic. **SaveBrain** will demonstrate the impact of the emotional environment, its elements and time windows on brain development during a vulnerable period of brain growth and development. We will also learn which elements or time windows are resistant to change; future studies will, then, be needed to tackle the change-resistant elements, as it is also essential to know who should receive additional support and when.

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UNIVERSITY OF TURKU

Commitment of the host institution for ERC Calls 2020[1, 2, 3]

The University of Turku, which is the applicant legal entity, confirms its intention to sign a supplementary agreement with **Liisa Lehtonen**
in which the obligations listed below will be addressed should the proposal entitled **SaveBrain: Emotional environment modulation to optimize the brain development in preterm infants** be retained.

Performance obligations of the *applicant legal entity* that will become the beneficiary of the H2020 ERC Grant Agreement (hereafter referred to as the Agreement), should the proposal be retained and the preparation of the Agreement be successfully concluded:

The *applicant legal entity* commits itself to hosting *[and engaging]* the *principal investigator* for the duration of the grant to:

a) **ensure that the work will be performed under the scientific guidance of the *principal investigator* who is expected to devote:**
- *in the case of a Starting Grant at least 50% of her/his total working time* to the ERC-funded project (action) and spend at least 50% of her/his total working time in an EU Member State or Associated Country;
- *in the case of a Consolidator Grant at least 40% of her/his total working time* to the ERC-funded project (action) and spend at least 50% of her/his total working time in an EU Member State or Associated Country;
- *in the case of an Advanced Grant at least 30% of her/his total working time* to the ERC-funded project (action) and spend at least 50% of her/his total working time in an EU Member State or Associated Country.

b) **carry out the work to be performed, as it will be identified in Annex 1 of the Agreement, taking into consideration the specific role of the *principal investigator*;**

c) **enter — before signature of the Agreement — into a '*supplementary agreement*' with the *principal investigator*, that specifies the obligation of the *applicant legal entity* to meet its obligations under the Agreement;**

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[1] A scanned copy of the signed statement should be uploaded electronically via the Funding and Tenders Portal Submission Service in PDF format.
[2] The statement of commitment of the host institution refers to most obligations of the host institution, which are stated in the H2020 ERC Model Grant Agreement (MGA). The H2020 ERC MGA is available on the Funding & Tenders Portal. The reference to the time commitment of the Principal Investigator is stated in the ERC Work Programme 2020.
[3] This statement (on letterhead paper) shall be signed by the institution's legal representative indicating their name, function, and email address along with the stamp of the institution.

d) provide *the principal investigator* with a copy of the signed Agreement;

e) guarantee the *principal investigator's* scientific independence, in particular for the:

- **i) use of the budget to achieve the scientific objectives;**
- **ii) authority to publish as senior author and invite as co-authors those who have contributed substantially to the work;**
- **iii) preparation of scientific reports for the project (action);**
- **iv) selection and supervision of the other *team members* (hosted *[and engaged]* by the *applicant legal entity* or other legal entities), in line with the profiles needed to conduct the research and in accordance with the *applicant legal entity's* usual management practices;**
- **v) possibility to apply independently for funding;**
- **vi) access to appropriate space and facilities for conducting the research;**

f) provide — during the implementation of the project (action) — research support to the *principal investigator* and the team members (regarding infrastructure, equipment, access rights, products and other services necessary for conducting the research);

g) support the *principal investigator* and provide administrative assistance, in particular for the:

- **i) general management of the work and his/her team**
- **ii) scientific reporting, especially ensuring that the team members send their scientific results to the *principal investigator*;**
- **iii) financial reporting, especially providing timely and clear financial information;**
- **iv) application of the *applicant legal entity's* usual management practices;**
- **v) general logistics of the project (action);**
- **vi) access to the electronic exchange system (see Article 52 of the Agreement);**

h) inform the *principal investigator* immediately (in writing) of any events or circumstances likely to affect the Agreement (see Article 17 of the Agreement);

i) ensure that the *principal investigator* enjoys adequate:

- **i) conditions for annual, sickness and parental leave;**
- **ii) occupational health and safety standards;**
- **iii) insurance under the general social security scheme, such as pension rights;**

j) allow the transfer of the Agreement to a new beneficiary ('portability'; see Article 56a of the Agreement).

k) take all measures to implement the principles set out in the Commission Recommendation on the European Charter for Researchers and the Code of Conduct for the Recruitment of

Researchers[4] - in particular regarding working conditions, transparent recruitment processes based on merit and career development – and ensure that the *principal investigator*, researchers and third parties involved in the project (action) are aware of them.

l) respect the fundamental principle of research integrity and ensure that persons carrying out research tasks follow the good research practices and refrain from the research integrity violations described in the European Code of Conduct for Research Integrity[5]. If any such violations or allegations occur, verify and pursue them and bring them to the attention of the Agency.

For the host institution (applicant legal entity):

Date

14/08/2020

Name and Function

Kalle-Antti-Suominen; Vice-rector

Email and Signature of legal representative

kalle-antti.suominen@utu.fi; _____

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Stamp of the host institution (applicant legal entity)

IMPORTANT NOTE: In order to be complete all the above mentioned items are mandatory and shall be included in the commitment of the host institution.

[4] Commission Recommendation 2005/251/EC of 11 March 2005 on the European Charter for Researchers and on a Code of Conduct for the Recruitment of Researchers (OJ L 75, 22.3.2005, p. 67).

[5] The European Code of Conduct for Research Integrity of ALLEA (All European Academies) and ESF (European Science Foundation) of March 2011.

Humans

Does your research involve human participants? YES

Informed Consent Forms + Information Sheets will be prepared and the ethics approval from the Ethics Committees of the Hospital District of Southwest Finland, Finland; Hospital of Lithuanian University of Health Sciences Kaunas Clinics, Kaunas. Lithuania; and Ghent University Hospital, Ghent, Belgium will be obtained before the beginning of the project. The models for Informed Consent Forms and Information Sheets are available from previous studies using similar methods and having been accepted by hospitals in several European countries, and in Australia and in Canada. (Table). The ethical self assessment will be brought up to date in month two of the SaveBrain.

Name of the research	Ethics approval from the Hospital District of Southwest Finland
Developmental and Functional outcomes of very preterm Infants (PIPARI) – 17 Year follow-up	19.12.2017 §560
Developmental and Functional outcomes of very preterm Infants (PIPARI) – fMRI and functional outcome at 13 years of age	17.11.2015 §521
Developmental and Functional outcomes of very preterm Infants (PIPARI) – 6 Year Cohort Study	19.11.2019 §516
Early Human Milk Expression, Paternal Involvement, and Family-Centered Care	18.09.2018 §389
Turku-Uppsala NIV-NAVA and NAVA Research	21.08.2018 §381
The Parent-Infant Closeness and its' effect of the development of preterm infants	19.12.2017 §559
Parental Speech and Closeness during the Initial Hospitalization of Preterm Infant and the Language Development of the Preterm Infant During the Second Year of Life (LENA II)	24.10.2017 §428
Developmental and Functional outcomes of very preterm Infants (PIPARI) – Substudy: Mathematical skills	18.2.2014 §50
The Evaluation of the Effects of The Close Collaboration with Parents - Training Program in a National Study	15.5.2012 §152
Addendum: 7 centers added	16.9.2014 §308
Implementing Family-Based Care in Pediatrics	15.2.2011 § 51
Developmental and Functional outcomes of very preterm Infants (PIPARI)	19.12.2000 §333

Are they volunteers for social or human sciences research? YES

The parents and their preterm infants born at 22 to 32 weeks of gestation will be recruited to the study after the first day. The first day is considered critical time and therefore inappropriate for recruitment. The parents will receive both verbal and written information about the study during the second day of their child/children or when they are ready. The researchers will make sure that the mother is sufficiently recovered from the delivery before consent is asked. After the information delivery, they get at least 24 hours time to make questions and consider their participation. They will give the consent for participation on their own and their child's /children's behalf. The information about initial stabilisation and admission to neonatal unit will be obtained only after the consent.

Inclusion criteria are live birth from 22+0 weeks of gestation to 32+6 weeks of gestation and expected survival until discharge home. Exclusion criteria: chromosomal abnormalities and other congenital anomalies affecting brain development.

Are they persons unable to give informed consent (including children/minors)? YES

Details of the procedures for obtaining approval from the guardian/legal representative and the agreement of the children or other minors.

The parents of preterm infants born at 22 to 32 weeks of gestation will be recruited to the study after the first day. The first day is considered critical time for the parents and therefore inappropriate to approach them for recruitment. Both parents will receive both verbal and written information about the study during the second day of their child/children or when they are ready. After the information delivery, they are given at least 24 hours time make questions from the research team and consider their participation. They will give the consent for participation on their own and their child's /children's behalf. The information about initial stabilisation and admission to neonatal unit will be obtained only after the consent.

What steps will you take to ensure that participants are not subjected to any form of coercion?

The parents get both verbal and written information about the volunteer nature of participation, about confidentiality, and the right to withdraw. They are also told that their care is not affected by their decision. The consent form includes the following paragraph:

"The participation in the study is voluntary, you have the right to refuse to participate or withdraw from participation at any time. The information obtained in the course of the study will be treated as confidential and anonymous - the data collected in the study will be stored and disposed at the end of the study or at the time you decide to withdraw from it. Participation or refusal to participate in the study has no influence on the care and treatment of your child in the NICU. The study is carried out free of charge. The person responsible for the study is Professor Liisa Lehtonen from the Turku University Hospital, Finland."

Are they vulnerable individuals or groups? YES

Details of the type of vulnerability.

Preterm infants are extremely vulnerable medically as they have a high risk for death and severe morbidities, They are also vulnerable psycho-socially which is the reason to carry out this research project. There is no possibility to obtain their personal opinion about the consent but their parents have to take this responsibility.

Details of the recruitment, inclusion and exclusion criteria and informed consent procedures. These must demonstrate appropriate efforts to ensure fully informed understanding of the implications of participation

The parents of preterm infants born at 22 to 32 weeks of gestation will be recruited to the study after the first day. The first day is considered critical time for the parents and therefore inappropriate to approach them for recruitment. The parents will be contacted, usually in hospital, to give them both verbal and written information about the study. After the information delivery, they are given at least 24 hours time make questions from the research team and consider their participation. They will give the consent for participation on their own and their child's /children's behalf. The information about initial stabilisation and admission to neonatal unit will be obtained only after the consent.

The parents will be told that participation includes automated data collection such as the auditory environment of their baby during two separate days in hospital and tracking parents' location in the hospital to document the time they spend in the room of their infant. Automated data collection is preferred this study to reduce the burden for parents in the stressful hospital situation. During their hospital stay, they will also be asked to wear a sensor to record their heart rate, breathing pattern and activity for 72 hours every third week. They are asked to fill in questionnaires and diaries. Part of the data is collected from routine hospital documentation. After discharge to home, a parent is asked to come with their child/children to hospital for brain imaging at term age (40 week of gestation). The imaging last about 45 minutes during sleep after feeding. Both parents are asked to come to the second visit 4 months after term age when the parents are asked to play with their baby. The baby will be placed in a babysitter, and the parent will be placed face-to-face with the baby during the parent-infant free play situation lasting up to 10 minutes. The video-recorded interaction situation will performed with each parent. During the interaction, both the parent and the baby wears a cap to locate the brain activation. The video will be scored for the quality of parent-child relationship.

The brain outcome measures are safe for newborns. Both MRI and fNIRS are non-invasive and non-ionizing, and they will be performed without any sedation. Many hospitals have included MRI in the routine follow-up of very preterm infants. The parents will get additional information about their child through the methods used in the study. They have, however, the right to refuse the information about the MRI, if they wish.

A team of experienced nurses or doctors will be trained for data collection and tasked with ensuring clinical referral if the study measures reveal a situation that requires acute clinical intervention (like a parent reporting self-destructive thoughts).

Are they children/minors? YES

Details of the age range.

Preterm infants born at 22 weeks and 0 days of gestation to 32 weeks and 6 days of gestation and recruited during the day of life 3. They will be followed until 4 months of corrected age (i.e. 4 months after term age).

What are your assent procedures and parental consent for children and other minors?

The parents of preterm infants born at 22 to 32 weeks of gestation will be recruited to the study after the first day. The first day is considered critical time for the parents and therefore inappropriate to approach them for recruitment. Both parents will receive both verbal and written information about the study during the second day of their child/children or when they are ready. After the information delivery, they are given at least 24 hours time make questions from the research team and consider their participation. They will give the consent for participation on their own and their child's /children's behalf. *What steps will you take to ensure the welfare of the child or other minor?*

The intervention has been shown to improve parents' satisfaction to care and mother' psychological wellbeing. The data on infants will be collected only at term age and at 4 months of corrected age. The methods used in the data collection are safe and non-invasive for newborns.

What justification is there for involving minors?

This study is designed to improve the brain outcomes of the vulnerable group of very preterm infants. Therefore, the target population is very preterm infants and their parents.

Are they patients? YES

What disease/condition /disability do they have?

The infants in this study are born very preterm (below 33 weeks of gestation) and they might have a range of prematurity-related diagnoses such as intraventricular hemorrhages, bronchopulmonary dysplasia, infections, necrotizing enterocolitis, retinopathy of prematurity, apnea of prematurity, anemia of prematurity, and persistent patent ductus arteriosus.

The mothers of these infants are also patients after the delivery. Some mothers may suffer from infections or pre-eclampsia which common predisposing factors for preterm delivery.

Details of the recruitment, inclusion and exclusion criteria and informed consent procedures.

As mentioned before, the researchers will make sure that the mother is sufficiently recovered from the delivery before consent is asked.

What is your policy on incidental findings?

A team of experienced nurses or doctors will be trained for data collection and tasked with ensuring clinical referral if the study measures reveal a situation that requires acute clinical intervention (like a parent reporting self-destructive thoughts). The process of treatment referral is planned beforehand.

The parents have the right to refuse the information of MRI as they may consider the information of incidental findings stressful. However, earlier research shows that those parents who get the information have less anxiety compared to those who did not get the information (Edwards AD et al Arch Dis Child Fetal Ed 2018;103:F15-F21).

Personal Data

Does your research involve processing of personal data? YES

Details of the technical and organisational measures to safeguard the rights of the research participants. For instance: For organisations that must appoint a DPO under the GDPR: Involvement of the data protection officer (DPO) and disclosure of the contact details to the research participants. For all other organisations: Details of the data protection policy for the project (i.e. project-specific, not general).

University Data Protection is based on legal obligations as described in the EU General Data Protection Regulation (GDPR) and local Finnish Law, and as set forth in the University Data Protection Policy given by the University board on 2018-02-16 (English translation pending).

The Finnish Parliament is in the process of setting a National Law for specific derogations and national rules. The law will be published in its final form only weeks or perhaps days before coming into effect on May 25th. This is why clear guidelines especially about scientific and academic use of personal data is impossible to be given at this time.

Contact

For any questions and comments relating to Data Protection or University tools & guidelines, please contact tietosuoja@utu.fi service address.

The service address is staffed by the University's Data Protection Officer, Information Security Officer, Chief of University Records, and a legal team.

Details of the informed consent procedures.

The parents of preterm infants born at 22 to 32 weeks of gestation will be recruited to the study after the first day. The first day is considered critical time for the parents and therefore inappropriate to approach them for recruitment. The parents will be contacted, usually in hospital, to give them both verbal and written information about the study. After the information delivery, they are given at least 24 hours time make questions from the research team and consider their participation. They will give the consent for participation on their own and their child's /children's behalf. The information about initial stabilisation and admission to neonatal unit will be obtained only after the consent.

The parents will be told that participation includes automated data collection such as the auditory environment of their baby during two separate days in hospital and tracking parents' location in the hospital to document the time they spend in the room of their infant. Automated data collection is preferred this study to reduce the burden for parents in the stressful hospital situation. During their hospital stay, they will also be asked to wear a sensor to record their heart rate, breathing pattern and activity for 72 hours every third week. They are asked to fill in questionnaires and diaries. Part of the data is collected from routine hospital documentation. After discharge to home, a parent is asked to come with their child/children to hospital for brain imaging at term age (40 week of gestation). The imaging last about 45 minutes during sleep after feeding. Both parents are asked to come to the second visit 4 months after term age when the parents are asked to play with their baby. The baby will be placed in a babysitter, and the parent will be placed face-to-face with the baby during the parent-infant free play situation lasting up to 10 minutes. The video-recorded interaction situation will performed with each parent. During the interaction, both the parent and the baby wears a cap to locate the brain activation. The video will be scored for the quality of parent-child relationship.

The brain outcome measures are safe for newborns. Both MRI and fNIRS are non-invasive and non-ionizing, and they will be performed without any sedation. Many hospitals have included MRI in the routine follow-up of very preterm infants. The parents will get additional information about their child through the methods used in the study. They have, however, the right to refuse the information about the MRI, if they wish.

A team of experienced nurses or doctors will be trained for data collection and tasked with ensuring clinical referral if the study measures reveal a situation that requires acute clinical intervention (like a parent reporting self-destructive thoughts).

Details of the security measures to prevent unauthorised access to personal data.

All data will be stored in a secure hard drive that requires a username and password. The access will be granted to the SaveBrain research personnel only and it will be in pseudonymised form. Data will be securely safeguarded, encrypted, and appropriately protected from unauthorized access, use, theft or accidental loss. In case of withdrawal, the parents have a right to ask the researchers to delete their information.

How is all of the processed data relevant and limited to the purposes of the project ('data minimisation' principle)? Explain.

Only data that is relevant to the project will be collected.

Details of the anonymisation /pseudonymisation techniques.

Each individual will be given an ID code. The key to connect the ID code to the name and person number will be safeguarded in a hard drive of the recruiting hospital. The access to the archive requires a username and a password

Justification of why research data will not be anonymised/ pseudonymised (if relevant).

Not applicable.

Details of the data transfers (type of data transferred and country to which it is transferred – for both EU and non-EU countries).

MRI images will be archived in the electronic image archive Carestream PACS of the Hospital District of Southwest Finland. The access to the archive requires a username and a password. The images will be transferred via electronic channels pseudonymised (personal information will be removed and replaced with codes). The code key will be archived separately in the secured hard drive of the Hospital of the Lithuanian University of Health Sciences Kaunas Clinics, in Lithuania, and in Ghent University Hospital, Belgium.

Does it involve the processing of special categories of personal data (e.g. genetic, health, sexual lifestyle ethnicity, political opinion, religious or philosophical conviction.)? YES

Justification for the processing of special categories of personal data.

The patient group is heterogenous and their brain outcomes are dependent on the medical and psychosocial background factors. Therefore, it is crucial to adjust the analyses for the confounding factors related to both medical factors of the child and the mothers as well as psycho-social background factors of the family. The study permission will be obtained from the target hospitals to collect the data from the medical records of the child and the mothers.

Why can the research objectives not be reached by processing anonymised/ pseudonymised data (if applicable)?

The health data will be pseudonymised before the data is transferred to Finland.

Does it involve profiling, systematic monitoring of individuals or processing of large scale of special categories of data, intrusive methods of data processing (such as, tracking, surveillance, audio and video recording, geolocation tracking etc.) or any other data processing operation that may result in high risk to the rights and freedoms of the research participants? YES

Details of the methods used for tracking, surveillance or observation of participants.

During the hospital stay, parents' location will tracked by using the AeroScout Real-Time Locating System, a tag carried by parents and connected to hospital wifi. https://www.stanleyhealthcare.com/aeroscout-rtls, to get information about the parents' presence in the patient room throughout the hospital stay after recruitment.

Parents' will carry a Firstbeat sensor to document the quality of sleep and the level of stress for 72 hours every third week.

The auditory environment of the infant will be recorded, including speech, for 16 hours twice during the study.

At four months after the term age, mother-infant and father-infant interaction situations will video recorded with a simultaneous fNIRS and computer vision face recognition recording for about 10 minutes.

The infant and family background information will be connected to the follow-up measures of the study.

Details of the methods used for profiling.

Not applicable.

Risk assessment for the data processing activities.

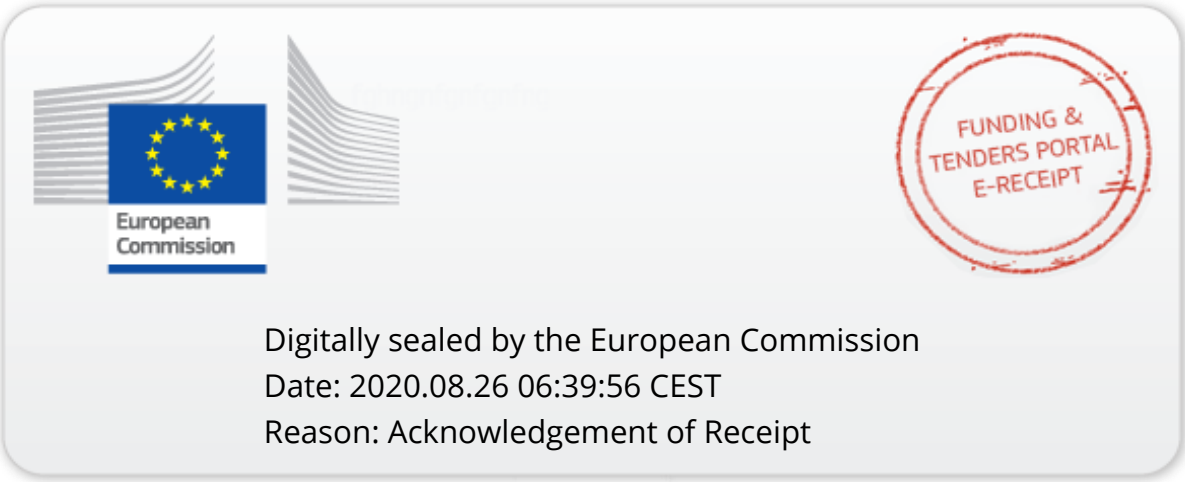
Data processing always will be in conformity with applicable rules concerning ethics and data protection.

How will harm be prevented and the rights of the research participants safeguarded? Explain.

Data will be securely safeguarded, encrypted, and appropriately protected from unauthorized access, use, theft or accidental loss. In case of withdrawal, the parents have a right to ask the researchers to delete their information.

Details on the procedures for informing the research participants about profiling, and its possible consequences and the protection measures.

The parents will receive both verbal and written information about the study during the second day of their child/children or when they are ready. The researchers will make sure that the mother is sufficiently recovered from the delivery before consent is asked. After the information delivery, they get at least 24 hours time to make questions and consider their participation. They will give the consent for participation on their own and their child's /children's behalf.



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