The impact of prematurity on the neural regulation of complex cognitive processes: Epigenetic Mechanisms

Linda Booij, PhD

Research Collaboration PUCRS / INScer
March 2012 -

PUCRS / INScer

Preterm births is a worldwide problem

Region/subregion[a]	Preterm births		Preterm birth rate	
	No. in 1000s	95% CI[b]	%	95% CI[b]
World total	**12 870**	**12 228–13 511**	**9.6**	**9.1–10.1**
More developed countries	1 014	982–1 046	7.5	7.3–7.8
Less developed countries	7 685	7 109–8 261	8.8	8.1–9.4
Least developed countries	4 171	3 891–4 452	12.5	11.7–13.3
Africa	**4 047**	**3 783–4 311**	**11.9**	**11.1–12.6**
Eastern	1 686	1 481–1 891	14.3	12.5–16.0
Middle	602	535–669	11.6	10.3–12.9
Northern	407	290–523	8.7	6.2–11.2
Southern	228	191–265	17.5	14.6–20.3
Western	1 125	1 036–1 215	10.1	9.3–10.9
Asia	**6 907**	**6 328–7 486**	**9.1**	**8.3–9.8**
Eastern	724	650–798	3.8	3.4–4.1
South-central	4 467	3 944–4 991	11.4	10.0–12.7
South-eastern	1 271	1 062–1 480	11.1	9.3–13.0
Western	396	290–501	7.9	5.8–9.9
Central	49	21–77	3.8	1.6–5.9
Europe	**466**	**434–498**	**6.2**	**5.8–6.7**
LA and the Caribbean	**933**	**858–1 009**	**8.1**	**7.5–8.8**
Caribbean	48	33–63	6.7	4.7–8.8
Central America	295	263–326	9.1	8.2–10.1
South America	591	524–658	7.9	7.0–8.8
North America[c]	**480**	**479–482**	**10.6**	**10.5–10.6**
Oceania				
Australia/New Zealand	20	20–20	6.4	6.3–6.6
Rest of Oceania	16	11–20	6.4	4.6–8.2

Beck et al. (2010). Bull World Health Organ 2010;88:31–38

Preterm birth in Brazil is on the rise

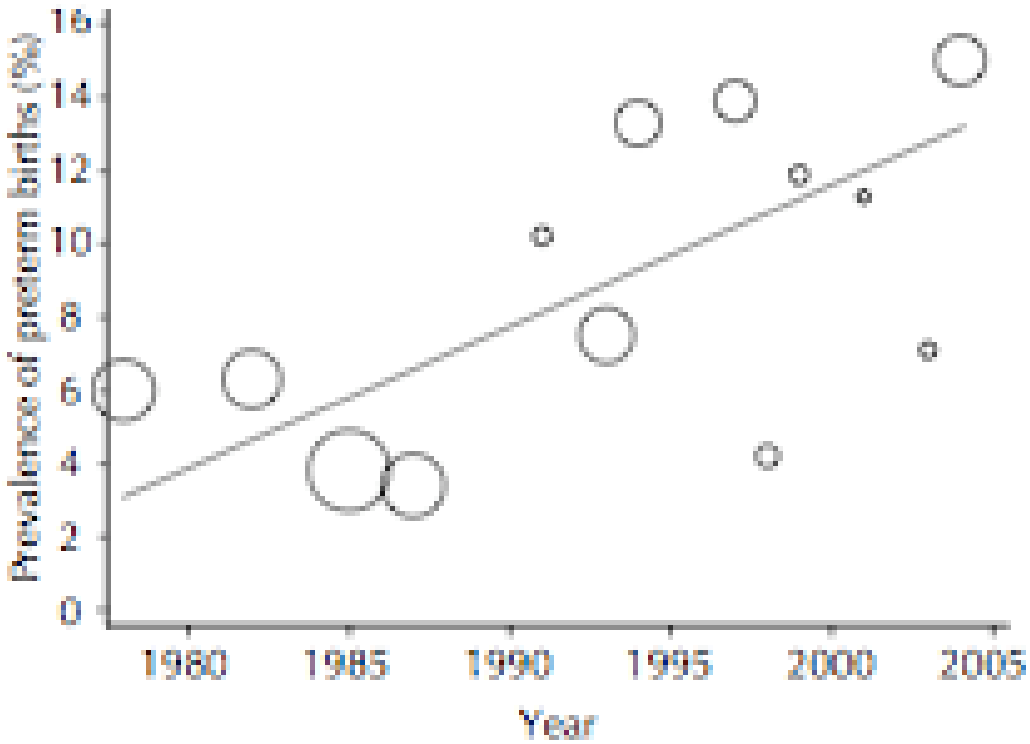


Figure. Prevalence of preterm births in Brazil, according to population-based studies, weighted by sample size.

Silveira et al. (2008), Rev Saúde Pública 2008;42(5)

Prematurity predicts mental health problems

- Large cohort study in Sweden (n=1301522).
- born at 32 to 36 weeks gestation: 1.3-2.7 times more likely to develop mental problems in adulthood.
- Born before 32 weeks: 2.5-3.7 times more likely

Nosarti et al. (2012). Arch Gen Psychiatry

Impact of prematurity on cognitive function (Brazil)

Subtests	Mean ± SD	% of children with abnormal results
Information	8.99 ± 3.05	10.0
Vocabulary	8.29 ± 2.23	7.5
Arithmetic	8.06 ± 4.02	**32.5**
Similarities	10.46 ± 2.56	5.0
Comprehension	7.96 ± 2.69	**17.5**
Animal pegs	7.78 ± 3.14	**27.5**
Picture completion	10.33 ± 2.96	6.3
Mazes	7.90 ± 2.65	**16.3**
Geometric design	8.04 ± 3.02	**16.3**
Block design	8.20 ± 2.59	**13.8**

Espírito Santo, Portuguez & Nunes (2009) J. Do Pediatria

Study 1: Meta-analysis

- Goal: quantify the impact of prematurity on cognitive and motor development in Brazilian cohort samples
- Investigation of the impact of age of assessment and putative other moderating variables.

Procedure / design

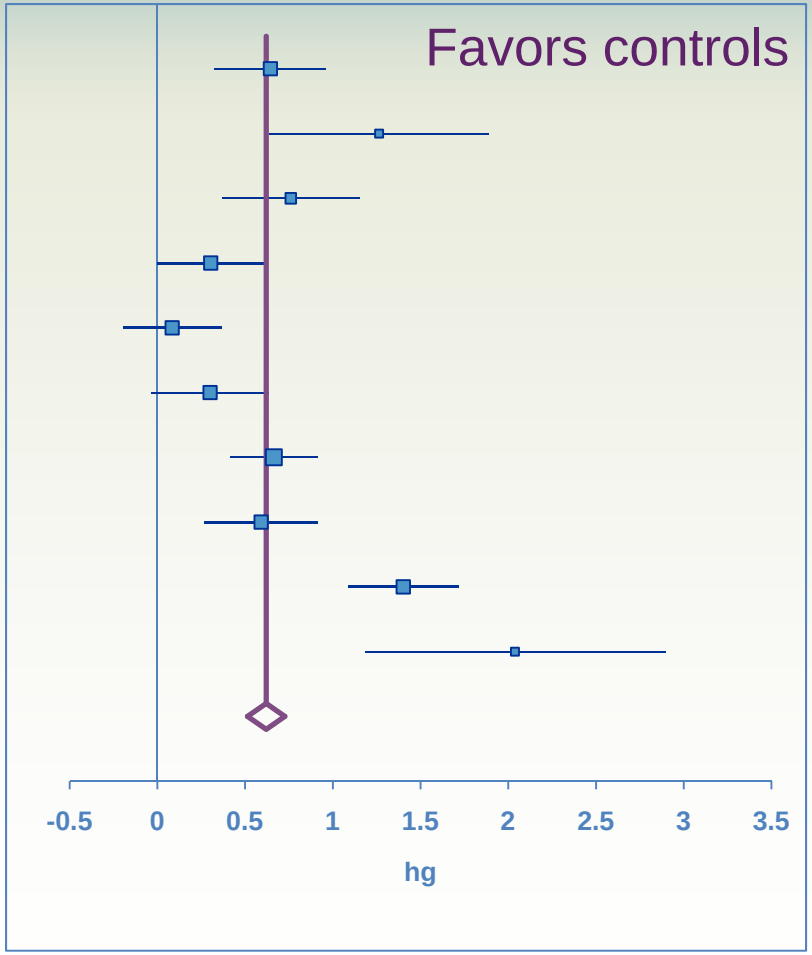
- 13 suitable studies identified via Pubmed, Web of Science and google scholar
- 3 single-group designs, 10 studies included a control group
- Age of assessments: 1-8 years

Outcome measures

- Wechsler Intelligence Scale
- Bayleys cognitive development
- Bayleys motor development
- Cognitive Development observation
- Test of Infant Motor Performance
- Alberta Infant Motor Scale

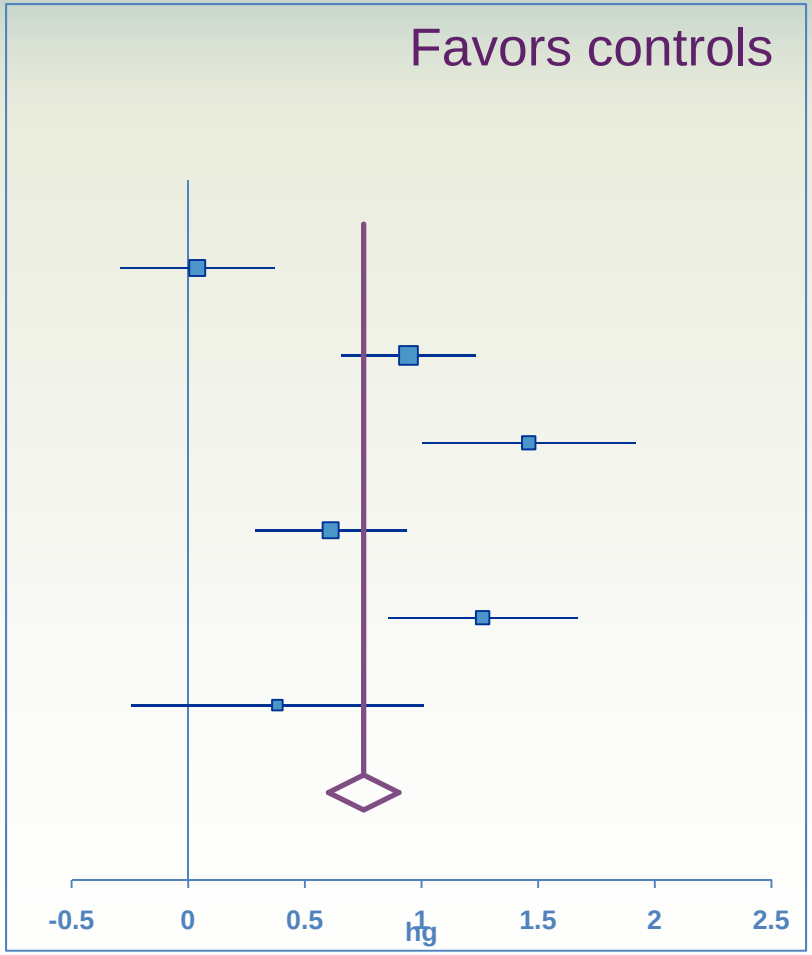
(Very) preliminary results

Impact on Cognitive Development



Z=4.913, p < 0.001

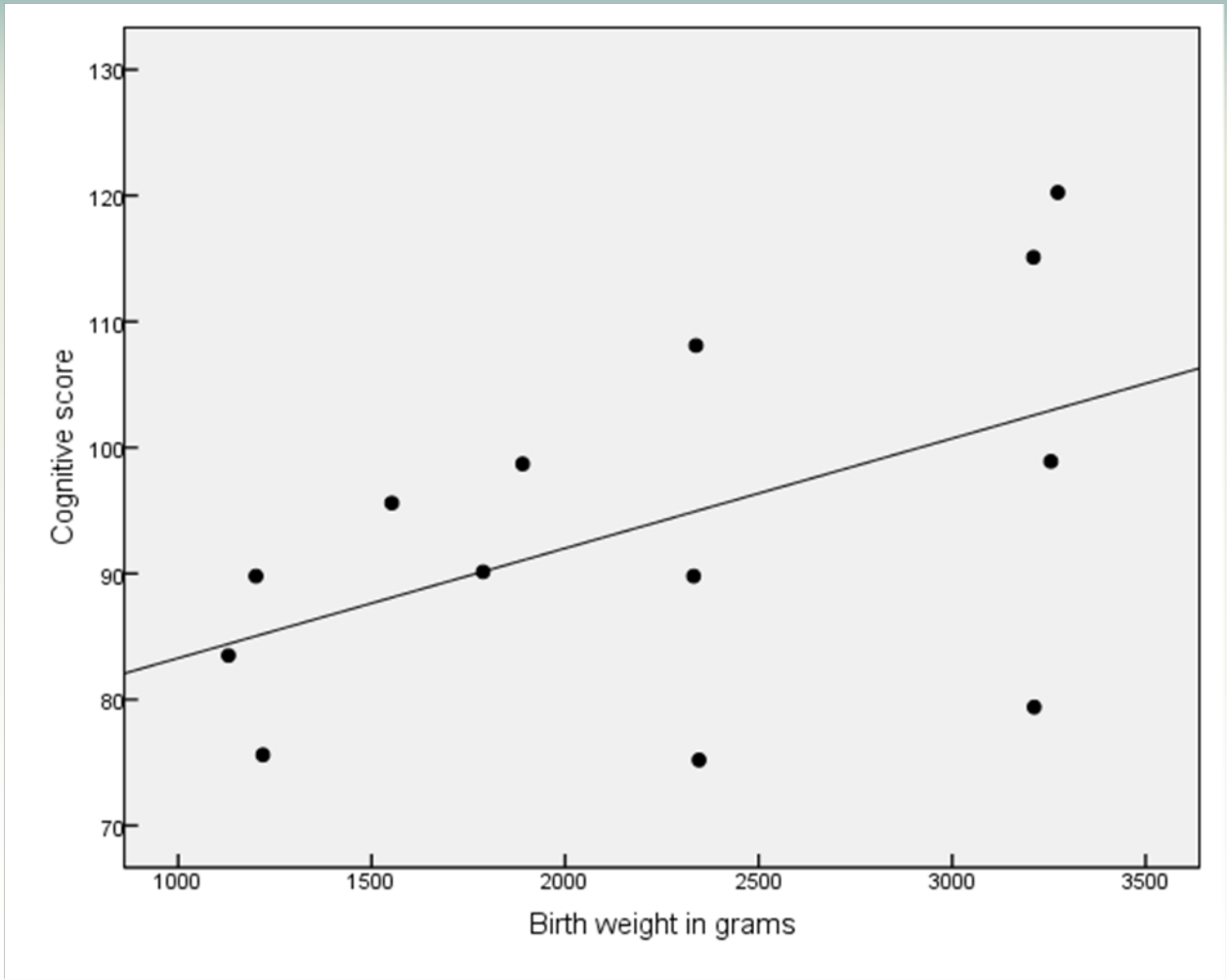
Impact on Motor Development



Z=3.64, p < 0.001

Booij, Mazza, Sudbrack, Nunes, in preparation

Birth weight & Cognitive function (across groups / studies)



$r = 0.50$
$p = 0.079$

No correlation with GA or age of assesment

Study in preparation

- Underlying neural and molecular mechanisms of these cognitive impairments, as a result of prematurity?

Structural brain alterations in youth & adults born premature

- Meta-analyses in US / European samples: smaller prefrontal cortex and hippocampus linked to prematurity, independent of age (de Kieviet et al., 2011)

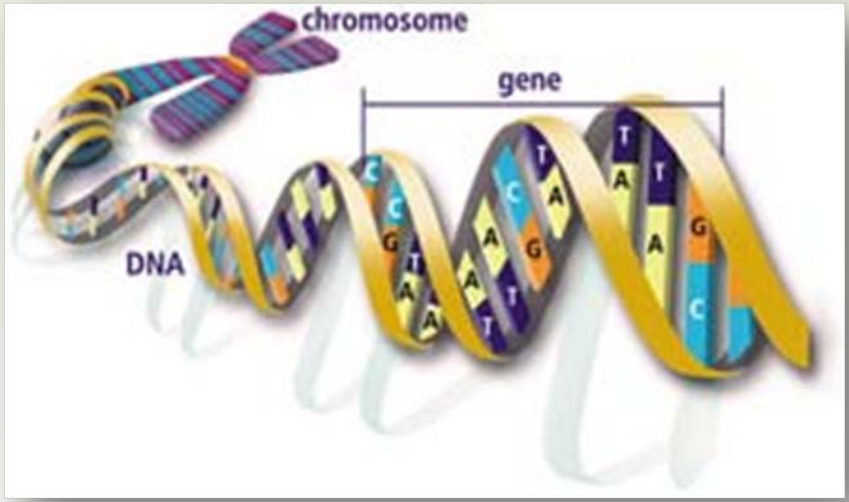
- Neural activation during cognitive processing?

Research Questions

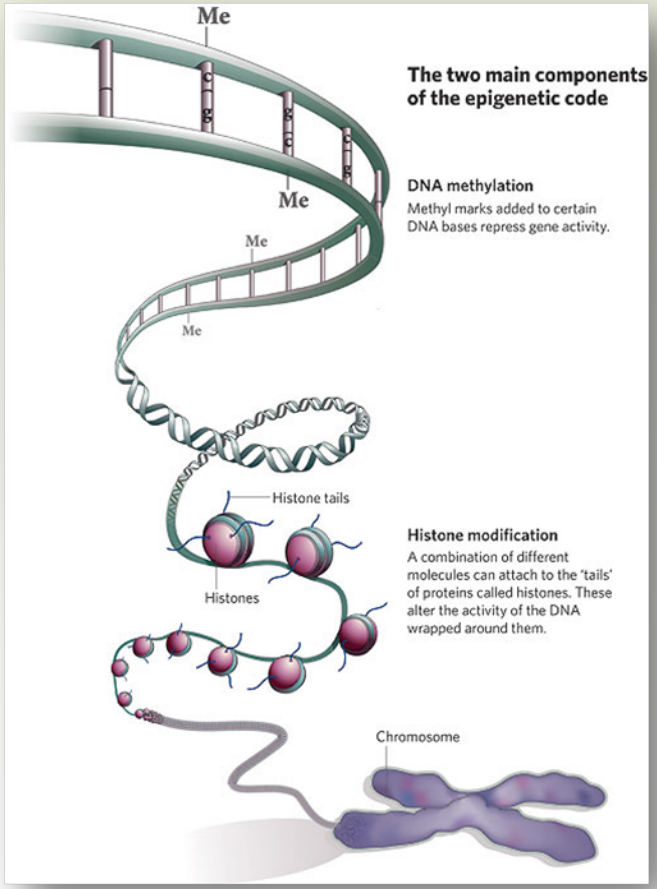
1. To study the impact of prematurity and low birth weight on brain mechanisms underlying complex cognitive processes.

Physiological mechanisms

Fixed Gene sequence (genotype)



Epigenetic modification



Environmental alterations of gene expression

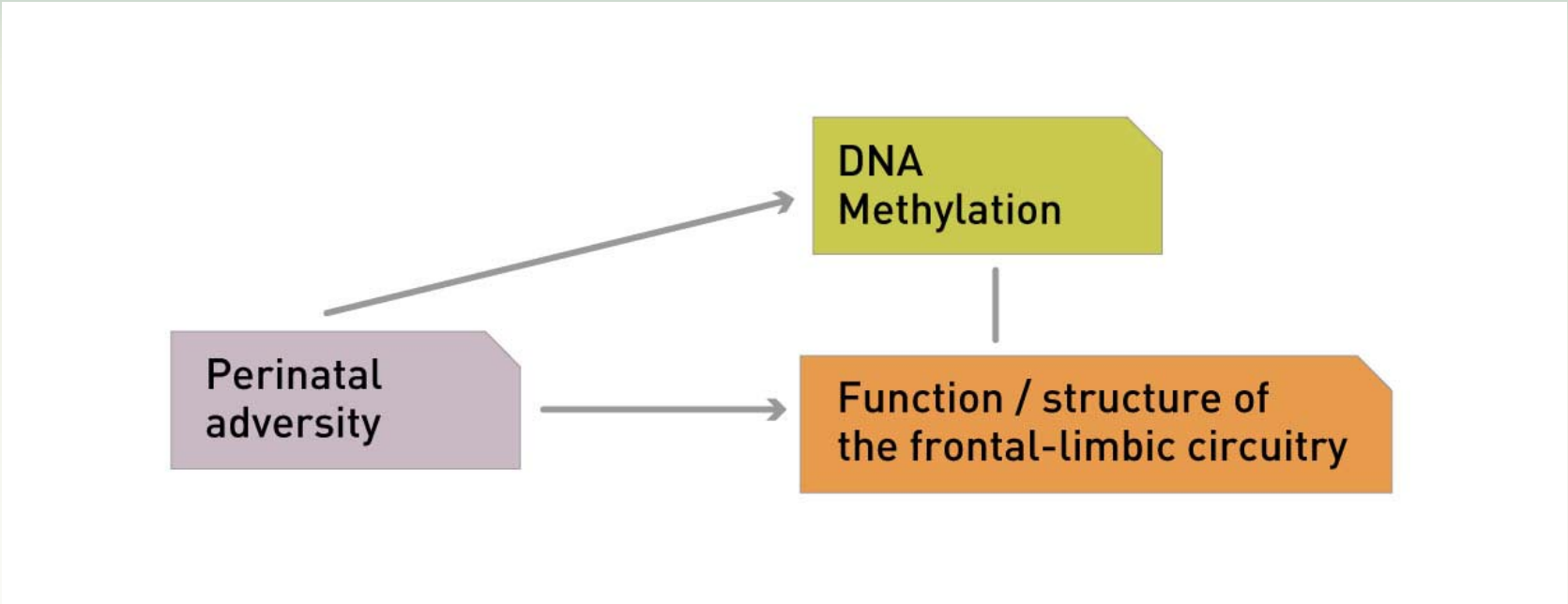
- Epigenetic code can alter gene expression without changing DNA sequences (DNA methylation)
- The DNA methylation pattern is largely set in the perinatal period, and thereby highly vulnerable.
- Impact of prematurity on DNA methylation?

Booij et al. (2012). Phil Transactions of Royal Soc B, in press.

Research Questions

1. To study the impact of prematurity on brain mechanisms underlying complex cognitive processes.
2. To study the effects of prematurity on DNA methylation patterns in late childhood.
3. To examine how DNA methylation and brain alterations are related.

Hypotheses



Does prematurity affect brain function via epigenetic changes?

Hypotheses

- Prematurity leads to altered activation in the prefrontal cortex on a working memory task, smaller frontal-limbic volumes.
- Prematurity leads to altered DNA methylation patters in later life.
- Increased DNA methylation mediates the link between prematurity and brain function/ structure

Methods

- 18 children born premature and low BW (i.e. born within 34 weeks of gestation and having a birth weight lower or equal to 1750 grams) and (previously(followed by the clinic in Porto Alegre.
- 18 healthy controls, normal term/weight.

- Matched on age, gender, SES.

Inclusion Criteria

- Born between 1999 and 2001
- Physically healthy
- No MRI exclusion criteria

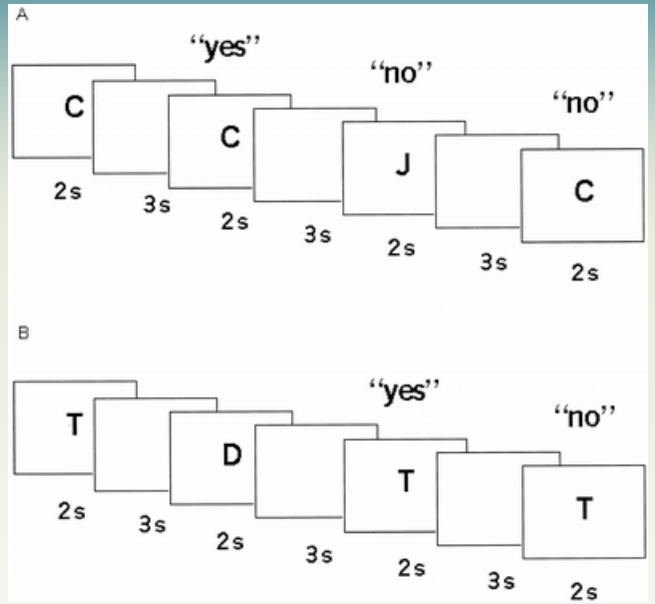
Procedure

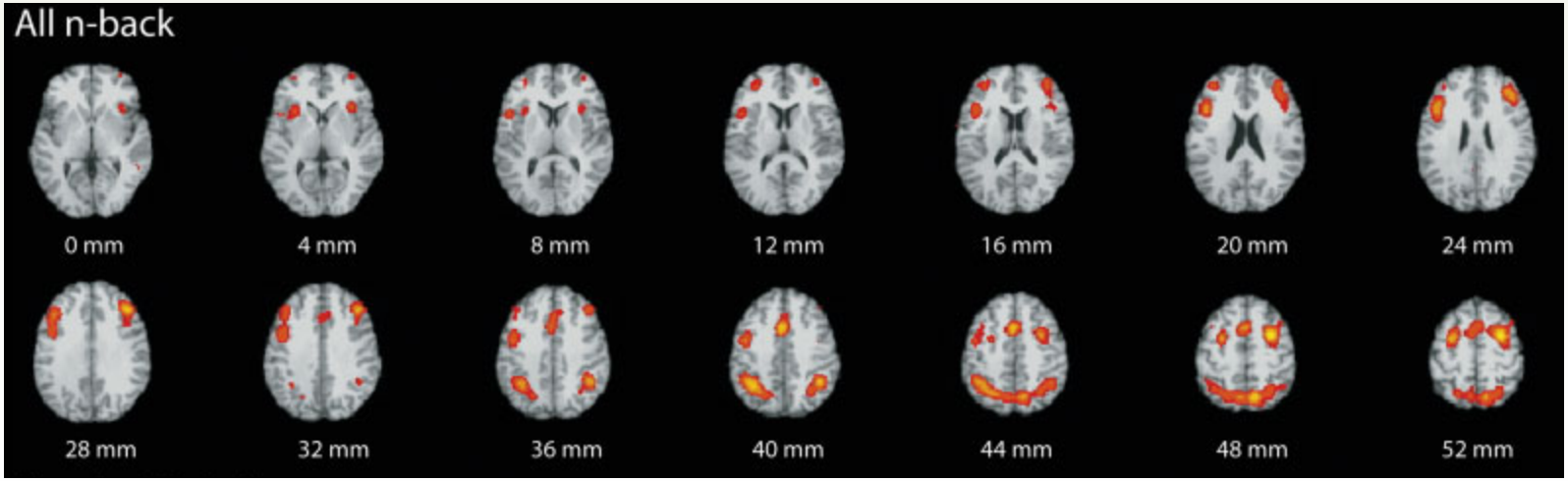
- Screening interview (CBCL)
- fMRI scan: anatomical, DTI, resting state, working memory task
- Questionnaires on parenting and family environment
- IQ testing (Wechsler)
- DNA methylation (saliva) in candidate genes

N-Back Task

- 12 experimental blocks, 3 rest blocks (30 s).
- Experimental blocks: 4 each of 0, 1 and 2-Back blocked trials.
- Each experimental block consists of 16 letters presented for 500 ms each, with a 1500 ms inter-stimulus interval.
- 0 back, 1 back, 2 back condition

fMRI paradigm





Owen et al.(2005) Human Brain Mapping 25:46 – 59

DNA Methylation

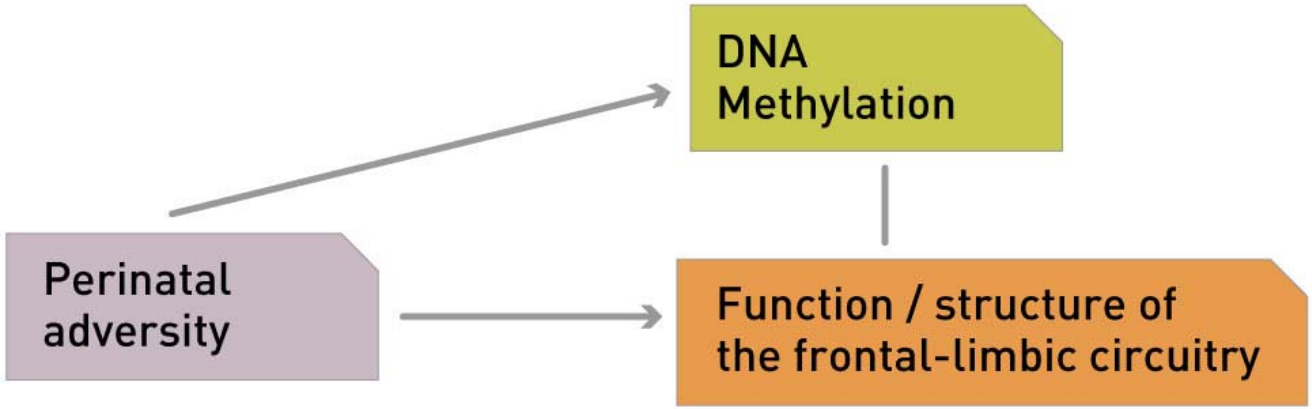
3-6 ml saliva

DNA extraction

DNA Methylation analyses:
Candidate genes?

In collaboration with ongoing epigenetic studies in Montreal cohorts

Hypotheses



Does prematurity affect brain function via epigenetic changes?

Logistics

- Imaging is taking place at INScer
- Epigenetic data will be analyzed in Montreal
- Further student / staff exchange between the two research sites
- Starting date: late 2012 (hopefully..)

Work in progress..

- Grant submitted to FAPERGS and CNPQ
- Project approved by PUCRS science committee, submitted to ethics

Planning

- Sept 2012: Bidirectional exchange (Dr. Sudbrack)
- Further goals: Obtaining funding, recruitment of student; future papers…

Implications

- Results may lead to a better understanding of the impact of the early environment and lead to the development of interventions fostering brain development and preventing cognitive problems.

Collaborators / Acknowledgements

- Dr. M.L. Nunes
- Dr. S. Sudbrack
- Dr. A. Palmini
- Dr. J. Da Costa
- Dr. A.R. Franco
- Dr. M. Portuguez
- Dr. H. Fiore
- Dr. R.E. Tremblay
- Dr. M. Szyf

GRIP

Université de Montréal

PUCRS