EURION

European Cluster to
Improve Identification
of Endocrine Disruptors

EURION cluster presentations at the ED Forum

17 December 2020 – ED Forum

Andreas Kortenkamp
Majorie van Duursen
Juliette Legler

These projects have received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 825161 (ATHENA), No. 825762 (EDCMET), No. 825759 (ENDpoiNTs), No. 825753 (ERGO), No. 825100 (FREIA), No. 825489 (GOLIATH), No. 825745 (SCREENED), No. 825712 (OBERON). This output reflects only the author's view and the European Union cannot be held responsible for any use that may be made of the information contained therein.

Three EURION cluster presentations

Thyroid hormone system – Andreas Kortenkamp

Female reproductive health – Majorie van Duursen

Metabolic disruption – Juliette Legler

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Common questions

What are the testing gaps and challenges today?

How does EURION address these?

What can be done immediately to improve the situation?

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Gaps in test methods for identifying thyroid hormone system disruption

17 December 2020 – ED Forum

Andreas Kortenkamp

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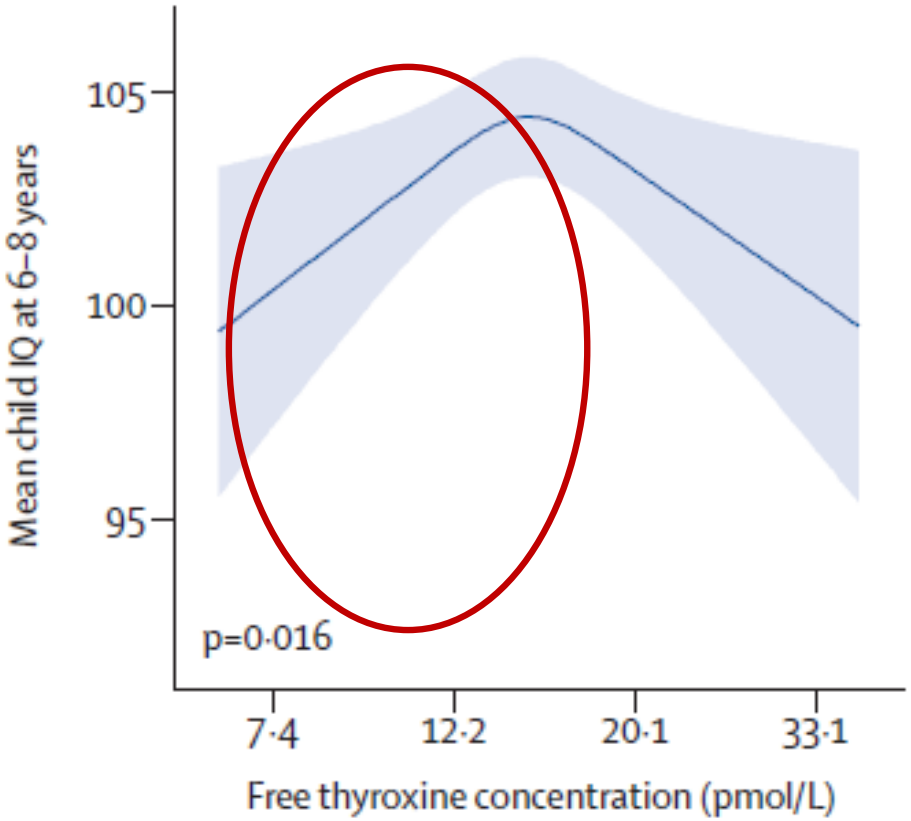
Low thyroid hormones in pregnancy = low IQ



3839 mother-child pairs

Korevaar et al. 2016, Lancet Diabetes Endocrinology

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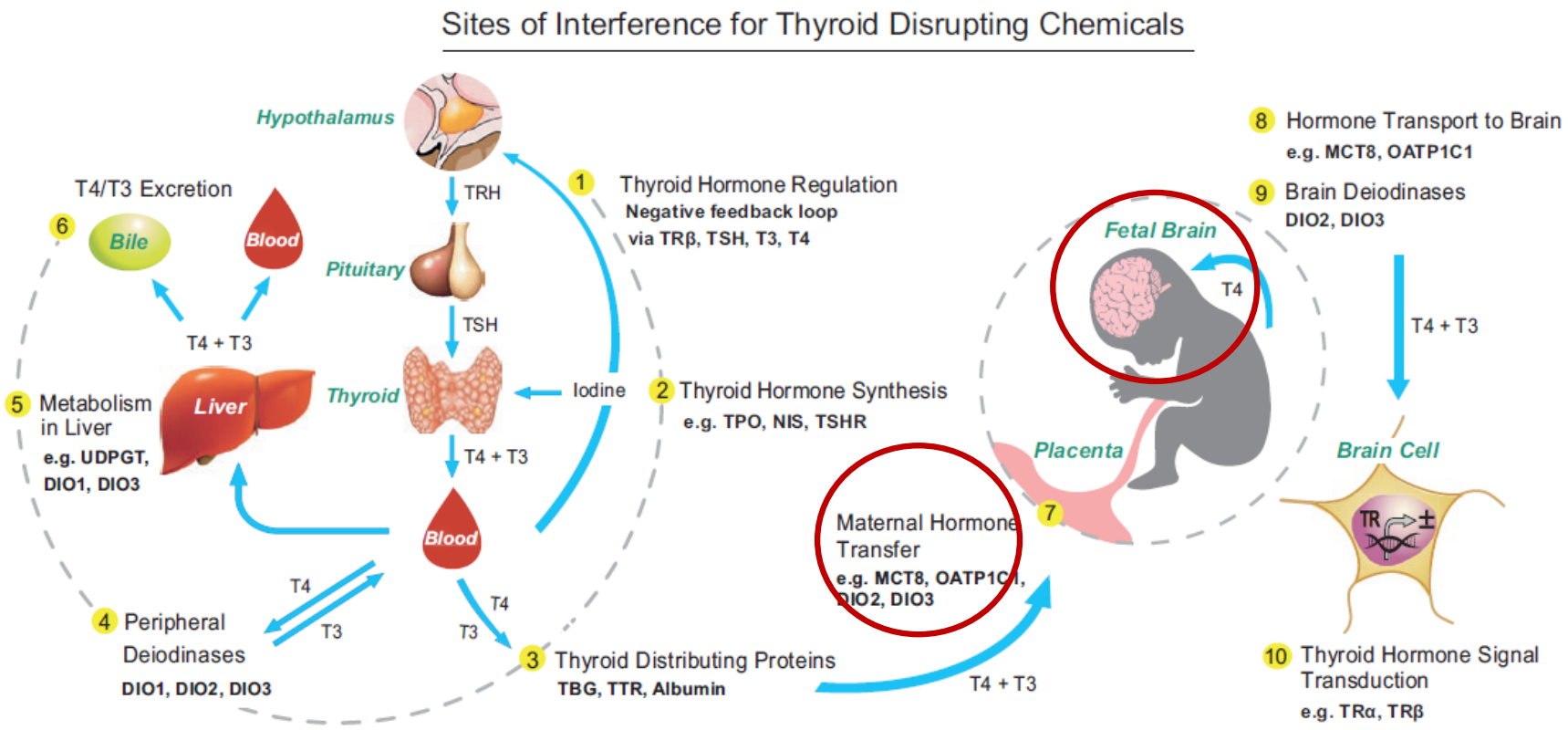

Gilbert, ME et al. 2020, Endocrinology 161, 1-17

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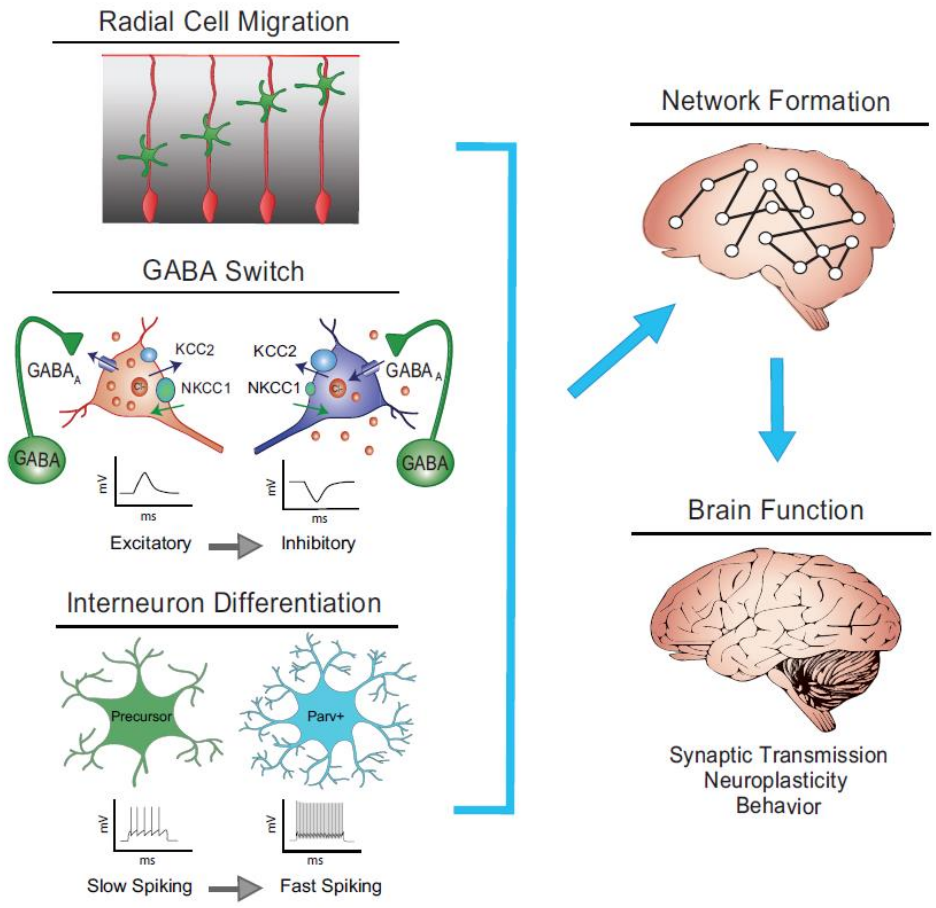
Thyroid hormones are essential for three steps of brain development



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Thyroid relevant tests in core data sets to be submitted for placing products on the EU market

Thyroid hormone serum levels

Thyroid histopathology

- Regulation 283/2013 for Plant Protection Products
- Annex II of Biocidal Products Regulation 528/2012
- Regulation 444/2008 for tests pursuant to REACH chemicals

No in vitro tests

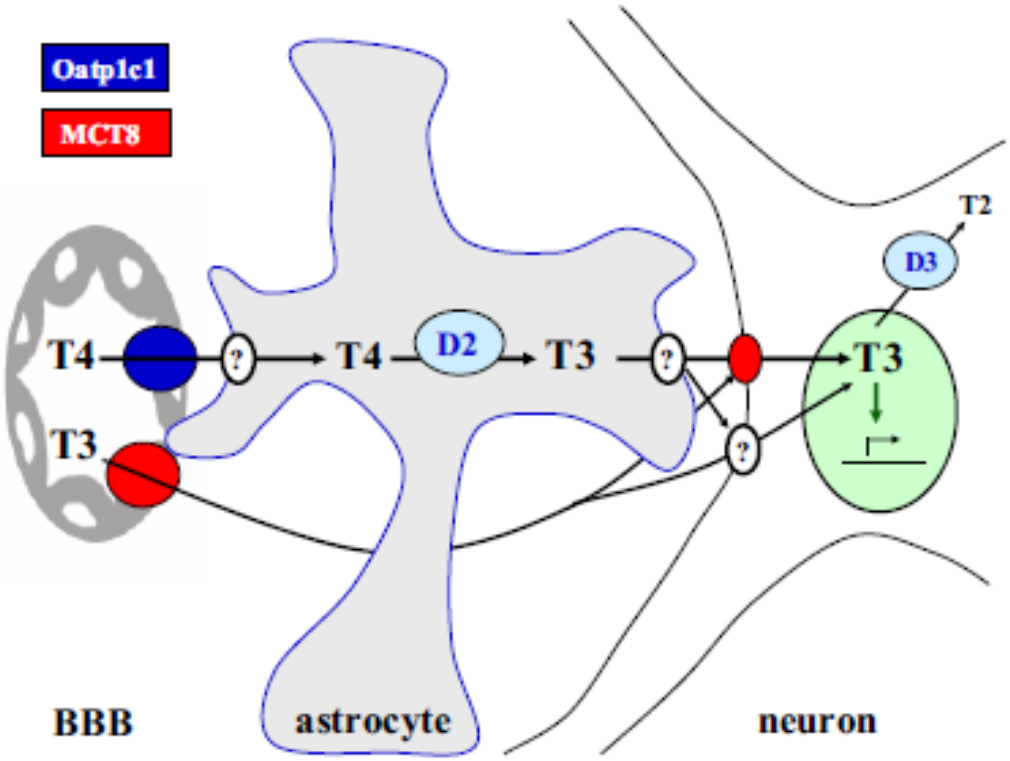
No tests for down-stream effects on the brain

Why thyroid hormone serum levels?

Assumption:

Diminished serum thyroid hormones = disrupted thyroid hormone action

Complex regulation of thyroid hormone action in target cells



Changes in serum thyroid hormone levels do not always translate into disrupted thyroid hormone action in tissues

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Severe defects in thyroid hormone action, but small changes in serum thyroid hormones

Mutated **Thyroid Hormone Receptor Alpha** = no response to hormone

- **Neurodevelopmental deficits, skeletal abnormalities**
- Low to normal T4, normal TSH

Measurements of serum thyroid hormone would not detect this disorder!

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Mutated thyroid hormone transporter MCT 8 – **Allan-Herndon-Dudley syndrome**

The brain cannot take up thyroid hormones

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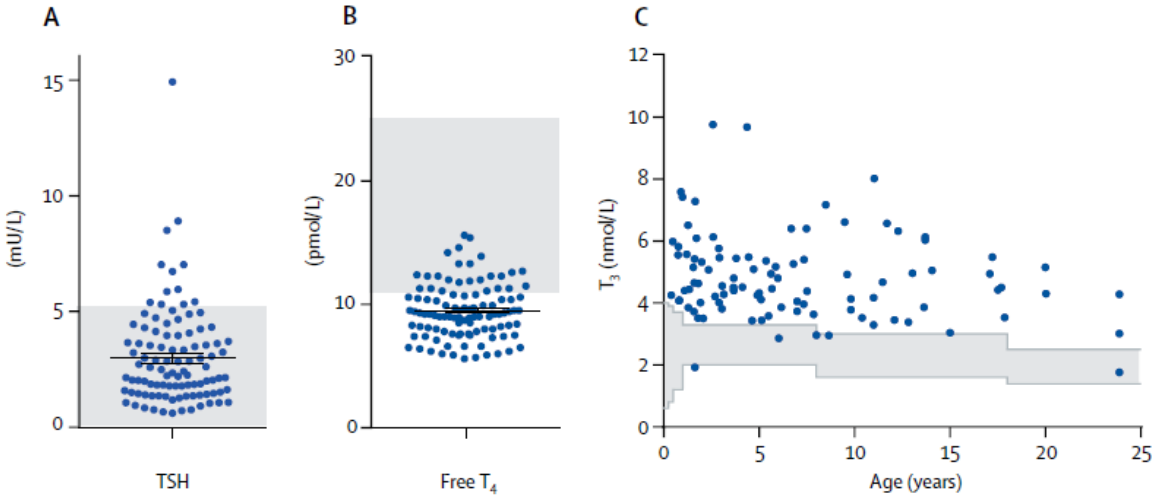

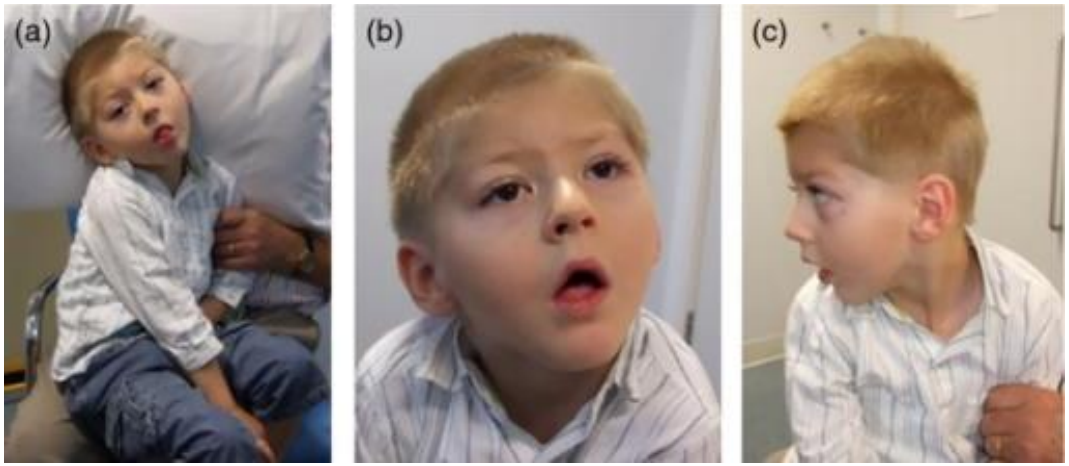

Groeneweg et al. 2020 Lancet Diabetes Endocrinology

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The dilemma

Changes in thyroid hormone levels alone cannot detect risks to neurodevelopment

But:

We have nothing else!

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Current consensus

In the absence of definitive biomarkers of altered neurodevelopment, thyroid hormone changes are appropriate **starting points** for risk assessment.

SOT 2017

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athena

ERGO

EndocRine Guideline Optimisation

SCREENED

SCREENING FOR ENDOCRINE DISRUPTORS

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How EURION cluster projects approach the challenges

- Development of ***in vitro assays***, including 3D models
- Development of **testing strategies** based on Adverse Outcome Pathway networks and read-across between vertebrate classes
- Development of **down-stream markers** of disrupted brain development

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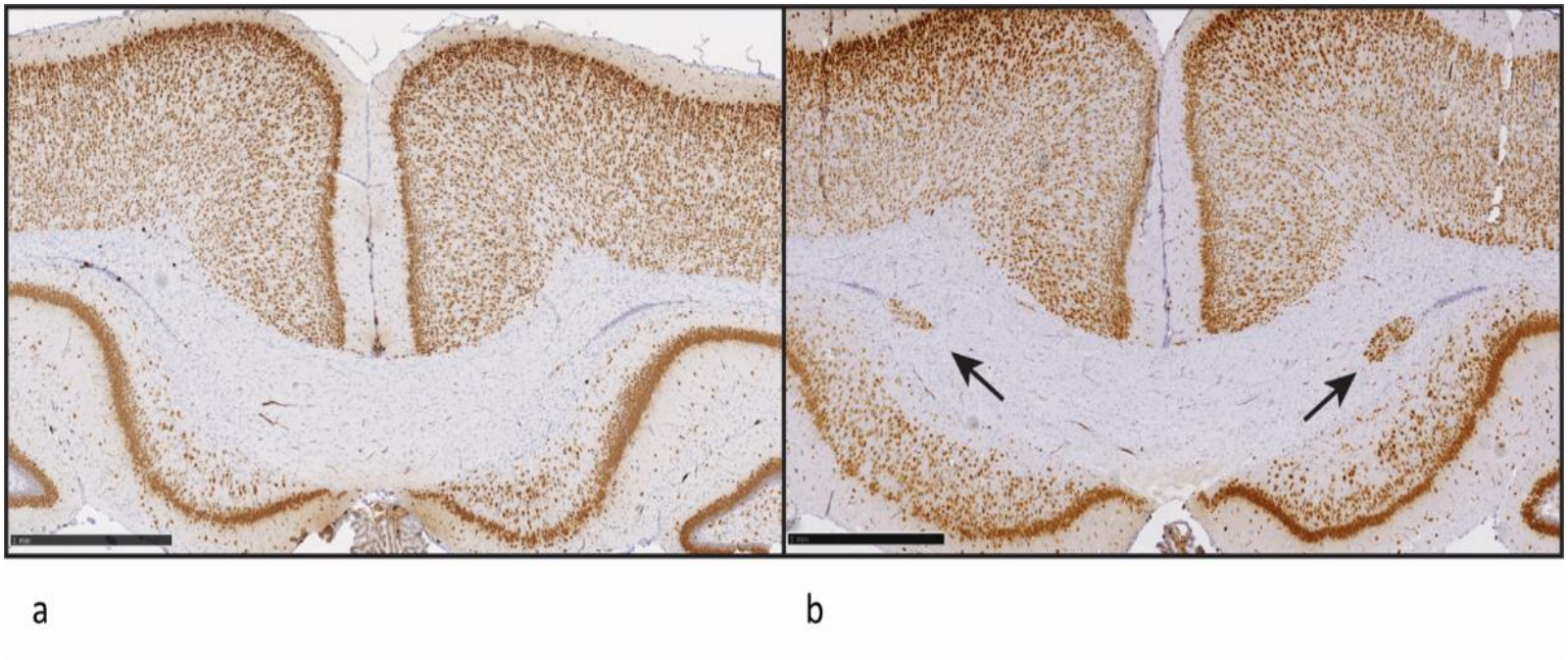
Misplaced neurons in the white matter

Control

Propylthiouracil, 2.5 mg/kg/d



Ramhoj et al. DTU

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Thank you!

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EURION Coordination April 2020 - July 2021

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