



Universiteit  
Leiden  
The Netherlands

## Early life experience : neuroendocrine adaptations to maternal absence

Enthoven, L.

### Citation

Enthoven, L. (2007, October 4). *Early life experience : neuroendocrine adaptations to maternal absence*. Retrieved from <https://hdl.handle.net/1887/12379>

Version: Corrected Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/12379>

**Note:** To cite this publication please use the final published version (if applicable).

# **Early life experience**

**neuroendocrine adaptations to maternal absence**

**Leo Enthoven**

Leo Enthoven

Early life experience; neuroendocrine adaptations to maternal absence

Thesis, Leiden University  
October 4, 2007

ISBN/EAN: 978-90-9022197-7

No part of this thesis may be reprinted or reproduced or utilised in any form or by any electronic, mechanical, or other means, now known or hereafter invented, including photocopying and recording, or in any information storage or retrieval system without written permission of the copyright owner.

© 2007, Leo Enthoven

Cover: RotsLeeuw Design, Leiden  
Painting "Depression" by Zsuzsanna Szegedi

Print: Ponsen en Looijen, Wageningen, The Netherlands

# **Early life experience**

## **neuroendocrine adaptations to maternal absence**

### **Proefschrift**

ter verkrijging van  
de graad van Doctor aan de Universiteit Leiden  
op gezag van de Rector Magnificus Prof. Mr. P.F. van der Heijden  
volgens het besluit van het College voor Promoties  
te verdedigen op donderdag 4 oktober 2007  
klokke 15:00 uur

door

**Leo Enthoven**

Geboren te Amsterdam in 1976

## Promotiecommissie

Promotoren:	Prof. Dr. E.R. de Kloet Prof. Dr. M.S. Oitzl (Universiteit Leiden & Amsterdam)
Referent:	Prof. Dr. S. Maccari (Université Lille, France)
Overige leden:	Prof. Dr. S. Levine (University of California at Davis, U.S.A.) Prof. Dr. R.R.J.M. Vermeiren Prof. Dr. A.J.W. van der Does Prof. Dr. F.J. Walther Prof. Dr. M. Danhof Prof. Dr. H. Pijl

The studies described in this thesis have been performed at the department of Medical Pharmacology, Leiden/Amsterdam Center for Drug Research (LACDR), Leiden University Medical Center (LUMC), Leiden, The Netherlands. This research is part of a collaboration between the Universities of Groningen and Leiden, the Hubrecht Laboratory (Utrecht) and N.V. Organon (Oss) and financially supported by the Netherlands Organisation for Scientific Research (NWO – NDRF / STIGON #014-80-005). Part of the study described in chapter 2 was performed at the Max Planck Institute of Psychiatry in Munich, Germany, and of the study described in chapter 3 at the department of Endocrinology and Metabolic Diseases at the LUMC in Leiden, The Netherlands.

Publication of this thesis was financially supported by:

- Leiden/Amsterdam Center for Drug Research
- Statistics Netherlands
- J.E. Jurriaanse Stichting

The statistician who supposes that his main contribution to the planning of an experiment will involve statistical theory, finds repeatedly that he makes his most valuable contribution simply by persuading the investigator to explain why he wishes to do the experiment, by persuading him to justify the experimental treatments, and to explain why it is that the experiment, when completed, will assist him in his research.

*Gertrude M. Cox.*

Voor Petra,  
mijn allerliefste



## Table of contents

	<b>Preface</b> .....	9
<b>Chapter 1</b>	<b>Introduction</b> .....	13
	Stress .....	17
	Adverse early life events in humans.....	20
	Characteristics of normal HPA axis development .....	23
	Adverse early life event modelling in rodents .....	28
	Scope and outline of the thesis .....	36
<b>Chapter 2</b>	<b>The pituitary-adrenal axis of the CD1 mouse infant desensitises to repeated maternal separations, but remains highly responsive to stress</b> .....	51
<b>Chapter 3</b>	<b>The role of brain corticosteroid receptors in HPA axis adaptation to repeated maternal separations of newborn mice</b> .....	77
<b>Chapter 4</b>	<b>Effects of maternal deprivation on performance in the water maze and swim stress</b> .....	95
<b>Chapter 5</b>	<b>Differential development of stress system (re)activity at weaning dependent on time of disruption of maternal care</b> .....	109
<b>Chapter 6</b>	<b>Ontogeny of the HPA axis of the CD1 mouse following 24 hours of maternal deprivation at pnd 3</b> .....	125
<b>Chapter 7</b>	<b>General discussion</b> .....	143
	Repeated maternal separations .....	147
	Maternal deprivation .....	154
	Implications of the findings .....	158
	Conclusions .....	159
	<b>Summary -Samenvatting</b> .....	167
	<b>List of abbreviations</b> .....	185
	<b>Glossary</b> .....	187
	<b>List of publications</b> .....	191
	<b>Curriculum Vitae</b> .....	193
	<b>Dankwoord</b> .....	195
<b>Appendix I</b>	<b>Plasma corticosterone responses reflect the degree of novelty in male and female CD1 mice</b> .....	197







## Preface



## Preface

An adverse early life event is considered a risk factor for stress-related psychiatric disorders in genetically predisposed individuals, probably because of its lasting effect on susceptibility to stress. The objective of this thesis research was to examine in the mouse CD1 strain the immediate and permanent effects of an adverse early experience on the neuroendocrine stress system. For this purpose the hypothalamic-pituitary-adrenal (HPA) axis was examined of mouse pups that were refrained from maternal care, a laboratory model for neglect mimicking aspects of abuse. The data show that the infants' stress response system readily adapts to daily repeated 8 hours of maternal separation, but that it continues to respond to a novelty stressor. The rapid adaptation to repeated maternal absence seems rather due to the ability to predict return of the mother than to adjust metabolism to episodic food deprivation. If maternal separation was extended to a single episode of 24 hours the immediate outcome was more profound but transient, although subtle effects on stress reactions and cognitive performance did persist. The findings demonstrate the amazing plasticity of the newborn brain and provide a basis to study the mechanistic underpinning of vulnerability or resilience to psychopathology.

