EXPLORING THE CONTRIBUTION OF PRENATAL STRESS TO THE PATHOGENESIS OF AUTISM AS A NEUROBIOLOGICAL DEVELOPMENTAL DISORDER: A DIZYGOTIC TWIN STUDY

by

MARLEEN CLAASSEN

Submitted in partial fulfilment of the requirements for the degree of

MAGISTER EDUCATIONIS

(specializing in Educational Psychology)

in the

DEPARTMENT OF EDUCATIONAL PSYCHOLOGY FACULTY OF EDUCATION

at the

UNIVERSITY OF PRETORIA

SUPERVISOR:

PROF. H. NAUDé (Department of Educational Psychology)

CO-SUPERVISORS:

PROF. E. PRETORIUS (School of Medicine, Faculty of Health Sciences)
PROF. M.C. BOSMAN (School of Medicine, Faculty of Health Sciences)

January 2006



ACKNOWLEDGEMENTS

My most sincere gratitude and appreciation is extended towards the following people:

- Prof. H. Naudé, my supervisor, for her guidance and supervision.
- Professors E. Pretorius and M.C. Bosman for their eloquent supervision.
- The parents and their twins for their willingness to participate in the study, and for support in collecting the data.
- My parents for all the sacrifices they have made to ensure my future, for their unfailing support, unlimited concern and words of encouragement.
- The principal and staff at Jeugland, Kempton Park, for their kindness and support that enabled me to complete this research project.
- Stephan Naudé for the graphics and technical support.
- Du Buisson, Bruinette & Kramer (Incorporated) Pathologists for expert consultation on blood plasma pathology results.

Psalm 119:130

'Wanneer U woord vir mense oopgaan; bring dit lig; Dit gee insig aan die wat nog onervare is.'

DECLARATION

I declare that **EXPLORING THE CONTRIBUTION OF PRENATAL STRESS TO THE PATHOGENESIS OF AUTISM AS A NEUROBIOLOGICAL DEVELOPMENTAL DISORDER: A DIZYGOTIC TWIN STUDY** is my own work and that all sources that I have used or quoted have been indicated and acknowledged by means of complete references.

MARLEEN CLAASSEN	DATE

EXPLORING THE CONTRIBUTION OF PRENATAL STRESS TO THE PATHOGENESIS OF AUTISM AS A NEUROBIOLOGICAL DEVELOPMENTAL DISORDER: A DIZYGOTIC TWIN STUDY

BY: MARLEEN CLAASSEN

DEGREE: MAGISTER EDUCATIONIS

(Specializing in Educational Psychology)

DEPARTMENT: EDUCATIONAL PSYCHOLOGY

SUPERVISOR: PROFESSOR H. NAUDÉ

CO-SUPERVISORS: PROFESSORS E. PRETORIUS and M.C. BOSMAN

SUMMARY

Exploring the contribution of prenatal stress to the pathogenesis of autism as a neurobiological developmental disorder: a dizygotic twin study

This research project explores the contribution of prenatal stress to the pathogenesis of autism as a neurobiological developmental disorder. The neurobiological impact of stress prior to the 28th week of gestation might produce structural neural changes, specifically regarding the cerebellum, the brain stem and limbic pathways, including the hippocampal area, which concept relates closely to the pathogenesis of autism. In this research project a significant focus is placed on prenatal hipothalamic-pituary-adrenal (HPA) activity due to the HPA axis' interactivity with cortisol, digoxin and serotonin, as these biochemicals are significantly implicated in programmed foetal development, postnatal cortical behaviour, postnatal learning, as well as in functional impairment of socialization, communication and imagery associated with autism. Based upon the rationale of this research project and the conceptualisation of the topic of interest, the research problem was formulated as follows: In what unique ways does prenatal stress contribute to the pathogenesis of autism as a neurobiological developmental disorder? Sub questions included: Did the mother of the dizygotic twins experience significant stress during the period of gestation? What structural brain differences can be observed among the dizygotic twins at hand of MR-imaging? To which periods of prenatal development can these structural differences be related? How do these differences account for sensory, motor, cognitive, and affective behavioural differences among the dizygotic twins? What plasma differences can be observed among the dizygotic twins at hand of blood sampling? How does elevation of pre- and postnatal

glucocorticoids relate to plasma difference among the dizygotic twins? How do these plasma differences account for sensory, motor, cognitive, and affective behavioural differences among the dizygotic twins? This research project represents **quantitative research**. The mode of inquiry is non-experimental at hand of a single dizygotic twin study. The following **data generating strategies** were employed: clinical intake interviews, administration of a diagnostic stress inventory and the 16-PF Questionnaire, MR-imaging, and the collection of blood plasma pathology results.

Key words: autistic disorder, prenatal stress, neurobiological developmental disorder, glucocorticoids, serotonin, digoxin, HPA-axis, intra-uterine deprivation, sub-optimal placental nutrient supply.

	University of Pretoria etd – Claassen, M (2006)
In anden to all 186	
	y the reading task the masculine gender is used within the text. This type of referenci
should not be see	en as a form of gender discrimination, since all references implicitly include the fema
gender, except if ir	ndicated otherwise.

CONTENTS

CHAPTER 1

INTRODUCTION, AWARENESS OF THE PROBLEM, RATIONALE FOR THE STUDY AND ANALYSIS OF THE RESEARCH PROBLEM, LITERATURE REVIEW, DEFINITION OF KEY CONCEPTS, PROBLEM STATEMENT, PURPOSE OF THE STUDY, THEORETICAL FRAMEWORK AND PARADIGMATIC PERSPECTIVE, RESEARCH DESIGN AND METHODOLOGY, ETHICAL CONSIDERATIONS AND CHAPTER OUTLINE.

1.1	INTRODUCTION	1
1.2	AWARENESS OF THE PROBLEM	3
1.3	RATIONALE FOR THE STUDY AND ANALYSIS OF THE RESEARCH PROBLEM	4
1.4	LITERATURE REVIEW	9
1.5	DEFINITION OF KEY CONCEPTS	13
1.6	PROBLEM STATEMENT	15
1.7	PURPOSE OF THE STUDY	16
1.8	THEORETICAL FRAMEWORK AND PARADIGMATIC PERSPECTIVE	16
1.9	RESEARCH DESIGN AND METHODOLOGY	18
1.10 E	ETHICAL CONSIDERATIONS	20
1.11C	CHAPTER PLANNING	22
1.128	SYNOPSIS	22
1.13L	IST OF REFERENCES	23

B	
I	
)(
$^{\sim}$ I	
\mathbf{H}	
\mathbf{E}	
V	
Ħ	
(
¹Α	
I	
,	
IN	
ΛĪ	
P	
1	
J	
C	
Δ	
\	
ΓΊ	
\mathbf{F}_{i}	
\mathbf{D}	
)	
n	
V	
I	
PΙ	
?	
\mathbf{C}	
(
H	
R	
Α	
ΛĪ	
٦	
Л	
F	
T	
)	
F	
7(
)	
F	
T	
`Δ	
١I	
Γ	
)Ī	
٦,۲	
V	
F	
I	
(
)]	
P	
M	
F	
1	
ď	
Т	

2.1	INTRODUCTION	30
2.2	NEUROTRANSMITTER, RECEPTOR SYNTHESIS AND NEUROCH	EMICAL
	CODING	30
2.2.1	Small molecule neurotransmitters	34
2.2.2	Peptide neurotransmitters	35
2.2.3	Transmitter gases	36
2.3 I	DEVELOPMENT OF NEUROTRANSMITTER SYSTEMS DURING CO	RTICAL
F	PERIODS	37
2.4 7	THE RELEVANCE OF THE HIPOTHALAMIC-PITUARY-ADRENAL(HI	PA) AXIS
I	N THE PATHOGENESIS OF AUTISM	39
2.4.1	Adrenaline	39
2.4.2	Noradrenaline	40
2.5]	THE RELEVANCE OF SERUM CORTICOL LEVELS IN THE PATHOO	GENESIS
(OF AUTISM	42
2.6 1	THE RELEVANCE OF SERUM DIGOXIN LEVELS IN THE PATHOGEN	ESIS OF
A	AUTISM	43
2.7 1	THE RELEVANCE OF SERUM SEROTONIN LEVELS IN THE PATHO	GENESIS
(OF AUTISM	45
2.8 S	SYNOPSIS	51
2.9 I	LIST OF REFERENCES	51

NEUROANATOMIC OBSERVATIONS OF THE BRAIN IN AUTISM

3.1	INTRODUCTION	62
3.2 N	ORMAL BRAIN DEVELOPMENT	62
3.2.1	Neurogenesis and gliogenesis	65
3.2.2	Cell migration and differentiation	66
3.2.3	Cell maturation (dendrite and axon growth)	68
3.2.4	Synaptogeneis, programmed cell death and synaptic pruning	69
3.2.5	Myelogenesis	70
3.3 S	TRUCTURAL ABNORMALITIES OF THE BRAIN IN AUTISM	71
3.3.1	Enlarged brain size in autism	71
3.3.1.1	l Elevated cerebral volumes	72
3.3.1.2	2 Enlarged head circumference	72
3.3.2	Reduction in the area of the corpus callosum	73
3.3.3	Abnormal patterns of cerebellar development	75
3.3.4	Abnormalities of the medial temporal lobe structures	77
3.4 T	HE IMPACT OF PRENATAL STRESS ON CORTICAL DEVELO	PMENT AND
A	GENESIS	79
3.4.1	The Hipotalamic-Pituitary-Adrenal Stress Response	80
3.4.2	The link between glucocorticoids and the pathogenesis of autism	82
3.4.3	Autistic expression in handwriting	84
3.4.4	Autistic expression in auditory and spatial functioning	85
3.4.5	Autistic expression in attentional and emotional processes	86
3.5 S	YNOPSIS	88
3.6 L	IST OF REFERENCES	88

EMPIRICAL STUDY

4.1	INTRODUCTION	97	
4.2	PROBLEM STATEMENT	97	
4.2.1	Sub questions	98	
4.2.2	Research hypothesis	98	
4.3	PURPOSE OF THE STUDY	98	
4.4	METHODS, MATERIALS AND PROCEDURES	99	
4.5	RESULTS OF THE CASE STUDY		100
4.5.1	Maternal clinical data		100
4.5.1.1	Gestational period		100
4.5.1.2	Blood-pressure readings		100
4.5.1.3	Blood plasma pathology reports		103
4.5.1.4	Perinatal period		106
4.5.1.5	Recorded stressors		108
4.5.2	Dizygotic twin obstetric and developmental data		112
4.5.2.1	Magnetic resonance imaging (MR-imaging)		113
4.5.2.2	Blood plasma pathology		113
4.6	DISCUSSION		114
4.7	REFLECTIVE VALIDATION OF RESEARCH HYPOTHESIS		116
4.8	SYNOPSIS		117
4.9	LIST OF REFERENCES		117

FINDINGS, CONCLUSIONS, AND RECOMMENDATIONS

5.1	INTRODUCTION	23
5.2	OVERVIEW	23
5.3	FINDINGS	24
5.3.1	Significant findings related to biochemicals implicated in programmed f	oetal
	development	24
5.3.2	Significant findings related to neuroanatomical observations of the brain in au	tistic
	disorder	27
5.3.3	Significant findings related to the impact of prenatal stress on cortical develop	ment
	and agenesis	29
5.3.4	Significant findings related to the dizygotic twin study	30
5.4	CONCLUSIONS	32
5.5	RECOMMENDATIONS	32
5.5.1	Educational psychological training	33
5.5.2	Prenatal primary health care	33
5.5.3	Further research	33
5.6	LIMITATIONS TO THIS STUDY	34
5.7	CONCLUDING REMARK	34
5.8	LIST OF REFERENCES	34

LIST OF ANNEXTURES	xiv
LIST OF FIGURES	XV
LIST OF TABLES	xvi

LIST OF ANNEXTURES

Annexture A: Letter of Informed Consent

Annexture B: Diagnostic Criteria for Autistic Disorder (DSM-IV-TR 2000)

Annexture C: Ethics and Research Statement

LIST OF FIGURES

Figure 2.1	The removal of the carboxyl (COOH) group from g procedures GABA	lutamate 32
Figure 3.1	The anatomical and functional differences between parasympathetic nervous systems	the sympathetic and 82
Figure 4.1	Table for tabulating maternal blood-pressure reduring period of pregnancy	eadings (BP/mmHg)

LIST OF TABLES

Table 1.1	Major premises of affective neuroscience	17
Table 1.2	Different modes of inquiry and research design	19
Table 2.1	Small molecule neurotransmitters	34
Table 2.2	Peptide neurotransmitters	35
Table 3.1	Potential neurotoxic agents and their teratogenic windows	65
Table 3.2	Possible sensorimotor learning deficits due to excess glucoco	rticoids
	during gestation	87
Table 4.1	Table for summarizing maternal blood-pressure values (unduring period of pregnancy	nits mmHg) 101
Table 4.2	Table for classifying blood-pressure values (units mmHG) a World Health Organization	according to
Table 4.3	Results of blood plasma analyses for Rubella antibodies duri week of gestation	ing the 6 th
Table 4.4	Results of blood plasma analyses for Rubella antibodies du week of gestation	ring the 7 th 104
Table 4.5	Results of the Rubella affinity index during the 8^{th} week 105	of gestation
Table 4.6	Results of maternal blood plasma analyses during the 32 gestation	2 nd week of 106
Table 4.7	Table for summarizing maternal 16-PF standardized 110	sten scores
Table 4.8	Table for summarizing dizygotic twins' blood plasma pathol reports	ogy 113