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

"Although some investigators still choose to believe that human emotions are unique and acquired through social learning, the data-based premise is that psychology is neurodynamics and that the ultimate sources of human cognition and feelings are biological, and that these foundations are essential for all of the many acquired complexities that characterize the detailed expressions of human emotions in the real world. The traditional distinction between bodily and psychological processes becomes blurred as we come to increasingly appreciate that mental abilities are bodily functions of the brain. Psychological and brain analyses must remain two-way streets. To understand the nature of the brain, we must understand emotions, but to understand the diversity of real-life emotions, we must understand the intrinsic operating systems of the brain" (Panksepp 1998:20).

1.1   INTRODUCTION

By means of this research project the contribution of prenatal stress to the pathogenesis of autism as a neurobiological developmental disorder will be explored.   Autism is characterised by serious functional impairment pertaining to socialisation, communication and imagery (Panksepp 1998:276; Trevarthen 2000: 4; Kates et al 2004:539).   In 1943 Kanner established the concept *autism* (also known as *Kanner's autism*) and remarked that children with autism "... have come into the world with an innate inability to form the usual, biologically provided affective contact with people" (Kanner 1943:50 cited in Panksepp 1998:276).   After a period during which claims were made that autism is caused by faulty parenting, researchers are currently united in their view that autism is primarily a neurobiological developmental disorder (Bauman & Kemper 1994; Herman 1996;

Panksepp 1998; Trevarthen 2000; Clark 2002; Courchesne 2002; Keller & Persico 2003; Schmidt & Rotenberg 2005). Research findings suggest that this neurobiological developmental disorder might be ascribed to disrupted neural development during the second trimester of gestation when the foetal brain stem, cerebellum and limbic pathways must be generated (Bauman & Kemper 1995:1-26). In keeping with these findings, Beversdorf in 2004 pointed out a significant relation between prenatal stress and the development of autism (Beversdorf 2004). 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 (Sapolsky 2000:925-935). Sapolsky (2000) found that programmed apoptosis is affected due to the neurobiological impact of stress on foetal development, which concept relates closely to the pathogenesis of autism. Sapolsky (2000:925-935) established that increased levels of cortisol in response to chronic stress (maternal or foetal) might kill nerve cells in the hippocampus. If hippocampal activity is thus compromised, excessive cortisol is secreted and, over time, the ability to turn off the stress response decreases, which leads to further atrophy of the hippocampus. These findings indicate that chronic stress leading to chronic secretion of cortisol may have long-lasting effects on physical functioning, including brain damage. Programmed apoptosis may be grossly interfered with, especially within the areas of the hippocampus and the cerebellum. MR-imaging confirmed structural differences of the cerebellum, the brain stem and limbic system associated with autism (Beversdorf 2004), and these structural differences were further associated with elevated levels of glucocorticoids and endogenous opiates during gestation (Bertram & Hanson 2002:459–467). Elevated glucocorticoids inhibit foetal growth and are associated with altered programmed foetal cortical development (Bertram & Hanson 2002:460). Thus, there appears to be a link between the pathogenesis of autism and prenatal endogenous and exogenous glucocorticoids as well as endogenous opiates (Panksepp 1998). In this research project a significant focus is placed on prenatal hipothalamic-pituary-adrenal (HPA) activity due to the HPA axis' interactivity with ß-endorphins, cortisol, oxytocin, insulin, endogenous opiates, digoxin and serotonin (Kurup & Kurup 2003:1537-1559), as these hormones 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 (APA 2000:75).

Recently various studies concerning monozygotic twins have been undertaken in order to investigate the neurobiological and cortical similarities and differences between children with and without autism (Trevarthen 2000; Clark 2002; Courchesne 2002; Bertram & Hanson 2002; Kurup & Kurup 2003; Keller & Persico 2003; Beversdorf 2004; Schmidt & Rotenberg 2005). This research project differs from previous studies by tracking the neurobiological and cortical differences and similarities in a pair of dizygotic twins, where only one of the pair meets the criteria for autism (APA 2000:75). Dizygotic twins develop from two different ovaries that were fertilized at the same time. Consequently, these dizygotic siblings share no more genetic similarities than normal siblings (Plug, Meyer, Louw & Gouws 1987:67). The reason why a dizogotic twin study was decided upon is to explore whether HPA activity manifests differently among a pair of dizogotic siblings, since it is expected that both dizygotic foetuses were exposed to elevated glucocorticoids during gestation, yet only one of the siblings is affected and meets the diagnostic criteria for autism (refer to Annexture B). In addition, a dizygotic twin study offers the ideal research control, since all significant variables are uniform and constant. If prenatal stress does play a role in the pathogenesis of autism, why was only one sibling affected? This phenomenon might only be explained by means of a neurobiological enquiry that forms the basis for a neuropsychological explanation of this complex phenomenon.

1.2   AWARENESS OF THE PROBLEM

During my training as student in psychology I was stationed at the Unica School for learners with Autism in Pretoria.   Following my observations of these children's behaviour, i.e., socialisation, communication, and learning, and after various discussions on the aetiology of autism with the psychologist employed at this school, I concluded that there must be a neural substrate to autism. I then started to investigate the foundations of human emotions, which led me to the field of affective neuroscience. With current advances in neurobiology, neuroscience, and neuropsychology, the bulk of literature pointed to the role of neurobiology in the understanding of human cognitive behaviour and emotions. The literature on these research findings provided me with recent information about the brain-operating systems involved in foetal brain development, how these brain-operating systems organize the fundamental emotional tendencies of all human beings, as well the neuropsychological implications of these findings.

Following this personal interest, the parents of a pair of dizygotic twins consulted me during my internship training this year. As this couple suffered significant emotional discomfort due to their personal guilt feelings and their misunderstanding of autism as a developmental disorder, I proceeded with in-depth reading in order to support the parents with accurate information about autism. The couple's misconceptions were demystified through information about the structural brain differences inherent to autism and how these differences relate to different affective, social, and cognitive behaviour in their two siblings. The parents found consolation through the power of knowledge, and were intrigued by the neurobiological basis underpinning autism as a developmental disorder. They concluded that they might contribute significantly to the demystification of autism and initiated further exploration by offering the participation of their dizygotic twins in a research project. Keeping in mind that they might later reconsider involvement, I discussed the advantages and disadvantages of such an endeavour with the parents; they anyway wanted to proceed and gave informed consent, upon which I discussed the proposed study with my supervisor.

1.3   RATIONALE FOR THE STUDY AND ANALYSIS OF THE RESEARCH PROBLEM

"To understand the basic operating systems of the brain, we have to begin relating incomplete sets of neurological facts to poorly understood psychological phenomena that emerge from many interacting brain activities. Why has it taken us so long to recognize the general organizational principles for mind and behaviour that are found within the primitive genetically dictated areas of the brain? It is partly because until recently we simply did not know enough about the brain. It is also because for a long time, 20th century psychology insisted that we should seek to explain everything in human behaviour via environmental events that assail human beings in their real-life interactions with the world rather than via the evolutionary skills that are constructed in their brains as genetic birthrights" (Panksepp 1998:4-5).

During various discussions with my supervisor and co-supervisors we envisioned that a research project of this nature might be met with resistance; however, the rationale for this study refutes potential resistance and arguments that a research project of this nature cannot be pursued within the field of Educational Psychology, although the rationale for this study cannot be defined using a single disciplinary approach. The premise of the rationale is that all human beings come into the world with a variety of abilities, i.e.,

intrinsic psycho-behavioural control systems, that do not require previous learning, but which provide immediate opportunities for learning to occur. Specific hormones activate these intrinsic psycho-behavioural control systems during gestation, as well as postnatally (Pretorius 2005). In each individual the influence of these intrinsic psycho-behavioural control systems varies as a function of the individual's life span. As these systems mature and interact with higher brain areas, where they undergo both re-representation and refinement, the individual learns to make effective behavioural choices. Emotional tendencies such as those related to fear, anger and separation distress, emerge at early developmental stages. Following gradual maturation these systems, through their effects on other parts of the brain, allow the individual to experience more subtle social feelings and to anticipate important events and deal with them in increasingly complex ways, i.e., one develops a certain 'theory of mind' or 'social cognition' (Kolb & Whishaw 2003:375). When these intrinsic psycho-behavioural control systems are overtaxed or operate outside the normal range, we call the end results *psychiatric* or *mental disorders*, in keeping with the diagnostic criteria for autism ([APA] American Psychiatric Association 2000:75). Under activity of certain systems may cause depression and variants of personality disorders. Over activity may contribute to mania, paranoid schizophrenia, anxiety, obsessive-compulsive, and posttraumatic stress disorders. Other disorders such as autism and schizophrenia appear to emerge from lesioned brain areas and associated "wiring" problems in brain circuits (Kolb & Whishaw 2003:602). Because of the social importance of these human problems, a substantive understanding of the neurobiological systems and the manner in which they can become compromised or overtaxed pre- and postnatally is of great scientific and societal concern, and therefore this research project becomes firmly based within the field of Educational Psychology.

Based upon the preceding premise, it is essential to synthesize biological, psychological, and neurological perspectives on the pathogenesis of autism as a developmental disorder, and this synthesis is reflected by the choice of supervisors/co-supervisors for this research project. Various disciplines have contributed towards this needed synthesis, but there is presently no umbrella discipline to bridge these neurobiological, neurological and psychological approaches, or have managed to synthesize the nature of neural systems within the human brain under one umbrella. The various cognitive sciences are beginning to address the complexities of the human mind (Eysenck 2001:5), but until recently these approaches have ignored the evolutionary neural systems upon which our vast cortical

potentials are built and to which those potentials may still be subservient.   The *experimental cognitive psychological approach* involves carrying out experiments on normal individuals, typically under laboratory conditions, whereas the *cognitive neuropsychological approach* involves studying patterns of cognitive impairment shown by brain-damaged patients in order to understand normal human cognition (Eysenck 2001:5).   The *cognitive neuroscientific approach* involves using several techniques for studying brain functioning (e.g., brain scans) in order to identify the processes and structures used in cognition (Eysenck 2001:5). *Clinical psychology* and *psychiatry* attempt to deal at a practical level with the underlying disturbances in brain mechanisms, but neither has an adequate neuroconceptual foundation of the sources of cognition and emotionality upon which systematic understanding can be constructed (Panksepp 1998:5). *Neuropsychology* aims to diagnose the presence of cortical damage or dysfunction and to localize it where possible. In doing so, there is an attempt to provide an accurate and unbiased estimate of a person's cognitive capacity (Kolb & Whishaw 2003:756).   The contribution of some of these approaches will be discussed under the heading that deals with the embedded paradigm; yet these approaches are mentioned here in order to illustrate the blurred distinctions and the complexities inherent to a suitable rationale. Nonetheless, this research project seeks to combine several elements of more than one approach; yet the missing piece that could bring all these disciplines together as part of a suitable rationale is a neurobiological understanding of the basic pre- and postnatal cognitive and emotional operating systems of the human brain, without compromising the psychological inputs. This synthesis could be found in the *affective neuroscience* (Panksepp 1998:5). Affective neuroscience is deeply rooted within *physiological psychology*, *behavioural biology*, and *behavioural neuroscience,* and provides the modernized umbrella label for various physiological, affective, and cognitive psychological approaches to disorders.   The affective neuroscience deals with pre- and postnatal neurobiological development and provides a suitable premise for the rationale of this study, as it will become clear from the following paragraphs.

Affective neuroscience offers a unique perspective on autism, which approach supplements the Educational Psychological perspective, since autism is defined as a developmental disorder first evident in early childhood (APA 2000:75). Why do we define autism as a developmental disorder *per se*? Almost all disorders included in the DSM-IV-TR (APA 2000) could be defined as developmental disorders, since with time the characteristic

symptoms undergo certain changes, and since the condition in itself often only develops over time – most disorders originate in childhood, although the full presentation of the condition only manifests itself much later during adulthood. In layperson's terminology this group of disorders is called 'adult psychopathology', mostly because the full clinical image is only met during adulthood, namely after the age of 18 years. In contradistinction, there is a group of developmental disorders that manifest early in life, the full clinical image is met during the early developmental years, and the disorder often persists as the individual grows older. The concept 'early developmental disorder' or 'childhood disorder' therefore seems to be a misnomer, because these conditions are relatively permanent in nature and the duration thereof persists through adulthood (Barlow & Durand 2002:455). Thus, the majority of these 'childhood' developmental disorders are by nature not unique to early childhood, e.g., autism (Barlow & Durand 2002:455). However, Educational Psychologists take special interest in these developmental disorders, since significant focus is placed on the social, affective and cognitive development of children diagnosed with these disorders. These disorders are of clinical significance within the field of Educational Psychology, since the child's normal development is affected by the condition, implicating compromised mastery of developmental milestones. What are the differences between these two categories of disorders then? When the full range of diagnostic criteria only manifests as a disorder during adulthood, the mastery of basic developmental skills is not compromised; yet, adult psychopathology might contribute to sensory, motor or cognitive impairment or deterioration. In addition to non-mastery of certain developmental milestones, developmental disorders usually first diagnosed in infancy or childhood also affect family life, educational needs, education planning and provision (Naudé 2005).

"Autism is characterized by markedly abnormal or impaired development in social interaction and communication and a markedly restricted repertoire of activity and interests. The impairment in reciprocal social interaction is gross and sustained. The impairment in communication is also marked and sustained and affects both verbal and nonverbal skills" (APA 2000:70). This brief description of impairment relates to a compromised neural substrate, in keeping with affective neuroscience, which approach deals with pre- and post neurobiological development. In addition, if speech does develop in children with autism, the pitch, intonation, rate, rhythm, or stress may be abnormal (APA 2000:70), which points to compromised neural involvement, specifically cerebellum

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involvement (Naudé, Marx, Pretorius & Hislop-Esterhuyzen 2006). "In most cases, there is no period of unequivocally normal development, although in perhaps 20% of cases parents may report relatively normal development for one or two years. In such cases, parents may report that the child adquired a few words and lost these or seemed to stagnate developmentally. By definition, if there is a period of normal development, it cannot extend past age three years" (APA 2000:71). It is thus concluded that autism is characterised by developmental delays, in keeping with compromised or overtaxed neurobiological systems, which seems to occur prenatal, as suggested by various researchers (Trevarthen 2000; Clark 2002; Courchesne 2002; Bertram & Hanson 2002; Kurup & Kurup 2003; Keller & Persico 2003; Beversdorf 2004; Schmid & Rotenberg 2005).

The following principles thus underlie the rationale for this research project namely, developmental delay or a total lack of mastery of certain developmental skills characterise autism (APA 2000:70–75; Kolb & Whishaw 2003:375); it is suggested that this developmental delay or lack of mastery of developmental skills might be ascribed to compromised neural development during the second trimester of gestation when the foetal brain stem, cerebellum and limbic pathways must be generated (Bauman & Kemper 1995:1-26); research findings point towards a significant relation between prenatal stress and the development of autism (Beversdorf 2004); autism deals primarily with development in the areas of socialisation, communication, and imagery, and exploration of this phenomenon is therefore firmly based in both the Affective Neuroscience and the Educational Psychology. If prenatal risk factors associated with the pathogenesis of autism could be identified, such findings might inform Educational Psychologists to better understand and provide for children with autistic disorder. In addition, such data might significantly implicate prevention and treatment regimes (Burd, 1999: 441). The rationale of this study is in keeping with Barlow and Durand's' views, "… we cannot study behavioural, cognitive, or emotional processes without appreciating the contribution of biological and social factors to psychological and psychopathological expression. Thus, we have abandoned the traditional compartmentalized approach to psychopathology. Instead, we use a more accessible approach that accurately reflects the current state of our clinical science" (Barlow & Durand 2002:xvii).

1.4   LITERATURE REVIEW

Recent research projects focused on the role of glucocorticoids in programmed foetal development (Benediktsson, Lindsay, Lindsay & Seckl 1993:339-341; Coleman 1994:104; Levitt, Lindsay, Holmes & Seckl 1996:1200-1204; Nyirienda, Lindsay, Kenyon, Burchell & Seckl 1998:2174-2181; Levitt, Lambert, Woods, Hales, Andrew & Seckl 2000:4611-4618; Courchesne 2002:21-23; Bertram & Hanson 2002:459; Clark 2002:7-10).   An increase in foetal exposure to maternal glucocorticoids can cause increased glucocorticoid receptor density and disruption of programmed neural development (Lindsay et al 1996:1200-1204; Bertram & Hanson 2001:103-121), yet despite these adverse risks it has become common practice to administer glucocorticoids to pregnant mothers to promote foetal maturation of organs if they are in danger of pre-term delivery (Matthews 2001:309-317).

Various studies point to the involvement of the hypothalamic–pituitary–adrenal (HPA) axis in neural programming. This is not surprising as glucocorticoids produced in the adrenal cortex in response to signals from the HPA axis have wide-ranging effects on a number of systems both in foetal and adult life, playing key roles in regulation of salt and water homeostasis, blood pressure, immunological responses and metabolism. The HPA axis is controlled by a classic negative feedback system, in which glucocorticoids released into the circulation by the adrenal gland interact with glucocorticoid receptors (GRs) located in the pituitary, hypothalamus and hippocampus. Thus over-activity at any stage along this pathway should result in negative feedback to the corticosteroid releasing hormone (CRH) corticotrophins in the hypothalamus and consequent reduced CRH release.

Pre-clinical research conducted over the past decade has shown that excess levels of glucocorticoids can result in functional and morphological hippocampal changes (Sapolsky 1994:294; Gould 1994:73; Miller et al 1993:391; Squire & Zola-Morgan 1991:1380; Zola-Morgan & Squire 1993; Zola-Morgan et al 1994; Alvarez et al 1995:3976). In addition, McEwen in 1997 noted that hippocampal shrinkage is usually accompanied by deficits in declarative, episodic, spatial and contextual memory performance, in keeping with the associated features of autistic disorder. These hippocampal changes provide a neural substrate for changes in cognitive functioning among children with autistic disorder (APA

2000:75). MR imaging revealed decreased benzodiazepine receptor binding in the medial prefrontal cortex, as well as reduced hippocampal volumes due to over-exposure to glucocorticoids (Stein et al 1997:951; Villarreal & King 2001:131). In addition to this, PET-scans demonstrated decreased N-acetyl aspartame (NAA) ratios and absolute concentrations in the medial temporal lobe and hippocampus, in keeping with the structural brain differences observed in autistic disorder (Panksepp 1998:358). Furthermore, fMRI studies demonstrated different patterns of limbic and paralimbic structure activation due to an excess of glucocorticoids. Of theoretical importance are findings of failure to activate the anterior cingulate, as well as amygdala activation during symptom provocation studies, in keeping with similar observations that were made in autistic disorder (Panksepp 1998). Villarreal and King (2001) suggested that anterior cingulate dysfunction produces failure to inhibit amygdala activation and/or an intrinsic lower threshold of amygdala response to fearful stimuli. These observations are in keeping with research findings implicating disrupted neural development, i.e., brain stem, cerebellum, hippocampal and limbic pathway abnormalities among individuals with autistic disorder (Bauman & Kemper 1995:1-26; Sapolsky 2000:925-935). In addition, Sapolsky (2000:925-935) found that programmed apoptosis is affected due to the neurobiology of stress, which concept relates closely to the pathogenesis of autism (Kalat 2001:346).

Glucocorticoids in the foetus can be derived from three sources: (i) through increasing basal secretion as the foetal adrenal system matures, or in response to foetal stress; (ii) from the mother by transplacental transfer; or (iii) by maternal glucocorticoids crossing into the foetal blood brain barrier, with toxic effects on foetal development (Edwards et al 1993:355). By allowing the high glucocorticoid concentrations to cross the placenta, the foetal HPA feedback system that regulates the foetal adrenal output may be overwhelmed. Not only will this have an immediate effect on development, but it may also result in long term 'resetting' of the foetal HPA axis, which may persist into adulthood, because the normal negative feedback system that regulates normal homeostasis is permanently altered (Edwards et al 1993:355).

As the foetal HPA axis regulates the response of the foetus to acute episodes of intrauterine stress and is central to other processes such as organ maturation, growth, neural programming, myelination and cardio-vascular regulation, any disturbance is likely to affect a wide range of foetal systems (Phillips et al 2000:1301). In the foetus,

glucocorticoids inhibit tissue expansion and growth. Foetal plasma cortisol concentrations are low until late gestation, when the HPA axis is activated, producing increased secretion of cortisol from the foetal adrenal gland and a progressive increase in cortisol concentrations, consequently there is a marked cortisol surge prior to delivery (Challis et al 2001:135). The rate of foetal growth normally decreases towards term delivery, which may be linked to the increase in plasma cortisol that occurs at this time, because high foetal glucocorticoid concentrations reduce foetal size. Inappropriate activation of the HPA axis or movement of maternal glucocorticoid across the placenta could therefore increase foetal glucocorticoid concentrations, thus influencing foetal growth. Glucocorticoids act as transcription factors with wide-ranging effects during development. Many genes are activated by glucocorticoids, and any disruption in HPA axis functioning could have subtle or overt effects on development of many tissues in the cardiovascular, pulmonary, renal and central nervous systems (Byrne 2001:153).

In addition, prenatal glucocorticoid exposure permanently programmes several central nervous system functions such as dopamine and serotonin sensitivity, as well as hippocampal formation. Prenatal exposure to glucocorticoids was associated with restricted foetal growth, and delayed myelination of the central nervous system. Barbazanges and coworkers (1996:3943) found that prenatal stress in the final third of gestation caused decreased expression of hippocampal mineralocorticoids receptors, but not glucocorticoid receptors. In humans, prenatal stress has been reported to induce mental retardation and sleep disturbances (Shell 1981:63-70; Barbazanges et al 1996:3943).

Exposure to excessive levels of glucocorticoids during pregnancy is detrimental in terms of brain structure (Uno et al 1994:336), and might even alter postnatal cortisol concentrations (Sapolsky 1996:294-304). Most evidence cited are now showing reduced birth weight, head circumference and more severe chronic lung disease (French et al 1999:114-121) among children who were treated with multi-dose glucocorticoids in utero. In addition to structural central nervous system changes due to high levels of glucocorticoids, the neuroendocrine system also seems to be disrupted. Research findings implicate both central nervous system and neuroendocrinological alterations in the pathogenesis of autism (Bertram & Hanson 2002:459-467).

The preceding literature study suggests that over exposure to glucocorticoids during gestation might affect the foetus adversely. Glucocorticoids act as transcription factors with wide-ranging effects on the foetus during gestation. Many genes are activated by glucocorticoids, implicating that organogenesis might be partly controlled by glucocorticoids, with specific focus on foetal central nervous system development (Perrotta et al 2003; Ross et al 2000; Maden 2001; Colbert 2002). In addition, the balanced supply of glucocorticoids to the foetus is essential, especially during the latter stages of gestation, due to the involvement of glucocorticoids in neural growth and cellular differentiation (Zachman 1995; Debier & Larondelle 2005), but an excess of glucocorticoids might alter central nervous system formation and adversely impact on post-natal sensorimotor learning and cognitive functioning. Disproportionate levels of glucocorticoids have also been implicated in disrupted programmed apoptosis, with specific focus on hippocampal, cerebellar and limbic formation. Structural differences, e.g., densely packed areas and lesser dendritic growth in other areas, are implicated in autistic disorder, and the cerebellum is of particular interest, due to involvement in almost all forms of motor learning and vestibular functioning, which areas once again are implicated in autistic disorder. The cerebellum consists of the cerebellar hemispheres, vermis and the flocculi, and forms part of the motor system that participates in post-natal sensorimotor functioning. The flocculonodular lobe receives projections from the vestibular system (the sensory receptors in the middle ear) and takes part in the control of balance and eye movements (Kolb & Whishaw 2003:217). Lesions to the midline areas of the cerebellum might disrupt balance, eye movements, upright posture and walking, but do not substantially disrupt other movements such as reaching, grasping and using the fingers (Kolb & Whishaw 2003:217). It is thus suggested that attainment of developmental milestones, particularly crawling and walking, might be delayed due to over exposure to glucocorticoids during gestation. Sensorimotor learning during the early post-natal developmental years might thus be adversely affected.

Considering the preceding literature on the adverse effects of glucocorticoids during gestation, as well as the structural and functional brain alterations that result from over-exposure, it is suggested that prenatal stress might play a significant role in the pathogenesis of autism. The various impairments associated with autism also suggest that excess levels of glucocorticoids might be implicated, i.e., speech deviations such as pitch, intonation, rate, rhythm, odd hand movements and body posture, high threshold for pain,

emotionality, abnormalities in sleep, deviant fear response, and so forth (APA 2000:75-77), because many of these behaviours are mediated by the brain stem, the cerebellum, the hippocampus, the limbic system and its relays.

1.5   DEFINITION OF KEY CONCEPTS

1.5.1   Prenatal

Wevell (1996:435) defines the concept *prenatal* as the period of gestation, relating to the duration of pregnancy, from conception to birth. The gestation period of humans is approximately 40 weeks.

1.5.2   Stress

The concept *stress* is defined as a transaction between a person and the environment that includes the person's appraisal of the challenges posed by the situation and available coping resources, along with the psychological responses to those perceived challenges (Bishop 1994:126). This type of stress thus refers to the subjective stress experienced by the mother during pregnancy. However, prenatal stress might also include foetal stress, e.g., strangling by the umbilical cord, placentae insufficiency, or abruptio placentae (Edwards et al 1993:355).

1.5.3   Pathogenesis

The prefix *patho* comes from Greek and means 'deviant' or 'pathological', while the concept *genesis* means 'origin' or 'beginning' (Wevell 1996:433). Within the context of this study the concept *pathogenesis* is indicative of the etiology of a certain disorder, namely autistic disorder (APA 2000:75).

1.5.4   Autism

Autism is defined as a developmental disorder first evident in childhood, and characterised by serious functional impairment pertaining to socialisation, communication and imagery (APA 2000:75; Panksepp 1998:276; Trevarthen 2000:4; Kates et al 2004:539). "The

median rate of Autistic Disorder in epidemiological studies is 5 cases per 10 000 individuals, with reported rates ranging from 2 to 20 cases per 10 000 individuals" (APA 2000:73). The onset of this disorder is prior to age 3 years, and there is an increased risk of Autistic Disorder among siblings of individuals with the disorder, with approximately 5% of siblings also exhibiting the condition (APA 2000:73; Kaplan & Sadock 1998:1182).

1.5.5   Neurobiological

The concept *neurobiological* refers to the study of "… a diversity of coherently operating brain systems which can generate psychologically meaningful classes of adaptive behavioural tendencies" (Panksepp 1998:12). In addition, the concept *neurobiological* also refers to the study of neural pathways and related electrophysiological and neurochemical activities. One of the best examples of neurochemistry comes from research findings implicating the role of serotonin in controlling human mood, including aggression and depression (Young 1996:313).

1.5.6   Developmental disorder

A developmental disorder manifests itself during the early developmental years, and often persists as the person grows older, e.g., Autistic Disorder. The concept 'early developmental disorder' or 'childhood disorder' therefore seems to be a misnomer, because these conditions are relatively permanent in nature and the duration thereof persists through adulthood (Barlow & Durand 2002:455). The majority of developmental disorders are by nature not unique to early childhood (Barlow & Durand 2002:455). However, Educational Psychologists take special interest in these developmental disorders, since significant focus is placed on the social, affective and cognitive development of children diagnosed with these disorders. These disorders are of clinical significance within the field of Educational Psychology, since the child's normal development is affected by the condition, implicating compromised mastery of developmental milestone. When the full range of diagnostic criteria only manifests during adulthood, the mastery of basic developmental skills is not compromised; yet, adult psychopathology might contribute to sensory, motor and cognitive impairment or deterioration. In addition to non-mastery of certain developmental milestones, developmental disorders usually first diagnosed in

infancy or childhood also affect family life, educational needs, education planning and provision (Naudé 2005).

1.5.7   Dizogotic

Dizygotic twins develop from two different ova that were fertilized at the same time. Consequently, these dizygotic siblings share no more genetic similarities than normal siblings (Plug, Meyer, Louw & Gouws 1987:67).

1.6   PROBLEM STATEMENT

Based upon the rationale of this research project and the conceptualisation of the topic of interest, the research problem can be formulated as follows:

In what unique ways does prenatal stress contribute to the pathogenesis of autism as a neurobiological developmental disorder?

1.6.1   Sub questions

- Did the mother of the dizygotic twins experience significant stress during the period of gestation?
- What blood plasma differences can be observed among the dizygotic twins at hand of blood sampling?
- Does HPA activity manifest differently among this pair of dizogotic siblings?
- How does elevation of glucocorticoids disrupt programmed foetal development?
- How do blood plasma differences account for sensory, motor, cognitive, and affective behavioural differences among the dizygotic twins?
- Does the MR image of the sibling diagnosed with autism differ in respect of structural brain development from what is normally expected?
- To which periods of prenatal development can these structural differences be related?
- How do these structural differences account for sensory, motor, cognitive, and affective behavioural differences among the dizygotic twins?

1.6.2   Research hypothesis

The research hypothesis can be formulated as follows:

Elevation of glucocorticoids due to prenatal stress disrupts programmed foetal development and contributes to the pathogenesis of autism as a neurobiological developmental disorder.

1.7   PURPOSE OF THE STUDY

The purpose of this research project is to explore at hand of dizygotic twin study the contribution of prenatal stress to the pathogenesis of autism as a neurobiological developmental disorder.

1.8   THEORETICAL FRAMEWORK AND PARADIGMATIC PERSPECTIVE

This research design is firmly embedded in a positivistic paradigm. Positivism is based upon the utilization of research methods and practices derived from the natural sciences and application of these to the social sciences. Research findings are interpreted in terms of quantifiable units, and deviations are reported as significant deviations at 0.001 or 0.005 levels or reliability (Cohen, Lui, Schutz et al 2003:8). Data is viewed to be linear and objective in nature, as well as relatively free from researcher contamination or bias. Reality is perceived as external and scientific data is objective and quantifiable, follows the medical approach, experimental in nature and seen as irrefutable or refutable.

In addition, this research project is firmly embedded in the cognitive science. Eysenck (2001:7) defines the cognitive science as follows: 'Cognitive scientists develop computational models to understand human cognition. A good computational model … allows us to predict behaviour in new situations. This is a clear advantage over many previous theories in cognitive psychology, which were expressed so vaguely that it was not clear exactly what predictions were supposed to follow from them.'

However, the cognitive science to a great extent lacks interpretation of the neurobiological systems that underlie affective human behaviour. Affective neuroscience developed from

the cognitive science and seeks to provide conceptual bridges that can link our understanding of basic neural circuits for the emotions with straightforward *cognitive* and p*sychological* views of the human mind and, most importantly, developmental disorders first evident in infancy and early childhood. Affective neuroscience is deeply rooted within *physiological psychology*, *behavioural biology*, and *behavioural neuroscience,* and provides the modernized umbrella label for various physiological, affective, and cognitive psychological approaches to disorders (Panksepp 1998:9). This interdisciplinary approach strongly draws upon our introspective-linguistic access to our subjective feelings. "Because of this small psychological window, and because the key emotional circuits are conserved in the human brain, the two can be linked in such a way that we can finally understand the neurobiological underpinnings of our human emotions" (Panksepp 1998:304). Thus, our introspective access to emotions supplements "hard" scientific data, resulting in an in-depth psychological understanding of developmental disorders. Panksepp's (1998) summary of the major premises of affective neuroscience is captured in table 1.1 below.

Table 1.1   The major premises of affective neuroscience (Panksepp 1998:14-15)

"Emotional processes … play a key role in the causal chain of events that control the actions of humans. They provide various types of natural internal values upon which many complex behavioural choices in humans are based. However, such internal feelings are not simply mental events; rather, they arise from neurobiological events. In other words, emotional states arise from material events at the neural level." "Emotional feelings not only sustain certain unconditioned behavioural tendencies but also help guide new behaviours by providing simple value-coding mechanisms that provide self-referential salience, thereby allowing humans to categorize world events efficiently so as to control future behaviours."
"A series of basic emotional processes arises from distinct neurobiological systems and everyday emotional concepts such as anger, fear, joy, and loneliness are not merely the arbitrary taxonomic inventions of noncritical thinkers. These brain systems have several common characteristics. The core function of emotional systems is to coordinate many types of behavioural and physiological processes in the brain and body."
"When such neural activities continue at low levels for extended periods of time, they generate moods and, ultimately, such personality dimensions as the differential tendency to be happy, irritable, fearful, or melancholy. These systems help create a substantial portion of what is traditionally considered universal "human nature".
"A complete study of emotional systems is also essential for understanding the many psychiatric disturbances that assail humans – schizophrenia, autism, mania, depression, anxiety, panic, obsessive-compulsive disorders, post-traumatic stress disorders, neuroses, and other vexations of the human spirit."
"We will not understand the underlying neurodynamics of emotional systems without a great deal of

concurrent brain research."

Affective neuroscience forms the paradigmatic conceptual bridge needed for this research project, since this approach can yield clear empirical predictions in both directions - from neuroscience to social science and vice versa, and it serves as an intellectual highway for productive interaction between the psychosocial and neurobiological sciences (Panksepp 1998:304). This paradigmatic conceptual bridge might facilitate an in-depth understanding of autism as a neurobiological developmental disorder.

1.9   RESEARCH DESIGN AND METHODOLOGY

This research project represents quantitative research. Quantitative research is deductive in nature and the research hypothesis, which flows from the research problem, directs the scientific inquiry, leading to hypothesis-testing.   This approach deals with relations, correlations and covariance of variables. Pertaining to this research project, the mode of inquiry is non-experimental at hand of a single dizygotic twin study, which is *ex post facto* in nature i.e., 'after the fact'. Dizygotic twins come from different ova and have only about 50% of their genes in common, as do all first-degree relatives (Barlow & Durand 2002:104). The advantage of including dizygotic twins is that all prenatal variables are uniform and constant, therefore this research design provides for experimental control which heightens validity of the results because future studies can be replicated at hand of similar dizygotic twins. Replicating findings usually convince researchers that the findings cannot merely be ascribed to coincidence (Cohen et al 2000:181). "The strength of a research program is in its ability to replicate findings in different ways to build confidence in the results" (Barlow & Durand 2002:104). A stress survey will be utilized, which is also non-experimental in nature.

Research involves establishing a hypothesis that is then tested. In abnormal psychology, research focuses on hypotheses meant to explain the nature and causes of disorders (Barlow & Durand 2002:110).

The following data generating strategies will be employed: intake interviews coupled with a diagnostic stress inventory, retrieval of diagnostic records where applicable, administration of the 16-PF Questionnaire, MR-imaging, and blood plasma sampling.

Both the mother and father of the dizygotic twins will be required to complete the diagnostic stress inventory, because they might have different perspectives on the significance of various stressors that were endured during pregnancy.

Magnetic resonance imaging (MR-imaging) of the sibling diagnosed with autistic disorder will be done in order to identify whether structural brain development was altered, compared to what is normally expected. These structural differences will be interpreted in light of prenatal neural programmed neural development, the impact of endocrine system changes on foetal central nervous system development, and the consequent manifestations of autism. MR-imaging is a procedure using radio signals generated in a strong magnetic field and passed through body tissue to produce detailed, even layered, images of brain structures, which are useful in detecting very small brain lesions (Eysenck 2001:9).

Blood plasma sampling of both siblings will complement the research hypothesis and allow exploration of the contribution of prenatal stress to the pathogenesis of autism as a neurobiological developmental disorder, since endocrine system changes might contribute to disruption of programmed neural development, and these plasma differences between siblings might continue to be present postnatally. The different modes of inquiry and research design that will be followed are presented in table 1.2 below.

Table 1.2   Different modes of inquiry and research design

	QUANTITATIVE		QUALITATIVE	
	Experimental	**Non-experimental**	**Interactive**	**Non-interactive**
Research design	True experimental	Descriptive	Ethnographic	Concept analysis
	Quasi-experimental	Comparative	Phenomenological	Historical analysis
	Single-subject	Correlational	Case study	
		Survey	Grounded theory	
		Ex post facto	Critical studies	

(Adapted from: McMillan & Schumacher 1997: 31.)

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1.9.1 Data analysis and Interpretation

The data will be quantified and interpreted along linear lines of thought, i.e., according to specific conceptual schemes and parameters of pre- and postnatal endocrinological and central nervous system development. Where applicable, significance of deviations will be calculated at the 0.001 and 0.005 levels of reliability.

In addition to my appointed supervisor and co-supervisors from the Faculty of Health Sciences, additional external expertise will be provided by dr. Becker, independent statistical analyst employed by the Medical Research Board, towards the statistical calculations. Du Buisson, Bruinette & Kramer (Incorporated) Pathologists will assist in analysing the blood plasma samples. Dr. Van Rensburg, radiologist, will provide MR-imaging services at the MR-centre at Willows Hospital.

1.10 ETHICAL CONSIDERATIONS

Planning a research project involves much more than selecting the appropriate design – it also includes ethical considerations. The ethics of doing research in developmental disorders deserve special attention and a child-sensitive approach. It is of utmost importance that informed consent is obtained prior to commencement of the research project. Informed consent involves a research participant's formal agreement to cooperate in a study following full disclosure of the nature of the research and the participant's role in it (Simon in Hales, Yudofsky & Talbott 1999:1493-1534). The basic components of informed consent are competence, voluntarism, full information, and comprehension on the part of the research participant (Imber et al 1996:137-146). In other words, research participants must be capable of consenting to participation in the research, they must volunteer or not be coerced into participating, they must have all the information they need to make the decision, and they must understand what their participation will involve. Children and individuals with cognitive impairments, for example, often do not fully appreciate what will occur during research, nor will they understand their role or their rights as participants.

Considering the preceding principles, certain general protections will be implemented to ensure that these concerns are properly addressed. First, approval of the research project by the review board of the Department of Educational Psychology was sought before commencement of the study. The purpose of seeking approval was to ensure that the research procedures provide for the adequate protection of the research participants' rights, welfare and dignity, in keeping with the Ethical Principles of Psychologists (APA 1992:1597-1611). To safeguard those who participate in psychological research and to clarify the responsibilities of researchers, these ethical principles include general guidelines for conducting research, which will be adhered to. This means that participants will be protected from both physical and psychological harm. These principles also emphasize the researcher's responsibility for the research participants' welfare, because the researcher ultimately must ensure that the welfare of the research participants is given priority over any other consideration, including research design.

In addition to the principles of informed consent, protection against potential harm, and the right to confidentiality, the Society for Research in Child Development (1990) has endorsed ethical guidelines for research that address some of the issues unique to research with children. Not only do these guidelines call for confidentiality, protection from harm, and debriefing, but they also require informed consent from children's caregivers and from the children themselves if they are age seven and older. These guidelines specify that the research must be explained to children in language they can understand so they can decide whether they wish to participate.

Many other ethical issues extend beyond protection of the participants, including the proper way to give credit to other researchers and co-workers. These concerns will be adhered to, as depicted in the ethical principles of the Faculty of Education, University of Pretoria (2003) attached to this dissertation as Appendix C.

1.11   CHAPTER PLANNING

Chapter one consists of the orientational introduction and actualisation of the research problem, the problem statement, the research hypothesis, as well as the research methodology and research design. Ethical considerations are also included.

Chapter two describes the relevance of a selection of hormones that are implicated in the pathogenesis and/or manifestation of autism, as well as how these hormones link to the different stages of programmed foetal development.

Chapter three describes the relevance of structural brain differences found among individuals diagnosed with autistic disorder, as well as how these differences link to different stages of programmed foetal development.

Chapter four describes the empirical research and related findings. Based upon the findings, the research hypothesis will be accepted or rejected.

Chapter five gives an overview of the research findings, as well as deductions and conclusions derived at. Relevant recommendations will be made, and shortcomings inherent to the design will be pointed out.

1.12   SYNOPSIS

In Chapter One the theoretical framework and paradigmatic perspective, as well as the research design and methodology directing this research project were outlined. The actuality of the research project, i.e., the contribution of prenatal stress to the pathogenesis of autism as a neurobiological developmental disorder, was emphasized. An analysis of the research problem was done and ambiguous concepts were defined. The research project was clearly demarcated at hand of relevant problem statements. **Chapter Two** describes the relevance of a selection of hormones that are implicated in the pathogenesis and/or manifestation of autism, as well as how these hormones link to the different stages of programmed foetal development.

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