CHAPTER 3

NEUROANATOMICAL OBSERVATIONS OF THE BRAIN IN AUTISM

3.1 INTRODUCTION

This chapter first describes normal brain development, followed by neuroanatomical observations of the brain in autism. Steffenburg (1991:495) found that almost 90 percent of a sample of autistic children had evidence of a brain abnormality. Recently it has been reported that a substantial proportion of cases are associated with megalocephaly, an abnormal enlargement of the head (Courchesne 2004:106). Various other anatomical sites in the brain have been hypothesized as the primary source of pathology, such as enlarged brain size, reductions in the area of the corpus callosum, and abnormalities of the cerebellum and the medial temporal lobe structure, therefore 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 are reviewed in this chapter. Because this research focuses on prenatal stress and autism, findings related to brain abnormalities as well as altered neural programming due to prenatal stress will complement the review.

3.2 NORMAL BRAIN DEVELOPMENT

The brain develops through a series of overlapping stages (Teicher et al 2002:397). Embryonic and foetal stages of development of the human brain are characterised by a series of changes that take place in a relatively fixed sequence, i.e., cell birth (neurogenesis and gliogenesis), cell migration, cell differentiation, cell maturation (dendritic and axonal growth), synaptogenesis (formation of synapses), programmed cell death (apoptosis) and synaptic pruning, and myelogenesis (formation of myelin) (Kolb & Whishaw 2003:610). A[1]t the time that an egg is fertilized by a sperm, a human embryo consists of just a single cell, which starts to divide, and by the 14th day the embryo consists of several sheets of

[1]The conversion of DNA to RNA is called transcription. The conversion of RNA to proteins is called translation (Panksepp 1998:98).

cells with a raised middle area, representing the primitive body. At about 18 days after conception the human brain starts to develop from the neuroectoderm, a placode of cells that are induced to differentiate from the surrounding ectoderm. This differentiation is induced by factors such as retinoids and follistatin (Clark 2002). Retinoic acid can alter the pattern of transcriptional factors in neuroepithelial cells, explaining some of the craniofacial defects seen in retinoid embryopathy (Clark 2002:3). Almost all steps in organogenesis are controlled by retinoic acids, thus suggesting that retinol is necessary for normal development of embryonic tissues, neuronal growth and cellular differentiation (Zachman 1995:1634S; Perrotta et al 2003:457; Debier & Larondelle 2005:153).[2] Retinal lesions include atrophy and gliosis of the ganglion cell layer and the nerve fibre layer (Van der Lugt & Prozesky 1989:99). At three weeks after conception the human embryo has a primitive brain, essentially consisting of a sheet of cells (neural plate), which rolls up to form a structure called the neural tube (Kolb & Whishaw 2003:611). The neural tube forms in axial fusion, with closure occurring in a simultaneous caudal and cranial progression at 22 days of gestation (Clark 2002:2). This event practically represents the start of the central nervous system (CNS). Even before the neural tube is seen on gestational day 21, critical events in the formation of the CNS have taken place. Gastrulation establishes a midline, axes for dorsal-ventral and anterior-posterior orientation, and symmetry. The notochord and somites develop during this phase to induce the ectoderm to form the neural plate and to establish segmental organization. During this process of neurulation, the cranial neuropore of the neural tube closes by 24 days of gestation and serves as the foundation for further brain development. The caudal neuropore of the neural tube closes by gestational day 26 and serves as the foundation for further spinal cord development (Schmid & Rotenberg 2005:4).

The body and nervous system change rapidly during the next three weeks of gestation. After neurulation described in the preceding paragraph, subsequent processes such as cell migration and differentiation, dendritic and axonal growth, synaptogenesis, programmed apoptosis and myelogenesis start after gestational day 28, but some of these processes continue postnatally, for example glial and synapse formation that continue to vigorously until approximately three years of age (Schmid & Rotenberg 2005:4). By seven weeks of gestation (49 days), the embryo starts to resemble a miniature person, and by about 100

days after conception, the brain looks distinctly human; however, it does not begin to form gyri and sulci until about seven months. At full term, i.e., 40 weeks, the brain grossly resembles the adult brain, though its cellular structure is different (Kolb & Whishaw 2003:611).

This programmed prenatal cortical development may be disrupted by deficits in the genetic program, intrauterine trauma, the influence of toxic agents, or other factors that may lead to the pathogenesis of developmental disorders in childhood. It is postulated that specific toxins may have mechanisms to exploit certain periods during development, as illustrated in **table 3.1** below (Schmid & Rotenberg 2005:5).

As depicted in table 3.1, neural proliferation is vulnerable to ethanol, organophosphates, and MeHg disruption. It follows that if proliferation is altered, migration may also be altered, leading to ectopic tissues. Cell differentiation may be changed and or interrupted by ethanol, nicotine, MeHG, and lead. Some of the same agents, ethanol, lead, MeHg, parathion, permethrin, di-isopropyl fluorophosphates and PCB compounds are involved in altering synaptogenesis. These insults may continue to disrupt programmed cortical development for years (Schmid & Rotenberg 2005; Courchesne 2004; Levitt 2003; Nicolson & Szatmari 2003; Dawson et al 2002; Clark 2002; Sparks et al 2002; Schultz & Klin 2002; Teicher et al 2002). Myelination peaks during the third trimester in humans and continues into the young adult years, accounting for the developing brain's longer period of vulnerability (Coleman 1994:107). Myelination disturbances have been linked to malnutrition, iron deficiency, alcohol, and lead exposures (Schmid & Rotenberg 2005:5). In addition, programmed cell death or apoptosis might also be disrupted by toxic exposures through a shift in the balance of neurotrophic signals, resulting in an increase or decrease in the number of cells. Ethanol, lead, MeHg, and PCBs have been implicated in altered cell numbers (Schmid & Rotenberg 2005:5). Each of these developmental processes is now discussed in more detail.

Table 3.1 Potential neurotoxic agents and their teratogenic windows

Age	Process in development	Potential neurotoxic agents	Altered outcomes
0 to 4 weeks of gestation	Gastrulation-notochord and somite formation.	Retinoic acid.	Disordered polarity, malformations of the hindbrain and spinal cord.
4 weeks of gestation	Neurogenesis in spinal cord and hindbrain.	Hot tubs; Folic acid antagonists.	Anencephaly, hydrocephaly.
28 to 35 weeks of gestation	Migration.	Ionizing radiation; MeHg.	Ectopia, Cerebral palsy, Learning disorders.
Middle-late pregnancy	Neuron proliferation and synaptogenesis.	Lead; PCBs; MeHg.	Neurobehavioral deficits.
Third trimester	Neurogenesis in cerebellum, hippocampus cell migration, myelination, synaptogenesis.	Pesticides.	Multiple: poor motor control, emotional lability, cognitive deficits and delays.
Infant to 3 years of age	Development of executive functions in the prefrontal cortex.	Lead (postnatal); Alcohol (prenatal); Cigarettes (prenatal).	Behavioral impairments, possible increased criminality.
4 to 17 years of age	Increase in fiber tracts of motor and speech functions; ability to build on previous learning; improved sensory function, specifically auditory.	Organophosphates; Lead, PCBs; MeHg; Lead.	Poor axonal outgrowth. Lowered IQ. Impaired concentration.

Source: Schmid & Rotenburg 2005:5

3.2.1 Neurogenesis and gliogenesis

The genesis of glia cells begins at the time of neuron genesis (early gestation), and the glia continue to differentiate and proliferate long after the migration of neural cells is complete (Teicher et al 2002:398; Clark 2002:5). The cells lining the neural tube are known as neural stem cells due to these cells' capacity for self-renewal. When a stem cell divides, two stem cells are produced, of which one dies and the remaining one continues to divide

again – a process that is repeated throughout an individual's lifespan. In an adult, neural stem cells line the ventricles to form the ventricular zone, and they also generate progenitor (precursor) cells. These progenitor cells can also divide, but they eventually produce nondividing neuroblasts and glioblasts that mature into neurons and glia. Neurogenesis (production of new neurons) ceases in most brain regions at birth, although stem cells continue to generate neurons and glia into adulthood, even in an aging brain, at least within the olfactory bulb and the hippocampal dentate gyrus throughout life (Eriksson, Perfilieva & Bjork-Eriksson 1998:1313; Teicher et al 2002:398; Kolb & Whishaw 2003:612). This cell division is programmed, resulting in the appropriate number of cells for the future cortex. Abnormalities in the number of proliferative units or in the total number of divisions can lead to disorders of the brain manifested by abnormal brain size and, therefore, an unusaually small or large head circumference (Clark 2002:5). From birth to five years of age, the brain triples in mass. Much of the gain in brain size stems from the vigorous myelination of fiber tracts (Teicher et al 2002:398).

3.2.2 Cell migration and differentiation

Cell migration starts shortly after the first neurons are generated. Clark (2002:7) provided the following simplified discription of cell differentiation and migration. At the completion of general neurogenesis, cell differentiation begins, the process in which neuroblasts become specific types of neurons. At the time of neuronal differentiation the neural tube consists of four consecutive layers: (a) the innermost layer is called the ventricular zone and gives rise to neurons and all of the glia of the CNS; (b) the adjacent more superficial layer is the subventricular zone, which is the staging area from which postmitotic neurons begin to differentiate and to migrate; (c) the adjacent intermediate zone is destined to become the cortical plate and the future cerebral cortex; and (d) the marginal zone, which is the outermost zone and which is composed of the cytoplasmic extensions of ventricular neuroblasts, corticopetal fibers, and the terminal processes of radial glia (which, at this time, are completely spanning the neural tube). Differentiation of neuroepithelial cells begins in the subventricular layer at approximately gestational day 26. The older, larger pyramidal cells are the first cells to be born and probably differentiate early to act as targets in the migration of the nervous system (Clark 2002:7). Disorders such as tuberous sclerosis, cortical dysplasia, cortical migration abnormalities, cortical

dysgenesis and the development of giant-cell astrocytomas might be due to "faulty" neuronal differentiation (Clark 2002:8).

The genesis of neuroblasts predestined to construct the cerebral cortex largely reach completion at about 4½ months of gestation, whereas cell migration to various regions continues for a number of months, even postnatally, with some regions not completing cell migration until about eight months after birth (Kolb & Whishaw 2003:613). At the most rostral end of the neural tube in the 40-to-41-day-old foetus, the first mature neurons, Cajal-Retzius cells, begin to migrate to the cortical surface. Radial glial fibers extend from the ventricular zone to the cortical surface, and neurons migrate along the radial glial fibers, which take them from the protomap in the ventricular zone to the corresponding region in the cortex (Kolb & Whishaw 2003:613). These migrating neurons accomplish this task by attaching to and migrating along radial glial in a process known as *radial migration* or by *somal translocation* in a neuronal process (Clark 2002:7). In the process of migration, the deepest layer of the cortical plate migrates and deposits before the other layers. Therefore, the first neurons to arrive at the future cortex are layer VI neurons. More superficial layers of cortex then are formed - the neurons of layer V migrate and pass the neurons of layer VI; the same process occurs for layers IV, II, and I. The cortex therefore is formed in an inside-out fashion (Clark 2002:7). Although most cortical neurons follow the radial glial fibers, a small number of them appear to migrate by following some type of chemical signal (Kolb & Whishaw 2003:613). Migration can stop prematurely, leaving a group of cells that belong in an outer layer scattered among inner layers of cells.

Disorders of migration can be identified by means of MR-imaging, and the most common effect of faulty migration in humans are disorders such as dyslexia or epilepsy (Kolb & Whishaw 2003:614). Some relatively unknown migration disorders are lissencephaly spectrum disorders (smooth brain), which refers to the external appearance of the cerebral cortex in which a neuronal migration aberration leads to a relatively smooth cortical surface, for example classic lissencephaly, isolated lissencephaly, X-linked lissencephaly, lissencephaly with cerebellar hypoplasia, cobblestone lissencephaly, polymicrogyria, and heterotopias (Clark 2002:8-16).

3.2.3 Cell maturation (dendritic and axonal growth)

After neurons have migrated to their final destinations and differentiated into specific neuron types, they begin the process of growing dendrites to provide the surface area for synapses with other cells (Kolb & Whishaw 2003:614). This process is illustrated in figure 3.1 *(page inserted)*.

As illustrated in figure 3.1 dendritic development involves dendritic arborization (or branching), and the growth of dendritic spines. Arborization commences with dendrites that start to protrude from the cell body and then develop into increasingly complex extensions that resemble the branches of a tree. These dendritic branches then start to form spines, on which most dendritic synapses take place (Kolb & Whishaw 2003:614). Although dendritic development begins prenatally in humans,there is a marked expansion of axonal and dendritic arborizations and a rapid increase in synaptic contacts during the postnatal phase and during childhood. This process mirrors the earlier overproduction and elimination of neurons (Teicher 2002:398). Axons develop at the rate of a millimeter per day, whereas dendritic growth happens at a slow rate, measurable in micrometers per day. This disparate development allows the developing axon to contact the target cell before the dendrites of that cell are completely formed, thereby enabling the axon to play a role in dendritic differentiation (Kolb & Whishaw 2003:615). The formation of these neural pathways can be disrupted by perinatal lesions, while early postnatal lesions can result in the axon failing to reach its target. Axonal development can also be adversely affected by neurotoxins, malnutrition, lesioned target cells, and genetic mutations (Kolb & Whishaw 2003:615; Courchesne 2004:106; Schmid & Rotenberg 2005:5).

A series of complex peptide molecules have been indentified that govern the maturation and development of specific neural systems such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), epidermal growth factors, fibroblast growth factors, glial-derived growth factors, insulin-like growth factors, and many others (Panksepp 1998:114). These molecules control specific growth processes in the brain, and they can also protect neurons against various forms of toxicity, for example BDNF and NGF can protect cerebellar granule cells and Purkinje cells (Tatter, Galpern & Isacson 1995:286-297). These are the types of neurons known to be deficient within cerebellar tissues of many autistic children (Panksepp 1998:114; Bailey, Luthert, Harding et al 1998:880-905).

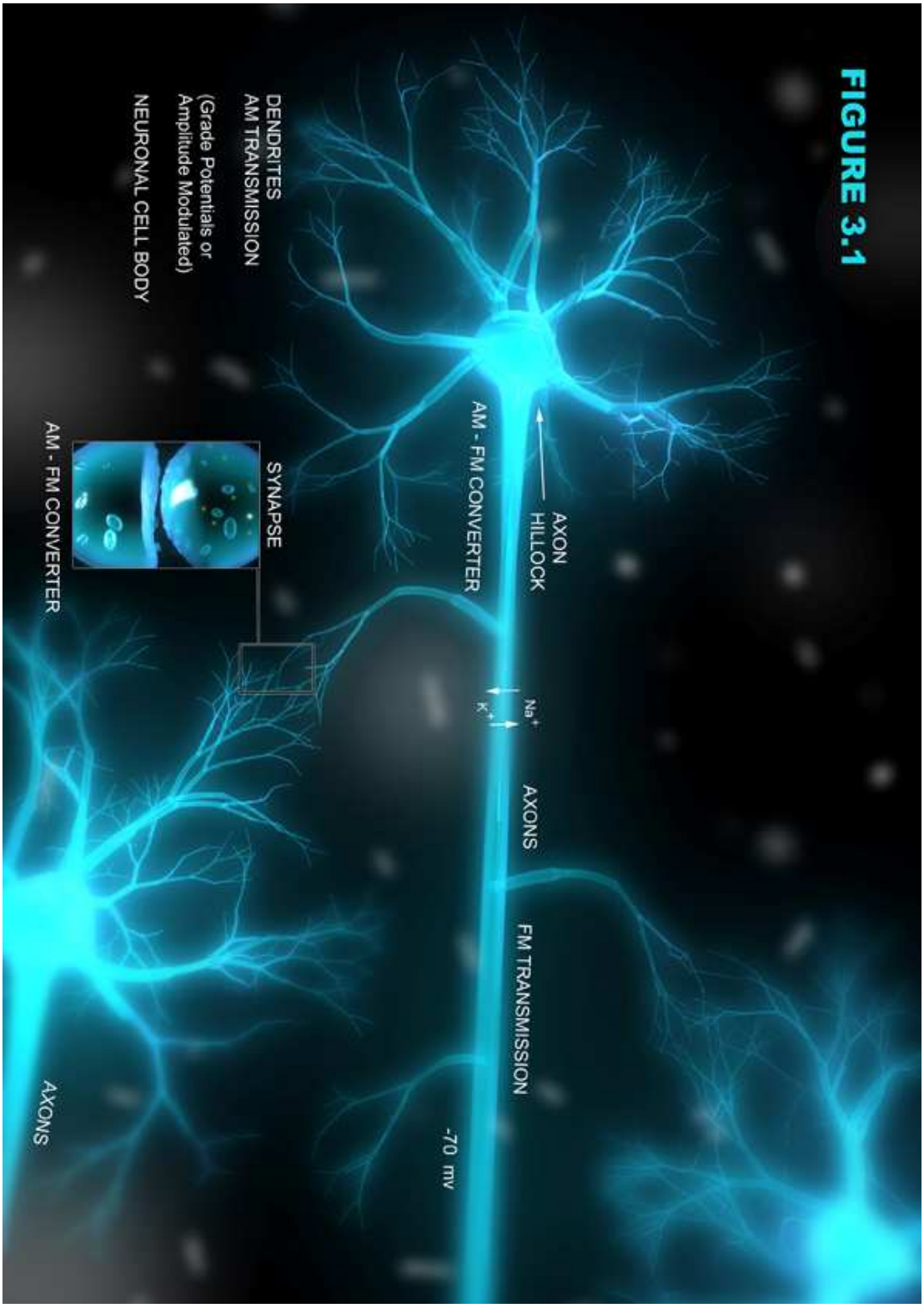


FIGURE 3.1
AXON HILLOCK
AM - FM CONVERTER
DENDRITES
AM TRANSMISSION
(Grade Potentials or Amplitude Modulated)
NEURONAL CELL BODY
SYNAPSE
AM - FM CONVERTER
Na+
K+
AXONS
FM TRANSMISSION
-70 mv
AXONS

3.2.4 Synaptogenesis, programmed cell death and synaptic pruning

Teicher and coworkers (2002:399) reported on *neuronal modification by selective depletion*, which refers to the genetically programmed overproduction of synapses. According to these researchers programmed synapse formation takes place according to distinct phases, and the final configuration of the circuitry occurs by elimination of synapses based on cell interactions, i.e., programmed cell death and synaptic pruning, also known as apoptosis, which process is illustrated in figure 3.2 *(page inserted)*.

As illustrated in figure 3.2, synaptogenesis in humans starts during early embryonic life and this phase is characterized by the generation of low-density synapses. The next phase of synapse formation starts before birth, continues until nearly two years of age, and is characterized by a rapid growth in the number of synapses, i.e., this phase peaks at about 40 000 synapses per second. During the next phase synaptogenesis initially reaches a plateau in numbers, followed by a rapid elimination of synapses, i.e., synaptic pruning (apoptosis) (Kolb & Whishaw 2003:616). Because there is a substantial overproduction of synapses, receptors, dendrites and axons, some are pruned back during the transition into adulthood without cell death (Teicher et al 2002:398). Synaptic pruning peaks during puberty, and the number of synapses may be pruned at a rate of 100 000 per second to 50% of the number present at age two. The final phase is characterized by a plateau in synapse number through middle age, followed by a slow but steady decline in the density of synapses with advancing age. There is a rapid drop during senescence before death (Kolb & Whishaw 2003:616).

Some of these synapses are experience dependent (Teicher et al 2002:399). Schmid and Rotenberg (2005:5) reported abnormal patterns of apoptosis after neurotoxic exposure. The teratogenic effect of exposure to neurotoxic agents can lead to a shift in the balance of neurotrophic signals, resulting in an increase or decrease in the number of cells. Overproduction and elimination specifically affects excitatory synapses and the density of glutamate, dopamine, and neurotensin receptors. The rate and degree of pruning vary from region to region (Teicher 2002:398).

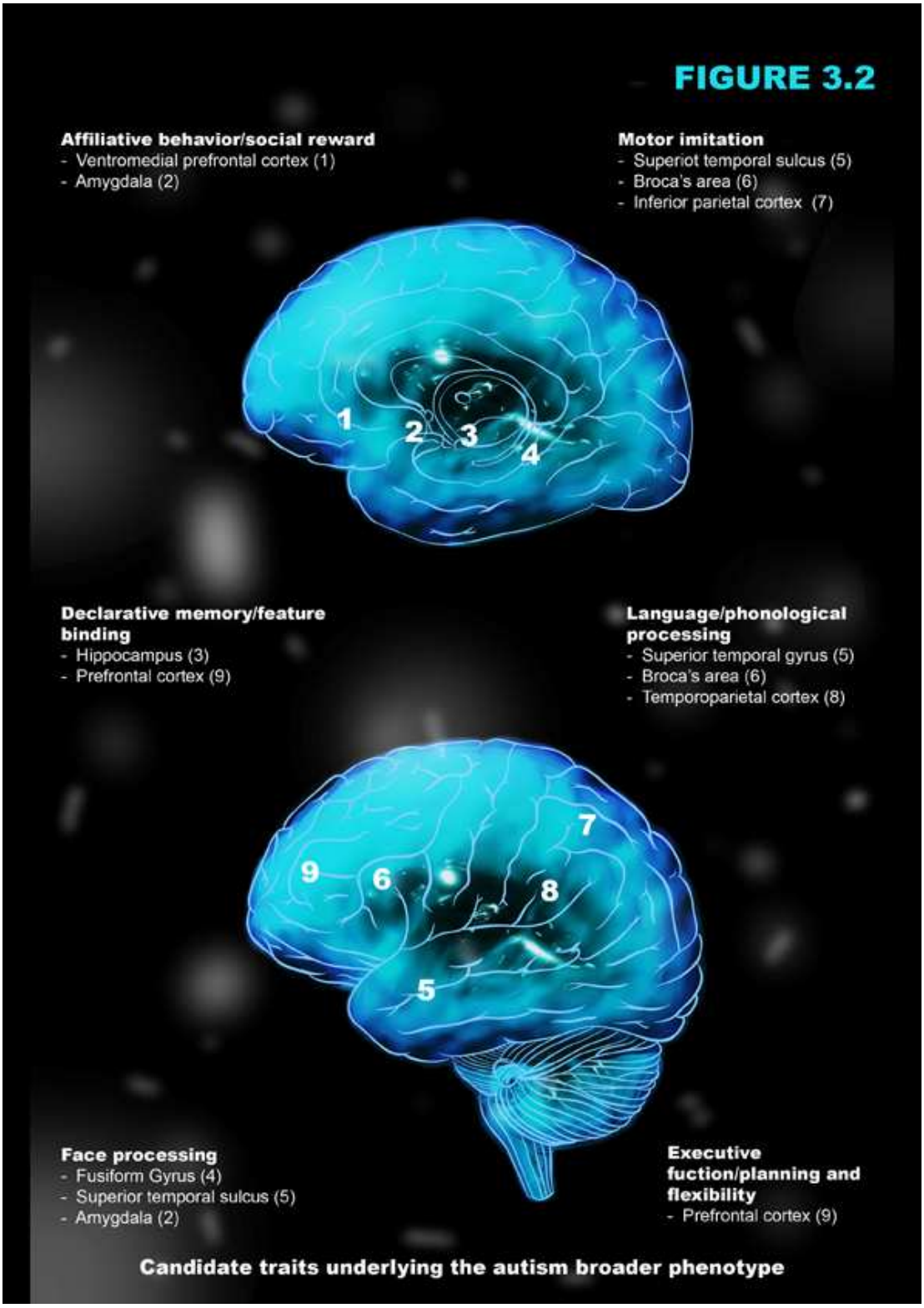


FIGURE 3.2
Affiliative behavior/social reward
- Ventromedial prefrontal cortex (1)
- Amygdala (2)
Motor imitation
- Superiot temporal sulcus (5)
- Broca's area (6)
- Inferior parietal cortex (7)
1
2
3
4
Declarative memory/feature binding
- Hippocampus (3)
- Prefrontal cortex (9)
Language/phonological processing
- Superior temporal gyrus (5)
- Broca's area (6)
- Temporoparietal cortex (8)
7
9
6
8
5
Face processing
- Fusiform Gyrus (4)
- Superior temporal sulcus (5)
- Amygdala (2)
Executive fuction/planning and flexibility
- Prefrontal cortex (9)
Candidate traits underlying the autism broader phenotype

3.2.5 Myelogenesis

Myelination begins prenatally and continues in the CNS through childhood and into adulthood. Myelination markedly increases the speed of information exchange (Teicher 2002:398). The vestibular system is primarily myelinated prenatally, whereas association cortices continue to be myelinated into the second decade (adolescence) (Schmid & Rotenberg 2005:1). Myelination and axonal growth are substantial throughout childhood, and the myelination rate varies markedly between brain regions, for example, frontal grey matter volumes increase 20% between early childhood and the end of childhood (Carper et al 2002:1038). Cerebral white matter volumes increase 59% between two to three and sixteen years of age (Courchesne et al 2001:245). Maximum brain volumes are not reached until about 10 to 12 years of age (Courchesne 2004:109), while cerebral white matter volume continues to increase through middle age (Courchesne et al 2000:672), and the corpus callosum continues to grow throughout childhood and into adulthood (Pujol, Vendrell, Junquae, et al 1993:71). Critical motor systems myelinate at an early age, whereas the process is quite protracted in the prefrontal cortex, and gender also affects myelination rate in some regions, such as the corpus callosum and the hippocampus (Teicher 2002:398).

According to recent MRI studies, this slow and differential maturation of the brain does not happen in autism – there is rather a relatively brief period of overgrowth, followed by reduced or arrested growth (Courchesne 2004:109). Oversized brain structures in the two-to-three-year-old autistic brain stop growing at an accelerated rate (Courchesne et al 2001:251), consequently the volume of typically developing children eventually "catches up" to the autistic brain (Courchesne 2004:109), i.e., volumetric differences between the autistic and the typically developing brain disappear almost completely during adolescence and adulthood. The only exception is the amygdala, which remains larger in autism compared to a typically developing brain (Aylward, Minshew, Field, Sparks & Singh 2002:176). Courchesne (2004) conducted MRI studies and demonstrated that maximum brain size in autism is reached by about three to five years of age – about six to ten years earlier than in typically developing children.

3.3 STRUCTURAL ABNORMALITIES OF THE BRAIN IN AUTISM

Research findings reported by Courchesne (2004), Nicolson and Szatmari (2003), Levitt (2003), Sparks, Friedman, Shaw and coworkers (2002), Schultz and Klin (2002), Dawson et al (2002), and Herman (1996) all demonstrated abnormal developmental processes early in the clinical course of autism, particularly implicating increased cerebellar volume, as well as bilateral enlargement of amygdalae and hippocampi due to early overgrowth followed by premature arrest of growth. Structural abnormalities and candidate traits underlying the autism broader phenotype are illustrated in figure 3.3 *(page inserted).*

Referring to figure 3.3, certain structural and functional studies have detected a variety of brain abnormalities in autism suggesting the underdevelopment of the neocortical neural networks, including the circuitry of the frontal systems (Hardan et al 2000:1033; Minshew 1996:205; Bauman & Kemper 1994:54; Zilbovicius, Garreau, Samson, et al 1995:248; Minshew, Luna & Sweeney 1999:917). Reduced metabolic correlations have been reported in a group of mostly high-functioning individuals with autism involving the frontal and parietal cortex and subcortical structures (Bauman & Kemper 1994). A PET study of blood flow in preschool autistic children revealed evidence of delayed maturation of the frontal lobes (Zilbovicius et al 1995:251). Recently, a study of saccadic eye movements in high-functioning individuals with autism reported significant abnormalities in volitional saccades subserved by the circuitry of frontal systems (Minshew et al 1999:921).

3.3.1 Enlarged brain size in autism

In his seminal paper describing autism, Kanner (1943) cited in Panksepp (1998:276) noted that five of his original eleven patients appeared to have relatively large heads. Over the past ten years, MRI studies have consistently found elevated brain volume, and estimates suggest that up to 20% of individuals with autism may have head circumferences above the 97th percentile (Nicolson & Szatmari 2003:531). Elevated brain volume and enlarged head circumference are consequently discussed in more detail.

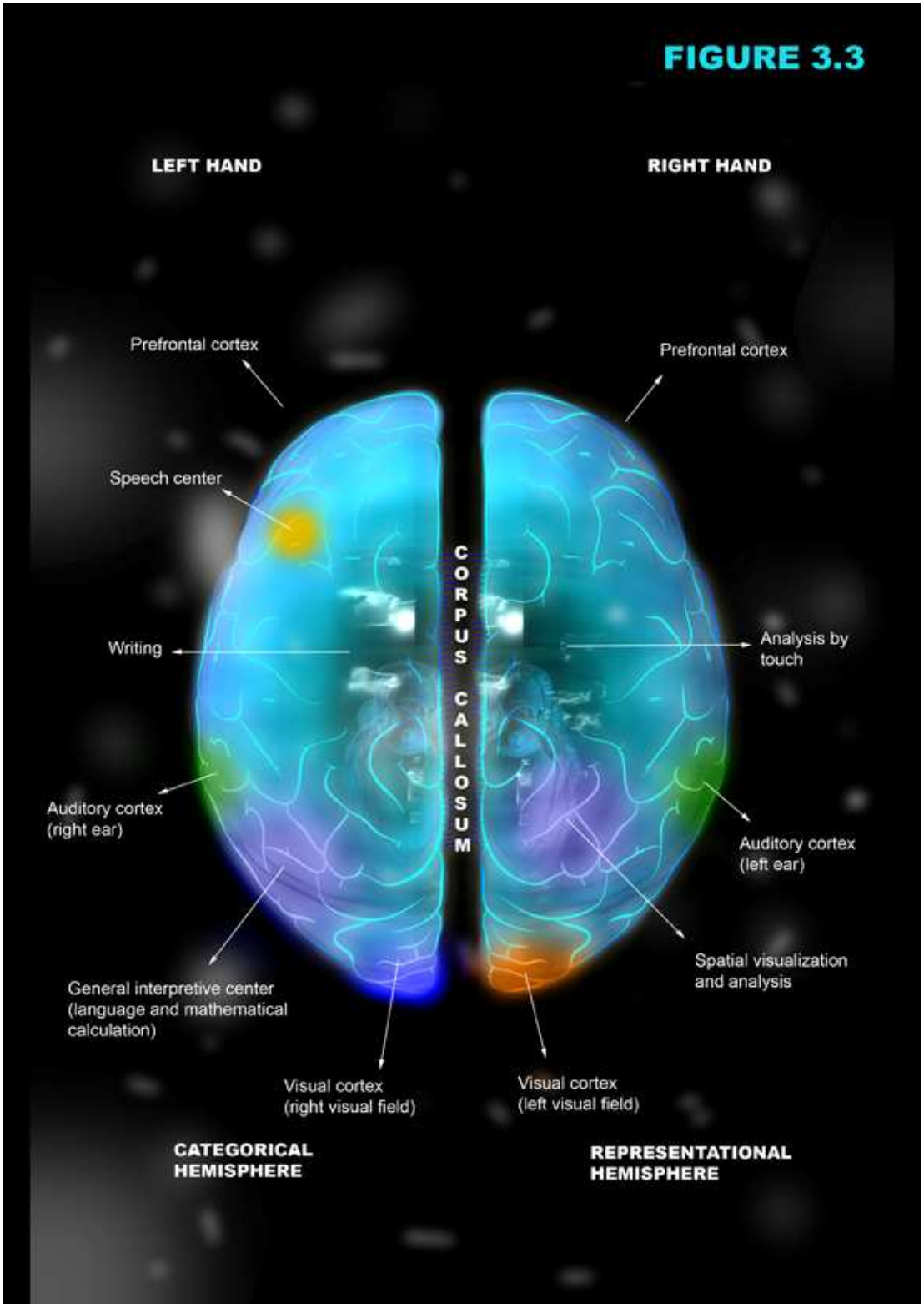


FIGURE 3.3
LEFT HAND
RIGHT HAND
Prefrontal cortex
Prefrontal cortex
Speech center
CORPUS CALLOSUM
Writing
Analysis by touch
Auditory cortex (right ear)
Auditory cortex (left ear)
Spatial visualization and analysis
General interpretive center (language and mathematical calculation)
Visual cortex (right visual field)
Visual cortex (left visual field)
CATEGORICAL HEMISPHERE
REPRESENTATIONAL HEMISPHERE

3.3.1.1 Elevated cerebral volumes

Children diagnosed with autism were found to have an overall 9.8% increase in cerebral volumes compared to typically developing children and an overall 12.5% increase compared to developmentally delayed children (Sparks et al 2002:10). Piven and coworkers (1997:546-555) reported increased brain volume in 22 male subjects with autism, compared with 20 male subjects without the disorder. In a follow-up study with an overlapping sample, Piven and coworkers (1998:105-110) again reported increased brain volume in patients with autism, with a regional subanalysis indicating that the volumetric elevation was most pronounced in posterior brain regions and that frontal regions did not differ between the groups. Elevated brain volume appears to be unique to autism, as most neurodevelopmental disorders and mental retardation are associated with a reduced brain volume (Nicolson & Szatmari 2003:531). Research findings published by Courchesne (2004:106-111) suggest that elevated brain volume in autism is associated with accelerated brain growth early in development, followed by arrested brain growth.

Three different MRI studies demonstrated that head circumference in autistic infants beyond normal head circumference of typically developing infants can be associated with abnormally large brain volumes. In the first MRI study of brain size in autistic toddlers, Courchesne et al (2001:245-254) reported that 90% of autistic subjects had brain volumes exceeding typically developing average by 10%. In keeping with these findings, Sparks et al (2002:184-192) also found brain volumes of autistic three-to-four-year-olds to be about 10% larger than typically developing controls. In 2004 Piven produced similar research results in support of the previous two studies. In a recent MRI study of two-to-five-year-olds Courchesne et al (2004:489) found that both girls and boys with autism had significantly enlarged whole-brain volume. At age two-to-four years a 10% greater brain volume represents a 1.5 centimeter greater head circumference in children with autism as compared to typically developing controls (Courchesne, Carper & Akshoomoff 2003:337-344; Bartholomeusz, Courchesne & Karns 2002:239-241).

3.3.1.2 Enlarged head circumference

Courchesne et al (2004:489-496) reported results from a longitudinal study of changes in head circumference during the first two years of life in a sample of children diagnosed with autism. As compared to the head circumference norms from the Center for Disease Control and Prevention (CDC), the head circumference of autistic children was at the 25th percentile at birth and then increased rapidly to the 84th percentile by six to fourteen months of age. This period of abnormally accelerated head circumference increase is thought to be largely concluded by the end of the second year of life. These researchers found that by 15 to 28 months, headcircumference was only two percentile points higher than that at 6 to 14 months. In a follow-up paper Courchesne (2004:107) concluded that the process of abnormally accelerated brain growth seems to be finished off during the second year of life; however, regional differences in overgrowth in autism were reported, based on the earlier research conducted by Courchesne and coworkers (2001:245-254). This earlier study already demonstrated overall brain enlargement due to significant increases in cerebral white matter by 18%, in cerebral grey matter by 12%, and in cerebellar white matter by 39%. Cerebellar grey matter was found not to be affected significantly. Carper and coworkers (2002:1038-1051) implicated early hyperplasia involvement in autism. According to these researchers abnormalities were found within the cerebrum, dorsolateral and medial frontal regions among two-to-four-year-old children diagnosed with autism. In addition, temporal grey matter and parietal white matter volumes were significantly enlarged. However, the occipital lobes were not significantly different from that of typically developing controls. Consistent with research findings showing regional differences in overgrowth among children with autism, Levitt and coworkers (2003:728) reported MRI results that demonstrated anterior and superior shifting of several sulci, with the greatest deviations seen in the superior frontal, inferior frontal, and superior temporal sulci and the lateral fissure.

3.3.2 Reduction in the area of the corpus callosum

The various regions of the neocortex are interconnected by three types of axonal projections, i.e., relatively short connections between one part of a lobe and another, longer connections between one lobe and another, and interhemispheric connections (commissures) between one hemisphere and another (Kolb & Whishaw 2003:67). The different areas of the brain are illustrated in figure 3.3 *(page inserted)*. As depicted in figure 3.3 the two interhemispheric commissures are the corpus callosum and the anterior

commissure. Research conducted by Bauman and Kemper (1995:1-26) provided evidence of a brain disconnection syndrome in autism, especially between cerebellar and limbic zones with other higher brain areas. In keeping with a brain disconnection syndrome, neural systems that should be working in close unison appear not to have developed normal synaptic interchange in various brain areas that control socialization, communication, and imagination in autism (Panksepp 1998:113).

All studies within the past decade have reported reductions in the area of the corpus callosum in autism (reviewed by Nicholson & Szatmari 2003:532). The corpus callosum is topographically organized and matures throughout childhood into young adulthood. Gender differences, testosterone levels, and handedness have been reported to affect corpus callosum anatomy (Witelson 1989:799; Moffat, Hampson, Hickett, et al 1997:297). Studies of autistic subjects with a wide range of functioning have documented quantitative abnormalities of the corpus callosum and reported the presence of an overall size reduction (Bauman & Kemper 1994; Egaas, Courchesne & Saitoh 1995; Piven, Bailey, Ranson & Arndt 1997). A smaller body and posterior subregions of the corpus callosum were also observed in two different studies examining individuals with autism with and without mental retardation (Egaas et al 1995; Piven et al 1997). Higher-level cognitive functions, such as language and linguistic processes and the ability to represent the action of others, depend upon hemispheric specialization, as the callosal pathways are involved in integrating these processes. Autism is often associated with abnormal motor and language lateralization, including left- and mixed-handedness and an unusual pattern of cerebral dominance for language (Kolb & Whishaw 2003:657). These findings implicate cerebral asymmetry and disrupted callosal pathway involvement in autism, particularly when one considers the importance of cerebral asymmetry in functions such as language that are impaired in autism.

Recent neuroanatomical studies of the corpus callosum that represent an index of neural connectivity between brain regions, provide impetus for investigating its role in autism. Hardan, Minshew & Keshavan (2000:1033-1036) measured the size of the seven subregions of the corpus callosum on MRI scans from 22 non–mentally retarded autistic subjects and 22 individually matched controls. These researchers reported smaller anterior subregions in the autistic group. In a subsample, measurements were adjusted for intracranial, total brain, and white matter volumes and the differences between groups

remained significant. No differences were found in the other subregions. This observation is consistent with the frontal lobe dysfunction reported in autism previously.

Hardan et al (2000:1035) reported a decrease in the size of the anterior regions of the corpus callosum, and a strong trend toward a decrease in the overall size of the corpus callosum. The greatest reduction in corpus callosum area in the autistic participants was found in the genu (region 2), involving the projections from prefrontal cortex. This is consistent with the cognitive, neurophysiological, and behavioural evidence of frontal lobe dysfunction reported recently in the literature (Bauman & Kemper 1994; Minshew et al 1999:920). There have been reports of deficits in executive function (Bauman & Kemper 1994), spatial working memory (Bauman & Kemper 1994), and the capacity for suppressing context-inappropriate responses in autism (Minshew et al 1999:921). Interestingly, the orbitofrontal cortex, which projects through the rostrum (region 1), has not been investigated in autism but is thought to play a significant role in the ritualistic behaviour of obsessive-compulsive disorder and may make a similar contribution to such behaviour in autism (Rosenberg, Keshavan & O'Hearn, et al 1997:824). Furthermore, Hardan and coworkers' findings of decreased size of the anterior regions of the corpus callosum may reflect the regional enlargement of parietal, temporal, and occipital but not the frontal regions (Piven, Arndt, Bailey & Andreasen 1996:530). This discrepancy may also reflect an increase in intrahemispheric connectivity and a decrease in the interhemispheric one. The reduction in the total cross-sectional area of the corpus callosum observed relative to total brain volume may indicate a decrease in interhemispheric connectivity, in keeping with Kolb and Whishaw's observations (Kolb & Whishaw 2003:67).

3.3.3 Abnormal patterns of cerebellar development

Sparks and coworkers (2002:10) observed that cerebellar volume in four-to-five-year-old children diagnosed with autism was increased compared with typically developing children, although some researchers reported normal or reduced cerebellar volumes in older populations (Courchesne, Townsen & Saitoh 1994:214-223; Piven, Saliba & Bailey 1997:546-555; Courchesne, Karns, Davis et al 2001:245-254).

Marked decreases in the number of Purkinje cells and granule cells throughout the cerebellar hemispheres were observed (Tatter et al 1995:286-297; Panksepp 1998:114; Bailey et al 1998:880-905). The most significant cell decrease was found in the posterior inferior neocerebellar cortex and adjacent archicerebellar cortex. Atrophy of the neocerebellar cortex was noted in the biventral, gracile, tonsillar, and inferior semilunar lobules, as well as abnormalities in the emboliform, fastigial, and globose nuclei in the roof of the cerebellum. Therefore, the normal circuitry of the cerebellum does not develop, and the deep cerebellar nuclei and olivary nucleus show a reduction in cell size and number (Herman 1996:5). Some changes were observed in the neurons of the deep cerebellar nuclei of autistic subjects, with younger subjects having abnormally large neurons and older subjects having abnormally small neurons in these nuclei (Nicholson & Szatmari 2003:533). These findings suggest that the cerebellar abnormalities occurred at or prior to 30 weeks gestation, suggesting atypical brain development in children diagnosed with autism.

Allen and Courchesne (2003:272-273) used fMRI to explore cerebellar function in autism at hand of eight autistic patients and eight control subjects. Relative to controls, the autism patients demonstrated increased cerebellar activation during a motor task and less cerebellar activation during an attentional task, suggesting that abnormal cerebellar development might have different implications for motor and attentional functioning.

The results of several autism studies reviewed by Bauman and Kemper (1994) suggest that various brain abnormalities, particularly temporal and cerebellar abnormalities, might correlate with the degree of impairment displayed in autism. Temporal lobe abnormalities are implicated in compromised explicit memories (i.e., memories for daily events), whereas cerebellar abnormalities are implicated in implicit memory (i.e., skills and conditioned responses) (Kolb & Whishaw 2003:658).

Roder (2000:56-63) found that an area of the brainstem in the caudal part of the pons is small in autistic subjects and that several nuclei in this area, including the facial nucleus, which controls facial musculature, are small or missing. In addition, many children with autism have subtle facial abnormalities that may be due to abnormalities of the facial nerve (Kolb & Whishaw 2003:658). The preceding findings suggest a strong biological basis in the pathogenesis of autism.

3.3.4 Abnormalities of the medial temporal lobe structures

Bauman and Kemper (1994:119-145) examined neuropathology among patients ranging in age from 9 to 29 years and diagnosed with autistic disorder. These researchers reported subtle alterations in the size of neurons and the complexity of their processes were confined to the limbic system and cerebellum. In the limbic system, the hippocampal complex, subiculum, entorhinal cortex, amygdala, mamillary body, anterior cingulate gyrus, and septal area are connected by neuronal circuits. In comparison with the brains of control subjects, the autistic brains showed reduced neuronal cell size and increased cell-packing density in these areas.

Bailey et al (1998:885) reported that neurons in parts of the limbic system of autistic patients, particularly in the hippocampus and amygdala, were unusually small and densely packed, pointing to deficient maturation in these areas. Sparks and coworkers (2002) confirmed bilateral enlargement both of the amygdalae and hippocampi in four-to-five-year-old children with autism compared with typically developing children. This notion was also observed among adults diagnosed with autism (Howard, Cowell, Boucher et al 2000:2931-2935). Bauman and Kemper (1994:125) also observed that CA1 and CA4 pyramidal cells in the hippocampus showed decreased complexity and extent of dendritic arbors, characteristic of an immature brain, suggesting constraint of normal development in these structures in autism.

Howard et al (2000) hypothesized that bilateral enlargement of the amygdala reflected incomplete neuronal pruning in early development. Pertinent to this observation, postmortem findings from adults with autism revealed increased cell packing density of the amygdala (Bauman & Kemper 1994:119). Other investigators reported normal or reduced size of these structures in samples of children and adults with autism (Pierce, Muller, Ambrose et al 2001:2059; Haznedar, Buchsbaum, Wei et al 2001:157; Aylward, Minshew, Goldstein et al 1999:2145; Piven, Bailey, Ranson et al 1998:105).

These observed differences might be ascribed to age differences among subjects included in different samples. Sparks and coworkers (2002) concluded that observed size differences of amygdalae and hippocampi in four-to-five-year-old children with autism (compared to adolescent or adult size) might be ascribed to arrested development or increased apoptosis of these structures over time, resulting in a reduction of size. Functional studies using fMRI consistently found abnormalities in activation of the amygdala and the fusiform gyrus, which contains the *fusiform face area*, so called because of its involvement in facial processing and social cognition. These fMRI studies demonstrated limited or no activation of the amygdala and the related fusiform gyrus in autism, and it appeared that autistic patients use brain regions not typically associated with facial processing. It was suggested that autistic patients were performing the task of facial processing, but that they were using alternate and idiosyncratic regions to do so, including regions more typically used for object perception (Nicolson & Szatmari 2003:533). These fMRI studies demonstrated that patients with autism do not use brain regions typically involved in social cognition in the same way that control subjects do (Nicolson & Szatmari 2003:533).

Individuals diagnosed with autism consistently fail theory-of-mind tasks, and Baron-Cohen (1995) theorized that the extreme abnormalities in social cognition in autism result from an abnormality in an amygdaloid-prefrontal circuit. The prefrontal cortex, the amygdala, the superior temporal sulcus and the insular cortex form part of the neural network underlying social cognition (Kolb & Whishaw 2003:602). Panksepp (1998:272) theorizes that specific regions such as the cingulate gyrus, septal area, bed nucleus of the stria terminalis, preoptic area, dorsomedial thalamus and the periaqueductal grey (PAG) all play an important role in social cognition and social bonding.

The limbic system, particularly the amygdala, plays a crucial role in behavioural responses to emotional stimuli and in emotional learning (Du Preez, Naudé & Pretorius 2004:27; Naudé, Pretorius, Van Schoor & Becker 2005:47; Pretorius, Naudé & Pretorius 2005:310). Autistic children have too many densely packed small neurons within parts of the limbic system (Bauman & Kemper 1994:119), suggesting that selective cell death (or apoptosis) has not progressed normally (Margolis, Chuand & Post 1994:946). This also means that neurons do not interconnect with the rest of the brain as well as in typically developing children, which suggest that a biochemical program for neuronal development has

malfunctioned (Panksepp 1998:276). Amygdalar damage impairs recognition of emotional faces (Adolphs, Tranel, Damasio et al 1994:669) and has been implicated in an impaired ability to link visual perception of emotionally relevant stimuli among individuals with autism (Adolphs, Sears & Piven 2001:232).

From the preceding discussion it is clear that human brain development follows a programmed continuum, and programmed development might be disrupted at any stage along this developmental continuum. Considerable progress has been made in unravelling the nature of the stress response and in understanding the neurobiological and neuroendocrine underpinnings of prenatal and postnatal stress on programmed cortical development.

The impact of prenatal stress on cortical development will be discussed in the following paragraphs.

3.4 THE IMPACT OF PRENATAL STRESS ON CORTICAL DEVELOPMENT AND AGENESIS

The concept *agenesis* refers to developmental failure in certain cortical regions (Kolb & Whishaw 2003:Glossary). Age is an important determinant of the effects of early lesions and general cortical development. Three critical age divisions have been identified: gestational period up until before one year of age, between one and five years, and older than five years (Kolb & Whishaw 2003:626). Kates, Burnette, Eliez et al (2004:539-546) postulated that agenesis might occur due to prenatal, perinatal or postnatal environmental events, which might include prenatal trauma in the form of reduced blood flow or oxygen and exposure to toxins and elevated levels of glucocorticoids due to prenatal and postnatal stress. In psychobiology the concept *stress* is anything that activates the pituitary-adrenal system (the ACTH-cortisol axis). Everything that is typically considered to be a stressor in humans generates this brain response (Suchecki, Nelson, Oers & Levine 1995:169).

Teicher and coworkers (2002:399) have postulated a cascade model for explaining the neurobiological effects of prenatal stress on programmed cortical development. Their cascade model is built on five fundamental premises. First, exposure to stress early in life activates stress-response systems and fundamentally alters their molecular organization to

modify their sensitivity and response bias. Second, exposure of the developing brain to stress hormones affects myelination, neural morphology, neurogenesis, and synaptogenesis. Third, different brain regions differ in their sensitivity, which depends, in part, upon genetics, gender, timing, rate of development, and desity of glucocorticoid receptors. Fourth, there are enduring functional consequences that include attenuated left hemisphere development, decreased right/left hemisphere integration, increased electrical irritability within limbic system circuits, and diminished functional activity of the cerebellar vermis. Fifth, there are associated neuropsychological consequences and vulnerabilities, which lead to enhanced risk for the pathogenesis of autism. In the following paragraphs the hipotalamic-pituitary-adrenal stress response (also known as the HPA-axis) will be discussed.

3.4.1 The Hipotalamic-Pituitary-Adrenal Stress Response

A variety of neuroemotional influences converge on cells of the paraventricular nucleus (PVN) of the hypothalamus, which contain corticotrophin releasing factor (CRF) (Suchecki et al 1995:172). The stress response thus consists of an alarm phase (the pituitary-adrenal stress response system), as well as a resistance phase (the sympathoadrenal stress response system), depicted in figure 3.4 *(page inserted)*.

As illustrated in figure 3.4, the piruitary-adrenal response is instigated by CRF from the PVN of the hypothalamus, which via axons descending toward the pituitary, can trigger ACTH release from the pituitary (Panksepp 1998:118). ACTH, which is released into the bloodstream, seeks out target tissue in the adrenal cortex, where it triggers the release of cortisol. Cortisol helps promote energy untilization in the body, and obviously more bodily resources need to be used in all stressful situations. This perpheral system is aroused in response to essentially all emotional stressors. The central CRF pathways within the brain help organize and coordinate various negative emotional responses.

Cortisol also feeds back onto brain tissue, where there are specific receptors for the steroid hormone, especially in the hippocampus (which controls cognitive processing), as well as on the CRF neurons of the PVN. Cortisol normally exerts an inhibitory effect on the PVN cells and thereby reulates the intensity of the stress response. This HPA axis may be permanently altered, resulting in this self-regulatory, negative feedback mechanism to no

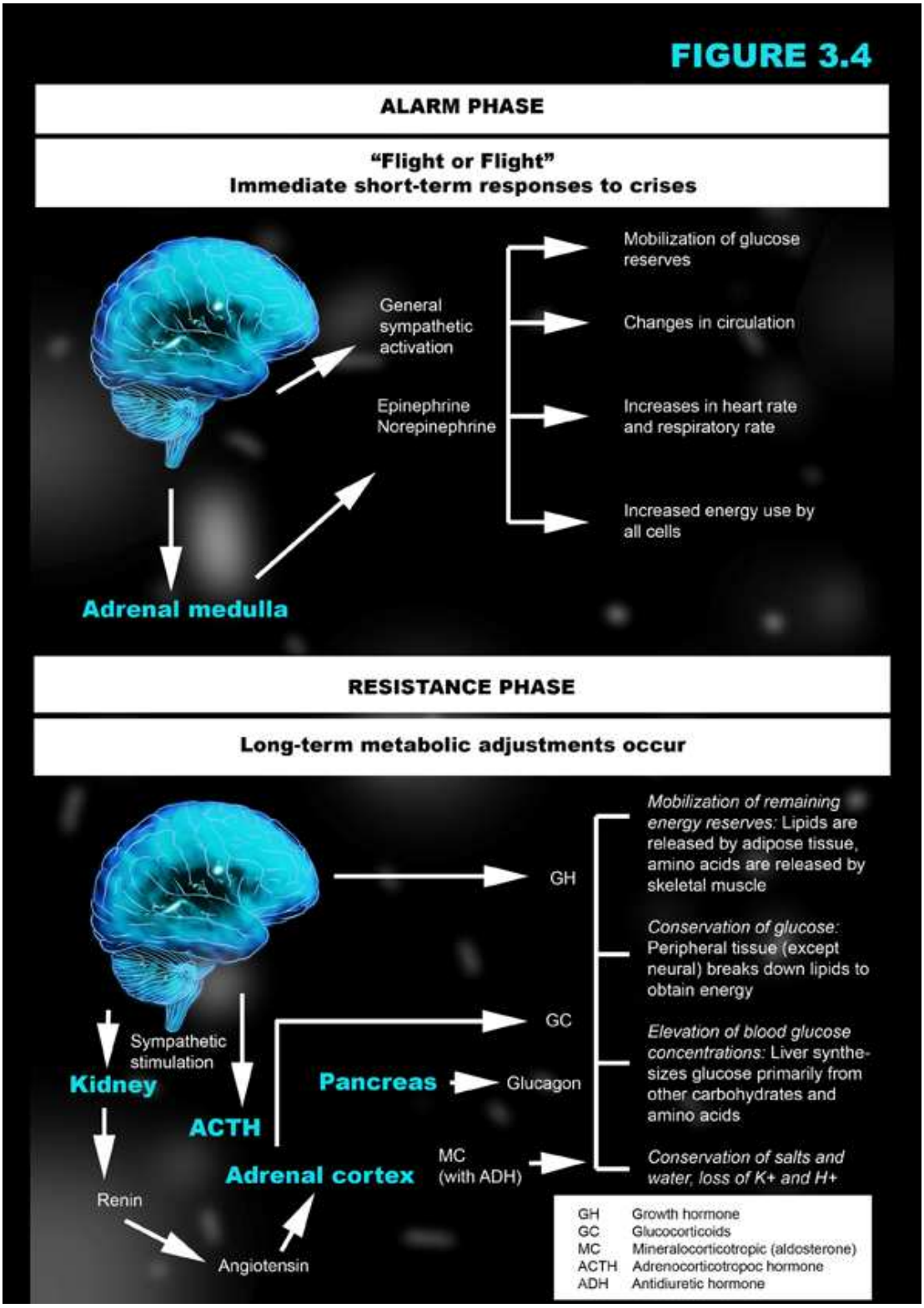


FIGURE 3.4
ALARM PHASE
"Flight or Flight"
Immediate short-term responses to crises
General sympathetic activation
Epinephrine
Norepinephrine
Mobilization of glucose reserves
Changes in circulation
Increases in heart rate and respiratory rate
Increased energy use by all cells
Adrenal medulla
RESISTANCE PHASE
Long-term metabolic adjustments occur
GH
GC
Sympathetic stimulation
Kidney
Pancreas
Glucagon
ACTH
Adrenal cortex
MC (with ADH)
Renin
Angiotensin
Mobilization of remaining energy reserves: Lipids are released by adipose tissue, amino acids are released by skeletal muscle
Conservation of glucose: Peripheral tissue (except neural) breaks down lipids to obtain energy
Elevation of blood glucose concentrations: Liver synthesizes glucose primarily from other carbohydrates and amino acids
Conservation of salts and water, loss of K+ and H+
GH Growth hormone
GC Glucocorticoids
MC Mineralocorticotropic (aldosterone)
ACTH Adrenocorticotropoc hormone
ADH Antidiuretic hormone

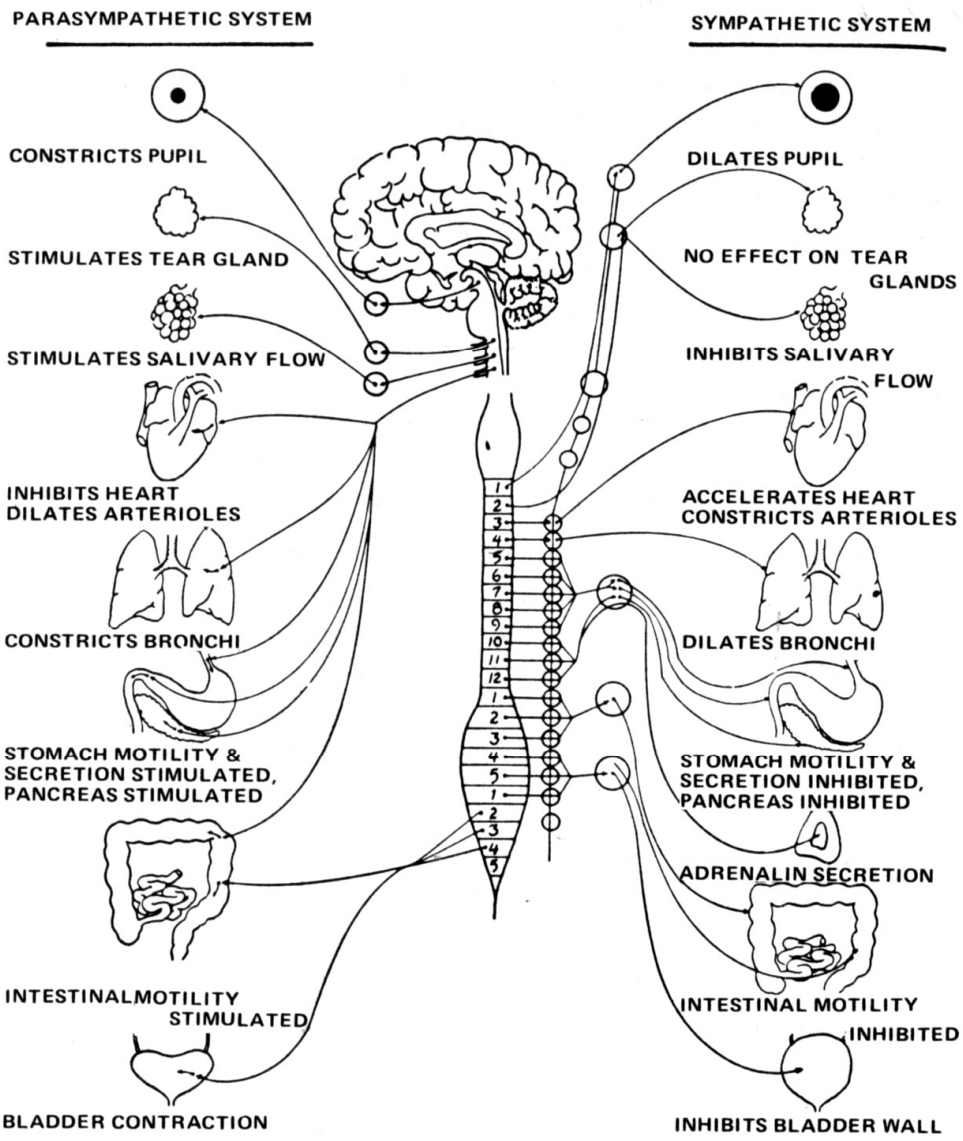
longer operate properly, consequently stress responses do not diminish normally once a stressful episode is over.

The feedback of cortisol onto hippocampal tussues also modifies cognitive abilities relevant to stress. It is postulated that cortisol might help promote cognitive strategies to cope with stressors (Panksepp 1998:118). This feedback mechanism is also subject to imbalances. The neurons that contain the cortisol receptors can tolerate only so much stimulation. If cortisol secretion is sustained at excessive levels, the metabolic resources of hippocampal neurons become depleted and die prematurely (McCubbin, Kaufmann & Nemeroff 1991; Sprott, Huber, Warner & Williams 1993; Friedman, Charney & Deutch 1995). Since brain cells are not replaced, this mechanism might impact on programmed foetal cortical development (Panksepp 1998:119).

A second major limb of the stress response is via a neural pathway arising from the hypthalamus and descending to the spinal cord, which via sympathetic efferents, activates the release of adrenaline (epinephrine) and noradrenaline (norepinephrine) from the adrenal medulla, as depicted in figure 3.1 below.

Adrenaline (epinephrine) and noradrenaline (norepinephrine) from the adrenal medulla help to break down liver glycogen rapidly and make abundant blood sugar available for the stressed individual. Practically all visceral organs and many other brain and immune responses are recruited during stress (Friedman et al 1995). These visceral, or enteric, nervous system is critical for elaborating organ responses during stress (McCubbin et al 1991) and consists of an endogenous plexus of nerves that line the gastrointetinal system and other organs; they are rich in various neuropeptides, which have some influence back into the brain via afferent neural and humoral routes. The brain itself contains many similar neural systems spread throughout the limbic system and related brain areas that govern the central integration of emotional responsivity, and autism might arise from overtaxed emotional responses prenatally (Panksepp 1998:119).

Figure 3.1 The anatomical and functional differences between the sympathetic and parasympathetic nervous systems



Source: Bruce, R.L. (1977:77)

3.4.2 The link between glucocorticoids and the pathogenesis of autism

There appears to be a link between the pathogenesis of autism and prenatal endogenous and exogenous glucocorticoids as well as endogenous opiates (Panksepp 1998). Research

findings implicate elevated levels of cortisol in the pathogenesis of autism (Beversdorf et al 2004), resulting in 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).

In addition, 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).

The preceding review of research findings demonstrate that various factors may contribute to disrupted programmed neurogenesis, and because this research focuses on the role that prenatal stress plays in the pathogenesis of autism, it follows that the critical age at which developmental failure occurs due to prenatal stress will determine the effects thereof. Exposure to excessive levels of glucocorticoids prenatally results in arrested programmed development in certain cortical regions, as summarized in table 3.3 at the end of this discussion. These regions are particularly implicated in the pathogenesis of autism, and abnormalities are closely linked to expression of autistic behaviour, as discussed in the following paragraphs.

3.4.3 Autistic expression in handwriting

Lesions to the lateral parts of the cerebellum disrupt arm, hand and finger movements, because of cerebellar involvement in the timing and accuracy of movements, which are also implicated in autistic disorder (APA 2000:75). According to Thatch and co-workers (1992:429) the primary role of the cerebellum is to help make fine adjustments needed to keep movements accurate. In addition to an inability to maintain movement accuracy, the child's error restoration might also be impaired. Traditionally these types of difficulties were ascribed to inadequate fine motor control. However, writing and drawing partially depend on movement-to-movement learning and adjustments that are made by the cerebellum (Kolb & Whishaw 2003:218). These authors explain error detection and restoration involved in handwriting as follows: Suppose a child performs a specific hand skill involved in letter formation, but finds that the shape is entirely incorrect. The child's next attempt is aimed at correcting the original error, resulting in two different versions of the same manoeuvre, i.e., the movement that the child intended to make, and the actual movement as recorded by sensory receptors in the fingers, arm and shoulder. If the first attempt at letter formation is successful, the child does not need to correct the next attempt; however, if the first attempt is incorrect, an adjustment is required. "One way in which the adjustment might be accomplished is through the feedback circuit that allows the cerebellum to correct movements. The cerebellum receives information about the

instructions sent to the motor neurons by the inferior olivary nucleus. It receives information about the actual movement through the spinocerebellar tract. By comparing the message for the intended movement with the movement that was actually performed, the cerebellum can send an error message to the cortex to improve the accuracy of the subsequent movement" (Kolb & Whishaw 2003:219). In keeping with this explanation, the cerebellum uses information about the intended movement as well as the actual movement to calculate the error and projects to the cortex how to correct the movement. Information about this correction is incorporated into the child's next attempt at letter formation. The rhythm involved in handwriting might also be disrupted.

3.4.4 Autistic expression in auditory and spatial functioning

Excessive exposure to glucocorticoids during gestation may also result in auditory and spatial deficits, because vestibular-temporal system abnormalities are implicated (Hendrickx & Hummler 1992; Emmanouil-Nikoloussi et al 2000). The receptors in the inner ear detect differences in air pressure as changes in pitch, loudness, and timbre, and these differences in pressure are conveyed from the inner ear to the brain as action potentials. These action potentials are interpreted in areas of the cortex in the temporal lobe as sounds, language, and music. The auditory system is composed of tonotopic maps, and it locates sound in space by comparing the time of the sound's arrival at each ear, which is subject to the perception of the space around the body (Kolb & Whishaw 2003:187). In autism this perception of space around the body seems to be compromised. In addition, when perception of timing and length of an auditory stimulus is compromised, post-natal sound location might be compromised as well, which is especially significant in autism. The inner ear also contains the receptor system that mediates static and dynamic balance, and once again, these functions seem to be compromised in autism. Apart from cerebellar involvement in eye movement control, the pathways projecting from the balance receptors to nuclei in the brainstem also aid in controlling eye movements (Kolb & Whishaw 2003:188), and therefore eye muscle control might also be impaired.

In addition, a child who suffers from disorders of the cerebellum might suffer a loss of timing, both in movement and in perception (finger tapping, judging rhythm and the length of an auditory stimulus) (Kolb & Whishaw 2003:217). This might manifest as poor time perception, e.g., embedded rhythm associated with speech sounds involved in language

acquisition, awareness of syllables in words, difficulty memorizing songs and poems, and these might easily be mistaken for temporal lobe lesions. Timing, rhythm and length of an auditory stimulus are closely linked to accurate perception of speech. Language is spoken at a rate of up to 12 phonemes per second, and one can understand speech at a rate of 50 to 60 sounds per second (Werker & Tees 1992:377). Eysenck (2001:243) asserts, "speech typically consists of a continuously changing pattern of sound with few periods of silence." When the perception of the length of sounds and silences are disrupted, the child might find it difficult to decide how the continuous stream of sound should be divided up into words, in keeping with Eysenck's proposed "segmentation problem" (Eysenck 2001:243). In addition, the child might have difficulty detecting the prosodic patterns of speech necessary for working out syntactic or grammatical structures. It is further suggested that synchronisation of visual and auditory information is closely related to the perception of timing, rhythm and length of auditory stimuli mediated by the cerebellum, and lip-reading might thus be compromised. Eysenck (2001:246) asserts that even individuals with normal hearing make use of visual information from lip movements to make sense of speech sounds. However, when perception of timing, rhythm and length of auditory stimuli is impaired, this might lead to the so-called McGurk effect (McGurk & MacDonald 1976:746-748). This McGurk effect might easily be misdiagnosed as auditory discrimination difficulties.

3.4.5 Autistic expression in attentional and emotional processes

The cerebellum was long believed to simply control motor coordination, but it is now known to contribute to attentional and emotional processes as well (Panksepp 1998:204; Heath, Llewellyn & Rouchell 1980:254-256). Along with the ganglion cells that play a part in vision, there are some other specialized ganglion cells that form the retinohypothalamic tract to the suprachiasmatic nucleus, which play a role in regulating circadian rhythms (Barlow & Durand 2002:203), implicated in sleep rhythm disturbances. The suprachiasmatic nucleus (SCN) might be viewed as the "major pacemaker for the daily clock" (Panksepp 1998:130), and is situated in the hypothalamus above the optic chiasm. The multiple output pathways from the SCN practically control all behavioural rhythms, from feeding and sleep to arousal and cortical energy balance regulation (Panksepp 1998:174). In addition, circadian rhythms are thought to have some relationship to mood and emotional processes (Barlow & Durand 2002:203). It thus follows that

lesions to the cerebellum and the SCN might result in defective arousal regulation, circadian rhythms, and mood irregularities, which are all implicated in autistic disorder.

Table 3.2 Possible sensorimotor learning deficits due to excess glucocorticoids during gestation (Naudé, Marx, Pretorius & Hislop-Esterhuyzen 2006 (in press)

Affected area	Sensorimotor deficits
Cerebellum	All forms of motor learning and vestibular functioning; Compromised movement-to-movement learning such as handwriting.
Flocculonodular lobe	Poor static and dynamic balance; Eye movement deficits.
Midline areas of the cerebellum	Disrupted balance, eye movements, upright posture and walking.
Lateral parts of the cerebellum	Disrupted arm, hand and finger movements; Compromised timing and accuracy of movements; Inability to detect and restore errors of movement.
Ganglion cell layer	Deficits in encoding of visual information; Faulty saccades and fixations; Compromised reading fluency and comprehension; Segmentation problems; Difficulty detecting the prosodic patterns of speech; Difficulty detecting syntactic or grammatical structures of speech; Faulty lip-reading; McGurk effect.
Suprachiasmatic nucleus (SCN)	Cortical energy balance dysregulation; Disturbed circadian rhythms; Altered mood and emotional processes; Defective arousal regulation; Altered attentional processes.

It is thus concluded that the supply of glucocorticoids should be carefully monitored during gestation to ensure that the developing fetus is exposed to neither too little nor too much, because either condition can disrupt programmed development.

3.5 SYNOPSIS

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.

In the following chapter the data of the empirical investigation will be discussed and analysed.

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