SUMMARY

Schizophrenia is a severe mental disorder with a chronic aetiology. The illness usually sets on during early adulthood and affects 0.1 to 1% of the population worldwide. Patients typically experience hallucinations and delusions, and may present with a variety of other positive symptoms such as incoherence, looseness of association, disoriented or bizarre behaviour and agitation. Also characteristic of the disorder are negative symptoms, such as flattened, or inappropriate affect, apathy and movement disorder (e.g., catatonia, postures, mutism, stupor) often accompanied by social withdrawal. The positive or psychotic symptoms tend to occur episodically, while in the intermittent periods negative symptoms prevail. Unmedicated patients are generally not capable of maintaining employment, interpersonal relationships or sufficient self-care.

Today, most hypotheses on the pathogenesis of schizophrenia include the notion of disturbed neurodevelopment. Indeed, a considerable body of evidence shows brain abnormalities in schizophrenic subjects, which appear to be of prenatal origin. Convergent epidemiological reports indicate that, besides genetic factors, 'environmental' circumstances of prenatal development influence the risk of developing schizophrenia. Brain abnormalities in schizophrenia have been found in limbic and association areas of the brain; most notably in the mediotemporal, prefrontal and anterior cingulate region. The mediotemporal displasias appear to be larger than those in other regions, while the mediotemporal area most consistently implicated is the entorhinal cortex.

The present thesis investigates possible neurodevelopmental aspects of the pathogenesis of schizophrenia in an animal model. One of the first questions to be addressed was how the type of neuropathology associated with schizophrenia might arise from developmental failure. It was hypothesised that relatively isolated maldevelopment of some regions implicated in schizophrenia might occur in view of their precocious formation. Notably, formation of the lateral and frontal mesocortex precedes the genesis of most other cortical regions and, indeed, of most other brain regions in general. Hence, an interruption of the earliest phases of cortical development may preferentially affect these areas. A consequence of such an early developmental failure would presumably be the connectional maldevelopment of areas that originate somewhat later in ontogeny. This may occur particularly in closely linked regions, such as the dorsolateral frontal cortex and the hippocampus proper, which have also been implicated in schizophrenia. Alternatively malfunction of these regions may result due to abnormal input from maldeveloped afferent areas.
As the parahippocampal cortex is a higher order association cortex, involved in maintaining transient representations of stimulus-context relationships (in which the context may also consist in an endogenous event), it was expected that malfunction of this structure may lead to cognitive impairment. The other early developing mesocortical regions, namely the anterior cingulate and prefrontal cortices, may also be regarded as multimodal association regions, which, in case of malfunction, may lead to disturbed cognition and executive control of behaviour. Moreover, it was envisaged that hypoplasia of the lateral and mediofrontal mesocortex would hamper the normal flow of information between the prefrontal cortex and the hippocampus. Such disconnection might impair the associative integration of new stimuli with previously stored, related information, leading to the subject’s inability to test its perception of reality against previous experience. The consequences of such an information-processing deficit may be misinterpretation of stimuli and reality distortion, both of which are hallmark symptoms of schizophrenia.

The experimental approach involved the induction of prenatal maldevelopment in rats. A developmental insult was effectuated using MAM, a brief acting antimitotic agent, which was administered in gestating rats at a time when the parahippocampal cortex and other early proliferating regions were expected to originate in the foetuses. The effects of the proliferative insult were investigated at the morphological, biochemical and behavioural level. Moreover, as abnormal brain asymmetries occur in schizophrenic brains and in other putatively developmental neuropsychiatric disorders, the above approach was used to investigate if and how such abnormalities may result from a developmental failure.

The experimental findings showed that interruptions of cell proliferation during early corticogenesis induce preferential damage to mesocortical regions in the brain, such as the entorhinal cortex, anterior cingulate, and prefrontal regions. Tissue reductions were, furthermore, found in the medial septal complex. The localisation and type of brain abnormality concorded to a notable degree with observed neuropathology in schizophrenic subjects. For instance, the entorhinal region was affected more severely than the frontal mesocortex, while hypoplasias were accompanied by mild to moderate cytoarchitectural disorganisation and cortical thinning. Furthermore, abnormal asymmetries resulted, particularly in the parahippocampal region. Our observations suggested that the left and right cerebral hemisphere develop asynchronously, with left hemisphere development lagging behind right hemispheric growth. Consequently, the prenatal insult impinged on different phases of development in the two hemispheres, affecting them differentially.

At the biochemical level, maldevelopment was reflected in abnormal transmission over the entorhinal and frontal cortex, as reflected in altered levels of the second
on cortex, involved in... ships (in which the... ned that malfunction of developing mesocortical... may also be regarded as... malformation of... may lead to disturbed... was envisaged that... super the normal flow of... Such disconnection... previously stored, related... tion of reality against... -processing deficit may... of which are hallmark...atal maldevelopment in... brief acting antimitotic... ten the parahippocampal... origin in the foetuses. At the... at the morphological,... in asymmetries occur in...ropsychiatric disorders,... abnormalities may result... cell proliferation during... regions in the brain, such... regions. Tissue reductions... alisation and type of brain... ed neuropathology in... affected more severely... ed by mild to moderate... Furthermore, abnormal... region. Our observations... asynchronously, with left... growth. Consequently, the... in the two hemispheres,... in abnormal transmission... ed levels of the second... messenger protein kinase C. The data suggested hyperactivity in the entorhinal and hypofunction in the frontal region. The dopamine system was only mildly or not notably affected (depending on the exact timing of the developmental insult), while no abnormalities were found in serotonin expression by the Raphé nuclei. Interestingly, nerve growth factor (NGF) levels were increased in the developmentally manipulated animals, possibly reflecting a stressed state of the affected cortical regions. These findings provide a first indication that NGF may represent a biochemical marker for prenatal brain maldevelopment.

The behavioural studies indicated that maldevelopment of the early developing associative regions of the brain results in impairments that may be related to schizophrenic symptoms, namely: sensory gating deficits, abnormal attention with behaviour suggestive of increased distractibility, social inadequacy and decreased social priming, a reduced pain response, impaired acquisition of passive avoidance, delayed motor development and subtle adult neurological impairment.

We have herewith provided a model that combines pathogenetic, neuropathological and symptomatological aspects of schizophrenia into a single approach. The unique advantage of this approach is that it presents with a neuropathology that has similar characteristics to brain abnormalities in schizophrenia, and that it proposes a developmental mechanism by which this neuropathology might come about. As a consequence, the emergent behavioural and biochemical properties of the model are more likely to be based on neurobiological mechanisms similar to those acting in schizophrenia, than is the case in other proposed models. The combined results from these experiments offer substantial support for a neurodevelopmental pathogenesis of schizophrenia, and for involvement of the mesocortex in this disorder.