Rough beginnings: Executive function in adolescents and young adults after preterm birth and repeat antenatal corticosteroid treatment

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Rough Beginnings
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Abstract

This thesis investigates long-term cognitive outcome in two cohorts of adolescents and young adults exposed to stressors during the perinatal period: one group born preterm (<37 weeks of gestation and birth weight <1,500 g), and one group exposed to two or more courses of antenatal corticosteroids (ACS), to stimulate lung maturation in the face of threatening preterm birth. In fetal life the brain undergoes dramatic development, in a regulated yet dynamic process. A disruption to the early establishment of functional neural networks may interrupt typical brain development in ways that are difficult to predict. Executive function refers to a set of cognitive processes that are important for active and purposeful regulation of thought, emotion, and behavior, and even a subtle depreciation may influence cognitive, social, and academic functioning. Study I investigated the stability and prediction of executive function development after preterm birth. Executive functions were differentiated into working memory and cognitive flexibility. Both components were highly stable from preschool age to late adolescence, and showed different developmental pathways. In Study II, we identified subgroups within the group children born preterm with respect to cognitive profiles at 5½ and 18 years, and identified longitudinal streams. Outcome after preterm birth was diverse, and insufficiently predicted by biological, perinatal, and family factors. Individuals performing at low levels at 5½ years were unlikely to improve over time; individuals who performed at norm were unlikely to fall far below norm. Indeed, a group of individuals performing at or above norm at 5½ years had improved their performance relative to term-born peers by age 18. Studies I and II pointed to the need for developmental monitoring and identification of those at risk, prior to formal schooling. Study III investigated long-term cognitive outcome after repeat ACS treatment. The study did not provide support for the prevailing concern that repeat ACS exposure will have a major adverse impact on cognitive function and psychological health in young adulthood. In sum, exposure to perinatal stressors resulted in great variation in outcome. However, for many, their rough beginnings had not left a lasting mark.

*Keywords*: cognitive flexibility; cluster analysis; development; latent variable analysis; longitudinal studies; parental education; perinatal medical complications; person-oriented approach; structural equation modeling; working memory.
List of studies


The first and second author contributed equally to this study.


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Abbreviations

ACS Antenatal Corticosteroids
ACTORDS The Australasian Collaborative Trial of Repeat Doses of Steroids
ASED Average Squared Euclidean Distance
CANTAB Cambridge Neuropsychological Test Assessment Battery
CFI Cognitive Flexibility Index
CFI Comparative Fit Index
D-KEFS Delis-Kaplan Executive Function System
DNA Deoxyribonucleic Acid
ESS Error Sum of Squares
FAST Fetal Antenatal Steroid Treatment Study
HPA Hypothalamic-Pituitary-Adrenal
IVH Intraventricular Hemorrhage
LICUR Linking of Clusters after Removal of a Residue
M Sample Mean
MACS Multiple Courses of Antenatal Corticosteroids for Preterm Birth
NICHD US National institute of Child Health and Human Development
PFI Performance Function Index (non-verbal ability)
PVL Periventricular Leukomalacia
QoLI Quality of Life Inventory
RMSEA Root-Mean-Square Error of Approximation
ROP Retinopathy of Prematurity
SD Standard Deviation
SDS Standard Deviation Score
SES Socioeconomic Status
SMRA Standardized Root Mean Square Residual
SNP Stockholm Neonatal Project
WAIS Wechsler Adult Intelligence Scale
VFI Verbal Function Index (verbal ability)
WISC Wechsler Intelligence Scale for Children
WMI Working Memory Index
WPPSI Wechsler Preschool and Primary Scale of Intelligence
I would like to gratefully acknowledge Elsevier Ltd., Professor Adele Diamond, and Professor Akira Miyake for permission to use and reproduce their figures in my thesis:


*Figure 3.* adapted from A. Miyake and N. P Friedman (2012). The nature and organization of individual differences in executive functions: Four general conclusions. *Current Directions in Psychological Science, 21*(1), 8–14. By permission of Akira Miyake.
Introduction

The development of a child, from an infant that is totally dependent on the care of others, to a young adult capable of abstract reasoning and able to fill out an income tax form, is a complex process resulting from the intricate multidirectional interaction between genes, brain, cognition, behavior, and environment. Executive function is an umbrella term for a set of higher order cognitive processes, which are crucial for the ability to purposefully control thought, behavior, and emotion. Executive functions are important for reasoning, problem-solving, social awareness, and adaptive behavior. They exhibit protracted development extending from birth well into young adulthood. These functions are also the most easily disrupted and prone to deficits in the face of brain injury, and executive dysfunction is implicated in many learning and developmental disorders. This thesis aims to investigate how perinatal stress, caused by preterm birth or repeat antenatal glucocorticoid exposure, affects development and ultimately executive functioning in adolescence and young adulthood.

The thesis rests on three studies, based on data from the Stockholm Neonatal Project and the Fetal Antenatal Steroid Treatment Study. Background information on these projects and the aims, results, and major conclusions of each study form the central part of the thesis. Bracketing the studies is an introductory section which gives a theoretical backdrop to the studies, and a discussion which aims to set the results in the wider context. The introductory section covers three topics: cognitive development, including a brief description of brain development and plasticity; executive functions, their theoretical and operational definitions, development, and relation to other cognitive constructs; and, finally, an introduction to two interrelated causes of perinatal stress: preterm birth and repeat antenatal corticosteroid treatment.
Cognitive development

Over time, our view of children has changed. In the ancient and medieval depiction, a child was seen as a small version of an adult, with expectations to take part in the adult world as early as the age of six or seven years. The concept of childhood was alien. Later views held that the child was born either pure, only to be corrupted by the world, or as a clean slate, that could be steered into a form acceptable to society (Gillibrand, Lam, & O’Donnell, 2011). Only in the last century have our views been informed by systematic observation and investigation of the children themselves: how they think, act, feel, relate, and construe their worlds.

With regard to cognitive development, Jean Piaget (1896-1980) has played a pivotal role. He developed groundbreaking theories and experimental approaches that transformed the field of developmental psychology, as well as how psychologists looked at and saw children. Although developmental researchers of today have moved beyond the original Piagetian theory, his analyses and findings remain a source of inspiration and continued investigation.

Piaget (1952) concluded that children are active in their development; they take notice of their environment and interpret their observations. They construct meaning and learn through the processes of accommodation and assimilation. His cognitive developmental theory outlines four main stages of development. In Stage 1, Sensorimotor intelligence (birth to 2 years), the infant coordinates sensory perception and motor abilities to acquire knowledge and understanding of the world. The child interacts with the environment by physically manipulating objects. Towards the end of the period, the child knows that objects exist, although they are out of view, and mental images of how to reach goals emerge. During Stage 2, Preoperational thought (age 2 to 7 years), actions are internalized as mental operations. The abilities of imaginative play and the use of symbols burgeon, and language develops dramatically. The child is still limited to understanding her world from her own perspective, and reasoning is limited by the physical appearance of objects and places. In Stage 3, Concrete operational thought (age 7 to 11 years), the child begins to use logic to understand her world and solve actual problems that involve more than one salient feature. However, reasoning remains on the concrete level, limited to objects and phenomena that are
real or can be seen. Abstract problem-solving and deductive reasoning are characteristics of Stage 4, Formal operations (age 11 to adulthood). At this stage, the youngster becomes able to consider all relevant aspects necessary to find a solution to a problem and systematically explore options. The youth can also understand that what is said may not match what is meant in a conversation and can engage in discussions that are purely hypothetical. Piaget’s theory holds that each stage is characterized by a qualitatively different understanding of the world that is more advanced and rational at each stage. This implies that certain specific abilities have to be successfully acquired before progressing to the next stage. The stages are presumed to be discrete, invariant in order, and irreversible.

Over the years, Piaget’s theory has been challenged and several weaknesses have been identified. The main flaws pointed out are that the theory describes rather than explains development and that Piaget did not distinguish between competence (i.e. understanding the task) and performance (being able to demonstrate the ability). In addition, Piaget’s assumption that children construct their understanding by acting on the environment, underestimates the contribution of the social environment to a child’s learning (Slater & Bremner, 2011). It has been shown that Piaget underestimated the abilities of the children in the early stages of development and overestimated the abilities of adults. If tasks are better adapted to the child’s experience, infants and young children have been found to be able to perform many of the tasks Piaget claimed they were not yet able to master. It has also been shown that not all individuals progress to the stage of formal operations, and in everyday life, adults’ thinking is often irrational. The issue of stages – the mind developing uniformly – is also debated (Flavell, 1992). Indeed, very often adults initially respond in line with a lower stage of thinking, only to inhibit this response in order to give a response that is better adapted to the situation. Nonetheless, the theory still holds well as a description of cognitive development, although the process is neither invariate nor necessarily irreversible (Gillibrand et al., 2011).

More contemporary researchers have addressed the questions raised by Piaget from various standpoints. By adapting an information processing perspective, changes within and between the stages proposed by Piaget could be understood in terms of increased memory capacity and efficiency in information processing (e.g. Case, 1988). By studying the strategies children use to solve problems, variations between children as well each child’s developmental progress could be understood (Siegler, 1976). Theories to understand cognitive development in terms of skills acquisition have also been presented (Fischer, 1980). Increasingly, the dynamic interplay between the child and her environment, as well as the role of social interaction in cognitive development have been emphasized. More recently, knowledge of brain
development and brain function have contributed to our understanding of the mechanisms behind cognitive development.

**Brain development**

Central nervous system development commences a few weeks after conception and by the end of the embryonic period the rudimentary structures of the brain have been defined (Stiles & Jernigan, 2010). The early fetal period, from eight weeks after conception to mid-gestation, is a critical period in brain development by the end of which most neurons have been generated, have migrated to their positions in the cortex, and have begun to make connections.

There are two major types of cells in the nervous system: neurons and glial cells. The glial cells function primarily as support and supply cells to the neurons. Cell generation, or neurogenesis, begins in the sixth week of gestation and is virtually complete by mid-gestation; cell proliferation peaks between the third and fourth prenatal month (Stiles & Jernigan, 2010; Volpe, 2000). During this short period of time virtually all of our 100 billion neurons are generated, and with the exception of a small number of cells in the olfactory bulb, the hippocampi, and possibly parts of the neocortex, no more neurons are ever formed (Nelson, de Haan, & Thomas, 2006). The vast majority of all neurons are produced in the proliferative zones and migrate to predetermined locations in the brain. The process of neuron generation and migration appears highly regulated, with an appropriate number generated in specific regions at predetermined times (V. A. Anderson, Northam, Hendy, & Wrennall, 2001). As the newly formed neurons migrate, most follow a pattern whereby newer neurons move past older neurons, building the cortical layers from the inside out. The different layers of the cortex contain different types of neurons (Stiles & Jernigan, 2010). At 20 weeks of gestation, three layers have been formed; all six layers are present by the seventh prenatal month (Nelson et al., 2006). In order to fit the growing cortex in the skull, the cortex folds, moving from a smooth structure to the mature patterns of gyri and sulci. The folding follows a set sequence beginning with the fissure separating the hemispheres. The primary sulci are formed by 26 weeks of gestation, the secondary sulci emerge during weeks 30 to 35, and finally, the tertiary sulci are completely formed postnatally (Stiles & Jernigan, 2010).

After neurogenesis and once neurons have completed their migratory journey the processes of cell differentiation begin. During the differentiation the cells in specific group of neurons begin to make connections. This “wiring” of the brain creates the information networks that enables cognition. In order
to be able to communicate with other neurons and become part of a network, axons and dendrites are developed and synapses formed. The axon is the principal means of sending signals from the neuron and the dendrites receive input from other neurons. The connections between axons and dendrites from other neurons are called synapses (Stiles & Jernigan, 2010). Chemicals in the brain, neurotransmitters such as glutamate, GABA, serotonin, dopamine, and norepinephrine, influence the transmission and modulation of neural signals (M. H. Johnson & de Haan, 2011). Axons that connect different parts of the brain form fiber bundles. Such fiber tracts unite the cortex with the lower part of the brain and the spinal cord (projection fibers), connect the two hemispheres (commissural fibers), and connect parts of the brain within the same hemisphere (association fibers) (Stiles & Jernigan, 2010).

Dendritic growth continues rather slowly into childhood; synaptic development, commencing in the fifth prenatal month, becomes more elaborate and complex postnatally (V. A. Anderson, Northam, et al., 2001). During prenatal brain development, there is an overproduction of neurons, and those that do not become part of a network are deemed redundant and are eliminated (programmed cell death, apoptosis). There is also an excess of synaptic connections, which are subsequently pruned. This dynamic process of progressive and regressive events in brain development is dependent on stimulation and activity. Different systems have different timetables for synaptic pruning and the process is not completed until the mid-teen years. Both programmed cell death and synaptic pruning are essential for establishing well-functioning, complex networks (Stiles & Jernigan, 2010).

Finally, a critical aspect of brain development is the process of myelination. Myelin, a substance which forms an insulation of the axon, increases the speed of neuronal conduction and thus is important for efficient functioning. It is a class of glial cells, the oligodentrocytes, that myelinate the axons. The process begins in the late prenatal period and in a non-linear pattern; different areas of the brain show different timing and rates of myelination. The most rapid period is in the first three years of life. The process unfolds in a specific spatio-temporal pattern that typically proceeds in an inside out and back to front manner. The primary motor and sensory areas are the first to be myelinated, and the process progresses gradually to areas supporting more complex functions. The prefrontal area is the last to be fully myelinated, continuing into the mid-twenties – thus completing brain development (Nelson et al., 2006).

Myelination and the growth of white matter (the myelinated fiber bundles) continue throughout development and well into adulthood. In contrast, neurogenesis vs. programmed cell death and synaptogenesis vs. synaptic prun-
ing, show a “rise and fall” developmental pattern. This pattern also holds for a number of neurotransmitters, for brain metabolism, and cortical thickness. Brain glucose metabolism increases after birth, peaks at approximately age 4 to 5, and comes down to adult levels for most cortical regions at 9 years of age. Gray matter volume increases rapidly to about age four, and shows a slight decline that continues into adulthood (M. H. Johnson & de Haan, 2011). The dynamic process involving regressive and progressive changes in brain development is shown in Figure 1.

There is accumulating evidence in support of a step-wise rather than continuous development, with growth spurts occurring prenatally (gestational week 24 to 25), in early infancy, at around 7 to 9 years of age, and again in adolescence. Although Piaget, in developing his theory, did not explicitly consider brain development, the transitions between the stages he proposed coincide well with the non-linear development and growth spurts identified in brain development (V. A. Anderson, Northam, et al., 2001).

Much of the early research relating brain development to behavior held a maturational viewpoint, which worked under the assumption that the information necessary to build the brain lies within the genes. With some individ-

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**Figure 1.** Approximate timeline and rise and fall pattern for human brain development. From (Casey, Tottenham, Liston, & Durston, 2005).
ual variation, the brain functions are innately specified and emerge according to a maturational time-line. In adult neuropsychology, brain insult or degeneration are often linked to loss of specific functions. Functional brain development in children was conceived as the reverse process, and research focused on the time at which a specific brain area would become functional for a specific behavioral task (M. H. Johnson & de Haan, 2011). The maturational viewpoint on brain development has increasingly been abandoned in favor of today’s more commonly accepted view: that development is the result of complex multidirectional interactions between genes, brain, cognition, behavior, and environment (M. H. Johnson & de Haan, 2011; Karmiloff-Smith, 2009; Nelson et al., 2006). Genes are probabilistic rather than deterministic. Development is dependent on external environmental influences, some common to all individuals (experience-expectant environmental influences) and some unique (experience-dependent). Brain development involves the progressive restriction of possibilities for the organization of function. That is, a number of mechanisms that do not start out as domain-specific become more specific over time (M. H. Johnson & de Haan, 2011). Early in development there is a range of possible end-states, and these end-states may be reached through different developmental pathways. In typical development the same end-point will be reached even if there are small variations in environmental input. However, an early or large disturbance to the on-going process may result in development along a different path (M. H. Johnson & de Haan, 2011). The lack of specialization and interconnectivity of early cortical development would imply that a small interruption could affect all parts of the cortex (Annaz, Karmiloff-Smith, & Thomas, 2008). Abandoning the maturational view implies that atypical development should not be seen in terms of impaired and spared functions where non-affected functions develop independently of the affected functions (Karmiloff-Smith, 1998). The adult framework referring to intact and impaired functions does not take the immature brain’s interconnectivity into account – it is unlikely that one part of the brain can develop in isolation from atypically developing parts (Annaz et al., 2008). Explaining development deficits with reference to the final outcome and comparing them to a typical adult system disregards the fact that the adult system is a product of development (Sirois et al., 2008). The developmental aspect is paramount.

Injury and plasticity

In a broad sense, plasticity refers to the ability of the brain to adapt to change – shifts in the strength of existing connections or modifications to connections in response to stimuli. In this broad use of the term plasticity, everyday learning reflects the plasticity of the brain. In a narrower sense, the term plasticity is reserved for describing adaption and change in the initial functional connections, or after an injury to more established systems. Applying
a narrow sense of the term plasticity, and with a view that the brain in early development is less specialized and that the development of functional brain regions are characterized by tuning and increased specialization, plasticity would be possible as long as function is not yet fully specialized (Sirois et al., 2008). Because of the lack of “hard-wiring”, the immature brain was previously seen as more resistant to insult. Early findings implied that an immature brain had the potential to transfer functions from damaged to healthy tissue. However, this proposed transfer seems more complicated than previously believed, as damaged tissue may work ineffectually or the transfer may lead to crowding, by which most functions are depressed (V. A. Anderson, Northam, et al., 2001). There is growing evidence that disruption in early brain development is irreversible and that the injury may interrupt development in ways that are difficult to predict. Also, although there is evidence of neuronal plasticity, this does not necessarily translate to recovery of function or unaffected development (V. A. Anderson et al., 2009).

It seems as if primary functions such as visual, sensori-motor skills, and simple language more often tend to functionally recover after injury. There is presumably a greater capacity for neural reorganization in the more discrete and simpler neural networks on which these functions rely. However, for functions such as attention, working memory, or social cognition, which rely on more complex and diffuse neural networks, functional recovery or development is less likely (V. A. Anderson, Spencer-Smith, & Wood, 2011). The age of injury affects outcome, and is related to developmental maturity of the function at that time. Functional outcome is also related to time elapsed since injury. An early assessment might not reveal deficits in functions that are under development – a child might ‘grow into’ a dysfunction as expected development fails. These development dynamics stress the importance of long-term follow-up and longitudinal research. Longitudinal research of typically developing children contributes to our understanding of how functions develop and interact, which is important for evaluating the effects of insult. Long-term follow-up after injury, and of developmental disorders, is critical for understanding how disruptions in typical development will alter functioning from both short- and long-term perspectives. By studying atypical development we can also gain new insights into what typical development entails, and also into the robustness and variations of normality.

The “how” of cognitive development has certainly been enlightened by research progress in genetics, neurobiology, neurology, neuroscience, and developmental neuropsychology. Although Piaget’s stage theory in many ways described the essential features of cognitive development, understanding has been furthered by investigating how primary functions develop and interact, and how they successively come under volitional control. Moreo-
ver, failure to develop in the typical manner can be traced to aberrations to this primary functions in very early development, aberrations that in interaction with the external world may lead to a variety of developmental trajectories. Cognitive development thus entails the development and interaction of core processes such as attention and working memory and, with frontal lobe maturation, an increased volitional control. The construct of executive functions in the next section is of interest in this respect.
Executive function

Executive function is an umbrella term for several cognitive processes that are important for active and purposeful regulation of thought, emotion, and behavior. These processes are especially important in novel situations or when automatic responses are maladaptive. There is no universally accepted definition of executive function, but key elements discussed include: attention, impulse control, planning and organization, mental flexibility, initiation and monitoring of activities, and working memory (P. J. Anderson, 2008). Executive functions are critical for cognitive and social development and affect schooling and life outcome (Diamond, 2013). The early models of executive function were based on clinical data from adults with known brain injuries. Executive function was theorized as a unitary concept and no specific subcomponents were identified; neuropsychologically, the abilities were found to be mediated by the frontal lobes (Fuster, 1989; Shallice, 1990; Stuss & Benton, 1992). However, “frontal lobe” patients proved to vary in behavioral profiles, and these variations could not be sufficiently understood in the context of the unitary models. Today, executive functions are regarded as a set of highly interrelated and complex processes or abilities which include cognitive as well as social and affective aspects (V. A. Anderson, Jacobs, & Anderson, 2008). However, the question of whether executive function is a unitary construct with constituent subprocesses, or a set of independent dissociable components, is still unresolved. The functions are dependent on the prefrontal cortex and closely related structures such as the anterior cingulate cortex and the basal ganglia (Pennington, 2009). In adults, there is evidence linking specific executive functions with focal lesions within the prefrontal cortex (Stuss, 1992). However, for children, where functional specialization is still in the process of development, effective function is dependent on the integrity of the entire brain (V. A. Anderson, Jacobs, & Anderson, 2008).

It is only in the past 25 years that focus has shifted from the study of adult executive function to early executive function, and executive function development (Welsh, Pennington, & Groisser, 1991; Welsh & Pennington, 1988). Contrary to what was previously believed, early studies of infants showed that the human prefrontal cortex was operative, rather than silent, in the first year of life (Diamond & Goldman-Rakic, 1989; Diamond, 1985). Major obstacles to overcome for the emerging field of developmental cognitive
neuroscience have been to adapt executive function tasks designed for adults to children of different ages, and to find agreement on what actually should fall under the executive function umbrella. Assessment of executive functions is often based on tasks that are complex. Making a task more age-appropriate implies simplification and it is difficult to ascertain if the simpler task actually reflects the same basic function (Garon, Bryson, & Smith, 2008). Executive function is also dependent on more primary functions such as visual perception, fine-motor skills, and early language, which, if deficient, will adversely affect performance. In assessments, a seemingly attenuated executive function can result from a deficit in a primary function, which should be taken into consideration when interpreting outcome. Another problem in clinical executive function assessment, in children and adults alike, is the fact that the standardized testing situation *per se* is structured and reduces executive function requirements, with the risk of masking actual difficulties (V. A. Anderson, Anderson, Northam, Jacobs, & Catroppa, 2001). Although mature results of test performance are often achieved prior to completed brain development, it is likely that in real life, or under stress, some immaturity would be apparent.

Although assessment of executive functions is often limited to cognitive tasks, the importance of executive function in motivation, affect regulation, and social interaction must not be overlooked. Indeed, the neural systems supporting cognitive executive functions such as attention, working memory, and inhibition are integrated with those that are involved in response to stress and emotional reactivity. This implies that executive function deficits are likely to adversely impact self-regulation of cognition, emotion, and behavior (Blair, 2006; Rothbart, Sheese, Rueda, & Posner, 2011). Importantly, the social aspects of executive dysfunction are often more burdensome in day-to-day living than the cognitive deficits. The focus of this thesis is on cognitive rather than socio-emotional development and outcome. Thus affective aspects of executive function and the link between social, emotional, behavioral, and cognitive aspects are left aside; however, by doing this I do not wish to imply that the cognitive aspects are more important.

In a recent review, a useful framework of executive functions and related terms was presented by Diamond (2013); see Figure 2.

In this framework, three commonly accepted core executive functions – inhibition, working memory, and cognitive flexibility – are basics on which more complex executive functions such as planning, problem-solving, and reasoning, are built. The framework presents an overview of the construct and can serve as a guide to discuss the development of the separate parts, as well as their relation and interdependence.
Figure 2. Executive functions and related terms. From Diamond (2013).
Development of executive function

Theories of executive function development in early childhood generally describe an increasing ability to deal with conflict when processing information, and the associations with the changes in underlying neural networks. During the preschool years, executive functions develop rapidly. The ability of the infant to focus attention on a selected stimulus, and to successively extend the ability to maintain focus and resist distractions, emerges in early infancy, and is under some volitional control towards the end of the first year. These early abilities to selectively focus attention form the basis for executive function development (Garon et al., 2008; Rueda, Posner, & Rothbart, 2005).

Inhibition

Inhibition refers to the ability to withhold a motor response or override a strong internal urge or external temptation. Simple forms of inhibition, such as adhering to “don’t” or delaying gratification, can be seen in the latter half of the first year, indicating an ability to impose cognitive control over behavior. More complex tasks involve holding an arbitrary rule in mind and responding according to the rule while inhibiting a dominant response. Young 3-year-olds have problems with complex response inhibition tasks, while children almost 4 years old perform much better (Garon et al., 2008). Inhibition continues to improve, especially on tasks that combine inhibition and working memory, between the ages of 5 and 8 years, and also later. The early gains in inhibition are more qualitative in nature, reflecting conceptual gains, whereas later development is more characterized by quantitative improvements in accuracy and refinement of skills (Best & Miller, 2010).

It can be noted that Diamond in her framework, regards focused attention as an aspect of inhibition. Also, inhibition is separated into interference control and response inhibition. Response inhibition refers to the ability of self-control (such as keeping at a task though wanting to do something else) while interference control encompasses cognitive inhibition and selective attention. Cognitive control is intimately related to working memory (Diamond, 2013). Barkley (1997) in his hybrid model of executive function placed inhibition at the top, regarding it as the primary component on which other executive function components depend. He also proposed that inhibition was composed of three interrelated processes; inhibiting the prepotent response, interrupting an ongoing response, and interference control.
Inhibition, thus, appears not to be a uniform construct, but rather to be composed of distinct processes with their own rates of development. Assessment at different ages might therefore involve measuring slightly different aspects of inhibition. To complicate things further, in certain tasks, inhibition is also dependent on other cognitive components and skills, such as working memory and reading (Best & Miller, 2010).

Neuropsychologically, inhibition in infants is associated with global brain activity. By early school age, complex response inhibition tasks give rise to a more localized activity in the prefrontal cortex; increased myelination of the frontostriatal pathways is correlated with maturation of inhibition in childhood and adolescence. It also appears as if task performance and underlying neural activity do not correspond – in fact, performance of inhibition tasks improves little from school age to adulthood, whereas neural activity changes profoundly. The global pattern of activation becomes localized activation in the task-specific regions in the prefrontal cortex, reflecting a greater efficiency and less effort (Best & Miller, 2010).

**Working memory**

Working memory, the ability to hold information in mind and mentally work with it, is the executive function component that has the most protracted development (V. A. Anderson, Anderson, Jacobs, & Spencer-Smith, 2008). Working memory is essential for making sense of sequential events, for spoken and written language, for being able to relate ideas to one another, or for breaking down problems into smaller parts. Working memory and inhibition are highly interdependent and are usually recruited in concert (Diamond, 2013). Although holding simple representations in mind can be seen in six-month-old infants, working memory tasks such as recalling a sequence of words or digits in reverse order begin to emerge at around age 3 years. These more complex tasks often require multiple operations to be performed at the same time (i.e. remember digits AND reversing their order). Mastery of the simpler tasks is achieved in early school years, whereas performance of the more demanding tasks continues to improve into adolescence and even young adulthood (Best & Miller, 2010; Brocki & Bohlin, 2004; Huizenga, Dolan, & van der Molen, 2006).

In contrast to inhibition, working memory appears to have a more linear developmental trajectory, with gradual refinement through adolescence. Verbal and spatial tasks rely on different neural networks in the prefrontal cortex; these networks become more specialized over time, and as with inhibition, the dramatic and prolonged neural specialization and increased efficiency translate into limited improvements in test performance (Best & Miller, 2010).
Cognitive flexibility

Cognitive flexibility, shifting, or mental set-shifting are all terms that relate to the ability to flexibly adjust to new demands or priorities and the ability to change perspectives. This core executive function component is the last to emerge and builds upon inhibition and working memory abilities. Indeed, in preschoolers working with complex executive function tasks, shifting may not be differentiated from inhibition and working memory. Children younger than 4½ to 5 years tend to get stuck on one dimension on sorting-tasks, and not until they are aged 7 to 9 can children flexibly switch between dimensions on a trial-by-trial basis (Diamond, 2013). Shifting reaches adult levels at around age 15. Younger children tend to activate executive functions reactively, whereas adolescents and adults are more anticipatory in their activation. With increasing complexity, adolescents slow down in order to maintain performance, whereas children typically fail to appropriately adjust speed. Thus, in shifting tasks, error detection and monitoring, as well as meta-cognition are employed in order to be successful. In children, there is evidence of increased activation in the dorsolateral prefrontal cortex compared to adolescents, who typically employ networks in the inferior frontal, parietal, and anterior cingulate cortex. Maturation of the conflict monitoring processes reduces the compensatory activation shown in children (Best & Miller, 2010).

Overall, executive function development in the preschool years takes place in two main stages. Prior to age 3 years, the basic skills emerge and the years after age 3 are characterized by increasing coordination of the executive function components. Inhibition follows a growth curve that is steeper up to age 8 years and then tapers off, whereas working memory and shifting follow a more linear development, albeit with different timing. Younger children’s neural activation is more global, with increased employment of localized networks as functions mature. The increased specialization and effectiveness of the neural networks continue even after fairly mature performance levels are achieved, and presumably less effort needs to be expended.

Higher order executive function and intelligence

Several models of human intelligence have been proposed in order to understand and predict individual differences in school and occupational settings. General cognitive ability, a latent construct that is usually operationalized and assessed with an IQ score, is a global index which reflects outcome in a broad range of cognitive skills. The outcome is affected by and dependent on the individual’s genes, neural make-up, environment, and life experiences. Overall ability is also linked to school success, health, and life outcome
In assessing cognitive developmental outcome, measures of general ability give a relevant measure of overall level. However, the broad measure also masks underlying intraindividual differences and thus gives little information on relative strengths and cognitive profiles, which can be of clinical as well as personal value. Although the debate is still ongoing as to how intelligence should be defined and assessed, intuitive notions of what it means to be smart—being good at solving new problems or knowing a lot—are in line with the concepts of fluid and crystallized intelligence (Horn & Cattell, 1966). Abstract reasoning, the ability to see patterns and relationships between entities, and being able to solve (novel) problems are often considered to represent fluid intelligence. Fluid intelligence is viewed as inherently influenced by biological factors and incidental learning. In contrast, crystallized intelligence to a higher degree reflects education and experience. The notion that fluid intelligence is unrelated to experience and learning, and in that sense is a purer measure of innate ability can be questioned (Lohman, 2005). Fluid intelligence has been found to be statistically inseparable from the overall general ability (Gustafsson, 1984), although this seems to be more true for healthy adults and in typically developing children than in clinical populations (Blair, 2006).

Increasing maturity and coordination of the core executive functions enables higher order executive functions. Reasoning, problem-solving, strategic organization, planning and creativity all, to greater or lesser extent, rely on core executive functions. Indeed, it is difficult to imagine any cognitive task that does not involve some aspect of executive function. Friedman and colleagues found that executive functions were differentially related to intelligence in young adults. Updating (working memory) accounted for approximately 40% of the variability in measurements of both fluid and crystallized intelligence. Inhibition and cognitive flexibility did not contribute to the intelligence measurements over and above what was shared with working memory. In a sample of typically developing children of 8 to 13 years, working memory, shifting, and inhibition were all correlated with intellectual capacity; in working memory and shifting the correlations were stronger (Lehto, Juujärvi, Kooistra, & Pulkkinen, 2003). Tillman and colleagues (2008) found in children of 6 to 13 years that both storing and executive components of working memory independently contributed to fluid intelligence.

In her framework, Diamond equates the complex executive functions reasoning and problem-solving with fluid intelligence (Diamond, 2013). Although Diamond’s proposition that the two are indeed the same is not necessarily accepted by all; in these terms two research traditions, psychology and cognitive neuroscience, converge.
The fluid abilities are more easily impaired as a result of brain injuries, and also as part of normal aging. And vice versa, crystallized abilities peak late in development and often remain intact after injury in adult age. In young children, the crystallized abilities to a large extent reflect the family environment – children growing up in enriched environments will perform better than children from more impoverished homes on tasks assessing language and knowledge. With age, this effect diminishes but home and schooling continue to exert an influence on crystallized abilities. The fluid abilities in the developing child, however, are fundamental for learning and a child with poor fluid abilities will face more challenges in acquiring knowledge and in developing an understanding of the world. The measure of intelligence takes on a rather different meaning when seen from a developmental perspective, and in particular in relation to outcome after neurodevelopmental disorders or childhood brain injury (Karmiloff-Smith, 2009). In children with neurodevelopmental disorders or early brain insult, intelligence scores reflect and are confounded with the effects of the insult and cannot be partialled out (Dennis et al., 2009).

Processing speed

Individual differences in intelligence have, through time and in diverse lines of research, been linked to fundamental differences in working memory as well as in processing speed (M. Anderson, 2008). In statistical analyses of factors of intelligence, speed is often found to account for an important part of the variation (Gustafsson, 1984). Information processing efficiency and speed differ between individuals, improve with age, and are related to performance in many cognitive tasks (Cepeda, Blackwell, & Munakata, 2013; Kail & Salthouse, 1994). In an attempt to parse out the distinctive contributions of age, speed, and working memory on fluid intelligence, Fry and Hale (2000) conclude that age-related improvements of working memory and intelligence are almost completely mediated by the effect of speed.

Although generally agreed as important, there is a lack of consensus on whether processing speed is an independent aspect of executive function, or an ingredient thereof (P. J. Anderson, 2008; Cepeda et al., 2013; Kail, 1991). Executive function task performance is improved with fluency, automaticity, and speed of information processing; and also, improved executive functions facilitate efficiency and speed of information processing (P. J. Anderson, 2008). In most assessments of executive function, information processing efficiency and speed affect task outcome; and vice versa, in most assessments of processing speed, demands are also placed on executive function. Thus all executive functions and fluid intelligence measurements are at least
in part polluted by processing speed and the pure speed measurements can be difficult to tap (Cepeda et al., 2013).

Thus, whether seen as a distinct domain, or an ingredient in, perhaps all cognitive abilities, processing speed is an important aspect of intelligence and executive function. Processing speed is dependent on the integrity of white matter tracts, and is linked to orientation of white matter in the whole brain (Ferrer et al., 2013; Turken et al., 2008). Slow processing speed is an indication that efficiency of, particularly, the prefrontal neural networks are suboptimal.

The integrative framework of executive function

Diamond (2013) depicts the three core executive functions as separate processes, with working memory and inhibition being dependent on each other, and cognitive flexibility occurring later in development and building on the two others. Another view on how to model executive function is the integrative framework proposed by Miyake and colleagues (2000). Their analyses of young adults led them to the conclusion that executive function was best modeled as three correlated but partially independent executive function components. Executive function thus shows both diversity (in the three clearly distinguishable components) and unity (the components share some underlying commonality). The three executive function components in the framework were those that had been most frequently studied at the time, namely Shifting, Updating, and Inhibition. The Shifting component corresponds to cognitive flexibility. Updating is related to working memory, the ability to not only keep in store, but actively manipulate information. It also reflects the ability to monitor and keep in mind information relevant to the task at hand. Finally, Inhibition refers to the ability to deliberately inhibit automatic responses, and more widely, it encompasses behavioral as well as cognitive control (Miyake et al., 2000). In a recent development of the model (Friedman et al., 2008; Friedman, Miyake, Robinson, & Hewitt, 2011; Miyake & Friedman, 2012), Inhibition did not explain variance over and above the common factor. The simplified model thus consisted of a common executive function factor as well as a Shifting Specific and an Updating Specific factor (see Figure 3). The common factor could be interpreted to reflect the ability to, during processing and specifically in the face of interference, maintain a goal; i.e. a form of executive or top-down attention (Friedman et al., 2011; Garon et al., 2008).
Although the integrative framework of executive function was based on young adult data, it has been successfully applied to populations with children. Letho and colleagues (2003) found that in 8- to 13-year-olds, a model with three separable and correlated factors provided the best fit for the data. Huizinga, et al. (2006) adapted the framework to assess executive function development. They found support for the latent factors of working memory and set-shifting, but not inhibition, over four age groups (7-, 11-, 15-, and 21-year-olds). A systematic review of executive functions from childhood to adolescence suggested that Miyake’s model serves as a suitable theoretical framework for investigating executive function development (Best & Miller, 2010). The framework is also used in a review of executive function in preschoolers (Garon et al., 2008). Although some evidence is accumulating as to the value of using the framework proposed by Miyake and colleagues for describing typical executive function development, its use on clinical child populations has been less investigated. To date, the framework has been applied to cross-sectional rather than longitudinal data.

In the framework of executive functions proposed by Diamond as well as in the more recent development of the executive function framework proposed by Miyake and colleagues, inhibition at the level of attention (also referred
to as selective attention or executive attention) is crucial. The development of the attention systems and their connectivity with other neural networks involved in the executive function components, is proposed to serve as a basis for all executive function development. In this development, attention might be a factor shared by the core executive function components or the factor common in all executive function tasks (Friedman et al., 2011; Garon et al., 2008). If attention is a basis on which all executive functions rest, then attention problems, whenever they initially occur, are likely to adversely affect other executive function components throughout development. This could also imply that very early brain insult presumably would impact development of attention, with more global or diffuse effects on executive functions later in development (Garon et al., 2008).

It is well established that an aberration, developmental or acquired, to typical brain development places the child at risk of executive dysfunction. Poor attention and self-regulation may impair reasoning abilities and flexible thinking, and negatively impact the capacity to learn and interact with the environment (V. A. Anderson, Anderson, et al., 2008). Executive dysfunction has been reported in children with autism spectrum disorders, attention-deficit disorders, after traumatic brain injury and cranial radiation, and in children born preterm (V. A. Anderson, Anderson, et al., 2001; Pennington & Ozonoff, 1996; Pennington, 2009). Functioning of the prefrontal cortex seems to be dependent on the integrity of the entire brain during development. Disruptions in other brain areas may disrupt typical prefrontal development and adversely affect connections and function. In children, it is likely that injury anywhere in the brain will lead to executive dysfunction (V. A. Anderson, Jacobs, & Harvey, 2008).
Perinatal stress and disruptions in brain development

The long-term effects of two perinatal stressors, which can lead to disruptions in brain development, are investigated in this thesis. These stressors are preterm birth and repeat antenatal corticosteroid treatment.

Preterm birth

Being born preterm, and especially very or extremely preterm, is a serious stressor to the organism and hence to brain development. During the time in gestation, the brain is in a rapid state of development and is vulnerable to insults. Through premature birth, the immature brain is exposed to an environment that is very different to that of the womb. Light, noise, and the stress and pain of medical interventions, and possibly further complications, may alter typical brain development and place the preterm infant at risk of suboptimal development (Perlman, 2001).

Definitions and prevalence

A pregnancy reaches term after 40 weeks’ of gestation; the expected due date is based either on the date of the last menstrual period, or ultrasound dating at 17-18 postmenstrual weeks. As conception occurs approximately two weeks after menstruation, the fetus is in effect 34 weeks old at the gestational age of 36 weeks. Preterm birth is defined as delivery before 36 completed weeks of gestation, and is further classified as moderately (32-36 weeks), very (28-31 weeks), or extremely (≤ 27 weeks) preterm. Sometimes, and especially historically in research, birth weight was used as a proxy for preterm birth. Low birth weight, < 2,500 g, very low, < 1,500 g, and extremely low birth weight, <1,000 g, are commonly seen classifications. However, birth weight is a function of both gestational age and individual fetal growth, and infants born with low birth weight are not necessarily born preterm.

In Sweden, about 6 percent of all pregnancies end in preterm birth, and one to two percent end prior to the gestational age of 32 weeks. Overall, neonatal
mortality, i.e. death in the first four weeks of life, has decreased in the last four decades, and this is especially true for infants born very or extremely preterm. Advances in neonatal medical care and centralization of care to specialized neonatal care units lie behind reductions in mortality rates, and have also changed the spectrum and rates of morbidity among the preterm-born children. Neonatal mortality and morbidity is inversely related to gestational age, and of the tiniest infants, weighing less than 500 g (average gestational age 23 weeks), only 17 % survive (Johansson & Cnattigius, 2010). Neonatal intensive care has developed rapidly over the past fifty years, shifting the border of viability to lower gestational ages and limiting neurological damage. Survivors of preterm birth who today have reached adulthood, thus reflect neonatal care practices that have since changed profoundly. Conclusions drawn from long-term follow-up studies should therefore be generalized with caution (Wyatt, 2010).

**Neonatal medical complications**

Very and extremely preterm infants have immature lungs, brains, and digestive systems – all which require monitoring and care. Although providing sufficient nutrition, maintaining temperature and avoiding infections are essential, limiting or preventing injuries to the vulnerable brain is paramount. In this vein, supporting the immature lungs of an infant born very or extremely preterm is extremely important. Prior to managed care with antenatal corticosteroids, postnatal surfactant treatment, and more gentle ventilation, episodes of cardiovascular collapse and recovery were frequent, with detrimental effects to the brain as a consequence.

Intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL) are common medical complications of preterm birth. IVH, i.e. bleeding in highly vascularized tissue in the vicinity of the ventricles, is associated with fluctuations in cerebral perfusion and venous pressure. If localized, poor outcome can be avoided, whereas bleeding extending into the brain tissue often has poor prognosis and might even lead to a decision to end care. Administration of antenatal corticosteroids to pregnant women at risk of delivering prior to 34 weeks of gestation has proved highly beneficial for fetal lung maturation. The reduction of respiratory distress decreases the incidence of IVH, but the steroids also seem to have a protective effect on cerebral vasculature (D. Roberts & Dalziel, 2006). PVL, a type of damage to brain white matter, is related to hypoxia and inflammation shortly after birth, or during a clinical deterioration, and develops over the following weeks. White matter injury is often accompanied by changes in the cortex, suggesting secondary consequences for cortical development (Volpe, 2009). Some forms of PVL are linked to cerebral paresis (Wyatt, 2010). Severe, cystic, PVL was more common ten to 15 years ago, but with advances in neonatal
care, rates are reducing. Instead, the most common form of brain lesions are diffuse white matter abnormalities (Back, Riddle, & McClure, 2007; Volpe, Kinney, Jensen, & Rosenberg, 2011). These are reported to range from mild to severe and they affect up to 70% of children born very preterm (Cheong et al., 2009; Volpe et al., 2011). Hypoxia and problems with oxygenation may also lead to Retinopathy of prematurity, ROP, an overgrowth of blood vessels in the retina of the eye which can in turn lead to visual impairment or blindness. Although the incidence of IVH and the negative effects of oxygenation on the brain and eyes have been reduced as a result of improved care, chronic lung disease is still a significant problem in preterm birth. Other medical conditions common in preterm birth are heart problems, inflammations, sepsis, and necrosis of the bowel (Johansson & Cnattigius, 2010).

Neurodevelopmental outcome

There is a risk of neurodevelopmental deficits after preterm birth, and particularly so if the child has suffered medical complications. Major disabilities are often identified early and include moderate or severe intellectual disability, cerebral palsy, visual or auditory impairments, and epilepsy. The more common milder deficits become obvious with increasing age as expected development is hampered. These more subtle dysfunctions are found in 50-70% of children born very preterm (Aylward, 2010), and may affect behavioral, intellectual, and educational outcome. Cognitive deficits reported in children born preterm include low intelligence, visual motor problems, deficient memory, delayed language skills, and executive dysfunctions. Social and emotional difficulties, specifically withdrawal and poor social skills, are also more common. Increased prevalence of ADHD and autism spectrum disorders has been reported. The group also has high rates of learning disabilities (P. J. Anderson, Howard, & Doyle, 2010).

Milder dysfunctions may be a result of the disruption to typical brain development that premature birth \textit{per se} involves. Vulnerable processes, such as cortical alignment and layering, synaptogenesis, and the migration and proliferation of the precursor cells that are instrumental for myelination (the oligodentrogial cells), are affected by the abnormal extrauterine environment. Thus, the brain of an infant born preterm presumably does not have the same organization as that of the full-term infant (Aylward, 2005). Even without apparent early injury (such as IVH or cystic PVL), aberrations in brain volume and structure are found. Reported abnormalities include reduced volumes of cerebral gray matter, hippocampi, amygdalae, and basal ganglia; enlarged ventricles; white matter lesions, reduced white matter volume, and thinning of the corpus callosum (P. J. Anderson & Doyle, 2003; Aylward, 2005; Nagy et al., 2009; Peterson et al., 2000). In relatively recent follow-up reports, diffuse white matter abnormalities have been specifically...
linked to executive deficits (Hart, Whitby, Griffiths, & Smith, 2008; Woodward, Clark, Pritchard, Anderson, & Inder, 2011).

With regards to general cognitive ability, as measured by IQ, the majority of school-aged children born very or extremely preterm perform within the normal range (Aylward, 2005; Bhutta, Cleves, Casey, Cradock, & Anand, 2002; Böhm, Katz-Salamon, Smedler, Lagercrantz, & Forssberg, 2002; S. Johnson, 2007). However, their mean scores are lower than is the case for their term-born peers, with reported differences typically ranging from 0.3 to 0.6 standard deviations when children with major disabilities are excluded. Also, there is a higher percentage of IQ-scores in the range bordering on intellectual disability, i.e. scores in the 70-85 span (Aylward, 2005). On a group level, IQ scores are negatively correlated with gestational age and birth weight (Bhutta et al., 2002). The pattern seems to hold for children born in the 1990s, when surfactant and antenatal steroids became prevalent (P. J. Anderson & Doyle, 2003). At gestational ages < 33 weeks, mean IQ scores decrease by an average of 1.5 to 2.5 points per gestational week (S. Johnson, 2007). However, there seems to be indications that among the moderately preterm, intrauterine growth restriction is more strongly associated with cognitive depreciation than preterm birth per se (Lundequist, Böhm, Forssberg, Lagercrantz, & Smedler, 2014; Lundequist, 2012). Non-verbal reasoning and visuo-spatial abilities are often attenuated and a discrepancy between verbal IQ and non-verbal (performance) IQ is common (Aylward, 2005; Böhm et al., 2002; S. Johnson, 2007). In individuals born preterm and subject to the care provided in the late 1970s or early 80s, the low but within normal range of general cognitive ability seems to persist into adulthood (Allin et al., 2008; Hack, 2009; Hack et al., 2002).

As discussed earlier, general cognitive ability is an aggregate measurement, which can mask intraindividual variability in function. In order to increase understanding of outcome after preterm birth, executive function has received increasing attention. Even a subtle depreciation in executive function may influence cognitive, social, and academic functioning. Executive function deficits are related to lower IQ scores, have generalized effects on knowledge acquisition, and also affect social interaction and adaptive functioning.

Consequences for executive functions

Studies reporting executive function outcome in children born preterm vary in terms of sample selection and chosen outcome measures, making it difficult to draw definite conclusions. Samples differ on inclusion criteria (gestational age and birth weight cut-offs), birth years, ages at follow-up, representativeness of groups (hospital vs. geographic), socioeconomic status, and
sample size. Perhaps more challenging when comparing results across studies is the great variation in operationalization and choice of tasks in measuring executive functions. The functions reported thus represent very different aspects of executive and often also non-executive functions (Howard, Anderson, & Taylor, 2008). Also, although a more perilous outcome is associated with lower gestational age and perinatal medical complications, the individual variability is large, with children of similar background exhibiting very different outcomes (P. J. Anderson et al., 2010; Lundequist, Böhm, & Smedler, 2013). A meta-analysis of children born preterm and older than 5 years at follow-up found that executive functions (verbal fluency, working memory, and cognitive flexibility) were significantly poorer in the preterm group compared to controls. The effect sizes were small to medium, ranging from -0.36 to -0.57 standard mean differences (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosterlaan, 2009).

There are few studies on executive function in infants and toddlers born preterm, but those available indicate that attention and working memory deficits are present in the group at this early age, and may be related to diffuse white matter abnormalities (P. J. Anderson et al., 2010).

Studies of executive function in preterm-born children in the preschool and school years are more common. When summarized, at least subtle deficits in all aspects of executive function are reported, and the difficulties are more pronounced among the most preterm-born and where perinatal complications are recorded (P. J. Anderson et al., 2010; Mulder, Pitchford, Hagger, & Marlow, 2009). Our research group reported deficits in impulse control and working memory as well as more complex executive function in a group of 182 5½-year-old children born preterm and with very low birth weight (Böhm, Smedler, & Forssberg, 2004). Bayless and Stevenson (2007) in a study of 40 children aged 6 to 12 years and born ≤ 32 gestational weeks found significantly lower results in measurements of shifting and inhibition but not working memory compared to age-matched peers. Anderson and Doyle (2004) found in their study of 275 8-year-olds born preterm (<28 gestational weeks or <1,000 g) in the late 1990s significantly lower scores on a range of executive function measurements compared to a matched control group. The measurements used in Anderson and Doyle’s follow-up included more complex executive function tasks such as planning and reasoning.

The few studies of adolescents and adults that do exist show that the risk of executive function deficits remains, and that executive dysfunction may mediate the relationship between preterm birth and below average academic achievement and social competence (P. J. Anderson et al., 2010; Burnett, Scratch, & Anderson, 2013; Luu, Ment, Allan, Schneider, & Vohr, 2011). At age 16, those born with a birth weight of <750 g performed below full-term
controls in all executive function tasks. Those born with a higher birth weight (750 – 1,499 g) did not significantly differ in performance compared to the controls, although a gradient effect of birth weight could be observed (Taylor, Minich, Bangert, Filipke, & Hack, 2004). Saavalainen and colleagues (2007) found that in adolescents born preterm, working memory and processing speed were at the same level as term-born peers. In contrast, Wilson-Ching and colleagues (2013) found that attention remained a weakness at age 17 for extremely preterm-born adolescents, and that the association with perinatal medical complications was limited. In our study group, executive functions also remained a specific weakness at age 18 and this was exacerbated by perinatal medical complications (Lundequist et al., 2014; Lundequist, 2012). Among young adults born very preterm in the late 1970s and early 80s, executive function deficits, identified at school age, persisted. The deficits were not linked to perinatal medical complications (Nosarti et al., 2007). In sum, the question of whether executive function deficits identified in younger children persist into adolescence and adulthood or if there is a reduction in deficits, perhaps as a result of compensatory strategies or brain plasticity, remains unanswered.

In infants and toddlers born preterm, information processing, including attention and processing speed, has been reported as a specific weakness. Processing deficiencies were also linked to lower general cognitive ability (Rose, Feldman, & Jankowski, 2002, 2009), and processing speed deficits explained some, but not all, executive deficits (Aarnoudse-Moens, Smidts, Oosterlaan, Duivenvoorden, & Weisglas-Kuperus, 2009). Processing speed, via executive function and particularly working memory, mediated the relationship between preterm birth and school achievement in pre-adolescence (Rose, Feldman, & Jankowski, 2011). Also among children born very preterm and without obvious brain abnormalities, reductions in white matter density were present; and these white matter reductions were associated with deficits in processing speed (Soria-Pastor et al., 2008).

Antenatal corticosteroid treatment

One of the most significant developments in perinatal care in the last 30 years has been the administration of antenatal corticosteroids (ACS) to pregnant women at risk of delivering prior to 34 weeks of gestation. Since Liggin’s and Howie’s seminal study in 1972 accumulated evidence has shown that a single course of ACS significantly reduces neonatal mortality and severe neonatal morbidity - such as respiratory distress and IVH - without adverse long-term effects (Crowley, Chalmers, & Keirse, 1990; Dalziel et al., 2005; National Institutes of Health Consensus Development Panel, 1995; D. Roberts & Dalziel, 2006). Due to difficulty in predicting preterm birth
combined with indications that the positive effect of ACS treatment on promoting lung maturation diminishes after about a week, it became practice to repeat the treatment, weekly or biweekly until birth or 33 completed weeks of gestation. In the late 1990s repeat courses had become common practice in the USA. However, animal models and early follow-up studies on humans indicated that repeat courses were associated with unwanted effects on growth, behavior, and stress response, which in the early 2000s led to recommendations to confine repeat courses to controlled clinical trials (Kapoor, Petropoulos, & Matthews, 2008; National Institutes of Health Consensus Development Panel, 2001).

Corticosteroids and developmental programming

Low birth weight is associated with metabolic and cardiovascular as well as affective and cognitive disorders in adult life (Harris & Seckl, 2011; Matthews, Owen, Banjanin, & Andrews, 2002; Osterholm, Hostinar, & Gunnar, 2012; Reynolds, 2013). Birth weight per se is not regarded as the cause of these disorders, but is seen as an indication of an adverse fetal environment, such as fetal under-nutrition and fetal exposure to excess glucocorticoids (Harris & Seckl, 2011). The association between an environmental challenge in utero, altered fetal growth and development, and subsequent development of disorders is referred to as developmental programming. Glucocorticoids, the main hormonal mediator of stress, have strong programming properties (Welberg & Seckl, 2008). Elevated levels of endogenous glucocorticoids in the fetus can result from under-nutrition, high maternal anxiety, or the stress of preterm birth; synthetic glucocorticoids (betamethasone or dexamethasone) are administered in ACS treatment.

Cortisol, the most important human glucocorticoid, plays an important part as the end-product of the Hypothalamic-Pituitary-Adrenal (HPA) axis endocrine system. The hippocampus and amygdalae also take a role in the control of HPA activity (Welberg & Seckl, 2008). The HPA axis is often referred to as the stress system, as it is active in coping with and adapting to stressful situations. The system is also vital in maintaining homeostasis, where the glucocorticoids influence metabolism, and regulate cardiovascular, neurobiological, and immunological functions. Because of the damaging effects of extended tissue exposure to glucocorticoids, the HPA axis is tightly regulated (Kapoor, Dunn, Kostaki, Andrews, & Matthews, 2006), and in non-stress conditions, 95% of the cortisol is bound in the plasma and is then biologically inactive (Tegethoff, Pryce, & Meinlschmidt, 2009). Prenatal stress has long-lasting effects on the adult HPA axis, programming the endocrine system to be a hyperactive system (Welberg & Seckl, 2008). Elevated concentrations of cortisol have been associated with anxiety disorders, depression, hyperactivity, autism spectrum disorders, immunosuppression, incidence of
diabetes, and cognitive impairment (Harris & Seckl, 2011; Tegethoff et al., 2009).

Endogenous glucocorticoids play a vital role in typical brain development. They exert their influence on a wide range of processes such as neuronal maturation and interaction, and synaptic stabilization. However, too high or too low levels may be detrimental to these processes, resulting in permanent changes in structure and function (Matthews et al., 2002). Glucocorticoids also interact with the brain neurotransmitter systems (serotonin, dopamine, epinephrine, and norepinephrine) in modulating HPA activity. The effects of prenatal stress on behavior and cognition could be mediated by permanent alterations to the transmitter systems (Welberg & Seckl, 2008). Poor regulation of HPA activity is linked to disrupted dopaminergic activity in the prefrontal cortex (Rodrigues, Leão, Carvalho, Almeida, & Sousa, 2011). Dopamine plays an important role in regulating executive functions in the prefrontal cortex (Blair, 2006; Diamond & Amso, 2008; Diamond, Prevor, Callender, & Druin, 1997).

Under normal circumstances, access of maternal endogenous glucocorticoids to the fetus is low. In the placenta, the enzyme 11β-HSD2 selectively regulates the transplacental passage of endogenous glucocorticoids. Therefore, typically the fetus has much lower concentrations of these glucocorticoids than its mother (Tegethoff et al., 2009). However, disturbances to the system can occur due to malfunctioning of the barrier, high levels of maternal stress, or poor nutrition. High maternal anxiety levels are linked to poorer emotional and cognitive outcome in children, possibly mediated by HPA activity (Talge, Neal, & Glover, 2007; Van den Bergh, Mulder, Mennes, & Glover, 2005). In addition, synthetic corticosteroids are hindered in the placenta to a much lesser degree than the mother’s endogenous stress hormones, allowing for a higher concentration passing to the fetus. The synthetic glucocorticoids also widely affect the developing brain, primarily modulating neuroendocrine function and delaying myelination rather than exerting modifications to brain structure. The timing and dose is related to outcome. (Harris & Seckl, 2011; Matthews et al., 2002).

Outcome after repeat ACS treatment

In a review of the effect of repeat vs. single courses of corticosteroids on animal models (monkeys, sheep, rabbits, and mice), Aghajafari and colleagues (2002) concluded that although benefits to lung function were found in sheep and mice, there was an effect of growth restriction in all species. There were also indications of restrictions to brain maturation and brain growth, although the consequence of this remained unknown. In sheep specifically, repeat courses of corticosteroids improved lung maturation and
function and adversely affected birth weight and brain size. Repeat courses were linked to reduced myelination in, among other areas, the corpus callosum. It is likely that the corticosteroids alter glial cell (oligodentrocyte) function, thereby inhibiting myelination (Huang, Harper, Evans, Newnham, & Dunlop, 2001; Moss et al., 2001; Newnham & Jobe, 2009). A study of common marmoset monkeys indicated that fetal overexposure to glucocorticoids was associated with abnormal development of motor, affective, and cognitive behaviors and that outcome differed with regard to the timing of exposure (Hauser et al., 2008).

An early American follow-up study of children exposed to ACS indicated that the incidence of lung disease and brain hemorrhages did not decrease with repeat courses; rather the repeat courses were associated with reductions in birth weight and increased mortality for those exposed to ≥ 3 courses (Banks et al., 1999). Likewise, in a Western Australian cohort, repeat courses did not lead to decreased morbidity, but were instead associated with decreased weight and smaller head circumference (French, Hagan, Evans, Godfrey, & Newnham, 1999). Neurodevelopmental follow-up of the Western Australian cohort at ages 3 and 6 years, found that an increased number of courses was associated with a reduced incidence of cerebral palsy and that there were no differences in general cognitive ability, or in internalizing behavior. However, repeat courses were associated with an increased risk of aggressive-destructive behavior, hyperactivity, and distractibility (French, Hagan, Evans, Mullan, & Newnham, 2004). Spinillo and colleagues (2004) found that repeat courses could have adverse effects on neurodevelopmental outcome in 2-year-old infants, but that this was true primarily for those exposed to dexamethasone rather than betamethasone.

Large randomized controlled trials have reported conflicting results with regards to morbidity and neonatal anthropometrics. The Australasian Collaborative Trial of Repeat Doses of Steroids (ACTORDS) study group found that repeat courses reduced neonatal morbidity (Crowther, Haslam, Hiller, Doyle, & Robinson, 2006). By contrast, the Multiple Courses of Antenatal Corticosteroids for Preterm Birth (MACS) randomized controlled trial and the National Institute of Child Health and Human Development (NICHD) study could not confirm improved outcomes after repeat courses of ACS (Murphy et al., 2008; Wapner et al., 2006). However, all three trials reported that repeat treatments were associated with decreased weight, length, and/or head circumference at birth. The latest Cochrane review concluded that repeat courses of ACS were associated with a reduction in the incidence and severity of neonatal lung disease, and a small reduction in size at birth (Crowther, McKinlay, Middleton, & Harding, 2011). Follow-up at 18 months to five years of age, found no effect on morbidity, anthropometrics, or general cognitive ability (Asztalos et al., 2010, 2013; Crowther et al.,
ACTORDS reported that although overall child behavior was similar between the treatment groups, a higher proportion of children exposed to repeat courses reached the clinical range of scores for attention problems (Crowther et al., 2007). The NICHD study reported that, although not a statistically significant over-representation, five of six cases of cerebral palsy were found in the repeat group (Wapner et al., 2007).

The possible beneficial effect on respiratory function after repeat ACS treatment thus seems accompanied by a reduction in fetal growth. The smaller head circumference at birth raises questions as to effects on brain development, in particular myelination. Long-term effects, and outcome beyond the early school years, are still largely unknown (Newnham & Jobe, 2009) and long-term follow-up studies on behavior, cognition, and stress response are still pending.

Moderating factors: sex and parental education

The increased risk of adverse outcome with lower gestational age and lower birth weight has been discussed above, as have the risks associated with perinatal medical complications as well as excess glucocorticoid exposure. Sex of the infant and socioeconomic conditions are factors known to influence individual development and to moderate the effects of disruptions in brain development.

Sex

There is evidence that females have an advantage over males in the perinatal period, in particular in the face of preterm birth. The death rate is higher for male fetuses and boys are more likely to be delivered prematurely. Perinatal death is also more prevalent among males, especially at lower gestational ages. In addition, boys have less favorable cognitive development as compared to girls following IVH (Ingemarsson, 2003). Boys also may have an increased risk of developing cognitive problems after extremely preterm birth, although evidence is inconclusive (Marlow, Wolke, Bracewell, & Samara, 2005; Mulder et al., 2009; Serenius et al., 2013). With regards to executive functions, the effects of sex are inconsistent. However, boys seem to be more at risk of executive or attention deficits, although not conclusively so (Lundequist, 2012; Marlow, Hennessy, Bracewell, & Wolke, 2007; Martel, Lucia, Nigg, & Breslau, 2007; Mulder et al., 2009). In typical brain development, timing and function seem to vary between sexes, primarily due to hormonal factors (Kolb & Wishaw, 1996). The female brain is presumably more diffusely organized and may therefore hold greater potential for reorganization of function and perhaps ability to cope with early insults (V.
A. Anderson, Northam, et al., 2001). The effect of synthetic glucocorticoids also has sex-specific implications, indicating that in developmental programming of the HPA axis, several other endocrine systems, including the transmitter systems, are involved (Kapoor et al., 2006; Matthews et al., 2002).

Parental education

Parents’ socioeconomic status (SES) – income, education, and occupation – affect a child’s life outcome, with children raised in low SES families showing poorer cognitive and academic development on a group level (Davis-Kean, 2005; G. Roberts, Bellinger, & McCormick, 2007). This may be especially true for children born preterm, where negative effects of perinatal medical complications may be exacerbated for children from low SES families (Aylward, 1992; Ford et al., 2011). Higher maternal education is reported to be associated with a lack of deterioration in cognitive outcome over time, and improvement in cognitive scores were reported as more likely in children living in more well-off neighborhoods (Wong & Edwards, 2013). In Sweden, where maternal and child medical care is publicly funded and universally provided, differences in outcome after preterm birth can hardly be explained by differences in the quality of care related to family income. Rather, the implication may be that well-educated parents are more likely to ensure and provide favorable learning environments for their children, including providing practice in sustained attention and development of strategies for planning and problem-solving (Davis-Kean, 2005; Ford et al., 2011). Blair (2006) has suggested that families with higher SES may be able to provide an environment that enables HPA axis deactivation, and thus enhancing connections between the prefrontal cortex and limbic regions. On a group level and in an egalitarian society such as Sweden, parents with higher education are likely to reflect a genetically based cognitive advantage. This, in combination with the family environment, might in children with more highly educated parents leave some room for attenuation in cognitive function without this becoming a liability.
Aims of the thesis

This thesis investigates long-term developmental outcome in two cohorts of adolescents and young adults who were exposed to stressful events during the perinatal period. The first cohort consisted of children born preterm - prior to 37 weeks of gestation and with a birth weight of less than 1,500 g. The second cohort consisted of children exposed to two or more courses of ACS treatment as they were at risk of being born preterm. Cognitive outcome after preterm birth is fairly well researched; however, longitudinal studies of executive function development are important contributions to the field. Moreover, although on a group level, evidence of outcome after preterm birth is accumulating, there is little knowledge about individual cognitive patterns and developmental trajectories among those born preterm. Previously, there have been no follow-up studies beyond the early school years on the effect of exposure to repeat courses of ACS on cognition and psychological functioning. The general aim of this thesis was to investigate how exposure to perinatal stress, as exemplified by preterm birth or excess fetal glucocorticoid exposure, might affect development and, as a result, executive function. Specifically, my aim was to study:

- Stability and prediction of executive function development from early childhood to late adolescence after very or extremely preterm birth.
- Individual cognitive patterns and developmental trajectories after preterm birth.
The empirical studies

Studies I and II are based on data from the Stockholm Neonatal Project (SNP). Study III is based on data from the Fetal Antenatal Steroid Treatment Study (FAST). I was invited to do research within the SNP after the data collection at 18 years was completed. My contribution to Study I was taking the lead in the statistical analyses and write-up. In Study II, I formulated the research question, led the statistical analyses and was the main author. In FAST, the research aim was broadly defined and the index participants identified when I came aboard. In this project I contributed to study design, identified reference group participants, coordinated the data collection, and conducted the psychological assessment of all participants. For Study III, I was responsible for the statistical analyses and took a lead in the write-up.

Below, the projects, their participants, data collections, and test variables are described, and some ethical points are discussed. That is followed by a section on statistical methods and considerations. Study aims, results, and major conclusions are presented for each study separately.

Stockholm Neonatal Project

The Stockholm Neonatal Project (SNP) is a longitudinal prospective population-based study of preterm children (gestational age < 37 weeks) with a birth weight less than 1,500 g, born in Stockholm, Sweden. In the initial recruitment process, all children who met these inclusion criteria and were born between September, 1988 and March, 1993 at Karolinska Hospital and at Löwenströmska Hospital in Stockholm were invited through their parents to participate from birth and onwards. In addition, during the same time period, all children from the entire county of Stockholm who were born with a birth weight less than 1,000 g and who were in need of neonatal intensive care at Karolinska Hospital were invited to participate. A total of 291 newborns were invited, of which eight percent declined to participate, and another 18 percent died during the neonatal period, leaving 213 children in the initial cohort.
During the perinatal period, extensive medical data was obtained from these 213 participants. At age 10 months (age corrected for preterm birth), a developmental assessment using Griffiths’ Mental Development Scales (Lindstam, 1968) was conducted.

The 213 children from the initial cohort were invited for a follow-up at age 5½ years. At that time, 19 families had moved away from the area and 13 declined to participate, leaving 181 preterm-born children available for assessment. The assessment took place at Astrid Lindgren’s Children’s Hospital at 5½ ± 2 weeks corrected age. All the children were assessed during morning hours by the same child neuropsychologist, Birgitta Böhm. The NEPSY 4-7 (Korkman, 1990) and Knox Cubes (Arthur, 1947) were administered the first morning and the WPPSI-R (Wechsler, 1999) the next day. The full WPPSI-R was not originally part of the test protocol and 16 of the preterm participants were assessed prior to its introduction. Results from the 5½ year assessment have been reported previously (Böhm et al., 2002; Böhm, Lundequist, & Smedler, 2010; Böhm et al., 2004; Lundequist et al., 2013).

All the children who participated in the 5½ years assessment were again invited for another follow-up at 18 years. Ten families had moved and their address could not be found, and twelve declined to participate. In addition, 24 failed to reply. One preterm male was unable to complete the test protocol due to intellectual disability. Hence 134 preterm-born 18-year-olds completed the assessment. We assessed the participants individually at Astrid Lindgren’s Children’s Hospital at age 18 years ± 3 weeks. The assessment lasted for 3.5 to 4 hours and tests were administered in the same order, starting with eight subtests from WISC-III (Wechsler, 1991), followed by selected tests from D-KEFS (Delis, Kaplan, & Kramer, 2001), and Corsi Blocks from WAIS-III NI (Wechsler et al., 2004). Brief descriptions of the tests used in Study I and Study II are presented in Tables 1 and 2. Fifteen master level students who were in their last year of the clinical psychology program at Stockholm University performed the assessments. They were trained and supervised by Birgitta Böhm, Aiko Lundequist, and Ann-Charlotte Smedler. Results on cognitive outcome at age 18 are in the process of being published (Lundequist et al., 2014).

At age 5½, a control group (n = 125) was recruited and assessed. The controls were children born at term on the same day, at the same hospital as the preterm children. To be eligible for inclusion, the child had to be born ≥ 37 weeks of gestation, have a birth weight over 2,500 g, and be classified as a healthy baby at birth. After invitation to the follow-up study at age 18, 94 of the controls chose to participate, and went on to complete the assessment. The control group scores are used as reference scores in studies I and II.
Table 1.
SNP Included test variables and indices at age 5½ years.

<table>
<thead>
<tr>
<th>Functions and tests</th>
<th>Test description</th>
<th>Study I</th>
<th>Study II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Index</td>
<td>Index</td>
</tr>
<tr>
<td><strong>Verbal Ability</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comprehension (WPPSI)</td>
<td>Questions about social situations or common concepts.</td>
<td>VFI-5</td>
<td></td>
</tr>
<tr>
<td>Information (WPPSI)</td>
<td>General knowledge questions.</td>
<td>VFI-5</td>
<td></td>
</tr>
<tr>
<td>Similarities (WPPSI)</td>
<td>The child is asked to explain how two words (nouns) are similar.</td>
<td>VFI-5</td>
<td></td>
</tr>
<tr>
<td>Vocabulary (WPPSI)</td>
<td>The child is asked to define words of increasing difficulty.</td>
<td>VFI-5</td>
<td></td>
</tr>
<tr>
<td><strong>Non-Verbal Ability</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Block Design (WPPSI)</td>
<td>The child is asked to put together red-and-white blocks in a pattern according to a displayed model.</td>
<td>PFI-5</td>
<td></td>
</tr>
<tr>
<td>Geometric Designs (WPPSI)</td>
<td>The child is asked to copy simple geometric designs.</td>
<td>PFI-5</td>
<td></td>
</tr>
<tr>
<td>Object Assembly (WPPSI)</td>
<td>The child is presented with the pieces of a puzzle in a standard arrangement and fits the pieces together to form a meaningful whole within 90 seconds.</td>
<td>PFI-5</td>
<td></td>
</tr>
<tr>
<td>Picture Completion (WPPSI)</td>
<td>The child is shown artwork representing common objects with a missing part, and asked to identify the missing part by pointing to and/or naming it.</td>
<td>PFI-5</td>
<td></td>
</tr>
<tr>
<td><strong>Working Memory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arithmetic (WPPSI)</td>
<td>Simple arithmetic problems.</td>
<td>Working Memory 5½</td>
<td></td>
</tr>
<tr>
<td>Digit Span (NEPSY)</td>
<td>The child is asked to repeat in exact order an increasing number of digits.</td>
<td>Working Memory 5½</td>
<td>5</td>
</tr>
<tr>
<td>Knox Cubes</td>
<td>The examiner taps a sequence on four cubes attached horizontally to a wooden board and the child has to repeat it in the correct order.</td>
<td>Working Memory 5½</td>
<td>5</td>
</tr>
<tr>
<td><strong>Cognitive Flexibility and Speed</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Animal Pegs (WPPSI)</td>
<td>Requires the child to, as fast as possible, match animals to colored pegs on a board according to a code.</td>
<td>Cognitive Flexibility 5½</td>
<td>CFI-5</td>
</tr>
<tr>
<td>Verbal Fluency (NEPSY)</td>
<td>The child has to list as many animals he or she can think of in one minute, followed by generating a list of things you can eat or drink.</td>
<td>Cognitive Flexibility 5½</td>
<td>CFI-5</td>
</tr>
<tr>
<td>Color Shape (NEPSY)</td>
<td>The child is requested to point out a path across a board by alternating between similar shapes and similar colors.</td>
<td>Cognitive Flexibility 5½</td>
<td>CFI-5</td>
</tr>
<tr>
<td>Coding (WPPSI)</td>
<td>The child is asked to mark rows of shapes with different lines according to a code. Speed test.</td>
<td>CFI-5</td>
<td></td>
</tr>
</tbody>
</table>

*Note.* WPPSI refers to WPPSI-R; NEPSY to NEPSY 4-7; Swedish versions.
Table 2.  
SNP Included test variables and indices at age 18 years.

<table>
<thead>
<tr>
<th>Functions and tests</th>
<th>Test description</th>
<th>Study I Index</th>
<th>Study II Index</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Verbal Ability</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Similarities (WISC)</td>
<td>The participant is asked to explain how two words (substantives) are similar.</td>
<td></td>
<td>VFI-18</td>
</tr>
<tr>
<td>Vocabulary (WISC)</td>
<td>The participant is asked to define words of increasing difficulty.</td>
<td></td>
<td>VFI-18</td>
</tr>
<tr>
<td><strong>Non-Verbal Ability</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Block Design (WISC)</td>
<td>The participant is asked to put together red-and-white blocks in a pattern according to a displayed model.</td>
<td></td>
<td>PFI-18</td>
</tr>
<tr>
<td>Picture Completion (WISC)</td>
<td>The participant is asked to name the pertinent detail that is missing from a picture.</td>
<td></td>
<td>PFI-18</td>
</tr>
<tr>
<td><strong>Working Memory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arithmetic (WISC)</td>
<td>Arithmetic problems of increasing difficulty, are solved mentally within a time limit.</td>
<td>Working Memory 18</td>
<td></td>
</tr>
<tr>
<td>Cori Block Backwards (WAIS)</td>
<td>A spatial memory task whereby the participant is requested to point to blocks on a board in the exact opposite order as to the test administrator.</td>
<td>Working Memory 18</td>
<td>WMI-18</td>
</tr>
<tr>
<td>Digit Span Backwards (WISC)</td>
<td>An increasing number of digits have to be repeated in the exact opposite order as given by the test administrator.</td>
<td>Working Memory 18</td>
<td>WMI-18</td>
</tr>
<tr>
<td><strong>Cognitive Flexibility</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal Fluency 2 (D-KEFS)</td>
<td>Semantic categories. List as many words as possible in one minute that fit into the given category (animals and boys names, respectively).</td>
<td>Cognitive Flexibility 18</td>
<td>CFI-18</td>
</tr>
<tr>
<td>Trail Making 4 (D-KEFS)</td>
<td>Connect by drawing a line every other letter and every other digit. Letters in alphabetical order, digits in increasing order.</td>
<td>Cognitive Flexibility 18</td>
<td>CFI-18</td>
</tr>
<tr>
<td>Color-Word 3 (D-KEFS)</td>
<td>Stroop test. When reading the name of colors printed in different colors, the task is to name the printed color rather than read the print.</td>
<td>Cognitive Flexibility 18</td>
<td>CFI-18</td>
</tr>
<tr>
<td>Coding (WISC)</td>
<td>The task is to transcribe a digit-symbol code and complete as many as possible in 2 minutes.</td>
<td>Cognitive Flexibility 18</td>
<td>CFI-18</td>
</tr>
<tr>
<td>Symbol Search (WISC)</td>
<td>Rows of symbols and target symbols; the participant is asked to mark whether or not the target symbols appear in each row, and complete as many as possible in 2 minutes.</td>
<td>Cognitive Flexibility 18</td>
<td>CFI-18</td>
</tr>
</tbody>
</table>

*Note.* WISC refers to WISC-III, Swedish version; WAIS to WAIS-III NI.
In addition to the assessments and instruments listed above, a wide range of data has been collected within the SNP. This includes a motor development assessment in the preschool years, self-reports on psychological health and adjustment, parental questionnaires, brain imaging, and blood samples for DNA analysis. Results have been and are continuously being published.

Study I included the 115 participants born after a gestational age < 32 weeks, who participated in the assessments at both ages 5½ years and 18 years. Participant characteristics are presented in Table 3.

Study II included the 118 participants, born preterm (gestational age < 37 weeks) with a birth weight less than 1,500 g, who participated in the assessments at both ages 5½ years and 18 years, and who had been given the full WPPSI-R at age 5½ years. (Sixteen participants for whom WPPSI-R data were missing were excluded.) Participant characteristics are presented in Table 3.

Fetal Antenatal Steroid Treatment Study

The Fetal Antenatal Steroid Treatment Study (FAST) emanated from neurocognitive as well as clinical queries, and was a cross-disciplinary venture. The prospective cohort study was designed to ascertain compatibility with translational studies and with the SNP cohort.

Danderyd’s Hospital, Stockholm, was the first hospital in Sweden to implement ACS treatment for women with threatening preterm delivery. During the years 1983 to 1996, the standard ACS treatment consisted of an initial course of betamethasone 24 mg intramuscularly (8mg q 8h), followed by weekly courses of 12 mg betamethasone continued until delivery or until pregnancy reached 34 gestational weeks. From a prospectively collected hospital registry including all mothers undergoing antenatal care and all infants admitted for neonatal care, 94 infants exposed to repeat (two to nine) courses of ACS were identified. Predefined exclusion criteria included maternal steroid use for other medical conditions, fetal anomalies, congenital viral infections, and chromosomal aberrations. In the cohort, the majority were born moderately preterm or at term, and there were no subjects who suffered from significant IVH or who developed PVL. One subject suffered from ROP. Neonatal anthropometric analyses of the cohort found a dose-dependent reduction in weight, length, and head circumference at birth (Norberg et al., 2011).
<table>
<thead>
<tr>
<th>Study I (n = 115)</th>
<th>Study II (n = 118)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>M ± SD or No (%)</strong></td>
<td><strong>Range</strong></td>
</tr>
<tr>
<td><strong>Gestational age at birth (weeks)</strong></td>
<td>27.0 ± 2.0</td>
</tr>
<tr>
<td>Extremely preterm (≤ 27 weeks)</td>
<td>73 (63.5%)</td>
</tr>
<tr>
<td>Very preterm (28-31 weeks)</td>
<td>42 (36.5%)</td>
</tr>
<tr>
<td>Moderately preterm, low birth weight (32-36 weeks; &lt;1,500 g)</td>
<td>-</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>971 ± 236</td>
</tr>
<tr>
<td>Intrauterine growth (BWSDS)</td>
<td>-1.3 ± 1.4</td>
</tr>
<tr>
<td>Male sex</td>
<td>53 (46.1%)</td>
</tr>
<tr>
<td><strong>Perinatal medical complications</strong></td>
<td>-</td>
</tr>
<tr>
<td>0 risk factors</td>
<td>77 (67.0%)</td>
</tr>
<tr>
<td>1 risk factor</td>
<td>28 (24.0%)</td>
</tr>
<tr>
<td>2 risk factors</td>
<td>9 (7.8%)</td>
</tr>
<tr>
<td>3 risk factors</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>Mother’s age at child’s birth (years)</td>
<td>32.3 ± 5.5</td>
</tr>
<tr>
<td>Mother’s educational attainment</td>
<td>4.1 ± 1.4</td>
</tr>
<tr>
<td>Father’s educational attainment</td>
<td>4.1 ± 1.5</td>
</tr>
<tr>
<td>Griffiths’ Mental Development Scales at 10 months’ (n = 99), sum of A-E scales’ stanine scores</td>
<td>24.6 ± 9.1</td>
</tr>
</tbody>
</table>


Perinatal medical complications are defined as severe levels of Intraventricular hemorrhage (IVH; grade III-V), periventricular leukomalacia, (PVL; grade III-IV), chronic lung disease (CLD), and retinopathy of prematurity (ROP; 3+).

Parental education attainment level as classified by Statistics Sweden (2000). 0 = no education, 1 = non-complete compulsory education, 2 = completed compulsory education (9 yrs), 3 = two years secondary education, 4 = graduated from secondary school (12 yrs), 5 = Bachelor degree, 6 = Master degree, 7 = Doctoral degree.
For the follow-up study, four of the 94 subjects exposed to repeat courses of ACS could not be found or had moved from Sweden. The remaining 90 were invited to participate. Fifty-eight (36 boys) accepted and completed the assessment. Of these, 19 were exposed to two courses, 14 were exposed to three courses, and 25 were exposed to four to nine courses. At follow-up, ages ranged from 14 to 26 years, with a mean of 18 years.

In order to get an age- and sex-matched reference group of unexposed subjects, we identified and invited 103 subjects born at the same gestational age as the study group from the hospital’s birth registry. Of these, 44 accepted and completed the assessment. For dose-response analyses, we also included a group of subjects exposed to a single course of ACS (n = 48) by using the same criteria as for the reference group; 25 completed the assessment. Subjects in the single-course group were born prior to the administration of the second course, and, as a result, the group was slightly more preterm than the other groups. In total, we invited 241 participants to the follow-up, and 127 accepted and were assessed according to the protocol. Maternal, pregnancy and participant (neonatal and at follow-up) characteristics are presented in Table 4.

I assessed all participants between October 2008 and April 2010 at Astrid Lindgren’s Children’s Hospital, and was at that time blinded to exposure group and gestational age at birth. The assessments were performed in the same room and at approximately the same time of the day for all participants. The tests were administered in uniform order and the entire assessment process lasted 2.5 to 3 hours. The neuropsychological test battery included tests from the Wechsler scales WISC-III and WAIS-III, Swedish versions (Wechsler, 1991, 2003), from the Delis-Kaplan Executive Function System (D-KEFS; Delis et al., 2001), and the Cambridge Neuropsychological Test Assessment Battery, CANTAB (Fray, Robbins, & Sahakian, 1996). All tests were administered and scored in accordance with manual instructions. The tests included in the neuropsychological test battery are shown in Table 5. Measures on psychological health were obtained from self-report forms: the Achenbach Adult or Youth Self-reports (Achenbach & Rescorla, 2001, 2003); the World Health Organization’s screen for ADHD (Kessler et al., 2007); and a Quality of Life Inventory (QoLI) (Berglund, 2006; Frisch, Cornell, Villanueva, & Retzlaff, 1992).

The study protocol also included blood sampling for lipids, glucose, cholesterol, and DNA analysis. A research nurse registered the participants‘ weight, height, and waist circumference as well as blood pressure and arterial pressure. Results from the analyses of long-term outcome of repeat ACS on blood pressure, arterial stiffness and metabolic profile have been published elsewhere (Norberg, Stålnacke, Nordenström, & Norman, 2013).
Table 4
*FAST Maternal, pregnancy and participant (neonatal and at follow-up) characteristics in relation to number of weekly courses of antenatal corticosteroids (ACS) for preterm birth*

<table>
<thead>
<tr>
<th></th>
<th>Unexposed</th>
<th>1 course</th>
<th>2 or more courses</th>
<th>Total</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invited – no.</td>
<td>103</td>
<td>48</td>
<td>90</td>
<td>241</td>
<td></td>
</tr>
<tr>
<td>Participants – no.</td>
<td>44</td>
<td>25</td>
<td>58</td>
<td>127</td>
<td></td>
</tr>
<tr>
<td>Maternal age – yr</td>
<td>30.5 ± 5.3</td>
<td>28.8±4.8</td>
<td>32.0± 5.0</td>
<td>30.8±5.2</td>
<td>0.03</td>
</tr>
<tr>
<td>Parental education†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.24</td>
</tr>
<tr>
<td>High school or less</td>
<td>11 (25.0)</td>
<td>10 (40.0)</td>
<td>19 (32.8)</td>
<td>40 (31.5)</td>
<td></td>
</tr>
<tr>
<td>Professional</td>
<td>6 (13.6)</td>
<td>6 (24.0)</td>
<td>6 (10.3)</td>
<td>18 (14.2)</td>
<td></td>
</tr>
<tr>
<td>Academic</td>
<td>27 (61.4)</td>
<td>9 (36.0)</td>
<td>33 (56.9)</td>
<td>69 (54.3)</td>
<td></td>
</tr>
<tr>
<td>Multiple pregnancy</td>
<td>9 (20.5)</td>
<td>5 (20.0)</td>
<td>28 (48.3)</td>
<td>42 (33.1)</td>
<td>0.004</td>
</tr>
<tr>
<td>Maternal smoking</td>
<td>8 (18.2)</td>
<td>7 (28.0)</td>
<td>10 (17.2)</td>
<td>25 (19.7)</td>
<td>0.50</td>
</tr>
<tr>
<td>Gestational age at 1st course – wks</td>
<td>31.1±1.2</td>
<td>29.1±2.0</td>
<td>29.7±2.0</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Total betamethasone dose – mg</td>
<td>–</td>
<td>23.2±2.8</td>
<td>55.2±20.5</td>
<td>45.5±22.6</td>
<td></td>
</tr>
<tr>
<td>Gestational age at birth – wks</td>
<td>34.9±2.9</td>
<td>32.6±2.9</td>
<td>34.1±2.5</td>
<td>34.0±2.8</td>
<td>0.005</td>
</tr>
<tr>
<td>Male sex</td>
<td>25 (56.8)</td>
<td>14 (56.0)</td>
<td>36 (62.1)</td>
<td>75 (59.1)</td>
<td>0.82</td>
</tr>
<tr>
<td>Birth weight – g</td>
<td>2,526±686</td>
<td>1,888±590</td>
<td>2,286±565</td>
<td>2,291±650</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Birth weight SDS</td>
<td>-0.2±1.0</td>
<td>-0.8±1.2</td>
<td>-0.4±1.1</td>
<td>-0.4±1.1</td>
<td>0.62</td>
</tr>
<tr>
<td>Major perinatal complications‡</td>
<td>5 (11.4)</td>
<td>6 (24.0)</td>
<td>7 (12.1)</td>
<td>18 (14.2)</td>
<td>0.29</td>
</tr>
<tr>
<td>Age at follow-up – yr</td>
<td>18.5±2.9</td>
<td>18.0±3.4</td>
<td>17.8±3.0</td>
<td>18.1±3.0</td>
<td>0.57</td>
</tr>
<tr>
<td>Swedish not first language</td>
<td>5 (11.4)</td>
<td>1 (4.0)</td>
<td>2 (3.4)</td>
<td>8 (6.3)</td>
<td>0.23</td>
</tr>
<tr>
<td>Glasses or lenses</td>
<td>11 (25.0)</td>
<td>7 (28.0)</td>
<td>21 (36.2)</td>
<td>39 (30.7)</td>
<td>0.45</td>
</tr>
</tbody>
</table>

*Note.* Data are means ± SD or numbers (proportion).
†The parent with the highest level of education is represented.
‡Includes at least one of the following: mechanical ventilation, neonatal seizures, sepsis, bronchopulmonary dysplasia (defined as need for supplemental oxygen at an age corresponding to 36 gestational weeks), any degree of retinopathy of prematurity or intraventricular hemorrhage.
### Table 5.

**FAST Neuropsychological test battery. Tests listed in order of administration.**

<table>
<thead>
<tr>
<th>Test</th>
<th>Source</th>
<th>Brief description</th>
<th>Cognitive domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOT, Motor Screening</td>
<td>Cantab</td>
<td>Screens for visual, movement and comprehension difficulties and also acquaints the participant with the system.</td>
<td>Reaction Time; Attention</td>
</tr>
<tr>
<td>RTI, Reaction Time</td>
<td>Cantab</td>
<td>Measures speed of response and movement in single and 5-choice paradigms. Simple and choice reaction time</td>
<td>Attention (Sustained)</td>
</tr>
<tr>
<td>RVP, Rapid Visual Processing</td>
<td>Cantab</td>
<td>Measures visual sustained attention. It is also a sensitive measurement of general performance.</td>
<td>Attention</td>
</tr>
<tr>
<td>SWM, Spatial Working Memory</td>
<td>Cantab</td>
<td>A test of the participant’s ability to retain spatial information and to manipulate items in working memory. It is a self-ordered test, which also assesses heuristic strategy.</td>
<td>Working Memory</td>
</tr>
<tr>
<td>SST, Stop Signal Task</td>
<td>Cantab</td>
<td>A stop signal response inhibition test. Uses staircase functions to generate an estimate of stop signal reaction time. Also gives a measurement of the ability to inhibit a prepotent response.</td>
<td>Response Inhibition</td>
</tr>
<tr>
<td>IED, Intra/Extra Dimensional Set Shift</td>
<td>Cantab</td>
<td>A test of rule acquisition and reversal featuring visual discrimination and attentional set formation as well as maintenance, shifting and flexibility of attention.</td>
<td>Cognitive Flexibility</td>
</tr>
<tr>
<td>Trail Making Test (TMT)</td>
<td>D-KEFS</td>
<td>Connect by drawing a line: i) Digits in increasing order; ii) Letters in alphabetic order; iii) every other letter and every other digit. Letters in alphabetical order, digits in increasing order.</td>
<td>Cognitive Speed Flexibility; Speed Memory</td>
</tr>
<tr>
<td>RAVL-R</td>
<td></td>
<td>Examiner reads a list of 15 words in 5 consecutive trials and participants repeat all the words they remember. After 30 mins, the participant is again asked to list all words they remember.</td>
<td>Verbal Learning and Retention</td>
</tr>
<tr>
<td>Block Design</td>
<td>WISC</td>
<td>Requires the participant to view a constructed model or a picture in the stimulus book, and use red-and-white blocks to re-create the design within a specified time limit.</td>
<td>General Ability (non-verbal)</td>
</tr>
<tr>
<td>Vocabulary</td>
<td>WISC / WAIS</td>
<td>The participant is asked to name or define words of increasing difficulty.</td>
<td>General Ability (verbal)</td>
</tr>
<tr>
<td>Coding</td>
<td>WISC</td>
<td>The task is to transcribe a digit-symbol code and complete as many as possible in 2 minutes.</td>
<td>Attention; Speed Cognition</td>
</tr>
<tr>
<td>Digit Span</td>
<td>WISC</td>
<td>An increasing number of digits must be repeated in i) the exact same order and ii) in the exact opposite order as that given by the test administrator.</td>
<td>Working Memory</td>
</tr>
<tr>
<td>Symbol Search</td>
<td>WISC</td>
<td>Rows of symbols and target symbols are shown. The participant is asked to mark whether or not the target symbols appear in each row and to complete as many as possible in 2 minutes.</td>
<td>Attention; Speed Cognition</td>
</tr>
<tr>
<td>Design Fluency</td>
<td>D-KEFS</td>
<td>The participant is asked to connect 5 dots with lines to create as many unique patterns as possible within one minute i) only black dots ii) white dots iii) alternate between white and black dots.</td>
<td>Cognitive Flexibility</td>
</tr>
<tr>
<td>Verbal Fluency</td>
<td>D-KEFS</td>
<td>The participant is asked to list as many words as possible in a minute that i) begin with the letters F, A, and S respectively ii) fit into the given semantic category (animals’ and boys’ names, respectively) iii) alternate between two semantic categories (fruits and furniture)</td>
<td>Cognitive Flexibility</td>
</tr>
</tbody>
</table>
Ethical points

Long-term follow-up studies after clinical complications or interventions are of the utmost importance to build knowledge, improve clinical practice, and identify and plan supportive interventions. However, for the participants, being invited to follow-up assessment may cause distress related to being identified as an individual at risk. For the SNP cohort, participation was originally based on parental consent, and the 5½ year follow-up assessment was also primarily a parental decision. At 18, however, the youngsters themselves were approached and informed about the study, and consented to participate. The parents of those who chose to participate in the follow-up assessment were subsequently invited to fill out questionnaires on the behavior and psychological health and development of their now grown-up child.

For the FAST participants, who probably had not experienced difficulties which they might link to treatment given before birth, the invitation to be part of a follow-up presumably came as a surprise. For their parents, follow-up on a treatment given while pregnant and which they might not have realized was potentially detrimental to growth and cognitive development, could have been distressing. The lower than ideal rate of participation might indicate that the invited did not view themselves as part of a clinically interesting group. For some, participation in the SNP or FAST study might have been motivated by wanting to know whether there was reason to be worried; if the perinatal complications actually had led to functional deficits. Clearly, a few of the participants from both studies were motivated by the monetary compensation (SEK 500 ≈ USD 80).

With clinical research populations, the questions and worries from participants and their families should be anticipated and need to be sensitively managed. As a rule, we did not give the participants feedback on individual assessment results. In SNP, especially at age 5½ years, and after discussion with the parents, referrals to the clinic were sometimes made. Upon request from a few participants, representing both cohorts, we shared their test results with clinical psychologists whom they were consulting outside of the studies. In the FAST study there were several calls from, particularly, the mothers with questions regarding the study and treatment, and these queries were answered by Lena Swartling, the study research nurse.

Both SNP and FAST have been approved by the Ethical Review Board in Stockholm. Participation is based on informed consent; for SNP the consent was obtained for each data collection.
Statistical methods and considerations

All three studies included in this thesis used powerful statistical methods. Yet, the sample sizes were smaller than ideal for these analyses. With this in mind, the application of the methods and interpretation of results have been performed with caution. The analyses have been conceptually driven. A p-value of less than 0.05 (two-sided) was considered to indicate statistical significance, and no corrections for multiple analyses were made. Corrections for multiple comparisons are critical to reduce the problem of mass-significance, i.e. limiting the risk of type-I error. However, correcting for multiple comparisons inflates the risk of a type-II error, i.e. the risk that possible effects would remain undiscovered. We have been restrictive in drawing conclusions from our analyses, and statistical significances have not uncritically been presumed to reflect real phenomena.

Analyses of variable and participant descriptive statistics were performed in SPSS Statistics 18 (PASW), 20, and 22 for windows (SPSS, inc., Chicago, Illinois) using Fisher’s exact test or analysis of variance (ANOVA). All analyses were performed by the present author.

Structural Equation Modeling

Structural Equation Modeling allows a complete and simultaneous test of complex relationships. The method makes it possible to test hypothesized causal relationships between manifest (directly measured) and latent variables. The latter are unobserved variables or constructs that are manifested by two or more measured variables (Tabachnick & Fidell, 2007). By using a latent variable approach, two measurement problems can be circumvented. First, the latent constructs (in our case Working Memory and Cognitive Flexibility) extract what is common in the manifest test variables, which reduces the problem of test impurity. All tasks designed to measure executive function tap both executive and non-executive processes to a greater or lesser extent. Our constructs thus reflect the shared process tapped by the tasks included, and are, in that sense, purer measurements. Secondly, the latent approach also alleviates the construct validity problem of executive functions (Miyake et al., 2000).

The fit of the measurement model, i.e. whether our chosen test variables adequately loaded on the intended latent constructs, was analyzed using a Confirmatory Factor Analysis. In the full model, hypothesized relationships between the latent variables as well as the impact of perinatal characteristics on the latent variables were added and the model fit was tested using Structural Equation Modeling analysis. The analyses were performed in the Lavaan package in R (R Core Team, 2012; Rosseel, 2012).
In Study I, as we had a rather small sample size with some missing values and not all variables filled the criteria for normal distribution, the estimation was based on full information maximum likelihood with robust standard errors and Yuan-Bentler scaling (MLR estimator) (Yuan & Bentler, 2008). The mean vector, as well as the covariance matrix, was thus used in the model fit estimation. Goodness-of-fit measures used were: (a) The chi-square test as a measurement of the discrepancy between the model-implied moments and the sample moments (a non-significant chi-square implies a good model fit). The chi-square is a function of sample size, and a rough rule of thumb is that a well-fitting model may be indicated when $\chi^2/df < 2$; (b) The Comparative Fit Index (CFI). The CFI assesses fit relative to other models and also works well for small sample sizes. It ranges from 0 to 1, and CFI values greater than .95 are indicative of a well-fitting model (Hu & Bentler, 1999); (c) The Root-Mean-Square Error of Approximation (RMSEA). The RMSEA estimates the lack of fit in a model compared to a saturated model. A value less than .06 indicates a good fit relative to the model degrees of freedom (Hu & Bentler, 1999). Confidence intervals (90%) of RMSEA are provided as well as a p-value associated with testing if RMSEA $\leq .05$; (d) The Standardized Root Mean Square Residual (SRMR). The SRMR is based on the residuals, reflecting the average differences between the sample and model implied variances and covariances. It ranges from 0 to 1, and values of .08 or less are desired (Hu & Bentler, 1999).

Classification and linkage across time
A person-oriented approach to analyzing human development works under the assumptions that functioning and development are, at least in part, specific and unique to the individual, and that the process is complex. (Bergman & Andersson, 2010; Magnusson & Töbestad, 1993). In a variable-based analysis, relationships among factors (e.g. cognitive strengths and weaknesses) and their role in the make-up of an individual are assumed to be the same for all individuals. Each variable reflects what is characteristic of the average person. In the person-oriented approach the meaning of the involved factors is determined by the interactions among these factors. Molenaar (2004) argues that for most psychological processes, such as development, learning, and adaptation, an analysis of the structure of interindividual variation will yield results that differ from an analysis of intraindividual variation. To reveal the heterogeneity of behavior and development, the more common variable-oriented approach thus needs to be complemented with a person-oriented approach (Bergman, Magnusson, & El-Khoury, 2003; Magnusson & Törestad, 1993). In study II, we have taken a person-oriented approach.
One method for studying development processes in an interindividual context is the Linking of Clusters after Removal of a Residue (LICUR) analysis, (Bergman et al., 2003). In this method of cross-sectional classification analysis followed by linkage over time, individual patterns and their stability and change over time can be discerned. The method involves four steps. First, identification of multivariate outliers (residue) separately for each age. Second, cluster analyses of the subjects separately at each age. Third, linking of the classifications at each age to one another. Fourth, analysis of individuals’ movements across the two time points.

The cluster analyses used Ward’s cluster analysis, a hierarchical agglomerative method. The agglomerative method initially assumes each individual case to be a cluster and, at iteration, the two clusters with the most similar scores on all indices, in our case four, (as measured in squared Euclidean distance) are fused. The Ward method fuses the two clusters that result in a minimum increase in variance, that is, the total within-group error sum squares (ESS). There are several criteria for choosing the optimal number of clusters. First, each cluster should be theoretically meaningful (normally this implies between five and fifteen clusters). Second, a sudden drop in the explained ESS may indicate that a solution with too few clusters has been reached. Third, the explained ESS for the chosen cluster solution should ideally exceed two-thirds of the total ESS. Fourth, each cluster in the chosen solution should also include similar cases, preferably a homogeneity coefficient not exceeding 1.00 (Bergman et al., 2003). The cluster analyses, based on the four index z-scores, were performed after excluding multivariate outliers separately for the ages 5½ and 18 years.

The structural stability of the clusters between the two points in time was investigated. This analysis compared clustering solutions by matching each cluster centroid in the 5½-year solution to the most similar cluster centroid from the 18-year solution, discovering what clusters were similar and to what extent. The centroids were represented by the means of the indices computed across the subjects that formed the cluster. Similarity was measured as the average squared Euclidean distance (ASED); a smaller ASED implied more similar clusters. The clusters were matched pair-wise step by step. The two clusters from different time points that were most similar with regard to centroids were matched first, then, from the remaining clusters, the most similar clusters were matched, etcetera. If there were the same number of clusters at both points in time, the two remaining clusters formed the last pair.

To study individual movements between clusters at the two points in time, exact analysis of single cells in a contingency table was used. In these anal-
yses the typical and a-typical longitudinal streams could be examined (Bergman et al., 2003).

The LICUR analysis was performed in Sleipner (Bergman & El-Khoury, 2002).

Multilevel linear regression modeling
Multiple linear regression allows for assessing the relationship between a dependent variable and a number of independent variables that may be correlated with one another (Tabachnick & Fidell, 2007). By using dummy variables to assign group membership (in our case the number of courses of ACS treatment), the effect of the number of courses on outcome can be assessed, while simultaneously taking into account the covariates. The method also allows for different numbers of participants in each group, as was true in our study. A necessary assumption for multiple regression is that all cases are independent. As our cohort included several pairs of twins and triplets, each individual could not be seen as an independent case. A mixed regression model was therefore used, where the lack of independence in multiple gestations was adjusted for as a random effect.

The mixed regression model corrected for age-at-testing, which compensated for the age component in the raw test scores. Parental education – a strong indicator of socioeconomic status which impacts test score outcome – was also included in the model. In order not to over-specify the model, and given the size of the cohort (n = 102; 58 exposed to multiple courses and 44 unexposed to ACS), no further covariates were included. With our given sample, we had a power of 0.8 to detect a group difference of 0.56 or more, i.e. a medium effect size.

The analyses were performed in SPSS Statistics 18 (PASW) and 20 for windows (SPSS, inc., Chicago, Illinois).
Study I

Aims and methods
The aims of this study were to investigate executive function development, specifically:

- Stability and differentiation in working memory and cognitive flexibility, from preschool age to late adolescence, in children born very and extremely preterm.
- To what extent gestational age at birth, intrauterine growth, sex, perinatal medical complications, and parental education predict executive functions at 5½ years and at 18 years.

Executive function tasks were categorized as related to either working memory or cognitive flexibility, in line with Miyake and Friedman’s (2012) framework. Four latent variables (Working Memory and Cognitive Flexibility at 5½ years, and Working Memory and Cognitive Flexibility at 18 years) were formed, each measured by three manifest test variables. The tests included were chosen with the aim of reflecting the same abilities at the two points in time. The preterm group performed lower on the included test variables as compared to the term-born control group. The group differences were statistically significant for almost all included variables. The latent variables and their manifest test variables are depicted in Figure 4.

Figure 4. Manifest test variables and latent constructs.
To test the measurement model’s fit to theory, the model for executive functions was specified and subjected to a preliminary Confirmatory Factor Analysis. The stability and predictions were tested using Structural Equation Modeling. The prediction variables of gestational age at birth, intrauterine growth, sex, perinatal medical complications (PVL, IVH, ROP, and CLD), and parental education, and the associations with the latent executive function variables were included and the model was subjected to a full analysis. The analyses were performed separately for the preterm and term group.

Results

The Confirmatory Factor Analysis of the measurement model showed that executive functions could be successfully modelled by the latent variables (Working Memory 5½, Cognitive Flexibility 5½, Working Memory 18, and Cognitive Flexibility 18) each measured with three manifest variables as specified above. For the preterm group, our data showed a good fit to the theoretical framework. The full model had a good fit and the model and the significant associations for the preterm group are depicted in Figure 5.

![Figure 5](image)

*Figure 5.* Full model with significant associations. For simplicity, error terms and test variables and their factor loadings are not shown.

For the term-born control group, the full model had a moderately good fit. Working Memory 18 was largely predicted by Working Memory 5½. However, Cognitive Flexibility 18 was less strongly predicted by Cognitive Flexi-
ibility 5½, and the regression coefficient was not statistically significant (p = .09). For the term group, sex did not impact outcome at either point in time. Parental education had a positive impact on both Working Memory and Cognitive Flexibility.

Conclusions

Executive functions proved to be differentiable and highly stable from preschool age to late adolescence. Working memory and cognitive flexibility were differentiated from each other at the ages of both 5½ and 18 years, and also followed slightly different pathways over time. Working memory performance at 5½ years essentially predicted working memory performance at 18 years. The prediction of cognitive flexibility performance at age 18 years was more complex. The impact of performance at age 5½ years was considerable, but intrauterine growth restriction and perinatal medical complications were also influential.

Among the very or extremely preterm-born, higher parental education, higher gestational age, and female sex were related to better overall executive functioning at late preschool age. The consequences of perinatal medical complications and restricted intrauterine growth had a continued detrimental effect specifically on cognitive flexibility in late adolescence. With increasing age, the problems of the affected children became apparent as they failed to master complex executive function tasks. On the other hand, executive function performance from preschool to late adolescence was stable enough to imply that significant catch-up effects in preterm children should not be expected beyond the late preschool years. The study poses an argument for identification of executive deficits before school entry among children born preterm, as such deficits are unlikely to diminish as a consequence of maturation. It also points to the importance of providing extra support to families with low educational attainment.
Study II

Aims and methods
The aim of this study was to identify individual cognitive patterns at pre-
school age and at late adolescence, and to assess development over time, in a
cohort of individuals born preterm. The research questions addressed were:

- Are there clinically meaningful subgroups within the group of pre-
term-born with respect to cognitive profiles at age 5½ years and age
18 years, respectively?
- Do the subgroups show developmental stability from preschool age
to adolescence?
- To what extent can these subgroups be predicted by sex, perinatal
factors and parental levels of education?

Four cognitive indices at each age were formed, based on the data from age
5½ years and age 18 years. Two indices were aimed at reflecting the indi-
vidual’s general ability (IQ). The first, verbal ability (VFI) reflects verbal
reasoning and knowledge; the second, non-verbal ability (PFI), reflects non-
verbal, visuospatial, and abstract reasoning and is less dependent on learning
and experience. For the operationalization of these indices, the raw scores of
tests included in the Wechsler verbal and performance scales, respectively,
were used. Two other indices were aimed at reflecting executive functions.
A model proposed by Miyake and colleagues (Miyake & Friedman, 2012;
Miyake et al., 2000) posits a common factor for all executive function abili-
ties as well as a specific updating and a specific shifting ability. Based on
this model we formed a working memory index (WMI), reflecting the ability
to hold in mind and manipulate information, and a cognitive flexibility index
(CFI), reflecting the ability to flexibly adjust to new demands or priorities,
and the ability to change perspectives. The latter index also reflected mental
processing speed. Tables 1 and 2 above give a short description of the tests
used, and the test composition of each index.

For each age separately, a Confirmatory Factor Analysis was performed to
ensure that the theoretically composed indices fit the data. At age 5½, the
model fit was reasonably good and at age 18, the model fit was good. At
both ages, the models with four indices had a better fit compared to allowing
all tests to load on one common factor. We thus concluded that our opera-
tionalizations were valid for use in further analyses.
To create the indices used in the pattern analysis, each test’s raw score was z-transformed using the mean and standard deviation from the SNP control group scores. The z sum for each index was divided by the number of test scores included, resulting in an average z-score for each index. The index score thus reflects performance relative to the term-born control group.

A method for cross-sectional classification analysis followed by linkage over time, LICUR (Bergman et al., 2003), was performed to discern patterns, and their stability and change over time.

Results
At age 5½ the 6-cluster solution best matched the criteria. The clusters were labelled from 5A to 5F in order of level of performance, 5A being the highest performing cluster. Again, at age 18, the 6-cluster solution was deemed the most meaningful. The clusters were labelled 18A+, 18A, 18B, 18D, 18E, and 18F in level of performance. The solutions are presented in Figures 6 and 7.

![Figure 6. Cognitive profiles of identified clusters at age 5½ years.](image-url)
Figure 7. Cognitive profiles of identified clusters at age 18 years.

The pair-wise matching of similar clusters across time revealed that five of the clusters at age 5½ corresponded well or rather well to a cluster at age 18. The exceptions were clusters 5C – which had no match at age 18, and cluster 18A+, which was essentially a breakout from cluster 18A.

The individual movements between clusters across time are depicted in Figure 8. All participants in cluster 18A+ came from the 5A cluster. The remaining 5A participants almost all formed part of cluster 18A. Participants from cluster 5B typically moved to cluster 18B. The large cluster 5C split up, with almost half of the participants improving in performance relative to term-born peers (18A), and the rest maintaining or deteriorating in performance over time. Movements from clusters performing at norm to low clusters, i.e. from the 5A or 5B cluster at age 5½ years to clusters 18D, 18E, or 18F at age 18 were extremely rare. Likewise, movements from the low clusters at age 5½ to the higher clusters at age 18 were unusual. There were no transfers from clusters 5D, 5E, or 5F to clusters 18A+ or 18B; only a few transfers occurred to 18A.
Figure 8. Longitudinal streams

The clusters were analyzed to identify membership background characteristics. At age 5½ years and 18 years, there were no statistically significant differences in sex, gestational age at birth, birth weight, or intrauterine growth between clusters. Perinatal medical complications and level of parental education attainment showed some association with cluster membership. Cluster membership was associated with the 10-months Griffiths scores (p < .001): post hoc analyses revealed that cluster 5A performed significantly better than clusters 5D, 5E, and 5F, and cluster 5F performed significantly worse than clusters 5A, 5B, and 5C and that cluster 18A+ scored significantly better than cluster 18F, and cluster 18A scored significantly better than clusters 18D and 18F.
Conclusions

We were able to identify meaningful subgroups within the group of preterm-born, with respect to cognitive profiles at age 5½ and age 18 years. There were six subgroups at both ages, based primarily on overall level of performance in the tests that constituted our cognitive indices. However, at both ages individual variations with regard to cognitive strengths and weaknesses were also apparent. In some subgroups, the pattern was even, with individuals performing at the same level relative to term-born controls on all four index measurements, whereas individuals in some subgroups were characterized by wide variability in relative performance. Those with a relative strength or relative weakness in verbal ability, or a relative strength in working memory at 5½ years, tended to show the same strength or weakness at age 18. Individuals with even cognitive profiles at 5½ years continued to exhibit even profiles at age 18. Cognitive ability at 5½ years was highly predictive of ability at age 18 for all subgroups: individuals performing at low levels at age 5½ years were unlikely to improve over time, and individuals who performed at norm were unlikely to fall far below norm over time. However, the study also showed that there were improvements in performance among a group of individuals performing at or above norm at age 5½ years. Among those in lower performing clusters, there was a slight reduction in relative performance over time. Also, the often reported relative strength in verbal ability among preterm-born seemed to be true for those who generally functioned within the normal range, whereas individuals with more pronounced deficits did not show this verbal advantage. Importantly, the present study shows that executive dysfunction was by no means characteristic of all individuals born preterm.

The relationship between the background characteristics and cluster membership was investigated. The analyses revealed that cluster membership could not be predicted by the background variables, either at age 5½ years or at age 18 years. This means that perinatal data alone cannot predict outcome in preschool years or adolescence.

The cognitive outcomes after preterm birth in late adolescence are diverse, with a large group being seemingly unaffected by the bumpy start while others exhibit specific or general cognitive deficits. Already at late preschool age, however, developmental trajectories are fairly well established. Therefore, developmental monitoring and identification of those at risk of a less favorable outcome is imperative. Interventions could thus be initiated early, prior to school entry, to limit the effects that even mild cognitive deficits may have on learning and overall development.
Study III

Aims and methods
The objective of this study was to investigate whether repeat courses of ACS have long-term effects on cognitive and psychological functioning. The neuropsychological tests, grouped into five broadly defined domains, included: i) General cognitive ability; ii) Memory and learning; iii) Working memory; iv) Attention and speed; and v) Cognitive flexibility and inhibition. The last three domains (iii, iv and v) reflect executive functions. Measurements on psychological health were obtained from self-report forms.

In order to investigate group differences in outcome variables, the unexposed group was initially compared to those exposed to two or more courses using Student’s t-test. Outcomes that differed significantly (p < .05) in the univariate tests were included in a mixed regression model that controlled for age at testing, level of parental education, and clustering effects due to multiple gestations.

Results
Among the 21 outcome measurements included to tap executive functions, four revealed significant univariate group differences between unexposed subjects and subjects exposed to two or more courses of ACS (p < .02; t-test of mean differences; see Table 6). All four were found in the domain of attention and speed and included Symbol Search, Coding, Digit Span Forward, and Rapid Visual Processing (RVP A’). After adjusting for covariates and multiple gestations, only Symbol Search and Digit Span Forward remained significant; the other two measurements reached near statistical significance; see Table 6. In both Symbol Search and Digit Span Forward the difference was slightly above half a standard deviation; a medium effect size. The additional variance explained in these two outcomes by adding exposure in a multiple regression model was four to six percent. In addition, these two group differences were not dose-dependent. In fact, when comparing the unexposed group to those exposed to a single course, to two courses, to three courses, and to four or more courses, the subgroup exposed to two courses had the lowest means and those exposed to three courses had the highest. The group exposed to two courses performed statistically significantly below the unexposed group on both Symbol Search and Digit Span Forward. For the other multiple exposure groups, the difference was not statistically significant.
Table 6.
Selected neuropsychological outcomes in 14 to 26 year-old subjects exposed to repeat weekly courses of antenatal corticosteroids (ACS)

<table>
<thead>
<tr>
<th></th>
<th>Unexposed (n = 44)</th>
<th>Repeat ACS (n = 58)</th>
<th>P-value</th>
<th>Adjusted mean difference [95% CI] (n = 102)</th>
<th>Adj p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Cognitive Ability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Block Design*</td>
<td>47.7 ±9.8</td>
<td>46.4 ±11.5</td>
<td>0.54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vocabulary†, normed z-score</td>
<td>-0.19 ±1.2</td>
<td>-0.20 ±0.99</td>
<td>0.96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memory and Learning</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAVL‡</td>
<td>54.0 ±6.6</td>
<td>54.9 ±7.0</td>
<td>0.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAVL‡ - Retention</td>
<td>12.5 ±1.9</td>
<td>12.8 ±1.8</td>
<td>0.43</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working Memory</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spatial Working Memory§, Between errors</td>
<td>10.9 ±8.8</td>
<td>12.6 ±11.1</td>
<td>0.41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit Span* Backward</td>
<td>7.0 ±1.9</td>
<td>6.4 ±2.0</td>
<td>0.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention and Speed</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Rapid Visual Processing§, A'</td>
<td>0.90 ±0.05</td>
<td>0.88 ±0.05</td>
<td>0.02</td>
<td>-0.02 [-0.04 to 0.00]</td>
<td>0.05</td>
</tr>
<tr>
<td>Trail Making Test</td>
<td></td>
<td>TMT-A, Digits</td>
<td>28.7 ±11.1</td>
<td>32.6 ±12.5</td>
<td>0.11</td>
</tr>
<tr>
<td>Digit Span* Forward</td>
<td>9.7 ±1.9</td>
<td>8.7 ±1.8</td>
<td>0.007</td>
<td>-0.91 [-1.65 to -0.17]</td>
<td>0.02</td>
</tr>
<tr>
<td>Symbol Search*</td>
<td>40.3 ±6.5</td>
<td>35.8 ±7.8</td>
<td>0.003</td>
<td>-3.88 [-6.76 to -1.01]</td>
<td>0.01</td>
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<tr>
<td>Coding*</td>
<td>74.2 ±13.5</td>
<td>67.1 ±16.1</td>
<td>0.02</td>
<td>-5.63 [-11.73 to 0.48]</td>
<td>0.07</td>
</tr>
<tr>
<td>Cognitive Flexibility and Inhibition</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Trail Making Test</td>
<td></td>
<td>TMT-B</td>
<td>64.6 ±23.5</td>
<td>72.2 ±21.4</td>
<td>0.10</td>
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<tr>
<td>Verbal Fluency</td>
<td></td>
<td>Semantic Category</td>
<td>42.6 ±9.0</td>
<td>42.7 ±9.2</td>
<td>0.95</td>
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<tr>
<td>Design Fluency</td>
<td></td>
<td>Total</td>
<td>31.1 ±6.7</td>
<td>29.1 ±6.7</td>
<td>0.15</td>
</tr>
<tr>
<td>Intra/Extra dimensional shift§, Adjusted errors</td>
<td>21.6 ±18.3</td>
<td>26.6 ±19.4</td>
<td>0.19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Signal Stop Time§, Signal Stop Reaction Time</td>
<td>178 ±33</td>
<td>190 ±47</td>
<td>0.16</td>
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<td></td>
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Note. Plus-minus values are means ± SD; Significant mean differences were adjusted for age at testing, level of parental education and clustering effects due to multiple gestations.
* From WISC-III
† WISC-III Vocabulary was administered to those born 1992 to 1996; WAIS-III Vocabulary to those born 1983 to 1991
‡ Rey Auditory Verbal Learning; Retention after 30 mins.
§ From CANTAB
|| From D-KEFS
There were no significant associations between repeat corticosteroid exposure and verbal or nonverbal ability 14 to 26 years later. Memory and learning were also unrelated to repeat exposure to ACS; see Table 6.

Essentially, there were no differences between the repeat corticosteroid and unexposed groups in scores from self-report inventories on psychological health. Self-reported ADHD symptoms were not increased with repeat corticosteroid courses. Life satisfaction, obtained by self-rated quality of life, did not reflect any differences among groups, or any dose-dependent relationships.

Conclusions
In this study on the long-term cognitive and behavioral outcome in adolescents and young adults exposed to repeat courses of ACS, we found no indication of adverse effects of this treatment on higher cognitive functions and behavior. Indeed, there were no significant differences between the repeat and unexposed groups in their ability to learn, understand and manage meaningful material. However, the mean scores obtained in two tests, Symbol Search and Digit Span Forward, were significantly lower for the repeat group when compared to the unexposed group, even after controlling for covariates and multiple gestations. Both measurements fall within the executive domain of attention and speed. These mild deficits did not seem to have an impact on more complex cognitive task performance, self-reported attention, adaptability, or overall psychological functioning.
Discussion

Being born preterm, or being exposed to antenatal corticosteroids when at risk of being born preterm, disrupts the typical process of fetal brain development. The long-term consequences of the disruptions to future cognitive functions are not fully understood. The aim of this thesis has been to study how exposure to perinatal stress in the long term might affect executive function. My specific aims have been threefold: To investigate if executive functions in individuals with a history of preterm birth can be differentiated into components, and if these components show differences with regard to developmental pathways and vulnerability to perinatal factors; to investigate if subgroups with respect to cognitive profiles among the preterm-born can be identified, and if these subgroups display differences in developmental pathways; and to investigate the long-term effects of repeat exposure to antenatal corticosteroid treatment.

Stability of executive function development

Executive function is often reported as being a specific weakness among children with a history of preterm birth. However, whether this weakness persists over development or whether the weakness is primarily an expression of delayed maturation, is still unresolved. Also, as executive function is a concept that encompasses many interrelated abilities, it is of interest to investigate whether different components of executive functions show different developmental pathways and if they are differentially influenced by known biological, perinatal, and familial factors. By differentiating the executive functions into working memory and cognitive flexibility, we were able to investigate stability, pathways, and determinants separately. The major conclusion drawn from Study I was that executive functions proved to be differentiable and highly stable from preschool age to late adolescence. Working memory and cognitive flexibility were differentiated from each other at both age 5½ and 18 years, and also followed slightly different pathways over time. Working memory performance at 5½ years essentially predicted working memory performance at 18 years. The prediction of cognitive flexibility performance at age 18 years was more complex. Level of performance was largely determined already at 5½ years, but the perinatal factors
intrauterine growth restriction and medical complications, continued to influence development.

Executive functions in children develop gradually; basic and simple processes are available to the child at an earlier age than the more complex functions (P. Anderson, 2002). Although tasks assessing working memory or cognitive flexibility can be varied in level of complexity, the cognitive flexibility tasks depend on inhibition and working memory – they are, almost by definition, of a higher level of complexity. The lower predictive power of cognitive flexibility at age 5½ years might be a reflection of the continued maturation of these aspects of executive functions after the preschool years. In other words, tasks requiring more advanced cognitive flexibility cannot be meaningfully assessed in preschool children, as they are typically not yet mature enough to solve the tasks. This finding is corroborated from other studies of cognitive flexibility in preschoolers (Woodward et al., 2011). In fact, task performance might then primarily reflect response inhibition, sustained attention, or the child’s working memory capacity. Neurodevelopmentally, this can be understood to be an effect of early disturbances of brain circuits underlying more advanced executive functions which first become apparent at the age when these functions typically develop and increasing demands are placed on the individual.

Previous research, including earlier studies from our own group, has already demonstrated that school aged children born preterm are at risk of executive functions deficits (Böhm et al., 2004; Howard et al., 2008; Taylor et al., 2004). In Study I, the preterm group performed lower on the included executive function test variables as compared to the term-born control group. The group differences were statistically significant for almost all included variables. The stability in executive function performance shown in this study implies that assessment at late preschool age will give a good indication of the child’s continued executive function performance. The notion of a catch-up effect after late preschool age (e.g. Saavalainen et al., 2007; H. G. Taylor et al., 2004) is not supported by our findings. Rather, they imply that catch-up among preterm children would occur before the age of 5 years. This is also in line with findings regarding typical executive function development during the first five years of life, in normative groups of children (Diamond, 2013; Garon et al., 2008). Further investigation is warranted to establish patterns of catch-up effects prior to 5 years in children born preterm. An implication of our results is that support and interventions to limit the effects of executive function deficits on learning and social interaction should be initiated before school entry. A wait and see approach will more likely lead to secondary effects of a deficit rather than a catch-up over time.
Suboptimal intrauterine or perinatal conditions are linked to long-term negative developmental impact on cognitive outcome (Raz, Debastos, Newman, & Batton, 2012; Roze et al., 2009; Vohr et al., 2000). In this study, restricted intrauterine growth had a negative impact on cognitive flexibility task performance in late adolescence, although it did not influence outcome at 5½ years. Seemingly, the effects became apparent with age, when expected development did not occur; in effect, the children grew into their problems. Perinatal medical complications influenced outcome of working memory at 5½ years, and had a negative influence on cognitive flexibility at 18 years. Again, perhaps this protracted effect reflects the long-term vulnerability of complex cognitive flexibility, which depends on neural substrates that develop during adolescence.

Individual patterns of development

The aim of Study II was to investigate the long-term stability in cognitive outcome patterns and developmental trajectories of subgroups of individuals born preterm, i.e. prior to 37 weeks of gestation and with a birth weight less than 1,500 g. The person-oriented approach enabled us to look at the variability in individual cognitive profiles and development and thus ascertain that individual outcome patterns are not disguised by group outcomes. These analyses truly showed that outcome after preterm birth is diverse. The six subgroups identified at 5½ years and 18 years, respectively, were based primarily on overall level of performance. However, individual variation with regard to cognitive strengths and weaknesses were also apparent, and the pattern of relative strengths and weaknesses tended to remain the same over time. At 18 years, almost half the participants (clusters 18A+ and 18A) performed at or above norm on all four indices; that is, in essence these individuals were cognitively rather well-functioning despite their suboptimal start in life. The individuals in one cluster (18B) displayed a pattern of at norm performance in general ability but with a weakness in executive functions, especially working memory. This profile is in line with studies that have reported executive function to be a specific weakness among those born preterm (Aarnoudse-Moens, Weisglas-Kuperus, et al., 2009; P. J. Anderson et al., 2010; Bayless & Stevenson, 2007; Böhm et al., 2004; Howard et al., 2008; Lundequist et al., 2014). However, executive dysfunction was not a general pattern although at 18 years there were subgroups, demonstrating both higher and lower levels of performance, whose cognitive profiles showed a clear relative weakness in working memory and/or cognitive flexibility. Verbal ability is often cited as a relative strength among those born preterm (Aylward, 2005; Böhm et al., 2002; S. Johnson, 2007). In our study this was not a typical profile. Notably, for those subgroups performing significantly below the norm, verbal ability was instead a relative weakness.
Perhaps this can be understood in terms of verbal ability reflecting the ability to learn and accumulate knowledge, which in turn requires non-verbal and executive abilities. Thus, for those whose preterm birth has had a clear negative impact on brain development, the ability to learn is hampered.

An indication of developmental stability is that the same individuals tend to be classified into clusters of similar level and profile at the two time points. By studying the longitudinal streams, i.e. how individuals moved from one cluster at age 5½ years to a cluster at 18 years, individual stability in cognitive patterns could also be analyzed. In our sample, most individuals moved to a cluster of similar level and profile. Indeed, movements from the higher clusters to a lower cluster were extremely rare, as were movements from a low to a high cluster. Those who were performing at low levels at age 5½ years did not improve relative to peers; rather, their problems remained or became more pronounced. In the low functioning clusters, executive dysfunction was accompanied by very low general ability. Presumably, in individuals forming these subgroups, the impact of early disruptions was not limited to aspects of executive functions but profoundly affected learning and understanding. The positive finding was that among those who at 5½ years performed close to or above norm, a fairly large number improved their performance vis-a-vis peers. For these individuals, the early disruption had the consequence of slightly delayed development. Presumably, critical networks were sufficiently unaffected to allow for a beneficial developmental process.

Of interest was the group of individuals in the largest cluster at 5½ years (5C), whose continued development was particularly difficult to predict. At 5½ years their cognitive profile was even, with performance slightly below norm; this profile was not matched by any cluster at age 18. Almost half of the members of this cluster at 5½ years improved their performance, and by age 18 formed part of a cluster with performance above norm. Others exhibited a general ability at norm at 18 years, with an executive weakness, whereas approximately one third had deteriorated in relative performance. These respective developmental trajectories could not be predicted from perinatal medical history, sex, or family education levels.

The relationship between the background characteristics and cluster membership was investigated. The analyses revealed that cluster membership could not be predicted by the background variables, either at age 5½ years or at age 18 years. This means that perinatal data alone cannot predict outcome in preschool years or adolescence. Our findings stress the importance of follow-up and continued monitoring before the preterm-born enter school, even after a seemingly uneventful perinatal period and when no obvious signs of cognitive deficits have presented themselves early in development.
Early interventions such as training programs to strengthen executive functions might benefit some, but perhaps more important is information and support to families, and ensuring a school environment where adjustments and compensations are made for possible cognitive weaknesses. In the face of cognitive deficits, such early support might allow for optimal development and prevent the child from falling further behind.

Cognitive outcome after repeat ACS treatment

The study of young adults exposed to repeat courses of ACS showed that, on the whole, the treatment had not had a negative impact on their neurodevelopment. Fourteen to 26 years after their fetal exposure, there were no apparent detrimental effects on cognitive or psychological functioning. However, mean scores obtained on two tests, Symbol Search and Digit Span Forward, were significantly lower for the repeat group when compared to the unexposed group, even after controlling for covariates and multiple gestations. Both measurements fall within the domain of attention and speed. In addition, prior to controlling for covariates, group differences were also present in the tests Coding and Rapid Visual Processing. Rapid Visual Processing is a test which assesses sustained attention, working memory, and inhibition. Coding tests speed, attention, and some working memory. The fundamental function affected in all four measurements seems to be the ability to maintain an appropriate level of attention. These mild deficits did not seem to impact the ability to learn, understand, or manage meaningful material reflected in other, more complex tests, nor did they affect self-reported attention, adaptability, or overall psychological functioning. The slight deficits in these most basic executive functions seen in those exposed to repeat ACS are illustrative. In this group, the dysfunction seems to be so subtle that it does not impact the more complex functions.

The lower scores could reflect increased sensitivity of certain neural circuits to programming effects by corticosteroids during fetal life. A recent study in nonhuman primates investigating the long-term effects of fetal glucocorticoid overexposure on prefrontal cortex gene expression found significant effects of this treatment on the expression of glucocorticoid receptors. These effects were more pronounced in neonates than in adults (Diaz-Heijtz, Fuchs, Feldon, Pryce, & Forssberg, 2010). In guinea pigs prenatally exposed to excess levels of corticosteroids, the effect on stress response and function varied as a function of age, pointing to the need for studying outcome at different times over the course of life (Matthews et al., 2004). It is tempting to speculate that the modest effects observed in our cohort of adolescents and young adults are remnants of deficits that were more clearly expressed in the younger preschool children in previous studies of repeat exposure to...
ACS (Crowther et al., 2007; French et al., 2004), but have been compensated for in later development.

The FAST study could potentially have informed us about threshold or timing effects of ACS treatment. It is therefore worth noting that we did not detect any dose-response effects. Prolonged exposure to excess glucocorticoids did not increase the magnitude of the subtle differences we identified. In part, the lack of effect might be explained by the increased gestational age of those exposed to a higher number of courses, that is, the negative effects of increased exposure are off-set by the additional time spent in the more suitable environment of the womb. The lack of a dose-response effect could also be a result of sampling bias, given the small number of participants in each subgroup.

The effect of sex and parental education

In the preterm SNP cohort, male sex had a negative impact on both working memory and cognitive flexibility at age 5½ years, but did not further influence outcome beyond this time. This could be because the male brain, relative to the female, is more vulnerable. It might also be a reflection of the differences in timing of brain development between the sexes. In the term-born control group in Study I, sex was not associated with outcome in either executive function component, at either point in time. Sex was not a determinant for subgroup membership in the cluster analysis, although at 5½ years, in the lowest performing subgroup four out of five were boys. Sex (although not reported) did not affect outcome after repeat ACS exposure. From these studies, no conclusive remarks on the interactive effects of sex and perinatal stress on cognitive development can be made, although indications are that male sex is probably associated with worse outcome. At least, we might state that being female does not entail an increased risk of adverse outcome.

In all three studies, having well-educated parents proved to be a developmental advantage. The strong effect of parental education on outcome points to the importance of environmental factors (Wong & Edwards, 2013). As previously stated, in Sweden, where maternal and child medical care is publicly funded and universally provided, differences in outcome after preterm birth are probably related to well-educated parents providing favorable learning environments for their children (Davis-Kean, 2005). This has implications for interventions. Health professionals working with preterm children born to less educated parents are advised to be aware of a possible need for increased support, even during the preschool years, in order to ensure an optimal learning environment. Another aspect of the level of parental educa-
tion is that it, at least in part, reflects parental cognitive ability. The children born to well-educated parents might presumably also have a hereditary advantage with regard to general cognitive ability. An insult can thus lead to a lower than expected functioning without leading to problems with life adaptation. Stated differently, although well-functioning as they are, they might have performed at higher levels had they not been exposed to abnormal levels of stress in the perinatal period. For the term-born control group in Study I, parental education was highly influential on the outcome of particularly working memory, but also on cognitive flexibility, at age 5½ years. This indicates that, in typically developing children, genetics and family education are the two factors that account for variability in outcome, exerting a determining influence even at a very young age.

Thoughts on underlying mechanisms

Our brains are formed in fetal life, in an intricate process. Although brain maturation continues into the third decade of life, neuronal migration and the basic structure are to a large extent completed by the end of the second trimester. During these early months, the brain is especially vulnerable to changes in fetal environment. The participants in the studies included in this thesis had been exposed to one or more stressors in the perinatal period. One stressor investigated was the occurrence of very or extremely preterm birth. Being born and exposed to the world outside the womb prior to the time when nature has deemed the brain systems mature enough to handle the surge of stimuli, is a major stressor. The immature infant often struggles with breathing, maintaining temperature, receiving sufficient nutrition, and fighting infections, placing the infant under additional stress. Some participants have also experienced another stressor prior to being born preterm, namely a suboptimal intrauterine environment. Prolonged restricted nutrition places the fetus under stress, and infants who are smaller than expected for their gestational age have increased levels of the stress hormone cortisol, a glucocorticoid. The third stressor investigated is the exposure of the fetus to synthetic glucocorticoids, which may be administered to the pregnant woman to hasten maturation of the fetus’ lungs when preterm delivery is threatening. In all three cases, the increased level of stress, affecting glucocorticoid levels, is likely to change the fetal milieu for a rapidly developing brain.

Glucocorticoid levels are typically well-regulated, as levels that are too high or too low may disrupt brain development. Both oligodentrocyte development, related to the process of myelination, and dopaminergic activity are presumably adversely affected by excess glucocorticoids. The dopaminergic neurons are formed during early development, and are highly sensitive to perturbations, such as a change in the levels of glucocorticoids. The dopa-
minergic systems projecting to the frontal lobes are linked to cognitive control and executive functions, and prenatal disruptions may alter these circuits and predispose an individual to dopamine-related disorders, such as attention deficit disorders (Rodrigues et al., 2011). An increased incidence of attentional deficits among those born preterm may thus be perceived as a sign of early life programming effects on the dopamine systems due to excess levels of stress. In the SNP studies included in this thesis, we did not specifically study attention (although self-report behavior data has been collected), and have not tested data in line with these theories. However, the notion that the common executive function factor can be thought of in terms of attention, could imply that the executive function deficits identified among the preterm-born in our studies, might be related to disruptions to typical dopamine system function.

Diffuse white matter abnormalities are the most common cause of brain injury affecting children born preterm (Back et al., 2007). It has been proposed that the disturbances to the myelination could be due to death of the cells that are to develop into the oligodentroglial cells, i.e. the myelinating glial cells (Volpe et al., 2011). Gestational weeks 23 to 32, a time during which the oligodendrocytes are early in their maturational cycle, coincides with the developmental window when risk of diffuse white matter injury is highest. During this period the precursors to the mature oligodendrocytes are extremely vulnerable (Back, 2006; Volpe et al., 2011). In the literature investigating white matter injuries in the preterm-born, oxidative stress resulting from ischemia-hypoxia or maternal-fetal infections, rather than glucocorticoids is in focus. However, there are links between corticosteroids and other steroids activated by ischemic-hypoxic insults (Hirst, Kelleher, Walker, & Palliser, 2014; Spedding, Evrard, & Gressens, 2008). The link between white matter abnormalities and executive function deficits is gaining increasing support (Nagy et al., 2003; Skranes et al., 2009; Woodward et al., 2011; Woodward, Clark, Bora, & Inder, 2012).

Executive functions revisited

In interaction with her environment, the newborn infant gradually conquers her world. External stimuli are necessary for brain connections to build and strengthen. The increasing number and efficiency of connections allow for a gradually more deliberate, precise, and coherent interaction with the environment. In typical development the neonate is equipped with the basic mechanisms for organized perception, attention, and learning from which further development springs. The effects of a disruption to ideal fetal conditions could potentially upset the developmental process and have severe long-term ramifications, or the disruption could be merely a blip, and in the
long-term may pass without notice. The complex executive functions are vulnerable, as they are, in effect, the end product and relies on the integrity of diffuse and complex neural networks. The basic attention processes have been singled out as together they represent one key function that is essential for working memory, inhibition, and cognitive flexibility. These processes in turn, are important for learning and for making sense of the world and the individual’s role in it. By late preschool age, the restrictions entailed by a deficiency in the still rather immature executive functions will become apparent in comparison to typically developing peers. However, some of the more complex functions, which are not expected to be at the youth’s disposal until the teenage years, may not be obviously deficient until this later time. Brain imaging studies of typically developing children show that task fulfillment is achieved prior to the emergence of adult patterns of brain function. This implies that a task (at least in test situations) can be solved using a less mature and presumably more taxing set of networks. More attention and energy is required to achieve the same result. It is worth pointing out that our analyses do not give insight into how the results were achieved; that is, whether task accomplishment came about by employing alternate neural systems than is typically the case. It cannot be ruled out that, on a group level, those born preterm use alternate neural systems, and at a higher cost to attention and energy systems than their term-born peers.

The importance of executive functions for cognitive, social, and psychological development, and the impact of these functions on success in school and in life are well established. Indeed, executive functions are emerging as more crucial for successful development than general ability – although the concepts are fundamentally linked to each other. Small children’s ability to withhold the urge for immediate gratification in waiting for a greater treat is more strongly linked to positive life outcome than IQ (Moffitt et al., 2011). The very early abilities to inhibit an external temptation to achieve a distant and less tangible goal are fundamental for cognitive control. Executive functions are many-faceted and interrelated and show protracted development across childhood and into young adulthood. The skills that require executive functions are mastered in succession as functions are challenged. An infant can maintain focused attention only for very short periods, a young child can hold only a few objects or rules in working memory, but may effectively solve a task when the working memory load is lowered. Hypothetical and abstract reasoning is effortful, and even adults’ thinking is characterized by relying on rules of thumb or automaticity; only occasionally do we actually apply the logical thinking characterized in Piaget’s fourth stage, formal operations. In order to accomplish reasoning at a higher level, however, the core executive function components have to be adequately developed. Without a satisfactory ability to attend, inhibit, hold in working memory, and shift
between response sets, reasoning, problem-solving, and decision making are difficult, or perhaps even impossible.

As formal schooling commences, the attentional abilities are challenged. The school situation is designed for typically developing children who therefore can meet the demands in a way that works in concert with brain maturation, which results in strengthening of the executive skills. For children who, for various reasons, have subnormally developed skills – where attending, inhibiting, and remembering instructions is not yet at the level that the situation demands – the challenge is too high. If demands are not at a developmentally appropriate level, the opportunity to build and strengthen skills may be forfeited, increasing the gap between these children and same age peers. Interventions for children (and indeed adults) facing executive difficulties have to meet the individual at her level of functioning rather than at age expectations. With executive difficulties, an extra effort is required to maintain attention and focus, making sustained attention a reasonable expectation only for a limited duration of time. School can be very taxing, and for children with executive function deficits this should be understood and heeded to when planning interventions or compensations.

These studies have given further insight into executive function differentiation, stability, development, and vulnerability, particularly for individuals whose fetal environment or perinatal experiences are less than optimal.

Miyake and colleagues (2000) have proposed a model for executive functions – explicating both their unity and diversity. Rather than investigating executive functions as one all-encompassing construct, or look further into single tasks or tests, we opted to use their proposed theoretical framework to investigate executive functions’ stability and development among the very and extremely preterm-born. By taking this approach, we hoped to clarify the more generally reported results of executive function deficits in these groups. The latent variable analyses enabled us to circumvent the problems of task impurity and construct validity; in effect we studied the constructs rather than the tests. In Study I, we showed that executive functions, although closely related, could be differentiated into working memory and cognitive flexibility at both age 5½ years and at 18 years. In fact, our model separating executive functions into these two components proved to fit our data better than allowing the included test variables to load on a single executive function construct. However, there are difficulties involved with effectively measuring particularly cognitive flexibility at early ages. Using the framework we could also show that working memory ability at 18 years was almost completely mediated by working memory performance at age 5½ years, and that cognitive flexibility also was highly stable. The differences in mediation of the 5½-year performance reveal that the two constructs exhibit
slightly different developmental pathways. In Diamond’s (2013) framework, cognitive flexibility is firmly established at a later point in development and is dependent on working memory and inhibition. In our study group, the effects of perinatal medical complications and restricted intrauterine growth had not run their full course at age 5½ years, which is in line with the later development of these functions. Overall, the study design and results adds to our knowledge of executive function deficits among the preterm-born which gives valuable input to clinical practice. Also, the study contributes to our general understanding of executive function, how it may be differentiated and how subcomponents develop with maturation.

The results from Study I inform us about outcome on the group level, but says little about differences in outcome within the group. With the person-oriented approach used in Study II, a more nuanced spectrum of outcome emerged. In these analyses, for methodological reasons, the indices used (two for general ability and two reflecting executive functions) were based on the average score of the included test variables, rather than the latent constructs. The index scores reflect both the abilities presumed to form the index as well as the skills common to all cognitive tests. The average index scores are thus less pure measures of the abilities than could have been obtained if a latent variable approach had been possible. The fact that our clusters to a large extent were separated on overall level is probably a reflection of this interrelatedness of test scores. Learning and non-verbal reasoning are not clearly distinguished from executive functions, and more basic functions such as processing speed, fine motor skills and attention, which were not specifically measured here, are likely to affect all test scores, although in different ways. Nonetheless, the analyses shed light on the diversity of outcome among the preterm-born, and the difficulty of predicting outcome from perinatal data, and indeed, for some individuals even from assessment data in late preschool age. The identified subgroups effectively modify the general statements that verbal ability is a relative strength and executive functions a specific weakness among the preterm-born. In line with Diamond’s (2013) framework, the link between executive functions and higher cognitive functions was also apparent in this study. Significant executive function deficits were accompanied by deficits in verbal and non-verbal cognitive ability. Both studies lead to the conclusion that actions to support executive function development, or alleviate the effects of deficits, should be introduced prior to formal school entry. There is no point in waiting to see if a deficit is merely a reflection of a developmental delay.

Early outcome studies on children exposed to repeat courses of ACS, as well as findings from animal models, led us to hypothesize that multiple courses of ACS would be associated with executive deficits in adolescence and young adulthood. However, our results warrant the conclusion that cognitive
and psychological function is not related to repeat ACS treatment. Nevertheless, the slight deficits in the most basic executive functions seen in those exposed to repeat ACS are illustrative. In this group, the impairment seems to be so subtle that it does not impact the more complex functions. However, we do not know if more effort was required to achieve the outcome or if there is a difference in the neural networks employed. It is interesting though, that although overall functioning seems unaffected, some very basic attention abilities show a slight attenuation.

The construct of executive functions – how they are defined, operationalized, and how they relate to other psychological and neurocognitive constructs – are important issues that are still not fully understood. Executive functions is a construct of interest within a diverse field of research ranging from genetics to developmental psychology, and the different research traditions adhere to a variety of theoretical frameworks. Confusion with regard to nomenclature is one consequence: identical terms can be used without necessarily reflecting the same underlying ability, and abilities that to all intents and purposes are identical can be referred to by different terms. With increased knowledge, perhaps a clearer and more universal understanding of what executive functions entail will emerge. I hope that the definitions and operationalization of executive functions used in these studies have worked within an emerging consensus rather than added to the plethora of terms in practice, and that the findings pertaining to executive functions contribute to their understanding.

Limitations and strengths

The primary limitation of all three studies is the less than ideal number of participants, given the powerful statistical methods applied. This limitation is addressed in the statistical considerations section. The statistical methods, on the other hand, have provided results that contribute to current knowledge. Not least, the application of a theoretical framework of executive functions and drawing conclusions based on latent constructs are a methodological strength.

The SNP cohort has been followed longitudinally over almost two decades with several points of data collection. The low attrition rate, the inclusion of a control group of demographically matched children born at full term, and comprehensive data constitute clear strengths and enable true longitudinal studies, as opposed to cross-sectional interpretations. In FAST, the prospective cohort design to a certain degree limits the generalizability of the results, and gives less control than randomized studies. Also, the attrition rate was
higher than ideal. However, the matched control group strengthens the design and lends credibility to the results.

The participants were all born in the late 1980s to the mid-90s; a time after which perinatal medical care has continued to improve. The spectrum of medical and cognitive effects of being born preterm has shifted with time. ACS treatment practice has also become more fine-tuned since the time of the FAST participants’ birth; routine administration of more than one or two courses is not in line with current knowledge. These cohort effects should be taken into account when discussing the implications of our findings for the clinical practice of today.

It was stated earlier that the cohorts under investigation have benefitted from universal and publically funded maternal and child medical care. Young mothers, minority groups, or underprivileged families may be overrepresented in other samples, but that is not the case in our cohorts. For SNP, this means the effect of preterm birth per se can be studied. The absence of major pregnancy and neonatal complications in the FAST cohort, where most individuals were born moderately preterm or at term, makes it possible to uncover effects of ACS exposure, without significant interference from severe maternal and perinatal morbidity or postnatal steroid exposure. The study is an important contribution to the knowledge of repeat administration of ACS and gives valuable input on the delicate balance between shorter-term benefits and potential longer-term detrimental effects of the treatment.

Lessons learned and directions for future research

The neuropsychological follow-up assessments in the studies are primarily based on clinical test batteries. The tests chosen give insights into cognitive functioning and indicate specific areas of strength and weakness, making them sensitive tools for detecting cognitive dysfunction. However, they all are impure with regard to exactly what they measure, and in that sense are wanting in specificity. A given result on a specific task can come about in many different ways, and we cannot always parse out what might underlie a performance below norm, or indeed identify compensatory strengths that might result in a performance at norm. From a developmental and neurocognitive perspective, earlier assessments, in infancy and the toddler years, of very basic functions would increase the possibility of identifying more specifically how perinatal stress alters the conditions under which continued development occurs. The current assessments inform us of outcome at a particular age, but give little input into the mechanisms that cause the pattern of strengths and weaknesses.
The notion that disturbances to the development of white matter adversely impacts connectivity and increases the risk of executive deficits is an area for further research. As we do have brain imaging data from the SNP cohort, an interesting line of research would be to see if we can find a relationship between the identified subgroups of preterm-born and the integrity or volume of white matter.

In retrospect, for the SNP cohort, additional assessments at around age 3 as well as in preadolescence, would have greatly added to understanding of at what age, what functions, and for which subgroups development stabilizes. For the FAST cohort, neuropsychological and behavioral data from the preschool years would have been extremely valuable. We still have no knowledge of the effect of repeat courses of ACS on the processes of aging. It could be that prenatal programming effects on the HPA axis may become more apparent in aging systems. Following the effects to old age is of clinical as well as theoretical interest.

Conclusions

Rough beginnings, which provide suboptimal conditions for early brain development, are related to great variation in cognitive outcome in late adolescence and early adulthood. The consequences of being born preterm have been subjected to a fair amount of research and many general conclusions have been drawn. These studies adds to our knowledge by using an established theoretical framework to differentiate executive functions into working memory and cognitive flexibility and by investigating the stability and developmental pathways from late preschool age to late adolescence separately. Apart from contributing to the construct of executive function itself, the stability in functions that the study elucidates, leads us to claim that executive function deficits exhibited in early childhood are likely to be lasting, and are not an expression of a developmental delay. The diverse outcomes, and the differences in developmental trajectories, become apparent in the longitudinal cluster analysis of Study II. The attenuation in cognitive function seen in group level studies was representative only for some subgroups of the preterm-born, indeed, almost half of the participants in this study performed at 18 years at levels at or above their term-born peers. Stability in outcome was true in this study as well; however, stability existed at very different levels of performance. To our knowledge, we are the first to report long-term outcome after repeat courses of antenatal corticosteroids. Study III shows that repeat exposure seems to have few long-term ramifications. This fact is an important contribution to our knowledge and is valuable when weighing the well-documented benefits of the treatment on neonatal health against possible adverse effects of long-term cognitive functioning.
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References


Obstetrics & Gynecology, 98(1), 144–150. doi:10.1016/S0029-7844(01)01410-7


