Irina Rannikko

CHANGE IN COGNITIVE PERFORMANCE AND ITS PREDICTORS IN GENERAL POPULATION AND SCHIZOPHRENIA IN EARLY MIDLIFE

THE NORTHERN FINLAND BIRTH COHORT 1966 STUDY
IRINA RANNIKKO

CHANGE IN COGNITIVE PERFORMANCE AND ITS PREDICTORS IN GENERAL POPULATION AND SCHIZOPHRENIA IN EARLY MIDLIFE
The Northern Finland Birth Cohort 1966 Study

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University of Oulu Graduate School; University of Oulu, Faculty of Medicine; Medical Research Center Oulu; Oulu University Hospital
University of Oulu, P.O. Box 8000, FI-90014 University of Oulu, Finland

Abstract
The aim of this study was to provide novel information on the change of cognitive performance and its predictors in early midlife between ages of 34 and 43 years. The change in verbal episodic memory between non-psychotic and schizophrenia samples was compared in the Northern Finland Birth Cohort 1966. In the non-psychotic sample, associations between primary school performance, sociodemographic factors and body mass index (BMI), and in the schizophrenia sample, between premorbid school performance and severity of illness with the change in cognitive performance were evaluated.

There was no evidence of greater decline in verbal episodic memory in the schizophrenia sample, compared to the non-psychotic sample, though the schizophrenia sample had an overall lower cognitive performance at the baseline. In the non-psychotic sample, male gender, poorer school performance, increases in BMI and having no children predicted a decline in verbal episodic memory; poorer school performance and low vocational education and occupational class predicted a decline in visual episodic memory; and having children predicted a decline in executive function. In the schizophrenia sample, poorer premorbid school performance, but not the later course of illness, was related to a decline in cognitive performance.

This study is one of the few studies to investigate the predictors of change in cognitive performance in the early middle-aged general population, and the first to investigate the predictors of cognitive change in early midlife schizophrenia.

To summarize; poor cognitive performance in adolescence may be considered as a vulnerability marker for a later impairment in cognitive functioning. In schizophrenia, cognitive ability possibly declines mostly in a normative fashion with aging at the same rate as in the general population rather than as a result of neurodegenerative processes. These results might improve our understanding of midlife change in cognitive functioning and may also help to develop effective interventions of cognitive impairment in schizophrenia.

Keywords: cognitive decline, cognitive performance, general population, midlife, predictor, review, schizophrenia
Rannikko, Irina, Kognitiivisen suorituskyvyn muutos ja siihen liittyvät tekijät yleisväestössä ja skitsofreniassa varhaisessa keski-iässä. Pohjois-Suomen vuoden 1966 syntymäkohorttitutkimus

Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta; Medical Research Center Oulu; Oulun yliopistollinen sairaala

Oulun yliopisto, PL 8000, 90014 Oulun yliopisto

Tiivistelmä

Tutkimuksen tavoitteena oli tuoda uutta tietoa kognitiivisen suoriutumisen muutoksesta sekä siihen liittyvistä tekijöistä varhaisessa keski-iässä ikävuosien 34 ja 43 välillä. Tutkimuksessa verrattiin kielellisessä muistisuoriutumisessa tapahtuvaa muutosta yleisväestön ja skitsofrenia-aineiston välillä Pohjois-Suomen vuoden 1966 syntymäkohortissa. Lisäksi yleisväestössä tutkittiin koulumenestysten, sosiodemografisten tekijöiden ja painoindeksin yhteyttä ja skitsofrenia-aineistossa koulumenestysten ja sairauden varhaisen kulun yhteyttä kognitiivisen suoriutumisen muutokseen.


Tämä on yksi harvoista tutkimuksista, joissa on selvitetty kognitiivisen suoriutumisen muutosta ennustavia tekijöitä varhaisessa keski-iässä, ja ensimmäinen, jossa on tutkittu kognitiivisen suoriutumisen muutosta ennustavia tekijöitä skitsofrenia-aineistossa varhaisessa keski-iässä.

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Asiasanat: ennustetekijä, keski-iä, kirjallisuuskatsaus, kognitiivisen suoriutumisen muutos, skitsofrenia, yleisväestö
In loving memory of my dearest father-in-law Kari Rannikko
Acknowledgements

I started to write this dissertation more and less by chance. I got an unforgettable opportunity to participate in the Northern Finland Birth Cohort 1966 study and to be a part of the invigorating research group, to get to know the wonderful people involved and to do some innovative and important work together. During the years that this study has been carried out, the research itself and the mutual and kind interaction with the colleagues involved have given me a wealth of experiences in both my professional and personal life.

This work is a part of the Northern Finland Birth Cohort 1966 study, started by Professor Paula Rantakallio (1930–2012) in 1965, and it was carried out at the Department of Psychiatry, at the University of Oulu. There are several persons, without whose help and support this dissertation study would not exist.

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Oulu, April 2016

Irina Rannikko
**Glossary of abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tbody>
<tr>
<td>AIM</td>
<td>Abstraction Inhibition and Working Memory</td>
</tr>
<tr>
<td>APA</td>
<td>American Psychiatric Association</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>CRCH</td>
<td>Care Register for Health Care</td>
</tr>
<tr>
<td>CRT</td>
<td>Cognitive Remediation Therapy</td>
</tr>
<tr>
<td>CVLT</td>
<td>California Verbal Learning Test</td>
</tr>
<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
</tr>
<tr>
<td>e.g.</td>
<td>exempli gratia, for example</td>
</tr>
<tr>
<td>ICD-10</td>
<td>International Statistical Classification of Diseases and Related Health Problems</td>
</tr>
<tr>
<td>IQ</td>
<td>Intelligence Quotient</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<tr>
<td>NFBC 1966</td>
<td>Northern Finland Birth Cohort 1966</td>
</tr>
<tr>
<td>PANSS</td>
<td>Positive and Negative Syndrome Scale</td>
</tr>
<tr>
<td>SCID</td>
<td>The Structured Clinical Interview for DSM disorders</td>
</tr>
<tr>
<td>SOFAS</td>
<td>Social and Occupational Functioning Assessment Scale</td>
</tr>
<tr>
<td>VOLT</td>
<td>Visual Object Learning Test</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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## Definitions

<table>
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<th>Term</th>
<th>Description</th>
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<tr>
<td>Cognitive functions</td>
<td>Separable but interrelated processes of acquiring, processing, storing and acting upon information.</td>
</tr>
<tr>
<td>Cognitive psychology</td>
<td>Study of mental activity as an information-processing condition.</td>
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<tr>
<td>Cognitive reserve theory</td>
<td>Suggests that access to education and other social resources conveys resilience to later life brain lesions, insults, and degeneration.</td>
</tr>
<tr>
<td>Cognitive impairment/deficit</td>
<td>An inclusive term to describe deficits in global intellectual performance or specific deficits in cognitive abilities.</td>
</tr>
<tr>
<td>Crystallized ability</td>
<td>An ability to use skills, knowledge, and experience.</td>
</tr>
<tr>
<td>Fluid ability</td>
<td>A capacity to think logically and solve problems in novel situations, independent of acquired knowledge.</td>
</tr>
<tr>
<td>Mental state examination</td>
<td>Examination of appearance and general behaviour.</td>
</tr>
<tr>
<td>Metamemory</td>
<td>An individual’s capacity to evaluate his/her own memory functions.</td>
</tr>
<tr>
<td>Neuropsychological assessment</td>
<td>Tasks that have been designed to assess specified cognitive functions and are administered in a standardized fashion defined in a test manual.</td>
</tr>
<tr>
<td>Social cognition</td>
<td>Ability to act wisely in social interactions.</td>
</tr>
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</table>
List of original publications

This thesis is based on the following publications, which are referred throughout the text by their Roman numerals:


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1 Introduction

Cognitive ability, a set of various intellectual processes, is an essential requirement in the contemporary information society and in the vocational life of a person. Cognitive development occurs from childhood through adolescence into adulthood and refers to how a person perceives, thinks, and gains understanding of his/her world through the interaction of genetic and learned factors (e.g. Johnson 2005). Among the areas of cognitive development are mental abilities related to information processing, attention, reasoning, judgment and evaluation, problem solving and decision making, language development, and memory.

When using the term cognitive ability, we need to limit the range of cognitive activities to those that centrally involve mental functions not only in the understanding of the intended end results but also in the performance of the task, most particularly in the processing of mental information (Carroll 1993). Thus, a cognitive task is any task in which the correct or appropriate processing of mental information is critical to successful performance and a cognitive ability is any ability that concerns some class of cognitive tasks (Carroll 1993).

Longitudinal population-based studies (Hultsch et al. 1998, Schaie 1996, Sliwinski & Buschke 1999) suggest that as we get older, our cognitive abilities gradually deteriorate. However, cognitive change over a lifespan is gradual, suggesting that cognitive changes may be an ordinary developmental process. Further, a change of cognitive ability is not unitary. Crystallized abilities increase up to the sixth or seventh decade, and may decrease in late old age. In contrast, memory and cognitive speed generally show continuous linear decline during adulthood, with further acceleration in late old age (Christensen 2001).

Systematic reviews have linked a wide range of theoretical areas, such as biological, social, emotional, and sociodemographic factors (e.g. age, education, occupation class, and social engagement) to a cognitive decline in late life (e.g. Prince et al. 2012; Marioni et al. 2012). However, there is a paucity of studies focused on predictors of change in cognition in the general population and schizophrenia in early midlife, which is a crucial period of a person’s life cycle with regards to key social everyday life.

In addition to normative cognitive deterioration, cognitive impairments may be caused by environmental factors such as brain injuries, neurological disorders, or mental illness such as schizophrenia. The course and consequences of schizophrenia, and cognitive impairment as a core feature of schizophrenia, are of great scientific and public health importance.
Reports of cognitive deficits in schizophrenia date back to the pioneering efforts of Emil Kraepelin (Kraepelin 1919) and Eugen Bleuler (Bleuler 1911). Meta-analyses and other recent literature have linked schizophrenia to a broadly based cognitive impairment that varies in severity in different patients across all phases of the illness (Bora & Murray 2014) and also varies in severity across neuropsychological domains (Heinrichs & Zakzanis 1998). Further, cognitive impairment has been found already at the onset of the disorder (Hoff et al. 2005) and even long before psychosis becomes manifest (David et al. 1997, Reichenberg et al. 2002). There is also some evidence that cognitive impairments continue into the chronic stages of the illness (e.g. Bilder et al. 1992, Heaton et al. 1994). Despite increasing interest, the longitudinal course and predictors of cognitive deterioration in schizophrenia are not understood (e.g. Bora & Murray, 2014, Nuechterlein et al. 2014).

The topic of this present doctoral thesis is the change in cognitive ability and its predictors in the general population and schizophrenia in early midlife. The aim was to compare the change in cognitive performance and its predictors in non-psychotic subjects and individuals with schizophrenia 10–20 years after the illness onset during a nine-year follow-up between ages 34 and 43.
2 Review of the literature

2.1 Human neuropsychology

2.1.1 History of human neuropsychology

The highest levels of the human brain engage in processes of almost unfathomable complexity and flexibility: processes such as perceiving, thinking, remembering, feeling, and speaking. These cognitive or mental processes and their underlying behavior constitute the mind (Lezak et al. 2004). Simply knowing that the brain controls behavior is not enough. Modern thinking about the question of how the brain controls behavior began with the French anatomist and philosopher Rene Descartes (1596–1650). Described as nonmaterial and without spatial extent, as Descartes saw it, the mind was seen as being different from the body and determined what movements the body should make (Kolb & Whishaw 2009). By the mid-nineteenth century, another, evolutionary theory of the brain and behavior was developed by two English naturalists, Alfred Russell Wallace (1823–1913) and Charles Darwin (1809–1892). This theory was based on the idea that rational behavior can be fully explained by the working of the nervous system, without any need to refer to a nonmaterial mind (Kolb & Whishaw 2009).

Beginning in the early 1800s, scientists began to test their ideas about brain function by examining and measuring the brain and by developing methods to describe behavior quantitatively. One of the important neuropsychological ideas that resulted from these experimental approaches is that significant development of the central and peripheral nervous systems occurs throughout early life, with major alterations being observed from infancy to adolescence, and that both genetic and experiential factors play a role in how brain networks develop (Nelson 2000, Williamson et al. 2003). Both structural and functional changes in these systems permit the rapid improvements in cognitive abilities observed from infancy through late adolescence, as well as into adulthood (Huttenlocher 1994). Thus, examination of normative cognitive development, as well as pathological patterns, such as delays or impairments in cognitive function, is crucial to identifying individual profiles of cognitive performance deficits later in life, or detecting risk factors for the onset of psychiatric illness later in life.

Cognitive psychology – the study of mental activity as an information-processing condition – has made considerable progress over the last few decades
and has developed sophisticated theories and models about specific cognitive domains or processes (such as object perception, word recognition, syntactic parsing, etc.). Cognitive psychology rests on the assumption that we do not directly perceive and act in the world (Cazzaniga et al. 2008). Rather, our perception, thoughts, and actions depend on internal transformations or computations. Information is obtained by sense organs, but our ability to comprehend that information, to recognize it as something that we have experienced before, and to choose an appropriate response depends on a complex interplay of processes.

By the end of the 1950s, psychologists had a secure role in all aspects of the neuropsychological assessment and rehabilitation of patients with cognitive disorders (Kolb & Wishaw 2009). Furthermore, age-related changes in cognitive ability occur regarding normative development in childhood, including quantitative increments in cognitive performance. Over the past 50 years, a number of studies have been conducted to examine neuropsychological performance in children, with the goal of identifying areas of cognitive function that might be associated with the onset of neuropsychiatric conditions. Deficits in cognitive development as a risk of schizophrenia have been studied extensively in children of parents with schizophrenia, with such studies examining a wide range of clinical, experimental and cognitive measures.

### 2.1.2 Cognitive domains

A cognitive process in general is an action in which mental contents are operated on to produce some form of a response (Lezak et al. 2004). These mental contents may be representations or encodings either of external stimuli or of images, knowledge, rules, and similar materials from memory (Carroll 1993). Various domains of cognitive process are generally associated with a neuropsychological evaluation. These domains include traditional components of a neuropsychological evaluation, such as memory, verbal skills, visuospatial functions, attention, processing speed and executive functions (Zillmer & Spiers 2001).

**Memory**

Memory is central to all intellectual functions and probably all that is characteristically human in a person’s behavior is the capacity for memory and learning (Johnson 2005). It is characterized as an ability to store and recall information or as an active process that records information from the past so that it
may be used in the present. It involves a number of processes including encoding or registration (receiving, processing and combining of received information), storage (creation of a permanent record of the encoded information) and retrieval or recall (calling back the stored information in response to some cue for use in a process or activity). (Green & Kopelman 1997).

Memory is commonly divided into short-term and long-term memory, with both types further fractionated into declarative and procedural memory. Declarative memory (also explicit or cognitive) refers to conscious recollection and recall that can be brought to mind as an image or proposition. Procedural memory (also implicit or habit) does not require the intentional or conscious recollection of an experience. It refers to memory that is embedded in a skill or procedure and includes priming, classical conditioning and skill-based learning (Squire 1986).

Working memory is the ability to apprehend and hold information in immediate awareness while simultaneously performing a mental operation. It is a central component to the development and functioning of many other cognitive processes including attention, language and executive functioning. This also permits the integration of other information from long-term memory during the performance of cognitive tasks (Lezak et al. 2004). Because working memory requires the individual to have direct intent and the strategic or controlled allocation of attentional resources to perform working-memory tasks, it has been considered a part of executive functioning.

Behavioral development in memory functioning may be due to the emergence of functions in non-memory-related brain systems (Murray 2000). It is however known, that several types of procedural memory are probably dependent on subcortical structures such as the cerebellum and hippocampus, whereas the declarative memory system may involve regions of the temporal cortex becoming coordinated with the hippocampus, possibly through a process of increasing, input-dependent specialization (Johnson 2005). Table 1 presents one classification of memory systems and developmental memory functions, and brain structures related to them based on the analysis of Nelson and Webb (2003).
Table 1. The major memory systems and developmental memory functions (Nelson & Webb 2003)

<table>
<thead>
<tr>
<th>General memory system</th>
<th>Subsystems</th>
<th>Function</th>
<th>Neural systems related to memory function</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Pre-explicit memory</td>
<td>Novelty detection in habituation and pared comparison tasks</td>
<td>Hippocampus</td>
</tr>
<tr>
<td></td>
<td>Semantic (generic knowledge)</td>
<td>Semantic retrieval, word priming, and associative priming</td>
<td>Left prefrontal cortex, anterior cingulate hippocampal cortex</td>
</tr>
<tr>
<td></td>
<td>Episodic (autobiographical)</td>
<td>Episodic encoding</td>
<td>Left prefrontal cortex, left orbitoprefrontal cortex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recall and recognition</td>
<td>Right prefrontal, anterior cingulate, parietal, cerebellum, hippocampal cortex</td>
</tr>
<tr>
<td>Procedural memory</td>
<td>Procedural learning</td>
<td>Serial reaction time tasks</td>
<td>Striatum, supplementary motor association, motor cortex, frontal cortex</td>
</tr>
<tr>
<td></td>
<td>Conditioning</td>
<td>Visual expectation paradigm</td>
<td>Frontal cortex, motor areas</td>
</tr>
<tr>
<td></td>
<td>Perceptual representation system</td>
<td>Perceptual priming paradigms</td>
<td>Modality-dependent: parietal cortex, occipital cortex, inferior temporal cortex, auditory cortex</td>
</tr>
</tbody>
</table>
Language and verbal skills

People communicate and share information by using verbal skills. The *language domain* itself is extremely complex and there are many different aspects to knowing and using a language. Thus, if a person has trouble with verbal skills, it can be difficult to find the reason for it. There is, however, a sense in which all language abilities tend to cohere, separately from other abilities (Carroll 1993). From the developmental perspective, a prominent portion of an individual’s very early life is spent learning to speak and understand the spoken form of the native language, that is, in acquiring an implicit knowledge of the structure and vocabulary of that language. Individuals differ in their rates of language acquisition, but their common experience is to develop by the age of about five years what can roughly be characterized as the competence of a ‘native speaker’ (Carroll 1993). In the “normal” child, this kind of language development takes precedence over the acquisition of skills in reading, writing, and certain more specialized skills. Individuals tend to become differentiated in levels of those other skills only at ages beyond the age of five or so. By the time of adulthood, however, the individual differences in various specialized language skills can become quite pronounced, and substantially independent of each other.

In the language domain, it can be expected that abilities tend to become differentiated with age, as was first suggested by H. E. Garrett in 1938 (Carroll 1993). Further, all language abilities tend to be highly correlated; individuals tend to differ – certainly over different ages, and also within groups of the same age – in their general level of language development. Rates of acquisition differ also with respect to specific aspects of language development, for example, vocabulary, grammar, reading comprehension, reading speed, oral production ability, etc. But there is also some specialization of abilities: some individuals are specialized in speaking skills, other are specialized in reading and writing skills, and so on (Lezak et al. 2004).

Some of the key brain structures involved are in language processing. the so-called *Broca’s area* in the inferior frontal gyrus in the dominant cerebral hemisphere (which is the left hemisphere in about 95% of right handed individuals and 60% of left handed individuals) is largely responsible for language processing and speech production, and *Wernicke’s area* in the posterior section of the superior temporal gyrus of the dominant hemisphere (usually the left) is important for speech comprehension (Lezak 2004).
Visuospatial function

Visuospatial perception may be defined as the ability to generate, retain, and manipulate abstract visual images. Often visual abilities have been discussed under the heading of ‘spatial/visuospatial ability’, because at least some of them have to do with how individuals deal with materials presented in space – whether in one, two or three dimensions, or with how individuals orient themselves in space (Carroll 1993). In concrete terms, the brain, not the eyes, processes the visual world, including things like symbols, pictures and distances. As such, visuospatial abilities have to do with the individual’s abilities in searching the visual field, apprehending the forms, shapes, and positions of objects as visually perceived, forming mental representations of those forms, shapes, and positions, and manipulation such representations ‘mentally’ (Kolb & Wishaw 2009). Visual processing deficits may impact the ability to perform ordinary tasks such as sorting visual material or may even affect how a person learns.

Although recent research offers a considerable amount of knowledge about individual differences in the domain of visuospatial perception, there are still many gaps in this knowledge. Several psychometrically major discriminable factors in the domain of visuospatial perception have been applied (Carroll 1993): (1) Visualization or ability in manipulating visual patterns, as indicated by the level of difficulty and complexity in visual stimulus material. (2) Spatial relation, which means a speed in manipulating relatively simple visual patterns, by mental rotation, transformation, or otherwise. (3) Closure speed or speed in apprehending and identifying a visual pattern, without knowing in advance what the pattern is, when the pattern is disguised or obscured in some way. (4) Flexibility of closure, a speed in finding, apprehending, and identifying a visual pattern, knowing in advance what is to be apprehended, when the pattern is disguised or obscured in some way. (5) Perceptual speed or speed in finding a known visual pattern, or in accurately comparing one or more patterns, in a visual field such that the patterns are not disguised or obscured.

Visual image processing begins in the primary visual cortex, which is primarily located on the medial side of the occipital lobe (Kolb & Wishaw 2009). The visual pathway from the eyes to the primary visual cortex passes through the center of the brain. From the primary visual cortex, two pathways transfer information forward to visual association areas, where visual signals are further interpreted and given additional meaning.
Attention

The ability to focus attention on a task is a requirement for the achievement of an individual’s goals. Attention refers to the processes of selecting and attending to a limited amount of material for enhanced processing while filtering out other information (Chun et al. 2011), where the attention span is the amount of concentrated time the subject can spend on a task without becoming distracted. Acknowledging the pioneering research of Lev Vygotsky (1978) and Alexander Luria (1973), attention is identified as one of the three major co-active processes of the working brain: attention, memory, and activation.

It is clear that attention is not a unitary construct. Posner and Petersen (1990) proposed that attention should be broken down into three main functions: alerting, orienting, and executive control. Alerting is defined as achieving and maintaining an alert state; orienting is the selection of information from sensory input; and executive control is defined as resolving conflict among responses (Fan et al. 2002). Further, estimates for the length of attention span are highly variable and depend on the precise definition of the components of attention being used: (1) Divided attention, is the ability to perform two tasks simultaneously; when the two simultaneous tasks use the same modality it is much more difficult to concentrate on both because the tasks are likely to interfere with each other. (2) Selective sustained attention, also known as focused attention, is the ability to filter out irrelevant information to focus on the task and to maintain attention producing consistent results over an extended time. (3) Attentional switching, is the ability to switch between attention sets and to perform two or more tasks simultaneously.

Attention is a very basic function that is often a precursor to all other neurological/cognitive functions and other variables, such as anxiety, arousal, task difficulty, skills, and culture, play a part in a human being’s ability to pay attention to and concentrate on many tasks at once (Kolb & Wishaw 2009). In many cases attention produces changes in the electroencephalography (Baldauf & Desimone 2014). Alerting, the process involved in becoming and staying attentive toward the surroundings, appears to exist in the frontal and parietal lobes of the right cerebral hemisphere (Coull et al. 1996), and the executive control of attention may take place in the anterior cingulate cortex (Fan et al. 2001).
**Processing speed**

*Processing speed* relates to an individual’s ability to perform simple repetitive cognitive tasks quickly and automatically (Schneider & McGrew 2012). The term ‘processing speed’ refers to the speed with which different cognitive operations can be executed. This is the ability to select and initiate the appropriate response relative to a received stimulus in a situation where more than one stimuli are possible, and where the appropriate response is selected from more than one alternatives (Smith 1991). In other words, processing speed is the pace at which we take in information, make sense of it and begin to respond. This information can be visual, such as with letters and numbers. It can also be auditory, such as when hearing spoken language.

Because *multiple brain regions* are involved in this function, the processing speed tasks are often relatively cognitively complex; they include useful field-of-view perception, digit-symbol substitution, identical picture identification, lexical decision tasks, and sentence verification (Ritchie et al. 2013).

The importance of processing speed lies in the fact that many higher cognitive operations – including perceptual processes, encoding and retrieval operations, transformation of information held in active memory, and decision processes – involve internal dynamics that are speed-dependent to some extent (Reichenberg 2010). Hence, reaction time measurements, particularly those derived from tasks involving the more complex forms of encoding and decision processes, tend to be correlated with various tests of cognitive ability (Carrol 1993).

Slow processing speed relates to a reduced ability to automatically or fluently perform complex cognitive tasks (Wendling & Mather 2009). Thus, changes in *white matter* that are associated with a reduction in processing speed may also be a sign of affected performance in other cognitive domains, such as attention and working memory. As a result, areas of difficulty for individuals with poor processing speed may include: (1) *Perceptual speed* which involves psychomotor speed, and means how fast something is copied, written or manipulated. (2) *Visual discrimination*, which means how quickly identical items, such as letters, numbers, objects, pictures, or patterns in a series or array are identified.

**Executive functioning**

The concept of *executive functioning* has its historical roots in attempts to delineate the higher cognitive functions of human information processing (Miyake *et al.*...
Executive functions are integrated cognitive processes that are involved in the maintenance and shifting of cognitive and behavioral responses to environmental demands permitting the control of action and long-term goal-directed behavior (Palmer & Heaton 2000). Further, executive functions are superordinate in the orderly execution of daily life functions. This includes the ability to formulate goals; to initiate behavior; to anticipate the consequences of actions; to plan and organize behavior according to spatial, temporal, topical or logical sequences; and to monitor and adapt behavior to fit a particular task or context. Abilities underlying such activities are thought to include: searching long-term knowledge stores, abstraction and planning, reasoning and problem-solving skills, initiation, self-monitoring, mental flexibility, and inhibition of immediate responses in pursuit of longer-term goals (Palmer & Heaton 2000).

Executive functions have been used synonymously with the term *frontal-lobe functions* implicating that these functions have historically been associated with multiple cortical networks including the brain’s prefrontal cortex. More recent conceptualizations of executive functioning include fractionation into various sub-processes (Miyake et al. 2000), and the view that not all executive processes are uniquely sustained by the frontal cortex. Specifically, some executive processes may be sustained by a distributed cortical network, rather than by a unique frontal region which may or may not be associated with the frontal lobes (Andres & Van der Linden 2001).

### 2.1.3 Neuropsychological assessment

Cognitive psychology focuses on understanding how objects or ideas are represented in the human brain and how these representations are manipulated. Thus, the primary goals of cognitive psychology include identifying how various human mental processes may be defined and measured, and exploring limitations in task performance (e.g. Carroll 1993, Cazzaniga et al. 2008).

A valid *neuropsychological assessment* is required for an adequate estimate of cognitive performance. Neuropsychological assessment was traditionally carried out to assess the extent of impairment to a particular skill and to attempt to determine the area of the brain which may have been damaged following brain injury or neurological illness (Lezak 2004).

Many *cognitive tasks* are complex, but can often be divided into distinct processes, stages, or components. Further, many tasks are imposed by others, such as when an individual is asked a question, presented with an item on a
psychological test, or requested to perform some action. The specifiability of the end results of a particular task is crucial because the individual performing the task must have some notion of what type of end result is to be attained and possibly of the criterion or criteria by which attainment of the end result is to be assessed.

Psychometric tests have been designed to assess specified cognitive functions and are administered in a standardized fashion defined in a test manual (Carroll 1993). Such tests are given to a normative sample group in order that the performance of the patient can be compared with that of a representative reference (i.e. individuals who have not suffered any form of neurological or neuropsychiatric conditions). The typical scores of the normal control group are used to produce norms. A test is considered to have reliable norms if the reference group is representative of the general population in terms of all the factors likely to influence test performance (e.g. age, gender, level of education). Test scores are expressed in terms of a “standard score”. A standard score is a measure of the distance of the subject’s score from the average of the reference group.

From the early 1950s until now, batteries of tests were developed, each with a different focus (Kolb & Wishaw 2009). A comprehensive neuropsychological assessment should address the practical or functional consequences of cognitive impairment for the individual (Kolb & Wishaw 2009). It should be conducted in terms of the disabilities caused and the likely handicapping effect of those disabilities in relation to activities of daily living, work, education, leisure, and social relationships. Thus, neuropsychological assessment has several main purposes (Groth-Marnat 1999): (1) To help with diagnosis in the context of other observations and findings from the background history, clinical and mental state examination, and the results of physical investigations. (2) To identify and quantify the pattern and severity of cognitive impairment. (3) To plan strategies of cognitive rehabilitation.

2.2 Schizophrenia and other schizophrenia spectrum psychoses

Over the past 40 years, it has become clear that psychiatric disorders have biochemical, anatomical, and genetic bases (Randolph et al. 1993). Schizophrenia, the most common severe psychotic disorder, is a major public health problem afflicting about 1% of humans, and beginning in early adult life. It is third of all causes of disability adjusted life-years in the world among people aged 10–24 years (Gore et al. 2011). The nature of this mental illness consists of multiple interacting genetic and environmental causes and a heterogenic set of psychotic symptoms (e.g.
hallucinations, delusions, thought disturbances), cognitive impairment, social and occupational withdrawal, restricted affects and poor motivation.

Schizophrenia appears in early adolescence and can drastically impair everyday functional abilities and has extensive negative social and personal consequences on social life, vocational education and employment (Harvey & Strassing 2012, Tuulio-Henriksson et al. 2004). Compared to the general population, individuals with schizophrenia have increased rates of physical illnesses (Crump et al. 2013). They also suffer from a 2–4-fold higher mortality risk, and their life expectancy is about 10 to 25 years shorter than in the general population, mostly by natural causes of death (Laursen et al. 2012). Antipsychotic drugs relieve symptoms and prevent relapses, but have limited efficacy, particularly on negative and cognitive symptoms, as well as neurological and metabolic side effects. The proportion of recoveries has decreased during the last decades (Jääskeläinen et al. 2013), despite the invention of antipsychotics.

The health care and social assistance costs incurred as a result of psychotic disorders are high. The estimated total costs due to non-affective psychoses F20–F29 in the year 2004 in Finland being 1.3 billion euros, and the roughly estimated total costs due to schizophrenia being 900 million euros (Wahlbeck & Hujanen 2008). Further, according to the World Health Organization (WHO 2008), in 2004 there were 26.3 million people suffering from schizophrenia worldwide, thus representing a serious global public health problem. Although there are a variety of environmental and cultural influences that impact everyday functioning in both positive and adverse directions, most impairments in schizophrenia are homogeneous across different countries and cultures, indicating that it is not caused by cultural factors (Jablensky et al. 1992). Rather, the fact that the symptoms observed in different patients are heterogeneous, suggests that the biological correlations will also be heterogeneous (Randolph et al. 1993).

The heterogeneity of schizophrenia as a syndrome appears not only in its core psychopathology but also in terms of the course of the disorder (Reichenberg 2010, Shmukler et al. 2015). Through careful and comprehensive research, it has become increasingly apparent that, in addition to the diverse symptoms that form the clinical definition of the illness, the disorder is to a variable degree accompanied by a generalized cognitive impairment (Tuulio-Henriksson et al. 2011, Reichenberg & Harvey 2007). The extent of the cognitive defects with their role as a key predictor of functional disability in schizophrenia, and its effective prevention and rehabilitation are major clinical challenges (Henderson & Malhi 2014).
2.2.1 Epidemiology, aetiology, symptoms and diagnosis of schizophrenia

Epidemiology of schizophrenia

Schizophrenia is one of the most severe mental illnesses afflicting all known human societies and cultures with an often unfavorable prognosis. The life-time prevalence of psychoses – i.e. the total number of individuals known to have had the disease for at least part of their lives – is estimated between 0.2 and 3.5% (Perälä et al. 2007, Saha et al. 2005). In Northern Finland it is estimated to be as high as 1.8% (Perälä et al. 2008). The annual incidence of schizophrenia is the number of new events, e.g., new cases of a disease in a defined population within a specified period of time (Last 2001). It varies markedly across and within populations between 0.01 and 0.035 % (Schultze-Lutter et al. 2015), with growing numbers reported in Europe, where within one year approximately 3.7 million adults (0.8%) had been affected in 2005 and as many as 5 million (1.2%) in 2011 (Kirkbride et al. 2006, Wittchen et al. 2011). In the Northern Finland Birth Cohort 1966 (NFBC 1966), the cumulative incidence of schizophrenia by the age 44 years was 1.4% (Keskinen et al. 2013).

The course of schizophrenia is very individual and often chronic. It can occur at any age, but in women incidence peaks at age 18–28 years, in general 3–4 years later than in men (Sutterland et al. 2013). However, a greater rise in the incidence of psychoses among women older than 40 than among men has been found (Kirkbride et al. 2006). Approximately 10–15% of all psychoses are early-onset psychoses manifesting before the age of 18, and approximately 1–3% are very-early-onset psychoses with an onset before the age of 13 (Wittchen et al. 2011). Despite the infrequency of very-early-onset psychoses, schizophrenia is one of the ten main causes of disability-adjusted life years in 10–14-year-old boys and 15–19-year-old girls (Gore et al. 2011).

Somatic comorbidity (Alaräisänen et al. 2009), as well as a high risk of metabolic syndrome (Saari et al. 2005) and obesity (Hakko et al. 2006, Saari et al. 2006) are common in schizophrenia, already at a relatively early age. Especially due to suicides, the rate of mortality in schizophrenia is two to three times as high as for the general population (Alaräisänen et al. 2009, Bushe et al. 2010, Saha et al. 2007).

Some individuals with schizophrenia are able to achieve symptomatic remission, which ranged from 7% to 52% (Lang et al. 2013), or even recovery from
the illness after the first episode (Jääskeläinen et al. 2013). However, according to a recent meta-analysis of 50 studies since 1921, the median percentage of recovery in schizophrenia was 13.5%, and disappointingly it has decreased during the last decades (Jääskeläinen et al. 2013).

Cognitive impairments, which vary in severity in different patients, have proven to be a major predictor of overall functional deficit in schizophrenia (Reichenberg 2010) including a steep decline in socioeconomic status and social life alongside the onset of illness (Aro et al. 1995). In addition to high direct non-medical and indirect costs, the burden caused by stigma and discrimination is among the highest in psychosis (Rössler et al. 2005).

**Aetiological models for schizophrenia**

The etiology of schizophrenia has been the focus of intensive research for a long time. Several aetiological models for schizophrenia have been detected. The pathogenesis of schizophrenia seems to be greatly influenced by both genetic risk factors as suggested by the vulnerability-stress model (van Os et al. 2010) and interactions between different genes and the environment as defined by the inheritance model of schizophrenia (Mittal et al. 2008, Cardno & Owen 2014).

Clinical observations started by Kraepelin (Kraepelin 1919) are now being complemented by epidemiological, neuroimaging and genetic studies to prove the neurodevelopmental hypothesis, according to which schizophrenia is a result of insufficient brain development starting from the fetal period of life (Rapoport et al. 2012) and affecting brain maturation in a way that is different from healthy aging (Douaud et al. 2014). A neurodevelopmental hypothesis claims that schizophrenia is a disorder of brain development. It views schizophrenia as a lifetime disorder of development, plasticity, and ageing with windows of vulnerability at all stages of life (Perkins et al. 2005). By definition, the disease should be early-onset not late onset, untreatable not treatable, and static not progressive (Gupta & Kulhara 2010). Certain aspects, however, such as the effectiveness of antipsychotic medication and the possibility of recovery (median 13.5% of cases, Jääskeläinen et al. 2013) go against the neurodevelopmental hypothesis (Gupta & Kulhara 2010).

At the same time, neuropathological and longitudinal studies of schizophrenia often support a neurodegenerative hypothesis. The neurodegenerative model of schizophrenia identifies progressive neurodegeneration as a core attribute of the disease (Gupta & Kulhara 2010, Kochunov & Hong 2014). By definition, the disease should have both characteristic histopathological features and a
histopathological progression. However, the absence of histological evidence of degeneration is the strongest argument against neurodegeneration.

Another hypothesis called the *progressive neurodevelopmental model* has also emerged from the recent research findings. It brings together two previous hypotheses, the neurodevelopmental and neurodegenerative hypotheses, and claims that schizophrenia is a complex and unique disorder (Gupta & Kulhara 2010, Isohanni *et al.* 2010, Kobayashi *et al.* 2014). Thus, it cannot be explained by a single process of development or degeneration and possibly requires a unique biological explanation. Regarding the treatment aspects, it should be emphasized that approaching schizophrenia as having *components of various dynamic processes* involved in neurodevelopment and neurodegeneration is therapeutically more optimistic.

**Symptoms of schizophrenia**

The symptoms of schizophrenia can be divided into positive symptoms (hallucinations, delusions and dissociative speech and behavior) and negative symptoms (apathy, restricted affects, passive social withdrawal and anhedonia) (WHO 1992; APA 2013). There is no one symptom that is essential to schizophrenia, thus the clinical picture varies from one person to another. Variations in symptoms occur even in the same patient. However, there is still one core feature of psychosis, which is a loss of contact with reality.

In the individuals who develop schizophrenia a line of subtle early sings, such as cognitive, social, and motor impairments, can already be seen in childhood. These early subtle symptoms have been noticed in adolescence and early adulthood before the onset of the first actual psychotic episode and the period is often called the prodromal state or clinical high-risk state (Du 2015).

The *symptomatic course* of schizophrenia is very individual. It can be either continuous or episodic with various deficits from progressive to stable and might include complete or incomplete remission (Farangou 2008, Jääskeläinen *et al.* 2013).

**Diagnosis of schizophrenia**

A variety of diagnostic systems have been used over the past 100 years, leading to much confusion. *Criteria* to diagnose the disorder continue to develop and evolve over time. The *DSM-5* (Diagnostic and Statistical Manual of Mental Disorders;
APA 2013) and *ICD-10* (International Statistical Classification of Diseases and Related Health Problems; WHO 1992) are both currently used in diagnosing schizophrenia.

With time, the diagnostic criteria of the two systems have approached one another; however, in ICD-10 one of the features is for the key symptoms to have been present for a significant portion of time more than a one-month-period, whereas the DSM-5 requires that continuous signs of the disturbance persist for at least six months, including at least one month of active symptoms. Additionally, the diagnostic criteria of the DSM-5 no longer identify subtypes of schizophrenia, such as paranoid, disorganized, or catatonic schizophrenia.

In Finland, clinicians use the ICD-10 diagnosis whereas the DSM-system is more common in research. The diagnostic systems employed in this doctoral thesis are the DSM-III-R, which is the revised version of the DSM-III introduced in 1987 (APA 1987), and the DSM-IV, which was published in 1994 (APA 1994). DSM-5 is the current version of the DSM-guidelines (APA 2013), thus it is also discussed below.

There are several differences in the diagnosis criteria for schizophrenia between the DSM-III-R, DSM-IV diagnosis systems and the currently used DSM-5 system (Bhati 2013, Tandon *et al.* 2013). In the DSM-5, the duration of characteristic symptoms is extended to a minimum of one month compared to one week in the DSM-III-R diagnosis. Further, subtypes of schizophrenia are eliminated and negative symptoms are added to the characteristic symptoms.

The diagnostic criteria for schizophrenia according to the DSM-III-R, DSM-IV and DSM-5 systems are represented in Table 2 (APA 1987, 1994 and 2013).
<table>
<thead>
<tr>
<th>Description</th>
<th>DSM-III-R</th>
<th>DSM-IV</th>
<th>DSM-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis code:</td>
<td>295 (except 295.4 and 295.7)</td>
<td>295 (except 295.4 and 295.7)</td>
<td>295 (except 295.4 and 295.7)</td>
</tr>
<tr>
<td>Duration of the characteristic symptoms:</td>
<td>≥ 1 week</td>
<td>≥ 1 month</td>
<td>≥ 1 month</td>
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**Characteristic symptoms and signs:**

**Criterion A:**

1. Bizarre delusions
2. Somatic, grandiose, religious, nihilistic or other delusions without persecutory or jealous content
3. Delusions with persecutory or jealous content if accompanied with hallucinations of any type
4. Auditory hallucinations
5. Prominent hallucinations of a voice with content having no apparent relation to depression or elation, or a voice keeping up a running commentary on the person’s behavior or thoughts, or two or more voices conversing with each other.

At least two of the following:

1. Delusions
2. Hallucinations
3. Disorganized speech (e.g., frequent derailment or incoherence)
4. Grossly disorganized or catatonic behavior
5. Negative symptoms

Note: Only one Criterion A symptom is required if the delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person’s behavior or thoughts, or two or more voices conversing with each other.
<table>
<thead>
<tr>
<th>Description</th>
<th>DSM-III-R</th>
<th>DSM-IV</th>
<th>DSM-5</th>
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<tbody>
<tr>
<td>6. Incoherence, marked loosening of associations, markedly illogical thinking, or marked poverty of content of speech if associated with blunted, flat or inappropriate affect/delusions or hallucinations/catatonic or other grossly disorganized behavior</td>
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<tr>
<td><strong>Criterion B:</strong> During the course of the disturbance functioning in such areas as work, social relations, and self-care is markedly below the highest level achieved before the onset of the disturbance.</td>
<td>Social/occupational dysfunction: For a significant portion of time since the onset of the disturbance, one or more major areas of functioning such as work, inter-personal relations or self-care are markedly below the level achieved prior to the onset.</td>
<td>Disturbances in at least one major area of social/occupational functioning</td>
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<tr>
<td><strong>Criterion C:</strong> Duration</td>
<td>Continuous signs of the disturbance persist for at least six months, including active phases of criterion A-symptoms for at least one week, with or without prodromal or residual symptoms.</td>
<td>Continuous signs of the disturbance persist for at least six months including at least one month of active symptoms (or less if successfully treated) and periods of prodromal or residual symptoms.</td>
<td>Continuous signs of the disturbance persist for at least six months, including active phases of criterion A symptoms for at least one month.</td>
</tr>
<tr>
<td><strong>Criterion D:</strong></td>
<td>A full depressive or manic syndrome, if present, developed after any psychotic symptoms or was brief in duration relative to the duration of the psychotic symptoms in A.</td>
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<tr>
<td><strong>Criterion E:</strong> Onset of the prodromal or active phase of the illness before age of 45.</td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Exclusion criteria:</strong> Criterion F:</td>
<td>Criterion D:</td>
<td>Criterion D:</td>
<td></td>
</tr>
<tr>
<td>Organic mental disorder or mental retardation</td>
<td>Schizoaffective or mood disorder</td>
<td>Schizoaffective and mood disorder</td>
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<td></td>
<td>Substance use or other medical condition</td>
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<tr>
<td>Description</td>
<td>DSM-III-R</td>
<td>DSM-IV</td>
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<tr>
<td>Criterion E:</td>
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<td>Substance use or other medical condition</td>
</tr>
<tr>
<td>Relation to Global Developmental Delay or Autism Spectrum Disorder - the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least one month (or less if successfully treated).</td>
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</table>

Criterion F: If there is a history of Autistic Disorder or another Pervasive Developmental Disorder, the additional diagnosis of Schizophrenia is made only if prominent delusions or hallucinations are also present for at least one month (or less if successfully treated).

DSM = Diagnostic and Statistical Manual of Mental Disorders; APA = American Psychiatric Association.
2.2.2 Other schizophrenia spectrum psychoses

Schizophrenia spectrum disorders are a group of other non-affective psychoses including mostly and in this study the schizophreniform disorder, persistent delusional disorder, and schizoaffective disorder.

In the schizophreniform disorder (F20.81; ICD-10), there are similar symptoms as in schizophrenia, but they are present for a significant portion of the time but for no more than six months. When compared to the often gradual onset of schizophrenia over a number of months or years, the onset of the schizophreniform disorder can be relatively rapid (DSM-5; APA 2013). A decline in overall functioning is not required for the diagnosis of the schizophreniform disorder. However, most individuals with this diagnosis have social or occupational impairments and some will also fulfill schizophrenia criteria in a long follow-up.

Persistent delusional disorder (F22; ICD-10) is a less common psychotic disorder, in which the presence of one or more non-bizarre delusions that persist for at least for three months is required. These delusions are not due to another psychotic or a mood disorder (ICD-10; WHO 1992). The presence of delusions of at least one month’s duration are required for this diagnosis. Furthermore, the patient’s functioning must not be affected except for the immediate consequences of the delusions experienced.

Schizoaffective disorder (F25; ICD-10) is one of the more common, chronic, and disabling mental illnesses marked by psychotic symptoms that occur separately and concurrently over time with major mood episodes. For this diagnosis these symptoms must be present for at least half of the illness duration. In the ICD-10, psychotic symptoms are required to be present most of the time during a period of at least two weeks. In the DSM-5, the diagnosis of schizoaffective disorder can be made only if full mood disorder episodes have been present for the majority of the total active and residual course of illness, from the onset of psychotic symptoms up until the current diagnosis.

An active organic brain disorder or serious metabolic disturbances affecting the central nervous system should be excluded for the diagnosis of all the illnesses mentioned above. Additionally, psychosis diagnoses should not be made during or while under drug/alcohol intoxication, dependence or withdrawal. (WHO 1992, APA 2013).
2.2.3 Neuropsychological features of schizophrenia

The clinical observations

In the early 20th century, the conceptual development of modern studies of cognitive ability started from the ground-breaking works of Emil Kraepelin and Eugen Bleuler (Green & Harvey 2014). Kraepelin maintained a lifelong interest in psychological phenomena and their applications to psychiatric disorders. It is Kraepelin’s distinction between schizophrenia and bipolar disorder that continues to be reflected in the key diagnostic systems up to the present time. Furthermore, Bleuler made many conceptual contributions, but perhaps most important is his view that psychotic symptoms were secondary to fundamental symptoms which are essentially cognitive in nature. However, the focus shifted to the more dramatic psychotic symptoms and the importance of cognitive phenomenon in schizophrenia was temporarily forgotten.

The assessment-based approaches

One of the post-World War II (1950–1980) views of the cognitive problems in schizophrenia was shaped by experimental psychology. It tried to characterize and understand schizophrenia in terms of basic psychological phenomenon. The goal was to closely measure deficits in schizophrenia in precise experimental paradigms, and then infer what the results mean regarding underlying deficits in the disorder based on existing experimental models. However, at the same time another measurement focused, but distinctly different approach, which had its roots in clinical neuropsychology, was taking hold.

Typically, the neuropsychologist was asked to determine whether cognitive impairments in a patient were “organic” (meaning neurological) versus “functional” (meaning not neurological). This type of question assumes that cognitive deficits are not a core part of schizophrenia and that cognitive deficits for psychiatric patients are not brain-based.

After a very large number of studies, a few notable thinkers (Goldstein, 1986; Heaton et al., 1978) concluded, that neuropsychological tests could not distinguish cognitive impairments that accompany schizophrenia from those that accompany head injury (Green & Harvey 2014). Although problems in differential diagnosis could be attributed to the tests themselves, the measures for the most part were reliable and would have been informative for different types of research questions;
the problem was the conceptual framing and the stated goals, not the assessment methods.

The neuroscientific approaches

The variety of neuroscientific methods used to study schizophrenia during the latter part of the 20th century has changed the view for cognitive functioning in schizophrenia by demonstrating that the cognitive performance in schizophrenia is available for rigorous study, as it is in any other brain-based disorder (Green & Harvey 2014).

Early brain structural findings reported a ventricular enlargement in patients with schizophrenia versus controls. Further, more sophisticated functional neuroimaging studies (positron emission tomography studies, PET) forced a reconsideration of brain morphology and functioning in schizophrenia; a common observation was that schizophrenia patients did not activate their frontal lobes as much, and as reliably, as control samples (Buchsbaum et al. 1992). Additionally, functional magnetic resonance imaging (fMRI) replaced PET for cognitive activation studies in schizophrenia.

Cognitive ability in schizophrenia

Nowadays, studies in schizophrenia have yielded a wide array of correlations between structural and functional brain changes and clinical and cognitive symptoms. The behavioral disorganization, emotional changes, and working memory impairments seen in schizophrenia lead to the suggestion that deficits in functioning of the frontal brain structures might cause the cognitive impairments (Callicott et al. 2000). Findings on dysfunctions in the hippocampal and medial temporal lobe, and in basal ganglia functioning are consistent with the ideas of disturbances in episodic memory and poor processing speed (Saykin et al. 1991). However, recent research on brain activity in schizophrenia has shown that no changes in the function of any single region can explain the range of cognitive and affective impairments in this illness. Neural circuits that support sensory, cognitive, and emotional processes are being investigated as substrates for cognitive and affective impairments in schizophrenia (Repovs et al. 2011). The most consistent suggestion has focused on network relationships, where disruptions in any one of these linked regions can lead to cognitive impairment (Harvey 2007).
Cognitive deficits in schizophrenia are common and almost universal (O’Carroll 2007, Rund 2007, Shmukler et al. 2015) occurring in about 80% of patients (Meesters et al 2010) with impairments in nearly every cognitive domain (Schaefer et al. 2013). Cognitive dysfunctions rather than positive symptoms are considered to be core features of schizophrenia, since they are strongly correlated with poor functional outcomes (Keefe et al. 2011), as well as being predictors of general outcome and rehabilitation effectiveness (Lesh et al. 2011). However, the association between cognitive deficits in schizophrenia and the risk factors of the impairments in cognitive ability has not received extensive attention in research, thus the etiology of cognitive deficits in schizophrenia is still unknown (Dickinson & Harvey 2009).

It has been suggested that cognitive impairments are already present in the premorbid phase of schizophrenia (Heinrichs & Zakzanis 1998, Henry & Crawford 2005, Woodberry et al. 2008) and their degree may be associated with the onset age of the disorder (Tuulio-Henriksson et al. 2004). Cognitive deficits are thought to be a strong predictor of adverse social and occupational outcomes for schizophrenia (Bowie & Leung 2008, Van Winkel et al. 2007). The most predictive in this respect are the disturbances in social cognition (Sprong et al. 2007, Penn et al. 2008, Van Hooren et al. 2008, Vauth et al. 2004) which lead to worse outcomes in terms of a range of everyday behaviors, including social functioning (Smith et al. 1999), self-care (Harvey et al. 1998), community-living skills (Palmer et al. 2002), and employment (McGurk & Meltzer 2000).

The most recent suggestion is that cognitive impairments in schizophrenia are multidimensional (Dickinson et al. 2008, Harvey 2007, Lencz et al. 2006). It is already known that individuals with schizophrenia often perform very poorly on most neuropsychological tests. The neuropsychological profile of schizophrenia, however, is also characterized by prominent specific deficits in verbal learning and memory (Achim & LePage 2005, Aleman et al. 2003, Ranganath et al. 2008, Tuulio-Henriksson et al. 2004), working memory (Barch & Smith 2008, Laws 1999, Lee & Park 2005, Reichenberg et al. 2010), verbal fluency (Henry & Crawford 2005), executive functions (Barch et al. 2008, Laws 1999, Lee & Park 2005, Reichenberg et al. 2010), attention (Floravanti et al. 2005), and processing speed (Dickinson et al. 2007), whereas social cue perception, affect recognition, attribution, and the theory of mind are the sociocognitive domains most affected (Wolwer & Frommann 2011). Thus, it has been suggested that there are multidimensional cognitive deficits, which produce reduced performance in other measured cognitive domains. This possibility is consistent with the generally
overlapping nature of the cognitive ability areas evaluated across cognitive tasks (Harvey 2007).

In considering the rehabilitation of the daily life functioning of person with a diagnosis of schizophrenia, it is important to take account of any specific cognitive difficulties that are related to functioning outcomes. Since the degree of impairments especially in attention, verbal memory, and executive functioning predict the ability to achieve functional goals through treatment (Bowie et al. 2010, Nuechterlein et al. 2011), improving metacognitive skills needs to be a prior goal for rehabilitation to avoid frustration and to maximize the treatment outcome.

**Memory in schizophrenia**

Memory, particularly episodic (declarative) memory and working memory deficits are a consistent and robust finding in schizophrenia. Of 110 studies reviewed by Cirello and Seidman (2003), 101 found evidence of impairment among individuals with schizophrenia on measures of verbal episodic memory. Further, meta-analyses consistently report severe impairments in immediate and delayed verbal and nonverbal memory in schizophrenia (Dickinson et al. 2007, Fioravanti et al. 2005, Mesholam-Gately et al. 2009).

Reductions of grey matter volume in the prefrontal and temporal cortex have been consistently found in schizophrenia, which are crucial for the development of positive and negative symptoms and impaired working memory (Zierhut et al. 2013). More specifically, grey matter volume reductions in the superior temporal gyrus were associated with positive symptom severity as well as working memory impairment. Furthermore, the absolute grey matter volume of ventrolateral prefrontal cortex was strongly related to negative symptoms, which predicted working memory performance as well as processing speed.

These findings suggested, that two distinct pathomechanisms are responsible for impaired memory in schizophrenia: (1) Grey matter volume reductions in the ventrolateral prefrontal cortex predict the severity of negative symptoms. Increased negative symptoms in turn are associated with a slowing down of processing speed and predict an impaired working memory. (2) Grey matter volume reductions in the medial temporal and medial frontal cortex are involved in the development of positive symptoms and impair working and long-term memory performance, too (Tanskanen et al. 2005, Zierhut et al. 2013).

Verbal memory played a mediating role in the change processes (Penadés et al. 2010). Both longitudinal and cross-sectional studies of individuals with diagnosed
schizophrenia suggest that cognitive performance particularly in memory is poor and remains poor over the course of the disorder. Such deficits limit functioning outcomes and the rehabilitation effectiveness of particular life skills such as work and social functioning (Wykes et al. 2007). Cognitive remediation therapy (CRT) is associated with durable improvements in memory, which in turn are associated with social functioning improvements in people with diagnosed schizophrenia (Wykes et al. 2007).

Executive functions in schizophrenia

A great deal of research has focused on executive dysfunction in schizophrenia (Barnett et al. 2007a, Pantelis et al. 1997). First, many of the clinical features of schizophrenia are phenomenologically similar to those associated with frontal lesions, such as reduced spontaneity, avolition, mental rigidity, and lack of social judgment (Benson & Miller 1997). A second reason has to do with the dominant view about the etiology of schizophrenia. The so-called “neurodevelopmental hypothesis” postulates that schizophrenia arises from early, possibly fetal brain abnormalities of genetic and/or environmental origin which remains largely “static” or “silent” until it interacts with normal brain maturation processes, namely, those of the frontal lobes (Murray & Lewis 1987).

The findings of recent research on brain activity in schizophrenia suggest that individuals with schizophrenia show reduced distal and somewhat enhanced local connectivity between the cognitive control networks (frontal-parietal, cingulo-opercular, and cerebellar) compared to control subjects. Better cognitive performance and fewer symptoms of disorganization among subjects with schizophrenia seem to be robustly predictive of greater connectivity between the frontal-parietal and cerebellar regions (Repovs et al. 2011). These results suggest that impairments of executive function and cognitive control result from disruption in the coordination of activity across brain networks and additionally suggest that these might reflect impairments in normal patterns of brain connectivity development.

Attention and processing speed in schizophrenia

Meta-analytic studies suggest moderate to severe impairments in the domain of attention in schizophrenia (Dickinson et al. 2007, Fioravanti et al. 2005). Clear evidence for a top-down network activated even before the presentation of to-be-
attended stimuli has been shown (Corbetta et al. 2000). Posner and Pettersen (1990) proposed that the sources of attention form a specific system of anatomical areas, which can be further broken down into three networks which carry out the functions of attention, orienting, and executive control (Fan et al. 2002). Thus, as a part of cognitive functioning is regulated by the heteromodal association cortex, attentional impairments may disrupt many other cognitive functions (Kolb & Whishaw 2009). However, previous studies have generally demonstrated that attentional dysfunction explains only a small proportion of the variance in other cognitive functions in schizophrenia (Goldberg et al. 2003, Keefe et al. 2006).

Regarding processing speed, according to meta-analyses (Dickinson et al. 2007, Mesholam-Gately et al. 2009, Knowles et al. 2010), the processing speed for both simple and more complex tasks show a severe and substantial impairment in schizophrenia. Poor processing speed can have a significant effect on academic performance in children with a high risk of schizophrenia and future employment outcomes, and can further affect most aspects of everyday living. Researchers are yet to identify the specific aspects of neurophysiology that underpin information processing but believe it may be influenced by the speed at which information passes along neural circuits (Schwartz 2011).

Other specific cognitive abilities in schizophrenia

As indicated by the meta-analytic studies, language and verbal skills are relatively well preserved in schizophrenia, with only mild impairments (Dickinson et al. 2007, Mesholam-Gately et al. 2009). Further, meta-analyses suggest moderate to severe deficits in tasks requiring simple psychomotor speed (Dickinson et al. 2007, Mesholam-Gately et al. 2009), though the magnitude of these deficits is smaller than the one evident for memory or executive functions. Also moderate to severe impairments have also been observed in perceptual problems (Dickinson et al. 2007, Heinrichs & Zakzanis 1998, Mesholam-Gately et al. 2009).

Cognitive remediation can also produce improvements in cognitive domains that are not the main target of intervention, such as verbal skills, psychomotor speed or social cue perception during remediation since improvements have been observed while there was no training exercise on these specific cognitive processes (Masson et al. 2015).
The assessment of cognitive ability in schizophrenia

Various results of recent research have led to the hypothesis that *impaired cognitive functioning is a core feature of schizophrenia* and not an artifact of other symptoms, treatment for the illness, or aspects of the course of the illness (Kremen et al. 2000). It has further been proposed that the well-known diversity of schizophrenia in terms of its functional outcome and recovery from the illness is best characterized by the associated cognitive deficits, not by the classical symptoms (Bowie & Leung 2008, Green et al. 2000, Van Winkel et al. 2007). Therefore, obtaining a formal neuropsychological evaluation in individuals with psychosis is recommended (Reichenberg et al. 2010).

Most neuropsychological assessment batteries used in schizophrenia studies have been adapted from clinical neuropsychology, which assesses a profile of cognitive strengths and weaknesses of an individual. General measures of the *intelligence quotient (IQ)* and *composite scores or profiles* derived from test batteries comprising multiple neuropsychological tests are widely used indices of *generalized cognitive performance* in schizophrenia. According to recent meta-analytic studies, impairments in general cognitive ability seem to be almost as severe as those observed for more *specific neuropsychological functions*, such as attention, executive functions, episodic and working memory, and processing speed (Dickinson et al. 2007, Henry & Crawford 2005, Fioravanti et al. 2005, Mesholam-Gately et al. 2009).

The neuropsychological tests described in Table 3 have been selected to represent diverse cognitive domains that have been shown to be the most consistently correlated with functional outcomes in schizophrenia.
### Table 3. Neuropsychological assessment batteries in relation to the assessment of cognition in schizophrenia.

<table>
<thead>
<tr>
<th>Assessment method</th>
<th>Cognitive domain</th>
<th>Type</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wisconsin Card Sorting Test</td>
<td>Executive functioning</td>
<td>Standardized</td>
<td>Heaton et al. 1993</td>
</tr>
<tr>
<td>Trail Making Test Parts A and B</td>
<td>Motor speed, speed of mental processing and mental flexibility</td>
<td>Standardized</td>
<td>Reitan 1958, Reitan &amp; Wolfson 1993</td>
</tr>
<tr>
<td>Learning Trials 1-5 from the Rey Auditory Verbal Learning Test (RAVLT)</td>
<td>Short-term auditory-verbal memory, rate of learning, learning strategies, retroactive and proactive interference, presence of confabulation of confusion in memory processes, retention of information, and differences between learning and retrieval</td>
<td>Standardized</td>
<td>Spreen &amp; Strauss 1998 (originally developed in the 1940s)</td>
</tr>
<tr>
<td>Boston Naming Test (BNT)</td>
<td>Any language processes</td>
<td>Standardized</td>
<td>Kaplan et al. 1983</td>
</tr>
<tr>
<td>Digit Span (subtest of WAIS-III, Wechsler Adult Intelligence Scale, 3rd edition)</td>
<td>Short-term memory, attention, and concentration</td>
<td>Standardized</td>
<td>Psychological Corporation 1998</td>
</tr>
<tr>
<td>Letter-Number Sequencing (subtest of WAIS-III, Wechsler Adult Intelligence Scale, 3rd ed.)</td>
<td>&quot;Working memory,&quot; the ability to simultaneously recall and organize stimuli of different, similar types of information</td>
<td>Standardized</td>
<td>Psychological Corporation 1998</td>
</tr>
</tbody>
</table>

The interpretation of assessment methods has been composed by utilizing the article by Reichenberg et al. 2010.
2.2.4 Treatment and early interventions in schizophrenia in the context of cognitive functioning

Cognitive deficits are present already before the onset of psychosis (Heinrichs & Zakzanis 1998, Henry & Crawford 2005, Woodberry et al. 2008). In relation to positive, negative, and disorganization symptoms associated with schizophrenia, cognitive ability is the strongest predictor of functional outcome (Green et al. 2000). Unlike the psychotic symptoms, cognitive deficits do not improve during periods of remission (Keefe et al. 2007). Thus, early prevention and cognitive intervention are important to reduce conversion rates in adult clinical high risk (CHR) patients and thus to reduce the burden of mental disorders across the individual’s lifespan.

A successful preventive intervention and then further treatment for schizophrenia rely on the accuracy of early detection of CHR states of psychoses. Therefore, there is a need for prediction and early detection of the psychotic disorder with an emphasis on potential developmental aspects.

The significant heterogeneity of conversion rates between CHR samples (Schultze-Lutter et al. 2015), and results of recent meta-analysis showing that 73% of subjects do not convert to psychosis during a two-year follow-up (Simon et al. 2013), and the significant proportion of remitting CHR subjects (46%; Simon et al. 2013) possibly accounted for by the effective treatments received, strongly suggests the presence of a dynamic aspect to psychosis risk and psychoses. Future early detection approaches should define different CHR groups that are identified with the aim to develop more sophisticated prediction models. These models should be easily translated into clinical practice and help to provide individualized rehabilitation options for different patient groups with special characteristics and treatment needs.

Early prevention is an approach that targets help-seeking individuals who experience early signs of emerging psychosis, but do not meet diagnostic criteria (Schmidt et al. 2015). The main goal of this approach is to prevent this condition from converting to psychosis. However, the accurate identification of the target population and their effective treatment are challenging. The ultra-high risk and the basic symptom approach (Fusar-Poli et al. 2013, Klosterkötter et al. 2011) have been developed for the purpose of early detection. Fulfilling these criteria however only indicates an increased risk for developing psychosis and raises debates about the risk of negative effects such as stigmatization and the side effects of medication,
which are associated with the identification and treatment of CHR states of psychoses (Schmidt et al. 2015).

In order to improve the rate of limitations associated with cognitive deficits in subjects with diagnosed schizophrenia, cognitive remediation was developed to improve cognitive deficits with the aim of increasing the likelihood of improved functional outcomes (Wykes et al. 2007). Cognitive remediation therapy (CRT) is a treatment approach derived from neuropsychology and is a sort of umbrella for a number of different interventions defined by their procedural characteristics.

CRT contains various techniques defined by their procedural characteristics and methods of training. CRT involving psychoeducation and metacognitive strategies has proved to be effective on crucial cognitive domains and seems to provide a benefit for schizophrenia patients with low baseline performance (Pillet et al. 2015). When CRT is provided together with other psychiatric rehabilitation treatments, this benefit seems to be generalized to the functional outcome for schizophrenia patients (Wykes et al. 2011). Thus, including metacognitive learning strategies in cognitive remediation might increase the value of the approach and enhances participant improvement. This is possibly because strategies using verbalization can lead to improvement even in not targeted cognitive domains.

2.3 Change in cognitive performance and its predictors in the general population and in schizophrenia

2.3.1 Change in cognitive performance and its predictors in the general population

Change in cognitive performance in the general population

Change in cognitive ability and cognitive aging has long been the focus of previous scientific research. There is heterogeneity in the findings regarding the specific types of changes in cognitive functioning that occur over a human lifespan. Many studies have demonstrated that cognitive change is not unitary, and that some abilities decline more rapidly than others (Hultsch et al. 1998, Salthouse 1991, Schaie 1996). Further, this change remains gradual, suggesting that the cognitive changes may be an ordinary developmental process.

With respect to the morphological perspective, researchers are investigating a number of changes related to healthy aging. As a person gets older, changes occur
in all parts of the body, including the brain. Numerous changes in brain morphology have been reported in postmortem studies such as decreased cortical volume and thickness (Kemper 1994), shrinking of neurons (Haug 1985), reduced neuron density in the cerebral cortex, hippocampus and cerebellum (Pakkenberg & Gundersen 1997), as well as decreased density of neuron synapses (Morrison & Hof 1997), and a decreased amount of myelin in subcortical areas (Pakkenberg & Gundersen 1997). Increases have been reported of lipofuscin or age pigment (Terman & Brunk 1998), as well as contracted density of blood vessels (Riddle et al. 2003), deprivation of sensory input to the brain (Bertoni-Freddari et al. 2002), impaired mitochondrial function (Brunk & Terman 2002) and increased amounts of damage due to neuronal deoxyribonucleic acid (DNA) (Rutten et al. 2003).

According to a meta-analysis from six studied samples from the USA, Norway and Sweden with age variations from 18 to 93 years (Walhovd et al. 2011) decreases were found in cerebral cortex, cerebral white matter, cerebellum white matter, cerebellum cortex, thalamus, caudate, putamen, pallidum, hippocampus, amygdala, accumbens, brain stem and total brain volume, while increases were noted in lateral ventricles and the inferior horn of lateral ventricles as well as 3rd and 4th ventricles, and sulcal cerebrospinal fluid (CSF).

In relation to cognitive functioning, shrinking of certain parts of the brain (especially in the area of prefrontal cortex and limbic system) which are associated with learning, memory, planning, and other complex mental activities, as well as degradation of white matter and reduced communication between neurons, and reduced blood flow in the brain’s blood vessels may all cause impairments in cognitive ability.

Recent research on the change of cognitive ability throughout a human lifespan has demonstrated that cognitive performance increases with age through childhood and adolescence (Korkman et al. 2001) until the third or fourth decade of life (Clark et al. 2006) and gradually declines in the fifth decade and beyond (Colsher & Wallace, 1991, Hahn & Lachman 2015, Richards et al. 2004, Schaie 1994, Tomaszewski Farias et al. 2011, Zelinski & Burnight 1997). Data from large longitudinal cohort studies provides recent evidence of significant deterioration in working and long-term memory, reasoning, selective attention and speed of processing mainly in the age group of 60 years and over (e.g. Agrigoroaei & Lachman 2011, Bielak et al. 2012, Cournot et al. 2006, Hultsch et al. 1998, Schaie 1996, Sliwinski & Buschke 1999) and further decline in global cognitive performance in the elderly population (e.g. Johansson et al. 2004, Matthews et al. 2012, Muniz-Terrera et al. 2009, Nguyen et al. 2002). Crystallized cognitive ability
seems to remain unchanged with increasing age: e.g. Park & Reuter-Lorenz (2009) found that performance is preserved over age for world knowledge.

**A systematic review of studies on change in cognitive performance and its predictors in the general population**

To summarize the results of longitudinal studies into change in cognitive ability, a systematic literature search was completed in August 2015 using the electronic database PubMed and a number of manual searches (Figure 1). The search produced 4525 results. Based on the information in the abstracts, 84 articles were selected for comprehensive evaluation. 22 articles met the inclusion criteria and were included in the systematic review.
Fig. 1. Flowchart diagram of the literature search and selection of studies on the predictors of change in cognitive performance in the general population (Modified from Figure 1, original study II).

Methods of the systematic literature review:
The literature search was completed in August 2015 using electronic database PubMed and manual searches. The search strategy included keywords limited to title and abstract search:
(cognit*[Title/Abstract] AND change*[Title/Abstract] AND predict*[Title/Abstract])
(NOT traumatic[Title/Abstract] NOT injury[Title/Abstract] NOT surgery[Title/Abstract]) limited to human; English.
The articles included in the current systematic review were required to meet the following criteria:
• sociodemographic and/or clinical predictors of longitudinal change in adult cognitive performance were analyzed (e.g. studies analyzing only neurobiological predictors were excluded);
• the sample was not delineated to subjects with certain illness or disorder (i.e. general population samples or samples that included mostly individuals without any diagnosed neuropsychiatric disorders / dementia / mild cognitive impairment);
• standardized neuropsychological tests were used;
• the sample size was 20 or more;
• cognitive performance was measured at least two times with same tests;
• period between the tests was at least five years.

Records identified through database searching (n = 4517)  Additional records identified through other sources (n = 8)
Records identified through database searching, and screened (n = 4525)
Records excluded by title and abstract (n = 4441)
Full-text articles assessed for eligibility (n = 84)
Full-text articles excluded, with reasons (n = 62)
• Change of cognitive performance not analyzed (n=3)
• Period between the tests less than five years (n=1)
• Neurological disorder or other serious medical condition (n=9)
• Only neurobiological predictors of cognitive change (n=8)
• Predictors of cognitive change not analyzed (n=4)
• Only baseline cognitive performance as a predictor of cognitive change (n=14)
• Review (n=5)
Studies included in qualitative synthesis (n = 22)
As a result of the systematic literature review, Table 4 summarizes studies on change in cognitive ability with a follow-up of five years or longer, presenting results of longitudinal cognitive changes in healthy adults or adults from general population samples.

The 22 general population-based studies have been published between 1991 and 2015, their follow-up times range from 5 to 38 years, and their sample sizes vary from 76 to 5000. The included studies consisted of participants aged between 12 and 102 years. The studies administered several neuropsychological tests including the Mini-Mental State Examination (MMSE), the California Verbal Learning Test-I and II (CVLT-I and CVLT-II), the Wechsler Adult Intelligence Scale (WAIS), and the Benton Visual Retention Test. Most of the studies demonstrated a cognitive decline from the age of 53 onwards in non-psychotic subjects (e.g. Colsher & Wallace 1991, Hahn & Lachman 2015, McDonald-Miszczak et al. 1995, Richards et al. 2004, Schaie 1994, Tomaszewski Farias et al. 2011, Zelinski & Burnight 1997). There was a wide variability regarding the extent of this decline (Table 4).
Table 4. Studies and results concerning the change in cognitive performance in the general population. Only studies with at least five years of follow-up are included (Modified from Table 1, original study II).

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study design and sample</th>
<th>Follow-up length</th>
<th>Neuropsychological assessments/domains</th>
<th>Change in cognition</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agrigoroaei &amp; Lachman (2011)</td>
<td>N=151 (43.7% F) persons from the Midlife in the United States study (MIDUS), who also participated in a satellite Boston Longitudinal Study (BLOS), Boston, U.S. -Average age at follow-up 60 years -Began between 1995 and 1996; follow-up between 2004 and 2005</td>
<td>10 years</td>
<td>Brief Test of Adult Cognition by Telephone, Short-term memory, Speed of processing, Reasoning (Ravens Advanced Progressive Matrices) Vocabulary (Wechsler Adult Intelligence Scale (WAIS)/vocabulary task)</td>
<td>Decline in short-term memory, speed of processing and reasoning.</td>
<td>Strengths: Longitudinal, interdisciplinary study with a long follow-up period Limitations: The generalizability of the findings is limited to some extent by the positive selection of the longitudinal participants in MIDUS and BLOS.</td>
</tr>
<tr>
<td>Bielak et al. (2012)</td>
<td>N=7,125 (appr. 50% F in each age cohort) drawn from the PATH Through Life Project, Australia -Average age at follow-up 50 years -Baseline in 1999–2001; follow-ups in 4 and 8 years</td>
<td>8 years</td>
<td>Symbol Digit Modalities Test, California Verbal Learning Test, Digit Span Backward from the Wechsler Memory Scale (WMS), Spot-the-Word Test</td>
<td>The 60s cohort declines in cognition with each additional year of being in the study The 20s and 40s cohorts: improvement in cognition</td>
<td>Strengths: According to the authors, this is the first investigation of the association between activity and cognitive change.</td>
</tr>
<tr>
<td>Carmelli et al. (1997)</td>
<td>N=566 men; a subsample of the cardiovascular epidemiologic study (the Western Collaborative Group Study), San Francisco Bay and Los Angeles areas, U.S.</td>
<td>6 years</td>
<td>Digit Symbol Substitution test, Benton Visual Retention Test, Controlled Oral Word Association Test</td>
<td>20% of subjects declined and 17% improved in cognitive performance</td>
<td>Strengths: Relatively large population-based sample Limitations:</td>
</tr>
<tr>
<td>Authors (Year)</td>
<td>Study design and sample</td>
<td>Follow-up length</td>
<td>Neuropsychological assessments/domains</td>
<td>Change in cognition</td>
<td>Comments</td>
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<tr>
<td>Colsher &amp; Wallace (1991)</td>
<td>$N=1,768$ (67.1% F) drawn from Iowa Rural Health Study, U.S.</td>
<td>6 years</td>
<td>Modified version of Pfeiffer's short portable mental status questionnaire</td>
<td>Decrements in free recall of a word list</td>
<td>The study including only men limits generalizability</td>
</tr>
<tr>
<td></td>
<td>-Age 65+ years</td>
<td></td>
<td>Memory (Word list)</td>
<td></td>
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<td></td>
<td>-Began in 1981</td>
<td></td>
<td>A measure of self-related memory/metamemory (in-person interviews)</td>
<td></td>
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<tr>
<td>Cournot et al. (2006)</td>
<td>$N=2,223$ drawn from Vieillissement et Sante au Travail (aging and health at work; VISAT) Study, French.</td>
<td>5 years</td>
<td>Word-list learning (four recalls)</td>
<td>Decline in cognition</td>
<td>Large population-based sample</td>
</tr>
<tr>
<td></td>
<td>-Age at baseline from 32 to 62 years</td>
<td></td>
<td>Digit Symbol Substitution Test</td>
<td></td>
<td>Functional scales used in elderly people were not adapted to the healthy working population of this sample.</td>
</tr>
<tr>
<td></td>
<td>-Baseline in 1996; follow-up in 2001</td>
<td></td>
<td>Selective attention test</td>
<td></td>
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<tr>
<td>Furuäng et al. (2013)</td>
<td>N=211 elderly men from a cohort of the population study &quot;Men born in 1914&quot;, Malmö, Sweden</td>
<td>14 years</td>
<td>Test of Synonyms</td>
<td>Decline in cognition</td>
<td>Large population-based sample</td>
</tr>
<tr>
<td></td>
<td>-Age at baseline 68 years</td>
<td></td>
<td>Block Design</td>
<td></td>
<td>Functional scales used in elderly people were not adapted to the healthy working population of this sample.</td>
</tr>
<tr>
<td></td>
<td>-Began in 1968</td>
<td></td>
<td>Digit Symbol Substitution test</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Benton Visual Retention Test</td>
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</table>

Strengths: Long 14-year follow-up
Limitations: High loss to follow-up and the study including only men limits generalizability
<table>
<thead>
<tr>
<th>Authors</th>
<th>Study design and sample</th>
<th>Follow-up length</th>
<th>Neuropsychological assessments/domains</th>
<th>Change in cognition</th>
<th>Comments</th>
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<tr>
<td>Giambra et al. (1995)</td>
<td><em>N</em>=1,721 (32.4% F) from the Baltimore Longitudinal Study of Aging (BLSA), U.S.</td>
<td>28 years</td>
<td>Immediate visual memory (Benton Visual Retention Test) Crystallized intelligence (WAIS/Vocabulary subtest)</td>
<td>Decline in immediate visual memory from 6 to 25 years of follow-up for men and over 6 years follow-up for women between 65–74-year-old subjects</td>
<td>Strengths: Large, well-characterized sample Use of combined longitudinal and cross-sectional data Limitations: The sample consisting only of very highly educated participants may limit generalizability High drop-out</td>
</tr>
<tr>
<td>Glynn et al. (2004)</td>
<td><em>N</em>=2,068 drawn from the East Boston component of the Established Populations for the Epidemiologic Study of the Elderly (EPESE) and the Hypertension Detection and Follow-Up Program (HDFP)</td>
<td>6 years</td>
<td>Short Portable Mental Status Questionnaire East Boston Memory Test</td>
<td>Cognitive decline over time.</td>
<td>Strengths: Longitudinal population-based study Large, well-characterized sample Limitations: Crude cognitive measures</td>
</tr>
<tr>
<td>Hahn &amp; Lachman (2015)</td>
<td><em>N</em>=103 (44% F) from the Midlife in the United States study (MIDUS), who also participated in a satellite Boston Longitudinal Study (BOLOS), Boston, U.S.</td>
<td>10 years</td>
<td>Working memory factor included tests of forward and backwards digit span and serial sevens (counting backwards by subtracting sevens).</td>
<td>Decline in memory</td>
<td>Strengths: Longitudinal interdisciplinary study Limitations: Measure of cognitive change focused on tasks of working memory, rather than other cognitive domains or other aspects of cognition.</td>
</tr>
<tr>
<td>Authors (Year)</td>
<td>Study design and sample</td>
<td>Follow-up length</td>
<td>Neuropsychological assessments/domains</td>
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<tr>
<td>Johansson et al. (2004)</td>
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<td>6 years</td>
<td>WAIS (General knowledge; Synonyms test; Digit–Symbol Substitution Test; Digit Span Forward and Backward Test) WMS (The Prose Recall test) The Figure Logic task Koh's Block Design Test</td>
<td>Cognitive decline over time.</td>
<td>Measure of working memory was not a pure measure of working memory. Strengths: Longitudinal interdisciplinary study Large, well-characterized sample of monozygotic and same-sex dizygotic twin pairs Limitations: High loss to follow-up limits generalizability</td>
</tr>
<tr>
<td>Johnson et al. (2010)</td>
<td>N=717 from the registers of 10 general medical practices located in diverse geographic and sociodemographic areas throughout the city of Edinburgh, UK</td>
<td>12 years</td>
<td>The National Adult Reading Test (NART) Logical Memory Raven’s Progressive Matrices Verbal Fluency Digit Symbol</td>
<td>Cognitive function declined 0.04 standard deviation per year over the period between cognitive assessments</td>
<td>Strengths: Longitudinal interdisciplinary study Large, well-characterized sample Long 15-year follow-up Limitations: High loss to follow-up limits generalizability</td>
</tr>
<tr>
<td>Kobayashi et al. (2014)</td>
<td>N=76 (39.5% F) non-psychotic, general population subjects drawn from the Northern Finland Birth Cohort 1966 Study, Finland</td>
<td>9 years</td>
<td>Executive function (Abstraction, Inhibition, and Working Memory, AIM) Visual learning and memory (Visual Object Learning, VOLT)</td>
<td>Cognition was found to stay constant</td>
<td>Long 9-year follow-up</td>
</tr>
</tbody>
</table>

(Note: The table is truncated for brevity, but the full table is as follows:)

<table>
<thead>
<tr>
<th>Authors (Year)</th>
<th>Study design and sample</th>
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<tr>
<td>MacDonald et al. (2004)</td>
<td>N=125 drawn from the Victoria Longitudinal Study (VLS), Canada</td>
<td>12 years</td>
<td>Verbal Learning (California Verbal Learning Test, CVLT)</td>
<td>Age-related cognitive decline</td>
<td>Strengths: Large population-based cohort study Long 12-year follow up Limitations: High loss to follow-up limits generalizability</td>
</tr>
<tr>
<td>Matthews et al. (2012)</td>
<td>N=13,004 drawn from the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS) from six centers in England and Wales</td>
<td>10 years</td>
<td>Verbal processing speed Working memory Reasoning, episodic memory Semantic memory</td>
<td>Age-related cognitive decline</td>
<td>Strengths: Large population-based cohort study Long 10-year follow up Limitations: MMSE may be relatively insensitive to differential patterns of change in cognitive ability.</td>
</tr>
<tr>
<td>Muniz-Terrera et al. (2009)</td>
<td>N=2,053 (65% F) drawn from the Cambridge City over 75s Cohort Study, UK</td>
<td>9 years</td>
<td>MMSE</td>
<td>Age-related cognitive decline as measured by the MMSE</td>
<td>Strengths: Large population-based cohort study Long 9-year follow up Limitations:</td>
</tr>
<tr>
<td>Authors (Year)</td>
<td>Study design and sample</td>
<td>Follow-up length</td>
<td>Neuropsychological assessments/domains</td>
<td>Change in cognition¹</td>
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<tr>
<td>Nguyen et al. (2002)</td>
<td>N=1,759 (65% F) drawn from the Hispanic Established Population for the Epidemiological Study of the Elderly (Hispanic EPESE), U.S. -Age 65+ years -Baseline in 1993–1994; follow-up in 1998–1999</td>
<td>5 years</td>
<td>MMSE</td>
<td>Cognitive decline as measured by the MMSE</td>
<td>Large population-based cohort study</td>
</tr>
<tr>
<td>Osler et al. (2013)</td>
<td>N=11,532 men drawn from the Danish person identification system, Copenhagen, Denmark -Cognitive assessments at ages 12, 18 and 57 years -Began in 1965; follow-ups in 6 and 45 years</td>
<td>45 years</td>
<td>1965: Härnquist test battery At 45-follow-up: Intelligent-Struktur-Test</td>
<td>Decline in cognitive function between 18 and 57 years</td>
<td>Large population-based cohort study Long 45-year follow up</td>
</tr>
<tr>
<td>Payne et al. (2014)</td>
<td>N=698 drawn from the Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE), U.S. -Mean baseline age 73.6 years -Baseline between 1999 and 2001; follow-up period over 10 years</td>
<td>10 years</td>
<td>Rivermead Behavioral Memory Test, version 2 Schaele-Thurstone Adult Mental Ability Test Kit of Factor-Referenced Cognitive Tests</td>
<td>Annual decline in these variables was not statistically significant after adjustment for covariates</td>
<td>Large population-based cohort study</td>
</tr>
<tr>
<td>Authors and Year</td>
<td>Study design and sample</td>
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<td>Neuropsychological assessments/domains</td>
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<tr>
<td>Richards et al. (2004)</td>
<td>N=2,058 (51.2% F) drawn from the National Survey of Health and Development (NSHD), a Birth Cohort 1946 Study, UK -Age 53 years -Began in 1999</td>
<td>38 years</td>
<td>Heim AH4 test Watts-Vernon reading test A three trial 15 item word list Timed letter search National adult reading test (NART)</td>
<td>Decline in memory</td>
<td>Cognition in childhood and data on a range of potential confounders and the use of repeated cognitive measures in mid-life Limitations: High loss to follow-up Repeated measures were obtained for only two cognitive tasks.</td>
</tr>
<tr>
<td>Schaie (1994)</td>
<td>N=5,000 drawn from the Seattle Longitudinal Study, Seattle, Washington, U.S. -Average age 53 years in 1991 -Began between 1956 and 1991</td>
<td>7-years (for the longitudinal data)</td>
<td>Verbal meaning, space, reasoning, number, and word fluency, perceptual speed</td>
<td>Modest gain from young adulthood to age 60 years. Average decrement for age 67 years.</td>
<td>Strengths: Large general population sample Broad population representation Limitations: Longitudinal gradients were evaluated only for 7-year-follow-up</td>
</tr>
<tr>
<td>Authors</td>
<td>Study design and sample</td>
<td>Follow-up length</td>
<td>Neuropsychological assessments/domains</td>
<td>Change in cognition¹</td>
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</tr>
<tr>
<td>Sturman et al. (2008)</td>
<td>N=3,885 (61.0% F) drawn from the Chicago Health and Aging Project (CHAP), U.S.</td>
<td>Average follow-up</td>
<td>MMSE, East Boston Tests of Immediate Memory and Delay Recall, Symbol Digit Modalities Test</td>
<td>Decline in global cognition over time.</td>
<td>Strengths: Large population-based study, Relatively long follow-up</td>
</tr>
<tr>
<td></td>
<td>-Age 65 and older</td>
<td>of 6.4 years</td>
<td></td>
<td></td>
<td>Limitations: Relate to the predictors (see Table 5)</td>
</tr>
<tr>
<td></td>
<td>-Conducted from 1993 to 2003; follow-up twice at 3-year intervals</td>
<td></td>
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<tr>
<td>Zelinski &amp; Burnight (1997)</td>
<td>N=106 (54.7% F) drawn from the membership list of Family Health Plan, California, U.S.</td>
<td>16 years</td>
<td>Verbal memory, Intelligence scores from the Schaie-Thurstone Adult Mental Abilities Test (STAMAT)</td>
<td>Reliable decline in list and text recall, reasoning and space after age 55</td>
<td>Strengths: Long 16-year follow-up and large population-based study, Used both cross-sectional and longitudinal data</td>
</tr>
<tr>
<td></td>
<td>-Age 30-36 and 55–81 years at baseline</td>
<td></td>
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<tr>
<td></td>
<td>-Began in 1978; follow-up in 1994</td>
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</table>

¹ Significant results presented in the articles.

F = females
Predictors of change in cognitive performance in the general population

Many factors have been investigated in association with cognitive ability. A large body of literature has demonstrated that basic sociodemographic predictors, such as vocational education, gender, and acculturation (Alley et al. 2007), and a variation of clinical physical health conditions, such as obesity (Nilsson & Nilsson 2009), smoking (Anstey et al. 2007) and having alcohol problems (Lopes et al. 2010), and psychological factors (Colcombe & Kramer 2003, Seeman et al. 2001) can affect cognitive ability.

There are also numerous studies with different clinical or population-based cohort samples about predictors of cognitive change, mostly examining longitudinal cognitive decline in elderly groups. There is longitudinal evidence that faster age-related cognitive decline occurs in those with a poor vocational education (Agrigoroaei & Lachman, 2011, Colsher & Wallace 1991, Hahn & Lachman 2015, Matthews et al. 2004, Nguyen et al. 2002, Osler et al. 2013, Richards et al. 2004, Schaie 1994). Also gender (Matthews et al. 2012, Muniz-Terrera et al. 2009), clinical condition (BMI, blood pressure, diabetes) (Cournot et al. 2006, Furuång et al. 2013, Glynn et al. 2004), marital status (Nguyen et al. 2002) and social class (Osler et al. 2013) have been associated with cognitive decline. Instead, psychological factors including a sense of control and quality of social support were positively related to cognitive change (Agrigoroaei & Lachman 2011).

To summarize, although understanding more about the predictors of change in cognitive functioning throughout a human lifespan is of theoretical and potential practical importance, there remains a gap in the literature regarding studies of the factors and nature of cognitive change during early midlife, a developmental period of the human life cycle with key social everyday life challenges that have major influences on cognitive development. Based on the literature review, Table 5 summarizes the results of studies concerning predictors of change in cognitive performance in the general population.
Table 5. Studies and results concerning predictors of change in cognitive performance in general population. Only studies with at least five years follow-up are included (Modified from the Table 1, original study II).

<table>
<thead>
<tr>
<th>Authors1 (Year)</th>
<th>Analyzed predictors2</th>
<th>Predictors of change in cognition3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agrigoroaei &amp; Lachman (2011)</td>
<td>Baseline basic demographic variables, Health status (e.g. diabetes), Physical exercise, Quality of social support</td>
<td>A composite index of the number of adaptive psychosocial and behavioral factors was positively related to change in reasoning abilities. Higher educated participants experienced smaller memory decline.</td>
</tr>
<tr>
<td>Bielak et al. (2012)</td>
<td>Activity level</td>
<td>Between-person activity and within-person variation in activity level were both not significantly associated with change in cognitive test performance.</td>
</tr>
<tr>
<td>Carmelli et al. (1997)</td>
<td>Baseline basic demographic variables, Physical health and cardiovascular history</td>
<td>Poor self-perceived health ratings, depression scale scores, and self-reports of physical activity predicted decline in cognitive performance.</td>
</tr>
<tr>
<td>Colsher &amp; Wallace (1991)</td>
<td>Baseline basic demographic variables</td>
<td>Higher age predicted decline in memory.</td>
</tr>
<tr>
<td>Cournot et al. (2006)</td>
<td>Baseline basic demographic variables, Clinical characteristics (e.g. BMI)</td>
<td>Lower levels of educational attainment were predictive of more rapid declines in the mental status examination and recall memory test among women. Higher BMI at baseline was associated with a higher cognitive decline in word-list learning. No significant association was found between changes in BMI and cognitive function.</td>
</tr>
<tr>
<td>Furuläng et al. (2013)</td>
<td>Baseline basic demographic variables, Clinical characteristics (e.g. BMI)</td>
<td>Subjects with enlarged left ventricular internal dimension in diastole at age 68 had poorer results on verbal and visuospatial tests in the follow-up.</td>
</tr>
<tr>
<td>Giambra et al. (1995)</td>
<td>Baseline basic demographic variables</td>
<td>Higher age predicted a decline in memory (longitudinally, the decline in cognition did not reach a magnitude sufficient to be significant until after 64 years).</td>
</tr>
<tr>
<td>Glynn et al. (2004)</td>
<td>Baseline basic demographic variables</td>
<td>There was little evidence for the effect of blood pressure on a change in cognitive function with either test, or for an effect on level of function in the memory test.</td>
</tr>
<tr>
<td>Hahn &amp; Lachman (2015)</td>
<td>Baseline basic demographic variables, Functional health (by asking participants whether their health limits them in daily activities)</td>
<td>Participants who were older, or had lower levels of education, or lower general perceived control, and higher initial working memory span at Time 1 were more likely to experience greater memory decline.</td>
</tr>
<tr>
<td>Authors1 (Year)</td>
<td>Analyzed predictors2</td>
<td>Predictors of change in cognition3</td>
</tr>
<tr>
<td>----------------</td>
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</tr>
<tr>
<td>Johansson et al. (2004)</td>
<td>Baseline basic demographic variables</td>
<td>Chronological age and time to death were consistent predictors of decline in measures of memory, reasoning, speed, and verbal abilities.</td>
</tr>
<tr>
<td>Johnson et al. (2010)</td>
<td>Marital status and housing</td>
<td>None of the covariates had any significant effect on cognitive change.</td>
</tr>
<tr>
<td>Johnson et al. (2010)</td>
<td>Covariates (e.g. age/gender)</td>
<td>The ankle–brachial index (ABI) was not associated with change in cognitive function.</td>
</tr>
<tr>
<td>Kobayashi et al. (2014)</td>
<td>The ankle–brachial index (ABI)</td>
<td>None of the covariates had any significant effect on cognitive change.</td>
</tr>
<tr>
<td>Johnson et al. (2010)</td>
<td>Developmental data at the age of 1 year of the infant when he/she was first able to stand without support</td>
<td>No significant association between the age of learning to stand and change in cognition.</td>
</tr>
<tr>
<td>MacDonald et al. (2004)</td>
<td>Biological and chronological age</td>
<td>Biological age predicted actual cognitive change (decline) independent of chronological age.</td>
</tr>
<tr>
<td>Matthews et al. (2012)</td>
<td>Baseline basic demographic variables</td>
<td>Women show greater change in MMSE scores with age than men.</td>
</tr>
<tr>
<td>Muniz-Terrera et al. (2009)</td>
<td>Occupation-based social class</td>
<td>Lower education levels and manual work show greater change in MMSE with age.</td>
</tr>
<tr>
<td>Nguyen et al. (2002)</td>
<td>Social class and education</td>
<td>Women and participants with better mobility were found to experience a slower decline with age than men and participants with poorer mobility.</td>
</tr>
<tr>
<td>Payne et al. (2014)</td>
<td>Information about activities of daily living</td>
<td>Biological age predicted actual cognitive change (decline) independent of chronological age.</td>
</tr>
<tr>
<td>Osler et al. (2013)</td>
<td>Baseline basic demographic variables</td>
<td>Biological age predicted actual cognitive change (decline) independent of chronological age.</td>
</tr>
<tr>
<td>Payne et al. (2014)</td>
<td>Impact of birth characteristics and childhood activities</td>
<td>Age, education, marital status, and household predicted decline in cognition.</td>
</tr>
<tr>
<td>Richards et al. (2004)</td>
<td>Social class</td>
<td>Age, education, marital status, and household predicted decline in cognition.</td>
</tr>
<tr>
<td>Richards et al. (2004)</td>
<td>Baseline basic demographic variables</td>
<td>Age, education, marital status, and household predicted decline in cognition.</td>
</tr>
<tr>
<td>Schaie (1994)</td>
<td>Physical and social activity</td>
<td>Increasing educational attainment was associated with slower decline in memory independent of ability in childhood.</td>
</tr>
<tr>
<td>Schaie (1994)</td>
<td>Health history records</td>
<td>Increased level of formal education predicted increments in inductive reasoning, spatial orientation, verbal ability and verbal memory for successive cohorts.</td>
</tr>
</tbody>
</table>
Baseline basic demographic variables and race

In a mixed model adjusted for age, gender, race, and education, higher BMI was associated with less cognitive decline in both black and non-black subjects.

Baseline basic demographic variables

Higher age predicted decline in list and text recall, reasoning and spatial perception.

Significant results presented in the articles.

Study design and characteristics of the sample are presented in Table 4.

1 Significant results presented in the articles.

2 Basic sociodemographic variables consist of age, gender, and education unless otherwise stated.
2.3.2 Change in cognitive performance and its predictors in schizophrenia

Change in cognitive performance in schizophrenia

There is evidence that cognitive impairment is a better predictor of work and social function in schizophrenia than are positive and negative symptoms (Kaneda et al. 2010, Miles et al. 2014). For example, improvements in the domains of verbal working memory were found to be a better predictor of employment outcome than other cognitive functions, whereas a decline in cognitive and adaptive functioning was found over time even when there was no change in schizophrenic symptoms (Kaneda et al. 2010). These findings indicate that cognitive decline may predict deterioration in overall functional status in schizophrenia, which emphasizes the importance of identification and treatment of cognitive impairment aiming to achieve a beneficial effect on the global functional status in schizophrenic sufferers (Harvey et al. 1999). However, the long-term course of cognitive functioning in schizophrenia and its predictors are not fully understood (Nuechterlein et al. 2014).

Studies show evidence of longitudinal brain volume decreases in schizophrenia underling the changes in cognitive performance. Some studies have suggested that individuals with schizophrenia with the worst clinical outcomes may also exhibit the most extensive brain atrophy over time (Andreasen et al. 2013). Some cross-sectional studies (with less than three years follow-up) associate cognitive impairment with smaller brain volumes (Hulshoff & Kahn 2008). Consistently, poor cross-sectional cognitive performance was associated with progressive brain volume decrease (Andreasen et al. 2011). A recent study of the NFBC 1966 (Veijola et al. 2014) reported brain volume reduction in schizophrenia especially in the temporal lobe and periventricular area, however with no association found with decline in cognitive performance.

A so-called connectomic approach grounded in network science is integral to understanding the neuropathology of syndrome-specific brain atrophy (Fornito et al. 2015). More precisely, pathological perturbations of the brain are often spread via axonal pathways to influence other regions. Patterns of such disease propagation are constrained by the extraordinarily complex, yet highly organized, topology of the underlying neural architecture; the connectome. Thus, network organization fundamentally influences brain disease. However, recent research
suggests that syndrome-specific brain volume decreases develop following the course of spontaneous functional connectivity in the general population (Fornito et al. 2015). Gray matter volume reductions have been found in the right angular gyrus, right frontoinsular cortex, left premotor cortex, left temporal pole, and left inferior frontal gyrus in both patients with specific neurodegenerations (such as Alzheimer disease and behavioural-variant frontotemporal dementia), and in healthy individuals. Additionally, consistent with previous findings on morphological changes in normative aging, impaired mitochondrial function in psychiatric disorders (Manji et al. 2012) and decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia (Glantz & Lewis 2000) have been reported. Put together, these findings indicate that the similar morphological processes are possibly associated with age-related changes in cognitive ability in the general population and schizophrenia.

According to recent suggestions, cognitive impairments in schizophrenia do not deteriorate significantly during the lifespan (Hoff et al. 2005, Censits et al. 1997). In the majority of cases, cognitive impairment remains unchanged throughout the disease (Bozikas & Andreou 2011, Goldberg et al. 1993, Heaton et al. 2001, Hoff et al. 2005, Szöke et al. 2008, Zipusky et al. 2013). Further, the meta-analysis by Irani and colleagues (2010) showed large and generalized cognitive deficits in older individuals with schizophrenia, but there was no decline over a six-year follow-up period. A first-episode study with a 20-year follow-up reported impairment in some cognitive domains already by the first-episode without further deterioration over time; on the other hand, some of the cognitive domains were spared during the first-episode but declined with time (Stirling et al. 2003).

Recent evidence also suggests that there is considerable variability between individuals with schizophrenia in the trajectory of cognitive impairment (Barnett et al. 2007). Given that schizophrenia is not a single disease with a predictable outcome, but that the concept of schizophrenia is one of a group of disorders with heterogeneity in their symptomatic presentation and also in their clinical outcome (Craddock & Owen 2005), different combinations of factors underpinning schizophrenia cause different presentations of symptoms and outcomes (Shmukler et al. 2015), and as a result, there is difficulty in describing a single trajectory for the development of cognitive defects in all subjects with schizophrenia.

Neuropsychological investigation typically focuses rather on the assessment of fluid cognitive abilities (e.g. memory, executive functions, and attention) than on crystallized cognitive abilities. In the case of fluid cognitive ability, especially in
the domains of verbal episodic memory and learning, findings on the change of
cognitive performance vary from deterioration (Albus et al. 2006, Hill et al. 2004,
Hoff et al. 2005) to improvement (Addington et al. 2005) for at least some studied
measures. This is possibly due to length of follow-up, practice effects or
improvement in symptoms.

A systematic review of studies on change in cognitive performance and its
predictors in schizophrenia

To summarize the results of longitudinal studies of change in cognitive ability in
schizophrenia, a systematic literature search was completed in September 2015
using the electronic database PubMed and a number of manual searches. The search
produced 4517 results. Based on the information in the abstracts of the articles, 53
articles were selected for comprehensive evaluation. Two articles met the inclusion
criteria and were included in the systematic review. A detailed description of the
literature search procedure is presented in Figure 2.
Methods of the systematic literature review:
The literature search was completed in August 2015 using electronic database PubMed and manual searches. The search strategy included keywords limited to title and abstract search:
(cognit*[Title/Abstract] AND change*[Title/Abstract] AND predict*[Title/Abstract])
(NOT traumatic[Title/Abstract] NOT injury[Title/Abstract] NOT surgery[Title/Abstract]) limited to human; English.
The articles included in the current systematic review were required to meet the following criteria:
• sociodemographic and/or clinical predictors of longitudinal change in adult cognitive performance were analyzed (e.g. studies analyzing only neurobiological predictors were excluded);
• standardized neuropsychological tests were used;
• the sample size was 20 or more;
• cognitive performance was measured at least two times with same tests;
• period between the tests was at least five years.

Fig. 2. Flowchart diagram of the literature search and selection of studies on the predictors of change in cognitive performance in schizophrenia.
As a result of the systematic literature review, two articles met the inclusion criteria and were included in the systematic review. Table 6 summarizes studies on change in cognitive ability with a follow-up of five years or longer presenting the results of cognitive changes in schizophrenia. In the recent research by Barder et al. (2015) 89 first-episode psychosis patients of 15–65 years of age were followed for ten years with a comprehensive neurocognitive test battery including three subtests from WAIS-R (Wechsler, 1981). No longitudinal decline was found in this sample (Table 6).

Secondly, in their over four decades long follow-up study, Jones et al. (1994) investigated associations between adult-onset schizophrenia and childhood behavioural, social, intellectual, and developmental characteristics. Their sample consisted of 30 subjects with schizophrenia, whose mean age at onset was 24 years. Non-verbal, verbal, and arithmetic abilities, reading and vocabulary were explored. Weaker performance over time was observed in all studied cognitive measures in the schizophrenia sample compared to controls (Table 6).
Table 6. Studies and results concerning change in cognitive performance in schizophrenia. Only studies with at least five years follow-up are included.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study design and sample</th>
<th>Follow-up length</th>
<th>Neuropsychological assessments/domains</th>
<th>Change in cognition</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Barder et al. (2015)</td>
<td>N=89 (47% F) drawn from the Early Treatment and Intervention in Psychosis Study (TIPS), carried out in four Scandinavian health care sectors; Oslo, Stavanger, Haugesund and Roskilde.</td>
<td>10 years</td>
<td>IQ-estimate (subtests Similarities, Block Design, and Digit Span from the Wechsler Adult Intelligence Scale-Revised (WAIS-R))</td>
<td>Non-significant improvement in IQ performance</td>
<td>Relatively long follow-up. The IQ calculation is based on three subtests only. Data on the duration of psychosis were collected retrospectively, and will automatically imply an element of uncertainty. The study sample is heterogeneous in terms of baseline diagnosis, which enabled an investigation, and subsequently a rejection of the hypothesis that the diagnostic category may discriminate between performance on IQ measures over time. The present study has no normal controls, and therefore cannot account for possible changes in controls.</td>
</tr>
<tr>
<td>Authors (Year)</td>
<td>Study design and sample</td>
<td>Follow-up length</td>
<td>Neuropsychological assessments/domains</td>
<td>Change in cognition(^1)</td>
<td>Comments</td>
</tr>
<tr>
<td>---------------</td>
<td>------------------------</td>
<td>------------------</td>
<td>----------------------------------------</td>
<td>--------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Jones et al. (1994)</td>
<td>N=30 (33% F) drawn from the Medical Research Council National Survey of Health and Development (NSHD), U.K. -Age 16–43 years -Began in 1970</td>
<td>Continues</td>
<td>Non-verbal, verbal, and reading abilities at ages 8, 11 and 15 years Arithmetic at ages 11 and 15 years Vocabulary at ages 8 and 11 years</td>
<td>Lower scores in all studied cognitive variables at ages 8, 11 and 15 years for cases than for controls.</td>
<td>Strengths: General population sample Limitations: Relatively small study sample The lack of standard diagnostic assessments at disease onset</td>
</tr>
</tbody>
</table>

\(^1\) Significant results presented in the articles.
Predictors of change in cognitive performance in general population

Understanding the role of predictors of cognitive change in schizophrenia is of theoretical and potential practical importance, but there is a paucity in the investigation of the impact of predictors on the course of cognitive change in schizophrenia (Bora & Murray 2014, Bozikas & Andrepi 2011, Irani et al. 2010). The relation between the duration of untreated psychosis and the change of global cognitive functioning has been observed (Barder et al. 2015). There has been no association between the duration of untreated psychosis and a change in cognitive performance, but a subgroup with a long duration of active psychosis after the start of treatment has demonstrated a significant cognitive deterioration. Out of sociodemographic factors, low education has been associated with a decline in selective attention (Ekerholm et al. 2012) and episodic memory (Han et al. 2012).

Based on conducted systematic literature review, very few studies with different clinical or population-based cohort samples have analyzed predictors of cognitive change in schizophrenia during relatively long follow-up times. In Table 7 the results of studies of different sociodemographic and clinical predictors of change in cognitive performance in individuals with diagnosed schizophrenia are summarized. Several predictors of change in cognitive ability have been examined including baseline basic sociodemographic variables (age, gender, education), social class, municipal characteristics of birth place, health visitors’ comments on home, child, and mother, and clinical characteristics (e.g. duration of untreated psychosis, PANSS, alcohol abuse, drug abuse, and diagnosis). None of the covariates had any significant effect on cognitive change (Table 7).
Table 7. Studies and results concerning predictors of change in cognitive performance in schizophrenia. Only studies with at least five years of follow-up are included.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Analyzed predictors</th>
<th>Predictors of change in cognition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barder et al. (2015)</td>
<td>Covariates at baseline, Clinical characteristics at baseline</td>
<td>None of the covariates had any significant effect on cognitive change.</td>
</tr>
<tr>
<td>Jones et al. (1994)</td>
<td>Covariates at baseline, Social class, Municipal characteristics of birth place, Health visitors’ comments on the home, child, and mother</td>
<td>There was no evidence that a low social class at birth or population size of the place of birth were associated with later schizophrenia.</td>
</tr>
</tbody>
</table>

1 Basic sociodemographic variables consist of age, gender and education unless otherwise stated.

2 Significant results presented in the articles.
2.3.3 Earlier cognition related studies in the Northern Finland Birth Cohort 1966

Cognitive performance, longitudinal change in cognitive ability, and their associations with infant motor developmental markers, brain volume change, and antipsychotic medication have all been studied and reviewed in the NFBC 1966 in schizophrenia in comparison with non-psychotic controls (Jääskeläinen et al. 2015) (Table 8).

Previously, three studies showed the results concerning early developmental markers and cognitive ability: (1) The age of learning to stand in infancy at about one year of age significantly inversely predicted later deterioration of executive functions in memory in adults with schizophrenia between 34 and 43 years of age (Kobayashi et al. 2014), suggesting that the connection between delayed infant development and general cognitive decline in adulthood may be a link between abnormal neurodevelopmental and neurodegenerative processes in schizophrenia. (2) Earlier motor development, better adult executive functions, and higher grey matter density in fronto-cerebellar systems were associated with each other in controls, but there was a disruption of these normative associations in schizophrenia at 34 years (Ridler et al. 2006). (3) Delayed infant motor development was associated with poorer adult cognition in schizophrenia at the age of 34 years in executive functions, verbal learning, and visuospatial working memory, but not in visual learning (Murray et al. 2006).

Cross-sectionally, cognitive performance has been observed in six previous studies: (1) Global cognitive functioning as well as performance in domains of executive functions, working memory, and visual and verbal memory were lower in subjects with schizophrenia in comparison to control subjects cross-sectionally, both at the age of 34 (Husa et al. 2014, Kobayashi et al. 2014, Murray et al. 2006, Rannikko et al. 2012, Ridler et al. 2006, Veijola et al. 2014) and 43 (Husa et al. 2014, Kobayashi et al. 2014, Veijola et al. 2014). (2) However, the longitudinal course of cognitive change in schizophrenia followed a mostly normative aggregated decline; e.g. no significantly greater decrease in overall cognition (Veijola et al. 2014) or visual learning, or executive functions without a memory component (Kobayashi et al. 2014) was observed during midlife in schizophrenia, compared to the controls. The only exception to this pattern was the significant deterioration of executive functions with the memory component in cases compared to controls (Kobayashi et al. 2014).
The association between antipsychotic medication and cognitive performance has been analyzed in three studies: (1) Higher lifetime antipsychotic medication exposure was associated with poorer verbal learning and memory performance at the age of 34 (Husa et al. 2014, Rannikko et al. 2012) and greater decline in verbal learning and memory between the ages of 34 and 43 years (Husa et al. 2014). (2) Although antipsychotic exposure also predicted brain volume reduction in schizophrenia during that time, this volume reduction was not associated with a decrease in overall cognition or specific cognitive processes (Veijola et al. 2014), so the associations between antipsychotic medication, cognition, and longitudinal brain changes seem complex in schizophrenia.
### Table 8. Studies and results of cognition analyses from the NFBC 1966

<table>
<thead>
<tr>
<th>Authors (Year)</th>
<th>Study sample</th>
<th>Results and conclusions of the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Husa et al. (2014)</td>
<td>N=40 schizophrenia subjects N=73 non-psychotic controls age 34 years at first cognitive assessment in 1999–2001 age 43 years at second cognitive assessment in 2008–2010</td>
<td>Higher antipsychotic dose-years at the baseline were associated with poorer baseline performance and a larger decrease in several dimensions of episodic memory. Higher antipsychotic dose-years during the follow-up were associated with a larger decrease of immediate free recall for trials 1–5. Compared to controls, the decline was greater among those using high-doses, but not among those using low-doses. <strong>Conclusion:</strong> The use of high doses of antipsychotics may be associated with a decrease in verbal learning and memory in schizophrenia years after the onset of the illness. The results do not support the view that antipsychotics in general prevent cognitive decline or promote cognitive recovery in schizophrenia.</td>
</tr>
<tr>
<td>Kobayashi et al. (2014)</td>
<td>N=36 schizophrenia subjects N=76 non-psychotic controls age 34 years at first cognitive assessment in 1999–2001 age 43 years at second cognitive assessment in 2008–2010</td>
<td>Compared to controls subjects with schizophrenia showed greater deterioration in executive functions, but there were no differences between schizophrenia and control groups in the rate of change of verbal or visual episodic memory. The age of learning to stand in infancy significantly inversely predicted later deterioration of executive functions in adult schizophrenia. <strong>Conclusion:</strong> Later infant development is linked to greater subsequent cognitive deterioration during adulthood, suggesting a link between abnormal neurodevelopmental and neurodegenerative processes in schizophrenia.</td>
</tr>
<tr>
<td>Murray et al. (2006)</td>
<td>N=61 schizophrenia subjects N=104 non-psychotic controls age 33–35 years at first cognitive assessment in 1999–2001</td>
<td>Subjects with schizophrenia achieved neuromotor milestones later and performed worse than the control group in the domains of executive function, verbal and visual episodic memory, and visuospatial working memory. <strong>Conclusion:</strong> In schizophrenia mild infant motor development delays and adult cognitive deficits at least in some domains are age dependent manifestations of the same underlying neural process. Thus, they may be better considered as part of a single longitudinal syndrome.</td>
</tr>
<tr>
<td>Authors (Year)</td>
<td>Study sample</td>
<td>Results and conclusions of the study</td>
</tr>
<tr>
<td>---------------</td>
<td>--------------</td>
<td>-------------------------------------</td>
</tr>
</tbody>
</table>
| Rannikko et al. (2012) | N=57 subjects with schizophrenia spectrum disorders  
N=94 non-psychotic controls  
age 33–35 years at first cognitive assessment in 1999–2001 | Individuals with schizophrenia spectrum disorders demonstrated explicit verbal learning and episodic memory impairments.  
Poorer verbal memory strategies were associated with a longer duration of illness and heavier use of antipsychotic medication.  
**Conclusion:** In schizophrenia substantial verbal learning and memory strategy impairments exist: cases are impaired in the use of certain memory strategies, and they instead use other less efficient information encoding strategies, suggesting a compensation mechanism to remember the verbal material using ineffective information processing strategies. |
| Ridler et al. (2006) | N=49 schizophrenia subjects  
N=93 non-psychotic controls  
age 33–35 years at first cognitive assessment in 1999–2001 | In the non-psychotic sample, earlier motor development in infancy was correlated with superior executive function, increased gray matter density in the adult premotor cortex, striatum, and cerebellum and increased white matter density in frontal and parietal lobes.  
Adult executive function was normally associated with increased gray matter density in the frontal-cerebellar system that partially overlapped, but was not identical to, the gray matter regions normally associated with infant motor development.  
The schizophrenia sample had relatively delayed infant motor development and impaired adult executive function in adulthood. They also demonstrated no normative associations between frontal-cerebellar structure, infant motor development, or executive function.  
**Conclusion:** Frontal cortico-cerebellar systems correlated with adult executive functions are anatomically related to systems associated with normal infant motor development. Disruption of this anatomical system may underlie both the early developmental and adult cognitive abnormalities in schizophrenia. |
### Authors (Year)

<table>
<thead>
<tr>
<th>Study sample</th>
<th>Results and conclusions of the study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Veijola <em>et al.</em> (2014) N=33 schizophrenia subjects N=71 non-psychotic controls age 33–35 years at first cognitive assessment in 1999–2001 age 43 years at second cognitive assessment in 2008–2010</td>
<td>The mean annual whole brain volume reduction was 0.69% in schizophrenia subjects (especially in the temporal lobe and periventricular area), and 0.49% in controls. Symptom severity, functioning level, and decline in cognition were not associated with brain volume reduction in the schizophrenia group. The amount of antipsychotic medication over the follow-up predicted brain volume loss. <strong>Conclusion:</strong> Brain volume reduction continues in schizophrenia patients after the onset of illness, and antipsychotic medications may contribute to these reductions.</td>
</tr>
</tbody>
</table>

Interpretation of the studies has been composed by utilizing results of the article by Jääskeläinen *et al.* (2015).
To summarize, the relation of cognitive decline to early development at age 1 (Kobayashi et al. 2014), brain volume reduction after the onset of illness (Veijola et al. 2015), and potential harmful effects of long-term high-dose antipsychotic medication to brain volume loss (Veijola et al. 2014) and to decline of cognitive function (Husa et al. 2014) have been observed in the NFBC 1966 in schizophrenia in comparison to non-psychotic controls.

The results of three original papers included in this doctoral thesis extend similar findings from the previous cross-sectional (Rannikko et al. 2012) and longitudinal (Husa et al. 2014, Kobayashi et al. 2014, Veijola et al. 2014) studies from the NFBC 1966 on time-related memory decline in non-psychotic subjects and in individuals with schizophrenia. More specifically, out of all cognitive studies from the NFBC 1966, this is the first study examining the change in all domains of verbal episodic memory measured by CVLT and the role of sociodemographic and clinical predictors of cognitive change in non-psychotic and schizophrenia samples.

Further, one of the key advantages of the present doctoral thesis is the exploration of possible predictors of change in cognitive performance, not only among participants with schizophrenia but also in the general population sample. This makes possible the comparison of the rate in cognitive change during early midlife and the risk factors of this change in cognitive performance between these two groups.

2.3.4 Summary of the literature review

Intellectual development occurs from childhood through adolescence into adulthood, and refers to how a person perceives, thinks, and gains understanding of his/her world through the interaction of genetic and learned factors (e.g. Johnson 2005). Among the areas of cognitive development there are mental or cognitive abilities related to information processing, memory, language and verbal skills, visuospatial function, attention, processing speed, and executive function.

By applying a formal neuropsychological assessment with its standardized psychometric tests, cognitive psychology aims to identify how various mental processes and cognitive impairments may be defined and measured, and to explore limitations in task performance. Cognitive deficits may be caused by environmental factors such as brain injuries, neurological disorders, or mental illnesses such as schizophrenia, in which cognitive impairment is a core feature of the disease. In schizophrenia, cognitive issues, especially in the domains of verbal learning and memory, working memory, verbal fluency, processing speed, and executive
functions, have proven to be a major predictor of overall functional deficit (Reichenberg 2010).

Previous scientific research has focused on the change in cognitive ability in non-psychotic samples, mostly in aging and clinical case-control studies. Many studies have demonstrated that the change in cognitive ability remains gradual, suggesting that it may be an ordinary developmental process. In schizophrenia, findings regarding longitudinal changes in cognitive performance are extremely variable. Understanding the longitudinal changes in cognitive ability is important for the etiological investigation of schizophrenia and for treatment purposes, but the number of studies in this area is still small. Also, understanding more about the predictors of change in cognitive ability throughout a human lifespan is of theoretical and potentially practical importance. However, there remains a gap in the literature regarding studies of the factors and nature of cognitive change during early midlife, which is an essential developmental period of the human life cycle with key social everyday life challenges that have major influences on cognitive development.

Previously in the NFBC 1966 the longitudinal course of cognitive ability has been analyzed in three (Husa et al. 2014, Kobayashi et al. 2014, Veijola et al. 2014) studies. This doctoral thesis aims to extend findings on change of cognitive performance from these previous studies and also provide novel information on predictors of cognitive changes in the NFBC 1966 in middle-aged non-psychotic individuals and individuals with schizophrenia.
3 Aims and hypotheses of the study

3.1 Aims of the study

The overall aim of this doctoral thesis project was to examine change in cognitive performance and its predictors in the general population and schizophrenia in early midlife. The third or fourth developmental decade of life can be generally considered as a crucial period of a person’s life cycle, when cognitive development continues due to key social, family and occupational everyday life challenges. However, this essential developmental period of a human lifespan has been earlier overlooked. The original studies in this doctoral thesis, that utilized the data from the NFBC 1966 for individuals from the general population sample and subjects with schizophrenia spectrum disorders, aimed to:

I Compare the change in verbal learning and memory in individuals with schizophrenia 10–20 years after the illness onset and non-psychotic controls during a nine-year follow-up between ages 34 and 43 years in midlife (I).

II Analyze the predictors of change in cognition in midlife in a general population sample (II).

III Find out whether premorbid school performance and the severity of illness and functioning predict changes in cognition in schizophrenia in midlife (III).

3.2 Hypotheses of the study

The hypotheses of the original studies tested were:

I Subjects with schizophrenia experience less improvement, or more deterioration, in measures of verbal learning and memory when compared to non-psychotic controls.

II Female gender, single marital status, parenthood, higher body mass index, poorer primary school performance and vocational education, and lower occupational class are associated with a decline in cognitive ability in general population samples.

III Both poor school performance and lower levels of education, and more severe illness during the first episode and later course of illness, associate with more decline in cognition in schizophrenia.
4 Material and methods

4.1 The Northern Finland Birth Cohort 1966

The Northern Finland Birth Cohort 1966 (NFBC 1966) is a birth cohort which has been studied extensively with almost 1,000 peer-reviewed publications in various fields of medicine (http://www.oulu.fi/nfbc). The NFBC 1966 was collected during the mid-1960s by pediatrician and Professor of Public Health Paula Rantakallio (1930-2012), the first aim being to analyze perinatal health (Rantakallio 1969). In the 1980s, adolescent health and, in the 1990s, adult somatic and psychiatric disorders emerged as the main study objective.

The NFBC 1966 is based on 12,068 pregnant women and their 12,058 live-born babies in two northernmost Finnish provinces (Oulu and Lapland), with an expected date of birth during 1966 (Rantakallio 1969). The live-births in this study represent 96% of all births in the region. The data has been completed for all cohort members from the 24th gestational week onwards, at ages 1, 14, 31, and 46, and from psychoses and selected controls at ages 34 and 43. The sample includes 10,934 individuals living in Finland who were 16 years of age in 1982. The psychiatric and somatic outcomes have been ascertained through data linkage to the national social and health care registers, e.g. the Finnish Hospital Discharge Register (FHDR), currently known as the Care Register for Health Care, as well as through extensive clinical evaluations.

All cohort members over 16 years appearing on the FHDR until the end of 1997 for any mental disorder (i.e. ICD-8 diagnoses 290–309, ICD-9 290–316, and ICD-10 F00–F69, F99) were identified. All case records were scrutinized and diagnoses were validated for DSM-III-R criteria (Isohanni et al. 1997, Moilanen et al. 2003).

Schizophrenia research with the NFBC 1966 has been especially active and was started in 1990 by Professor Matti Isohanni (emeritus), with the first studies performed and reported in the mid-1990s. The first studies focused on early risk factors, but later clinical and social outcomes, cognitive ability, brain morphometry, somatic illnesses, and genetics have also been studied (reviewed recently by Jääskeläinen et al. 2015).
4.2 Participant identification

4.2.1 Baseline study at 34 years of age

The 34-year follow-up for psychoses was conducted in 1999–2001. Hereafter in this thesis the term “baseline study” is used for the 34-year follow-up study. NFBC 1966 cohort members with a psychotic episode by the end of the year 1997 were detected using the Care Register for Health Care, formerly known as the Finnish Hospital Discharge Register. The control subjects were selected randomly from the cohort members without a psychotic episode, living in the region of Oulu (Haaapea et al. 2007).

The baseline study consisted of structural magnetic resonance imaging (MRIs) of the brain, as well as measures of cognitive functioning, psychiatric diagnostic interviews, and questions related to, for example, the use of psychiatric medication, social background, and substance use. All 146 individuals with a psychotic episode (62 females, 42%) and 187 controls (71 females, 38%) were invited to participate in the field study. Altogether 91 individuals with psychosis (73 [79%] with schizophrenia spectrum disorders) and 104 non-psychotic control subjects participated.

The diagnoses of the participants of the baseline study were scrutinized and the diagnoses were validated in accordance with DSM-III-R (Isohanni et al. 1997, Moilanen et al. 2003), together with all available anamnestic information including individual hospital notes. The Structured Clinical Interview for DSM-III-R (SCID-I; Spitzer et al. 1989) was performed for all participants. After diagnostic interviews a total of 61 individuals with a lifetime diagnosis of schizophrenia and 12 with other schizophrenia spectrum disorders were detected. In this thesis, the schizophrenia spectrum disorder diagnoses were schizophreniform disorder, schizoaffective disorder and delusional disorder. The mean duration of illness was 10 years (standard deviation [SD] 4.3 years) at the baseline.

4.2.2 Follow-up study at 43 years of age

All the participants of the baseline study were invited to participate in the 43-year follow-up study conducted in 2008–2010 when the participants were around the age of 43 years. Hereafter in this thesis the term “follow-up study” is used for the 43-year follow-up. Of the participants, 54 subjects with a psychotic disorders (41 with schizophrenia spectrum disorder) and 76 non-psychotic control subjects
participated, both at ages 34 and 43 (Jääskeläinen et al. 2015). The original diagnosis in the follow-up study for all participants with schizophrenia were validated in accordance with the DSM-IV and upheld on the basis of the SCID-I (Spitzer et al. 1989), interview and case note review. The mean duration of illness up until the follow-up study was 20.0 years (S.D.4.1).

### 4.2.3 Study samples

The original study I included 73 control subjects and 41 subjects with schizophrenia spectrum disorder for whom CVLT data was available in both baseline and follow-up studies. The original study II included 75 control subjects and the original study III included 41 subjects with schizophrenia spectrum disorder for whom data on at least one of the three studied measurements of cognitive performance were available in both baseline and follow-up studies. A detailed description of the study samples (I - III) is presented in Figure 3 and Figure 4.

Hereafter in this thesis the term “schizophrenia” is used for schizophrenia and other schizophrenia spectrum disorders. In this thesis, the schizophrenia group included the following DSM-III-R diagnoses: schizophrenia 295.1 (n=9); 295.3 (n=8); 295.6 (n=1); 295.9 (n=16); schizophreniform psychosis 295.4 (n=1), schizoaffective disorder 295.7 (n=5) and delusional disorder 297.1 (n=1).
A sample of 187 non-psychotic NFBC 1966 members were invited to participate in the baseline study in 1999-2001. 83 non-participants in the baseline study. 104 participants in the baseline study. 1 with non-schizophrenic psychosis. 27 non-participants in the follow-up study. 76 participants in the follow-up study in 2008-2010. CVLT data: - no baseline data, n=2 - no follow-up data, n=1. VOLT data: - no baseline data, n=1 - no follow-up data, n=2. Complete VOLT data, n=72. 2 with VOLT and AIM, 1 with AIM. Complete AIM data: - abstraction without memory, n=71 - abstraction with memory, n=70. N=73 (I) 1 with organic psychosis. N=75 (II) VOLT data: - no baseline data, n=1 - no follow-up data, n=2. AIM data: - no baseline data, n=3 - score < 15: - abstraction without memory, n=1 - abstraction with memory, n=2. 27 non-participants in the follow-up study. 2 with VOLT and AIM, 1 with AIM. N=73 (I) 1 with organic psychosis. 76 participants in the follow-up study in 2008-2010.

Fig. 3. Procedure of invitation and participation for the non-psychotic sample (I-II). Abbreviations: CVLT = California Verbal Learning Test, VOLT = Visual Object Learning Test, AIM = Abstraction, Inhibition and Working Memory task.
Fig. 4. Procedure of invitation and participation of the schizophrenia sample (I, III). Abbreviations: CVLT = California Verbal Learning Test, VOLT = Visual Object Learning Test, AIM = Abstraction, Inhibition and Working Memory task.
Attrition analyses within non-psychotic subjects

In the original studies I and II, those who completed the cognitive measurements in the baseline and follow-up studies (completers) did not differ from those who did not participate or did not complete the cognitive measurements in the follow-up study (non-completers) in gender, vocational education, or selected cognitive measures at the baseline (Table 9).

There were no differences in primary school marks between the sample of original study II and the rest of the non-psychotic NFBC 1966 members or between those invited to participate in the baseline study and the rest of the non-psychotic NFBC 1966 members. The sample group was, however, more highly educated, when measured using information from the education register (nine years or less, 10-12 years, over 12 years by 1997) compared to the rest of the cohort (p=0.021).

Attrition analyses within schizophrenia

In the original studies I and III, the samples included the same subjects with schizophrenia. The completers did not differ from the non-completers in gender or cognitive measure at the baseline (Table 9). Altogether 34 (83%) of the completers and 27 (87%) of the non-completers had a diagnosis of schizophrenia (p=0.75). The completers did not differ from non-completers in their current use of antipsychotic medication or in the prevalence of alcohol use disorders based on the SCID-I interview. There was also no significant difference in displayed symptoms based on the PANSS at the time of the baseline study, or the onset age or number of psychiatric hospitalization days. Regarding education, the completers did not differ from the non-completers in vocational education, but the completers were more highly educated in 1997 compared to the non-completers based on the education register (p=0.041). Four cases with high levels of education did not participate in the follow-up study.

The sample of the original studies I and III had non-significantly higher primary school marks in theoretical subjects and significantly higher primary school marks in practical subjects compared to the rest of the NFBC 1966 members with schizophrenia. There was no significant difference in education based on the register data.
Table 9. Representativeness of the samples in respect to gender, education and primary school marks, and comparison of the samples with the baseline participants in respect to gender, vocational education and cognitive ability.

<table>
<thead>
<tr>
<th>Attition analyses</th>
<th>Non-psychotic sample</th>
<th>P-value</th>
<th>Schizophrenia sample</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Participants</td>
<td>Non-participants</td>
<td></td>
<td>Participants</td>
</tr>
<tr>
<td>Comparison with the NFBC 1966</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td>n = 75</td>
<td>n = 10524</td>
<td>0.08</td>
<td>n=41</td>
</tr>
<tr>
<td>Males</td>
<td>46 (61.3%)</td>
<td>5359 (50.9%)</td>
<td></td>
<td>22 (53.7%)</td>
</tr>
<tr>
<td>Females</td>
<td>29 (38.7%)</td>
<td>5165 (49.1%)</td>
<td></td>
<td>19 (46.3%)</td>
</tr>
<tr>
<td>Primary school marks, mean (SD)</td>
<td>n = 74</td>
<td>n = 10290</td>
<td></td>
<td>n = 39</td>
</tr>
<tr>
<td>All subjects</td>
<td>7.61 (0.89)</td>
<td>7.56 (0.95)</td>
<td>0.66</td>
<td>7.64 (0.95)</td>
</tr>
<tr>
<td>Theoretical</td>
<td>7.43 (1.07)</td>
<td>7.39 (1.11)</td>
<td>0.75</td>
<td>7.51 (1.11)</td>
</tr>
<tr>
<td>Practical</td>
<td>8.02 (0.61)</td>
<td>7.95 (0.73)</td>
<td>0.32</td>
<td>7.92 (0.77)</td>
</tr>
<tr>
<td>Education by 1997, n (%)</td>
<td>n = 75</td>
<td>n = 10512</td>
<td>0.021</td>
<td>n=41</td>
</tr>
<tr>
<td>9 years or less</td>
<td>3 (4.0%)</td>
<td>1588 (15.1%)</td>
<td></td>
<td>8 (19.5%)</td>
</tr>
<tr>
<td>10 to 12 years</td>
<td>48 (64.0%)</td>
<td>6253 (59.5%)</td>
<td></td>
<td>33 (80.5%)</td>
</tr>
<tr>
<td>Over 12 years</td>
<td>24 (32.0%)</td>
<td>2671 (25.4%)</td>
<td></td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Comparison with the baseline participants</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td>n = 75</td>
<td>n = 27</td>
<td>&gt;0.99</td>
<td>n=41</td>
</tr>
<tr>
<td>Males</td>
<td>46 (61.3%)</td>
<td>16 (59.3%)</td>
<td></td>
<td>46 (61.3%)</td>
</tr>
<tr>
<td>Females</td>
<td>29 (38.7%)</td>
<td>11 (40.7%)</td>
<td></td>
<td>29 (38.7%)</td>
</tr>
<tr>
<td>Vocational education at baseline, n (%)</td>
<td>n = 75</td>
<td>n = 27</td>
<td>0.48</td>
<td>n=41</td>
</tr>
<tr>
<td>Low</td>
<td>31 (41.3%)</td>
<td>9 (33.3%)</td>
<td></td>
<td>22 (53.7%)</td>
</tr>
<tr>
<td>Middle</td>
<td>15 (20.0%)</td>
<td>4 (14.8%)</td>
<td></td>
<td>12 (29.3%)</td>
</tr>
<tr>
<td>High</td>
<td>29 (38.7%)</td>
<td>14 (51.9%)</td>
<td></td>
<td>7 (17.1%)</td>
</tr>
</tbody>
</table>
## Attrition analyses

<table>
<thead>
<tr>
<th>Cognitive measures, mean (SD)</th>
<th>Non-psychotic sample</th>
<th>Schizophrenia sample</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Participants</td>
<td>Non-participants</td>
</tr>
<tr>
<td>Immediate free recall</td>
<td>59.7 (7.3)</td>
<td>60.0 (8.6)</td>
</tr>
<tr>
<td>Short delay</td>
<td>26.9 (3.5)</td>
<td>26.3 (5.6)</td>
</tr>
<tr>
<td>Long delay</td>
<td>27.7 (3.5)</td>
<td>27.6 (5.5)</td>
</tr>
<tr>
<td>VOLT</td>
<td>68.6 (5.4)</td>
<td>68.4 (4.8)</td>
</tr>
<tr>
<td>AIM, abstraction without memory</td>
<td>24.1 (2.5)</td>
<td>24.7 (2.2)</td>
</tr>
<tr>
<td>AIM, abstraction with memory</td>
<td>23.6 (3.4)</td>
<td>23.5 (3.2)</td>
</tr>
</tbody>
</table>

NFBC 1966 = Northern Finland Birth Cohort 1966. SD = standard deviation.


1 Significance from the independent samples t-test (continuous variables) or chi-square test (categorical variables).
4.3 Neuropsychological assessment in the non-psychotic sample (I-II) and the schizophrenia sample (I, III)

The neuropsychological assessment was selected to correspond to cognitive domains that have been consistently identified with areas of cognitive deficit in schizophrenia: memory and executive functioning.

A neuropsychological battery included the California Verbal Learning Test (CVLT; Delis et al. 1987), the Visual Object Learning Test (VOLT; Glahn et al. 1997) and the Abstraction, Inhibition and Working Memory task (AIM; Glahn et al. 2000). These tests were administered at both the baseline and at the follow-up (Rannikko et al. 2015).

The battery of cognitive tasks was administered in a fixed order by examiners who were trained in neuropsychological assessments. The training of the examiners was updated regularly throughout the follow-up phase of the study during 2008-2011. The examiner training throughout the follow-up period was supervised by two clinical neuropsychologists.

All participants were provided with feedback for each trial in each cognitive task. For the computerized tasks, instructions were presented on a computer screen for subjects to read at their own pace, and a number of practice trials were completed for each task before testing began.

The results of the cognitive task tests were run through Power Laboratory Player on an Apple 5300 laptop computer, with the exception of the CVLT, which was administered using a paper-pencil record form and scored manually.

In the case of the CVLT, the representativeness of the control group was ensured according to standardized norms for the CVLT at baseline and follow-up. The raw CVLT scores of the study sample were compared to normed CVLT scores for the same age group described in the manual for the CVLT (Delis et al. 1987). A comparison was made separately for males and females, and the raw CVLT scores of the study sample were similar to those presented in the CVLT manual.

Neither of the computerized tasks, VOLT and AIM, have been frequently used in research of cognitive performance among general population and schizophrenia. However, the VOLT has been shown to correlate with measures from other visual memory tasks (Glahn et al. 1997) and AIM has been shown to correlate with other most commonly used task tests of executive function, e.g. Wisconsin Card Sorting Test (Glahn et al. 2000).
4.3.1 Verbal episodic memory

The California Verbal Learning Test (CVLT) is a paper-and-pencil, auditory, verbal memory test. It provides a brief, individually administered assessment of multiple strategies, processes, and errors involved in learning and remembering verbal material. The CVLT comprises of a 16-item word list over a number of five trials and requires memorization of a word list consisting of items from four semantic categories, with four words per category (Delis et al. 1987). The words are presented so that a given word is never followed by another word from the same category. After each trial, the subject must repeat back as many items as he/she can remember. A detailed description of the variables obtained in the CVLT is presented in Table 10.

Table 10. Interpretation of variables obtained in the California Verbal Learning Test (CVLT) test (Appendix 1, original study I).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Span of apprehension</td>
<td>Performance (correct responses) on List A Trial 1 provides a gauge of initial learning/attention span.</td>
</tr>
<tr>
<td>Verbal learning</td>
<td></td>
</tr>
<tr>
<td>Immediate free recall</td>
<td>Performance (correct responses) on List A provides a sum of trials 1 through 5.</td>
</tr>
<tr>
<td>Learning slope</td>
<td>The rate of improvement from first to final trial indicates the amount of new learning per trial, i.e. reflects the increment in words recalled per trial over Trials 1–5.</td>
</tr>
<tr>
<td>Short-term memory</td>
<td></td>
</tr>
<tr>
<td>Short delay free recall</td>
<td>After interference List B (a second list containing 16 items, presented for one trial) the subject is asked to recall items from List A in any order.</td>
</tr>
<tr>
<td>Short delay cued recall</td>
<td>After interference List B (a second list containing 16 items, presented for one trial) the examinee is asked to recall items from List A by category.</td>
</tr>
<tr>
<td>Long-term memory</td>
<td></td>
</tr>
<tr>
<td>Long delay free recall</td>
<td>The number of correct responses on List A in any order after 15–20 min interval (in which the examinee is occupied with other tests to minimize interference) reflects the examinee’s ability to retain verbal information over time.</td>
</tr>
<tr>
<td>Long delay cued recall</td>
<td>The number of correct responses on List A by category after 15–20 min interval (in which the examinee is occupied with other tests to minimize interference) reflects the examinee’s ability to retain verbal information over time.</td>
</tr>
</tbody>
</table>
### Variable Interpretation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recognition discriminability</strong></td>
<td>An auditory recognition task designed to assess long-term retention and the ability to discriminate target words from distractor items, i.e. the examinee is tested for recognition of the List A items from a list which contains all the List A items and 28 distracters (8 List B items, 8 phonetic distracters, 4 distracters prototypical of the semantic categories and 8 unrelated distracters).</td>
</tr>
<tr>
<td><strong>Rate of forgetting</strong></td>
<td>To assess the degree of forgetting over a 20-min delay period a difference score is calculated for the number of words recalled during Short-Delay and Long-Delay Free Recall.</td>
</tr>
<tr>
<td><strong>Susceptibility to interference</strong></td>
<td></td>
</tr>
<tr>
<td>Proactive interference</td>
<td>Reflects the degree to which learning List A interfered with the subsequent learning of List B, i.e. the decremental effect of prior learning on the retention of subsequently learned material.</td>
</tr>
<tr>
<td>Retroactive interference</td>
<td>Reflects the degree that learning a second list interfered with later recall of the original list, i.e. the decremental effect of subsequent learning on the retention of previously learned material.</td>
</tr>
<tr>
<td><strong>Organization strategies</strong></td>
<td></td>
</tr>
<tr>
<td>Semantic cluster</td>
<td>Consecutive recall of List A words grouped by semantic category is the ratio of correct responses followed by another correct response from the same category, relative to the expected clustering by chance. This indicates the degree to which the examinee uses the active learning strategy of reorganizing the target words into categorical groups.</td>
</tr>
<tr>
<td>Serial cluster</td>
<td>Recalling words according to their order in the word list denotes the ratio of word pairs recalled in the same succession as the stimulus list relative to chance expected serial ordering. This indicates the degree to which the examinee recalls target words in the same order as they are presented.</td>
</tr>
<tr>
<td><strong>Recall</strong></td>
<td>The serial position effect is divided among primacy, middle and recency regions, related to the position of words in the list. Examinees typically recall a larger percentage of the words that are in the primacy and recency regions of a list than of the words in the middle regions.</td>
</tr>
<tr>
<td>Primacy</td>
<td>The percentage of correct responses from the primary region (the first 4 words on the target list) from Trials 1-5 of List A immediate Free Recall. Poor recall of primacy-region words in conjunction with considerably better recall of recency-region words may indicate a passive learning style.</td>
</tr>
<tr>
<td>Middle</td>
<td>The percentage of correct responses from the middle region (8 words on the target list) from Trials 1-5 of List A immediate Free Recall.</td>
</tr>
<tr>
<td>Recency</td>
<td>The percentage of correct responses from the recency region (last 4 words on the target list) from Trials 1-5 of List A immediate Free Recall.</td>
</tr>
</tbody>
</table>
Variable Interpretation

Recall consistency The ability to consistently recall the same words across repeated presentations of the same list. This index measures the percentage of target words recalled in one of the first four trials that are also recalled in the very next trial.

Recall errors

Perseverations The type of recall errors defined as a repetition of any response in the same trial.

Free recall intrusions The type of recall errors, which are responses not on the target list after a short and long delay.

Cued recall intrusions The type of recall errors, which are responses not on the target list after a short and long delay.

The interpretation of CVLT variables has been composed by utilizing the following references:

4.3.2 Visual episodic memory

The Visual Object Learning Test (VOLT) is a measure of visual-spatial learning and memory and was developed to examine aspects of visual-spatial learning and memory in a manner analogous to available verbal tests (e.g. CVLT). Like the CVLT, the VOLT has multiple learning trials, although the VOLT consists of four rather than five trials, followed by an interference list, as well as short and long delay trials (Glahn et al. 1997). The VOLT uses Euclidean shapes as stimuli with the same paradigm as the word.

Participants are shown a set of 10 visual objects – the learning set. In a forced choice paradigm, they are then required to recognize those stimuli from a group of 20 objects, of which 10 are distractors. After each trial, the learning set is presented.

The dependent variable is the total number of correct responses in the four trials summed. The participant’s score reflects the number of correctly recognized targets and correctly rejected foils. The procedure is repeated after a 20-minute delay. Two forms are available for each test. The VOLT score ranges from 0 to 80 points. Scores less than half of the maximum score (i.e. less than 40 points) are considered as below chance. Thus, participants who performed below chance, i.e. who had less than 50% correct answers, were excluded assuming they had not understood the test assignment.
4.3.3 Executive functions

The Abstraction, Inhibition, and Working Memory (AIM) task is a computerized rule-abstraction/category learning task that requires subjects to use information to group stimuli in a meaningful way on the basis of feedback received during the test. It is fundamentally a task of abstraction and categorization (Glahn et al. 2000). To perform the task successfully, the participant must be able to abstract information about shape and color, and use this information to make category judgements on the basis of shared characteristics.

In this task, manipulation of information is operationalized as a form of visual abstraction. Two pairs of stimuli are presented on the top of the screen: one pair in the top left, and one in the top right. The stimuli can be of various colors and shapes. Participants are shown five shapes: two shapes in the upper-right corner and two shapes in the upper-left corner of a computer screen. An additional stimulus, which can be called the target object, of variable shape and color, is presented at the bottom center of the screen.

The participant’s task is to pair the target object with the objects on either the left or right. This target stimulus can match one or more of the four stimuli at the top of the screen across one or more dimensions in such a way that the target and one of the pairs form three objects in a set. In some trials, an additional maintenance requirement was superimposed on this basic module by adding a delay between the presentation of the target and the other objects.

This task yields two outcome measures: total score on the abstraction trials and total score on the trials involving abstraction and memory (Glahn et al. 2000). The scores range from 0 to 30 points. The scores of less than half of the maximum score (i.e. less than 15 points) are considered as below chance. Participants who performed below chance were excluded.

4.4 Predictors of change in cognitive performance

In Table 11 primary school marks and clinical and basic demographic predictors of change in cognitive performance in non-psychotic and schizophrenia samples used in this doctoral thesis are described.
<table>
<thead>
<tr>
<th>Predictor of change in cognition</th>
<th>Definition</th>
<th>Source of information</th>
<th>Used in the original study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male/Female</td>
<td>National population register II</td>
<td>II</td>
</tr>
<tr>
<td>Primary school marks</td>
<td>The mean scores for all subjects and theoretical and practical subjects, calculated separately from the school reports at the end of compulsory primary school (at the age of 16 years).</td>
<td>National population register II</td>
<td>II-III</td>
</tr>
</tbody>
</table>
| Level of vocational education    | Non-vocational education (comprehensive school, 9 years; or general upper secondary school, 12 years with matriculation examination) and vocational education (lower level: none, course or school [up to 3 years]) in vocational institution, currently a student; or higher level: polytechnic or university) were combined as follows:  
  low = comprehensive school with lower level of vocational education;  
  middle = comprehensive school with higher level of vocational education  
  or upper secondary school with lower level of vocational education; and  
  high = upper secondary school with higher level of vocational education | Field study in 1999–2001; questionnaire II-III               | II-III                      |
| Occupational class               | Low = employee, student or unemployed; middle = official level employee; and high = managerial employee                                                                                                                                                                                                                                   | Field study in 1999–2001; questionnaire II                  | II                          |
| Marital status                   | Married or cohabiting; and single, divorced or widowed                                                                                                                                                                                                                                                                                    | Field study in 1999–2001; questionnaire II                  | II                          |
| Children                         | Having and not having children                                                                                                                                                                                                                                                                                                           | Field study in 1999–2001; questionnaire II                  | II                          |
| Body mass index (BMI)            | Calculated from self-reported height and weight.  
  The BMI at the baseline study and the change of BMI between the baseline and follow-up were used in the analyses.                                                                                                                                                                                                                   | Field studies in 1999–2001 and 2008-2010; questionnaires | II                          |
<table>
<thead>
<tr>
<th>Predictor of change in cognition</th>
<th>Definition</th>
<th>Source of information</th>
<th>Used in the original study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity of positive and negative symptoms around first episode</td>
<td>The presence of symptoms at the first psychotic episode was assessed retrospectively using the Operational Criteria Checklist For Psychotic Illness (OPCRIT) (McGuffin et al. 1991). The symptoms were categorized using the factors presented by Matsuura et al. (2004). The positive (items 73, 67, 61, 68, 75, 55, and 66), and negative (items 24, 29, 32, 33, and 25) symptoms were analyzed separately as continuous variables.</td>
<td>Medical records</td>
<td>III</td>
</tr>
<tr>
<td>Occupational functioning around first episode</td>
<td>Defined as a person achieving his/her premorbid occupational level: unemployed for all of the time, before and after the onset of the illness; employment decreased or was less than 50% of the time after the onset of the illness; and employment did not decrease or accounted for more than 50% of the time after the onset of the illness. Decreases and increases in employment were defined by the proportion of employment two years after the onset of the illness divided by the proportion of employment two years before the onset of the illness (Penttilä et al. 2013).</td>
<td>Finnish Centre for Pensions</td>
<td>III</td>
</tr>
<tr>
<td>Severity of positive and negative symptoms in later course of illness</td>
<td>Assessed by the Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987) at the baseline study. The positive and negative dimensions of the PANSS were used to measure the amount of psychopathological, especially psychotic symptoms during the previous week. This variable was analyzed as a continuous variable.</td>
<td>Field study in 1999–2001; interview</td>
<td>III</td>
</tr>
<tr>
<td>Occupational status in later course of illness</td>
<td>Good occupational outcome = not on disability pension and working at least 50% of time during the year 2000 (i.e. at around the age of 34 years); and poor occupational outcome = working less than 50% of time and/or on disability pension.</td>
<td>Social Insurance Institution of Finland and Finnish Centre for Pensions</td>
<td>III</td>
</tr>
</tbody>
</table>
4.5 Other characteristics of the samples

The background characteristics were selected to describe the psychiatric and somatic condition, and social and occupational functionality of the non-psychotic and schizophrenia samples, and the severity of psychotic symptoms of the schizophrenia sample. The age of illness onset was used as a confounder in original study III. The background characteristics used in this study are presented in more detail in Table 12.
Table 12. The background characteristics used in the original studies.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Definition</th>
<th>Source of information</th>
<th>Used in the original study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at psychosis onset</td>
<td>Age when first psychotic symptoms occurred. Due to the birth cohort design the age of illness onset also indicates the length of illness.</td>
<td>All available sources, i.e. different registers and available patient notes from hospital archives.</td>
<td>I, III</td>
</tr>
</tbody>
</table>
| Non-psychotic psychiatric diagnoses| **Non-psychotic sample:** anxiety disorder (n=4), alcohol abuse (n=1), alcohol dependence (n=2), anxiety disorder and alcohol abuse or dependence (n=2). Specific diagnoses: depression (n=1), panic disorder (n=1), depression and panic disorder (n=1).  
  **Schizophrenia sample:** specific diagnoses at baseline – depression (n=1), alcohol abuse (n=1), alcohol dependence (n=3), depression and alcohol dependence (n=1); and in controls: depression (n=1), panic disorder (n=1), depression and panic disorder (n=1). Specific diagnoses at follow-up – anxiety disorder (n=4), alcohol dependence (n=3), depressive disorder and alcohol dependence (n=2), anxiety disorder and bulimia nervosa (n=1), mood disorder due to general medical condition and anxiety disorder (n=1). | Field study in 1999–2001; SCID-I interview | II                          |
<p>| Current or earlier alcohol use disorder | Comorbid diagnosis of alcohol use disorder.                                                                                                                                                              | Field study in 1999–2001; SCID-I interview                                             | I, III                      |
| Current non-psychotic psychiatric diagnoses, including alcohol use disorder | Comorbid diagnosis of any psychiatric disorder.                                                                                                                                                         | Field study in 1999–2001; SCID-I interview                                             | I                           |
| Somatic illnesses                  | <strong>Non-psychotic sample:</strong> hypothyreosis (n=1), spondylarthritis acylopoetica (n=1), asthma (n=1), asthma, migraine (n=1), asthma, hypothyreosis, celiac disease (n=1), epilepsy, no medication or symptoms since age 16 years (n=1), lumbar disc prolapse operated years ago (n=1). | Field study in 1999–2001; interview                                                   | II                          |</p>
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Definition</th>
<th>Source of information</th>
<th>Used in the original study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Social and Occupational Functional Scale (SOFAS)</td>
<td>SOFAS assesses social activity and the ability to work. It ranges from 0 to 100, with higher scores indicating better functioning (Spitzer et al. 2000).</td>
<td>Field study in 1999–2001; interview</td>
<td>I, III</td>
</tr>
<tr>
<td>Positive and Negative Syndrome Scale (PANSS)</td>
<td>PANSS is used to measure psychopathological symptoms. The higher scores indicate more severe symptoms (Kay et al. 1987). Original study I: Total scale and positive, negative, disorganization, excitement and emotional subscales determined based on van der Gaag et al. (2006) were used. Original study III: Total scale and positive and negative subscales determined based on Matsuura et al. (2004) were used.</td>
<td>Field study in 1999–2001; interview</td>
<td>I, III</td>
</tr>
<tr>
<td>Remission</td>
<td>Defined based on the remission criteria by Andreasen et al. (2005) using PANSS without the duration criteria.</td>
<td>Field study in 1999–2001; interview</td>
<td>I</td>
</tr>
<tr>
<td>Cumulative number of hospital treatment days</td>
<td>Cumulative number of days in psychiatric hospitalization until the baseline study.</td>
<td>The Care Register</td>
<td>I, III</td>
</tr>
<tr>
<td>Antipsychotic medication before the baseline study and current use (last 3 months)</td>
<td>Long term medication: at least one year of regular use preceding the baseline study, low dose: ≤300mg CPZ/day, high dose: &gt;300mg CPZ/day.</td>
<td>Field study in 1999–2001; interview</td>
<td>I, III</td>
</tr>
</tbody>
</table>

SCID-I = The Structured Clinical Interview for DSM disorders; SOFAS = Social and Occupational Functioning Assessment Scale; PANSS = Positive and Negative Syndrome Scale; CPZ = Chlorpromazine equivalents.
4.6 Statistical methods

The characteristics of the samples are presented using frequency distributions, means with standard deviations (SD) and medians with interquartile ranges (IQR). The cognitive performance at the baseline and follow-up are presented using means with SDs, and were compared between the non-psychotic and schizophrenia samples using an independent samples t-test.

The change in the cognitive performance (CVLT, VOLT and AIM) from the baseline to follow-up was analyzed using a paired samples t-test separately for the non-psychotic and schizophrenia samples. The difference in the change in the CVLT, VOLT and AIM between the non-psychotic and schizophrenia samples, separately for each cognitive performance measure, was analyzed using linear regression analysis adjusted for the corresponding baseline cognitive performance measure, gender and education at the baseline.

In the non-psychotic sample, the predictors of change in the CVLT, VOLT and AIM (separately) were analyzed using linear regression analysis, adjusted for the corresponding baseline cognitive measure, in order to determine betas to express the effect sizes. The analyses for the non-psychotic sample were conducted using inverse probability weighting by gender and education in order to correct for their distribution in the sample. P-values are presented uncorrected for multiple comparisons. Additionally, the Benjamini-Hochberg (B-H) procedure was used to correct for multiple comparisons due to the large number of cognitive measures and predictors analyzed.

In the schizophrenia sample, to estimate the overall cognitive performance, a composite cognitive score was calculated using the non-psychotic sample as a reference sample, as in many earlier studies (e.g. Buckley et al. 2007, Emsley et al. 2007, Siegel et al. 2006). The composite cognitive score was formed by standardizing each individual score according to the mean and SD of the non-psychotic sample and taking the mean of these standardized scores. The predictors of change in the CVLT, VOLT, AIM and the composite cognitive score were analyzed using linear regression analysis adjusted for the corresponding baseline cognitive measure and the age of illness onset.

All the analyses were two-tailed tests with a probability level of P<0.05 indicating statistical significance. IBM SPSS Statistics 21.0 or 22.0 software was used to conduct the analyses.
5 Ethical considerations and personal involvement

5.1 Ethical considerations

The research plan for the NFBC 1966 34-year follow-up study was approved by the Ethical Committee of Oulu University, Faculty of Medicine on 30th March 1998, the 43-year follow-up on 18th February 2008, and the 46-years in 17.9.2012 by the Regional Ethics Committee of the Northern Ostrobothnia Hospital District. Data protection has been scrutinized by the Privacy Protection Agency and according to the principles of the Ministry of Health and Social Affairs. Informed consent has been obtained from all participants. The research up to date has been performed, and will be performed in the future following the Declaration of Helsinki and its later amendments.

5.2 Personal involvement

I started my doctoral studies in the research group of my supervisors, Docent Erika Jääskeläinen, MD and Professor (emeritus) Matti Isohanni in 2008 and in collaboration with my third supervisor, statistician Marianne Haapea, PhD. I have been a member of the NFBC 1966 research group since the spring of 2008. I was awarded the University of Oulu Graduate School doctoral study rights in June 2010 and performed this thesis for the Department of Psychiatry, at the University of Oulu, and for the Center for Life Course Health Research (formerly Institute of Health Sciences), at the University of Oulu. During my doctoral study I have participated in collecting cognitive data in the follow-up study 2008-2011. Additionally, I have trained our research group on neuropsychological issues, supervised the cognitive research group and also participated as co-author, or first or second author for other articles and manuscripts in the NFBC 1966 (e.g. Cowling et al. 2012, Husa et al. 2014, Isohanni et al. 2010, Isohanni et al. 2011, Rannikko et al. 2012).

Regarding my doctoral thesis, as first author I designed (in consultation with the co-authors) all the original studies, carried out all the literature searches, and participated in carrying out the statistical analyses of the original studies I and II supervised by statistician Marianne Haapea. The statistical analyses of original study III were mainly done by statistician Henri Salo supervised by Erika
Jääskeläinen. The additional analyses for the thesis were planned and executed under supervision by Marianne Haapea. I conducted the systematic literature reviews in consultation with my supervisors. I was in charge of writing the manuscripts of all three original studies. I was involved, in collaboration with the co-authors, in interpreting the results and creating the tables and figures for the original studies. As a first author of all and a corresponding author of two original studies (I-II), I was in charge of submission (I-II), revision (I-III) and resubmission (I-II) processes of the studies.
6 Results

6.1 Characteristics of the samples (I–III)

Twenty nine (39%) of the non-psychotic subjects and nineteen (46%) of the individuals with schizophrenia were females. The mean age of the onset of illness in the schizophrenia sample was 23.6 years (SD 4.4). The mean follow-up time was 8.5 years (SD 0.7) in the non-psychotic sample and 9.1 years (SD 0.6) in the schizophrenia sample. Detailed characteristics of the samples are presented in Table 13.
Table 13. Characteristics of the samples at the baseline.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Non-psychotic sample (I-II)</th>
<th>Schizophrenia sample (I, III)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up time, years (mean, SD)</td>
<td>8.5 (0.7)</td>
<td>9.1 (0.6)</td>
</tr>
<tr>
<td>Gender (n, %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>29 (39%)</td>
<td>19 (46%)</td>
</tr>
<tr>
<td>Males</td>
<td>46 (61%)</td>
<td>22 (54%)</td>
</tr>
<tr>
<td>Education (n, %)†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>31 (41%)</td>
<td>22 (54%)</td>
</tr>
<tr>
<td>Middle</td>
<td>15 (20%)</td>
<td>12 (29%)</td>
</tr>
<tr>
<td>High</td>
<td>29 (39%)</td>
<td>7 (17%)</td>
</tr>
<tr>
<td>Social and Occupational Functioning Scale (SOFAS) (mean, SD)</td>
<td>86 (5.3)</td>
<td>51 (16.5)</td>
</tr>
<tr>
<td>Current or earlier alcohol use disorder (n, %)</td>
<td>1 (1%)</td>
<td>9 (22.0%)</td>
</tr>
<tr>
<td>Current nonpsychotic psychiatric diagnoses, including alcohol use disorder (n, %)²</td>
<td>3 (4%)</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>Age of psychosis onset, years (mean, SD)</td>
<td>n/a</td>
<td>23.6 (4.4)</td>
</tr>
<tr>
<td>Positive and Negative Syndrome Scale (PANSS) (mean, SD)</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>52.4 (19.5)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>20.0 (5.7)</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>14.8 (9.2)</td>
<td></td>
</tr>
<tr>
<td>Cumulative number of hospital treatment days (median, IQR)</td>
<td>n/a</td>
<td>161 (44-753)</td>
</tr>
<tr>
<td>Current use of antipsychotic medication (last 3 months) (n, %)</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>No current medication</td>
<td>13 (31.7%)</td>
<td></td>
</tr>
<tr>
<td>Typical antipsychotic</td>
<td>15 (37%)</td>
<td></td>
</tr>
<tr>
<td>Atypical antipsychotic</td>
<td>9 (22%)</td>
<td></td>
</tr>
<tr>
<td>Both typical and atypical antipsychotic</td>
<td>4 (10%)</td>
<td></td>
</tr>
</tbody>
</table>

SD = standard deviation, n/a = not applicable

† Low = comprehensive school with a lower level of vocational education; middle = comprehensive school with a higher level of vocational education or upper secondary school with a lower level of vocational education; and high = upper secondary school with a higher level of vocational education. Information from questionnaire at age of 34.

² Specific diagnoses at baseline in the non-psychotic sample: depression (n=1), panic disorder (n=1), depression and panic disorder (n=1); and in the schizophrenia sample: depression (n=1), alcohol abuse (n=1), alcohol dependence (n=3), depression and alcohol dependence (n=1).
6.2 Cognitive performance at the baseline and follow-up (I-III)

Cross-sectionally, individuals with schizophrenia had poorer performance than non-psychotic subjects in CVLT, VOLT and AIM at both the baseline and follow-up (Table 14). Statistically significant differences occurred in most of the CVLT variables from different dimensions of verbal memory and learning.
Table 14. Original values of selected items for CVLT, and VOLT and AIM in the non-psychotic sample (n=75) and schizophrenia sample (n=41) in baseline and follow-up studies with comparison between non-psychotic and schizophrenia samples. The analyses were conducted separately for each cognitive measure. (Modified from Table 2, original study I and, Table 4, original study II, and some additional analysis have been added).

<table>
<thead>
<tr>
<th>Measure of cognitive performance</th>
<th>Baseline study</th>
<th>Follow-up study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-psychotic sample</td>
<td>Schizophrenia sample</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>CVLT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Span of apprehension</td>
<td>8.4 (2.0)</td>
<td>6.6 (2.0)</td>
</tr>
<tr>
<td>Immediate free recall</td>
<td>60.1 (6.8)</td>
<td>48.0 (13.8)</td>
</tr>
<tr>
<td>Short delay²</td>
<td>26.9 (3.5)</td>
<td>21.2 (7.2)</td>
</tr>
<tr>
<td>Long delay²</td>
<td>27.6 (3.5)</td>
<td>22.7 (6.7)</td>
</tr>
<tr>
<td>Recognition discriminability</td>
<td>97.7 (3.0)</td>
<td>92.7 (9.6)</td>
</tr>
<tr>
<td>Recall consistency</td>
<td>87.3 (7.0)</td>
<td>78.4 (15.3)</td>
</tr>
<tr>
<td>All intrusions³</td>
<td>1.5 (2.6)</td>
<td>2.9 (4.0)</td>
</tr>
<tr>
<td>VOLT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstraction without memory</td>
<td>71</td>
<td>24.1 (2.5)</td>
</tr>
<tr>
<td>Abstraction with memory</td>
<td>70</td>
<td>23.6 (3.4)</td>
</tr>
</tbody>
</table>


1 Significance from the independent samples t-test.
2 Free and cued recalls summed. 3 All intrusions summed.
6.3 Change in cognitive performance between the baseline and follow-up (I–III)

Both studied samples declined in cognitive performance between the baseline and the follow-up (Table 15). In the non-psychotic sample, there was a statistically significant decline in the span of apprehension, immediate free recall, short- and long-term memory, recognition discriminability, proactive interference, middle and recency recall, and recall consistency. There was a statistically significant increase in the number of intrusions and statistically non-significant increase in AIM, abstraction without memory. In the schizophrenia sample, only the number of cued recall intrusions increased statistically significantly and long-delay free recall decreased statistically non-significantly. There was no change in VOLT and AIM, abstraction with memory in either of the samples.

The schizophrenia sample decreased more than the non-psychotic sample in learning slope and recall consistency (beta = -0.19 for both; Table 15).
Table 15. The change in cognitive performance in the non-psychotic sample (original study I, n=73; original study II, n=75) and the schizophrenia sample (n=41). The baseline and follow-up cognitive measures were compared unadjusted. The change between the baseline and follow-up in each cognitive measure was compared between the non-psychotic and schizophrenia sample adjusted for the corresponding baseline cognitive measure, education and gender. The analyses were conducted separately for each cognitive measure. (Modified from Table 3, original study I, and some additional analysis have been added).

<table>
<thead>
<tr>
<th>Cognitive measures</th>
<th>Difference between the baseline and follow-up</th>
<th>Linear regression analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-psychotic sample</td>
<td>Schizophrenia sample</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>CVLT</td>
<td>-0.82 (2.3)</td>
<td>-0.20 (2.4)</td>
</tr>
<tr>
<td>Span of apprehension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verbal learning</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate free recall</td>
<td>-5.1 (6.8)</td>
<td>-2.9 (13.0)</td>
</tr>
<tr>
<td>Learning slope</td>
<td>-0.04 (.81)</td>
<td>-0.26 (1.3)</td>
</tr>
<tr>
<td>Short-term memory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short delay free recall</td>
<td>-1.2 (2.0)</td>
<td>-0.27 (3.2)</td>
</tr>
<tr>
<td>Short delay cued recall</td>
<td>-1.2 (2.0)</td>
<td>-0.37 (2.9)</td>
</tr>
<tr>
<td>Long-term memory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long delay free recall</td>
<td>-1.2 (2.1)</td>
<td>-0.90 (3.1)</td>
</tr>
<tr>
<td>Long delay cued recall</td>
<td>-0.95 (1.7)</td>
<td>-0.49 (2.7)</td>
</tr>
<tr>
<td>Recognition discriminability</td>
<td>-1.6 (4.1)</td>
<td>-0.33 (8.9)</td>
</tr>
<tr>
<td>Rate of forgetting</td>
<td>0.62 (18.4)</td>
<td>-7.0 (27.7)</td>
</tr>
<tr>
<td>Susceptibility to interference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proactive interference</td>
<td>-13.0 (42.7)</td>
<td>4.0 (47.8)</td>
</tr>
<tr>
<td>Retroactive interference</td>
<td>-1.5 (19.1)</td>
<td>0.71 (31.1)</td>
</tr>
<tr>
<td>Organization strategies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Semantic cluster</td>
<td>-0.16 (.78)</td>
<td>0.00 (.88)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive measures</td>
<td>Difference between the baseline and follow-up(^1)</td>
<td>Linear regression analysis(^2)</td>
</tr>
<tr>
<td>--------------------</td>
<td>-----------------------------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td></td>
<td>Non-psychotic sample</td>
<td>Schizophrenia sample</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>P-value</td>
</tr>
<tr>
<td>Serial cluster</td>
<td>-0.20 (1.9)</td>
<td>0.39</td>
</tr>
<tr>
<td>Recall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primacy</td>
<td>0.28 (4.2)</td>
<td>0.57</td>
</tr>
<tr>
<td>Middle</td>
<td>-1.6 (5.4)</td>
<td>0.014</td>
</tr>
<tr>
<td>Recency</td>
<td>1.3 (5.1)</td>
<td>0.031</td>
</tr>
<tr>
<td>Recall consistency</td>
<td>-0.03 (.09)</td>
<td>0.014</td>
</tr>
<tr>
<td>Recall errors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perseveration</td>
<td>0.14 (5.4)</td>
<td>0.83</td>
</tr>
<tr>
<td>Free recall intrusions</td>
<td>0.70 (2.7)</td>
<td>0.031</td>
</tr>
<tr>
<td>Cued recall intrusions</td>
<td>0.47 (1.4)</td>
<td>0.007</td>
</tr>
<tr>
<td>VOLT</td>
<td>0.18 (5.0)</td>
<td>0.76</td>
</tr>
<tr>
<td>AIM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstraction without memory</td>
<td>0.61 (2.6)</td>
<td>0.051</td>
</tr>
<tr>
<td>Abstraction with memory</td>
<td>0.50 (3.4)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

SD = standard deviation, CVLT = California Verbal Learning Test, VOLT = Visual Object Learning Test, AIM = Abstraction, Inhibition, and Working Memory task.

\(^1\) Unadjusted comparisons between baseline and follow-up, p-value from paired samples t-test.

\(^2\) Comparison of the change between the samples, adjusted for the corresponding baseline cognitive measure, education and gender.

Statistically significant results are **bolded.**
6.4 Predictors of change in cognitive performance (II-III)

6.4.1 Association between primary school marks at the age of 16 years, change in BMI and sociodemographic factors with changes in cognitive performance in early midlife in the non-psychotic sample (II)

Male gender predicted statistically a significantly decrease in episodic memory measured by CVLT (Table 16). Males had a larger decrease compared to females in their span of apprehension, immediate free recall, and short delay free recall. Also poor school marks in practical subjects were associated with a decrease in two domains of verbal episodic memory – immediate free recall and short delay – though not significantly after B-H correction. Likewise, increasing memory strategy biases during the episodic memory task measured with all intrusions was associated with having no children and an increase in BMI.

Better school marks in theoretical, practical and all school subjects, and belonging to a higher occupational class were significantly associated with preserved performance in visual object learning measured by VOLT: performance decreased among those with lowest primary school marks, lowest vocational education or lowest employment status; whereas performance increased among those with highest primary school marks, highest vocational education or highest employment status, (Table 17).

Having children predicted decreased performance in executive functioning measured by AIM abstraction with memory, but non-significantly after corrected for multiple comparisons. Marital status did not associate with a change in cognitive ability (Table 17).
Table 16. Predictors of change in CVLT, adjusted for the corresponding baseline cognitive measure and weighted by gender and education (n=75). The analyses were conducted separately for each cognitive measure. (Modified from Table 6, original study II).

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Span of apprehension</th>
<th>Immediate free recall</th>
<th>Short delay</th>
<th>Long delay</th>
<th>Recognition discriminability</th>
<th>Recall consistency</th>
<th>All intrusions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beta</td>
<td>P-value</td>
<td>Beta</td>
<td>P-value</td>
<td>Beta</td>
<td>P-value</td>
<td>Beta</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.28</td>
<td>0.004*</td>
<td>0.35</td>
<td>0.033*</td>
<td>0.35</td>
<td>0.003*</td>
<td>0.20</td>
</tr>
<tr>
<td>Primary school marks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All subjects</td>
<td>0.18</td>
<td>0.067</td>
<td>0.14</td>
<td>0.25</td>
<td>0.19</td>
<td>0.12</td>
<td>0.12</td>
</tr>
<tr>
<td>Theoretical subjects</td>
<td>0.17</td>
<td>0.080</td>
<td>0.11</td>
<td>0.39</td>
<td>0.16</td>
<td>0.20</td>
<td>0.10</td>
</tr>
<tr>
<td>Practical subjects</td>
<td>0.17</td>
<td>0.086</td>
<td>0.27</td>
<td>0.032</td>
<td>0.28</td>
<td>0.023</td>
<td>0.14</td>
</tr>
<tr>
<td>Vocational education</td>
<td>0.14</td>
<td>0.15</td>
<td>-0.05</td>
<td>0.71</td>
<td>0.09</td>
<td>0.46</td>
<td>0.04</td>
</tr>
<tr>
<td>Occupational class</td>
<td>-0.03</td>
<td>0.79</td>
<td>-0.08</td>
<td>0.51</td>
<td>0.03</td>
<td>0.79</td>
<td>-0.80</td>
</tr>
<tr>
<td>Marital status</td>
<td>-0.02</td>
<td>0.87</td>
<td>-0.10</td>
<td>0.37</td>
<td>0.17</td>
<td>0.17</td>
<td>0.03</td>
</tr>
<tr>
<td>Children</td>
<td>0.06</td>
<td>0.51</td>
<td>0.03</td>
<td>0.82</td>
<td>0.11</td>
<td>0.35</td>
<td>0.17</td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At age 34 years</td>
<td>-0.06</td>
<td>0.56</td>
<td>-0.13</td>
<td>0.25</td>
<td>0.02</td>
<td>0.87</td>
<td>0.08</td>
</tr>
<tr>
<td>Change from age 34 to 43 years</td>
<td>-0.11</td>
<td>0.28</td>
<td>-0.09</td>
<td>0.47</td>
<td>-</td>
<td>0.33</td>
<td>-0.05</td>
</tr>
</tbody>
</table>

CVLT = California Verbal Learning Test; **Bolded** p-values marked with an asterisk are statistically significant after the Benjamini-Hochberg correction.
Table 17. Predictors of changes in VOLT and AIM, adjusted for the corresponding baseline cognitive measure and weighted by gender and education (n=75). The analyses were conducted separately for each cognitive measure. (Modified from Table 6, original study II).

<table>
<thead>
<tr>
<th>Predictors</th>
<th>VOLT</th>
<th>AIM, Abstraction without memory</th>
<th>AIM, Abstraction with memory</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beta</td>
<td>P-value</td>
<td>Beta</td>
</tr>
<tr>
<td>Gender</td>
<td>-0.14</td>
<td>0.20</td>
<td>-0.02</td>
</tr>
<tr>
<td>Primary school marks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All subjects</td>
<td>0.33</td>
<td>*0.002</td>
<td>0.03</td>
</tr>
<tr>
<td>Theoretical subjects</td>
<td>0.32</td>
<td>*0.002</td>
<td>0.04</td>
</tr>
<tr>
<td>Practical subjects</td>
<td>0.30</td>
<td>*0.004</td>
<td>0.01</td>
</tr>
<tr>
<td>Vocational education</td>
<td>0.28</td>
<td>0.007</td>
<td>0.02</td>
</tr>
<tr>
<td>Occupational class</td>
<td>0.31</td>
<td>*0.003</td>
<td>0.03</td>
</tr>
<tr>
<td>Marital status</td>
<td>0.11</td>
<td>0.29</td>
<td>0.18</td>
</tr>
<tr>
<td>Children</td>
<td>0.01</td>
<td>0.94</td>
<td>-0.09</td>
</tr>
<tr>
<td>Body mass index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At age 34 years</td>
<td>-0.20</td>
<td>0.053</td>
<td>0.07</td>
</tr>
<tr>
<td>Change from age 34 to 43 years</td>
<td>-0.01</td>
<td>0.91</td>
<td>-0.19</td>
</tr>
</tbody>
</table>

VOLT = Visual Object Learning Test. AIM = Abstraction Inhibition and Working Memory task.

**Bolded** p-values marked with an asterisk are statistically significant after the Benjamini-Hochberg correction.
6.4.2 Association between premorbid school performance and later course of schizophrenia with changes in cognition in midlife (III)

Lower primary school marks at age 16-years and lower education at age 34-years predicted more decline in cognitive performance. Measures of the severity of illness or functioning did not associate statistically significantly to a change of cognition.

Having a lower mean of all school marks at the age of 16 years predicted a greater decline in VOLT, and AIM, abstraction with memory. Lower school marks in both theoretical and practical school subjects predicted a decline in VOLT. Lower practical school marks were associated also with more decline in long delay free recall of CVLT, AIM, abstraction with memory, and cognitive composite scores. Having a low level of education at the age of 34 years was associated with more decline in AIM, abstraction with memory (Table 18).

When associations between the mean of all school marks and change of VOLT were adjusted additionally (to baseline cognition and onset age) for the level of education at the age of 34 years, the associations remained statistically significant. In this model, education at the age of 34 years did not remain statistically significant. When the same adjustments were made for abstraction with memory, none of the associations remained statistically significant.
Table 18. School marks and later education as predictors of change in cognitive performance between the baseline and follow-up in schizophrenia, adjusted for the baseline cognitive measure and age of the onset of illness. The analyses were conducted separately for each cognitive measure. (Table 2, original study III).

<table>
<thead>
<tr>
<th>Predictors</th>
<th>CVLT Immediate free recall</th>
<th>CVLT Long delay free recall</th>
<th>CVLT All intrusions</th>
<th>VOLT AIM, abstraction without memory</th>
<th>VOLT AIM, abstraction with memory</th>
<th>Composite score</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Beta</td>
<td>P-value</td>
<td>Beta</td>
<td>P-value</td>
<td>Beta</td>
<td>P-value</td>
</tr>
<tr>
<td>Mean of all school marks</td>
<td>0.19</td>
<td>0.25</td>
<td>0.20</td>
<td>0.18</td>
<td>-0.09</td>
<td>0.59</td>
</tr>
<tr>
<td>Mean of theoretical subject marks</td>
<td>0.15</td>
<td>0.35</td>
<td>0.15</td>
<td>0.34</td>
<td>-0.04</td>
<td>0.83</td>
</tr>
<tr>
<td>Mean of practical subject marks</td>
<td>0.25</td>
<td>0.13</td>
<td>0.36</td>
<td>0.017</td>
<td>-0.26</td>
<td>0.13</td>
</tr>
<tr>
<td>Low education at age 34 years</td>
<td>-0.27</td>
<td>0.51</td>
<td>-0.19</td>
<td>0.60</td>
<td>0.13</td>
<td>0.70</td>
</tr>
</tbody>
</table>

CVLT = California Verbal Learning Test, VOLT = Visual Object Learning Test, AIM = Abstraction, Inhibition and Working Memory task. Statistically significant results are **bolded**.
7 Discussion

7.1 Main results

The main findings of this doctoral thesis corresponding with the aims were:

I Both cases and controls declined in cognitive performance in the nine-year follow-up between ages 34 and 43 years. However, there was no major difference in the amount of change of verbal episodic memory over time in cases and controls, except that cases had more decline in the measures of learning slope and recall consistency. This difference was relatively small based on beta coefficients. The essential and novel finding of the study is that there was no evidence of significantly greater decline in verbal learning and memory in middle-aged individuals with schizophrenia compared to the general population. This leads to the suggestion that during midlife verbal learning and memory in schizophrenia possibly declines mostly in a normative fashion with aging at the same rate as the general population, rather than as result of neurodegenerative processes.

II There was a statistically significant decline in all studied measures of verbal learning and memory in the general population sample. Performance in visual object learning, as well as memory and executive functioning remained unchanged. Several key findings regarding predictors of change in cognitive ability in the general population in early midlife were observed. Male gender, poor school marks in practical subjects, having no children and an increase in BMI were associated with a decrease in episodic memory. Better primary school marks in all school subjects, or for theoretical and practical subjects, having a higher level of vocational education, and belonging to a higher occupational class were associated with preserved performance in visual object learning. Having children predicted decreased performance in executive function. Putting together, the decline in episodic memory in the relatively young age group with non-psychotic controls, the association between the decline in cognitive ability in the non-psychotic sample and poor adolescent cognitive performance, change of BMI, and several sociodemographic factors and can be considered as novel findings.

III In the schizophrenia sample, poorer adolescent cognitive performance measured by school marks at age 16-years and having a lower level of vocational education at age 34-years predicted more decline in cognitive performance. Measures of severity of illness or functioning were not associated statistically significantly with change in cognitive ability. Regarding the novelty of the study, this was the first
study, which showed that premorbid school performance, but, somewhat surprisingly, not the later course of schizophrenia, predict change of cognitive ability in early midlife.

7.2 **Comparison to earlier studies and theoretical discussion**

7.2.1 *Changes in verbal episodic memory in the general population and schizophrenia in midlife (I)*

The main finding of this study is that although the schizophrenia sample had poorer cognitive ability in many different dimensions of episodic memory in cross sectional analyses at age 34 and 43 years when compared to a non-psychotic sample, *both samples declined* in cognitive performance in the nine-year follow-up. In addition, one of essential and novel findings of this study is that *there was no major difference* in the amount of change in episodic memory in schizophrenia and non-psychotic samples, except that the schizophrenia sample had more decline in the measures of learning slope and recall consistency.

As suggested by the results of this study and in concordance with the previous findings from this same cohort sample (Kobayashi *et al.* 2014), there were no differences between schizophrenia and non-psychotic samples in the rate of change in verbal episodic memory showing that in early midlife schizophrenia the cognitive impairments, at least in the case of verbal learning and memory, appeared to remain relatively stable over time. These findings suggest that although there is evidence of abnormal neurodevelopment in schizophrenia (Bora & Murray 2014, Censits *et al.* 1997, Hoff *et al.* 2005), however it *may not be a progressing degenerative process.*

It is difficult to discuss why exactly across all 20 memory domains, as measured by CVLT, the learning slope and recall consistency show statistically significant deteriorations, and the cued recall intrusions display nearly significant deteriorations in the schizophrenia sample compared to non-psychotic controls. In addition to the possibility of being chance findings, it is possible that these domains have a true role in the course of the illness and cognitive skills in schizophrenia, or at least in a subgroup of individuals with schizophrenia.

Recently, the rate of improvement (learning slope) and poorer recall organization (recall consistency) have been associated with an encoding deficit or less sophisticated (serial recall) strategy for memory encoding in schizophrenia.
Recall errors measured by intrusions have been associated with poorer social functioning and independent living skills (Stip et al. 2007), and greater disorganized symptoms as well as lower self-reflectivity (Fridberg et al. 2010) in schizophrenia. The findings of this longitudinal study extend the previous cross-sectional findings on cognitive performance in schizophrenia and non-psychotic controls.

Further, one essential and novel finding of this study is the decline in episodic memory in the non-psychotic sample already during early midlife. Similarly, some of recent earlier studies reported memory decline in general population samples, though in the considerably later developmental decades – from the age of 53 onwards (e.g. Hahn & Lachman 2015, Richards et al. 2004, Tomaszewski Farias et al. 2011). According to the systematic literature review (Rannikko et al. 2015, original study II) there is still a gap in the evaluation of the longitudinal course of verbal episodic memory in early midlife in non-psychotic adults. Therefore, this work extended previous studies by indicating memory decline over a long follow-up time interval between age 34 to age 43 years in non-psychotic individuals from the general population.

In summary, no evidence of significantly greater decline in verbal learning and memory over a long follow-up period was found in a midlife schizophrenia sample compared to a non-psychotic sample. When compared to non-psychotic controls, the schizophrenia sample had lower cross-sectional test scores in cognitive performance at the baseline and follow-up, but the decline during the follow-up was similar in both studied samples, with the exception of learning slope and recall consistency which had a larger decline in the schizophrenia sample. These results imply that between ages 34- and 43-years verbal episodic memory in schizophrenia declines mostly in a normative fashion with aging at the same rate as in the general population rather than as a result of neurodegenerative processes.

### 7.2.2 Association between primary school marks at the age of 16 years, change in BMI and several sociodemographic factors with changes in cognition in early midlife in the non-psychotic sample (II)

Several key findings regarding predictors of change of cognitive ability were observed in the middle-aged non-psychotic sample. There was a statistically significant decline in all studied measures of verbal episodic memory predicted by male gender, poor school marks in practical subjects, having no children, and an
increase in BMI. Performance in the domain of visual object learning remained unchanged. Here, preserved performance was predicted by achieving better primary school marks in theoretical, practical and all school subjects, having a higher vocational education and belonging to a higher occupational class. In executive functioning there was no statistically significant change. However, parenthood was associated with decreased performance in the domain of executive function.

The previous findings on predictors of cognitive decline are heterogeneous and contain mostly findings from the late life decades (e.g. Marioni et al. 2012 Prince et al. 2012). Gender differences in cognitive ability have been purported to reflect biological (Gur et al. 2000, Cowell et al. 1992, Silverman et al. 1999) and social (Verma et al. 2011) factors that both contribute to daily functioning in the context of cognitive decline. Previously, large dementia risk analyses have linked female gender to greater cognitive deterioration (Launer et al. 1999). Thus somewhat surprisingly, and not supporting the hypothesis of this study, male gender predicted more decline in verbal episodic memory. These findings, however, consistently with the previous reports (Matthews et al. 2004, Muniz-Terrera et al. 2009), indicate that adults demonstrate progressive cognitive decline possibly moderated by specific gender differences. In addition, these findings extend previous findings by showing that gender-associated decline already occurs in early midlife.

In the case of adolescent intellectual ability as a predictor of change in cognitive performance in early midlife, there are no earlier studies of an unselected general-population sample. Here lower school marks at age 16-years predicted more decline of cognitive ability in middle-aged adults. It may be that according to the concept of cognitive reserve (Stern 2012) individuals with better adolescent cognitive skills can somehow compensate for age-related changes, perhaps by employing alternative cognitive and/or neural strategies to solve cognitive problems in unorthodox ways (Murray et al. 2010).

The protective effects of higher education and occupation-based social class on cognitive ability have been previously demonstrated in old age cohorts (Christensen 2001, Matthews et al. 2012). It has been suggested however that more recent birth cohorts are better educated and thus perform better cognitively (Matthews et al. 2012). Coupled with developing a broad level of physical illnesses and dementia, and the high loss of participants in follow-up, the findings from previous elderly studies need to be regarded with caution. As such, the findings of this work are not only consistent with the previous findings, but they also extend these works showing the benefits of association between higher vocational
education and belonging to a higher occupational class, and preserved cognitive performance in early midlife.

*Parenthood* seemed to have heterogeneous effects on cognitive change. This variable can be considered as a form of general well-being. In this way, the results of this study are consistent with previous studies on an association between cognitive changes and individual-difference factors, such as social conditions and general well-being (e.g. Rönnlund *et al.* 2005, Zelinski & Burnight 1997). Additionally, another well-being factor, an *increase in BMI*, was associated with increasing memory strategy biases in episodic memory. Much is already known about the association between baseline BMI and cognitive changes, though mostly in adults aged 65 years and older (e.g. Sturman *et al.* 2008, Tolppanen *et al.* 2014). This study further investigated the impact of BMI on cognitive status and extends previous findings by studying BMI change as a predictor for cognitive decline in middle-aged adults.

*To conclude*, there is evidence that cognitive decline increases with age and it even seems to occur in early midlife. This change in cognitive performance can be predicted by a number of risk factors such as specific gender differences, adolescent cognitive ability, parenthood, vocational education and occupational class, and change in BMI. Because the relatively modest sample size of this study might limit the generalizability of the findings, additional investigations of risk factors for cognitive change over time in large unselected population-based longitudinal studies with long follow-up periods are needed.

### 7.2.3 Association between school performance in adolescence and the later course of schizophrenia and changes in cognitive performance in midlife (III)

The main findings of this study are that *lower school marks at the age of 16 years* and having a *lower education at the age of 34 years* predicted more deterioration in cognitive ability in schizophrenia in midlife. Somewhat surprisingly, and not supporting the hypothesis of the study, the course of schizophrenia in the first episode and in the later course of schizophrenia did not predict a change of cognitive performance in midlife.

Based on results of a systematic review of the predictors of change in cognitive performance in schizophrenia (in the part 2.3.2 of this thesis), there are no earlier studies on school performance as a predictor for longitudinal change in cognitive ability in schizophrenia. In a previous study of this same NFBC 1966 sample, a
later age of learning to stand at age about one year associated with more decline in
cognitive performance in schizophrenia, suggesting a putative link between
developmental and degenerative aspects of the illness (Kobayashi et al. 2014). Here
this work extends the previous findings to consider adolescence, because it was
demonstrated that poorer school performance at the age of 16 years is associated
with a decline of cognitive performance in schizophrenia. As it has been suggested
by other previous studies, impairment in intellectual capacity may exist from early
in life, before the onset of illness (Bora & Murray 2014, Jones et al. 1994).

According to this, poorer cognitive ability as measured by primary scholastic
achievements but not severity of symptoms might predict poorer cognitive ability
at the first episode (Fuller et al. 2002). Consistently with these studies, the results
of this doctoral thesis show that cognitive ability deteriorates in schizophrenia
independently of the severity of illness.

The association between vocational education and cognitive performance has
This study demonstrates that having a poorer adult educational level had an effect
on the longitudinal change in cognitive ability after approximately 20 years of
illness, though this becomes non-significant after adjusting for the corresponding
baseline cognitive score and age at the onset of illness. However, this study has
been able to extend earlier research by suggesting that poorer school achievements
may contribute to poorer adult vocational education and in this way may be
associated with a change of cognitive performance in midlife.

The associations between the severity of illness and cognitive ability has been
previously investigated. A poorer cognitive performance especially predicted later
worse functional (Ventura et al. 2011) and clinical outcomes (Faber et al. 2011). In
this same NFBC 1966 sample, poorer cognitive performance at the age of 34 years
predicted poorer vocational and global outcomes at the age of 43 years in
schizophrenia (Juola et al. 2015). Now the results of this doctoral thesis have shown
that symptoms or functioning around the first episode or in the later course of the
illness do not greatly predict the change in cognitive ability at midlife. It may be,
that after the onset of the illness several other factors may become more important
(compared to the severity of the symptoms and functioning) regarding cognitive
functioning, such as treatments (e.g., the use of antipsychotic medication, Husa et
al. 2014).

One potential explanation for an association between primary school marks
and a later change in cognitive ability might be the ability of the mind to
compensate in some way for brain changes, known as the concept of cognitive
reserve as a protective factor for later life cognitive impairments. It is well established that low intelligence is a risk factor for schizophrenia, and in part this itself may relate to cognitive reserve because altered cognitive functions, such as attributional biases, or biases in data gathering and self-monitoring, may predispose towards the development of delusions and hallucinations. In this study, lower school marks at the age of 16 years and having a lower education at the age of 34 years predicted more decline in cognitive ability in midlife schizophrenia. It may be that individuals with schizophrenia with better premorbid cognition and better educational attainment can somehow compensate for illness-related deficits, perhaps by employing alternative cognitive and/or neural strategies to solve cognitive problems in unorthodox ways.

To summarize, this study showed in concordance with previous research on cognitive change in schizophrenia, that cognitive decline, predicted by poor premorbid cognitive capacity, occurs in schizophrenia even after approximately 20 years of illness. The concept of cognitive reserve as a protective factor for cognitive impairment might play an essential protective role and could possibly be used as an aspect of treatment and rehabilitation for cognitive and further functional impairments in schizophrenia.

7.3 Methodological discussion

7.3.1 Strengths of the study (I-III)

The main strength of this birth cohort based study is that it uses a population-based long-term follow-up design which may decrease the potential sample selection bias. As such, this study differs in aspects of its design from most of the other studies on the topic of cognitive ability in the general population and schizophrenia. In many studies schizophrenia samples are often from clinical, collected from one treatment setting, and non-psychotic controls are not included or consist of selected volunteers. The major benefit of this study is its prospective design and the opportunity to extensively register linkage with the inclusion of a heterogeneous schizophrenia sample including subjects with both good and poor clinical course and prognosis, and unselected matched control subjects. This design provides a unique opportunity for analyzing causal relationships between a number of baseline sociodemographic factors and change in cognitive ability in both, non-psychotic and schizophrenia samples.
The population-based and longitudinal design of this study also provides other advantages compared to many earlier studies: (1) The subjects are all the same age, which eliminates bias and inaccuracy from this factor. (2) Studies on cognitive ability on other birth cohorts have focused mostly on premorbid cognitive performance. This is the first birth cohort study which focused on change in cognitive ability and its predictors 10–20 years after the onset of the illness. (3) Acknowledging the study design, there was opportunity to receive prospective data from adolescent school marks and from changes in cognitive performance in midlife. (4) Previous studies of predictors of change in cognitive ability in non-psychotic subjects have tended to be drawn from specific populations, such as aging projects with a high loss of participants for the follow-up, populations with certain clinical conditions, or specific study samples (e.g. male/female or ethnic samples) with lack of generalizability of the findings. The sample of this doctoral thesis shows ethnic homogeneity (Rantakallio 1969) and a degree of socio-economic homogeneity. (5) Compared to previous studies with usually short follow-ups, a nine-year follow-up may contribute towards understanding the temporal correlations between individual-difference factors and change of cognitive ability in early midlife. (6) The re-test reliability was maximized by using identical cognitive measurements – the CVLT, VOLT and AIM – at both time points.

7.3.2 Limitations of the study (I-III)

The study has various limitations. Originally this birth cohort was not planned for schizophrenia studies specifically. Thus the number of participants is relatively modest. Owing to the small sample size the impact of the study may be lessened and may affect the interpretation of non-significant results. Further, not all relevant data regarding schizophrenia research has been collected in this study (e.g. childhood behavior and cognitive performance, symptoms or treatment aspects, especially regarding cognitive and psychosocial treatments).

Additionally, NFBC 1966 was not planned for studies on change in cognitive ability and its predictors. Thus, there are a limited number of sociodemographic and clinical predictors. There is no information on physical activity and there were no questionnaires on psychiatric symptomatology performed at the time of the examination of cognitive performance. The measures of height and weight used for forming BMI were determined by self-reports, which may not be completely accurate.
The schizophrenia sample had the disorder for approximately ten years and as cognitive assessment was not administered at the initial stage of the disorder, it is not possible to consider the temporal characteristics of changes in cognitive performance in the early stages of the illness.

The neuropsychological set utilized in this study was part of an extensive psychosis field survey (conducted in 1999-2001 and 2008-2010) also including diagnostic and health-related interviews, questionnaires and magnetic resonance imaging of the brain. Assessment of verbal and visual-spatial learning and memory, as well as rule-abstraction/category learning was performed at both the baseline and follow-up studies using the CVLT, VOLT, and AIM test batteries respectively. In addition to these three tests, the follow-up study also included many other cognitive tests, such as three subtests from the Wechsler Adult Intelligence Scale, 3rd edition (WAIS-III; Vocabulary, Digit Span and Matrix reasoning), Verbal Fluency Test, one subtest from the Wechsler Memory Scale, 3rd edition (WMS; Symbol Span), and the Grooved Pegboard Test. This neuropsychological battery can be considered a valid cognitive evaluation to provide a relatively specific view of a participant’s cognitive performance. However, because of the longitudinal design of this study a neuropsychological battery included only three tests (CVLT, VOLT, and AIM) which were administered at the time of both the baseline and follow-up studies. Thus, due to the relatively concise cognitive battery there was no possibility to evaluate a detailed cognitive profile of the participants, which might limit the generalizability and interpretation of the cognitive findings. The author of this study could not influence the content of the cognitive battery used in the study.

Also, any observed associations may be confounded by unmeasured factors. For example, it is impossible to control all the confounding factors occurring during the long follow-up interval, even though the most important confounders were taken into account. It is possible that the findings may reflect a true causal association, but they may also be explained by uncontrolled third factors and residual or latent confounding. Due to the relatively small sample size the analyses were not mutually adjusted and interaction effects were not analyzed.
8 Conclusion

8.1 Main conclusion

In summary, no evidence of significantly greater decline in verbal episodic memory was observed in midlife schizophrenia when compared to the non-psychotic population. In schizophrenia, there was lower cognitive performance in many different dimensions of verbal learning and memory in cross-sectional analyses at age 34 and 43 years when compared to non-psychotic controls. However, the amount of cognitive decline over time was similar in these two groups suggesting that in schizophrenia cognitive ability mostly declines in a normative fashion with aging at the same rate as the non-psychotic population.

In the non-psychotic sample, there was evidence of age-related cognitive decline which was predicted by a line of risk factors. This study extended the previous findings showing that cognitive decline seems to occur even in early midlife in relation to specific gender differences, adolescent cognitive ability, parenthood, vocational education, occupational class and change in BMI. These results indicate that deterioration of fluid cognitive ability occurs even in middle-aged individuals without any neuropsychiatric conditions.

In schizophrenia, primary school performance rather than the later course of schizophrenia seems to associate with a change in cognitive ability in midlife schizophrenia. These results suggest that the concept of a cognitive reserve as a protective factor for later life cognitive impairment in the non-psychotic population may be also relevant in the midlife course of schizophrenia. These results suggest that poor primary scholastic performance and post-onset cognitive decline may represent related processes as part of an endophenotype of schizophrenia.

Put together, it appears that the associations between adolescent intellectual ability and the course of cognitive change in middle-aged schizophrenia are similar to those in the general population. These results suggest that poor premorbid cognitive performance may be considered as a vulnerability marker for a later impairment in cognitive functioning in both the general population and schizophrenia. Thus, cognitive ability in schizophrenia possibly declines mostly in a normative fashion with aging at the same rate as in the general population, rather than as a result of neurodegenerative processes as it was recently suggested (Bora & Murray 2014). These results might improve the understanding of midlife changes in human cognitive functioning and the related predictors and may contribute to
attempts to develop effective interventions for cognitive impairment in schizophrenia.

8.2 Clinical implications and future research

Effective cognitive functioning is an unconditional requirement in the contemporary information society and in vocational life. Defining the nature and trajectory of cognitive development and finding predictors of change in cognitive ability may help in developing preventions of cognitive decline in both the general population and schizophrenia.

8.2.1 General population

In the non-psychotic population, cognitive ageing is an exciting area of research. However, the majority of these samples have mostly been selected as control groups for case-control clinical studies, e.g., on dementia, elderly studies, and schizophrenia as in this thesis. Thus, the generalizability and implication of the findings of these studies are limited and large studies on cognitive changes and their predictors in normal population based studies with long follow-ups are lacking.

Studies on cognitive aging have attempted to relate changes in cognitive ability to more fundamental biological processes, such as blood pressure, white matter lesions and brain volumes, e.g. hippocampal volumes. In the future, to provide the possibility of discussion about the nature of the processes behind cognitive deterioration in normatively developed individuals, the understanding of the causal relationships between biological processes and cognitive variables is needed.

The results of this doctoral thesis provide evidence of age-related cognitive decline in the non-psychotic population. This decline seems to occur even in early midlife and can be predicted by a number of sociodemographic and clinical risk factors. These results emphasize the importance of using samples derived from general population based studies with long follow-up periods. Additionally, the results of this doctoral thesis implicate that various psychosocial aspects must be taken into account when aiming to evaluate and further to rehabilitate cognitive impairments of individuals.

8.2.2 Schizophrenia

Schizophrenia in the past was a grim diagnosis with a poor prognosis. At the present time, it can probably be better described as a serious condition, with plenty of
reasons to be hopeful. One of the clinical implications of this doctoral thesis supports this optimistic view showing that in schizophrenia cognitive dysfunction mostly does not seem to deteriorate in early middle age.

There is a lack of information on the rate of cognitive impairment, and effectiveness of medication and clinical cognitive interventions in schizophrenia in naturalistic, general population based long-term follow-ups.

There are several national guidelines for the treatment of schizophrenia, but the evidence base for the treatment recommendations often relies on highly selected clinical trials with short follow-up periods.

In clinical samples, patients with schizophrenia are found to have cognitive impairments. However, the longitudinal change in cognitive ability and its predictors, and the long-term (tens of years) effects of treatments on cognitive skills in schizophrenia are impossible to study in clinical trials and there is lack of naturalistic general population based research of this kind.

The results of this doctoral thesis suggest that individuals with schizophrenia from a non-clinical general population based study may not have significant cognitive deterioration when compared to non-psychotic individuals. These results emphasize the importance of using control samples derived from the same population and examined similarly as those with psychotic disorders in evaluating changes in cognitive ability and its predictors in the future.

8.2.3 Cognitive interventions

In the field of clinical cognitive intervention, there are many treatment options available that can address cognitive issues and help individuals suffering from cognitive impairments to live balanced and healthy lives. One of the most frequently used forms of cognitive interventions is cognitive remediation therapy (CRT), which was developed especially for treating cognitive deficits in schizophrenia (Wykes et al. 2011). It is a type of a behavioral treatment that utilizes cognitive reserve concept-related activities, such as practice, and compensatory and adaptive strategies to facilitate improvement in targeted cognitive areas which are suggested as being highly associated with functional outcomes in schizophrenia (e.g., memory, attention, processing speed, executive function and problem solving skills, social cognition) (Wykes et al. 2011).

Recently, evidence of the effectiveness of CRT, especially when combined with other psychiatric rehabilitation, has been provided (Wykes et al. 2011). Especially
psychoeducation and metacognitive strategies – the most important components of CRT – appear to effective on crucial cognitive domains (Pillet et al. 2015).

Early detection of psychoses and implementing the treatment needs of children and adolescents might be confronted with additional challenges when compared to adults. These include different onset and when compare to progressive adult-onset psychoses a longer lag time to conversion (Ziermans et al. 2011), a more dynamic clinical picture (e.g., David et al. 2011, Fux et al. 2013, Rubio et al. 2012, Schultze-Lutter et al. 2012), a gradual decrease of attenuated psychotic symptoms (Kelleher et al. 2012), and spontaneous remediation in about 75% of cases (Bartels-Velthuis et al. 2011). In the future, it is important to concentrate on the individualization of treatment of patients with a high clinical risk. This treatment should involve an optimistic therapeutic approach with acknowledgement of components of various dynamic processes in schizophrenia. Treatment should also include long follow-ups because of the increasing conversion rates (Schultze-Lutter et al. 2015).

Cognitive remediation therapies tend to concentrate on the training emphasis, focusing mostly on target practice of cognitive skills or direct training of learning strategies (Wykes et al. 2011). However, clinical findings suggest that schizophrenia is a complex disease including various dynamic processes. These findings indicate, that the disorganized dimension of the symptoms seems to be associated with verbal memory and motor speed, and positive symptoms with verbal fluency (Altamura et al. 2015). Notably, negative symptoms and cognitive impairments showed to be closely related to functional outcomes, and contribute substantially to the overall illness burden (Carbon & Correll 2014). Thus, it is extremely important that, when designing an intervention, the etiology of schizophrenia and also the relationship between the psychopathology of the disease and cognitive issues are considered.

Despite the fact that there might be long cognitive interventions carried out, the impact of cognitive deficits is often harmful for the individual, especially in novel environmental circumstances if psychosocial aspects are not take into account during a treatment. Interventions should also include long follow-ups, especially with regard to the fact that prominent negative symptoms including problems with motivation, social interaction, affective experience and responsiveness, prosody and clarity of speech, as well as clinical relevant cognitive impairments affect individuals with diagnosed schizophrenia (approximately 40% and 80%, respectively; Carbon & Correll 2014) throughout their lifespan.

The results of this doctoral thesis imply that, when aiming to improve cognitive impairments predicted by a number of sociodemographic and clinical factors, the
whole person in his/her entirety must be taken into account. This study hopefully provides value for better understanding the risk factors affecting cognitive ability during the early decades of an individual’s lifespan that could potentially be used in future interventional studies and clinical interventions. A next step in the investigation process is to improve our knowledge about the association between a number of complex factors possibly underlying the treatment outcome, such as the clinical and sociodemographic characteristics of participants, specific and generalized cognitive impairments, and different effects of cognitive remediation therapies in large general population based studies with long-term follow-ups.

8.2.4 Concluding remarks

To conclude, nowadays impairment of cognitive ability seems to have a rising trend in relation to comorbidity of challenging social, somatic and psychiatric conditions. The costs of cognitive dysfunction are high on both, individual and societal levels. The results of this study hopefully provide relevant information on cognitive change and its predictors in the general population. This might be generalized and contribute to attempts to develop and adapt effective intervention strategies which aim to improve not only a quality of individual’s lives, but also to achieve financial benefits at the different functional levels of modern society.
References


Andreasen N (1983). The scale for the assessment of negative symptoms (SANS). University of Iowa; Iowa City.

Andreasen N (1984). The scale for the assessment of positive symptoms (SAPS). University of Iowa; Iowa City.


Glantz LA & Lewis DA (2000). Decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia. Archives of General Psychiatry 57(1): 65–73.


cognitive remediation for schizophrenia: Methodology and effect sizes. The American

remediation therapy in schizophrenia. The British Journal of Psychiatry 190(5): 421–
427.

Zelinski E M & Burnight KP (1997). Sixteen-year longitudinal and time lag changes in

Distinct structural alterations independently contributing to working memory deficits

Ziemans TB, Schothorst PF, Sprong M & van Engeland H (2011). Transition and remission
in adolescents at ultra-high risk for psychosis. Schizophrenia Research 126(1–3): 58–
64.

California.
Original Publications

This thesis is based on the following publications, which are referred throughout the text by their Roman numerals:


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Original publications are not included in the electronic version of the dissertation.
1342. Nanekar, Rahul (2016) Biochemical and biophysical studies on adenosine receptors and their interaction partners


1345. Pääkkölä, Fanni (2016) Thyroid function of mother and child and their impact on the child’s neuropsychological development

1346. Löppönen, Pekka (2016) Preceding medication, inflammation, and hematoma evacuation predict outcome of intracerebral hemorrhage: a population based study

1347. Koikkonen, Tuomo (2016) Endothelial FasL in lymph nodes and in intestinal lymphatic tissue


1349. Kelemenis, Anthi (2016) Genetic risk factors for intervertebral disc degeneration

1350. Näystä, Marjut (2016) Venous malformation causative mutations affect TIE2 receptor trafficking, downstream signaling and vascular endothelial cell functions

1351. Ruotsalainen, Heidi (2016) Elintapaohjausinterventtiöiden vaikuttavuus ylipainoisten ja lihavien nuorten fyysiseen sitoutumiseen

1352. Tuisku, Anna (2016) Tobacco and health: A study of young adults in Northern Finland

1353. Forsman, Minna (2016) Histological characteristics and gene expression profiling of Dupuytren’s disease


1355. Selkää, Eija (2016) Role of α-methylacyl-CoA racemase in lipid metabolism


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CHANGE IN COGNITIVE PERFORMANCE AND ITS PREDICTORS IN GENERAL POPULATION AND SCHIZOPHRENIA IN EARLY MIDLIFE

THE NORTHERN FINLAND BIRTH COHORT 1966 STUDY