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DISSERTATION

Association of childhood trauma, socio-economic status and neighborhood status with cognitive function

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Contents

List of abbreviations

5-HT	Serotonin
α.	Significance level
Aβ	Amyloid β
ACC	Anterior cingulate cortex
ACTH	Adrenocorticotropic hormone
AD	Alzheimer's disease
ANOVA	Analysis of Variance
AVLT	Auditory Verbal Learning Test
BDNF	Brain neurotrophic factor
BEFRI	Berlin Female Risk Evaluation
CNS	Central Nervous System
CRF	Corticotropin-releasing factor
CSF	Chronic Fatigue Syndrome
CTQ	Childhood Trauma Questionnaire
DA	Dopamine
DMN	Default mode network
DSM	Diagnostic and Statistical Manual of Mental Disorders
DTNBP1	Dystrobrevin binding protein 1
ECG	Electrocardiogram
ELS	Early life stress
ERP	Event related potential
ESSI	ENRICHD social support instrument
EU	European Union
FL	Frontal lobe
fMRI	Functional magnetic resonance imaging
GC	Glucocorticoid
GR	Glucocorticoid receptor
HPA	Hypothalamic pituitary adrenal
IPL	Inferior parietal lobe
LOR	Living environment areas „Lebensweltlich Orientierte Räume“
LOTG	Lateral occipito-temporal gyrus
MCI	Mild cognitive impairment

MFG	Middle frontal gyrus
MRI	Magnetic resonance imaging
NE	Norepinephrine
NMDA	N-methyl-d-aspartate
OFC	Orbitofrontal cortex
PFC	Prefrontal cortex
PHQ	Patient Health Questionnaire
PNV	Paraventricular nucleus
PTSD	Posttraumatic stress disorder
SD	Standard deviation
SES	Socio-economic status
SNPs	Single-nucleotide polymorphism
SPSS	Statistical Package for the Social Sciences
TAP	Test of Attentional Performance
US	United States
VLMT	Verbal Learning and Memory Test

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Abstract

Background The increasing prevalence of dementia-related diseases in an aging society poses a socio-economic burden on Germany. Since there is no curative therapy available at the moment, preventive psychosocial approaches aimed at optimizing cognitive health need to be developed in order to maintain cognitive function into old age.

Methods Based on a cross-sectional design, the present study (part of the BEFRI study) included a female urban probability sample aged 25-76 years (n=843) and examined the influence of childhood trauma and individual and neighborhood socio-economic status on different aspects of cognitive function. A full test series consisted of a medical history, clinical examination, blood tests and an extensive neuropsychological test battery (Verbal Learning Memory Test, TAP Alertness, Go/No-go, Working Memory and Flexibility Test).

Results The results indicate a significant relationship between higher exposure to childhood trauma and lower cognitive function, depending on the dimension of childhood trauma. Women with a history of physical neglect or abuse performed worse in the flexibility test compared to women who did not report trauma exposure (physical neglect: number of errors: p=0.031, median of reaction times: p=0.015; physical abuse: number of errors: p=0.043). Furthermore, there were statistical trends toward poorer performance in working memory with higher levels of physical abuse (p=0.078) and toward deficits in behavioral control with physical neglect (p=0.065). Emotional and sexual childhood trauma did not cause measurable deficits in cognitive function. Higher individual education and income were associated with better cognitive performance, while no significant differences could be detected for varying levels of neighborhood SES. Concerning individual SES, the independent adjusted education effect was stronger than the income effect. Higher education was significantly related to better cognitive function with regard to verbal learning memory (total learning score: p<0.001, corrected recognition score: p=0.018), behavioral control (p=0.039), working memory (number of omissions: p=0.017, number of errors: p<0.001) and flexibility performance (number of errors: p=0.001, median of reaction times: p<0.001). Income showed an adjusted measurable effect on verbal learning memory, working memory and flexibility performance.

Conclusions The present study suggests that childhood trauma and individual education and income have an effect on adult executive functions. The mechanisms underlying this association require further investigation. Therefore, future studies on markers of stress and stress response and their association with brain function or structure are needed to illuminate the underlying neurobiological mechanisms of the associations seen in this cross-sectional study.

Zusammenfassung

Hintergrund Die steigende Prävalenz dementieller Erkrankungen stellt eine zunehmende sozioökonomische Belastung der deutschen Gesellschaft dar. Aufgrund gegenwärtig nicht zur Verfügung stehender kurativer Therapieoptionen demenzassoziierter Erkrankungen müssen präventive Ansätze zur Verbesserung kognitiver Gesundheitsressourcen entwickelt werden mit dem Ziel des längerfristigen Erhalts kognitiver Funktionen im höheren Lebensalter.

Methoden Bei der vorliegenden Studie (Teil der BEFRI Studie) handelt es sich um eine randomisierte Querschnittsstudie, in die gesunde Frauen aus Berlin zwischen 25-76 Jahren einbezogen wurden ($n=843$). Gegenstand der Ergebnisanalyse waren der Einfluss des individuellen und nachbarschaftlichen sozioökonomischen Status sowie die Auswirkung von Kindheitstraumata auf kognitive Leistungen. Eine vollständige Studientestung umfasste eine Anamnese, eine medizinische Untersuchung, eine Blutuntersuchung und eine umfassende neuropsychologische Untersuchung (Verbaler Lern- und Merkfähigkeitstest, TAP Tests: Alertness, Go/No-go, Arbeitsgedächtnis und Flexibilität).

Ergebnisse Die Ergebnisse deuten auf einen signifikanten Zusammenhang zwischen Kindheitstraumata und schlechteren kognitiven Leistungen hin, abhängig von der Art des Traumas. Frauen, die körperliche Vernachlässigung (Anzahl der Fehler: $p=0,031$ bzw. Median der Reaktionszeiten: $p=0,015$) oder Missbrauch ($p=0,043$) angaben, erzielten im Flexibilitätstest verglichen mit den Frauen ohne frühkindliche Traumaerfahrung schlechtere Ergebnisse. Zudem zeigten sich statistische Trends für einen Zusammenhang zwischen körperlichem Missbrauch und einem schlechteren Abschneiden im Arbeitsgedächtnistest ($p=0,078$) sowie für eine Assoziation zwischen körperlicher Vernachlässigung und Defiziten in der Verhaltenskontrolle (Go/No-go Test) ($p=0,065$). Für emotionale und sexuelle Traumata war keine signifikante Verschlechterung kognitiver Funktionen messbar. Weiterhin zeigen die Ergebnisse, dass höhere individuelle Bildung und höheres Einkommen mit besseren kognitiven Leistungen assoziiert sind. Derweil konnte kein signifikanter Einfluss von nachbarschaftlichen sozioökonomischen Faktoren auf individuelle Kognitionsleistungen gemessen werden. Bezogen auf den individuellen sozioökonomischen Status war der unabhängige Effekt von Bildung stärker als der von Einkommen. Eine verbesserte kognitive Leistung in Zusammenhang mit höherer Bildung war signifikant für verbale Lern- und Merkfähigkeit (Gesamtlernleistung: $p<0,001$, korrigierte Wiedererkennungsleistung: $p=0,0018$), Verhaltenskontrolle ($p=0,039$), Arbeitsgedächtnis ($p=0,017$ bzw. $p<0,001$) und kognitive Flexibilität (Anzahl der Fehler: $p=0,001$ bzw. Median der Reaktionsgeschwindigkeiten: $p<0,001$). Im

Bezug auf den Einfluss von individuellem Einkommen zeigte sich ein messbarer Effekt auf verbale Lern- und Merkfähigkeit, auf Arbeitsgedächtnis und kognitive Flexibilität.

Schlussfolgerung Die Studie liefert Hinweise, dass Kindheitstraumata sowie individuelle Bildung und Einkommen einen Einfluss auf exekutive Funktionen im Erwachsenenalter zeigen. Die kausalen Mechanismen bedürfen dabei weiterer Untersuchung. Daher werden künftig Studien benötigt, die Marker von Stress und Stressreaktionen und deren Zusammenhang mit Hirnfunktionen und –Strukturen untersuchen, um neurobiologische Mechanismen, die den in der vorliegenden Querschnittsstudie angeführten Zusammenhängen zugrunde liegen, besser zu verstehen.

1 Introduction

General human cognitive ability is influenced and modulated both by genetic preconditions and social environment (24). While the impact of genetics on cognitive function will not be dealt with in the present work, the focus of analysis will be on the effect of psychosocial factors on the cognitive performance of healthy women. Three important dimensions will be examined: childhood trauma, individual socio-economic status (SES) and urban neighborhood status.

1.1 Dementia or related neurodegenerative diseases

Industrialized and post-industrial societies such as Japan, Italy and Germany are facing fundamental changes as they have undergone a process of demographic transition producing low death and birth rates with sub-replacement fertility. This brings about a radical transformation of the demographic structure with a higher proportion of older and fewer young people to support them. Demographic aging is a worldwide phenomenon ensuing from the success of improved hygiene and health care over the course of the 20th century. With more people living into old age, the prevalence of age-associated chronic conditions is concomitantly increasing. Dementia affects approximately 5 % of the population aged 65 and older (119). In studies from developed countries, meta-analyses have established dementia prevalence at approximately 1.5% for people aged 65 years, doubling about every four years to arrive at ca. 30% at 80 years (119). This clearly shows that the incidence of dementia increases with age and thus with demographic change in an aging population. As a consequence, it becomes more and more important to focus on preventive approaches aimed at optimizing cognitive health and maintaining cognitive function into old age.

The most common form of dementia is Alzheimer's disease (AD), accounting for an estimated 50-70% of all cases (14). Other frequent forms of dementia include vascular dementia, which accounts for approximately 20 % of dementias, primarily affects executive functioning and has an abrupt onset, and mixed dementia (associated with more than one type of dementia). Dementia with Lewy bodies (an estimated 10%) often shows fluctuating attention or visual hallucinations (103). Frontotemporal dementia, alcohol-related dementia and other types are less frequent.

While in 2013, 1.4 million people with AD or related diseases were living in Germany, it is estimated that this number will have doubled by 2050 (17), reaching a total of up to 2.8 million people. It is to be assumed that by then one in seven people will be 80 years or older (25). The estimated development of dementia diseases in Germany is illustrated in Figure 1.1. Globally, the organization “Alzheimer Disease International” predicts the number of dementia cases to triple from an estimated 44.4 million in 2013 to total of about 135.5 million in 2050 (1). Dementia has an exceptionally high disability weight, causing more years with disability than stroke, musculoskeletal disorders, cardiovascular disease or cancer in people aged 60 years and older (56).

YEAR	ESTIMATED NUMBER OF >65 YEAR OLDS (MILLION)	ESTIMATED NUMBER OF DEMENTIA DISEASES
2010	16,80	1450000
2020	18,70	1820000
2030	22,30	2150000
2040	23,90	2580000
2050	23,40	3020000

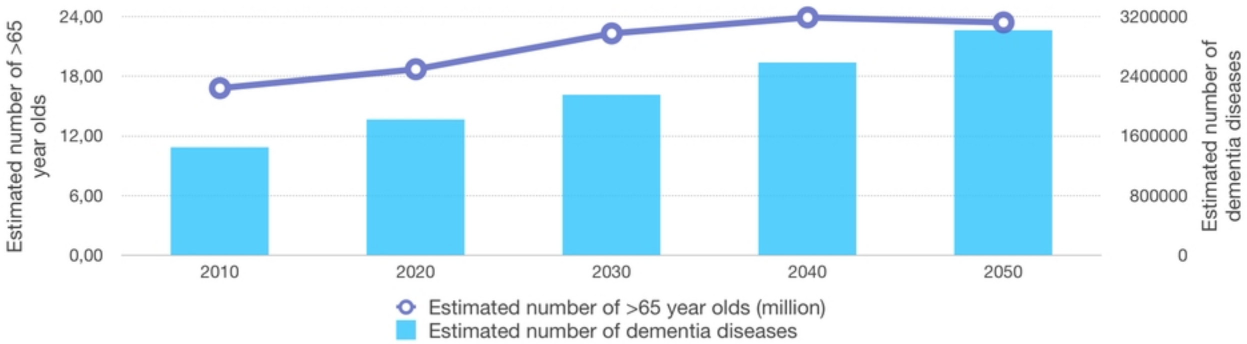

Figure 1.1: Future estimated development of dementia diseases in Germany. Based on (3).

Consequently it is crucial for healthcare systems to focus on dementia and related neurodegenerative diseases and to develop new therapeutic methods and prevention strategies in order to enable old people to live at home independently as long as possible. With the current knowledge of dementia, two different approaches have been developed for its prevention: one is based on primary prevention by altering modifiable lifestyle and risk factors, and the other is a pathophysiological approach aimed to identify subjects at a preclinical disease stage (e.g. mild cognitive impairment (MCI) and to treat them with drugs which are purported to act on the amyloid cascade (122). Currently, it is proposed that abnormal amyloid β (Aβ) and tau protein act as key factors in the development of AD. However, the exact pathogenesis of the disease remains elusive. So far, none of the drugs available (such as cholinesterase inhibitors and the N-methyl-d-aspartate (NMDA) receptor antagonist memantine) have proven disease-modifying and curative properties; treatments mainly offer symptomatic treatment (102) with small effect sizes and limited impact on long term outcomes. Despite massive efforts to develop disease-modifying treatments over the past decade, there is still no effective therapy for AD. Accordingly, it is important both to promote research in neuroscience and to find causal treatments and strategies for prevention that delay cognitive impairment in healthy older adults. Strategies suggested to preserve cognitive functions are physical activity (90), minimal exposure to stressful life events, constant mental stimulation (e.g. through education or cognitive training) and socially stimulating neighborhoods and environments. In this context, the present work aims to investigate the association between early stressful experience, individual or neighborhood socio-economic status and cognitive function.

1.2 Cognitive dimensions

Cognition is a set of mental processes and skills that can be subdivided into different dimensions including: alertness, short-term and long-term memory and executive function. Alertness is a basic aspect of attention and can be subdivided into tonic, intrinsic and phasic alertness. Tonic alertness refers to a state of general wakefulness. Intrinsic alertness represents cognitive control of this wakefulness and maintenance of responsiveness over a longer period of time; it is assessed through implementation of simple reaction time tasks. Phasic alertness enables a person to increase activation patterns subsequent to external demands and task requirements (138). It can be measured using reaction time tasks, which include a warning stimulus that precedes the target stimulus. Intrinsic and phasic alertness are pre-requisites for the more complex demands of attention selectivity and adequate reaction to given instructions.

Another dimension of cognition is memory, which refers to one's ability to retain learned information. The functioning of memory depends on specific brain structures such as hippocampus and amygdala, where information is stored into short-term and long-term memory. Short-term memory refers to temporary information storage (e.g. phone numbers) and can be tested inter alia by measuring the memory span, which is the number of items that a person can recall immediately after a preceding presentation (e.g. of word lists). Long-term memory stores data for a long period of time and can be divided into procedural and declarative memory. Procedural memory refers to unconscious implicit memories utilized for the execution of automated courses of action such as complex motion patterns (e.g. cycling) and cognitive activities (e.g. reading, writing). Declarative memory, on the other hand, corresponds to conscious explicit memories such as knowledge and facts and can be divided into semantic and episodic memory. Whereas semantic memory encompasses factual knowledge about objects, events and the use of language independent of individual experience, episodic memory contains memory of specific situations or episodes grounded in personal experience. Fast episodic memory involves the medial temporal lobe with the hippocampus and the slower semantic system being distributed across the neocortex with a gradual integration of new information (139). One way to measure long-term memory is delayed recall of words in a verbal learning test.

Executive functions are linked to the prefrontal cortex (PFC) and encompass working memory, flexibility of thinking, planning, problem solving, impulse control and inhibition of interfering stimuli. Working memory is a short-term memory and processing system that keeps various pieces of transitory information in mind and is used to design and execute (e.g. problem-solving) behavior. Cognitive flexibility is described as the ability to switch actively between different concepts and situations. It can be differentiated into spontaneous and reactive cognitive flexibility. Spontaneous cognitive flexibility involves one's capacity to switch between various concepts of thought on demand, and reactive cognitive flexibility includes one's ability to react adequately to changing extrinsic stimuli and cognitive sets, often also referred to as "set shifting" (127). Accordingly, its functioning can be tested through "set shifting" tasks (e.g. the computer-based Wisconsin Card Sorting Test or the Test Battery for Attentional Performance (TAP) flexibility test, which was also used in the present study). If cognitive flexibility is impaired, those affected might show symptoms such as perseverative processing, repetitive behavior and incapability to shift one's attentional focus and to process information efficiently. Impulse control and inhibition of interfering stimuli or prepotent responses are also conceptualized as executive functions and linked to the PFC. Deficits in general impulse or behavioral control generate an inability to perform appropriate reactions in a short time and to simultaneously suppress inadequate responses.

The normal process of aging results in local gray and white matter changes corresponding to an age-related cognitive decline, which is not generalized as in the case of dementia, but affects only certain cognitive executive and memory functions such as processing speed, working memory, recall and recollection of context, while implicit/semantic memory and recognition remain relatively stable (47, 73).

1.3 Interaction between genetics and environment

Even though the impact of genetics on cognitive function is not part of the examination of the present study, it still deserves attention as an important field of cognitive research. Estimates of heritability of cognitive skills are based on recent molecular genetic studies and on behavioral studies, which examine identical and fraternal twins raised either together or apart and adoptees (sharing environmental conditions but who are genetically dissimilar to their rearing family). The questions underlying all of these designs are whether genetic relatedness correlates with similarity in cognitive skills and to what degree variance in cognitive ability is caused by additive genetic differences or shaped by environmental aspects. It has been established that genes account for about 50 percent of cognitive variation at the population level (143) and twin studies have shown that cognitive ability has a strong heritability in adulthood (42). Using twin pairs from the Netherlands, assessed at different points during childhood and adolescence, *Hoekstra et al.* found a high degree of stability in nonverbal and verbal abilities indicative of genetic effects and a marked decrease in the heritability of verbal ability with age hinting at additional environmental effects (42). *Davies et al.* implemented a genome-wide analysis of about 3,500 unrelated adults with extensive data on single nucleotide polymorphisms (SNPs) as well as cognitive characteristics and claimed that about 40-50 percent of variation in human intelligence is related to common SNPs (40). General intelligence is often characterized by a cognitive factor (*g*) that is conceptualized based on a phenotypic overlap of several cognitive processes such as spatial or verbal ability and memory, with a large proportion of cognitive variation in ability being accounted for by "g" (26). Strong genetic associations have been reported for many brain structures such as, for example, overall brain volume, gray or white matter volumes and the hippocampus (114). However, the genes causing brain volume variation in humans are still largely unknown and no specific genes or genetic sequences that are directly associated with an intelligence phenotype could be identified yet (42), even though several candidate genes have been suggested in hypothesis driven gene studies. For example, there is evidence that variation in the apolipoprotein E allele causes higher risk of cognitive decline in old age. Another gene that has been suggested to be linked to variation in intelligence and cognitive ability is the schizophrenia-related and widely expressed gene for dysbindin-1 (dystrobrevin-binding protein 1 (DTNBP1)) (26). *Burdick et al.* (26) found that carriers of the haplotype DTNBP1 had a lower intelligence factor "g" when compared with non-carriers even though the mechanisms underlying its effect remained unclear. Genome-wide correlation studies have identified more potential loci, but most of these results remain tentative and unreplicable in spite of the advances in whole-genome sequencing (70).

1.4 Childhood trauma and cognitive function

The first of the psychosocial dimensions investigated in the present study is individual childhood trauma and its effect on cognition. Brain development goes through a series of sensitive periods during which early life stressors and inflammatory events can cause significant neurobiological alterations and lasting effects on cognitive function (45). In experiments with mice, it could already be shown that traumatic stress in early life was associated with an enhancement of long-term depression, an alleged alteration of brain plasticity and an impairment of cognitive functions such as long-term memory (18). Rhesus macaque monkeys raised in isolation showed significant impairments in learning and memory (12, 31).

Child abuse and neglect also cause neurobiological and social stress to the ones who experience it. For example, one study with a sample of female university students reported an impairment of working memory accuracy for positive emotional stimuli suggestive of differences in emotional control in women with a history of sexual or physical abuse (37). Apart from injuries or physical effects resulting from neglect the enduring effects of early maltreatment encompass alterations in emotional wellbeing, demeanor, interpersonal relationships and cognitive performance (63).

1.4.1 Trauma-related effects on cognition in children, adolescents and adults

Childhood trauma is hypothesized to cause changes in cortical growth and an alteration to brain function and structure (20, 147). Furthermore, it is assumed to trigger a stress reaction with an increased cortisol response and circulation of glucocorticoids (GCs) that mediate multiple effects on the brain, e.g. on the PFC and the hippocampus. Also, alterations of monoaminergic transmitter release and function have been suggested as potential mechanisms by which chronic stress might influence executive functions (9).

In general, notwithstanding slight differences in outcomes, depending on sample composition, examined categories of maltreatment, criteria for childhood trauma and testing procedures (110), studies of children experiencing neglect or abuse have shown significant differences in cognitive performance (13, 104). Previous studies with adolescents and adults retrospectively reporting abuse and neglect histories have also supported this idea, in some cases with mixed and diverse results for the different dimensions of maltreatment (144), but in general with extensive evidence for the negative effects of childhood trauma on academic achievement, executive functioning, IQ and post-traumatic stress disorder (110). *Spann et al.* showed that adolescents without identified psychiatric diagnoses, who had experienced physical abuse or neglect, exhibited an impaired cognitive flexibility (136). In line with this, *Navalta et al.* (109) investigated the association between abuse and memory and mathematic impairments in female college students and indicated significant deficiencies in abused subjects (109). For healthy adults with early experience of childhood trauma, *Majer et al.* (95) found physical neglect and emotional abuse to be associated with persistent deficits in visual and working memory (95). Another study conducted by *Gould et al.* (65) described a relation between childhood trauma and impaired cognitive function in adulthood, varying by the type of trauma experienced.

A large body of childhood trauma research focuses on persons with psychopathology and psychiatric disorders, especially post-traumatic stress disorders (13, 144), but also depression or in some cases chronic fatigue syndrome (CFS). Studies that only examine abused adults with PTSD or other psychiatric disorders cannot distinguish whether measured differences are a consequence of childhood trauma or whether they are a pre-existing risk factor for the development of a psychiatric condition such as PTSD. Also, it is to be assumed that not all of the people who experienced maltreatment in their childhood meet full DSM-IV-specific criteria for an Axis I disorder. For example, only about one third of the children who face abuse are diagnosed with PTSD when they are adults (148). This makes some of the past findings not applicable to subjects without lifetime diagnosis of a psychiatric disorder. Instead many of the abused subjects may develop more subtle deficits in their executive functioning, e.g. an alteration of cognitive flexibility (136).

These differences might be explained, inter alia, by glucocorticoid and catecholamine-induced changes in the PFC, which is critical for adjustment to alternating extrinsic stimuli (7). Some evidence indicates that the PFC with its high number of glucocorticoid receptors (GRs) and prolonged development is particularly vulnerable to stress effects (85). If one's cognitive flexibility is impaired, this could result in difficulty shifting focus from a previously trained response to a new set of tasks or cause an inability to maintain a new response pattern. A reduced cognitive flexibility involves inferior adaptive skills, limiting one's ability to adjust to quickly changing challenges (e.g. relating to communication competence: assertiveness and argumentation) in everyday life. So, childhood trauma might cause a dysfunctional but subclinical variation in adult real life behavior and educational functioning.

1.5 Individual socio-economic status and cognitive functioning

The second and third psychosocial factors examined in the present study were the associations of individual and neighborhood SES with cognitive performance. When considering the relation of SES to cognitive function, one has to differentiate mainly between the influence of educational attainment and the impact of economic factors such as income and wealth.

1.5.1 Education and cognitive performance

Education is often used as the main indicator of SES. There are several possible ways in which education could affect cognitive functioning. First, education could be a consequence of inherent intelligence, with intelligence predicting the level of educational achievement and educational achievement thus simply being a dependent variable (43). Second, education could determine an improvement of cognitive strategies, whereby one's ability to conduct cognitive tests with alternative test-taking strategies might yield better results partly compensating for possible deficits in case of cognitive decline (5). Also, higher levels of educational attainment often lead to an enriched environment and desire for mental stimulation throughout life, which might cause beneficial neurochemical or structural alterations in the brain (5). *Kelly et al.* (82) investigated the impact of cognitive training and mental stimulation on cognitive performance among a healthy population of older adults without known cognitive deficits. They observed that cognitive training and stimulation led to an improved performance in memory and cognitive functions compared to controls. Finally, education may have a direct effect on neural brain structure by increasing the number of neurons and improving the level of neural efficiency; thus providing a "cognitive reserve" against brain pathology and injury (142). According to the "reserve capacity hypothesis", this effect would not essentially change the vulnerability to disease but postpone the clinical appearance of cognitive deficits (5, 118). *Lee et al.* (92) administered six cognitive tests to a large number of educated and professional women aged 70 to 79 years twice between 1995 and 2000 and found significant relations between educational attainment and both cognitive function and decline with decreasing odds for poor cognitive function and for cognitive decline with higher level of education (92). In line with this, *Gallacher et al.* (59) examined cognitive functioning among 1,870 men from a general population aged 55-69 years as part of the Caerphilly Study showing a consistent trend towards better cognitive performance with higher educational attainment, which remained significant after adjusting for age, social class and mood (59).

However, education does not only provide protection against cognitive impairment in the elderly but also has a positive effect on cognitive preservation and performance in the younger. *Farmer et al.* examined the relationship between educational attainment and cognitive decline over the course of 1 year for subjects 18 years and older using the Mini-Mental State Examination (MMSE) as an instrument for assessment and found that education was an important predictor of cognitive decline in both young and old (54).

1.5.2 Income and cognitive performance

Income constitutes another indicator of SES reflecting the current economic and social position of the individual. It also has a significant effect on cognitive function, however to a lesser degree than education (29, 78). In a US-population-based study of the elderly, verbal memory, working memory and general knowledge scores were associated with education, wealth and household income, indicating a very strong positive effect of education and an attenuated effect of income and wealth on cognitive function after adjustment for education (29). *Lee, Buring et al.* (91) found that with higher income, mean cognitive performance increased significantly on three of the four cognitive measurements they conducted among a group of 6,314 US health professionals (91). One study even emphasized that while the impact of education on health and cognitive functioning was attenuated in older age, health and cognitive benefits associated with higher income persisted into advanced age (151).

Income can be seen as a surrogate for material circumstances and wealth partially influencing cognitive functioning independent of education. This association is to some extent mediated by a higher standard of living, which results in an improved access to health care, better health behavior (e.g. more varied and balanced diet, attending regular medical checkups) and favorable environmental lifestyle effects (e.g. in urban environments: less exposure to congestion, spending more time in green spaces). Also, a higher standard of living might reduce stress and enhance psychological wellbeing. In line with this, one study examined the limiting effect of poverty on cognitive performance, hypothesizing that poverty is causally associated with concerns (consuming mental resources and leaving less for other tasks) and so directly impedes cognitive capacity (98).

1.5.3 Unequal distribution of socio-economic resources

A person's or individual SES, for which income or wealth and education are proxies, affects society as a whole. In most parts of the world, educational and economic standards differ a lot across population groups with a global increase of inequities in wealth distribution and lifestyle. In Germany inequity has not been reduced in the past years after significantly rising during the 1990s.

A standard illustration of a nation's income distribution and statistical measurement for the level of income inequalities is the so-called Gini coefficient. The Gini coefficient can take on any value between 0 and 1 with higher values indicating a higher level of inequity. In 2012 the Gini index was 0.78 making Germany the country with the highest degree of income inequality within the eurozone (66). The one percent richest people in Germany hold private capital with a value of at least 800,000 EUR, whereas more than 20 percent work in the low-wage sector and 15 percent of the German population live below the poverty line (135). In the European Union (EU) and in many other countries, poverty is defined as access to a net income of less than 60 percent of the median income (153). The problem of poverty in urban areas is especially severe. The Institute of Economic and Social Research, which is part of the Hans Böckler Foundation, looked at the 15 most populous cities in Germany between 2005 and 2011 and found an increase of the poverty rate well above the national average (129). Accordingly, Berlin faced a rise in the poverty rate with a high level of childhood poverty and had the highest proportion of the population receiving public assistance (129).

In the face of this continuing overall income inequality, the topicality of the question "To what extent does per capita income modulate cognitive performance?" can clearly be seen.

1.5.4 The twofold association between wealth or income and education

As income and wealth determine living conditions and family background, they have an influence on educational attainment. Even though in Germany theoretically everyone has equal access to school services, and through educational achievement can modulate his or her job prospects and SES, the chances of succeeding in life still vary depending on a person's economic and social backgrounds. It has been shown that poor children face inferior educational opportunities (76). *Holz et al.* (76) found that children who had experienced or are currently experiencing poverty managed to get into Gymnasium (academic high school in Germany) considerably less frequently than children who had never encountered poverty. This can be seen as a consequence not only of material hardship but also as a lack of cultural capital/resources (in the sense of familiarizing children with high culture) and parental involvement.

However, the relation of material wealth and education is of a twofold and reciprocal kind. Not only does poverty diminish educational prospects, lack of education causes poverty. So an interference with both economic conditions and education could positively alter prospects and functioning within societal environment. These interventions would enhance individual health and wellbeing.

In order to stress the importance of social and political measures designed to alleviate poverty and unequal access to education, it is necessary to show its negative impact on individual health. The present work focuses on the cognitive dimension of health and aims to examine the association between SES and cognitive performance.

1.6 Neighborhood socio-economic status and cognitive function

It is rather difficult to distinguish between the effects of local communities and the characteristics of the people who live there. However, beside the exclusive focus on the impact of individual SES on mental health and wellbeing, it might be assumed that neighborhood-level SES also has an effect above and beyond individual-level characteristics, the idea being for neighboring communities to provide a contextual matrix for the development, shaping and preservation of mental skills. Every community in theory has its own unique social, crime and health environment with the neighborhood acting both as a role model for socio-educational attainments and as a possible source of mental stimulation. For children and adolescents, neighborhood professional and cultural achievements represent what they themselves may expect to achieve in school and university (101); and for the elderly an affluent cohesive social environment provides a source of sophisticated and stimulating intercourse, promoting mental engagement. Social engagement, social networking, contact and support might as “social capital” have protective effects and foster the maintenance of a cognitive reserve (58).

Other mechanisms by which lower quality communities might affect physical and cognitive health involve an inferior access to high-quality health care, excessive consumption of tobacco and alcohol and an increased exposure to environmental chronic stressors and pollutants (132).

1.6.1 Looking at poor neighborhoods

Previous studies indicate that lower quality neighborhoods are significantly associated with poorer cognitive functioning, even after adjusting for age, education and wealth (52, 89, 149). Many of the existing studies suggest that especially older people are subject to an increased risk for their cognitive performance to be modulated by neighborhood characteristics due to prolonged periods of residence in one neighborhood (38, 50, 51, 89, 131, 149). Also, they often spend more time in their neighborhoods when they are retired and develop frailty and disabilities, which further reduces their mobility (28, 105). In this respect, the local and immediate neighborhood setting is especially important for older adults. In line with this, *Lang et al.* found a significant inverse correlation between a low neighborhood SES and a higher rate of cognitive decline over time for an older national sample in England (89).

Also, possible negative effects of destitute environment might be seen most clearly in disadvantaged neighborhoods with low incomes and a poor living environment. In line with this, *Aneshensel et al.* (6) showed that neighborhood economic disadvantage had an especially strong negative effect on the cognitive function of people with low personal wealth. The influence of neighborhood SES on cognition is closely interwoven and interacting with the impact of individual SES. Consequently, when adverse individual and neighborhood circumstances meet, this has the most detrimental effect on cognition. According to this, *Wight et al.* found that older people with a low individual level of education living in a neighborhood with a high proportion of inhabitants without a high school degree achieved the lowest scores in cognitive testing (149).

1.6.2 Assessing neighborhood socio-economic status in Germany

To access neighborhood status it is easiest to rely on census tract statistical data. In the present study, neighborhoods were defined as socio-spatial units within a new concept of geographical planning areas that was introduced by the Senate in Berlin in 2006, enabling a continuous socio-economic monitoring of quarters and neighborhoods instead of census areas and traffic zones (72).

Even though previous Anglo-American studies have addressed the question to what extent neighborhood contexts modulate cognitive functioning especially among older adults, so far no one has investigated the impact of urban neighborhood settings in Germany. Especially compared to the US, Germany has an entirely different structure of local environments, which can mostly be seen as a result of its distinct health and welfare system. Also, especially the problems of urban black neighborhoods are central to US sociological and health research. As there is no such racial issue in German urban environments and no substantial residential segregation of one large minority group, investigations on the association between neighborhood and cognitive health by race do not apply. Instead there might be other individual-level migratory or demographic factors modifying the influence of neighborhood status on cognitive functioning. Therefore, the present study is unique, as it considers a yet uninvestigated geographic field of research.

Also, the survey is not limited to the association of neighborhood with cognition in a group of older adults but also considers women at a younger age, examining whether slight influences on cognitive function can already be seen at an earlier stage in life. Adding to that, studies such as the one conducted by *Wight et al.* (149) focus exclusively on the interaction of individual-level education with neighborhood-level education or on the interaction between individual-level and neighborhood-level SES (6). However, so far there has been very little investigation on other individual-level characteristics such as childhood trauma that could possibly modulate the positive and negative effects of neighborhood influences on cognitive function (132). The present work examines whether neighborhood SES is related to cognitive performance in a demographically diverse set of generally healthy women in Berlin, also considering possible health and psychosocial confounders such as childhood trauma, social support, and depression.

1.7 Outline of hypotheses on childhood trauma

The long-time influence of childhood trauma on cognitive functioning needs further investigation and scrutiny. So far, few studies (65, 95, 110) have explicitly examined whether abuse-related cognitive damage persists not only into adolescence but also further into adulthood.

The present study examines different dimensions of self-reported childhood trauma and of cognitive function and includes tests for short- and long-term verbal memory as well as executive functioning, using a standardized assessment. In order to evaluate childhood abuse and neglect, an internationally accepted questionnaire (84) was used, on the basis of which trauma scores were calculated. The aim was to assess the association between different dimensions of childhood trauma and cognition, considering the potential role of SES as a confounder.

- First, it was assumed that experiences of childhood emotional, physical or sexual abuse or neglect had a negative effect on cognitive function that was still measurable in adulthood.
- Second, it was hypothesized that there would be a difference in verbal and executive performance depending on the dimension and subtype of abuse.

1.8 Summary and main questions

Demographic changes in Germany (e.g. declining population with an increasing number of older people suffering from dementia) cause far-reaching effects on politics, economics, public finance, social security and healthcare systems. Also there is insufficient evidence on the benefits of pharmacologic or other treatments of age-related dementia. During the past decades, research has found a number of modifiable risk factors for dementia diseases as well as the means to deal with them on individual and population levels. As cognitive decline is slow and progressive, it starts long before people are diagnosed with dementia. Therefore, prevention strategies in clinically healthy subjects become increasingly important, as they might be able to moderate the consequences of age-related impairment. Factors, which have been suggested to influence cognition, apart from biological or genetic preconditions, are individual psychosocial factors (e.g. childhood abuse) and individual- and neighborhood-level socio-economic factors (e.g. education, income).

A handful of previous studies have established the idea of a measurable association between higher childhood trauma scores and lower neuropsychological function (13, 65, 95, 109). Based on this, the first aim of the present study was to examine the relationship between childhood trauma and cognition and to test whether cognitive performance differed depending on the subtype of trauma. Furthermore, existing research has suggested a positive effect of individual and neighborhood education and income on cognitive performance. In line with this, for the second and third aim, the present work focused on interactions of individual- and neighborhood-level socio-economic status with cognitive function. As the study sample consisted of a sample of generally healthy German urban women of different ages and socio-economic backgrounds, it allowed for an evaluation of cognitive functioning across diverse individual and neighborhood socio-economic contexts.

Finally, the author raised three main questions, the first two referring to individual-level and the third one to neighborhood-level psychosocial influences:

(1) In what way do subjectively evaluated experiences of emotional, physical, sexual abuse or neglect modulate different dimensions of cognitive function in adulthood? Does the subtype of abuse matter with regard to measured cognitive modification or impairment, possibly with different dimensions of abuse showing varying effects?

(2) To what extent do individual levels of education and income as indicators for one's socio-economic status show an impact on verbal and executive cognitive function?

(3) Extending beyond individual socio-economic status: Does neighborhood socio-economic status as an environmental influence also have an effect on individual cognitive functioning after adjusting for individual-level factors?

2 Materials and Methods

This study was conducted in accordance with the Declaration of Helsinki (amendment of 1996), which constitutes an international consensus on the ethical execution of human subject research. Approval by the ethics committee of the Charité was obtained and scientific quality standards of Good Clinical Practice (GCP) for the conduction and recording of clinical trials were upheld at all times. All subjects were explicitly informed about the setup and aims of the study and gave written informed consent to their participation and the anonymized analysis of their data.

2.1 Study design

This work is part of the larger scale Berlin Female Risk Evaluation (BEFRI) study, which consisted of different working groups and was carried out between November 2012 and November 2013 (112). It aimed to approximately represent Berlin's female population with a proportional representation of boroughs' inhabitant density (112), but with an artificially generated age distribution consisting of 5 equal age strata that do not reflect the real age distribution in Berlin. The main part of the BEFRI study investigated female cardiovascular risk factor distribution comparing subjective risk assessment to the cardiovascular risk estimate of a women-specific version of the Framingham score and analyzed risk distribution with regard to age, social, economic and medical risk factors.

The present study is based on the database of the BERFI study but puts it into context with neuropsychological testing. As several people were involved in the realization of the study, I will now briefly explain my part. Between November 2012 and November 2013, I was in the Working Group for Cognition, Aging and Neurorehabilitation under the direction of Professor Dr. med. Agnes Flöel and conducted neuropsychological tests with the BEFRI subjects including a verbal learning and memory test (VLMT) as well as computerized cognitive tests. This followed the informed consent and clinical examination of the participants. Another doctoral candidate, a student assistant and I carried out neuropsychological tests for 843 out of a total of 1065 study participants. I performed 342 neuropsychological examinations independently, each of them taking about 40 minutes. So I had personal contact to about 40 percent of the participants I refer to in the present work. All methods used for handling data and statistical analyses were applied independently after consultation with Dr. Ulrike Grittner from the Institute of Medical Biometrics and Clinical Epidemiology (Charité Universitätsmedizin, Berlin).

2.2 Participant recruitment

The present study was carried out on an urban age-stratified probability sample. 3600 healthy women from Berlin aged between 25 and 76 were randomly selected by the city census with densely populated areas contributing more women than sparsely populated districts (112). The rate of participation over all districts varied between 19 and 34 percent. All women selected were invited to participate through a letter of invitation and one other letter describing the study's purpose and examination procedures in case of acceptance (112). Of the 1199 women, who replied by notifying the study coordinator and were subsequently sent consent forms, a specifically designed questionnaire and further information sheets, 1066 (88.9 %) decided to participate (112). A non-blinded study manager, who was not involved in any of the clinical examinations or neuropsychological tests, randomized all personal data so that allocations of name, date of birth or address to questionnaire information, examination or test results were impossible.

2.3 Inclusion and exclusion criteria

We were able to conduct neuropsychological examinations in 844 out of the 1066 women (79.1 %), with 1 woman having to be excluded as a consequence of language and literacy problems. All of the 843 women that were included in the analysis of neuropsychological tests (mean age ± SD 50.6 years ± 14.3 years) were fluent in German, this being a prerequisite for conducting and comparing the results of the VLMT, and did not suffer from any untreated clinically significant disease. Severe untreated diseases of the brain, heart, liver, kidney, autoimmune or metabolic diseases, use of CNS-active medication and drug or alcohol abuse led to an exclusion from our study.

2.4 Testing procedure

An overview of the study design and of examinations can be seen in Figure 2.1. As a consequence of a cross-sectional study design, data were collected at only one specific point in time. Variable appointment times were offered during working days (and in exceptional cases even on weekends) in order to ensure that participants with long working hours would not be disadvantaged and could also be included. Most of the BEFRI participants were surveyed in examination rooms on the site of the Campus Charité Mitte, but we also went to the more remote districts for examinations and tests to facilitate participation for less mobile subjects. External appointments were scheduled based on the participant's preference. For their time, all participants received a reimbursement of 50 €. However, in order to prevent selection bias, women were only informed about the compensation after they had consented to participate (112).

After obtaining informed written consent, the first part of the testing procedure, which took about an hour, comprised a clinical examination, the taking of the medical history and a veni-puncture. After a short break, participants were, if possible and if they consented, instructed to go to the echocardiographic examination. The last part of the testing procedure was the neuro-psychological examination, which is described in section 2.8. It took about 45 minutes and con-sisted of 5 different tests, of which 4 were computer-based.

In the run-up to the examination all subjects were sent a specifically designed standardized questionnaire, which they completed at home and brought with them to the examination. The questionnaire is presented in detail in section 2.6. The socio-economic and psychosocial data gathered in the questionnaire were then put into context with the results of our computerized cognitive testing battery in statistical models.

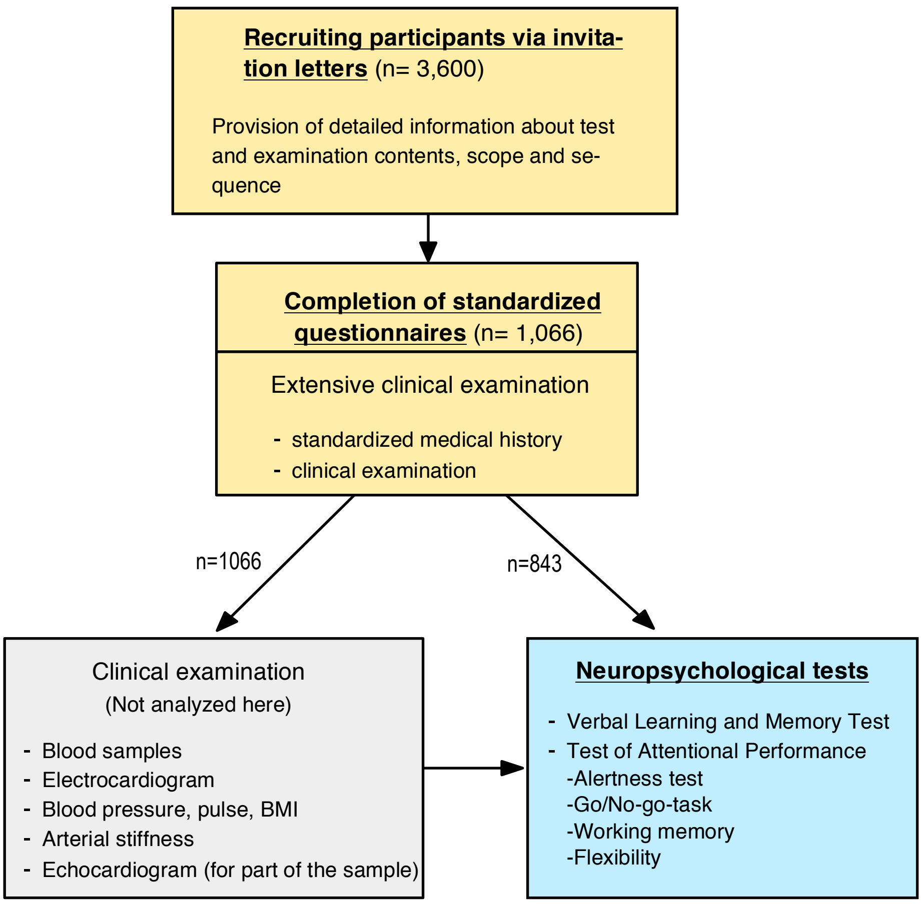

Figure 2.1: Study design and overview of examinations.

In order to reduce the potential influence of confounding factors on test results, we tried to provide standardized settings in a quiet, low-stimulus environment. At Charité hospital, exami-nations were generally carried out in the same rooms and, when testing externally at district-based local facilities, similar conditions and settings were ensured.

2.5 Medical examination

The extensive clinical examination consisted of:

- measurement of height (cm) using a stadiometer,
- determination of weight on a calibrated scale (kg), all women being lightly dressed without shoes,
- waist and hip circumference (cm),
- blood pressure (mmHg),
- pulse (1/min),
- a 12-led electrocardiogram (ECG),
- measurement of arterial stiffness (ankle brachial index),
- venous blood samples,
- a case history
    - regular intake of medications,
    - previous illnesses,
    - lifestyle factors.

All blood samples were immediately placed in the refrigerator at 4°C and processed at an external lab (Hospital Laborverbund Berlin-Brandenburg, Bernau, Germany) within 24 hours of collection (112). Data was collected in paper form and a database was designed using Microsoft Access.

2.6 Questionnaire

The questionnaire was sent to the participants in good time before the examination and completed by them at home. It consists of 72 items and provides information inter alia about mother tongue, citizenship, composition of the household, level of educational attainment, profession and income, medical history, physical fitness, health behavior, subjective cardiovascular risk estimation and psychosocial dimensions such as social support, mood, critical life events and childhood experiences. In order to be able to evaluate the influence of some of these parameters (economic, social, psychological information and childhood experiences) on cognition, they were statistically correlated with cognitive performance in the neuropsychological test battery.

Comprehension, feasibility and duration (average completion time being 75 minutes) of the full questionnaire had been tested before in a pilot setting of 50 women of various age groups and different educational and socio-economic background with single questions being adapted and altered based on the results of the pilot phase (112).

The questionnaire was created based on German versions of standardized measurements such as the short form of the Childhood Trauma Questionnaire (CTQ) measuring moderate to severe trauma exposure (77), the ENRICHD social support instrument (ESSI) indicating the extent of social support (145) and the self-administered Patient Health Questionnaire-9 (PHQ) as a measure for current depression (99).

2.6.1 The Childhood Trauma Questionnaire

The CTQ assesses severity and levels of trauma exposure. The CTQ-short form is a widely used (61, 113, 124) retrospective 28-item instrument developed by Bernstein and Fink (16, 124), whose validity and reliability as a screening tool has been supported by several studies (15, 81, 137, 150). Examining different dimensions of childhood abuse and neglect, it evaluates emotional, physical and sexual abuse, as well as emotional and physical neglect (49). All items start with "when I grew up…" and are rated on a 5-point Likert scale ranging from 1 ("never true") to 5 ("very often true"). Scores with a range of 5 (no experience of abuse) to 25 (extreme experience of abuse) are produced for every childhood trauma subscale (49), with higher values suggesting a more severe extent of abuse. For each subscale, scores are categorized into four cut-off scores, assessing the severity of maltreatment. For emotional abuse e.g. these are: 5-8 ("none to minimal"), 9-12 ("slight to moderate"), 13-15 ("moderate to severe") and 16-25 ("severe to extreme"). For each subscale, moderate-to-severe-cut-off was used to classify subjects as positive for a respective history of trauma. The aim of this cut-off was to increase specificity and to minimize misidentification of non-abuse cases (75).

Table 2.1: Evaluation of the severity of childhood trauma (16, 71).

	None-minimal	Slight-moderate	Moderate-severe	Severe-extreme
Emotional abuse	5-8	9-12	13-15	16-25
Physical abuse	5-7	8-9	10-12	13-25
Sexual abuse	5	6-7	8-12	13-25
Emotional neglect	5-9	10-14	15-17	18-25
Physical neglect	5-7	8-9	10-12	13-25

As can be seen in Table 2.1, moderate-to severe-cut-offs for the respective subscales are: 13 or more for emotional abuse; 10 or more for physical abuse; 8 or more for sexual abuse; 15 or more for emotional neglect and 10 or more for physical neglect. The internal consistency of the CTQ subscales has been demonstrated to be good (0.62-0.96) in community and clinical samples (16, 95). For statistical correlation categorized subscales were used, but also a continuous form of the CTQ data.

2.6.2 The ENRICHD Social Support Instrument

The ENRICHD social support instrument (ESSI) is a self-report survey consisting of 6 items that assess different aspects of social support such as emotional, instrumental and network support. Each item is rated on a 5-point Likert scale ranging from 1 = “never” to 5 = “to all the time”. A total score of less than 18 (lowest quartile) combined with a score less than 3 on two or more items, or irrespective of the total score, a score of no more than 2 on two items classified a subject as having a low perceived social support (27). The ENRICHD Social Support Instrument has been shown to correlate with other screening instruments for social support establishing its validity (106).

2.6.3 The Patient Health Questionnaire

The Patient Health Questionnaire-9 is frequently used and established in the detection and assessment of self-reported major depression in clinical studies. It is a 9-item screening instrument extracted from the full PHQ and based on the DSM-IV criteria for major depressive disorder, but has been specifically developed to screen for current depression in the past two weeks (87, 99). Major depression can be diagnosed if the PHQ score reaches 10 (often recommended as the cut-off score (96)) or more and if at least 5 of the 9 depression criteria have applied for “more than half the days" during the past 2 weeks, one of the symptoms being loss of interest or depressed mood (87). Sensitivity and specificity for major depression are 88 percent, respectively (87).

In order to measure depression severity, a total sum score with a possible range of 0-27 can be obtained by using the item responses. Thereby, the respondent rates the frequency of each of the 9 items on a 4-point Likert scale from 0 ("not at all"), 1 ("several days"), 2 ("more than half of the days") to 3 ("nearly every day") (87). Sum scores of 0 to 4 correspond to minimal symptoms, 5 to 9 to mild symptoms, 10 to 14 to moderate depression, 15 to 19 to moderately severe and 20 to 27 to severe depression. These cut-off values have been established in several studies (30, 69, 87) and were used for statistical analysis in the present work.

2.7 Living environment areas

Living environment areas (LORs or Lebensweltlich Orientierte Räume) form a spatial basis for the planning and monitoring of socio-demographic developments in Berlin. The concept consists of three related levels of spatial units: 447 planning areas (LORs), 138 intermediate areas and 60 prognosis areas. It was drawn up by the sociologist Dr. Häusermann and supported by the Senate Department for Urban Development in Berlin. In 2006, the Senate decided to replace the former Geographical Reference System by the new system of Living Environment Areas (72). Each planning are (LOR) has a mean size of 0.06 km^2 and includes an average of 7,500 inhabitants; introducing LORs has allowed a continuous monitoring of neighborhoods since 2007 (72). SES and development can be evaluated through a set of indicators, which are publicly available online on LOR and planning area-level (72). Since 2007, there has been a differentiation between indicators of "status" describing the social situation in a neighborhood and indicators of "dynamics" which characterize changes in the living area during the previous year (72). As the aim was to examine neighborhood SES, the status index was used. The status index is a composite variable consisting of 6 indicators: adult unemployment rates, youth unemployment (% of 15-25 year olds), unemployment with a reference period of over a year (long-term unemployed), portion of recipients of benefit, amount of child poverty and percentage of inhabitants under 18 with migration backgrounds (72). Through the ranking obtained using the status index, the planning areas can be divided into groups of 10 percent (deciles) each, with the two deciles with the best status index being categorized as "high" and the two lowest deciles being classified as "low to very low" (72). The intermediate 60% are categorized as having a "medium" social status. Corresponding to this, a 3-item status (very low/low, medium, high) was used in statistical analysis in order to compare neighborhood socio-economic position to individual cognitive outcomes. Neighborhood SES was considered not on LOR but on larger prognosis area level, as the study sample size did not cover smaller spatial units.

2.8 Neuropsychological Test Battery

In the following, I will describe and explain the set of neuropsychological tests that were used. All of them are standardized psychometric tests with published normative data and they were performed under uniform conditions with standard instructions. The tests covered various dimensions of cognitive performance such as: verbal learning memory, attentiveness and sustained attention, working memory and executive functions. The sequence of testing was conducted in this order: VLMT, Alertness Test, Go/No-go Test, Working Memory Test, Flexibility Test.

The German VLMT is a valid, standardized and reliable measure of declarative explicit memory with free recall, interference and delayed recall, modeled on the Rey Auditory Verbal Learning Test, which is widely used in scientific research as well as in clinical practice (107).

The computerized Test of Attentional Performance (TAP) was originally developed for the assessment of attentional impairments in people displaying cognitive deficits with reaction time tasks (measured in milliseconds) at the core of the procedure. It is a standardized and valid method for measuring executive cognitive performance and has been supported by institutions and studies related to executive and attentional performance (33, 36, 97, 100, 125).

2.8.1 Verbal Learning and Memory Test

The VLMT is designed as a serial list-learning task in paper form consisting of two semantically independent word lists (A, B) and a recognition list. The recognition list contains all words from lists A and B as well as 20 semantically or phonetically similar nouns. Before starting the test, instructions are read out loud and clear. There are two parallel test versions with different words for repeat examinations: The present study is based on version A.

At the beginning of the VLMT, the participant is asked to memorize as many words as possible and to repeat all of them after each subsequent trial as soon as the presentation stops with no restriction on the output. Starting the test, 15 unrelated nouns from the first list are read to the participant, followed by four more trials in identical order with free recalls. When the fifth iteration is completed, the subject is presented with a second “interference” list in the same manner and asked to repeat as many words from it as possible. Immediately after the interference trial, the participant is instructed to repeat the original list. After a 30-minute delay (during which in the present test set-up the subjects administered the computer-based tasks) and unexpected for the participants, the respondent must again recall as many words as possible from the original list. Following this “delayed recall” task, the recognition list is read to the participant, who has to decide for each word with yes/no whether it is part of learning list A or a new non-target addition. Stimulus words are presented for 1 second with an interval also of 1 second.

Based on the VLMT results, a number of scores was calculated: a total learning score from trials 1-5 (sum of correctly recalled words after each presentation), a recall difference score between trial 5 and 7 (performance after interference, measuring consolidated memory), a delayed recall score (number of words correctly repeated after the 30 minute interval) and a corrected recognition score (number of correctly recognized words minus the incorrectly assigned words). The summary scores for cognitive performance used in statistical analysis are the learning score and the corrected recognition score. While the learning score is a measure of one’s learning ability and of the short-term component of declarative memory, the corrected recognition score is a measure of the long-term component of declarative memory. It serves as an indicator for the amount of new information that can be transferred into long-term memory.

All VLMT data were collected either by the other doctoral candidate, a research assistant or me; we tried to ensure uniform test administration and data collection through constant dialogues and mutual visits during VLMT assessments. All of the paper form data was then entered into SPSS for evaluation purposes.

2.8.2 Test of Attentional Performance

In total, the TAP includes thirteen subtests, which allow for evaluation of a large variety of attention performance measurements. We administered four of these subtests covering a wide range of attentional and executive functions: Alertness, Go/No-go, Working Memory and Flexibility. Internal consistency for these subtests varies between about 0.60 and 0.83 (154).

The computerized TAP runs on PCs or laptops under MS-DOS mode within Windows 98 and results are automatically saved and presented as graphics/lists on screen. We used two laptops with TAP 2.3 (Copyright 2012, Zimmermann and Fimm) similar in hardware (both coming with two adapted responsive keys) and software configuration, as two of us were sometimes testing simultaneously (on the site of Campus Charité Mitte and in one of the districts). In all cases we ensured that neither daylight nor any kind of strong artificial light fell directly on the monitor in order create comparable conditions for brightness and contrast of the screen and to reduce eyestrain.

Before the start of each test and based on the display of instructions on the monitor, we gave clear verbal instructions using a predetermined sequence of phrases and answered subsequent questions. After this, a pre-test was done before the main test in order to ensure a complete understanding of the task. If a participant encountered difficulties in understanding, she was allowed to do the pre-test more than once until a full understanding and following of instructions was guaranteed. If repeated pre-test application ensued, this was always documented. As all of the TAP tests measured reaction time, the participant was required to maintain a continuous high level of attentiveness and responsiveness. To support this, the subject was reminded several times throughout the implementation to press the key as quickly as possible (154). During the course of the pre- and main test, it was always possible to interrupt the execution when the participant wished to do so because of having questions or feeling exhausted.

2.8.2.1 Alertness

The TAP alertness test assesses both tonic (basic level) and phasic alertness by instructing participants to respond as quickly as possible to the appearance of a visual stimulus on the monitor, occurring with or without warning signal. Phasic alertness becomes apparent through reduction of response time to a stimulus, which is preceded by a warning stimulus. It refers to one's ability to increase and maintain a higher level of response readiness following and in anticipation of a stimulus.

The TAP trial consists of four test rounds with 20 target stimuli each and is executed in an ABBA sequence (A without acoustic warning stimuli and B with acoustic warning stimuli). The target stimulus is the appearance of a cross on the monitor, to which the participant is instructed to react as quickly as possible by pressing a key ("key 1"). Each of the rounds starts with a note concerning the modality of the test and informing the respondent if it is a trial with or without warning signal.

The participant is told that if it is a trial with a warning signal, the warning signal comes first and then the cross appears, but that she must not press the key before the cross (visual stimulus) appears. Before starting the test, each participant has to complete at least one practice trial in order to ensure adequate understanding of test instructions. Without instructions and practice trials implementation time is 4 minutes and 30 seconds. Rounds one and four measure phasic alertness and thus general responsiveness, whereas rounds three and four are important in order to examine phasic alertness as a change in reaction time following a preceding stimulus.

For each alertness test, the TAP software provides the user with a list including mean score, median and standard deviation (SD) of reaction times, number of correct reactions, omissions, outliers (reaction times exceeding the mean reaction time plus 2.35 times the SD) and anticipations. A keystroke is counted as an anticipation if the pressing of the key occurs before the presentation of the stimulus or if reaction time is less than 100 ms. In addition, the program automatically calculates a standard score for phasic alertness composed of the difference of reaction times between the two parts of the trial (with and without warning signal) and divided by the median of all reaction times. This index of phasic alertness is calculated according to the following formula (154):

$$\frac{\mathbf{Median_{rt0} - Median_{rtw}}}{\mathbf{Median_{rtt}}}$$

$\mathbf{Median_{rt0}}$: Median reaction time without warning signal

$\mathbf{Median_{rtw}}$: Median reaction time with warning signal

$\mathbf{Median_{rtt}}$: Median of all reaction times (154).

This composite score was used for statistical analysis.

2.8.2.2 Go/No-go

The Go/No-go test measures sustained attention and response inhibition. Response inhibition is an important aspect of behavioral control, enabling individuals to react adequately under time pressure inhibiting externally triggered inappropriate responses (154). The TAP software provides two versions of the Go/No-go test; we applied the “1 of 2” option (one of the two stimuli is critical), where an upright “+” and a diagonal cross “x” are presented alternatively on the monitor (154). The participant is required to press a key (“key 1”) when given a certain stimulus (“x”) and to inhibit the action under a different stimulus (“+”). In total, 40 stimuli are presented on the screen including equal numbers of critical and uncritical stimuli. Presentation time is very short (200ms) in order to provoke a rapid response. Dependent measurements include reaction times for all critical stimuli and error frequencies.

The results output includes mean score, median and SD as specific parameters for reaction time and also the number of errors and omissions. Standard values are presented for comparison. In order to evaluate and analyze response control, we assessed the number of errors and the median of reaction times, which hints at the efficiency of the decision-making process.

2.8.2.3 Working memory

Working memory refers to cognitive processes associated with storing, updating and manipulating a limited amount of information over a short period of time. In the TAP working memory test a 2-back task is used which requires storage and processing at the same time. Out of three difficulty levels, the third (highest) level of difficulty is selected. A continuing sequence of single digit numbers is presented on the monitor and the participant is asked to decide for each number whether it corresponds to the preceding number. The critical stimulus requesting a response (pressing the key “key 1”) is the appearance of a number identical to the second last one.

As the sequence of numbers is continuous, the critical stimulus is constantly being redefined. In total, the test is comprised of 100 numbers, which are presented at 3 second intervals with each condition containing 15 critical stimuli and (without pre-test and instructions) it takes 5 minutes to complete (154).

The results output includes the number of omissions, errors, correct responses, outliers and reaction time parameters. In order to evaluate cognitive performance, the most important parameters are omissions and errors, as they hint at a loss of control and attention in the processing and updating of information. Reaction times are only of secondary importance in the working memory test.

2.8.2.4 Flexibility

The flexibility subtest is a set-shifting task. With cognitive flexibility being the ability to adjust one's reaction to changes in tasks or environment, this test measures the participant's ability to adapt responses to a changing set of circumstances. The complexity of the flexibility test stems from the continuing alternation of two types of critical stimuli.

The test requires the use of both adapted response keys (key 1 = left side and key 2 = right side) and the test person is instructed to control each key with one hand. The flexibility test can be performed under different conditions; we chose the complex nonverbal mode for all flexibility tests. In this mode the target stimulus, which is randomly placed and is not fixed but alternating. The subject is presented simultaneously with an angular shape and a round shape on the right and left center of the monitor (154). The participant is required to press either the right or the left key, depending on the side of the monitor the target stimulus appears on, the instructions being: "Please press as quickly as possible first the key on the side where the angular shape appears, then on the side where the round shape appears. Please switch each time between angular and round shape. Begin with the side with the angular shape." (154) If the test person gives a wrong response, one of the forms (angular or round) flashes instantly and is marked by a surrounding square, indicating that the angular-round alternating must be restarted. Trials with highlighted stimulus are not included in the evaluation. In total, the test consists of 100 trials and takes at least 3.5 minutes to complete.

With regard to the assessment of test performance, the crucial parameters are the median of reaction time and the number of errors, as they serve as indicators for speed and precision. There is an interdependence between the two parameters in the form of a "speed-accuracy trade off" (154) which means that depending on the chosen strategy, poor performance in the TAP flexibility test can either result from slowed down reaction times or from a high number of errors. Accordingly, both parameters were used for assessment of flexibility function.

2.9 Statistical analysis

All collected data were entered into SPSS for Windows, version 23.0 (SPSS Inc., Chicago, IL, USA) and analyses carried out in anonymized form.

For the present work, descriptive analyses and statistical tests were performed for all of the underlying hypotheses. In order to test for normal distribution, histograms and skewness were assessed. If skewness values were between -1.0 and +1.0, data were considered sufficiently normally distributed. If distribution deviated from normality, nonparametric tests were used. In order to decrease skewness before regression analysis, not normally distributed variables were transformed into variables with approximately normal distribution. I applied "log" transformations (lg10) to reduce right skewness and I used inverse/reciprocal and power transformations (x^4) to reduce left skewness.

In order to ensure that figures were not distorted by "outliers" scatterplots and box plots were applied. The strength of correlations between individual/ neighborhood SES and neuropsychological test results and childhood trauma and neuropsychological test results was tested using the Pearson's coefficient or the Spearman's rank-order coefficient, depending on the distribution of the variables.

To examine the association of different psychosocial parameters and the respective outcomes of the neuropsychological tests, ordinal regression models were used with the respective psychosocial parameter (education, income, social support, depression, experience of childhood trauma) as the dependent variable and neuropsychological test parameters (metric) as the independent variable. To account for confounding factors, I used multiple linear regression models with potential confounders such as age, education, income and depression as independent variables and the neuropsychological test parameters as the dependent outcome variables. Instead of using the total family income for statistical analysis, equivalised income, which weights the individual member and allows for a better comparison between incomes in different sized households, was calculated with SPSS according to the definition of the German Federal Statistical Office (44).

As the hypothesis was that neighborhood-level SES could have an influence on individual cognitive function, with women living in higher SES neighborhoods performing better than women living in lower SES, linear mixed models were used to investigate associations between psychosocial parameters and neuropsychological test outcomes (VLMT, TAP) additionally accounting for neighborhoods (as defined by the concept of planning areas for sub-districts in Berlin, see section 2.7). Random intercept models were used for every outcome variable separately. Mixed models allow for an analysis of unbalanced data by using all data available. In order to reduce the impact of skewed data, logarithmized values were used for mixed models.

Because of neuropsychological tests being conducted by three examiners, an ANOVA univariate test analysis was used for comparison of average test results with regard to the different examiners. Missings of individual-level cognitive outcome variables varied between 2.3 and 0.01 percent of the cases (Tables 3.4 and 3.5).

A two-sided significance level of $\alpha=0.05$ was considered. No adjustment for multiple testing was applied.

3 Results

3.1 Psychosocial characteristics of the study population

Sample characteristics of our total of 843 women are shown in Table 3.1. As can be seen in the table, 47.3% of the respondents displayed low (9.5%) to medium (37.8%) levels of education with older women more frequently reporting less years of formal education (112). 50.8% of the women in the study had achieved higher levels of education (general qualification for university entrance, 42.1%). Concerning personal income, 15.3% of the respondents could be classified as poor with an equivalised income of less than 856 euros/month. The rest of the subjects were evenly subdivided into groups of median (27.9%), high (22.9%) and very high income (21.5%). LOR-specific neighborhood SES corresponded to a median level in most of the cases (69.3%).

Concerning social support, 16.0% reported to receive low social support, while 79.0% reported normal to high levels of social support. Mean CTQ scores across all the women were in the none-to-moderate range. Nevertheless, a considerable proportion of respondents scored above the cut-off scores for moderate-to-severe abuse for each dimension. The most common forms of self-reported childhood maltreatment were emotional abuse (15.4%), emotional neglect (15.4%) and physical neglect (14.2%). Mean ratings for current depression were in the normal range (no depression). However, 10.7% of the respondents reported moderate levels of depression and 5.2% had depression in the moderate-extreme range.

Mean values and SDs of cognitive test outcomes in various covariate groups are shown in Tables 3.2, 3.3 and 3.4.

Table 3.1: Sample characteristics.

Sample characteristics	Sample (n=843), Mean ± SD or No. (%)
Cognitive Testing	
German version of the AVLT (VLMT)	
SumR_Dg1_5[1]	54.4 ± 10.1
W_korrdiff[2]	12.9 ± 3.0
TAP[3]	
Alertness Test[4]	0.098 ± 0.1
Go/No-go Test[5]	1.9 ± 2.3 / 428.6 ± 77.2
Executive working memory[6]	2.9 ± 4.3 / 2.4 ± 2.6
Flexibility[7]	2.4 ± 4.1 / 916.9 ± 379.3
Individual-level characteristics	

Sample characteristics	Sample (n=843), Mean ± SD or No. (%)
Age	50.6 ± 14.3
BMI (kg/m^2)	25.3 ± 5.2
Educational attainment	
Lower secondary education	80 (9.5)
Secondary school certificate	319 (37.8)
Qualification for universities of applied sciences	73 (8.7)
General qualification for university entrance	355 (42.1)
Wealth (income per person)	
Poor (<856 EUR/ month)	129 (15.3)
Median (857- 1427 EUR/ month)	235 (27.9)
High income (1428- 2141 EUR/ month)	193 (22.9)
Very high income (more than 2141 EUR/ month)	181 (21.5)
Neighborhood characteristics	
Social status (LOR[8]-specific)	
High	132 (15.7)
Median	584 (69.3)
Low/Very low	126 (14.9)
Vascular factors	
HbA1c levels (%)	5.4 ± 0.6
Systolic blood pressure (mmHg)	125.3 ± 20.7
Smoking, pack-years (n= 181)	19.0 ± 15.4
Psychosocial factors	
Social support score	
Low social support	135 (16.0)
Normal/high social support	666 (79.0)
Current depression (PHQ-Score)	
PHQ total score (0-27)	5.61 ± 4.38
Moderate (cut-off)	90 (10.7)
Moderate to extreme	44 (5.2)
Childhood trauma scores	
CTQ total score (5-125)	35 ± 11.5
Emotional abuse (5-25)	10.2 ± 2.7
Physical abuse (5-25)	6.1 ± 2.7
Sexual abuse (5-25)	5.7 ± 2.3
Emotional neglect (5-25)	9.7 ± 4.7

Sample characteristics	Sample (n=843), Mean ± SD or No. (%)
Physical neglect (5-25)	7.1 ± 2.1
Exposure to abuse	
Emotional abuse (Moderate to extreme/cut-off)	130 (15.4)
Physical abuse (Moderate to extreme/cut-off)	67 (7.9)
Sexual abuse (Moderate to extreme/cut-off)	77 (9.1)
Emotional neglect (Moderate to extreme/cut-off)	130 (15.4)
Physical neglect (Moderate to extreme/cut-off)	120 (14.2)

Notes. AVLT= Auditory Verbal Learning Test, VLMT= "Verbal leaning and memory test" [1] Learning: Sum of scores obtained on the five learning trials. [2] Recognition: Total correct minus false positive errors. [3] Test for Attentional Performance. [4] Index of phasic alertness. [5] Total number of errors/ Median of reaction times. [6] Total number of errors/ Total number of omissions. [7] Total number of errors/ Median of reaction times. [8] "Lebensweltlich orientierte Räume"; 447 planning areas in Berlin.

3.2 Confounding variables

As the aim was to examine the influence of particular psychosocial factors such as individual and neighborhood SES and self-reported experiences of childhood abuse on cognitive performance, it was necessary to control for variables that might have a spurious effect on cognitive outcome measurements. By means of correlation calculation, tests were performed for confounders that affected neuropsychological test outcomes. However, single correlation coefficients and significances are not presented in detail. The major confounder found was age, which had a strong effect on all of the administered cognitive tests. As was to be expected and has been shown in previous studies, older subjects performed significantly poorer compared to the younger ones in all reaction time, memory, and executive function tests. Other important confounding variables were education and income, which were significant in the VLMT test and in TAP executive tests. In order to account for confounding effects on the tested associations between psychosocial factors and the cognitive outcomes in question, adjustments were made for age, education, income and depression in linear regression and mixed model analysis.

3.2.1 The effect of current depression

As previous research has shown a relationship between mood and cognition (e.g. deterioration of memory function with severity of depression (10)), the influence of current depressive symptoms on cognitive performance was also considered. The PHQ-9 (see section 2.6.3 above) served as an instrument to make a tentative diagnosis of depression and to measure its severity. There were no significant effects of current depression on verbal memory (VLMT test), but there was an association between higher levels of self-reported depression and poorer behavioral control

(Go/No-go test): Women with “moderate” depression (cut-off value) made significantly more errors (mean of 2.3) compared to women without symptoms of current depression (mean of 1.7) (Table 3.3). Thus, they showed a reduced ability to perform appropriate reactions and inhibit inappropriate impulses under time pressure. However, this trend of poorer behavioral control with higher levels of depression did not show for moderate to severe levels of depression.

Furthermore, there was a significant relationship between depression and working memory performance with the “minimal“ depression group performing slightly better than the “mild” depression group (Table 3.4). But again this trend did not continue for moderate to severe depression. Since depression showed an influence on some dimensions of cognition, it was adjusted for it in linear mixed model analysis.

3.3 Childhood trauma

The present study provides evidence to support a relationship between self-reported childhood trauma and lower cognitive function in adulthood. Specifically, in adjusted linear regression analysis, three significant associations were found between physical abuse or physical neglect and executive flexibility (Tables 3.2-3.4).

In linear mixed model analysis, there was also a significant relation between physical abuse and poorer working memory performance (Table 3.7). Furthermore, physical neglect exhibited an association with performance in the TAP Go/No-go test (Table 3.6), which nearly reached significance in linear regression analysis (p=0.065) (Table 3.3).

Concerning the other types of childhood trauma (emotional/sexual abuse, emotional neglect), linear regression models showed no significant associations with cognitive performance in VLMT or TAP subtests. Before adjustment for confounders, there were associations between emotional abuse and two VLMT outcome variables (Sum_Dg1_5) (Diff_Dg5_7) (Table 3.2) and between emotional abuse and the TAP working memory test (wm3_err0) in linear regression analysis (Table 3.4). But these were attenuated below significance (p=0.720, p=0.179 and p=0.900) (Tables 3.2 and 3.4) after adjustment for age, education and income.

In summary, neither emotional or sexual abuse nor emotional neglect was significantly associated with cognitive performance, while physical neglect and abuse were related to deficits in executive cognitive function.

3.3.1 Verbal learning memory

Declarative verbal memory abilities were assessed by means of the VLMT. However, adjusted linear regression models revealed no associations between CTQ and VLMT scores. Even though there was a statistically significant trend for poorer total learning scores with higher levels of emotional and physical abuse and physical neglect (Table 3.2), this association lost significance after adjustment for age, education and income. Thus, no significant effect of childhood trauma scores on short- and long-term verbal memory could be confirmed.

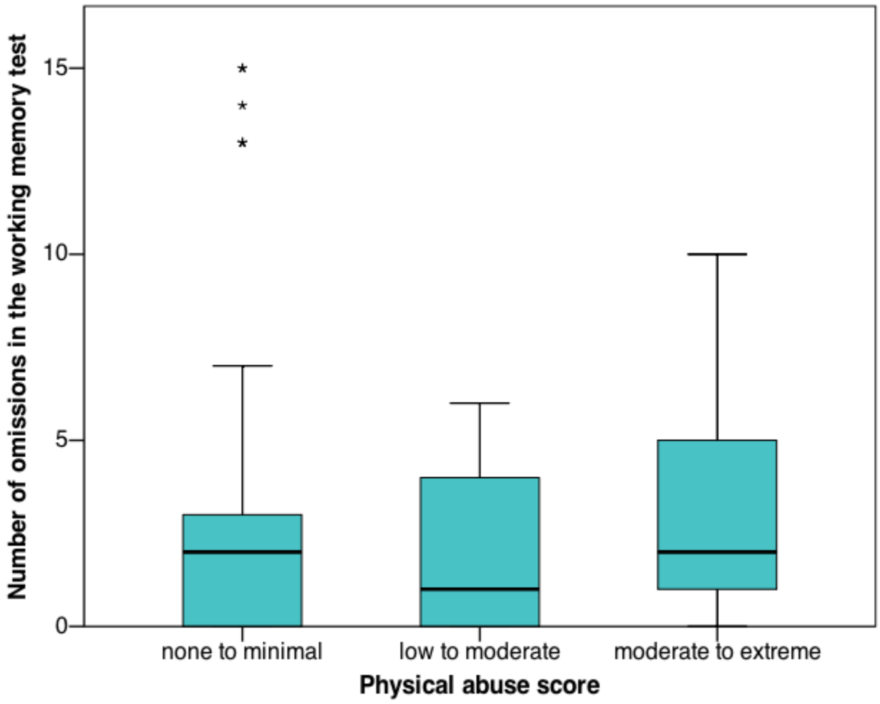

Figure 3.1: Association of physical abuse with TAP working memory performance, moderate to severe“ as cut-off score for physical abuse.

3.3.2 Working memory

Concerning short-term working memory (measured by the TAP working memory test), there was an association between physical abuse in childhood and poorer performance on the working memory task (Figure 3.1). While women with none to moderate experience of physical abuse had a mean of 2.3 or 2 omission errors in the TAP working memory test, the group of respondents who reported moderate to extreme physical abuse (cut-off value) had a mean of 3.5 omission errors (Table 3.4). This association retained significance in adjusted mixed models. In linear regression analysis after adjustment for age, education and income it showed a statistical trend, nearly reaching significance (p=0.078). The relation between higher physical abuse and poorer working memory performance supports the assumption that physical abuse in childhood might be related to cognitive deficits in adulthood.

3.3.3 Flexibility

Cognitive flexibility as component of executive functioning was measured by the TAP flexibility test. Concerning physical neglect, women with moderate to extreme experiences of physical neglect made significantly more errors in the flexibility test (mean value of errors being 3.5 in the "moderate to extreme" group compared to 1.9 in the "none to minimal" group, p=0.031, Table 3.4). The boxplot in Figure 3.2 shows that the group of women with "moderate to extreme" physical neglect has a 1-point higher median error score compared to the groups of women, who scored below the cut-off value for physical neglect. Median reaction times in the flexibility test were approximately 110 milliseconds longer for "moderate to extreme" physical neglect than they were for "none to minimal" physical neglect (Table 3.4). Flexibility was poorer with higher exposure to physical neglect. This trend is also indicated by the boxplot in Figure 3.3.

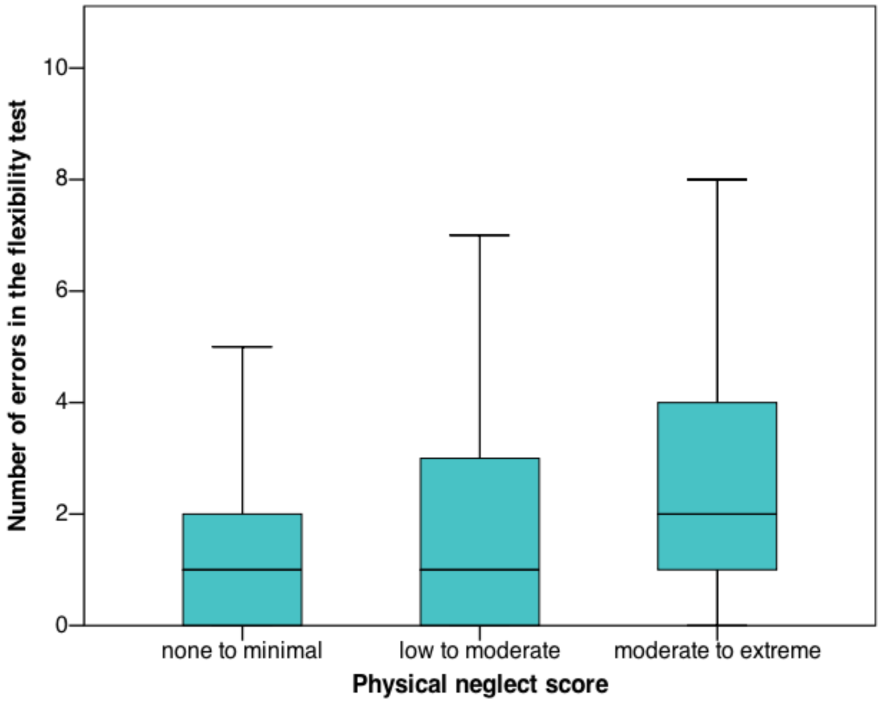

Figure 3.2: Association of physical neglect with TAP flexibility performance (number of errors), comparison of groups: "moderate to extreme" as cut-off value for physical neglect.

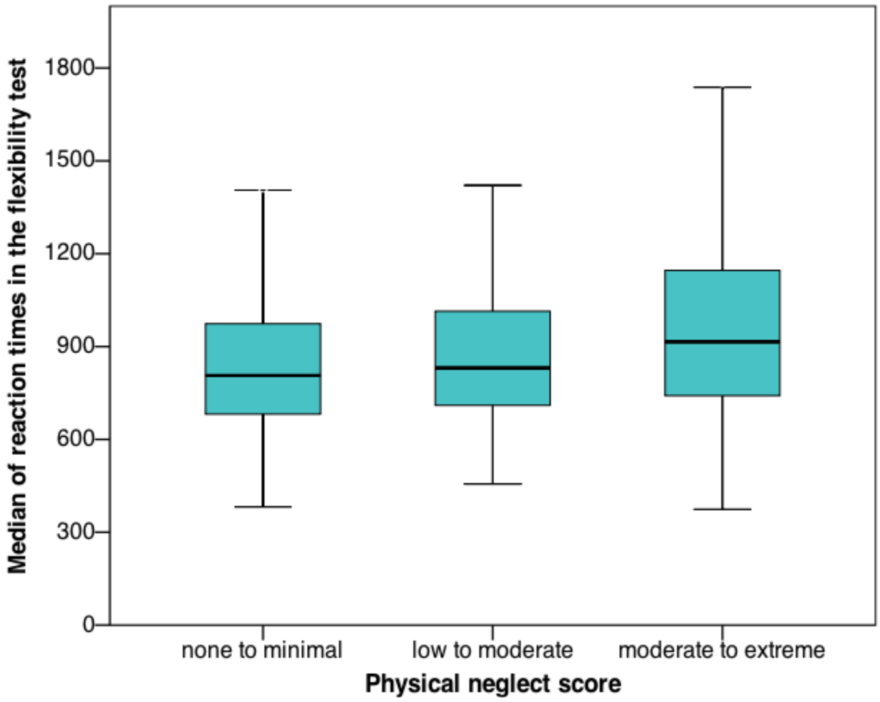

Figure 3.3: Association of physical neglect with TAP flexibility performance (median of reaction times), “moderate to extreme” as cut-off value for physical neglect.

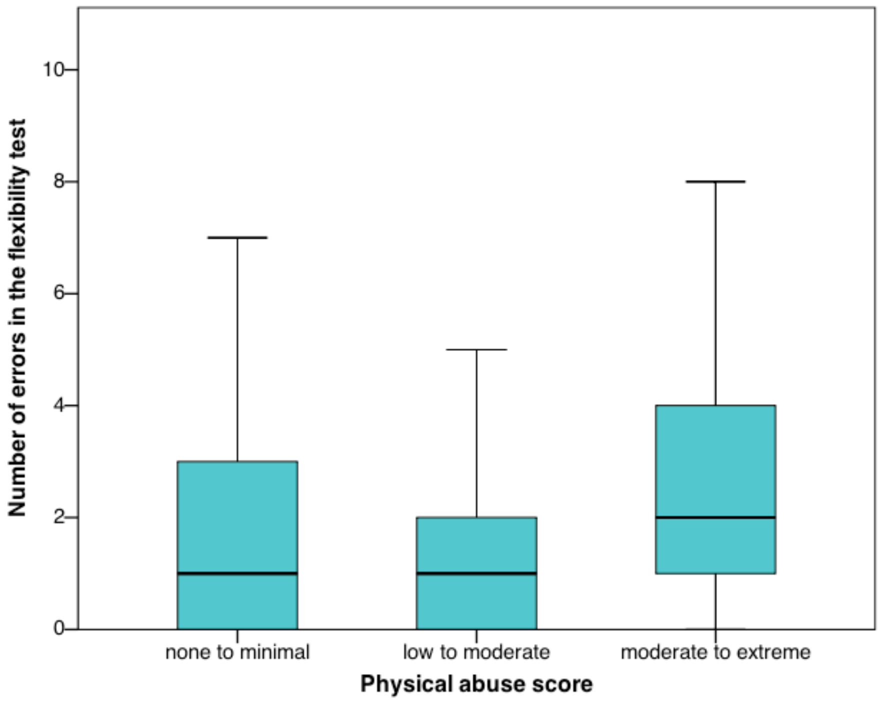

Figure 3.4: Association of physical abuse with TAP flexibility performance (number of errors), “moderate to extreme” as cut-off value for physical abuse.

Furthermore, higher physical abuse scores also exhibited an association with poorer cognitive flexibility. The mean value of errors made by the “moderate to extreme” group was 3.3 (Table 3.4) compared to 2.3 or 1.5 in the two groups of respondents who reported none to moderate physical abuse. In conclusion, physical neglect and abuse were found to be related to poorer flexibility performance, suggesting that they might have an adverse effect on the development of cognitive flexibility leading to altered functions in adulthood.

3.3.4 Behavioral control

The Go/No-go test served as a measure of the subject's capacity for response control and sustained attention. Here, subjects with experience of physical neglect showed a trend towards more errors compared to women without such experience. This is illustrated in Figure 3.5.

While women who reported none to moderate forms of physical neglect had a mean of 1.7 to 2.1 errors per trial, women who had experienced moderate to extreme physical neglect had a mean of 2.5 errors (Table 3.3). In mixed model analysis, the difference between the low-to-moderate and the moderate-to-extreme group reached significance ($p<0.05$) (Table 3.6). Equally, in adjusted linear regression analysis, the association between physical neglect and Go/No-go performance showed a statistical trend towards poorer performance, with higher levels of physical neglect in childhood nearly reaching significance ($p=0.065$). Thus, results suggest an association between higher childhood trauma scores and less behavioral control.

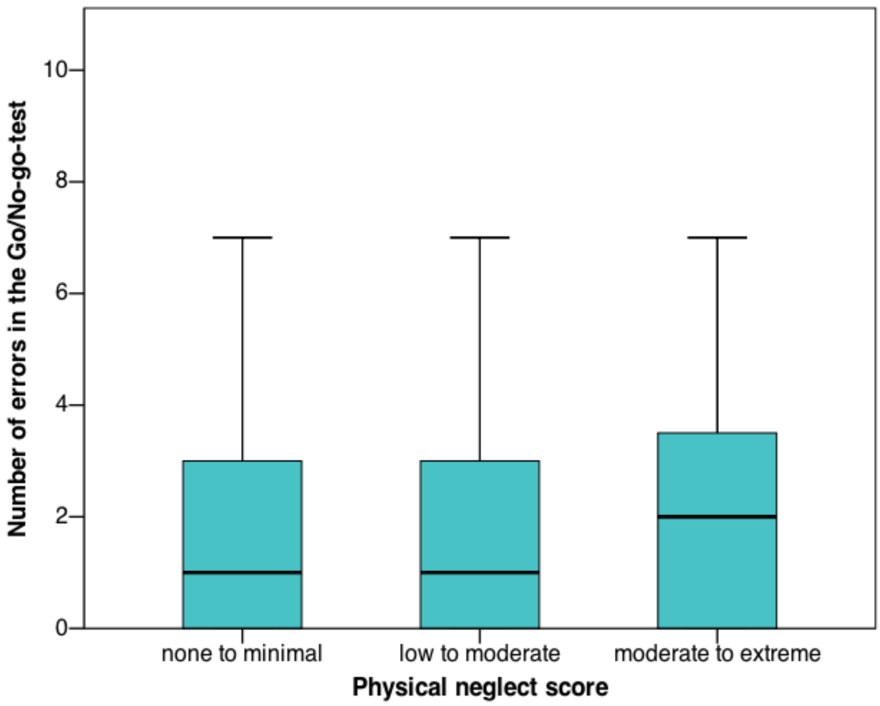

Figure 3.5: Association of physical neglect with TAP Go/No-go performance (number of errors), "moderate to extreme" as cut-off value for physical neglect.

Table 3.2: Descriptive statistics and linear regression analysis of the association between psychosocial factors and the VLMT outcome variables.
Notes. [1]p-value after adjustment for confounders (age, education, income) in ordinal regression analysis.

	n	**SumR_Dg1 _5** n=826 skewness= - 0.5 Mean ± SD	**p**	**n**	**Diff_Dg5_7** n=826 skewness =0.8) Mean ± SD	**p**	**n**	**W_korrDiff** n=826 skewness =- 2.4 Median (IQR) (Mean)	**p**
Educational attainment			**<0.001**			0.301[1]			**0.018[1]**
Lower secondary education	80	49.3 (11.1)		80	1.64 (2.1)		80	13 (11-15) (12.1)	
Secondary school certificate	318	52.1 (10.1)		318	1.67 (1.9)		318	14 (11-15) (12.3)	
Qualification for universities of applied sciences	73	55.2 (9.0)		73	1.21 (1.7)		73	14 (12-15) (13.2)	
General qualifica-tion for university entrance	355	57.8 (8.8)		355	1.12 (1.8)		355	14 (13-15) (13.6)	
Equivalised in-come			**0.057[1]**			0.212[1]			**0.006[1]**
Poor (<856 EUR/ month)	128	54.7 (10.7)		128	1.15 (2.0)		128	14 (12-15) (12.8)	
Median (857-1427 EUR/ month)	235	52.5 (10.8)		235	1.65 (2.0)		235	14 (11-15) (12.5)	
High income (1428- 2141 EUR/ month)	193	55.2 (9.5)		193	1.40 (1.8)		193	14 (13-15) (13.2)	
Very high income (more than 2141 EUR/ month)	181	55.9 (8.5)		181	1.20 (1.7)		181	14 (13-15) (13.3)	
ENRICHD social support instru-ment			0.189[1]			0.435			0.222
Low social sup-port	96	52.5 (10.2)		96	1.53 (1.7)		96	14 (12-15) (12.6)	
Normal/high social support	721	54.9 (10.0)		721	1.37 (1.9)		721	14 (12-15) (13.0)	
Childhood trau-ma scores									
Emotional abuse			0.720[1]			0.179[1]			0.089
None to minimal	182	53.0 (9.7)		182	1.6 (1.8)		182	14 (12-15) (12.6)	
Low to moderate	483	55.4 (9.9)		483	1.3 (1.9)		483	14 (12-15) (13.1)	
Moderate to ex-treme	130	55.1 (10.2)		130	1.0 (1.7)		130	14 (13-15) (13.1)	
Physical abuse			0.173[1]			0.625			0.067
None to minimal	699	55.0 (9.9)		699	1.4 (1.8)		699	14 (12-15) (13.0)	
Low to moderate	46	54.1		46	1.4 (1.8)		46	14 (12-15)	

	n		p	n		p	n		p
		(11.0)						(12.8)	
Moderate to extreme	67	51.9 (10.6)		67	1.2 (2.0)		67	13 (11-15) (11.3)	
Sexual abuse			0.321			0.463			0.849
None to minimal	677	54.7 (10.0)		677	1.4 (1.8)		677	14 (12-15) (13.0)	
Low to moderate	59	53.6 (10.4)		59	1.3 (1.9)		59	14 (12-15) (12.7)	
Moderate to extreme	77	53.8 (10.3)		77	1.2 (1.8)		77	14 (12.5-15) (13.1)	
Emotional neglect			0.272			0.725			0.429
None to minimal	471	55.2 (9.9)		471	1.3 (1.8)		471	14 (12-15) (13.0)	
Low to moderate	191	54.8 (9.9)		191	1.3 (1.8)		191	14 (12-15) (13.0)	
Moderate to extreme	130	54.1 (9.8)		130	1.4 (2.0)		130	14 (12-15) (12.8)	
Physical neglect			0.631[1]			0.106			0.076
None to minimal	544	55.4 (9.6)		544	1.3 (1.8)		544	14 (12-15) (13.1)	
Low to moderate	143	54.4 (10.6)		143	1.6 (1.9)		143	14 (12-15) (12.9)	
Moderate to extreme	120	52.1 (10.5)		120	1.5 (2.0)		120	14 (12-15) (12.4)	
Current depression (PHQ)			0.600			0.441			0.650
Minimal	343	54.6 (10.0)		343	1.4 (1.9)		343	14 (12-15) (13.0)	
Mild	265	54.9 (10.3)		265	1.4 (1.8)		265	14 (12-15) (12.9)	
Moderate	90	55.4 (9.7)		90	1.4 (1.8)		90	14 (12-15) (12.9)	
Moderately severe to severe	44	54.5 (9.8)		44	1.2 (2.0)		36	13.5 (13-14) (13.1)	

Table 3.3: Descriptive statistics and linear regression analysis of the association between psychosocial factors and TAP outcomes for the Alertness and Go/No-go test.
Notes. [1]p-value after adjustment for confounders (age, education, income) in ordinal regression analysis.

	n	**TAP alertness** (al_ex0) n=840 skewness =-0.514 Mean (SD)	p	n	**TAP go/no-go** (go2_err0) n=840 skewness= 2.17 transformed variable: go2_err0log Median (IQR) (Mean)	p	n	**TAP go/no-go** (go1_mdn0) n=840 skewness=0.646 Mean (SD)	p
Educational attainment			0.053[1]			**0.039[1]**			0.093[1]
Lower secondary education	80	0.038 (0.10)		80	1 (0-3) (2.2)		80	433.4 (82.3)	

Secondary school certificate	319	0.016 (0.09)		317	1 (0-3) (2.1)		317	428.1 (78.2)	
Qualification for universities of applied sciences	73	0.007 (0.80)		73	1 (0-4) (2.5)		73	425 (78.4)	
General qualification for university entrance	352	-0.002 (0.09)		353	1 (0-2) (1.6)		353	426.5 (74.4)	
Equivalised income			0.756[1]			0.159[1]			0.760[1]
Poor (<856 EUR/ month)	125	0.054 (0.10)		129	1 (0-3) (2.3)		129	422.7 (73.1)	
Median (857- 1427 EUR/ month)	235	0.010 (0.10)		235	1 (0-3) (2.1)		235	429.6 (75.7)	
High income (1428-2141 EUR/ month)	192	0.014 (0.09)		191	1 (0-3) (1.7)		191	431.3 (80.6)	
Very high income (more than 2141 EUR/ month)	180	0.005 (0.09)		180	1 (0-3) (1.7)		180	424.3 (79.5)	
ENRICHD social support instrument			0.527			0.070			0.455
Low social support	96	0.014 (0.09)		96	2 (0-3) (2.3)		96	433.8 (79.4)	
Normal/high social support	719	0.008 (0.09)		719	1 (0-3) (1.9)		719	426.85 (78.4)	
Childhood trauma scores			0.765			0.224			0.410
Emotional abuse									
None to minimal	181	0.014 (0.10)		181	1 (0-3) (2.2)		181	420.8 (78.7)	
Low to moderate	482	0.008 (0.09)		481	1 (0-3) (1.8)		481	430.9 (80.0)	
Moderate to extreme	130	0.012 (0.11)		130	1 (0-3) (1.9)		130	425.8 (73.1)	
Physical abuse			0.607			0.126			0.335
None to minimal	697	0.010 (0.09)		696	1 (0-3) (1.9)		696	429.1 (77.7)	
Low to moderate	46	0.028 (0.08)		46	1 (0-3) (2.1)		46	423.3 (63.1)	
Moderate to extreme	67	0.007 (0.12)		67	2 (0-3) (2.2)		67	420.2 (69.8)	
Sexual abuse			0.268			0.158			0.479
None to minimal	675	0.012 (0.09)		674	1 (0-3) (2.0)		674	427.0 (78.1)	
Low to moderate	59	-0.012 (0.09)		59	1 (0-3) (1.7)		59	429.4 (73.5)	
Moderate to extreme	77	0.012 (0.11)		77	1 (0-3) (1.7)		77	435.2 (73.2)	
Emotional neglect			0.383			0.157			0.234
None to minimal	471	0.014 (0.88)		471	1 (0-3) (1.8)		471	430.6 (78.5)	
Low to moderate	189	-0.001 (0.10)		188	1 (0-3) (2.0)		188	422.0 (73.5)	

Moderate to extreme	130	0.014 (0.10)		130	2 (0-3) (2.2)		130	424.0 (75.1)	
Physical neglect			0.840			0.065[1]			0.661
None to minimal	542	0.011 (0.09)		541	1 (0-3) (1.7)		541	427.1 (76.5)	
Low to moderate	143	0.008 (0.08)		143	1 (0-3) (2.1)		143	429.3 (79.4)	
Moderate to extreme	75	0.009 (0.13)		120	2 (0-3.8) (2.5)		120	430.5 (79.3)	
Current depression (PHQ)			0.793			**0.004[1]**			0.125[1]
Minimal	342	0.012 (0.10)		341	1 (0-3) (1.7)		341	437.3 (85.3)	
Mild	264	0.009 (0.09)		263	1 (0-3) (2.0)		263	418.0 (80.0)	
Moderate	90	0.016 (0.89)		90	2 (0-3) (2.3)		90	426.0 (78.2)	
Moderately severe to severe	44	0.019 (0.08)		44	1 (0-2) (1.7)		44	415.6 (63.8)	

Table 3.4: Descriptive statistics and linear regression analysis of the association between psychosocial factors and TAP outcomes for the working memory and flexibility test.
Notes. [1]p-value after adjustment for confounders (age, education, income) in ordinal regression analysis.

	n	**TAP working memory** (wm3_omi0) n=824 skewness=1.59 transformed variable: **wm3_omi0log** Median (IQR) (Mean)	p	n	**TAP working memory** (wm3_err0) n=824 skewness=3.60 transformed variable: **wm3_err0log** Median (IQR) (Mean)	p	n	**TAP flexibility** (fn3_err4) n= 837 skewness= 3.78 transformed variable: fn3_err4log Median (IQR) (Mean)	p	n	**TAP flexibility** (fn3_mdn4) n=837 skewness= 3.48 transformed variable: fn3_mdn4_trans Median (IQR) (Mean)	p
Educational attainment			**0.017[1]**			**<0.001[1]**			**0.001[1]**			**<0.001[1]**
Lower secondary education	78	3 (1-6) (3.7)		78	2 (0.8-5.3) (4.1)		80	2 (0-7) (5.2)		80	1004 (833-1399.25) (1219.6)	
Secondary school certificate	310	2 (1-4) (2.8)		310	2 (1-5) (3.8)		315	1 (0-3) (2.7)		315	863 (745.5-1053) (946.7)	
Qualification for universities of applied sciences	67	2 (1-4) (2.9)		67	2 (1-3) (2.9)		72	1 (0-3) (1.7)		72	866.5 (764.75-1027.88) (937.5)	
General	353	1 (0-2.5)		353	1 (0-3)		354	1 (0-2)		354	755.5 (644.5-	

qualification for university entrance		(1.8)			(1.8)			(1.5)			916) (813.0)	
Equivalised income			**<0.001**[1]			0.281[1]			**<0.001**[1]			**<0.001**[1]
Poor (<856 EUR/ month)	125	2 (1-3.5) (2.7)		125	2 (0-4) (3.0)		128	1 (0-3.75) (3.2)		128	818.5 (680.1-1052.9) (972.5)	
Median (857- 1427 EUR/ month)	231	2 (1-4) (2.8)		231	2 (1-4) (3.1)		232	1 (0-3) (3.0)		232	873.5 (728.6-1092) (966.9)	
High income (1428- 2141 EUR/ month)	189	2 (0-4) (2.3)		189	1 (0-4) (2.8)		192	1 (0-3) (2.0)		192	785.5 (678-957) (866.0)	
Very high income (more than 2141 EUR/ month)	179	1 (0-2) (1.7)		179	1 (0-3) (2.2)		181	1 (0-2) (1.4)		181	806.5 (684.5-974) (872.9)	
ENRICHD social support instrument			0.257			0.457			0.839			0.250
Low social support	95	2 (1-3) (2.5)		95	2 (1-4) (3.0)		94	1 (0-3) (2.1)		94	846.3 (729.9-1026.3) (948.8)	
Normal/high social support	706	2 (0-4) (2.4)		706	2 (0-3) (2.8)		718	1 (0-3) (2.3)		718	820.3(692.6-995.5) (908.4)	
Childhood trauma scores			0.781			0.900[1]			0.378			0.212
Emotional abuse												
None to minimal	178	2 (1-4) (2.4)		178	2 (1-4) (3.4)		180	1 (0-3) (2.7)		180	846.8 (728.9-980.3) (934.0)	
Low to moderate	475	2 (0-3) (2.4)		475	1 (0-3) (2.6)		481	1 (0-3) (2.1)		481	815 (679-997) (905.6)	
Moderate to extreme	126	1 (1-4) (2.4)		126	1 (0-3) (2.4)		129	1 (0-3) (2.3)		129	815 (688-1014.5) (855.1)	
Physical abuse			0.078[1]			0.567			**0.043**[1]			0.472
None to minimal	684	2 (0-3) (2.3)		682	1 (0-3.8) (2.8)		694	1 (0-3) (2.3)		694	825.5 (693-992.8) (912.9)	
Low to moderate	45	1 (0-4)(2.0)		45	2 (1-3.5) (2.4)		46	1 (0-2) (1.5)		46	817.5 (711.8-975) (874.2)	
Moderate to extreme	65	2 (1-5) (3.5)		65	1 (1-4) (3.3)		35	2 (1-4) (3.3)		67	874 (721.5-1095) (949.4)	
Sexual abuse			0.316			0.439			0.613			0.367
None to minimal	663	2 (0-4) (2.4)		663	2 (1-4) (2.9)		673	1 (0-3) (2.5)		673	831.3 (702.5-998.0) (922.0)	
Low to moderate	57	1 (0-3) (1.8)		57	1 (0-4) (2.4)		58	1 (0-3) (1.9)		58	792.8 (659.0-914.1) (809.3)	
Moderate to	75	2 (1-5)		75	1 (0-4)		77	1 (0-3)		77	840 (727.5-	

extreme		(3.1)			(2.9)			(2.0)			1072) (936.9)	
Emotional neglect			0.186			0.637			0.115			0.143
None to minimal	463	1 (0-3) (2.3)		463	1 (0-4) (2.8)		470	1 (0-3) (2.2)		470	806 (689.9-980.3) (898.5)	
Low to moderate	184	2 (0-4) (2.4)		184	1 (0-3) (2.5)		188	1 (0-3) (2.3)		188	840.5 (697.5-1013.6) (914.4)	
Moderate to extreme	127	2 (0-3) (2.6)		127	2 (1-3) (2.8)		129	1 (0-3) (2.4)		129	793.8 (665.3-887.5) (939.1)	
Physical neglect			0.450[1]			0.458[1]			**0.031**[1]			**0.015**[1]
None to minimal	534	1 (0-3) (2.2)		534	1 (0-3) (2.5)		541	1 (0-2) (1.9)		541	806.5 (681.5-974.5) (874.7)	
Low to moderate	142	2 (1-4) (2.6)		142	2 (0-4) (3.4)		141	1 (0-3) (2.8)		141	831 (709.8-1017.8) (935.5)	
Moderate to extreme	113	2 (1-5) (3.2)		113	2 (1-4) (3.2)		120	2 (1-4) (3.5)		75	915.5 (741.3-1148) (1046.3)	
Current depression (PHQ)			0.454			**0.001**[1]			0.315			0.060
Minimal	334	1 (0-3) (2.4)		334	1 (0-3) (2.5)		340	1 (0-3) (2.3)		340	836.5 (710.3-1007.9) (928.6)	
Mild	261	2 (1-4) (2.5)		261	2 (1-4) (3.4)		263	1 (0-2) (2.4)		263	805.5 (679-978) (898.0)	
Moderate	89	2 (0-4) (2.4)		89	1 (0-3) (2.4)		89	1 (0-3) (2.3)		89	799 (674.3-998) (890.1)	
Moderately severe to severe	43	1 (0-2) (1.9)		43	2 (1-4) (3.1)		44	2 (0-3) (2.5)		44	800 (652.5-975.6) (854.4)	

Table 3.5: Linear mixed model analysis (VLMT variables) with regard to the identification of neighborhood influences.
The coefficients [Beta (SE)] of linear mixed models for every outcome group separately (random intercept models)
* p<0.05; **p<0.01; ***p<0.001

VLMT Outcomes	**Sum_Dg1_5**	**Diff_Dg5_7**	**w_korrDiff** (log-transformed)
	n= 59 neighborhood groups/ 724 women	n= 59 neighborhood groups/ 779 women	n= 59 neighborhood groups/ 724 women
Fixed effects	**Beta (SE)**	**Beta (SE)**	**Beta (SE)**
Intercept	52.27 (1.37)***	1.08 (0.29)***	36.14 (2.42)***
Neighborhood SES Very low/ low social status	reference	reference	reference
Median	-0.06 (0.95)	0.25 (0.19)	-0.83 (1.68)

High social status	-1.03 (1.27)	0.39 (0.24)	-2.00 (2.25)
age in decades	-3.01 (0.24)***	0.32 (0.05)***	-4.5 (0.43)***
Educational attainment			
Lower secondary education	reference	reference	reference
Secondary school certificate	0.78 (1.20)	0.32 (0.24)	-2.69 (2.12)
Qualification for universities of applied sciences	3.90 (1.55)*	-0.11 (0.30)	2.18 (2.72)
General qualification for university entrance	4.14 (1.25)**	0.07 (0.24)	0.43 (2.20)
Income (in 1000€)	0.79 (0.40)*		1.73 (0.70)*
Emotional abuse score	--		--
None to minimal	--	reference	--
Low to moderate	--	-0.12 (0.15)	--
Moderate to extreme	--	-0.38 (0.21)	--
Random effects			
Variance between groups	1.42 (0.50)*	0.18 (0.13)*	2.64 (0.87)*
Residual variance	8.49 (0.24)*	1.74 (0.05)*	14.94 (0.41)*

Table 3.6: Linear mixed model analysis (TAP alertness and go/no-go-variables) with regard to the identification of neighborhood influences.
The coefficients [Beta (SE)] of linear mixed models for every outcome group separately (random intercept models).
* p<0.05; **p<0.01; ***p<0.001

TAP **Outcomes** (part 1)	**al_ex0**	**go2_err0** (log-transformed)	**go1_mdn0**
	n= 59 neighborhood groups/ 823 women	n= 59 neighborhood groups/ 628 women	n= 59 neighborhood groups/ 724 women
Fixed effects	**Beta (SE)**	**Beta (SE)**	**Beta (SE)**
Intercept	1.22^{-8}(3.29^{-8})	0.34 (0.05)	433.43 (11.93)
Neighborhood SES			
Very low/ low social status	reference	reference	reference
Median	0.01 (0.01)	-0.02 (0.03)	-7.38 (8.07)
High social status	0.01 (0.01)	0.03 (0.04)	-8.49 (10.43)
Age in decades	0.01 (0.002)*	0.03 (0.01)***	11.80 (2.15)***
Educational attainment			
Lower secondary education	reference	reference	reference
Secondary school certificate	-0.02 (0.01)	-0.03 (0.04)	4.53 (10.38)
Qualification for universities of applied sciences	-0.03 (0.02)	0.05 (0.06)	-3.25 (13.44)
General qualification for university entrance	-0.03 (0.01)**	-0.04 (0.05)	11.82 (10.67)
Income (in 1000€)	--	-0.02 (0.01)	--

Physical neglect score			
None to minimal	--	reference	--
Low to moderate	--	0.02 (0.03)	--
Moderate to extreme	--	0.08 (0.03)*	--
Current depression (PHQ)			
Minimal	--	reference	reference
Mild	--	0.06 (0.03)*	-16.35 (6.38)*
Moderate	--	0.13 (0.04)***	-4.55 (9.16)
Moderately severe to severe	--	0.02 (0.05)	-12.49 (12.56)
Random effects			
Variance between groups	1.22^{-8}(3.29^{-8})*	0.04 (0.02)*	1.95^{-11} (5.54^{-11})*
Residual variance	0.09 (0.02)*	0.29 (0.01)*	76.08 (2.00)*

Table 3.7: Linear mixed model analysis (TAP working memory and flexibility variables) with regard to the identification of neighborhood influences.
The coefficients [Beta (SE)] of linear mixed models for every outcome group separately (random intercept models).
* p<0.05; **p<0.01; ***p<0.001

TAP Outcomes (part 2)	**wm3_omi0** (log-transformed) n= 59 neighbor-hood groups/ 68 women	**wm3_err0** (log-transformed) n= 59 neighbor-hood groups/ 708 women	**fn3_err4** (log-transformed) n= 59 neighbor-hood groups/ 775 women	**fn3_mdn4** (transformed) n= 59 neighborhood groups/ 692 women
Fixed effects	**Beta (SE)**	**Beta (SE)**	**Beta (SE)**	**Beta (SE)**
Intercept	0.52 (0.05)	0.41 (0.05)	0.47 (0.05)	1.99 (0.01)
Neighborhood SES				
Very low/ low social status	reference	reference	reference	reference
Median	-0.03 (0.03)	-0.02 (0.03)	-0.03 (0.03)	-0.001 (0.01)
High social status	-0.01 (0.04)	-0.004 (0.04)	-0.04 (0.04)	0.0003 (0.01)
Age in decades	0.06 (0.01)***	0.07 (0.01)***	0.04 (0.01)***	0.02 (0.002)*
Educational attainment				
Lower secondary education	reference	reference	reference	reference
Secondary school certificate	-0.06 (0.04)	0.03 (0.04)	-0.08 (0.04)	-0.02 (0.01)**
Qualification for universities of applied sciences	-0.06 (0.06)	-0.01 (0.06)	-0.18 (0.06)*	-0.02 (0.01)*
General qualification for university entrance	-0.13 (0.04)*	-0.08 (0.05)	-0.16 (0.05)***	-0.03 (0.01)***
Income (in 1000€)	-0.04 (0.01)*	--	--	-0.005 (0.002)*

Physical abuse score				
None to minimal	reference	--	reference	--
Low to moderate	-0.04 (0.05)	--	-0.03 (0.05)	--
Moderate to ex-treme	0.10 (0.04)*	--	0.08 (0.05)	--
Physical neglect score				
None to minimal	--	--	reference	reference
Low to moderate	--	--	0.04 (0.03)	0.001 (0.01)
Moderate to ex-treme	--	--	0.10 (0.04)**	0.01 (0.01)*
Current depres-sion (PHQ)				
Minimal	--	reference	--	--
Mild	--	0.10 (0.03)***	--	--
Moderate	--	0.03 (0.04)	--	--
Moderately severe to severe	--	0.11 (0.05)*	--	--
Random effects				
Variance between groups	0.04 (0.02)*	4.57^{-8} (1.28^{-7})*	6.13^{-12} (1.63^{-11})*	1.97^{-8} (3^{-5})*
Residual variance	0.29 (0.01)*	0.32 (0.01)*	0.33 (0.01)*	0.05 (0.001)*

3.4 Individual-level socio-economic status: Education and income

As expected, higher educational attainment was related to better performance on different dimensions of cognitive tests (Figure 3.6). After adjustment for age and equivalised income, linear regression analysis revealed a significant association between educational attainment and the outcome variables “total learning score” (SumR_Dg1_5) and “corrected recognition score” (W_korrDiff) from the VLMT. Concerning the “total learning score”, respondents with higher education had higher scores (SumR_Dg1_5) (Table 3.2). The mean total learning score was between 49.3 (lower secondary education, SD=11.1) and 52.1 (secondary school certificate, SD 10.1) for women with lower levels of education and between 55.2 (SD 9.0) and 57.8 (SD 8.8) for women with greater educational attainment (Table 3.2).

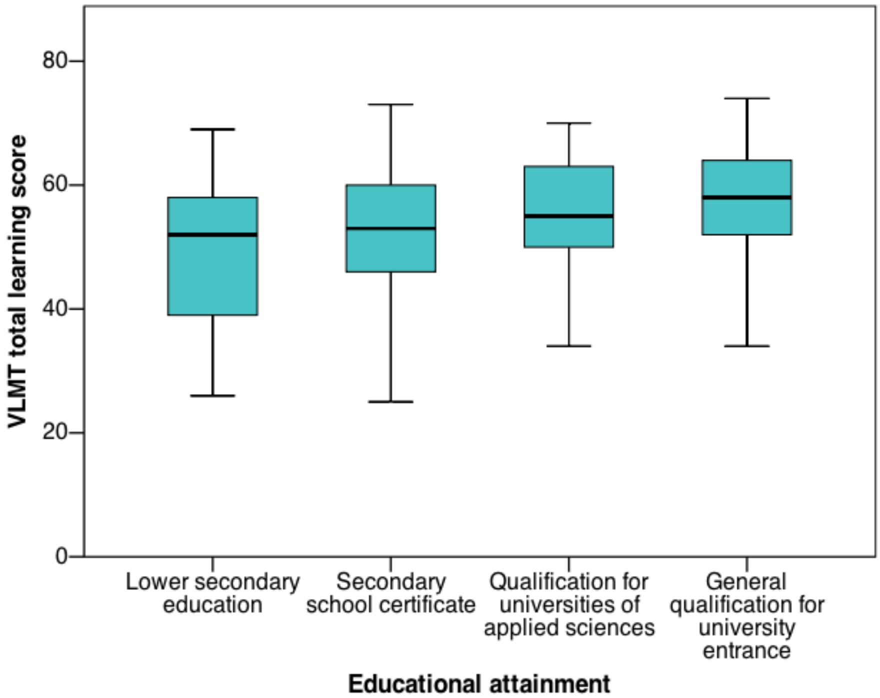

Figure 3.6: Comparison of education groups based on the VLMT total learning score.

Referring to the "corrected recognition score", subjects with higher levels of education yielded higher corrected recognition scores compared to women with lower levels of education (mean score of 12.1 in the lowest education group compared to a mean score of 13.6 in the highest education group) (Table 3.2) (Figure 3.7).

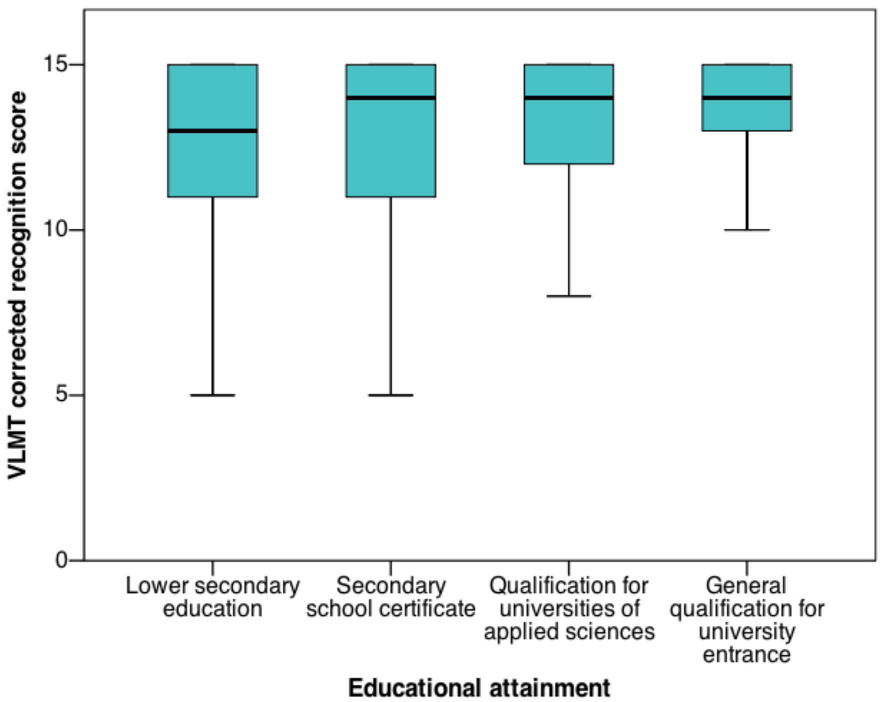

Figure 3.7: Comparison of education groups based on the VLMT corrected recognition score.

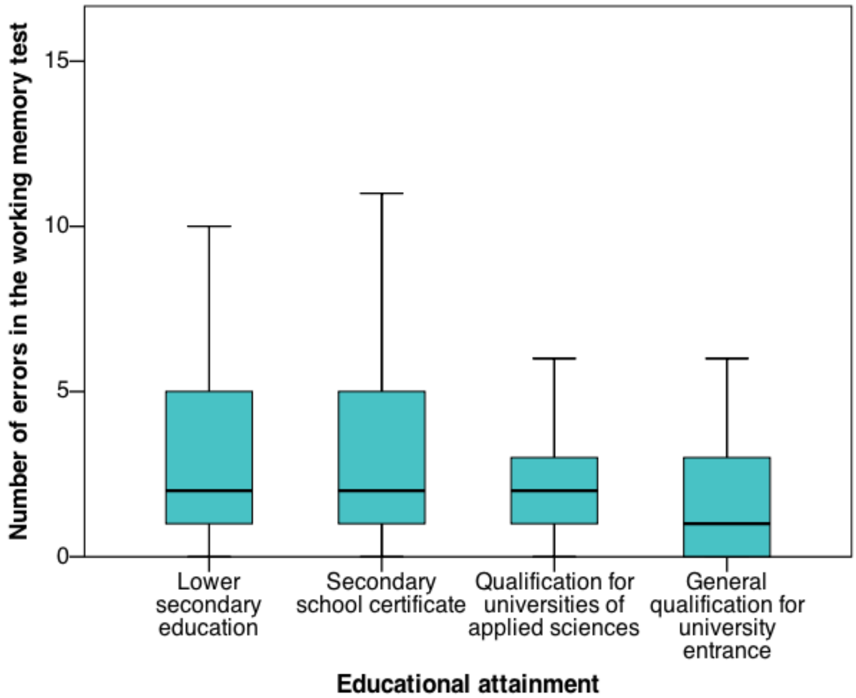

Figure 3.8: Comparison of education groups based on the number of errors in the working memory test.

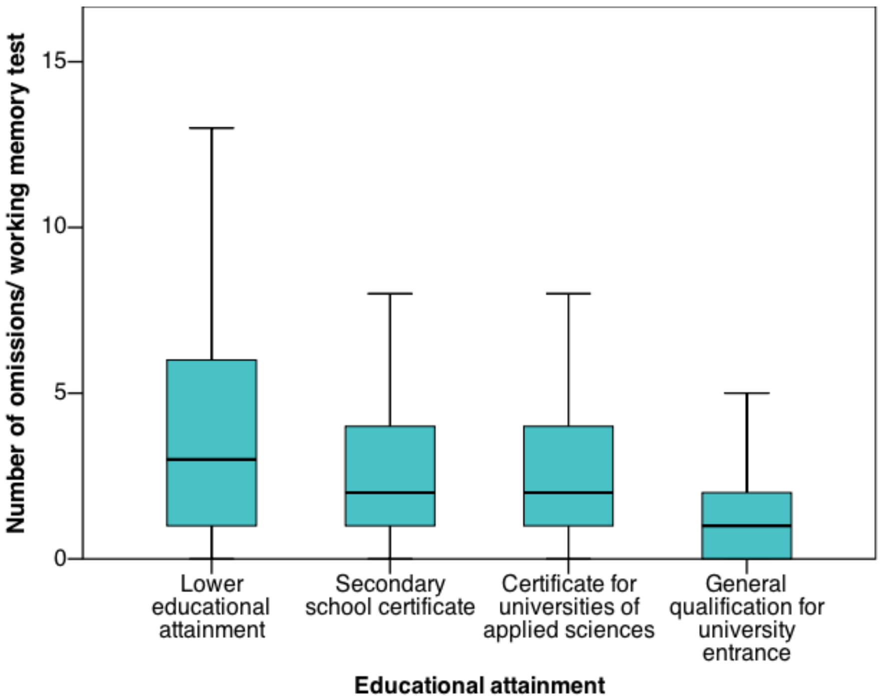

Figure 3.9: Comparison of education groups based on the number of omissions in the working memory test.

Concerning TAP outcomes, significant associations between higher education and enhanced cognition scores were found in three of the four administered tests (Go/No-go (go2_err0), working memory (wm3_omi0) and flexibility test (fn3_mdn4; fn3_err4)) (Tables 3.3 and 3.4). In the working memory test, better-educated women obtained more correct responses and made significantly less omissions (Figures 3.8 and 3.9). Compared to a median of three omissions (mean 3.7) in the lower secondary education group, there was only a median of one omission (mean 1.8) in the group with the highest educational attainment (Figure 3.9) (Table 3.4).

Considering the flexibility test, higher education was associated with less errors and shorter reaction times (Table 3.4) (Figures 3.10 and 3.11). Being in the low-education group was associated with on average 400 milliseconds longer reaction times compared to women in the high education group (Table 3.4).

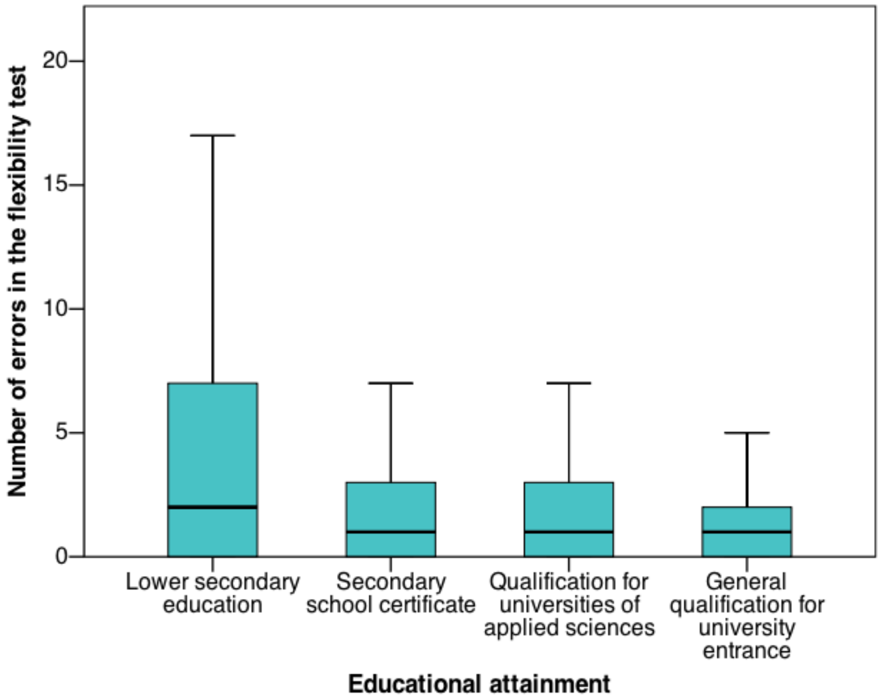

Figure 3.10: Comparison of education groups based on the number of errors in the flexibility test.

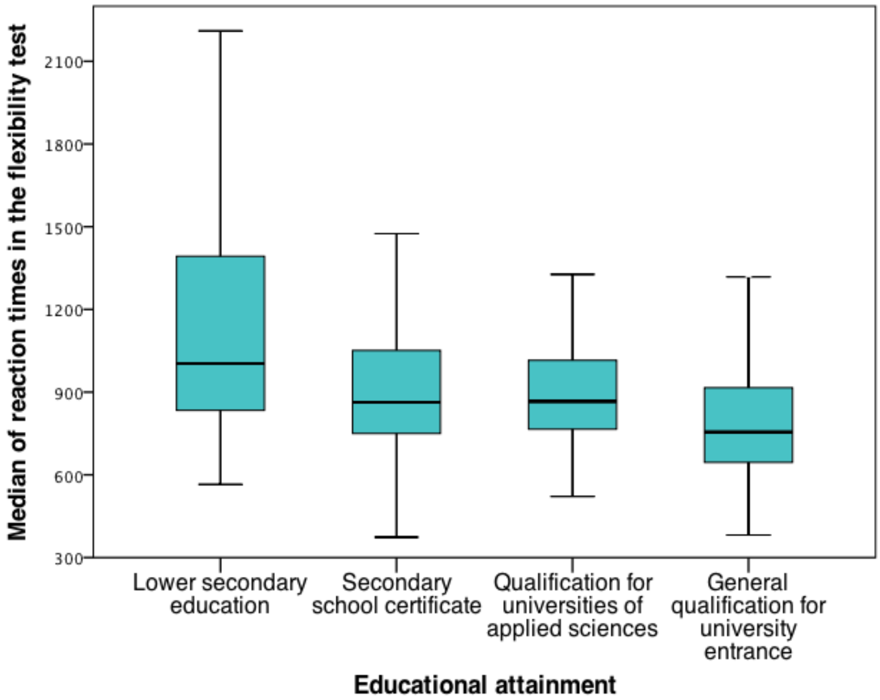

Figure 3.11: Comparison of education groups based on the median of reaction times in the flexibility test.

Also, the results provided evidence supporting a relationship between higher personal income as an indicator of current material circumstances and better cognitive abilities in adults.

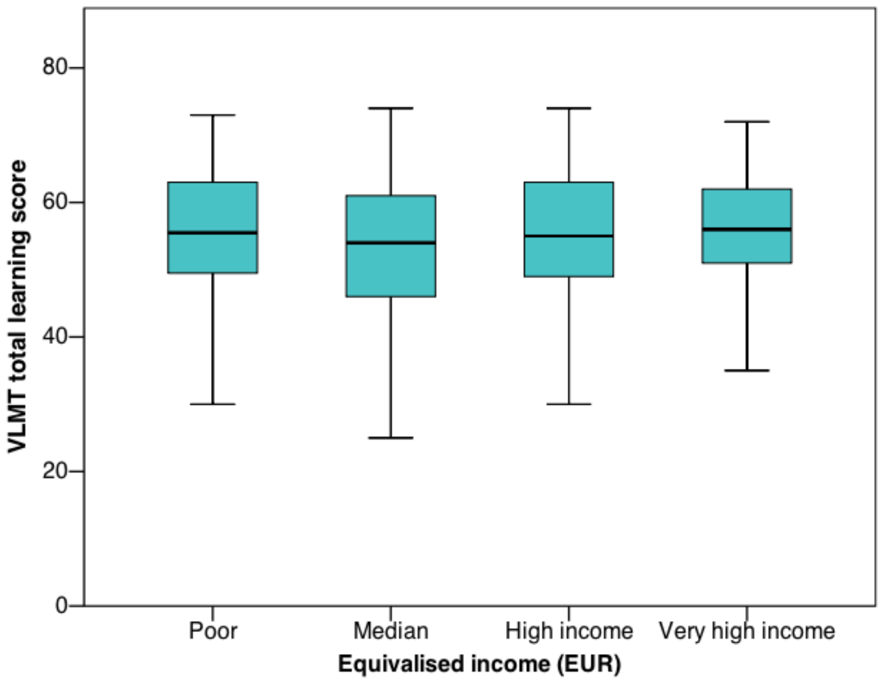

Figure 3.12: Association of equivalised income with VLMT learning score.

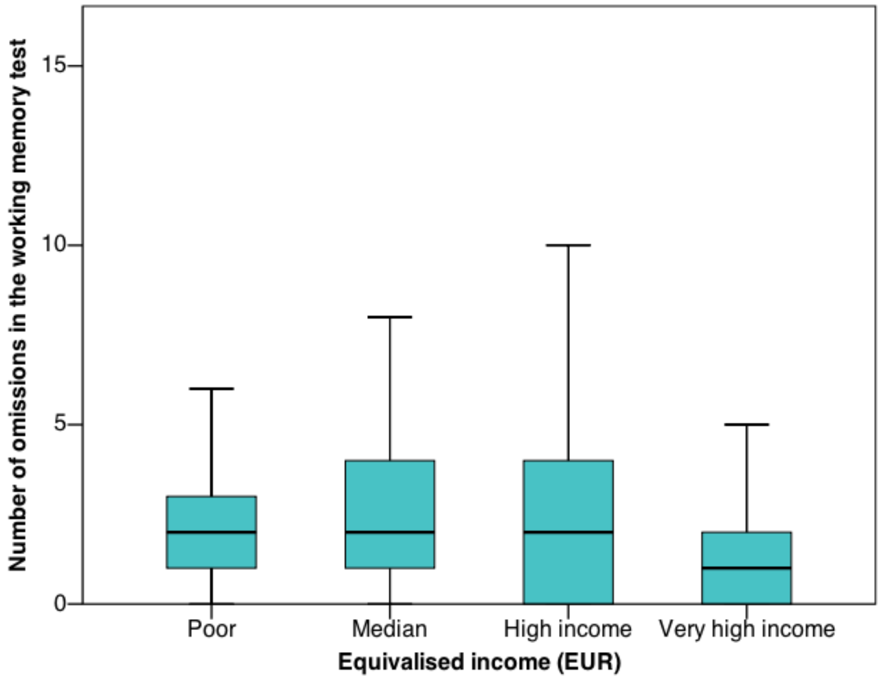

Figure 3.13: Association of equivalised income with the number of omissions in the working memory test.

Specifically, using adjusted linear mixed models showed higher amounts of income to be associated with higher VLMT total learning and corrected recognition scores (SumR_Dg1_5) (w_korrDiff) (Table 3.2). While respondents with median income achieved a mean total learning score of 52.5 (SD 10.8), women with high and very high income scored better, with means of 55.2 (SD 9.5) and 55.9 (SD 8.5) (Table 3.2). Associations between income and VLMT results are also illustrated in Figure 3.12.

Furthermore, higher income was significantly related to a better performance in the working memory test (less omissions (wm3_omi0), Table 3.4) (Figure 3.13) and less errors and shorter reaction times in the flexibility test (fn3_mdn4) (Table 3.4) (Figure 3.14). Adjusting for age and education as potential confounders, the difference in cognition scores was slightly attenuated but remained significant (working memory test: $p<0.001$, number of errors and median of reaction times in flexibility test: both $p<0.001$).

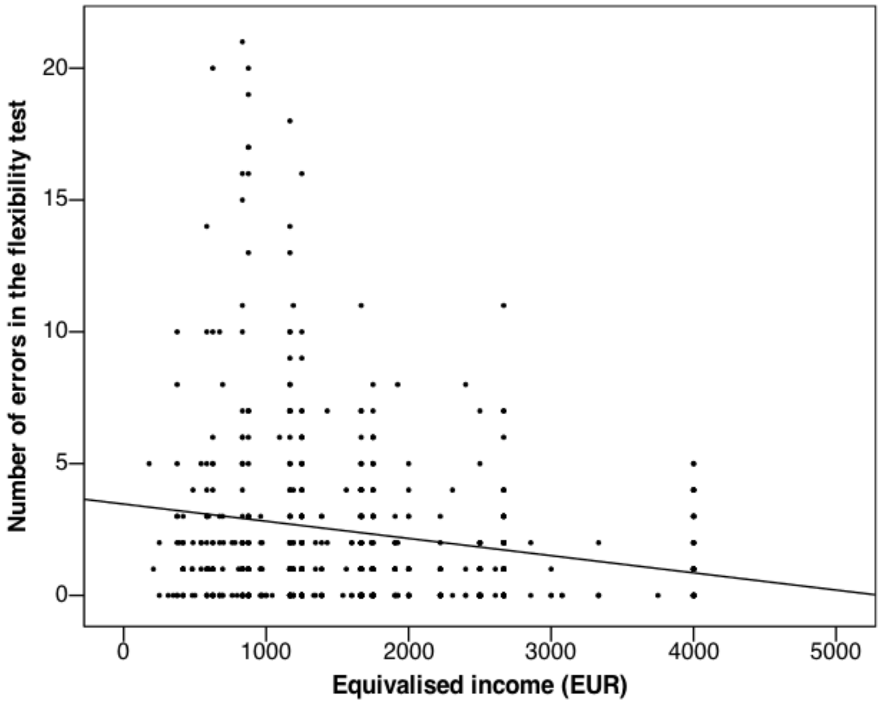

Figure 3.14: Association of equivalised income with the number of errors in the flexibility test.

A noticeable exception was the performance of the group with the lowest equivalence income ("poor", <856 €/month), as it did not follow the trend of higher levels of cognitive performance with income. Both in the VLMT (SumR_Dg1_5, W_korrDiff) (Figure 3.12) and less pronounced in the TAP working memory and flexibility test (wm3_omi0, wm3_err0, fn3_mdn4) the "poor" group performed respectively better than the higher level group with the median income, but its performance was in all cases inferior compared to the high income groups.

As mentioned above and observed in linear regression models (Tables 3.2-3.4), individual SES, of which personal education and income are main factors, is positively associated with cognitive function (VLMT, TAP scores). Comparing levels of interference, education showed a stronger direct association with cognitive performance than income.

3.5 Neighborhood-level socio-economic status

To account for potential neighborhood effects, linear mixed models were used to test whether neighborhood SES had an association with cognitive performance independent of individual SES. Therefore, linear mixed models were adjusted for age and individual SES. The result revealed no marked difference in cognitive performance in any of the outcome variables between women with different neighborhood SES ($p>0.05$) (Tables 3.5-3.7). In ordinal regression analysis, before adjustment for confounders and their potential attenuation effect, there was one significant correlation between neighborhood status and the recall difference score (Diff_Dg5_7, VLMT test). However, with adjustment for age, the relationship was attenuated below significance.

As previous studies have suggested that especially older people are influenced by their neighborhood environments due to longer residence in one place and a decrease in mobility, linear regression analysis was performed for a total of 178 women from our study who were 65 years or older, excluding all others. Using linear regression and adjusting for age and individual SES, a relationship between neighborhood SES and performance in the TAP working memory test (higher neighborhood status being associated with less omissions) with a trend towards significance ($p=0.092$) could be identified. Also a significant relationship ($p<0.05$) was determined between a higher number of errors in the TAP flexibility test and a lower-level neighborhood status. It stayed significant after adjustment for age, but lost significance after adjusting for individual SES, still showing a statistical trend however ($p=0.082$).

Correspondingly, the author found no valid evidence that the sole circumstance of living in a neighborhood with a higher level of SES is associated with better cognitive function in living environments in Berlin.

3.6 Further results

In addition, the effect of one's self-perceived social support (measured by the 7-item ENRICHD social support instrument) on cognitive performance was also examined. It was expected that social support would be linked to mental health and cognition. However, no significant associations were found in linear regression analysis. In descriptive statistics, women with low social support showed a poorer performance in verbal learning memory compared to subjects who reported normal to high social support (Table 3.2): While the "low social support" group had a mean total learning score of 52.5, the group with normal to high social support obtained a mean total learning score of 54.9. However, this was only a statistical trend, which was not significant after adjusting for age, education and income in linear regression analysis ($p=0.189$).

4 Discussion

In an aging society with a large increase in individuals with age-related diseases like dementia and its precursors, it is crucial to reduce psycho-developmental, social and economic risk factors.

To the author's knowledge, the present cross-sectional study with a large group of healthy women, randomly selected from the general population, is the first combined examination of individual- and neighborhood-level psychosocial influences on cognition in an urban setting in Germany. It focuses on possible changes in adult memory and executive functions (sustained attention, working memory and flexibility) caused by different subtypes of childhood trauma and socio-economic factors.

4.1 Main results

With regard to childhood trauma, results reveal an association between higher exposure to physical neglect or abuse and lower flexibility performance: Subjects with exposure to physical neglect demonstrated a higher error rate and longer response latencies, and women who reported physical abuse made more errors in the flexibility test. Furthermore, women with higher physical abuse scores showed poorer performance in the working memory test. Also, there appeared a small association between higher level of exposure to physical neglect and higher error scores in the TAP Go/No-go test.

Moreover, the results show an association between higher levels of individual SES (education, income) and better verbal learning memory and executive performance. Especially education was strongly associated with better performance in VLMT learning and corrected recognition, behavioral control (Go/No-go test), working memory and cognitive flexibility. On a neighborhood level, no significant associations were found after controlling for individual-level SES.

4.2 Discussion of methods

4.2.1 Selection of participants

Recruitment of randomly selected participants with proportional representation of population density in the different districts reached a great number of potential test persons across Berlin. Five equal age strata were generated artificially to include approximately even numbers of women aged between 25 and 76 and to reach a balanced representation of all age groups. In total, 843 women of 3,600, who were invited to participate, could be included in neuropsychological testing. Socio-economic indicators in the general population in Berlin were compared to the distribution of SES in the present study sample, confirming a valid representation of the city's socio-economic structure. As a consequence of this broad socio-economic spectrum, findings related to childhood neglect and abuse can be generalized to lower, middle and upper class women. Furthermore, selection of a generally healthy sample of a representative size allowed for the examination of trauma-related effects on adults without apparent psychiatric conditions.

4.2.2 Adjustment for confounders

As the current study aims to examine the influence of certain socio-economic and psychological parameters on cognitive function, other known influence factors on neuropsychological performance need to be considered. Previous studies (41, 64, 116) showed a strong correlation of age with cognition. Thus, age can be considered as a potential confounder and was used as a covariate in all statistical analyses performed in order to attenuate its confounding effect on the examined associations. Other covariates used to make the effect of the observed psychosocial factors on cognitive performance more transparent were education, income and depression. Through adjustment for potential confounders, valid conclusions can be drawn concerning the influence of individual-level and neighborhood-level SES as well as self-reported experience of childhood trauma on cognitive performance.

4.2.3 Reliability of self-reported data and cross-sectional design

During analysis and evaluation of questionnaires and quantification of psychosocial data, it has to be considered that the answers of respondents to questions are subjective and that participants can influence results consciously or unconsciously. Concerning the retrospective self-report of childhood maltreatment history there is also a potential recall bias. When collecting a subject's medical history, truthfulness and completeness of the information has to be assumed. This applies likewise to the self-reported experience of childhood maltreatment and information on individual education, income and mood.

When using self-report questionnaires, response bias and distortion cannot be completely prevented. It becomes especially relevant in studies with small sample sizes. But even though sample size in the current work was relatively large, a potential confounding effect cannot be excluded. However, as this effect cannot be objectified, it has not been considered in the context of the present work.

Another important aspect to be mentioned is the cross sectional design of the present study. Simultaneous assessment of exposure and outcome make it difficult to distinguish between cause and effect and to draw causal inferences. Consequently, one cannot definitely establish the asserted temporal relationships between trauma and adult cognitive function or between socio-economic factors and cognitive performance. The cross-sectional design is also important with reference to the examination of neighborhood influences on cognition. Because of the cross-sectional design the effects of neighborhoods on cognition are considered as contemporaneous and no causal pathways can be inferred between neighborhoods and cognitive development. Thus, connections between urban neighborhood and cognition that might evolve and change over time cannot be accounted for, even though impacts of the past neighborhood disadvantage might not be transmitted via the current neighborhood disadvantage (6). Furthermore, cognitive performance is only tested and assessed at one point in time and thus it is difficult to draw conclusions concerning its longitudinal stability.

4.2.4 Influence of test times

Performance in neuropsychological tests depends on variable parameters including blood glucose levels (83), test time and level of mental exhaustion. As time of testing varied from morning to afternoon slots, depending on participant's time preferences and working hours, the individual circadian typology could not generally be considered. Previous studies have demonstrated that there's a difference between morning-type individuals who go to bed and rise early, achieving their peak mental performance in the morning, and evening-type subjects who go to bed and rise late, reaching their best performance toward the end of the day (4). However, in the present study time slots were not selected based on circadian rhythms of performance but selected to fit individual schedules and working hours. Apart from circadian typology, a daytime variation in cognitive performance is also influenced by level of alertness or tiredness. It has been shown that tiredness exerts a negative impact on cognitive performance with decrements in selective attention and alertness (126). Subjects in the present study that completed neuropsychological tests after long working hours might have performed below their maximum due to higher levels of tiredness. In future studies, a standardized time of testing on non-working days or based on circadian typology could ensure more equal conditions and better control of possible confounders.

4.2.5 Examination procedures and tests

Validity and reliability of the internationally accepted and standardized tests used in the present study have been confirmed in previous works with representative samples (see sections 2.6 and 2.8 above).

To assess memory performance, the German version of the AVLT (VLMT) was used with maximum scores of 75 in total learning and 15 in corrected recognition. In the present work, mean values for cognitive performance were 54.5 (SD 10.1) for total learning and 12.9 (SD 3.0) for corrected recognition. As recognition performance was on a very high level with relatively small SDs, differences between groups were small.

The examination and testing procedure was standardized following a predefined sequence of steps, and even though we tested at different testing sites, a quiet low-stimulus environment in a separate room was always ensured. As a consequence, external influences on test results can be largely excluded except for mood parameters (e.g. current depression).

4.2.6 History of childhood maltreatment

The CTQ, which was used for childhood trauma assessment, has shown excellent reliability and validity in adult psychiatric and community samples (15, 95, 124). However, a limitation might be that even though associations between trauma history and cognition were adjusted for a number of individual-level covariates, it is still possible that the observed significant associations reflect unmeasured variables. The lack of data on the onset and duration of childhood trauma presents another limitation, as the effects of stressful experience on brain function might depend on whether it occurred during a critical window for the development of certain brain structures (55). Future studies in similarly sized samples which investigate specific ages of trauma occurrence will be important for understanding the critical periods during which childhood neglect or abuse influence adult cognitive dysfunction and the neurobiological mechanisms that mediate these changes (136).

4.2.7 Concept of neighborhoods

In the present work, neighborhoods were defined by spatial units according to the monitoring concept of living environment areas in Berlin. These artificial units might fail to depict social reality by not corresponding to neighborhood environments as experienced by residents. However, compared to previous studies that often used census tracts as a correlate for neighborhood units, the concept of living environment areas constitutes an advanced approach to neighborhood environmental reality, as these areas are defined by parameters such as formation of milieus and uniform building structures and only include an average of 7,500 inhabitants, allowing for a more precise monitoring of and approximation to, socio-economic neighborhood reality.

Furthermore, a limitation to acknowledge is that the length of residence in the respective neighborhood was not accounted for. Duration of residence in a particular neighborhood is associated with different levels of social integration and exposure to neighborhood effects and can thus determine varying effects on cognitive function, especially in older people, who have lived in one neighborhood for a longer period of time. Apart from that, this study was limited to women of different ages living in Berlin and findings might not be generalized to apply to other urban areas.

4.3 Discussion of results

4.3.1 Childhood trauma and cognitive performance

In the current study nearly one fifth of the sample reported at least one subtype of childhood trauma. Depending on the severity of trauma, physical neglect and abuse were associated with deficits in working memory, cognitive flexibility and behavioral control. Childhood and adolescence are crucial periods in the development of certain brain regions such as the hippocampus and the PFC, which promotes the development of executive functions. Previous structural and functional MRI studies have shown a reduced volume of the frontal brain in children with experiences of abuse (19, 146). Findings in adults with experience of childhood trauma have also suggested a trauma-related decrease in PFC volumes (146). It has already been indicated by former research that traumatized children have an increased risk of psychopathology and are more likely to develop psychiatric disorders (i.e. major depression, anxiety disorders, posttraumatic stress disorders, bipolar disorders, personality disorders or substance abuse) over their lifespan (140). The present study is one of the fewer studies evaluating whether early childhood trauma in the absence of a psychiatric condition also impacts adult cognitive performance.

It can be assumed that there are neurobiological mechanisms, which cannot be determined from the present work, mediating the effects of childhood trauma on the development of memory and executive functions. As childhood maltreatment is a form of early life trauma (ELS), it is associated with alterations to the functioning of the hypothalamic-pituitary-adrenal (HPA) axis and changes in the monoaminergic response.

The HPA axis consists of a complex set of feedback interactions among the hypothalamus, the pituitary gland and the adrenal, the major output of which is cortisol. Corticotropin-releasing factor (CRF), which is the principle regulator of the HPA axis (120), is secreted by neurons located in the paraventricular nucleus (PNV) of the hypothalamus and then released into hypophysial portal vessels accessing the pituitary gland (134). The circadian or stress-induced release of corticotropin-releasing hormone (CRH) then modulates adrenocorticotropic hormone (ACTH) secretion from the anterior pituitary, subsequently acting on the adrenal cortex to synthesize cortisol (134). Circulating glucocorticoids operate through ubiquitously distributed receptors (11) targeting the pituitary, the PFC and other CNS areas.

Stress also elicits monoamine release, increasing both dopamine (DA) and norepinephrine (NA) levels. The function of the PFC is suppressed through DA D1 receptor and NE alpha-1 receptor signaling (130). Because of the inhibitory function, the PFC has, with regard to HPA-related stress response, deficits in PFC function can result in an enhanced and prolonged cortisol release (130).

4.3.1.1 Short- and long-term verbal learning memory

In the present study, associations between childhood trauma and short- and long-term verbal memory lost significance after adjustment for age, education and income. In contrast, an earlier study by *Bremner et al.* suggested a negative relationship between childhood abuse and verbal memory function, depending on the severity of abuse (21). In a later study, *Bremner et al*. investigated verbal memory function in women with sexual abuse-related PTSD by use of the Wechsler Memory Scale and found that abused women with PTSD showed deficits in verbal declarative memory compared to women with history of abuse without PTSD and non-abused women without PTSD (22). This indicates that verbal memory dysfunction might be a result of trauma-related PTSD, but not of nonspecific effects of childhood abuse. The present results can be explained in line with this, as the focus was on women with history of abuse not necessarily suffering from PTSD. Thus effects of childhood trauma beyond PTSD were examined that might be smaller but still cause changes to cognitive functioning. The results of the present work suggest that these nonspecific effects of childhood trauma do not cause measurable deficits in declarative verbal memory function, but rather on executive functions (working memory, flexibility, sustained attention).

4.3.1.2 Working memory

Results showed that respondents with more exposure to physical abuse had higher omission rates in the working memory test compared to subjects below the cut-off score for physical abuse. Working memory represents one important function of the PFC and requires sustained attention and transient storage of information to develop a strategy for continuously identifying changing target stimuli. Higher omission rates in the TAP working memory test hint at a combination of organizational and memory deficits.

As regards the influence of trauma-related effects on cognition, it has been suggested that working memory is more sensitive to glucocorticoid-related changes than declarative memory (94). *Lupien et al.* found that after administration of glucocorticoids over a short period of time, subjects showed deficits in working memory performance, while their declarative memory function was unaffected (94). Assuming that childhood maltreatment is associated with exposure to elevated levels of glucocorticoids throughout crucial stages of brain development and that it causes sustained changes in adult HPA axis functioning, similar results were obtained for the present study sample. Another important part of the stress response system is the enhancement of monoamine release. Previous studies have shown that increased D1 DA receptor stimulation in the PFC results in an impairment of working memory function (9).

Recently, the effect of ELS on adult working memory function was evaluated in a neuroimaging (fMRI) study, in which the childhood trauma group demonstrated qualitatively and fundamentally different patterns of activation and deactivation across brain regions and decreased working memory accuracy compared to controls (115). Even though brain activity was not measured within the present work, it can be speculated that the observed executive deficits are linked to structural changes of function in some of the brain regions such as those found in the fMRI study by *Philip et al* (115). Also, it has been indicated that the association between higher exposure to childhood trauma and poorer working memory performance was modified by genetic differences. *Gatt et al.* found that carriers of polymorphisms in the brain neurotrophic factor (BDNF) alleles have a higher risk of developing trauma-related depression and associated alterations in cognition, along with poorer working memory performance (60).

4.3.1.3 Flexibility

Cognitive flexibility is attributed to the PFC and refers to one's ability to quickly adapt behavior to changes in the environment. In the present sample, childhood physical abuse and neglect exhibited a measurable effect on cognitive flexibility. Women with experiences of childhood maltreatment showed poorer flexibility performance with severity of abuse/neglect. The strongest association found was between physical neglect and flexibility performance. As physical neglect includes both aspects of emotional neglect and physical deprivation, it has the potential to affect neurobiological processes and FL development in a multifaceted way (136). It could be seen that self-reported experience of physical neglect had a negative impact on both reaction time and correctness of response in the flexibility task. Apart from that, women who reported physical abuse showed a higher error rate in the flexibility test. The deficit in flexibility of subjects with higher levels of physical childhood trauma cannot be explained solely by a general reduction of elemental cognitive processing and reaction speed, since there was no significant correlation between physical neglect and the TAP reaction time task (alertness test). Instead, poorer performance likely reflects an executive organizational deficit in adapting to a changing situation. The finding of a measurable effect of childhood physical neglect and abuse on flexibility performance in adulthood is relatively novel and has received little study. *Spann et al.* showed that trauma-related flexibility dysfunction persists at least into adolescence (136). Based on current results, it is probable that flexibility dysfunction can extend to adulthood. However, it is not clear if abuse- or neglect-related flexibility dysfunctions persist from childhood into adulthood in one form or if they undergo further alterations in the process. Therefore, future longitudinal studies of adults with exposure to childhood trauma are needed.

The causal neurobiological mechanisms moderating the association between childhood trauma and flexibility function cannot be determined from the present work. It is known that the PFC supports higher-order cognitive executive processes that underlie flexibility. In order to accomplish this task, there are interconnections between the PFC and various cortical and sub-cortical structures (117) such as the HPA axis and the monoaminergic system. While moderate levels of glucocorticoids and monoamines are important for proper functioning of the PCF, higher levels of these hormones may adversely affect executive functions. The impact of childhood abuse and neglect on flexibility could be explained both by the prominence of GRs in this brain area (93), making the PFC more susceptible to the effects of trauma-related stress, and by higher monoamine release during stressful experiences, causing dysregulation in the PFC (9). Under conditions of stress, CRF regulates monoaminergic systems with projection to the PFC, including the NE system in the locus coeruleus, the DA system within the ventral tegmental nucleus and the dorsal raphe serotonin (5-HT) neurons. One mechanism, by which glucocorticoids and monoamines are thought to interact, is an extraneuronal transport system, that usually helps to remove excess NE and DA from the synapse in order to maintain an optimal PFC stimulation, but which is blocked by higher levels of glucocorticoids resulting in an increased catecholamine release with PFC dysfunction (130). Hyporesponsiveness of the PFC in turn causes a lack of inhibitory signals to other brain regions and functional circuits such as the HPA axis, resulting in even higher glucocorticoid levels.

With respect to NE, it has been suggested that varying levels of NE activate different NE receptors (8). Whereas moderate NE release leads to an activation of alpha-2a-adrenergic receptors improving PFC function, high levels of NE stimulate lower-affinity alpha-1 and beta adrenoceptors, which impair PFC responsiveness and lead to a decrease in neuron firing (121). There is a similar situation with regard to DA receptors, where D1 and D2 receptors are engaged at different levels of DA activity (121). While moderate levels of DA are associated with D1 receptors that maintain PFC activity, high levels of D1-activation during stress cause a suppression of both preferred and detrimental inputs, resulting in a suppression of PFC neuronal firing (121). Furthermore, it has been suggested that D4 receptors might antagonize the positive effects of D1 and D2 receptors on executive functions via reduction of NMDA-mediated transmission in the PFC (57). The 5-HT system is also involved in the modulation of the PFC. However, the question of how 5-HT influences neuronal firing in the PFC during performance of executive tasks such as flexibility remains largely unresolved.

Studies in rodents have indicated that sustained exposure to stress also leads to a loss of spines and dendrites in the PFC, which might be associated with poorer flexibility function (9). In conclusion, stressful events such as physical childhood trauma can result in marked flexibility impairments because executive function depends on the maintenance of a neuronal interconnectedness and balanced neurochemical state in the PFC (130). However, further studies are needed to investigate the structural and neurochemical effects of physical childhood trauma on frontal development and the PFC.

4.3.1.4 Behavioral control

Furthermore, the present work examined the performance of a sample of female adults in a simple response-inhibition Go/No-go task from the TAP. Adjusted mixed model analysis showed a significant association between higher severity of childhood maltreatment and poorer performance in the Go/No-go test. This can be interpreted as a consequence of poorer modulation of impulses, sustained attention and self-control (e.g. to inhibit a prepotent response). Traumatized subjects are more likely to react, when reaction is not appropriate, hinting at a change in inhibitory mechanisms. So far, there has been little research on the enduring effect of childhood trauma on behavioral control. *Mezzacappa et al.* reported poorer inhibitory capacity in abused boys using a continuous Go/No-go/Stop task (104). In a functional MRI study by *Carrion et al.* adolescents with traumatic experience showed more widespread activation in the ACC and the PFC and poorer activation in the middle frontal gyrus (MFG), an area involved in response inhibition, during a response-inhibition Go/No-go task compared to controls, suggesting a trauma-related change in neurofunctional processes (32). Consequently, the present findings are in line with prior data suggesting that childhood trauma has an influence on the regulation of motor executive skills and might attenuate behavioral control into adulthood.

4.3.2 Other types of childhood trauma

The current work suggests that trauma-related cognitive impairments in adulthood vary depending on the dimension of childhood trauma. This is consistent with previous research that also suggests different subtypes of childhood trauma exposure to be associated with distinct anomalies in HPA-axis and cognitive functioning (65, 88). Concerning the present study, physical abuse or neglect was linked to cognitive impairments in certain areas of executive functioning, whereas no differences could be identified for emotional or sexual maltreatment.

4.3.2.1 Emotional abuse and neglect

In contrast to the present study, which found no association between emotional childhood trauma and cognitive deficits, two previous studies reported a significant association (65, 95). Both studies used the Cambridge Neuropsychological Automated Test Battery (CANTAB), involving seven tests and requiring about 60 minutes, whereas the present study used the TAP including four tests and taking approximately 40 minutes. As a consequence, the different results concerning childhood emotional abuse could be explained by varying methods of cognitive assessment. Also, due to a smaller number of neuropsychological tests in the present study, the evaluation of different domains of cognitive function might be less specific and thus not able to detect emotional abuse- or neglect-related deficits in certain domains of cognitive function. Another explanation could be that small sample sizes in both the above mentioned studies led to false positive results due to outliers and that the effect of the trauma subtypes "emotional neglect" and "abuse" on cognitive function is much smaller than the impact of physical neglect and abuse and might thus not be measurable with neuropsychological test batteries.

4.3.2.2 Sexual abuse

Concerning the childhood trauma subtype "sexual abuse", we found no evidence suggesting a relationship between history of childhood sexual abuse and adult cognitive function. This stands in contrast to a small body of previous studies indicating a relation between experience of sexual abuse and cognitive deficits such as increased response latency, reduced inhibitory capacity and memory deficits (21, 65, 74, 109).

The main age of participants in the present study (about 50 years) was relatively high, which could be associated with a smaller impact of childhood sexual abuse. On the other hand, negative effects on cognition cumulate in older age and the negative effects of early life trauma might also be exacerbated. In contrast to emotional abuse, which might be hypothesized as having a smaller effect on cognitive development compared to physical abuse and neglect, sexual abuse would be considered to have long-term effects on cognitive development. It is therefore surprising, that no effect of childhood sexual abuse on cognitive function could be detected in the present sample. Because there was no information available regarding duration and onset of abuse and as the effect of stress on the brain might depend on whether stressful experience occurs during critical periods for the development of particular brain structures (55), it is conceivable that some of the reported sexual abuse occurred during non-critical periods for brain development and thus did not show a long-term impact on cognitive function. Another explanation might be that the neuropsychological tests conducted were unable to assess the domains of cognitive function modulated by early experience of sexual abuse.

4.3.3 Disturbed family environment as a potential confounder

Concerning childhood trauma co-occurring adverse experiences are common and affect the majority of maltreated children (46). In subjects who grew up in disturbed family environments, cognitive disadvantages could – instead of being a sole consequence of childhood trauma – also result from being raised in families that lack education and educational support, organization, economic resources, parental monitoring or ethical values and thus fail to provide adequate opportunities for learning (86). Such a disadvantageous environment might – beyond the effect of childhood trauma – have an adverse effect on and act as a barrier for the development of higher cognitive functions. As a consequence, the cumulative effect of adversities could account for a greater risk of cognitive impairment, whereby there is some contention whether the effect of childhood trauma on cognition is independent or rather mediated by other forms of childhood adversities. Even though a potential benefit of a cumulative approach has been shown (128), there is an ongoing debate as to which methods are the best to estimate the effects of childhood trauma and chronic adversities (i.e. sum scores of specific experiences or the use of more cumulative measures) (108). Also, due to the complex and multifactorial association between psychosocial factors and cognition, it remains uncertain if using more advanced statistical models or different study designs, e.g. twin-based studies, may be able to fully disentangle the effects of emotional, physical and sexual abuse or neglect from other stressful environmental events. In the present study, while examining the potential effect of childhood trauma on cognition, it was adjusted for adult individual education and income in order to reduce the effect of economic and educational confounders. However, even though one's economic and educational achievements as an adult can function as an indicator for one's situation in childhood, the adjustment remains imprecise and the biasing effect of the socioeconomic and educational situation in which children were raised cannot be completely avoided. Consequently, the association between childhood maltreatment and cognition might be overestimated.

4.3.4 Individual socio-economic status and cognitive performance

In ordinal regression and mixed model analysis it could be shown at a significant level that especially individual education, but also income show a strong influence on cognitive performance. After adjustment for age, most of the associations remained highly significant. While previous studies have described language as one of the main domains affected by SES (39, 80, 111), the author found executive functions to be most affected.

Referring to the effect of income in the present study sample, the performance of the "poor" income group (<856 €/month) was very noticeable, as it was the only group not following the trend of better cognitive performance with each level of increase in equivalised income. Concerning the VLMT outcome variables total learning score, recall difference score, corrected recognition score and also the TAP outcomes from the Go/No-go, the working memory and the flexibility test, the “poor” income group scored respectively better than the one-level higher “median” income group. This could be explained by the fact, that the “poor” income group was more heterogeneous in terms of age than were the “median”, “high” and “very high” income group, as it also included younger women with a modest income who were still students. Because most students receive financial support for the duration of their degree programs and are not part of the workforce yet, their equivalised income cannot be considered as a valid measure of unfavorable SES as it is only a temporary condition, which does not reflect final income level. In addition to that, most of the students are still embedded in the socio-economic context of their families, shaping them during childhood and adolescence. Previous studies have investigated the relationship between childhood poverty and cognition, establishing low SES as a risk factor for cognitive growth due to an associated lack of psychosocial stimulation, adequate sanitation conditions and intellectually stimulating material resources (such as books and day care) (23, 123). However, as stated above, low personal income as a student does not indicate poor socio-economic conditions during childhood and adolescence and can thus not be used to examine or evaluate the relationship between poor SES and cognitive performance. Also, as the present study is cross-sectional and only includes adult women, no statement can be made concerning SES-dependent cognitive development from childhood to early adulthood.

As regards cognitive function in all periods of adulthood, findings in all but the “poor” income group are consistent with the existing body of literature, showing trends of better cognitive performance with both increasing education and income (91). In two large cross-sectional studies with men, *Cagney and Lauderdale* and *Gallacher et al* (Caerphilly Study) found a significant association between increasing cognitive performance and higher levels of education, after adjustment for age and household income/wealth (29, 59). While *Cagney and Lauderdale* used wealth and household income as indicators for one’s economic situation, the present use of equivalised income might have the advantage of taking into account different household sizes. Compared to *Cagney and Lauderdale*, who report a great attenuation of the effect of income and wealth after adjusting for education, the results for the BEFRI population were slightly different in that even though education was found to be the most important influence factor, the effect of income was attenuated to a lesser degree after adjustment for education and remained significant for declarative verbal memory, executive working memory and flexibility performance.

As the present study considers adult cognitive performance at one point in time, but does not include any follow-up examination, it assesses the current state of cognition and cannot determine the education- and income-related change in cognitive function over time. To address this question, there has been some previous research on the correlation between levels of SES and longitudinal change in cognitive function (53, 152). The findings suggest that greater educational attainment is associated with higher levels of cognitive functioning and slower cognitive decline, mediated by income (152). It would be very interesting to see, if the BEFRI study population, if followed up over time, would also show this trend of SES-dependent cognitive development.

4.3.4.1 Mechanisms of the effects of socio-economic status on cognitive function

There are different mechanisms that might elucidate the connections between variable levels of SES and cognitive performance. One explanation could be that there are SES-related differences in neural substrates leading to neurobiologically mediated alterations in memory and executive functions (152). According to this approach, differences in the activation of the PFC and cortical structures have been reported in subjects with different SES by use of electrophysiological measurements and magnetic resonance (MR)-based neuroimaging.

D'Angiulli et al. compared event related potentials (ERPs) for auditory selective attention in lower and higher SES-children and conducted an electroencephalographic power analysis, which revealed different patterns of brain response (39). Their results can be seen as a reference to a SES-dependent recruitment of specific and varying neural systems during (executive) cognitive processing (67). In another study, *Hanson et al.* suggested an association between higher levels of family income and higher grey matter density (measure of volume) in the hippocampus (68). This brain region is central to memory functioning, learning and emotional behavior. *Gianaros et al.* examined a mixed group of 100 men and women and indicated that low self-reported SES is associated with reduced grey matter volume in the perigenual area of the anterior cingulate cortex (ACC), which is part of the PFC and involves in the regulation of stress responses and the experience of emotion. As the PFC has a long developmental trajectory, it might be particularly susceptible to environmental conditions (67). *Tomarken et al.* investigated the relation between SES and frontal lobe (FL) functioning and found that higher SES predicted a relatively greater left frontal activity (141). All of these findings point to potential neural mediation between socio-economic conditions and the development of cognitive skills.

A causal pathway from SES differences to variations in brain development and functioning can be modeled using the effect of chronic exposure to stress and related alterations in the functioning of the HPA-axis and the monoaminergic system (see Sections 4.3.1 and 4.3.1.3). Having a lower SES is related to higher levels of stress and changes in the stress response system (67). *Gianaros et al.* suggested that higher levels of chronic stress are also associated with cellular changes leading to reduced hippocampal volumes in healthy adults (62). They used a prospective design over a period of approximately 20 years and found that higher levels of self-reported life stress presaged decreased grey matter volumes in the hippocampus and orbitofrontal cortex (OFC) (62).

However, the current understanding of the mechanisms of SES on cognitive function and development has to be considered as tentative. Therefore, further research is needed to improve our understanding of SES-related differences in cognitive performance across all ages. Cognitive neuroscientific studies in the field of SES provide the possibility of combining new insights into the functioning of the human brain with an approach to problems in society.

4.3.5 Neighborhood socio-economic status and cognitive performance

It was hypothesized that living in neighborhoods with lower-level SES would be associated with poorer cognitive functioning. However, in examining the association of cognitive function with neighborhood SES in the present sample of healthy adult women, no significant correlations were found after adjustment for potential confounders. Previous research suggests an influence of neighborhood characteristics on individual physical and cognitive function with a link between lower neighborhood-level SES and poorer cognitive performance above and beyond individual-level SES (89, 131, 132, 149). As people with low educational attainment are more likely to experience economic disadvantage and poverty compared to people with higher levels of education, an accumulation of people with little education consequently creates an environmental concentration of economic disadvantage potentially influencing cognitive health (149). Concentrated economic disadvantage in low-level segregated socio-economic urban neighborhoods has also been linked to higher probabilities of delinquency and criminality leading to social withdrawal and isolation of the residents with translation into poor cognitive functioning (6).

Older adults appear to be more susceptible to the effects of neighborhood environments as they are generally less mobile and have often spent a longer period of time in the respective neighborhoods (28). To test the effect of neighborhood SES on the cognitive functioning of older women (>65 years) in the present study sample, an additional statistical analysis was performed for this subgroup. After adjustment for confounders such as age and individual SES, trends towards poorer working memory and flexibility performance with lower levels of neighborhood SES were found, which however did not reach significance level. The deviation of results from previous Anglo American research might be explained in several ways. One explanation might be that the present study design was not able to dissect the influence of neighborhood SES on individual cognitive function (see section 3.5). Also, the social influence of neighborhoods might have been overestimated, as school and work contacts outside the area of residence could be more important for the respective individuals than contacts formed within neighborhoods (48).

Another possible explanation could be the different composition of urban German/Berlin neighborhoods. US society is very much shaped by immigration and also there is the growing impact of a large group of undocumented immigrants. Whereas US urban metropolitan areas are shaped by residential segregation of population groups, levels of residential segregation in Berlin are significantly lower. Concerning neighborhood effects on individual wellbeing, US studies have observed adverse effects of racial segregation on health and have shown that African Americans, for whom segregation in the US is more extensive than for other ethnic groups, have increased mortality rates in urban areas with higher levels of segregation compared to lower level segregation regions (79). The adverse effects on health are mediated through poorer socio-economic, school and environment quality of racially segregated residential areas. As Berlin neighborhoods are less shaped by residential segregation, it can be assumed that the socio-economic differences between neighborhoods as well as social and spatial divisions in general might not be as pronounced as in the US. Still, it seems important to have a closer look at neighborhood influences in future, as the current massive increase of immigration to Germany will alter societal structure and the composition of neighborhoods. Another argument for possibly less marked neighborhood differences in Germany is that it has a more generous social welfare system. Berlin in particular has a remarkable social housing sector, including a tradition of housing cooperatives. The cooperative apartments make up about 11 percent of all rental housing, which supports the cooperative idea of stable neighborhoods and long-term rental housing (2). In addition, following the pauperization of some of Berlin's districts during the 1990s, the government launched the program "The Socially Integrative City" in 1999 in order to improve the social structure of low SES boroughs, which often also face ethnic problems. Within the framework of the program, there have been a multitude of small social integration and neighborhood management programs in the different low-SES focus areas in Berlin aiming to improve educational and employment opportunities and to facilitate the integration process of different nationalities living in one neighborhood. Even though there undoubtedly is a lot of socio-economic inequality in Berlin, it may be less acute and less concentrated than in US urban segregated neighborhoods with more social exchange and interaction between people from different neighborhoods.

In addition, the US education system is class-ridden. On the one hand this is due to selective admission to private schools, that offer superior teaching with a wider range of academic programs, smaller class sizes and better qualified teachers, but come with higher costs, which only families with wealthier backgrounds can afford. On the other hand, with school admission being based on residency, there are great differences in public schooling between wealthy communities with high median incomes and higher property taxes and poorer neighborhoods (34). Ability to raise revenues for local schools differs a lot. In contrast, there are only few private schools in Germany with little impact on the education system and the public education system does not differ so much across residential areas. The compound of these educational differences might result in less pronounced neighborhood-related education disparities, attenuating the neighborhood effect on cognitive functioning. Still, even though these differences are less pronounced compared to previous studies in the US and do not reach statistical significance, the statistical trends found after adjustment for age and individual SES show that there is nonetheless the tendency for older people from lower SES- neighborhoods to perform worse in some areas of cognitive testing compared to respondents from higher-level neighborhoods.

A brief overview of the possible psychosocial factor-related mechanisms that might cause cognitive differences, but were not examined in the present study, can be seen in Figure 4.1.

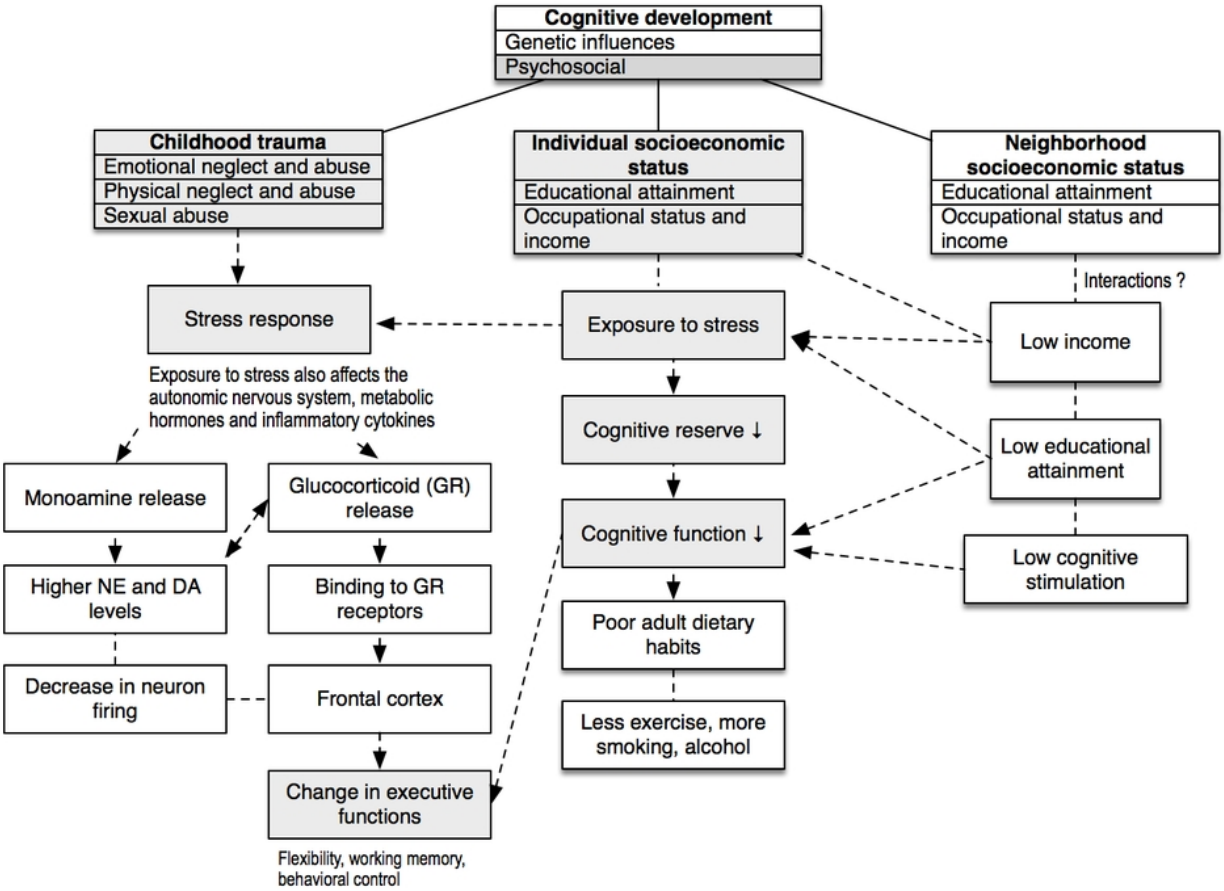

Figure 4.1: General hypotheses concerning the association between psychosocial factors and cognitive function.

4.4 Summary of strengths and limitations

Strengths and limitations of the present study have already been discussed in the part above, but the most important ones will be summarized here. Concerning methodology, a very important limitation is its cross-sectional design, which makes it difficult to evaluate temporal relationships as cause and effect are assessed at the same time. Furthermore, all the data from the questionnaire are self-reported data and thus the potential impact of response bias on the validity of results has to be acknowledged. With reference to childhood trauma, the study was limited by lack of assessment of respondents' cortisol levels and non-collection of data on the onset and duration of trauma.

Strengths of the study design include especially the large sample size (n=843) and the wealth of data it provides with regard to childhood trauma and individual and neighborhood socio-economic parameters. Also the use of valid and internationally accepted tests as well as the employment of standardized examination and testing procedures ensures that external influences on test results can be largely excluded. Finally, the study is the first to explore a combination of childhood trauma and individual and neighborhood socio-economic data for an urban female sample in Germany. With respect to the concept of neighborhoods, a new set of publicly available census and urban development data was used in order to assess the influence of neighborhoods on cognitive outcomes in Berlin. Furthermore, the results on individual SES and childhood trauma are consistent with earlier research pointing to the impact of individual psychosocial factors on cognitive function.

4.5 Conclusions and outlook

The results of the present study indicate that the individual socio-economic factors education and income and the psychosocial factor childhood trauma are independently related to cognitive outcome variables such as declarative verbal memory, working memory, flexibility and other areas of executive performance and that they can be detected through neuropsychological testing.

4.5.1 Childhood trauma

As statistical analysis was adjusted for individual-level factors such as age, education, income and depression, this study lends support to the hypothesis that the differences in cognitive performance found in women with self-reported child maltreatment are not a consequence of differences in current SES or symptoms of depression, but that childhood trauma has an independent adverse effect. However, taking into account that many survivors of childhood abuse are reared in ineffective families, statistical adjustment for age and adult individual socioeconomic status does not exclude the potential effect of a disturbed family-of-origin environment on cognitive functioning, because of which the impact of childhood trauma might be overestimated.

In the present study, especially physical abuse and neglect seem to be related to problems in adult working memory and flexibility performance, which are both domains of executive functioning and associated with the PFC. As suggested by previous research, stress-related alterations to the HPA axis and changes in brain structure can be assumed to act as potential mechanisms and causes.

Here, more studies with longitudinal design are needed in order to confirm the causal relationship between childhood trauma and cognitive deficits. Especially longitudinal studies with measurement of serum or salivary cortisol in abused children, adolescents and adults without psychological disorder are warranted in order to confirm the hypothesized causal neurobiological association between traumatic stress and changes in cortisol release. Apart from that, neuroimaging studies in traumatized children and adolescents will be important to explain executive deficits and to obtain more information on the acute and long-term effects of childhood trauma on the function and structure of certain brain regions.

So far, study samples have been composed mostly of female participants. It would be interesting to investigate gender-related differences regarding the cognitive effects and consequences of childhood trauma with a shift of focus also towards male subjects. Animal models have suggested sex-specific differences in susceptibility, resilience and adaptability to experiences of childhood maltreatment (133). Also there is the need for a standardization of the neuropsychological instruments used in the assessment of trauma-related dysfunctions and for less variability in study designs and techniques of data collection in order to ensure a better comparability of results. Furthermore, future studies with more comprehensive memory and executive function testing could make it possible to better define both the abilities most affected and the skills that are preserved and thus help researchers in the construction of intervention strategies for trauma-related cognitive deficits by drawing on intact cognitive abilities that could compensate for and reduce dysfunction (136). In this context, future large-scale intervention research could for example be dedicated to promoting the development of behavioral and self-control in subjects with experience of childhood trauma. Ideally, child welfare systems should develop more mechanisms for positive parenting, ensuring that patterns of chronic maltreatment do not occur in the first place (35). The current study begins to fill a gap in childhood trauma literature concerning effects of ELS on adults that do not meet DSM-IV criteria but show differences in executive functioning. Results indicate that trauma exposure even in the absence of diagnosed psychiatric illness has a measurable and significant impact on executive functions such as cognitive flexibility. As executive functions are important for planning, problem solving, adapting to changing situations and control of behavior, even small executive deficits can cause difficulties in exposed individuals' management of everyday life and changes in behavior, although this effect might not be visible at first glance.

4.5.2 Individual-level socio-economic factors

As already suggested by previous research, the present study confirms that higher levels of education and income are closely associated with better cognitive performance. The association between higher levels of education and better cognitive performance suggests that higher education levels in the population at large could ameliorate cognitive function. Although the impact of education on cognition is measurable, questions as to the mechanisms by which education improves cognitive function and in what way this association is modulated by genetics still remain.

In this context, cohort studies considering an interaction of genotype with non-genetic influences could enhance and improve the understanding of human intelligence and cognitive development across the life span. Apart from that, further large-scale candidate gene and genome-wide association studies are needed to identify genetic variations and single-nucleotide polymorphisms (SNPs) that show significant associations with cognitive function. The recognition of genetic variations that impact cognition and educational attainment would enable the initiation of tailored educational interventions that could improve outcomes in educational attainment. Also, it would be interesting for future longitudinal intervention studies to determine whether the beneficial effects of education can only be produced through exposure in early life or whether they can also result from mental stimulation later on; in the latter case strategies that employ cognitive stimulation would be an essential tool. Concerning early educational intervention, studies aimed at the schooling of low SES children could examine if additional teaching is able to improve cognitive skills of the intervention group compared to controls during and beyond the period of intervention. Standardized cognitive testing such as the one used in the present study would have to be conducted at various points in time to measure the (long-term) effects of education on cognitive development. Furthermore, it would be instructive to investigate other correlates of education and income/wealth such as parental education, occupation and property ownership and- as was done in the present study- neighborhood SES, as these factors might contribute to a mentally stimulating environment (29). These data could be obtained by standardized questionnaires or census data.

Generally, analyses with a longitudinal approach that examine socio-economic factors and their interactions over the life span could aid the understanding of the impact of education and income not just on current cognitive function, but also on cognitive development and decline, which appears crucial in an aging society. In addition, future early and late life educational intervention studies could confirm the causal effect of additional education in improving cognitive performance.

4.5.3 Neighborhood influence

Even though no significant association was found between urban neighborhood socio-economic context and cognition, it is still possible that neighborhood circumstances have an effect on individual cognition that was just not measurable with the neuropsychological test methods employed or with the spatial concept of neighborhoods used. Previous studies have suggested an independent effect of adverse (urban) neighborhood conditions on cognition beyond individual-level characteristics. Neighborhood-level improvement programs would have the potential to reach a large number of people compared to individual-level approaches. Therefore further and more detailed longitudinal analyses of different domains of cognitive function are needed in the neighborhood context in order to re-evaluate the possible effect of neighborhood differences on individual cognition. Future studies with a longitudinal design should also collect data concerning length of residence in one neighborhood and concentrate on a sample of older people who are more likely to be influenced by their neighborhood environments due to reduced mobility, age-related reductions of functional abilities and lengthened exposure (149). Also, a more comprehensive neuropsychological testing (e.g. also involving visual-motor functioning, visuo-spatial memory, spatial abilities, more complex problem solving and emotion regulation) might help to detect even small differences in cognitive performance.

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Eidesstattliche Erklärung

„Ich, Lisa Christine Adams, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Association of childhood trauma, socio-economic status and neighborhood status with cognitive function“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

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Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Betreuer/in, angegeben sind. Sämtliche Publikationen, die aus dieser Dissertation hervorgegangen sind und bei denen ich Autor bin, entsprechen den URM (s.o) und werden von mir verantwortet.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum Unterschrift

Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version dieser Arbeit nicht veröffentlicht.

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