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Diploma Thesis

HIV-infection and cognitive abilities

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Abstract

Background: People living with human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) often suffer from neurological disorders which are caused by the virus. The issue of HIV-associated neurocognitive disorders (HAND) is particularly relevant because of increasing incidences of milder forms of HAND. Therefore, early detection of neurocognitive deficits in HIV patients is becoming more and more important due to the implementation of pharmacological treatment.

Objective: The aim of this study was to examine cognitive abilities and deficits as well as self-rated levels of depression, forgetfulness, daily living skills and quality of life and sleep in HIV patients who were selected according to strict criteria and compare them to a healthy control group. The diagnosis of HIV-associated neurocognitive impairment was made by using different methods of classification.

Design: Explorative study.

Setting: HIV outpatient clinic.

Participants: 39 HIV patients who came to the HIV outpatient clinic at the Department of Dermatology of Vienna General Hospital (AKH) for their check-up appointments and met the inclusion criteria were included in the study. They were compared to 42 matching healthy controls of the Department of Neurology.

Results: HIV patients did not differ from healthy controls in their cognitive abilities or in self-rated levels of depression, forgetfulness, daily living skills and quality of life and sleep. Categorizing cognitive deficits of HIV patients according to the Frascati criteria revealed the following results: 8 HIV patients (20.5%) were classified as cognitively healthy, 11 subjects (28.2%) had nonamnestic asymptomatic neurocognitive impairment (ANI) and 20 (51.3%) met the criteria for amnestic ANI. By using the Diagnostic and Statistic Manual of Mental Disorders, fifth edition (DSM V) with minimum mode of determination, the total sample of 39 HIV-infected people consisted of 2 cognitively healthy subjects (5.1%), 18 (46.2%) were given the diagnosis nonamnestic mild neurocognitive disorder (NCD) and 19 HIV patients (48.7%) met the criteria for amnestic mild NCD. According to the DSM V with mean method of determination, 27 HIV patients (69.2%) were classified as cognitively healthy, 10 subjects (25.6%) met the criteria for nonamnestic mild NCD and 2 (5.1%) had amnestic mild NCD. The comparison of the subgroups of HIV patients and the control group in terms of their self-rated levels of depression, forgetfulness, daily living skills and quality of life and sleep revealed no significant differences in any method of classification.

Conclusion: HIV patients who are as comparable as possible to a healthy control group also show a similar cognitive performance and similar ratings of depression, forgetfulness, daily living skills and quality of life and sleep as the matched healthy sample. The prevalence of cognitive impairment is substantially affected by the criteria used for diagnosis. If the presence of impairment on cognitive measures in at least two different cognitive domains is required for diagnosis (Frascati criteria), 79.5% of people are classified as cognitively impaired. If the presence of impairment on a single cognitive measure is sufficient for the diagnosis (Minimum mode), the prevalence of cognitive impairment is 94.9%. By requiring the presence of impairment on a mean composite score of a certain domain as criterion for diagnosis (Mean mode), 30.8% of subjects are diagnosed

with cognitive impairment. These different prevalence estimations indicate the importance of developing guidelines for the operationalization of cognitive impairment due to HIV-infection.
Keywords: HIV-infection, cognitive abilities, HIV-associated neurocognitive disorders (HAND), Frascati criteria, DSM V, minimum and mean mode of determination, neuropsychological testing, Neuropsychological Test Battery Vienna (NTBV).

Abstract (Deutsch)

Hintergrund: Menschen, die das humane Immunodefizienz-Virus (HIV) oder erworbene Immunschwäche-Syndrom (AIDS) haben, leiden häufig auch an neurologischen Störungen, die durch diese Erkrankungen verursacht werden. Vor allem die Inzidenz der milderen Formen von HIV-assoziierten neurokognitiven Störungen (HAND) nimmt zu. Die Früherkennung neurokognitiver Defizite bei HIV-Patienten wird daher zunehmend wichtiger, vor allem im Hinblick auf die indizierte pharmakologische Behandlung.

Ziele: Das Ziel der Studie war die Untersuchung von kognitiven Fähigkeiten und Defiziten sowie dem selbst eingeschätzten Ausmaß an Depression, Vergesslichkeit, Alltagsfertigkeiten, Lebens- und Schlafqualität in einer nach strengen Kriterien ausgewählten Stichprobe von HIV-Patienten, welche mit einer gesunden Kontrollgruppe verglichen wurde. Für die Diagnose von HIV-assoziierten neurokognitiven Störungen wurden unterschiedliche Klassifikationsmethoden angewendet.

Design: Explorative Untersuchung.

Setting: HIV-Ambulanz des AKH Wien.

Teilnehmer: 39 HIV-Patienten, die zu ihren Kontrollterminen in die HIV-Ambulanz kamen und die Einschlusskriterien der Studie erfüllten, wurden getestet. Diese wurden mit 42 angepassten gesunden Kontrollpersonen verglichen.

Ergebnisse: HIV-Patienten unterschieden sich nicht von der gesunden Kontrollgruppe hinsichtlich ihrer kognitiven Fähigkeiten und des selbst eingeschätzten Ausmaßes an Depression, Vergesslichkeit, Alltagsfertigkeiten, Lebens- und Schlafqualität. Die Kategorisierung von HIV-Patienten hinsichtlich ihrer kognitiven Beeinträchtigungen mittels der Frascati Kriterien lieferte folgende Ergebnisse: 8 Patienten (20.5%) wurden als kognitiv gesund klassifiziert, 11 Personen (28.2%) hatten eine nonamnestische asymptomatische neurokognitive Beeinträchtigung (ANI) und 20 (51.3%) erfüllten die Kriterien für amnestisches ANI. Bei Verwendung des Diagnostic and Statistic Manual of Mental Disorders, fifth edition (DSM V) und der Minimum Methode bestand die Stichprobe der HIV-Patienten aus 2 kognitiv gesunden Personen (5.1%), 18 (46.2%) bekamen die Diagnose nonamnestische milde neurokognitive Störung (NCD) und 19 HIV-Patienten (48.7%) erfüllten die Kriterien für eine amnestische milde NCD. Nach dem DSM V und der Mean Methode wurden 27 HIV-Patienten (69.2%) als kognitiv gesund klassifiziert, 10 Personen (25.6%) erfüllten die Kriterien für eine nonamnestische milde NCD und 2 (5.1%) hatten eine amnestische milde NCD. Der Vergleich der Subgruppen von HIV-Patienten mit der Kontrollgruppe im Hinblick auf deren selbst eingeschätztes Ausmaß an Depression, Vergesslichkeit, Alltagsfertigkeiten, Lebens- und Schlafqualität zeigte keine signifikanten Unterschiede in einer der Klassifikationsmethoden.

Konklusion: HIV-Patienten, die so vergleichbar wie möglich mit einer gesunden Kontrollgruppe sind, zeigen auch ähnliche kognitive Leistungen und ein vergleichbares selbst eingeschätztes Ausmaß an Depression, Vergesslichkeit, Alltagsfertigkeiten, Lebens- und Schlafqualität wie die gesunde Stichprobe. Die Häufigkeit von kognitiven Beeinträchtigungen wird stark von den Kriterien beeinflusst, die für die Diagnose verwendet werden. Wenn eine Beeinträchtigung in kognitiven Tests in mindestens zwei verschiedenen kognitiven Domänen für die

Diagnose verlangt wird (Frascati Kriterien), werden 79.5% der HIV-Patienten als kognitive beeinträchtigt klassifiziert. Reicht das Vorhandensein einer einzigen unterdurchschnittlichen Testleistung für die Diagnose aus (Minimum Methode), so liegt die Prävalenz von kognitiven Beeinträchtigungen bei 94.9%. Wenn ein unterdurchschnittlicher Mittelwert einer kognitiven Domäne als Diagnosekriterium benötigt wird (Mean Methode), werden 30.8% der Personen als kognitiv beeinträchtigt eingestuft. Diese unterschiedlichen Prävalenzraten weisen auf die Wichtigkeit der Entwicklung von konkreten Anleitungen zur Operationalisierung von HIV-assoziierten kognitiven Beeinträchtigungen hin.
Schlüsselwörter: HIV-Infektion, kognitive Fähigkeiten, HIV-assoziierte neurokognitive Störungen (HAND), Frascati Kriterien, DSM V, Minimum und Mean Methode, neuropsychologische Testung, Neuropsychologische Testbatterie Vienna (NTBV).

1. Introduction

Human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) as well as the related HIV-associated disorders of all kinds have become intensively investigated issues since the discovery and description of the disease in the 1980ies. HIV and AIDS do not only impair people's immune systems and physical health but also have an impact on their cognitive abilities and mental health. When the brain gets affected by the disease, so-called HIV-associated neurocognitive disorders (HAND) can occur. As the number of people who are living with HIV as well as the life expectancy of those concerned increases, the diagnosis of HAND becomes more and more important in order to implement pharmacological treatment and prevent severe forms of neurocognitive disorders. Therefore, also different classification methods of cognitive impairment play an important role in generating diagnoses of HAND.

1.1 Human immunodeficiency virus (HIV)

Human immunodeficiency virus is a retrovirus that belongs to the lentivirus group which infects the human immune system and in the further course causes the acquired immunodeficiency syndrome (AIDS). AIDS was first described as new disease in 1981 and it was hypothesized that lifestyle factors are causally related to this illness. The initially affected population were men who had sex with men what led to a high stigmatization of the disease and those concerned from the very beginning. In 1983, the human immunodeficiency virus was finally identified as the true cause of AIDS (Hoffmann & Rockstroh, 2012). The virus weakens the immune system by destroying white blood cells, for example T helper cells, CD4 T cells and macrophages which usually fight and kill germs that enter the human body. The more white blood cells get destroyed, the less the human body is able to fight the germs in the environment and within the body. Without antiretroviral

treatment, people with AIDS mostly die of diverse diseases the body is not able to overcome any more (Douek, Roederer & Koup, 2009; WebHealthCentre, 2015). In 1987, the first antiretroviral drug (Zidovudine) against HIV was approved for the treatment which led to an alleviation of symptoms and delay of the onset of AIDS. After this medical breakthrough, AIDS which was believed to lead inevitably to death, turned out to be a disease that can be durably and effectively treated (Hoffmann & Rockstroh, 2012; Sepkowitz, 2001).

Worldwide, around 36.9 million people are infected with HIV, whereas almost half of those concerned (48%) know about their disease and 19 million people are not aware of their HIV-positive status. Generally, older people have higher levels of awareness of their HIV status compared to younger people living with HIV (The Gap Report, 2014). By now, people in almost all countries of the world have been affected by HIV, whereas the disease illustrates a rather minor health care problem in industrialized countries. In Sub-Saharan Africa, in contrast, where every fifth person dies of AIDS, it has become the most frequent cause of death (Hoffmann & Rockstroh, 2012). By the end of 2013, 24.7 million people living with HIV were located in Sub-Saharan Africa which made up about 71% of the global total. Since people are living longer because of antiretroviral therapy (ART), the number of persons who get infected is still increasing. Nevertheless, the new infections are already on the decline. In 2014, there were 2 million new infections which is a decline of 41% from 2001 where 3.4 million people got infected with HIV. Being infected with HIV does not mean certain death any more. People who are on antiretroviral therapy and live in a high-income setting have nearly the same life expectancy as people not infected with the virus. Globally, almost 12.9 million people received HIV treatment at the end of 2013 which is 27% more than in 2006. However, three out of five people are still not treated with antiretroviral therapy. Since 1995, HIV treatment has prevented 7.6 million deaths. The key populations that are at the highest risk of HIV-infection are gay men and men who have sex with men. Worldwide, gay men and men who have sex with men are 19 times more likely to be infected with HIV than the rest of the population. They often face a double stigma because of their sexual orientation and their HIV-positive status which increases their risk of being discriminated or becoming victims of violence (The Gap Report, 2014). Especially in industrialized countries, the most common transmission route is homosexual intercourse, whereas in Africa the majority of people get infected by heterosexual intercourse. Generally, the main transmission routes of

HIV are unsafe sex with an HIV-positive person as well as sharing injections with HIV-infected people (especially drug addicts) and transfer from the HIV-infected mother to the baby which is possible to occur prenatal, at birth or later due to breastfeeding (Hoffmann & Rockstroh, 2012).

One of the two main clinical staging systems to classify HIV and HIV-related diseases is the WHO disease staging system for HIV-infection and disease (World Health Organization [WHO], 2007) which has defined four stages of HIV-infection. In the course of HIV, without antiretroviral therapy, there arises a so-called acute retroviral syndrome shortly after primary infection. Unspecific symptoms such as fever, lymphadenopathy and muscular pain can occur but typically do not last longer than four weeks so that HIV-infection is usually not diagnosed without additional testing. The acute infection is followed by several years in which most HIV-positive people do not show clinical symptoms (stage I). As the disease progresses, symptoms and illnesses like herpes zoster can occur and a decrease of CD4 T cells is observed (stages II and III). HIV as possible cause should always be taken into consideration (Hoffmann & Rockstroh, 2012; WHO, 2007). Eight to ten years after infection, when the CD4 T cell count drops below 200 cells/µl and AIDS defining illnesses occur, HIV-infection has turned into AIDS (stage IV) (WHO, 2007). Without antiretroviral therapy, AIDS defining illnesses may be lethal at some point (Hoffmann & Rockstroh, 2012).

HIV and AIDS do not only affect people's physical health but also have an impact on their cognitive abilities (HIV-associated neurocognitive disorders, see chapter 1.2) and mental health. A study of Ciesla and Roberts (2001) found that the prevalence of major depressive disorder was nearly two times higher in HIV-infected people than in the healthy control group. Similar results to the extent that depression appears to be more common among HIV-infected persons than in the general population were also reported in other studies (e.g., Basu, Chwastiak & Bruce, 2005; Maj et al., 1994).

HIV-infection has also a negative effect on people's health-related quality of life (HRQoL). Miners et al. (2014) and Pozniak (2014) found that people living with HIV have a significantly lower HRQoL than HIV-negative persons.

Addressing the quality of sleep, it has been found that the prevalence of insomnia in HIV-infected persons is not significantly higher compared to healthy people (Crum-Cianflone et al., 2012).

1.2 HIV-associated neurocognitive disorders (HAND)

HIV-associated neurocognitive disorders (HAND) is a common term for neurological disturbances associated with HIV-infection and AIDS. They constitute one of the most common clinical disorders among people infected with HIV (Antinori et al., 2007).

1.2.1 History of HAND.

Before 1987, when Grant et al. published the first study of HIV-associated neurocognitive disturbances, the existence of neurological impairment caused by HIV was much disputed. There was only one definition of neurocognitive disorder due to HIV existing, which was known as the AIDS dementia complex (ADS) (American Academy of Neurology AIDS Task Force, 1991). The findings of Grant and colleagues (1987) proved that neurocognitive dysfunctions occur across all stages of HIV and affect several cognitive abilities, which will be explained in chapter 1.2.2. In 1991, the AIDS Task Force of the American Academy of Neurology (AAN) published the first diagnostic guidelines to classify the neurologic disturbances caused by HIV. Two categories of neurological impairment were defined: the HIV-associated dementia (HAD) and the minor cognitive motor disorder (MCMD). HAD was applied to patients who showed the most severe form of cognitive disturbances whereas MCMD represented patients that did not meet the criteria for HAD but had neurocognitive or behavioral impairments that affected their daily life (AAN, 1991). In 2007, a working group supported by the National Institute of Mental Health (NIMH) introduced a further revised classification of HAND (Antinori et al., 2007). The so-called Frascati criteria describe besides HAD two other HAND subtypes: mild neurocognitive disorder (MND) and asymptomatic neurocognitive impairment (ANI). HAD, the most severe form of HAND is defined by moderate to severe impairment in standardized neuropsychological tests (≥ 2 standard deviations (SD) below the mean of adjusted normative scores) in at least two different cognitive domains along with marked difficulties in activities of daily living (ADL). The impairment does not meet the criteria for delirium or is attributable to comorbidities. MND refers to a mild to moderate impairment in standardized neuropsychological tests (≥ 1 SD below adjusted normative means) in at least two cognitive areas with an additional everyday functioning impairment. The impairment does not meet the criteria for delirium or dementia or can be explained by comorbid conditions. ANI is marked by neuropsychological testing impairment (≥ 1 SD below the mean of adjusted norms) in at least two cognitive domains but without causing observable declines in

everyday functioning (Antinori et al., 2007).

The Frascati criteria specify that neuropsychological testing used for the diagnosis of HAND should cover multiple ability domains: “Ideally, the examination would include tests of the following ability domains (if possible, with at least two test measures per domain): verbal/language; attention/working memory; abstraction/executive; memory (learning; recall); speed of information processing; sensory-perceptual; motor skills (Antinori et al., 2007, p. 1796).

Although the incidence of HAD has declined due to the introduction of antiretroviral therapy (Sacktor et al., 2001), milder forms of HIV-associated disorders are still very common (Heaton et al., 2010). In various studies, the prevalence of HIV-associated dementia in the pre-ART era was estimated. In 1993, McArthur et al. found that the prevalence of HAD was 16% in people with AIDS who did not receive antiretroviral treatment. Other prevalence estimates of HAD five years later ranged from 10 to 15% among HIV-infected people (McArthur & Grant, 1998). Gonzales-Scarano and Martin-Garcia (2005) claimed that 20 to 30% of people with advanced HIV have developed HIV-associated dementia in the pre-ART era. According to Valcour, Paul, Chiao, Wendelken, and Miller (2011), HAD was observed in 6 to 30% of people with AIDS before the availability of antiretroviral therapy. In 2010, Heaton and colleagues carried out the CHARTER study to investigate the prevalence of HAND in the era of ART. They found that neuropsychological impairment occurred in 46.9% of the sample without severe comorbidities, whereas 32.7% of study participants had ANI, 11.7% met the criteria for MND and only 2.4% were diagnosed with HAD. These results show, that HIV treatment has greatly reduced HIV-associated dementia but seems to have less impact on milder forms of HIV-associated neurocognitive disorders.

A second more recent classification system of HIV-associated neurocognitive disorders is provided in the Diagnostic and Statistic Manual of Mental Disorders, fifth edition (DSM V) (American Psychiatric Association [APA], 2013). There, two forms of neurocognitive disorders (NCD) due to HIV-infection are differentiated: major and mild NCD. For the diagnosis of major or mild NCD due to HIV-infection a documented infection with human immunodeficiency virus is required. Major NCD corresponds to dementia in the DSM IV (APA, 1994) and caused by HIV-infection it is defined by impairment in one or more cognitive domains with performance that is typically 2 or more standard deviations below appropriate norms. The cognitive deficits have a negative impact on independence in

everyday activities and do not occur in the context of a delirium or due to other mental disorders (e.g., depressive disorder). Furthermore, the neurocognitive disorder is not better explained by non-HIV or other medical conditions. Mild NCD due to HIV-infection is marked by impairment in one or more cognitive domains with performance in the range of 1 to 2 standard deviations below appropriate norms. The cognitive deficits do not have an impact on independence in everyday activities and do not occur in the context of a delirium. Furthermore, they are not primarily attributable to other mental disorders (e.g., depressive disorder) or non-HIV conditions. For both, major and mild NCD the specifications with or without behavioral disturbance are specified (APA, 2013).

In the DSM V, there are six cognitive domains defined which form the basis on which the different neurocognitive disorders may be diagnosed: complex attention, executive function, learning and memory, language, perceptual-motor and social cognition (APA, 2013).

The estimated prevalence of mild NCD in people infected with HIV will be 25%, whereas in less than 5% the criteria for major NCD would be met (APA, 2013).

Regarding the classification of HIV-associated neurocognitive disorders by Antinori et al. (2007) and the criteria for the diagnosis of neurocognitive disorders due to HIV-infection presented in the DSM V (APA, 2013), it can be said that ANI corresponds to mild NCD and HAD is comparable with major NCD.

Because in the DSM V, there are no specifications of determination of the standard deviation higher than 1 below appropriate norms, it is possible to use two different methods of classification: minimum and mean mode of determination (Pusswald et al., 2013). Minimum mode means that a z-score less than -1 SD in at least one of the applied neuropsychological tests of the test battery is sufficient for the diagnosis of NCD. For the mean mode of determination, the mean z-score of all cognitive tests within one specific domain, for example attention, which is less than -1 SD is used for the diagnosis of NCD (Pusswald et al., 2013).

The Frascati criteria are more precise concerning the diagnosis of ANI and MND. They define a z-score less than or equal to -1 SD in neuropsychological tests in at least two cognitive areas which is required to diagnose the milder forms of HIV-associated neurocognitive disorders. This corresponds more likely to the minimum mode than to the mean mode of determination because scores of cognitive tests and not mean scores of cognitive domains are necessary for the diagnosis (Antinori et al., 2007).

Another classification of cognitive impairment that is considered in the

present study comes from Petersen (2004, 2011). He divided mild cognitive impairment (MCI) into two subtypes, namely amnestic MCI (aMCI) and nonamnestic MCI (naMCI). The term amnestic refers to impairment of people's memory with possible deficits in other cognitive functions, for example attention or executive functions. The term nonamnestic means that there are deficits in one or more cognitive domains but the memory itself is not impaired.

1.2.2 HAND and the brain.

HIV enters the brain early after primary infection and causes inflammatory reactions in the central nervous system (CNS) which lead to HIV-associated neurocognitive disorders (Powderly, 2000). Masliah, DeTeresa, Mallory, and Hansen (2000) found that the brain is the second most frequently infected organ after the lungs. The virus invades the brain by being carried in monocytes and lymphocytes that cross the blood brain barrier (BBB) via a so-called "Trojan Horse" mechanism (Hult, Chana, Masliah & Everall, 2008). After crossing the BBB, the HIV-infected monocytes differentiate into macrophages and replicate the virus in the CNS (Albright, Soldan & González-Scarano, 2003; Letendre, 2011).

The brain regions in which HIV is most prevalent are the basal ganglia and the thalamus as well as the frontal neocortex and the hippocampus (Bragança & Palha, 2001; Wiley et al., 1998). Findings of Archibald and colleagues (2004) show that white matter tracts which connect the basal ganglia and the neocortex are also affected by the virus. In the pre-ART era, the most common presentation of HAND was subcortical damage and cortical deficits occurred only in more advanced stages of HIV. Since the introduction of antiretroviral therapy, however, cortical functions are reported to be more and more involved (Heaton et al., 2011). Damage in the brain regions described above leads to deficits in the cognitive abilities learning and memory (episodic and semantic), attention and working memory, executive functions, language and speech, visuoperception, information processing and motor skills (Woods, Moore, Weber & Grant, 2009). Impairment in episodic memory occurs very often in the course of HIV and is said to be among the most sensitive indicators of HAND (Heaton et al., 1995; Carey et al., 2004), whereas only mild deficits in semantic memory (famous faces and public events) were observed in people with HAD (Sadek et al., 2004). The severity of impairment of attention, working memory and executive functioning depends on the stage of HIV. In early stages of the disease, the basic skills are hardly affected, whereas in advanced stages, people with HAND show mild to moderate deficits (Reger, Welsh,

Razani, Martin & Boone, 2002). Addressing the ability of language and speech, there are inconsistent findings concerning the impact of HIV on verbal fluency. The meta-analysis of Iudicello and colleagues (2007) found a small verbal fluency deficit which may increase to moderate severity with advanced disease stage. Action fluency (e.g., verbal production of "things that people do"), however, was found to be more severely impaired in HIV. A study of Woods, Carey, Tröster, and Grant (2005) revealed that approximately 60% of people with HAND show signs of impairment in action fluency. In addition, impaired action fluency is associated with declines in activities of daily living (Woods, Morgan, Dawson, Cobb Scott & Grant, 2006). The findings concerning visuoperception and spatial cognition seem to be inconsistent. Heaton et al. (1995) detected no significant visuospatial impairment, whereas an earlier, small investigation of Poutianien, Iivanainen, Elovaara, Valle, and Lähdevirta (1988) as well as a more recent study by Hardy, Castellon, and Hinkin (2004) found that mild deficits in spatial cognition and perceptual span are prevalent in people infected with HIV. Regarding information processing and motor skills, it is widely recognized that bradyphrenia (slowness of information processing) and bradykinesia (slowed movement) are characteristic for HIV-infection and HAND. Hardy and Hinkin (2002) claim that bradyphrenia and bradykinesia are the main symptoms of HIV-associated neurocognitive disorders.

1.2.3 Risk factors and predictors of HAND.

Researchers have found various risk factors and predictors which are associated with an increased probability of developing HAND. Risk factors include HIV disease factors and treatment factors, host factors as well as comorbidities (Letendre, 2011). Disease factors comprise for example low nadir CD4 T cell count (< 200 cells/µl), low current CD4 T cell amount, high plasma viral load and longer duration of HIV-infection. ART adherence, ART interruption and short ART duration rank among treatment factors. Host or demographic factors contain for example female sex, older age, lower levels of education, vascular disease and malnutrition. Comorbidities include infection with hepatitis C, syphilis, alcohol and/or drug abuse and mental illnesses (e.g., depression) (Heaton et al., 2010; Heaton et al., 2011; Letendre, 2011; McCombe, Vivithanaporn, Gill & Power, 2013; Mind Exchange Working Group, 2013). Whereas current plasma viral load and CD4 T cell amount were strongly associated with the risk of cognitive impairment in the pre-ART era, nadir CD4 T cell count constitutes the most important

predictor of HAND in the treatment era (Heaton et al., 2010; Heaton et al., 2011).

1.3 Aim of the study

The purpose of this study was to estimate the prevalence of amnestic/nonamnestic HAND and amnestic/nonamnestic mild NCD using the Frascati criteria and the DSM V with two different modes of determination (minimum and mean mode) in a sample of HIV patients that was selected according to very strict criteria. These strict criteria were used to ensure that possible cognitive impairment is not better explained by other factors than HIV-infection. This aspect of the study makes it innovative and unique because so far, no study is known where such a "clean" sample of HIV patients has been compared to a healthy control group. Besides the HIV patients, the healthy controls had to fulfill certain criteria too. The strict selection of the two groups also served to match certain characteristics of HIV patients and healthy controls and make them as similar and comparable as possible. As part of the diagnoses of HAND (specifically ANI) or mild NCD by using the Frascati criteria or the DSM V with minimum and mean mode of determination, Chi-square tests were conducted to compare the resulting prevalence rates. Furthermore, differences in cognitive abilities and questionnaires concerning depression, forgetfulness, daily living skills and quality of life and sleep between the experimental group and the control group were computed. Taking into consideration the diagnoses of HIV patients according to the different classification methods, the differences between their subgroups and the control group in the applied questionnaires were calculated. Furthermore, correlations between cognitive impairment and duration of HIV, current amount of CD4 T cells and nadir CD4 T cell count were computed for each classification method.

In the present study, it was hypothesized that the prevalence rates of neurocognitive impairment differ depending on which classification method is chosen for the diagnosis. It was assumed that there are more cognitively impaired persons among HIV-infected people by using the DSM V with minimum method of determination than classifying people according to mean method of determination. The prevalence of people with cognitive deficits diagnosed by using the Frascati criteria was expected to lie somewhere between the rates of DSM V minimum and mean mode.

Based on the literature above, it was hypothesized that HIV patients and healthy controls do not differ to a high extent in their cognitive abilities because of the strict inclusion criteria. Furthermore, worse subjective ratings of health-related quality of life and higher ratings of depression

among HIV patients were assumed, whereas quality of sleep was expected to be similar in both groups. Concerning cognitive impairment and duration of HIV-infection, a positive correlation was assumed, whereas the relationship between cognitive impairment and current amount of CD4 T cells or nadir CD4 T cell count should be negative.

2. Methods

2.1 Subjects and procedure

The data used for the present exploratory study were collected in the HIV outpatient clinic at the Department of Dermatology and the memory outpatient clinic at the Department of Neurology of the Vienna General Hospital (AKH). The investigation was carried out in accordance with the ethical principles of Helsinki's Declaration and approved by the Ethics Committee of the Medical University of Vienna. Furthermore, all participants of the study signed an informed consent. The data of the healthy control group were provided by the Vienna Conversion to Dementia Study (VCDS) of the Medical University of Vienna, administrated by the Department of Neurology. HIV patients were recruited when they came in the HIV outpatient clinic for their check-up appointments. It was agreed that they get a feedback of their cognitive abilities and deficits that were assessed by using the Neuropsychological Test Battery Vienna (NTBV) (Lehrner, Maly, Gleiß, Auff, & Dal-Bianco, 2007). HIV patients were selected by using a brief screening of the cognitive status and strict inclusion criteria. A Mini-Mental-State-Examination score (MMSE) (Folstein, Folstein & McHugh, 1975) greater than or equal to 24 that had to be reached ensured that only HIV patients that did not show evidence for dementia were participating in the study. Furthermore, age between 18 and 60 years, no hepatitis B- or C-infection, no alcohol or drug abuse, no mental illness (e.g., depression), no vascular pathologies, no syphilis, 500 or more CD4 T cells/µl at testing time, no nadir below 350 CD4 T cells/µl, HI-viral load below limit of detection and on treatment with antiretroviral therapy were requirements for HIV patients. Besides the HIV patients, the healthy controls had to fulfill certain criteria too: a Mini-Mental-State-Examination score of 27 or higher, age between 18 and 60 years, no hepatitis B- or C-infection, no alcohol or drug abuse, no mental illness, no vascular pathologies and no syphilis. To make the HIV patients and the control group as comparable as possible, they were matched in terms of sex, age, education and IQ that was assessed by the Wortschatztest (WST) (Schmidt & Metzler, 1992).

The resulting total sample of N = 81 included 39 HIV patients and 42 healthy controls between 20 and 60 years of age

(M = 41.6, SD = 12.3) of which 32 were female (39.5%) and 49 were male (60.5%). Years of education ranged from 8 to 20 (M = 13.8, SD = 3.8). The experimental group consisted of 7 women (17.9%) and 32 men (82.1%) between 20 and 57 years of age (M = 39.5, SD = 9.9). Mean years of education were 13.3 (SD = 3.7) and the mean MMSE score was 28.0 (SD = 1.7). HIV patients had a mean CD4 T cell amount of 844.2 cells/µl (SD = 235.0) and nadir CD4 cell count ranged from 350 to 896 cells/µl (M = 531.9, SD = 135.7). The mean duration of HIV was 48.6 months (SD = 66.6). In the control group, there were 14 women (40.5%) and 25 men (59.5%) between 21 and 60 years of age (M = 43.6, SD = 14.0). Years of education ranged from 9 to 20 (M = 14.2, SD = 4.0) and the mean MMSE score was 29.0 (SD = 1.0).

2.2 Neuropsychological measurement

2.2.1 Screening procedures.

For an overview of the cognitive status, a screening with the Mini-Mental-State Examination (MMSE) (Folstein et al., 1975) and the clock drawing test after Sunderland et al. (1989) were performed.

2.2.2 Assessment of objective cognitive performance.

After the brief screening, the standardized, validated and normed NTBV was applied. Actually designed to detect dementia in a clinical setting, the NTBV investigates a wide range of cognitive abilities that are impaired in individuals with cognitive decline (Lehrner et al., 2007; Pusswald et al., 2013). Therefore, this test battery was also used in the sample of HIV patients to diagnose cognitive deficits that could be due to HIV infection. The NTBV includes the following cognitive function domains: attention, executive functioning, language and memory with domain- and total z-scores across all tests (Lehrner et al., 2007; Pusswald et al., 2013).

The Alters-Konzentrations-Test (AKT) (Gatterer, 2008), the Digit-symbol subtest of the German Wechsler Adult Intelligence Scale- Revised (WAIS-R Zahlen-Symbol-Test) (Tewes, 1994), the Symbol counting task from the Cerebral Insufficiency Test (C.I.) (Lehrl & Fischer, 1997), the Trail Making Test B (TMT B) (Reitan, 1979) and the score difference of the Trail Making Test A (TMT A) and TMT B (Reitan, 1979) were applied to assess attention.

Executive functions were investigated by using the TMT A (Reitan, 1979), the Five-Point Test (Regard, Strauss & Knapp, 1982), the Maze test and the Stoop test from the Nürnberger Aging Inventory (NAI) (Oswald & Fleischmann, 1997) and the Interference subtest from the C.I. (Lehrl & Fischer, 1997). Additionally, the Phonematic Verbal Fluency Test (PWT)

was applied to tap lexical verbal fluency. In this test, participants were required to name as many words as possible beginning with the letters b, f, and l within one minute for each letter (Goodglass & Kaplan, 1983).

To test language functions, two tests were applied. The Semantic Verbal Fluency Test (SWT) in which participants should name as many animals, supermarket items and tools as the can within one minute for each task was used to tap semantic verbal fluency (Goodglass & Kaplan, 1983). Secondly, the modified Boston Naming Test (BNT) (Morris et al., 1989) was used for assessing naming capabilities.

Episodic memory was examined by using the Verbal Selective Reminding Test (VSRT) (Lehrner, Gleiß, Maly, Auff, & Dal-Bianco, 2006) with the subtests of immediate recall, total recall, delayed recall and recognition.

2.2.3 Additional testing and questionnaires.

In addition to the NTBV, the Wortschatztest for assessing the IQ and the City- and Face- Test (Lehrner, 2001) for assessing semantic memory were performed. Furthermore, questionnaires for self-evaluation of depression (Beck Depression Inventory Revision, BDI-II) (Hautzinger, Keller & Kühner, 2009), forgetfulness (Forgetful Assessment Inventory, FAI) (Lehrner et al., 2014), daily living skills (Bayer activities of daily living scale, B-ADL) (Erzigkeit & Lehfeld, 2010), health-related quality of life (Short-Form 36 Health Survey, SF-36) (Bullinger & Kirchberger, 1998) and sleep (Pittsburgh Sleep Quality Index, PSQI) (Buysse, Reynolds, Monk, Berman & Kupfer, 1989), (Epworth Sleepiness Scale, ESS) (Johns, 1991) were applied.

2.3 Classification procedure

The HIV patients were categorized in different groups of cognitive impairment based on their neuropsychological test results. For this classification, the raw scores of all subtests of the NTBV were transformed into z-values which were calculated depending on age, gender and education of a cognitively healthy control sample because it has been shown that demographic variables have an influence on cognitive variables (Chandler et al., 2005; Pusswald et al., 2013).

Based on the guidelines of HAND classification of Antinori and colleagues (2007) that were described earlier, the following subgroups of HIV patients resulted: cognitively healthy, nonamnestic ANI and amnestic ANI. In the present study, there were no patients with MND or HAD because of the strict inclusion criteria.

The categorization of NCD according to the DSM V with minimum mode of

determination (APA, 2013) led to the following subgroups of HIV patients: cognitively healthy, nonamnestic mild NCD and amnestic mild NCD. The same subgroups resulted by using the DSM V with mean mode of classification. Again, the more severe form of NCD, namely major NCD, was not prevalent among HIV patients in the present study.

As already mentioned, ANI is comparable with mild NCD because in both forms of neurocognitive impairment, everyday functioning is not impaired.

2.4 Statistical analysis

For the statistical analyses of the data, IBM SPSS statistics 22.0 for Windows was used. The sample and subgroup characterization was made by utilizing descriptive statistics and demographic variables and neuropsychological data were described by means and standard deviations. According to the central limit theorem, the sample's mean distribution is supposed to be normally distributed if the sample size exceeds N > 30 (Bortz & Döring, 2006; Field, 2009) Therefore, normal distribution in the experimental group as well as in the control group was assumed. The level of significance was set at 0.05% across all statistical procedures. For the comparison of HIV patients and the control group in terms of their cognitive abilities and the applied questionnaires, independent samples t-tests with Bonferroni correction were conducted. Thereafter, effect sizes were calculated. According to Cohen (1988), an effect size of d = 0.2 might be a small effect, d = 0.5 represents medium effect size and d = 0.8 a large effect. After the diagnosis of cognitive impairment according to the Frascati criteria and the DSM V with minimum and mean mode of determination, Chi-square tests and effect sizes were calculated to compare the resulting prevalence rates in HIV patients. An effect size of φ = 0.1 is considered a small effect, φ = 0.3 a medium effect and φ = 0.5 a large effect (Cohen, 1988). Thereafter, the differences between the three caused subgroups and the control group in the applied questionnaires were computed for each classification method (Frascati, DSM V minimum & DSM V mean mode) by using Kruskal-Wallis tests with Bonferroni correction. The assumptions for ANOVA were not fulfilled because of small and unequal group sizes and missing normal distribution (Field, 2009). To investigate the relationship between cognitive impairment and duration of HIV, current amount of CD4 T cells and nadir CD4 T cell count, point-biserial correlations were calculated for each classification method. The resulting effect sizes of the correlations were interpreted according to Cohen (1988) who classifies r = 0.1 as

small effect, r = 0.3 as medium effect and r = 0.5 as large effect.

3. Results

A total of 81 adults who came to the HIV outpatient clinic and the memory outpatient clinic participated in this study. The sample consisted of 49 men (60.5%) and 32 women (39.5%) between 20 and 60 years of age (M = 41.6, SD = 12.3). Mean years of education were 13.8 (SD = 3.6). In the experimental group, there were 39 HIV patients, whereas the control group consisted of 42 healthy subjects. In the sample of HIV-infected people, the lowest achieved MMSE score was 24 (SD = 1.7), whereas all healthy controls reached a MMSE score of at least 27 (SD = 1.0). For the comparison of cognitive abilities and differences in the applied questionnaires between the experimental group and the control group, the neuropsychological test variables of the NTBV as well as questionnaire variables represented the dependent variables. In table 1, means and standard deviations for demographic variables as well as for neuropsychological test variables of the total sample and the two main comparison groups (control group and HIV patients) are listed. Table 2 shows means and standard deviations of the applied questionnaires of the total sample and the two comparison groups.

After Bonferroni correction, the t-tests revealed no significant differences between HIV patients and healthy controls in terms of their cognitive abilities and the applied questionnaires. T-test results are listed in table 3 and 4.

Of the 39 HIV patients included in this study, 8 (20.5%) were classified as cognitively healthy, 11 subjects (28.2%) had nonamnestic ANI and 20 (51.3%) met the criteria for amnestic ANI according to the Frascati criteria. By using the DSM V with minimum mode of determination, the total sample of 39 HIV-infected people consisted of 2 cognitively healthy subjects (5.1%), 18 (46.2%) were given the diagnosis nonamnestic mild NCD and 19 (48.7%) met the criteria for amnestic mild NCD. According to the DSM V with mean method of determination, 27 HIV patients (69.2%) were classified as cognitively healthy, 10 subjects (25.6%) met the criteria for nonamnestic mild NCD and 2 (5.1%) had amnestic mild NCD. Chi-square tests were conducted to compare the prevalence rates of cognitive impairment in HIV patients resulting from different methods of classification. For this purpose, amnestic and nonamnestic cognitive impairment was summarized into one variable named ANI or mild NCD. The resulting dichotomous variable had the levels 0 = cognitively healthy and 1 = ANI or mild NCD, depending on which classification method was used. By comparing the prevalence rates of cognitive impairment in HIV patients who

were classified according to the Frascati criteria or the DSM V with minimum mode of determination a significant difference was found χ^2 (1) = 8.169, $p < .01$. The effect size of $\varphi = 0.458$ represents a moderate to large effect according to Cohen (1988). Classifying HIV patients according to the DSM V with minimum mode of determination led to a higher prevalence of cognitive impairment (94.9%) than using the Frascati criteria (79.5%). A second Chi-square test revealed a significant difference between the prevalence rates of cognitive impairment in HIV-infected subjects who were classified according to the Frascati criteria or the DSM V with mean method of determination χ^2 (1) = 4.473, $p < .05$. The effect size of $\varphi = 0.339$ can be classified as medium effect. Cognitive impairment was more likely to be diagnosed by using the Frascati criteria (79.5%) than the DSM V with mean mode of determination (30.8%).

Kruskal-Wallis tests with Bonferroni correction between the subgroups of each classification method and the control group showed no significant differences in the applied questionnaires. Kruskal-Wallis test results are summarized in table 5 (Frascati criteria), table 6 (DSM V with minimum mode) and table 7 (DSM V with mean mode).

The investigation on correlations between HIV patients and the variables of interest was carried out in the classification methods Frascati criteria, DSM V with minimum mode and DSM V with mean mode. For this purpose, point-biserial correlations were calculated by using the dichotomous variable of cognitive impairment. No significant relationships between cognitive impairment and duration of HIV, current amount of CD4 T cells and nadir CD4 T cell count in any classification method were detected (see Table 8).

4. Discussion

4.1 Summary of results and interpretation

This explorative study investigated whether there are differences in cognitive abilities and self-rated levels of depression, forgetfulness, daily living skills and quality of life and sleep between HIV patients and a healthy control group. Both groups were selected according to strict criteria to make them as comparable as possible and create a clean sample of HIV patients in terms of comorbidities and other factors that could explain cognitive impairment. Because of these strict inclusion criteria, it was expected that HIV patients do not differ from healthy controls their cognitive abilities. The present study confirmed this assumption since there were no significant differences in cognitive abilities between the comparison groups. The expectation that HIV patients show worse subjective ratings of health-related quality of life and higher ratings of depression was not met

because no significant differences in SF-36 and BDI-II between the experimental and the control group were detected. Although the result of the t-test revealed no significant difference between HIV patients and healthy controls in terms of their levels of depression, the effect size was d = 0.442 which represents a small to moderate effect according to Cohen (1988). The mean values of BDI-II show a trend towards higher levels of depression in HIV patients (see table 2). However, the present study provides evidence that the sleep quality of HIV-infected persons is similar to that of healthy people and therefore confirms the results of Crum-Cianflone et al. (2012).

Furthermore, the influence of different decision criteria on generating neuropsychological diagnoses was examined in the present study. The classification according to the Frascati criteria by Antinori and colleagues (2007) and the DSM V with two modes of determination revealed different prevalence rates of cognitive impairment. As expected, the strictest classification method was the DSM V with minimum mode of determination. Since performance in one single cognitive measure that lies in the range of 1 to 2 standard deviations below appropriate norms is sufficient for diagnosis of mild NCD, the prevalence is 94.9%. By using the DSM V with mean mode of determination, the prevalence of mild NCD was hypothesized to be much lower because the mean score of a certain cognitive domain served as criterion for diagnosis. According to this classification method, only 30.8% of HIV patients were diagnosed as being cognitively impaired. As the Frascati criteria require the presence of impairment on cognitive tests in at least two different cognitive domains, the prevalence of HIV patients with ANI was expected to lie somewhere between minimum and mean mode of determination. Since 79.5% of HIV patients were categorized as cognitively impaired, this assumption was confirmed. Chi-square tests revealed significant differences in the prevalence rates of cognitive impairment resulting of different methods of classification. These different prevalence estimations indicate the importance of developing guidelines for operationalizing cognitive impairment due to HIV-infection (Pusswald et al., 2013).

An interesting aspect of the present study concerns the inconsistency of t-test results and diagnoses of cognitive impairment. Although 94.9%, 30.8% or 79.5% of HIV patients were diagnosed with mild NCD or ANI, they did not differ significantly from the control group in any test of the NTBV. Only in the Phonematic Verbal Fluency Test and the Boston Naming Test in which HIV patients achieved better results than the healthy controls medium effect sizes were

observed (see table 1). Mean values and effect sizes of other tests of the NTBV (table 1) show that HIV patients often have even better results than the control group. For example in the Trail Making Test A, HIV patients were faster than the control group and the effect size of d = 0.527 indicates a medium effect. Also in the Maze test from the NAI, HIV patients performed better than the healthy controls. According to Cohen (1988), the effect size of d = 0.682 represents a moderate to large effect. Another test in which HIV patients achieved better results than the control group was the Interference test from the C.I. with an effect size of d = 0.403 that can be classified as small to moderate effect. Therefore, the diagnoses of cognitive impairment in HIV-infected subjects are not consistent with the results of the conducted t-tests. Especially executive functioning seems to be a cognitive ability in which HIV patients perform better than healthy controls.

In general, the non-significant outcomes with their moderate to large effect sizes indicate that the present study is underpowered and a higher number of subjects would have been required to achieve significant results.

Another important finding of the present study that should be given special consideration to is the high prevalence of ANI diagnosed by using the Frascati criteria. With 79.5% it far exceeds the prevalence rates of former studies. For example, in the CHARTER study (Heaton et al., 2010), 32.7% of HIV-infected subjects were diagnosed with ANI which is less than half of the number in the present study. Also the prevalence estimates in the DSM V that suggest that 25% of HIV-infected people will have mild NCD seem too low. According to the DSM V with minimum mode of determination, 94.9% of all HIV patients meet the criteria for mild NCD. By using mean method of classification, 30.8% of HIV-infected subjects are diagnosed with mild NCD which is close to the expected prevalence. These high frequencies of cognitive impairment due to HIV-infection may indicate that the Frascati criteria as well as the minimum mode of determination possibly lead to an overestimation of the real prevalence. Mean mode of determination, however, seems to be more suitable for the diagnosis of cognitive impairment since the prevalence of 30.8% in the present study is similar to that of former investigations.

Kruskal-Wallis tests for calculating the differences between the resulting subgroups of HIV patients and the control group in terms of their self-rated levels of depression, forgetfulness, daily living skills and quality of life and sleep revealed no significant results in any classification method. These outcomes show that HIV patients do not differ from healthy controls

even when they are classified according to different classification methods and get divided into certain subgroups.

The calculated correlations between cognitive impairment and duration of HIV, current amount of CD4 T cells and nadir CD4 T cell count revealed no significant results in any classification method which is contrary to the expectations. Since CD4 T cell amount and nadir CD4 cell count constitute important predictors of HAND in the pre-ART and treatment era (Heaton et al., 2010; Heaton et al., 2011), a significant negative relationship between cognitive impairment and these variables was assumed. For the classification according to the DSM V with minimum mode of determination, the correlations between cognitive impairment and CD4 T cell amount or nadir CD4 cell count were not significant and positive what is contrary to all findings of former studies. However, this positive correlation may be due to the high amount of cognitively impaired subjects resulting of this strict classification method. Also duration of HIV-infection was not significantly positively correlated with cognitive impairment but effect sizes of $r = 0.207$ for the classification according to the Frascati criteria and $r = 0.178$ for the DSM V with mean mode of determination show that there is at least a small effect.

4.2 Strengths and limitations

As most clinical studies, the present investigation has also strengths and limitations that should be considered. A particular strength of this study was the clean sample of HIV patients that resulted from strict inclusion criteria. These strict criteria were used to ensure that possible cognitive impairment is not better explained by other factors than HIV-infection. Furthermore, they also served to match certain characteristics of HIV patients and healthy controls and make them as comparable as possible. So far, no study is known where such a clean sample of HIV-infected subjects was compared to a healthy control group. Therefore, it could make a contribution to the scientific progress. Another strength of the study was the comprehensive neurocognitive and psychosocial testing the participants went through. With the help of the NTBV, a detailed assessment of cognitive deficits was possible. A further important strength of the study was the comparison of two classification methods including the well-tried Frascati criteria and the new DSM V criteria with two different modes of determination. The resulting prevalence rates that range from 30.8% to 94.9% may make a contribution to the essential development of consistent guidelines for operationalizing cognitive impairment.

Besides the strengths of the investigation, there also limitations that need to be addressed. Firstly, the samples

of the present study are very specific so that the generalization of the results to the general population is limited. Another limitation concerns the test battery that was used for the assessment of cognitive deficits. Since the NTBV was developed for dementia diagnostics, certain tests of it (e.g., BNT, VSRT Recognition) are not well suited for young samples because of ceiling effects. This leads to worse test results and false positive rates of cognitive impairment. Therefore, the NTBV as possible cause of the high prevalence rates of cognitive impairment in the present study should be considered. Furthermore, the development of reliable neuropsychological tests that are designed specifically for HIV patients would be clinically very useful. Another negative aspect was the long duration of the neuropsychological testing (between one and one and a half hours) that often led to decreasing concentration and demotivation. Also the current mood of the participants was not considered. Furthermore, the resulting sample sizes after dividing HIV patients in subgroups were relatively small. For example, according to the DSM V with minimum mode of determination only two subjects were classified as cognitively healthy. In view of these small sample sizes, no significant Kruskal-Wallis test results could be expected. Therefore, future research is recommended to include a larger number of subjects to rule out the possibility that significant results fail to appear because of small group sizes.

In conclusion, HIV patients did not differ from a healthy control group in their cognitive abilities and self-rated levels of depression, forgetfulness, daily living skills and quality of life and sleep. The classification of HIV patients according to the Frascati criteria and the DSM V with minimum and mean mode of determination revealed highly different prevalence rates of cognitive impairment.

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Table 1. Sample characteristics and neuropsychological test variables of total sample and two main comparison groups (N=81)

	Total (N=81)	control (n=42)	HIV (n=39)
Female (n/%)	32/ 39.5	14/ 40.5	7/ 17.9
Age (years)	41.6/ 12.3	43.6/ 14.0	39.5/ 9.9
Education (years)	11.8/ 3.6	14.2/ 4.0	13.3/ 3.7
MMSE	28.5/ 1.4	29.0/ 1.0	28.0/ 1.7
WST	106.3/ 10.6	108.1/ 9.3	104.3/ 11.6
AKT time	25.8/ 6.6	25.7/ 7.3	25.9/ 5.9
AKT total/time	2.2/ 0.6	2.3/ 0.7	2.2/ 0.6
Digit-symbol	55.8/ 11.3	54.1/ 11.8	57.7/ 10.6
Symbol counting	18.8/ 3.7	19.1/ 4.0	18.4/ 3.3
TMTA	29.2/ 10.9	31.9/ 12.2	26.4/ 8.6
TMTB	72.3/ 31.4	71.5/ 31.0	73.2/ 32.1
SWT	64.4/ 11.8	62.2/ 10.6	66.8/ 12.9
PWT	37.4/ 10.6	40.0/ 11.5	34.7/8.8
BNT	14.8/ 0.5	14.9/ 0.3	14.6/ 0.6
VST-IR	9.6/ 2.0	9.2/ 2.0	10.1/ 1.9
VSRT-TR	61.1/ 6.4	60.4/ 7.0	61.8/ 5.9
VSRT-DR	13.0/ 2.0	12.9/ 2.1	13.0/ 2.0
VSRT-RECOG	14.8/ 0.6	14.8/ 0.7	14.9/ 0.4
5-Point correct	38.5/ 10.3	39.0/ 11.9	38.0/ 8.6
5-Point perseverations	2.0/ 2.7	1.9/ 2.2	2.2/ 3.1
Stroop colors	21.6/ 4.4	21.2/ 4.2	22.1/ 4.6
Stroop words	38.0/ 12.4	38.7/ 12.9	37.3/ 11.9
Stroop total/time	1.0/ 0.3	1.0/ 0.3	1.0/ 0.2
Stroop interference	16.4/ 9.9	17.4/ 10.4	15.2/ 9.4
Maze test time	25.2/ 9.7	28.0/ 10.8	22.1/ 7.4
Maze test total/time	0.7/ 0.2	0.6/ 0.2	0.8/ 0.2
TMTB-TMTA	43.1/ 27.2	39.6/ 24.6	47.0/ 29.7
Interference time	18.8/ 3.7	19.3/ 3.8	18.2/ 3.6
Interference total/time	1.9/ 0.4	1.8/ 0.3	1.9/ 0.4

Note: variables are presented as mean & standard deviation; control, control group; HIV, experimental group - HIV patients; M, mean; SD, standard deviation; MMSE, Mini Mental State Examination; WST, Wortschatztest; AKT, Alters-Konzentrations-Test: AKT time, AKT total/time; Digit-symbol, Digit-symbol subtest WAIS-R; Symbol counting, symbol counting task C.I.; TMTA, TMTB: Trail Making Test A & B, SWT, Semantic Verbal Fluency Test; PWT, Phonematic Verbal Fluency Test; BNT, Boston Naming Test; VSRT, Verbal selective reminding test; VSRT-IR, VSRT- immediate recall; VSRT-TR, VSRT- total recall; VSRT-DR, VSRT-delayed recall; VSRT-RECOG, VSRT- recognition; 5-Point, Five-Point test: 5-Point correct, 5-Point perseverations; Stroop, Stroop test C.I.: Stroop colors, Stroop words, Stroop total/time, Stroop interference; Maze test NAI, Maze test NAI: Maze test time, Maze test total/time, TMTB-TMTA, TMTB-TMTA difference; Interference, Interference test C.I.: Interference time, Interference total/time

Table 2. Variables of the applied questionnaires of total sample and two comparison groups (N=81)

	Total (N=168)	control (n=42)	HIV (n=39)
BDI-II	5.7/ 6.6	4.4/ 5.2	7.2/ 7.5
GDS	2.3/ 3.2	1.8/ 2.9	2.8/ 3.5
Körperl. Funkt.	94.3/ 11.9	93.7/ 11.6	94.9/ 12.4
Körperl. Rollenfunkt.	89.8/ 23.1	89.3/ 27.1	90.4/ 18.7
Körperl. Schmerzen	90.8/ 18.3	91.6/ 16.2	89.9/ 20.5
Allg. Geswahrnehm.	75.1/ 19.6	75.8/ 22.0	74.4/ 16.8
Vitalität	65.0/ 16.1	64.5/ 16.0	65.5/ 16.5
Soz. Funkt.	88.1/ 17.8	89.9/ 15.4	86.2/ 20.0
Emot. Rollenfunkt.	89.3/ 25.2	90.5/ 22.4	88.0/ 28.1
Psych. Wohlbef.	76.2/ 18.4	76.5/ 17.2	75.9/ 19.9
Körperl. Skala	54.6/ 6.9	54.5/ 8.1	54.6/ 5.4
Psych. Skala	50.5/ 9.2	50.9/ 8.6	50.0/ 10.1
CITY	12.3/ 3.0	12.9/ 2.9	11.7/ 3.0
FACE	13.5/ 2.6	13.6/ 2.5	13.3/ 2.8
FAI	2.0/ 0.7	1.9/ 0.6	2.1/ 0.7
B-ADL	1.4/ 0.5	1.4/ 0.4	1.5/ 0.5
PSQI	4.5/ 2.7	4.0/ 2.5	4.9/ 2.9
ESS	6.8/ 3.5	6.2/ 3.2	7.3/ 3.7

Note: variables are presented as mean & standard deviation; control, control group; HIV, experimental group - HIV patients; M, mean; SD, standard deviation; BDI-II, Beck Depression Inventory Revision; GDS, Geriatrische Depressionsskala Kurzform; Skalen des SF-36, Short-Form 36 Health Survey: Körperliche Funktionsfähigkeit, Körperliche Rollenfunktion, Körperliche Schmerzen, Allgemeine Gesundheitswahrnehmung, Vitalität, Soziale Funktionsfähigkeit, Emotionale Rollenfunktion, Psychisches Wohlbefinden, Körperliche Skala & Psychische Skala; CITY, City-Test; FACE, Face-Test; FAI, Forgetful Assessment Inventory; B-ADL, Bayer activities of daily living scale; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale

Table 3. T-tests on neuropsychological test variables for control group and HIV patients (N=81)

	Control (n=42)		HIV (n=39)				
	M	SD	M	SD	t	p	d
AKT time	25.7	7.3	25.9	5.9	-0.141	0.888	0.031
AKT total/time	2.3	0.7	2.2	0.6	0.431	0.668	0.096
Digit-symbol	54.1	11.8	57.7	10.6	-1.428	0.157	0.318
Symbol counting	19.1	4.0	18.4	3.3	0.820	0.420	0.182
TMTA	31.9	12.2	26.4	8.6	2.372	0.020	0.527
TMTB	71.5	31.0	73.2	32.1	-0.250	0.803	0.056
SWT	62.2	10.6	66.8	12.9	-1.741	0.086	0.387
PWT	40.0	11.5	34.7	8.8	2.322	0.023	0.516
BNT	14.9	0.3	14.6	0.6	2.816	0.007	0.626
VSRT-IR	9.2	2.0	10.1	1.9	-2.091	0.040	0.465
VSRT-TR	60.4	7.0	61.8	5.9	-0.966	0.337	0.215
VSRT-DR	12.9	2.1	13.0	2.0	-0.316	0.753	0.07
VSRT-RECOG	14.8	0.7	14.9	0.4	-0.101	0.920	0.022
5-Point correct	39.0	11.9	38.0	8.6	0.433	0.666	0.096
5-Point perseverations	1.9	2.2	2.2	3.1	-0.423	0.674	0.094
Stroop colors	21.2	4.2	22.1	4.6	-0.987	0.327	0.219
Stroop words	38.7	12.9	37.3	11.9	0.499	0.619	0.111
Stroop total/time	1.0	0.3	1.0	0.2	-0.707	0.481	0.157
Stroop interference	17.4	10.4	15.2	9.4	0.987	0.327	0.219
Maze test time	28.0	10.8	22.1	7.4	2.874	0.005	0.639
Maze test total/time	0.6	0.2	0.8	0.2	-3.066	0.003	0.682
TMTB-TMTA	39.6	24.6	47.0	29.7	-1.231	0.222	0.274
Interference time	19.3	3.8	18.2	3.6	1.437	0.155	0.32
Interference total/time	1.8	0.3	1.9	0.4	-1.811	0.074	0.403

Note: control, control group; HIV, experimental group - HIV patients; M, Mean; SD, standard deviation; t, calculated t-score; significant at $p < .002$ (corrected α after Bonferroni); d, Cohen's d - effect size; MMSE, Mini Mental State Examination; WST, Wortschatztest; AKT, Alters-Konzentrations-Test: AKT time, AKT total/time; Digit-symbol, Digit-symbol subtest WAIS-R; Symbol counting, symbol counting task C.I.; TMTA, TMTB: Trail Making Test A & B, SWT, Semantic Verbal Fluency Test; PWT, Phonematic Verbal Fluency Test; BNT, Boston Naming Test; VSRT, Verbal selective reminding test; VSRT-IR, VSRT- immediate recall; VSRT-TR, VSRT- total recall; VSRT-DR, VSRT- delayed recall; VSRT-RECOG, VSRT- recognition; 5-Point, Five-Point test: 5-Point correct, 5-Point perseverations; Stroop, Stroop test C.I.: Stroop colors, Stroop words, Stroop total/time, Stroop interference; Maze test, Maze test NAI: Maze test time, Maze test total/time, TMTB-TMTA, TMTB-TMTA difference; Interference, Interference test C.I.: Interference time, Interference total/time

Table 4. T-tests on variables of applied questionnaires for control group and HIV patients (N=81)

	Control (n=42)		HIV (n=39)				
	M	SD	M	SD	t	p	d
BDI-II	4.4	5.2	7.2	7.5	-1.986	0.051	0.442
GDS	1.8	2.9	2.8	3.5	-1.491	0.140	0.332
Körperl. Funkt.	93.7	11.6	94.9	12.4	-0.444	0.659	0.099
Körperl. Rollenfunkt.	89.3	27.1	90.4	18.7	-0.211	0.834	0.047
Körperl. Schmerzen	91.6	16.2	89.9	20.5	0.392	0.696	0.087
Allg. Geswahrnehm.	75.8	22.0	74.4	16.8	0.317	0.752	0.07
Vitalität	64.5	16.0	65.5	16.5	-0.275	0.784	0.061
Soz. Funkt.	89.9	15.4	86.0	20.0	0.926	0.357	0.206
Emot. Rollenfunkt.	90.5	22.4	88.0	28.1	0.434	0.666	0.097
Psych. Wohlbef.	76.5	17.2	75.9	19.9	0.140	0.889	0.031
Körperl. Skala	54.5	8.1	54.6	5.4	-0.067	0.947	0.015
Psych. Skala	50.9	8.6	50.0	10.1	0.424	0.673	0.094
CITY	12.9	2.9	11.7	3.0	1.769	0.081	0.393
FACE	13.6	2.5	13.3	2.8	0.662	0.510	0.147
FAI	1.9	0.6	2.1	0.7	-1.440	0.154	0.32
B-ADL	1.4	0.4	1.5	0.5	-1.160	0.249	0.258
PSQI	4.0	2.5	4.9	2.9	-1.508	0.135	0.335
ESS	6.2	3.2	7.3	3.7	-1.459	0.149	0.324

Note: control, control group; HIV, experimental group - HIV patients; M, Mean; SD, standard deviation; t, calculated t-score; significant at $p < .0027$ (corrected α after Bonferroni); d, Cohen's d - effect size; BDI-II, Beck Depression Inventory Revision; GDS, Geriatrische Depressionsskala Kurzform; Skalen des SF-36, Short-Form 36 Health Survey: Körperliche Funktionsfähigkeit, Körperliche Rollenfunktion, Körperliche Schmerzen, Allgemeine Gesundheitswahrnehmung, Vitalität, Soziale Funktionsfähigkeit, Emotionale Rollenfunktion, Psychisches Wohlbefinden, Körperliche Skala & Psychische Skala; CITY, City-Test; FACE, Face-Test; FAI, Forgetful Assessment Inventory; B-ADL, Bayer activities of daily living scale; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale

Table 5. Kruskal-Wallis tests on variables of applied questionnaires for Frascati criteria diagnostic group of HIV patients and control group (N=81)

	Frascati (n=39)			Control (n=42)		
	cog healthy (n=8)	naANI (n=11)	aANI (n=20)			
	MR	MR	MR	MR	H	p
BDI-II	38.75	49.00	46.10	36.90	3.632	0.304
GDS	36.75	45.09	48.38	37.23	3.884	0.274
Körperl. Funkt.	55.50	43.59	39.03	38.50	5.171	0.160
Körperl. Rollenfunkt.	45.00	35.86	39.43	42.33	1.938	0.585
Körperl. Schmerzen	51.00	46.55	34.10	40.93	6.595	0.086
Allg. Geswahrnehm.	52.19	43.09	31.20	42.99	5.699	0.127
Vitalität	56.25	37.77	39.20	39.80	3.832	0.280
Soz. Funkt.	49.00	40.27	34.28	42.87	3.606	0.307
Emot. Rollenfunkt.	48.50	33.41	42.03	41.07	4.352	0.226
Psych. Wohlbef.	50.94	39.27	39.63	40.21	1.622	0.654
Körperl. Skala	50.00	41.64	31.65	43.57	4.839	0.184
Psych. Skala	52.25	38.45	39.95	40.02	2.070	0.558
CITY	44.56	36.55	31.73	45.90	5.661	0.132
FACE	38.56	53.27	32.38	42.36	6.141	0.105
FAI	46.56	41.32	45.80	37.57	2.175	0.537
B-ADL	36.00	42.32	44.95	39.73	1.089	0.780
PSQI	30.81	56.59	42.78	38.01	7.291	0.063
ESS	41.69	47.68	42.20	38.55	1.418	0.701

Note: Frascati, Frascati criteria; cog healthy; cognitively healthy; naANI, nonamnestic ANI; aANI, amnestic ANI; control, control group; MR, mean rank; SD, standard deviation; H, chi-square; significant at $p < .0027$ (corrected α after Bonferroni); BDI-II, Beck Depression Inventory Revision; GDS, Geriatrische Depressionsskala Kurzform; Skalen des SF-36, Short-Form 36 Health Survey: Körperliche Funktionsfähigkeit, Körperliche Rollenfunktion, Körperliche Schmerzen, Allgemeine Gesundheitswahrnehmung, Vitalität, Soziale Funktionsfähigkeit, Emotionale Rollenfunktion, Psychisches Wohlbefinden, Körperliche Skala & Psychische Skala; CITY, City-Test; FACE, Face-Test; FAI, Forgetful Assessment Inventory; B-ADL, Bayer activities of daily living scale; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale

Table 6. Kruskal-Wallis tests on variables of applied questionnaires for DSM V minimum mode diagnostic group of HIV patients and control group (N=81)

	DSMmin (n=39)			Control (n=42)		
	cog healthy (n=2)	namildNCD (n=18)	amildNCD (n=19)			
	MR	MR	MR	MR	H	p
BDI-II	51.75	47.31	42.95	36.90	3.178	0.365
GDS	60.50	38.83	49.34	37.23	5.332	0.149
Körperl. Funkt.	55.50	45.72	40.53	38.50	2.686	0.443
Körperl. Rollenfunkt.	49.50	41.17	37.00	42.33	1.871	0.600
Körperl. Schmerzen	51.00	43.58	37.66	40.93	1.680	0.641
Allg. Geswahrnehm.	66.75	44.14	30.92	42.99	6.541	0.088
Vitalität	23.00	48.06	38.87	39.80	3.085	0.379
Soz. Funkt.	37.75	41.11	37.11	42.87	1.049	0.789
Emot. Rollenfunkt.	48.50	38.86	42.03	41.07	0.855	0.836
Psych. Wohlbef.	18.25	43.89	42.39	40.21	2.284	0.516
Körperl. Skala	72.00	41.94	31.16	43.57	7.328	0.062
Psych. Skala	18.50	45.83	40.95	40.02	2.661	0.447
CITY	46.50	34.81	35.45	45.90	4.317	0.229
FACE	13.00	47.94	34.37	42.36	6.290	0.098
FAI	41.25	46.78	43.08	37.57	2.127	0.546
B-ADL	65.75	40.97	41.24	39.73	2.352	0.503
PSQI	46.00	48.75	39.74	38.01	2.842	0.417
ESS	42.75	45.06	42.39	38.55	1.081	0.782

Note: DSMmin; DSM V with minimum mode of determination; cog healthy; cognitively healthy; namildNCD, nonamnestic mild NCD; amildNCD, amnestic mild NCD; control, control group; MR, mean rank; SD, standard deviation; H, chi-square; significant at $p < .0027$ (corrected α after Bonferroni); BDI-II, Beck Depression Inventory Revision; GDS, Geriatrische Depressionsskala Kurzform; Skalen des SF-36, Short-Form 36 Health Survey: Körperliche Funktionsfähigkeit, Körperliche Rollenfunktion, Körperliche Schmerzen, Allgemeine Gesundheitswahrnehmung, Vitalität, Soziale Funktionsfähigkeit, Emotionale Rollenfunktion, Psychisches Wohlbefinden, Körperliche Skala & Psychische Skala; CITY, City-Test; FACE, Face-Test; FAI, Forgetful Assessment Inventory; B-ADL, Bayer activities of daily living scale; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale

Table 7. Kruskal-Wallis tests on variables of applied questionnaires for DSM V mean mode diagnostic group of HIV patients and control group (N=81)

	DSMmean (n=39)			Control (n=42)		
	cog healthy (n=27)	namildNCD (n=10)	amildNCD (n=2)			
	MR	MR	MR	MR	H	p
BDI-II	45.48	48.60	28.50	36.90	3.941	0.268
GDS	43.56	49.00	45.75	37.23	2.814	0.421
Körperl. Funkt.	45.70	35.90	55.50	38.50	3.800	0.284
Körperl. Rollenfunkt.	39.37	38.10	49.50	42.33	1.340	0.720
Körperl. Schmerzen	44.54	29.75	51.00	40.93	5.689	0.128
Allg. Geswahrnehm.	43.20	31.00	19.50	42.99	4.037	0.257
Vitalität	41.94	42.10	48.00	39.80	0.356	0.949
Soz. Funkt.	38.22	37.35	57.50	42.87	2.374	0.499
Emot. Rollenfunkt.	39.00	44.60	48.50	41.07	1.380	0.710
Psych. Wohlbef.	40.09	42.45	62.50	40.21	1.818	0.611
Körperl. Skala	46.22	19.00	26.50	43.57	11.336	0.010
Psych. Skala	39.78	44.90	58.50	40.02	1.527	0.676
CITY	38.50	27.80	37.75	45.90	5.412	0.144
FACE	41.30	32.60	50.50	42.36	1.814	0.612
FAI	43.63	42.50	70.00	37.57	4.311	0.230
B-ADL	39.83	51.85	29.25	39.73	2.831	0.418
PSQI	41.61	56.40	18.50	38.01	6.971	0.073
ESS	39.63	57.45	28.75	38.55	6.045	0.109

Note: DSMmean; DSM V with mean mode of determination; cog healthy; cognitively healthy; namildNCD, nonamnestic mild NCD; amildNCD, amnestic mild NCD; control, control group; MR, mean rank; SD, standard deviation; H, chi-square; significant at $p < .0027$ (corrected α after Bonferroni); BDI-II, Beck Depression Inventory Revision; GDS, Geriatrische Depressionsskala Kurzform; Skalen des SF-36, Short-Form 36 Health Survey: Körperliche Funktionsfähigkeit, Körperliche Rollenfunktion, Körperliche Schmerzen, Allgemeine Gesundheitswahrnehmung, Vitalität, Soziale Funktionsfähigkeit, Emotionale Rollenfunktion, Psychisches Wohlbefinden, Körperliche Skala & Psychische Skala; CITY, City-Test; FACE, Face-Test; FAI, Forgetful Assessment Inventory; B-ADL, Bayer activities of daily living scale; PSQI, Pittsburgh Sleep Quality Index; ESS, Epworth Sleepiness Scale

Table 8. Point-biserial correlations (r) between cognitive impairment and duration of HIV, current amount of CD4 T cells & nadir CD4 T cell count in all classification methods

	Frascati (n=39)		DSMmin (n=39)		DSMmean (n=39)	
	cog healthy (n=8)	ANI (n=31)	cog healthy (n=2)	mild NCD (n=37)	cog healthy (n=27)	mild NCD (n=12)
	p	r	p	r	p	r
HIV duration	0.207	0.207	0.904	0.020	0.277	0.178
CD4	0.815	-0.039	0.656	-0.074	0.450	0.125
Nadir CD4	0.796	0.043	0.161	-0.229	0.314	0.166

Note: Note: Frascati, Frascati criteria; DSMmin; DSM V with minimum mode of determination; DSMmean; DSM V with mean mode of determination; cog healthy; cognitively healthy; significant at $p < .05$; r, correlation coefficient; HIV duration, duration of HIV; CD4, amount of CD4 T cells at testing time; nadir CD4, nadir CD4 T cell count

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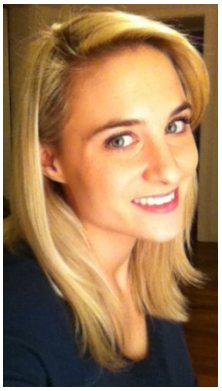
Curriculum Vitae



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Sprachkenntnisse

Englisch in Wort und Schrift (sehr gut)
Französisch in Wort und Schrift (gut)

Sonstige Qualifikationen

Sehr viel Erfahrung im Umgang mit Kindern & Jugendlichen
EDV-Grundkenntnisse für MS-Office, SPSS (Statistik Programm)
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