Ph.D. Thesis

The effects of aging and HIV infection on the relationship between the Resting State of the brain and neurocognitive functioning

Wpływ starzenia się i zakażenia wirusem HIV na związek pomiędzy stanem spoczynkowym mózgu a funkcjonowaniem poznawczym

Anna Rita Egbert, MA
anna.rita.egbert@gmail.com

Promoter:
Emilia Łojek, Professor, Ph.D.
University of Warsaw, Faculty of Psychology, Department of Neuropsychology

Co-Promoter:
Bharat Biswal, Professor, Ph.D.
New Jersey Insitute of Technology, Department of Biomedical Engineering

Auxiliary Promoter:
Agnieszka Pluta, Ph.D.
University of Warsaw, Faculty of Psychology, Department of Neuropsychology
Bioimaging Research Center in Kajetany

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Faculty of Psychology
University of Warsaw
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Index of the used abbreviations

AAN	American Academy of Neurology
AC	anterior commissure
ACC	anterior cingulate cortex
AFNI	Analysis of Functional NeuroImages software
AIDS	to acquired immunodeficiency syndrome
ALFF	amplitude of low frequency flunctuations
mALFF	amplitude of low frequency flunctuations divided by the mean
AngG	angular gyrus
Ant insula	anterior insula
APA	American Psychological Association
aPFC	anterior prefrontal cortex
ART	Aritfact Detection Tools
B	Beta Coefficient
BFI	Brief Fatigue Questionnaire
BMI	Biomedical Engineering
BOLD	blood oxygenation level dependent
BRC	Bioimaging Research Center
BSS	source separation problem
cART	combination anti-retroviral therapy
CD4	CD4 lymphocytes
CD4+T	CD4 T lymphocytes
CD8+T	CD8 T lymphocytes
CES-D	Center for Epidemiological Studies – Depression Scale
CHARTER	AntiRetroviral Therapy Effects Research
CI	Confidence Interval
CingG	cingulate gyrus
CNS	central nervous system
CON	Cingulo-Opercular Network
CRUNCH	Compensation-Related Utilization of Neural Circuits Hypothesis
CSF	cerebro-spinal fluid
CTT	Color Trails Test
CTT-1	Color Trails Test – Part 1
CTT-2	Color Trails Test – Part 2
CVLT	California Verbal Learning Test
dACC	dorsal anterior ACC
DAN	dorsal attention network
dFC	dorsal frontal cortex
DICOM	Digital Imaging and Communications in Medicine
DMN	default mode network
DSM-V	Diagnostic and Statistical Manual of Mental Disorders-V
DTI	Diffusion Tensor Imaging
FA	Fractional Anisotropy
FC	functional connectivity
FD	framewise displacement
FDR	false discovery rate

fMRI	functional Magnetic Resonance Imaging
FPN	fronto-parietal network
FWHM	full width half maximum
GPT	Groove Pegboard Test
Hz	Hertz
HAART	highly active antiretroviral therapy
HAND	HIV-associated neurocognititve disorder
HAROLD	Hemispheric Asymmetry Reduction in Old Adults
HIV	Human Immunodeficiency Virus
HIV-	Human Immunodeficiency Virus seronegative
HIV+	Human Immunodeficiency Virus seropositive
HIV RNA	Human Immunodeficiency Virus ribonucleic acid
HP	head position
GLM	General Linear Model
GM	grey matter
IC	independent component
ICA	Independent Component Analysis
IFG	inferior frontal gyrus
inf temporal	inferior temporal cortex
IPC	inferior parietal cortex
IPL	inferior parietal lobule
IPS	inferior parietal
IQ	intelligence quotient
KCC-ReHo	Kendall's Coefficient of Concordance
LOC	lateral occipital network
LP	lateral parietal
mALFF	amplitude of low frequency flunctuations divided by the mean
M	mean
MCP-1	monocyte chemoattractant protein-1
MD	median
MELODIC	multivariate exploratory linear optimized decomposition into independent components
mFC	medial frontal cortex
MidFG	middle frontal gyrus
MidTG	midle temporal gyrus
MMSE	Mini Mental State Examination
MNI	Montreal Neurological Institute
MoccG	middle occipital gyrus
mPFC	medial prefrontal cortex
MPRAGE	structural RS-fMRI data
MR	Magnetic Resonance
MTL	medial temporal lobe
NHANES	National Health and Nutrition Examination Survey
NIFTI	Neuroimaging Informatics Technology Initiative
NIJT	New Jersey Institute of Technology
ON	Occipital Network

OSU	Ohio State University
PASA	Posterior-Anterior Shift with Aging
PCC	posterior cingulate cortex
PoscG	postcentral gyrus
PostcentG	postcentral gyrus
PostCing	posterior cingulate
Prec	precunues
PrecentG	precentral pyrus
mPFC	medial prefrontal cortex
mReHo	regional homogeneity divided by the mean
pre-SMA	pre-supplementary motor area
ReHo	Regional Homogeneity
REST	Resting-State fMRI Data Analysis Toolkit
RFFT	Ruff Figural Fluency Test
ROI	region of interest
RS	resting state
RSC	retrosplenial cortex
RS-FC	resting state functional connectivity
ROI	region of interest
ROI-based	Region of Interest-based analysis
RS-fMRI	resting state fMRI
SAL	salience network
sCD14	soluble monocyte differentiation antigen 14
SD	standard deviation
SMA	sensory-motor area
SMN	sensori-motor network
SPM	Statistical Parametric Mapping
STAC	the Scaffolding Theory of Aging and Cognition
SupFG	superior frontal gyrus
SupTG	superior temporal gyrus
TE	echo time
TLRC	Talairach atlas
TPJ	temporal-parietal junction
TR	repetition time
UNAIDS	The Joint United Nations Programme on HIV/AIDS
WAIS-R	Wechsler Adult Intelligence Scale
WCST	Wisconsin Card Sorting Test
WHO	World Human Organization
WM	white matter
VBM	voxel-based morphometry
vFC	ventral frontal cortex
VFT	Verbal Fluency Test
vlPFC	ventral lateral prefrontal cortex
QA	quality assurance

Abstract

Rationale and objective: The aging HIV seropositive (HIV+) population struggles with the brain functional and structural abnormalities. Consequently, HIV+ individuals can experience decline in neurocognitive performance. The current state of knowledge informs on the neuroinfectious actions of the HIV virus to a limited extent. However, with the new methods of brain imaging, such as resting state functional magnetic resonance imaging (RS-fMRI), we can now better understand the functional brain bases of the clinical neurocognitive portrait in this specific patient population. Up to date, few scientific reports addressed the effects of age and HIV infection on the resting state (RS) of the brain and cognitive functioning. Due to previous inconsistent findings, the issue remains unclear. This study aimed to examine the effects of aging and HIV infection on the RS of the brain in relationship to the cognitive functioning.

Methods: This study analyzed data from a final number of 108 participants between 25 and 75 years of age, including 54 HIV+ individuals (age M=41; SD=12 years) and 54 demographically matched HIV-seronegative controls (age M=43; SD=12 years), with the mean of 16 years of education. All HIV+ participants were receiving HAART. The data retained for the current analyses included neuroimaging data of resting state functional magnetic resonance imaging (RS-fMRI), and neurocognitive data from a comprehensive battery of tests assessing attention, executive functions, memory, psychomotor functions, and semantic skills. RS data was analyzed using Regions of Interest-based approach, Independent Component Analysis, and Voxel-based analysis. Cognitive tests outcome T-scores were comprised into Neurocognitive Factor Scores. Between group differences in RS and neurocognitive data was assessed with *T*-unpaired test. Bivariate correlations examined relationships between age, RS measures, and neurocognitive factors. Multiple Linear Regression Analysis were performed in order to investigate the effects of

age and HIV infection on the relationship between RS brain activity and neurocognitive performance.

Results: Control group revealed patterns of aging in RS functional connectivity (FC) and neurocognitive decline comparable to the general population. HIV infection was related to decreases and increases in RS-FC and deterioration in attention and sematic skills as compared to controls. Interaction effects of age and HIV infection were exposed in terms of intra- and inter-network remote FC, which was weakening with age in HIV+ group, while strengthening with age in healthy comparators. No age-HIV interaction effects were observed on cognitive factors. Significant relationships were distinguished between RS-FC measures sensitive to age-HIV interaction effects and neurocognitive factors. Age had no significant moderator effects on majority of the revealed relationships in controls. HIV significantly moderated relationship between RS-FC and neurocognitive factors. Age in HIV+ group did not reveal significant moderator effects on the relationship between RS-FC and neurocognitive factors.

Conclusions: Current study provides evidence that RS-fMRI is a sensitive technique to reveal not only additive but also interaction effects of age and HIV infection on the functioning of the brain. The results confirm that age and HIV infection lead to brain reorganization and decline in neurocognitive performance. Importantly, the study finds evidence for the employment of brain compensatory mechanisms in aging HIV+ patient population. The current findings support the hypothesis of rather accentuated than accelerated aging in the individuals aging with HIV.

Key words: Resting State; RS-fMRI; aging; HIV; neurocognitive functions

Streszczenie (Abstract in Polish language)

Uzasadnienie i cel: Osoby starzejące się z infekcją HIV (HIV+) zmagają sią z zaburzeniami w strukturze jak i funkcjonowaniu mózgu. W wyniku tego, osoby HIV+ mogą doświadczać deterioracji w funkcjonowaniu neuropoznawczym. Obecny stan wiedzy jest ograniczony na temat neuroinfekcyjnych działań wirusa HIV. Jednak przy użyciu nowych metod neuroobrazowania mózgu, takich jak badanie spoczynkowej aktywności mózgu w funkcjonalnym rezonansie magnetycznym (ang. resting state functional magnetic resonance imaging) możemy coraz lepiej opisać funkcjonalne podstawy mózgu przyczyniających się do klinicznego portretu zaburzeń neuropoznawczych w tej szczególnej grupie pacjentów. Do tej pory niewiele doniesień naukowych skierowanych było na badanie wpływu wieku i zakażenia wirusem HIV na stan spoczynkowy mózgu w odniesieniu do funkcji poznawczych. W związku z niespójnościami dotychczasowych doniesień, zagadnienie to pozostaje niewyjaśnione. To badanie miało na celu zbadanie efektów starzenia się i zakażenia wirusem HIV na stan spoczynkowy mózgu (RS) w stosunku do funkcjonowania poznawczego.

Metoda: W badaniu przeanalizowano dane z ostatecznej liczby 108 uczestników między 25 a 75 rokiem życia, w tym 54 osoby HIV+ (średnia wieku = 41 lat; SD = 12 lat) oraz 54 demograficznie dopasowane osoby kontrolne HIV-seronegatywne (średnia wieku = 43 lata; SD = 12 lat), ze średnią 16 lat edukacji. Wszyscy uczestnicy HIV + byli na terapii HAART. Dane przeanalizowane w tym badaniu obejmowały dane spoczynkowego neuroobrazowania stanu mózgu (RS-fMRI) i dane neuropoznawcze z kompleksowego zestawu testów oceniających funkcje uwagi, funkcje wykonawcze, pamięć, funkcje psychomotoryczne i umiejętności semantyczne. Dane analizowano stosując podejście oparte na mózgowych regionach zainteresowania badawczego (ang. Regions of Interest-based analysis), analizy niezależnych

komponentów (ang. Independent Component Analysis), i analizy opartej na wokselach (ang. Voxel-based analysis). Na podstawie wyników przekształconych (T) z testów poznawczych zostały skomponowane czynniki neuropoznawcze. Różnice pomiędzy grupami w RS i funkcjonowaniu poznawczym oceniano testem t. Dwuwymiarowe korelacje były użyte do zbadania relacji między wiekiem, RS, a czynnikami neuropoznawczymi. Wielokrotna analiza regresji liniowej przeprowadzona została w celu zbadania wpływu wieku i zakażenia wirusem HIV na relacje między spoczynkowa aktywnością mózgu (RS) a neuropoznawczą wydajnością.

Wyniki: Grupa kontrolna, w zakresie połączeń funkcjonalnych (FC) w spoczynkowej aktywności mózgu oraz deterioracji funkcji neuropoznawczych, wykazała wzorce starzenia się porównywalne do ogólnej zdrowej populacji. Zakażenie wirusem HIV związane było z obniżeniem jak i z podwyższeniem RS-FC oraz pogorszeniem uwagi i umiejętności semantycznych w porównaniu z grupą kontrolną. Efekty interakcji wieku i zakażenia HIV były wykazane dla FC wewnątrz-sieciowych oraz między-sieciowych, które słabły wraz z wiekiem w grupie HIV+, a wzmacniały się wraz z wiekiem u zdrowych niezakażonych. Brak efektów interakcji wieku i wirusa HIV był wykazany dla czynników poznawczych. Wykazane zostały istotne relacje pomiędzy mocą połączeń RS-FC, które wykazały wrażliwość na skutki interakcji wieku i wirusa HIV, a wartością czynników neuropoznawczych. Wiek nie miał znaczącego wpływu jako moderator dla większości wykazanych relacji w grupie kontrolnej. Zakażenie wirusem HIV znacznie wpływało na związek między RS-FC a czynniki neuropoznawcze. Natomiast wiek w grupie HIV+ nie miał znaczących skutków jako moderator na relacje między RS-FC a czynnikami neuropoznawczymi.

Wnioski: Obecne badanie dostarcza dowodów na to, że RS-fMRI jest czułą techniką mogącą ujawnić nie tylko efekty niezależne, ale również efekty interakcji wieku i zakażenia wirusem

HIV na funkcjonowanie mózgu podczas braku jawnych procesów poznawczych. Wyniki tego badania dalej potwierdzają, że wiek i zakażenie wirusem HIV prowadzą do reorganizacji funkcjonalnej mózgu i spadku wydajności funkcji neuropoznawczych. Co ważne, badania to donosi o dowodach na wdrożenie kompensacyjnych mechanizmów mózgowych w populacji pacjentów starzejących się z wirusem HIV. Wyniki tego badania dowodzą o przeważającej słuszności hipotezy natężonego/skoncentrowanego (ang. accentuated) nad hipotezą przyspieszonego (ang. accelerated) starzenia się u osób żyjących z infekcją HIV.

Słowa kluczowe: stan spoczynkowy mózgu; RS-fMRI; starzenie się; HIV; funkcje neuropoznawcze

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INTRODUCTORY PART

Currently, one can observe a gradual enrichment of literature describing the functioning of people living with HIV (Human Immunodeficiency Virus). The growing interest in this subject reflects the changing portrait of the HIV infection. At least three aspects form the core of those changes and may be distinguished as follows: epidemiology, aging of the HIV-infected population, and the development of new research methods.

First, despite the announcement of the HIV epidemic and the numerous campaigns to educate the public about the risks of infection, the population of people living with HIV infection continues to grow. A global trend is still observed for the spreading of HIV, although there is a decrease in the number of new infections (UNAIDS, 2013). In addition, more social groups are becoming at risk of HIV infection. These socio-demographic changes in the HIV-infected population were described by Brennan, Karpiak, Shippy and Cantor (2009), who stated based on the American society that the infection in the "first decade of HIV" was associated almost exclusively with young homosexual men. In the "second decade of HIV," especially women and ethnic minorities have been affected by the epidemic. But currently, in the "third decade of HIV," infection prevalence begins to increase among older people. Report of the Joint United Nations Programme on HIV/AIDS (UNAIDS) from 2013 showed that the proportion of people aged over 50 has grown to about 33% of the total population living with HIV in the developed countries of Western and Central Europe and North America in 2012.

This transformation in the socio-demographic portrait of people living with HIV infection is associated mainly with the implementation of antiretroviral therapy - cART (combination anti-retroviral therapy) in the mid-90’s, which then developed into even more successful treatment, namely Highly Active Anti-retroviral Therapy (HAART) (UNAIDS, 2013). The application of

the therapy resulted in the transformation of HIV infection from a deadly disease into a chronic condition where life expectancy of infected individuals is more comparable to that of healthy individuals (Mills et al, 2011). However, that brought a new challenge for the health-care system, namely the health problems of aging HIV-infected patients. The primary challenge of the increased susceptibility to the diseases in geriatric patients (WHO, 2015) is magnified in individuals aging with HIV (Egbert et al., in press; Guaraldi et al., 2011). HIV invades the central nervous system (CNS) in the early asymptomatic phase after seroconversion (Chiodi, et al., 1988; Valcour et al., 2012) limiting the effectiveness of drugs that do not cross the blood-brain barrier. As a result, it is the CNS that is the most susceptible to the neuroinfectious actions of the HIV (Thurner et al., 2000).

The dynamic development of new technologies of neuroimaging of the brain enabled more in-depth research on the functioning of the brain. In combination with the growing interest in the field of HIV infection, this contributes to the increased understanding of the mechanisms of actions of the virus within the CNS (Thompson and Jahanshad, 2015). Studies using Magnetic Resonance Imaging (MRI) indicated the existence of brain atrophy in HIV infection (for example: Brew et al., 2009) and were soon supported by studies on the metabolic changes of the brain visible during cognitive tasks in the functional MRI (fMRI) (for example, Plessis et al., 2014). Currently, the research also involves studying of the brain activity during lack of overt cognitive functioning, so-called spontaneous, intrinsic activity or resting state of the brain with the Resting State fMRI (RS-fMRI) (Biswal et al., 1995).

The current Ph.D. dissertation was established to form a partial fulfillment of a larger collaborative research, here called the Major Study, entitled “The Effects of Aging on Cognitive and Chemosensory Functions of the Brain in HIV Infection” coordinated by prof. Łojek, Ph.D.

Description of the Major Study is provided in Section 3.1. In the context of this large research project, the current Ph.D. dissertation focuses on studying health disparities particularly in terms of resting state of the brain in relationship to neurocognitive functioning in aging HIV-infected population. The study gains from the recent developments in brain imaging technology and applies the RS-fMRI technique to study the independent and interaction effects of age and HIV infection on the functioning of the brain at no cognitive demand. Furthermore, the study addresses cognitive disparities in this population by examining the additive and synergistic effects of age and HIV infection on cognitive functions. Finally, the dissertation is committed to the subject of the effects and aging and HIV infection on the relationship between RS-fMRI measures and cognitive functioning in this growing aging HIV+ population. Description of the Ph.D. dissertation is provided in Section 2.2.

1. TECHNIQUE OF THE RESTING STATE FMRI

In this chapter the author provides a description of the technique of the Resting State fMRI, which conforms the neuroimaging method used in the current dissertation. First, the definition of the RS of the brain is given. Then, the methods of examining and analyzing RS data are explained. Finally, resting state brain networks are described in terms of the brain regions they consist of as well as their cognitive involvement.

1.1. Resting state of the brain definition

Resting State (RS) brain activity has been defined as the spontaneous neuronal and synaptic activity during lack of overt cognitive processing (Fox & Raichle, 2007). It was first observed in particular anatomically separate brain regions by Biswal et al. (1995). Later research has proved this finding to be generalized across the cortical regions (Zhang & Raichle, 2010). The ongoing intrinsic activity consumes possibly majority of the brain energy budget (Raichle & Mintun, 2006), which indicates its great importance in brain functioning (Zhang & Raichle, 2010).

RS brain activity can be investigated using RS-fMRI which examines spatial synchronization of spontaneous fluctuations in blood oxygenation level dependent (BOLD) signal during stimulus-independent thought (Fox, Halko, Eldaief, & Pascual-Leone, 2012; Fox & Raichle, 2007; Iglesia-Vaya, Molina-Mateo, Escarti-Fabra, Kanaan, & Martí-Bonmati, 2013; Lee, Smyser, & Shimony, 2012; Uddin, Supekar, & Menon, 2010). There is an empirical support to the interpretation of low frequency (0.01 – 0.1 Hz) RS-fMRI oscillations in BOLD signal as a consequence of the intrinsic neuronal and synaptic activity patterns (Damoiseaux et al., 2006; Greicius, Krasnow, Reiss, & Menon, 2003). Accordingly, most of the current research using RS-fMRI focused on the measurement of spontaneous BOLD signal frequencies in the range of 0.01-0.1 Hz. However, it is now possible to measure spontaneous activity of the brain associated

with higher frequencies, as described SLOW 1-5 (Penttonen and Buzsaki, 2003), which exhibits a consistent pattern of activation even at frequencies up to 1.2 Hz (Gohel and Biswal, 2015).

1.2. Resting state data assessment, examination and analysis

1.2.1. Resting state data assessment

Resting state of the brain can be assessed with RS-fMRI as stated earlier (see Section 2.3.1. Definition of the resting state of the brain). The imaging protocol of the resting state BOLD fMRI (REST) has the usual acquisition time of about eight minutes. The standard instruction given to the participant informs him/her not to move in the scanner, but to relax with eyes open/closed (depending on the research protocol) and not think of anything specific. The participant is placed in the fMRI scanner with no visual or auditory stimuli being presented during the scanning session.

In addition to the RS scans and in order to preprocess the RS data, the T1-weighted scans are also acquired for every participant using a magnetization-prepared rapid gradient echo sequence (MPRAGE). The acquisition time of the structural sequences is usually about five minutes. Participant is placed in the scanner and instructed not to move during the scanning session.

1.2.2. Resting state and structural data preprocessing

The standard procedure of preprocessing of the RS data the can be written as the following pipeline:

1. conversion of data from DICOM to NIFTI;
2. skull stripping of MPRAGE data;

3. alignment of MPRAGE and REST data to anterior commissure;

4. concatenation of 240 time points into one 4D rest.nii file;

5. refit TR=1 of rest.nii to TF=2;

6. realignment of REST;

7. coregistration of MPRAGE to rest.nii mean of images;

8. segmentation into white matter (WM), grey matter (GM), and cerebro-spinal fluid (CSF) tissue maps;

9. deformations and normalization to MNI space;

10. smoothening of [6 6 6] FWHM;

11. creation of WM and CSF masks;

12. create regressors: motion (6motion, 6previous, 6motion^2, 6previous motion^2), WM, and CSF;

13. temporal regression of first 5 principal components of WM and CSF, and 24 motion parameters;

14. temporal filtering (0.01-0.1 Hz).

As shown in the pipeline above, preprocessing of the RS data can be divided into consecutive steps as follows: conversion of the data from DICOM to NIFTI, skull stripping, alignment, concatenation, refit, realignment, coregistration, segmentation, deformations, normalization, and smoothening. Finally, regressors are created, followed by temporal regression and temporal filtering.

Preprocessing of the RS data starts with the conversion of data from DICOM to NIFTI. Data originally collected from the scanner needs to be converted into format read by the software

for further analysis.

Then, skull stripping is performed to allow for better coregistration of structural and functional images.

During the alignment, researcher manually redefines the center of the functional and structural images to the anterior commissure (AC). As a result, AC in each image is set in MNI space at coordinate of 0, 0, 0. This step is performed in order for all images to be equalized within each participant's data (i.e., functional and structural images of each subject) as well as between participants. It also allows for tissue probability maps to get registered more adequately later during the preprocessing.

Concatenation of the acquired time points into one 4D file enables easier maneuver of the subject's data in consequent analysis. If the concatenation is performed in Analysis of Functional NeuroImages software (AFNI), the repetition time (TR) needs to be then adjusted by refit to the original TR.

Next, realignment is performed. During this step the scans acquired for each person get aligned to one "representative scan" that is designated by the researcher. This step allows for each participants' data to be aligned together by eliminating movement artifact from the scanning session.

Coregistration is the step where structural image is registered on the functional images within each subject. This step allows for matching structural and functional images so that they are overlied with voxel-to-voxel specificity.

Segmentation is the following step in which each participants' data is separated into several tissue maps, i.e., white matter, grey matter, and cerebrospinal fluid (CSF).

Deformation and normalization is another step to be taken in order to write individuals'

data into a standard space predefined by a template supplied by software used for the analysis and further described in the atlas such as MNI brain or Talairach atlas (1988). This transformation of the images allows to label regions of the brain based on the MNI or TLRC space, depending on the atlas, and further enable comparisons at a group level.

Finally, smoothing is applied in order to suppress the noise which appears due to differences in functional and gyral anatomy in between-subject averaging.

1.2.3. Quality assurance

Measures of quality assurance (QA) include absolute and relative motion and framewise displacement (FD).

Absolute motion is based on the parameters derived from motion correction, a preprocessing step which can be performed in SPM12. The output reveals the absolute motion for every time point. The usual thresholds for absolute motion is at 2mm.

Relative motion can be analyzed using Aritfact Detection Tools (ART) toolbox (https://www.nitrc.org/projects/artifact_detect/) in SPM12. Analysis is based on the extracted voxel-wise time series for each participant separately. The threshold of relative movement for each time point is usually set at 0.5mm. The relative movement is checked for each consecutive slice, which results in noting slices exceeding the set threshold.

FD can be calculated for translation and rotation separately as previously described in Di & Biswal (2015) in the following equations:

$$FD_{translation,t} = \sqrt{(hp_{x,t} - hp_{x,t-1})^2 + (hp_{y,t} - hp_{y,t-1})^2 + (hp_{z,t} - hp_{z,t-1})^2}$$

$$FD_{rotation,t} = \sqrt{(hp_{\alpha,t} - hp_{\alpha,t-1})^2 + (hp_{\beta,t} - hp_{\beta,t-1})^2 + (hp_{\gamma,t} - hp_{\gamma,t-1})^2}$$

, where the parameters of head position (HP) are relative to the first volume as a function of scan

time t and denoted as $HP = [hp_{x,t}, hp_{y,t}, hp_{z,t}, hp_{\alpha,t}, hp_{\beta,t}, hp_{\gamma,t}]$. The x, y, and z represent three translation directions, while α, β, and γ represent three rotation directions (Di & Biswal, 2015). The threshold for FD of mean translation/rotation is usually set at 0.2mm/0.2degrees and of maximum translation/rotation at 1.5mm/1.5degrees.

1.2.4. RS-fMRI postprocessing

Postprocessing of resting state data can be approached in several ways as follows: Independent Component Analysis (ICA); Regions of Interest (ROI) based analysis; and voxel-based analysis.

1.2.4.a. Independent Component Analysis

ICA is a data-driven analytical technique, which, applied to RS-fMRI data, explores independent distribution of spatial patterns depicting source processes in the analyzed data set (McKeown, Makeig, Brown, Jung, Kindermann, et al., 1998). The advantage of this analysis is that it aims at directly solving the blind source separation problem (BSS). BSS is related to the fact that the analyzed signal source from fMRI includes different underlying sources of variability (such as machine artefacts or physiological noise) that only when accounted for allow for informed estimation of the source of interest (Beckmann & Smith, 2015). ICA analysis can be carried out using FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL) MELODIC software. In specific, this software uses the probabilistic ICA, which is developed based on the classical ICA decomposition. The probabilistic ICA further addresses BSS by additionally accounting for a varied number of regressors in the data sets by applying estimated instead of pre-specified number of regressors (Beckmann & Smith, 2015).

The usual implementation of ICA specifies 20 independent component (IC) maps, where

each of them represents a separate pattern of functional connectivity which can be further analyzed for revealing a brain network. In order to obtain between-group differences in each of the obtained components, voxel-wise comparisons for each of the ICs is performed using three stages of dual regression in FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL). The first stage results in obtaining one file per participant consisting of time series of each group-IC component. The second stage gives the result of one 4D image spatial map per participant consisting of one time point per group-IC component, i.e., the GLM parameter estimates which are used for between-subjects comparisons. This stage also results in one 4D image spatial map per component including one time point per participant, which are used for stage three of dual regression. In the third stage, analysis of the effects of independent variables are performed for each group-IC component and result in corrected p-value images for each component. The output of the third stage can be examined using AFNI software, which allows to read the exact corrected p-values for each IC.

1.2.4.b. Regions of Interest based analysis

The ROI-based analysis can be approached as an exploratory technique to discern the patern of the underlying activation signal across the brain regions (Poldrack, 2007). In specific, ROIs are selected *a priori*, which is one of the advantages for neurocognitive research studies since it is allows to specify regions of the brain based on their involvement in cognitive processes. Dosenbach et al. (2007) have performed meta-analysis on the functional cognitive involvement of the brain regions. Based on the results of this analysis, they have derived a set of 160 ROIs covering the cerebrum and cerebellum. Those regions were then functionally separated into six major brain networks (for further description of brain networks see Section 2.3.), which

fosters further correlational analysis with the cognitive performance scores.

RS data entered into ROI analysis has already gone under preprocessing steps which aim at eliminating the sources of noise from the activation signal. The ROI analysis commences with definition of ROIs which can be created as small spheres in MarsBaR region of interest toolbox (http://marsbar.sourceforge.net/; Brett et al., 2002) and extract the ROI time courses from RS data in SPM software. Then, the researcher can perform data-driven analysis and enter the entire set of the brain regions time courses (for example 160 ROIs from Dosenbach et al., 2010) into second-level analysis to obtain the correlation maps between the specified ROIs (in this example it would be 160x160 ROI pairs), which can be scripted in MatLab environment. Those resulting correlation maps represent the functional connectivity and can be derived for each of the studied groups (depending on the study design). In order to check the influence of the independent variables, one can perform further analysis with the resulting output presenting the p-values for each ROI pair.

1.2.4.c. Voxel-based analysis

Voxel-based analysis include the measures of Regional Homogeneity (ReHo) and Amplitude of Low Frequency Flunctuations (ALFF).

ReHo allows to study local functional connectivity, defined as FC at a local spatial scale, by measuring functional synchronization between the voxels within a radius of usually 10-15mm (Jiang & Zuo, 2015). ReHo analysis can also be expended to the Regional Homogeneity divided by the mean (mReHo).

Preprocessed RS data without temporal filtering can be prepared for voxel-based analysis in REST toolbox (http://restfmri.net/forum/index.php?q=rest). ReHo is commonly based on the

Kendall's Coefficient of Concordance (KCC-ReHo). In order to obtain KCC-ReHo map for each participant, data is first detrended in order to remove linear trend, and the band pass filter can be set at 0.01-0.08 Hz. Cluster size can be chosen for 27 voxels and mask adequate for the data set can be applied. In case of mReHo, an additional last step is implied where each participant's ReHo map is divided by the mean within the defined mask. The resulting output shows one ReHo map and one mALFF map per participant.

ALFF reflects neural activity in the low-frequency band usually between 0.01 and 0.8 Hz (Zang, He, Zhu, Cao, Sui, et al., 2007). Specific regional ALFF is found to be correlated with FC measures of ICA and ROI-based analysis (Di, Kim, Huang, Tsai, & Biswal, 2013). ALFF can also be expended to the Amplitude of Low Frequency Flunctuations divided by the mean (mALFF).

ALFF analysis data preparation includes detrending in order to remove linear trend, setting band pass filter for 0.01-0.08 Hz. Then a binary mask can be applied. In case of mALFF analysis, each participant's ALFF map is divided by the mean within the defined mask. This results in one ALFF map and one mALFF per subject.

Group-level analysis of ReHo and ALFF can be then executed using FSL. The output map shows the coordinates of regions presenting between-group differences at the specified significance threshold.

1.3. Resting state brain networks

The research using RS-fMRI has already shown the existence of the resting state brain networks. They consist of anatomically separate, but functionally linked brain regions showing activity during rest (Van den Huevel & Hulshoff Pol, 2010). There are several approaches used in

studying RS brain networks. Researchers can examine brain networks identified based on anatomically defined ROIs (Hagmann et al., 2008; Zalesky et al., 2010) or functionally defined ROIs from cognitive task activation (Dosenbach et al., 2007; Fair et al., 2009), based on independent component analysis (ICA) of BOLD signal (Damoiseaux et al., 2006; Greicius et al. 2003; Raichle et al. 2001), or seed-based correlations (in which correlation maps are calculated according to the picked brain region, with the results exhibiting regions showing simultaneous intrinsic activity and thus revealing the underlying RS network) (Zhang & Raichle, 2010). Even though the definition of the exact coordinates and the extent of coverage of the regions of interest (ROIs) on the brain images varies depending on these approach, the regions identified for each network show high overlap and consistency across the studies.

As described earlier (see Section 2.2.4.), Dosenbach et al. (2007) described six major brain networks based on functional cognitive involvement of the ROIs as follows: cerebellum, cingulo-opercular, default, fronto-parietal, occipital, and sensorimotor. Support for studying functionally defined brain networks comes from the analysis of Smith et al. (2009), who showed that functional architecture of the brain is corresponding between the task activation and resting state. Furthermore, functional definition of ROIs in the brain networks allows for more valid interpretation of the correlational analysis of resting state activity of the brain with the cognitive performance.

Using nomenclature after Dosenbach et al. (2007), RS networks in the cerebrum will be distinguished in the current dissertation between the following: cingulo-opercular network (CON), default mode network (DMN), fronto-parietal network (FPN), occipital network (ON), and sensorimotor network (SMN). They can be described as follows.

The widely studied RS network is the default mode network (DMN). It is defined by

Dosenbach et al. (2007) as comprising areas of the prefrontal cortex, regions of the frontal and inferior temporal cortex, angular gyrus, precuneus, and posterior cingulate cortex. The primary areas of interest are overlapping with the previous reports by Greicius et al. (2003), Raichle et al. (2001), and Zhang and Raichle (2010) as they have described the DMN to consist of the following brain areas: the posterior cingulate cortex (PCC); the precuneus; retrosplenial cortex (RSC); the inferior parietal cortex (IPC); the medial prefrontal cortex (MPFC); and the medial temporal lobe (MTL).

The DMN is unique in that it shows decrease in neuronal activity during performance of cognitive tasks and increase during rest in healthy individuals (Damoiseaux et al., 2006; Greicius, Supekar, Menon, & Dougherty, 2009; Raichle et al., 2001). Consequently, the research has mainly focused on the role of the DMN in cognitive functioning. Two main hypotheses, i.e., the "introspection" hypothesis and the "sentinel" hypothesis, have been developed. According to the "introspection" hypothesis, the DMN supports: executive functioning (Van den Heuvel, Mandl, Kahn, & Hulshoff Pol, 2009); integrating emotional and cognitive processing (Grecius et al., 2003); self-referential processing and episodic memory (Fox, Zhang, Snyder, & Raichle, 2009; Greicius et al., 2009; Mevel, Chetelat, Eustache, & Desgranges, 2011; Uddin et al., 2010); theory of mind and social cognition (Mevel et al., 2011); mind wandering and task-unrelated thoughts (Mason et al., 2007); thinking into the past (recollection of autobiographical events) and into the future (the "prospective brain" and the self-projection based on mental simulations) (Fox & Raichle, 2007; Greicius et al., 2003; Mevel et al., 2011), or linking past personal experiences with thinking of and evaluating possible perspectives (Van den Huevel & Hulshoff Pol, 2010).

Pursuant to the "sentinel" hypothesis, the DMN supports monitoring of the external world for unexpected events by sustaining a low-level focus of attention (Mevel et al., 2011;

Uddin et al., 2010; Van den Huevel & Hulshoff Pol, 2010).

Another RS network, the sensorimotor network (SMN), comprises regions of ventral frontal and parietal cortices, post-parietal areas, precetral gyrus, and mid insula (Dosenbach et al., 2007). Others report the primary sensorimotor network to encompass a group of brain regions consisting of precentral and postcentral gyri (Damoiseaux et al., 2006; Raichle et al., 2009; Zhang and Raichle, 2010). It is described to be involved in processing sensory and motor information (Dosenbach et al., 2007).

The cingulo-opercular network (CON) consists of basal ganglia, insula, thalamus, posterior cingulate, precuneus, and regions of prefrontal and parietal cortices (Dosenbach et al., 2007). It shows resemblance with the RS network described by Damoiseaux et al. (2006), i.e., consisting of dorsal anterior cingulate and regions of prefrontal and parietal cortices. This set of brain regions has been described to be involved in executive control, error-processing and working memory functions (Damoiseaux et al., 2006; Dosenbach et al., 2007). Similarly, Zhang and Raichle (2010) described executive control network, where the seed is placed in the dorsal prefrontal cortex.

The fronto-parietal network (FPN) is composed of the areas of the prefrontal and frontal cortex, inferior parietal lobule, and post parietal regions, and is prone to showing lateralization (Dosenbach et al., 2007). This set of brain areas corresponds with the network described by Damoiseaux et al. (2006) containing middle frontal and orbital areas and superior parietal regions, and also temporal gyrus and posterior cingulate. It is related to cognitive processes of memory functions, language skills (Damoiseaux et al., 2006; Dosenbach et al., 2007), as well as attention (Cocchi et al., 2013). Regions included in the FPN network partially overlap with the dorsal attention network (DAN) described by Zhang and Raichle (2010), who placed the seed in

the intraparietal sulcus. DAN evokes intrinsic activations primarily in the dorsal parietal and frontal regions and its cognitive involvement includes top-down processing and attention.

The occipital network (ON) described by Dosenbach et al. (2007) comprises areas of the occipital cortex and overlaps with the network described by Damoiseaux et al. (2006) which consists of lateral and superior occipital gyrus as well as peristriate area. It further shows resemblance to visual network described by Zhang and Raichle (2010), where the seed placed in the calcarine sulcus correlates with the other regions of visual cortex. This network is recognized to be involved in visual processing (Damoiseaux et al., 2006; Dosenbach et al., 2007; Zhang and Raichle, 2010).

To sum up, there are several ways of dividing brain areas into RS networks. However, in the context of research that is focused on examining the relations between RS networks and neurocognitive performance, one can follow the classification described by Dosenbach et al. (2007). Five cerebral RS networks are distinguished beteween cingulo-opercular network (CON), default mode network (DMN), fronto-parietal network (FPN), occipital network (ON), and sensorimotor network (SMN). Brain regions included in those RS networks highly overlap with other classifications described by Damoiseaux et al. (2006) or Zhang and Raichle (2010). Furthermore, cognitive involvement of those networks is characterized as follows: CON supporting executive functions and working memory; DMN supporting executive functioning, integration of emotional and cognitive processes, mind-wandering, prospective thinking; FPN supporting memory functions, verbal skills, and attention; ON supporting visuospatial processing; and SMN supporting sensory and motor information processing. Based on those descriptions of the previous literature, general relationships between RS functioning of the brain and neurocognitive processes can be determined for the general healthy population. The

estimation of RS – neurocognitive relationships in norm / health, allows for further comparisons with clinical populations. The observations in clinical studies can be then discussed due to the normative cognitive involvement of RS of the brain. Further speculations can be also made on the effects of particular diseases, such as in case of the current study, HIV infection, on the RS of the brain in relation to cognitive processes. The determination of the effects of the HIV infection leads to a better understanding of the functional consequences of the neuroinfectious actions of the HIV virus.

2. LITERATURE REVIEW ON AGING IN HIV

In this chapter, author provides the review on the effects of aging on the central nervous system (CNS). The author focuses particularly on brain alterations in terms of functional connectivity and supports the description by the results of the scientific studies. Next, the author provides a description of the effects of aging on the neurocognitive functioning. This widely studied subject is synthetized into a brief description of the commonly found cognitive deterioration in healthy aging. It is followed by a synopsis of the modulatory effects of age and HIV on the relationship between resting state of the brain and neurocognitive functions. The first chapter is concluded with a brief summary on the issues in brain and cognitive functioning in aging with HIV infection.

2.1. Effects of aging on the central nervous system and neurocognitive functioning

2.1.1. Effects of aging on the central nervous system

Aging is a widely addressed issue in neuroscience and multiple research teams have put their efforts to describe neural bases of aging. Considering the rapid evolution in brain structural

imaging, the revolutionized and numerous methodologies still bring inconsistent findings on the aging of the brain (Nakagawa et al., 2013). Furthermore, multiple factors may affect healthy aging, such as physical activity or education. It is, however, accepted that advancing age leads to both structural changes in the form of reductions in gray and white matter as well as functional changes in terms of both decreases and increases in brain activity depending on the brain region.

Studies focused on brain structure revealed that gray matter decreases in aging during adulthood (Pfefferbaum et al., 1994). Gray matter reductions can be observed in terms of reduction in cortical thickness as well as reduction in gray cortical volume (a function of cortical thickness and cortical surface) in aging individuals (Marstaller et al., 2015). However, education has recently been proven to be a protective factor. Higher education attainment was found to be related to lower loss of gray matter, especially in the left anterior cingulate and the left dorsomedial prefrontal cortex (Rzezak et al., 2015).

As for white matter, the overall degeneration is reported with decreases in fractional anisotropy accompanied by increases in mean diffusivity (Marstaller et al., 2015). The decrease in fractional anisotropy (FA)1 in advancing aging are notable especially in terms of an anterior-posterior gradation (Ardekani et al., 2007). The decline in FA occurs predominantly in the frontal WM, genu and anterior body of corpus callosum, superior part of splenium (Ardekani et al., 2007). More specific analysis of FA in healthy aging by Pfefferbaum and Sullivan (2003) revealed that the observed reductions in FA also arise from the increase of fluid between the

[1]FA examines the fraction of anisotropic diffusion, which shows it to be related to oriented structures (Le Bihan, 2001) and commonly used as a measure of WM integrity (O'Donnell & Westin, 2011).

cells, which is consistent with previous findings showing increase in CSF in late adulthood (Pfefferbaum et al., 1994).

Researchers using task fMRI have observed both, increases and decreases of brain activity. The increases are interpreted as a recruitment of additional brain resources in certain brain areas to compensate, or at least attempt to compensate, for the deficits in activation of some other brain regions (Sala-Llonch, Bartrés-Faz, & Junqué, 2015). Following this thought further, the level of success of this compensatory attempt will then translate to the quality of maintenance of the cognitive functioning at an optimal level (Sala-Llonch, Bartrés-Faz, & Junqué, 2015).

On the other hand, decreased brain activity in aging is mostly described in terms of the loss of functional specificity. The observed reductions in particular regions of interest while performing a cognitive task is accompanied by functional increases observed in other brain areas as described above. Based on task-fMRI studies, authors such as Park et al. (2004) and Rajah and D'Esposito (2005) state that the observation of decreases defines the loss of functional specificity of the cerebral regions. Consequently, particular regions of the brain, which are observed in young adults to be engaged in particular cognitive domains, fail to be activated due to cognitive demand in elderly. Furthermore, the failure to increase the activation in one region as well as failure to decrease activation in another brain region according to cognitive demands at the particular environmental conditions are related to cognitive deficits in working memory, processing speed, and visuospatial functions (for review see Sala-Llonch, Bartrés-Faz, & Junqué, 2015).

Research using task-fMRI and showing the patterns of such compensation-related mechanisms has led to the formulation of three models as follows: 1) The Hemispheric Asymmetry Reduction in Old Adults (HAROLD) model (Cabeza et al., 2002); 2) The

Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH; Reuter-Lorenz and Cappell, 2008; Schneider-Garces et al., 2010); and 3) The Posterior-Anterior Shift with Aging (PASA).

In the HAROLD model, Cabeza et al. (2002) describes interhemispheric dedifferentiation of the brain activity patterns in older adults while performing a cognitive task as compared to younger individuals. In their studies (Cabeza et al., 2002; Cabeza, 2004), older subjects were found to use less lateralized patterns of brain activity in prefrontal regions while performing cognitive tasks involving episodic retrieval (e.g., word and face recognition) or working memory (e.g., n-back). The results were interpreted in the form of compensatory mechanism of recruiting additional counter-hemispheric resources in the cognitive task execution. Later, researchers have provided further evidence to this pattern of changes in activation due to aging in frontal areas (Park and Reuter-Lorenz, 2009; Turner and Spreng, 2012).

Other researchers proposed the CRUNCH (Reuter-Lorenz and Cappell, 2008; Schneider-Garces et al., 2010), in which they also argue that in older age individuals recruit additional brain resources from other brain areas that younger adults do not need to maintain the cognitive processing at an optimal level. They further state that this type of excessive brain activity occurs mainly in prefrontal cortex, but also in parietal cortex, precuneus and posterior cingulate (Reuter-Lorenz and Cappell, 2008; Schneider-Garces et al., 2010). Spaniol and Grady (2012) have described those changes in brain activation during episodic memory task, while Mattay et al. (2006) and Reuter-Lorenz and Cappell (2008) reported it during working memory tasks.

The third main stream interpreting increased activity is PASA, which was described by Davis et al. (2008). Authors have implemented visuoperceptive task and episodic retrieval task. During those tasks older adults showed deficits to activate posterior regions at the level shown in

younger comparators (Davis et al., 2008). However, authors have also observed the shift of brain functional activity, where the decreases in the activity of the posterior midline cortex were shown together with the increases of the activity in the medial frontal cortex.

Following the dispute on cerebral aging by Park, Polk, Mikels, Taylor, and Marshuetz (2001), the above three compensatory models can also be interpreted in terms of contralateral recruitment, unique recruitment or substitution. The HAROLD model can represent a case of "contralateral recruitment", where additional brain resources are activated in the counter lateral hemisphere. The CRUNCH can hold a case of 'unique recruitment", as the additional neural activation is found to be specific to one region which is excessively exploited. While, the PASA model can represent a case of "substitution", where the weight of the proper activation in younger age is shifted to another region in older age.

A further interpretation to the described above compensatory brain mechanisms accounting for both increases and decreases in brain functioning is provided by the Scaffolding Theory of Aging and Cognition (STAC) (Park and Reuter-Lorenz, 2009). STAC further states that the additional brain resources may be understood in terms of network reorganization, which is engaged in healthy aging to maintain cognitive processing at the optimal level in case of brain structural atrophy and functional weakening (Park and Reuter-Lorenz, 2009).

Recent study by Marstaller, Williams, Rich, Savage and Burianová (2015) provides further evidence to the above interpretation of compensatory mechanisms in aging. Authors examined micro- and macro-structural aging of the brain in relation to the resting state functioning across the life span (Marstaller et al., 2015). They depicted RS-FC within fronto-parietal network to become less consistent with advancing age, in particular found that activity in frontal regions, especially in anterior medial and lateral prefrontal regions increases as a function

of decreases in cortical volume and reductions in white matter integrity in healthy aging (Marstaller et al., 2015). They interpreted it as further evidence for employment of functional compensatory mechanisms counterbalancing the decline in gray and white matter structure (Marstaller et al., 2015).

The results by Betzel et al. (2014) and Geerlings et al. (2014), both using network modeling techniques, provided evidence that whole-brain reorganization of resting state networks due to aging can be interpreted as a pattern of increases in inter-network functional connectivity together with decreases in intra-network functional connectivity. As further described by Betzel et al. (2014) the observed FC alterations go in line with the changes in structural connectitivty.

Literature provides further reports on the increases in RS activity in short-range connections to be accompanied by decreases in long-range FC in healthy aging. Tomasi and Volkow (2012) based their analysis on the dataset of 913 healthy participants (age mean and range not provided), including men and women. Using ROI-based analysis, they have found both, increases and decreases in FC due to advancing age, which were shown not to be related to sex of the participants. Increases were found in short-range connections of somatosensory and subcortical networks consisting of insula, caudate, hippocampus, thalamus, cerebellum and brain stem. On the other hand, decreases were observed in long-range connections within DMN (posterior cingulate, precuneus, angular gyrus and ventral prefrontal cortex) as well as between regions of middle orbitofrontal and middle and dorsolateral prefrontal cortices. Authors further noticed that long-range connections were more sensitive to aging than short-range connections.

Song et al. (2014) studied a total of 50 subjects including 26 younger adults (age M=24.6, SD=3.3 years), and 24 older adults (age M=58.0, SD=6.1 years). RS-fMRI data was extracted for

regions of interest and analyzed with graph metrics including local and global efficiency, modularity and strength of functional connections. Despite the differential methodology, their results show high resemblance to those of Tomasi and Volkow (2012). Song et al. (2014) described RS-FC to be increased in sensorimotor network and decreased in DMN with age. They have interpreted those results as presenting a shift in functional importance in particular brain regions in aging, thus revealing brain-wide network reorganization aiming at the compensation for cognitive decline.

Other reports focused on FC within particular networks. Mowinckel, Espeseth, and Westlye (2012) performed Independent Component Analysis on RS data obtained from 238 healthy participants ranging from 21 to 80 years of age. Their network-specific analysis showed the decreased FC due to aging in the DMN, visual and sensory networks. A study by Marstaller and co-workers (2015) using functional-structural covariance network analysis, further showed that aging accompanies decreases in the strength of functional connectivity in the DMN network as well as fronto-parietal network (FPN) and salience network (SAL).

Further literature also points to age effects on the decreases within the DMN (Andrew-Hanna et al., 2007; Damoiseaux et al., 2008; Mevel et al., 2011; Wu et al., 2011). Damoiseaux et al. (2008) focused their analysis on the effects of age on the DMN and based on the comparison of 10 younger (age M=22.8, SD=2.3) to 22 older participants (age M=70.73, SD=6.0). They have reported that the disconnections were observed in most of the DMN regions (superior and middle frontal gyrus, posterior cingulate, middle temporal gyrus, superior parietal regions). Others reported age-related DMN integrity reductions to be particularly observed in terms of anterior-posterior disconnections (Andrew-Hanna et al., 2007; Wu et al., 2011). It has been further shown that those disconnections are correlated to age-related deterioration in cognitive

functions as well as white matter changes (Andrew-Hanna et al., 2007). The observed disruptions in resting state functional connectivity are persistent after accounting for age-related structural changes such as brain atrophy (Damoiseaux et al., 2008; Ferreira & Busatto, 2013).

One of the mechanisms underlying the described above changes and functional organization may be the reduce perfusion and metabolism of the brain that accompanies aging (Kobari, Meyer & Ichijo, 1990). Another neurobiological explanation of this functional deterioration was proposed by Lietal et al. (2001), who related it to a process which could be started by a decline in dopaminergic neuromodulation which then provokes adequate increases and decreases in cerebral activation.

To sum up, it is widely described that healthy aging affects the brain structural and functional architecture. Literature depicts age related alterations to be observed in terms of gray matter and white matter degeneration. Structural changes go along with functional alterations showing anterior-posterior disconnection and gradation of regional recruitment in the execution of cognitive tasks. Further literature contributes with the evidence for the involvement of the compensatory mechanisms in healthy aging, where functional decline in certain brain areas can be compensated by the recruitment of additional neural resources from more or less distant brain regions. This mechanism may take form of dedifferentiation, unique recruitment or substitution, all of which describe a sort of change in the neural pattern underlying cognitive performance. Those compensatory mechanisms in brain functioning are also detected during the conditions of lack of overt cognitive processing. Increasing number of scientific reports describe decreases in RS activity in short-range connections to be accompanied by increases in long-range FC in healthy aging. The growing empirical evidence echoes in the development of models and theories providing theoretical account to the observed brain changes in healthy aging. One of the

most comprehensive explanations has been provided by the Scaffolding Theory of Aging and Cognition, which incorporates the observations of structural changes as well as both, decreases and increases in brain functioning and describes it together as a network reorganization in aging.

2.1.2. Effects of aging on the neurocognitive functioning

Numerous lines of evidence present neurocognitive functions to decline with aging in adulthood (e.g., Falkenstein, Gajewski, & Getzmann, 2013; Glisky, 2007; Goh, An, & Resnik, 2012; Salthouse, 2004; Semenov et al., 2015) and to be the lowest near the end of life (Smits et al., 1999). It was estimated in early 2000's that about 40% of population above 60 years of age worldwide is affected by some degree of cognitive decline, and the percentage is estimated to grow (Andrade & Radhekrishan, 2009). Longitudinal studies provide further evidence that rapid deterioration of global cognitive functioning is related to increased mortality risk on a 10-year interval (van Gelder et al., 2007).

Literature provides a wide range of scientifically proven cognitive alterations due to healthy aging. However, there are multiple factors which significantly moderate cognitive functioning of the elderly (Finkel et al., 2007). Those include sex, education, occupation (for meta-analysis see Opdebeeck, Martyr & Clare, 2016), engagement in cognitively stimulating leisure activities (Ferreira et al., 2015), nutrition (Wahl et al., 2016), physical activity (Fazeli et al., 2015), sleep hygiene (Vance, Heaton, Eaves, & Fazeli, 2011), medical conditions (Tucker-Drob, Briley, Starr, & Deary, 2014), social resources (Gow & Mortensen, 2016), depressive symptoms, positive well-being and exercising (Allerhard, et al., 2014). Apart from those factors, which will differentiate studied cohorts (Finkel et al., 2007), different methods of examining cognitive performance will contribute to the diversified results. Still, it is generally known that

age-related cognitive decline begins early in the adulthood and encompasses broad spectrum of functions (Salthouse, 2004).

Cognitive decline is usually observed in reasoning, memory, and speed, which comprises reaction time, sensorimotor, and perceptual speed (Earles & Salthouse, 1995; Salthouse, 2004). A variety of data presents aging to be also accompanied by decreases in psychomotor speed and executive functions, switching attention among multiple inputs, and perception (Falkenstein, Gajewski, & Getzmann, 2013; Glisky, 2007). Goh, An, and Resnik (2012) observed age to cause dysfunctions in long-term memory, visual processing, and executive functioning especially in terms of inhibition, manipulation, semantic retrieval, and switching. Lately, based on a large cohort from National Health and Nutrition Examination Survey – NHANES, Semenov et al. (2015) have provided further support to the deterioration of visuospatial and spatial memory functioning in older adults.

In sum, cognitive aging can be approached as a conglomerate of intra personal conditions such as health disparities, together with the outer personal life experiences, socio-economic conditions, demographic grounds, environmental influences. Even though the combination of cognitive decline is highly individual, the extensive literature provides descriptions of the healthy aging as generally leading to the deterioration in multiple cognitive domains. Numerous reports point to the complexity of the observed cognitive decline, which may involve degradation in attention, executive functions, memory, psychomotor, and semantic skills.

2.2. Effects of HIV infection on the central nervous system and neurocognitive functioning

In this chapter the author describes current state of knowledge on the effects that the HIV virus has on the central nervous system (CNS). A description of the general brain alterations is

followed by more in-depth description of the changes in the resting state brain connectivity with the supporting up-to-date research findings. Next, the author discusses the current state of knowledge on the subject of the effects of HIV on the neurocognitive functioning. Stable neurocognitive patters found in HIV are then described and followed by other reported cognitive alterations due to the HIV virus.

2.2.1. Effects of HIV infection on the central nervous system

Human immunodeficiency virus (HIV) enters the central nervous system (CNS) early in the course of infection (Chiodi et al, 1988; Davis et al., 1992; Ragin et al., 2012; Valcour et al., 2012). Despite the introduction of Highly Active Antiretroviral Therapy (HAART), the virus still causes abnormalities in the structure and functioning of the brain (Brew, Crowe, Landay, Cysique, & Gullemin, 2009; Cohen, Harezlak, Schifitto, et al., 2010; Young at al., 2014). In pre-HAART era, brain structure was reported to show atrophy primarily in subcortical regions (Aylward, Henderer, McArthur, Brettschneider, Harris, et al., 1993), while more recent study on subjects receiving HAART presents that atrophy persists in basal ganglia and is more profound with time since infection (Ances, Ortega, Vaida, Heaps, & Paul, 2012). Although the neuroinfectious mechanisms of the virus are not fully described yet, literature provides evidence that the HIV virus targets myeloid cells (Thomson et al., 2011; Williams et al., 2001), and CD8+T-cells which promote neuroinflammation (Schrier et al., 2015). Infection of astrocytes has also been reported (McArthur et al., 2010). Anderson et al. (2015) further showed that certain inflammatory markers, such as Monocyte Chemoattractant Protein-1 (MCP-1) and soluble monocyte differentiation antigen 14 (sCD14) significantly contribute to distinct patterns of brain atrophy in HIV infection.

Various methods have been implemented to study effects of HIV on the brain at both micro- and macrostructural levels. A growing body of research indicates the virus to cause gray matter volume reduction (Thompson et al., 2005; Wilson et al., 2015), followed by cognitive decline (Moore et al., 2006; Steindrink et al., 2013). Recently, the research has proved that HIV targets especially white matter structures (Ragin et al., 2015), with more advanced stages of infection leading to greater WM changes especially in corpus callosum, which can be observed with diffusion constant and anisotropy despite normal MR images (Filippi et al., 2001). Serostatus is shown to have additive and not synergistic effects with aging on measures of Diffusion Tensor Imaging, especially Fractional Anisotropy (FA) and Mean Diffusivity (MD)[2] (Nir et al., 2014). Furthermore, WM changes measured with FA and MD are in a positive relationship with the cognitive decline seen in HIV infection (Ragin et al., 2005; Gongvatana et al., 2009; Tate et al., 2012). To date, two articles provided a review of Diffusion Tensor Imaging (DTI) findings in HIV infection (Holt, Kraft-Terry, & Chang, 2012; Masters & Ances, 2014) and both concluded about the inconsistency in DTI findings in HIV population across the studies.

At a macrostructural level, functional MRI reports have consistently shown that HIV primarily affects the fronto-striatal circuitry (Plessis et al., 2014). Furthermore, task-fMRI findings revealed altered brain functional activity in response to cognitive processing involving working memory (Caldwell et al., 2014; Castelo et al., 2006, Chang et al., 2001; Ernst et al., 2002; Sundermann et al., 2015; Tomasi et al., 2008), verbal memory (Maki et al., 2009),

[2]MD is the average of the tensor's eigenvalues and shows the amount of diffusion in a voxel, which is related to the amount of water in the extracellular space (O'Donnell & Westin, 2011) and the presence of obstacles to diffusion (Le Bihan, 2001).

visual-spatial functions (Ernst et al., 2009; Schweinsburg et al., 2012), cognitive impulsivity (Meade et al., 2011), risk perception (Conolly et al., 2014; Hacker et al., 2015), reaction time (Ances et al., 2010; Ances et al., 2011; Ances et al., 2011; Chang et al., 2004; Chang et al., 2008; Ernst et al., 2002), and motor speed (Ances et al., 2011).

Most recently, resting-state (RS) fMRI studies in HIV+ population have also provided evidence showing alterations in functional connectivity within the lateral occipital network (Wang et al., 2011), the frontostriatal network (Ipser et al., 2015), between the striatum and the default mode network (DMN) and ventral attention network (Ortega et al., 2015), as well as a loss of positive RS correlations between the right lateral parietal (rLP) cortex and DMN and a loss of negative RS correlations between rLP cortex and salience network (Thomas et al., 2013).

Wang et al. (2011) examined 30 young individuals (age M=29.5, SD=6.2 years), including 15 HIV+ (average of 1 year post-infection) and 15 noninfected comparators, and analyzed RS data with ICA approach. They found that coactivation within the lateral occipital network (LOC), which included area from the occipital pole to the occipital-temporal junction and dorsally to the posterior regions of the parietal lobes, is significantly reduced as early as one year since the HIV infection in young adulthood. They noticed reductions especially in the inferior parietal cortex. They did not, however, observe such reductions within other RS networks (Wang et al., 2011). Becker et al. (2012) found that later in the course of the disease (i.e., approx. 10 years after HIV infection), the RS activity is altered across the brain.

Another study providing analysis of the resting state across the brain was carried out by Thomas et al. (2013). In their research, they analyzed RS of 52 HIV+ subjects (age M=41, SD=14 years) including 23 subjects on HAART; and 52 HIV-negative controls (age M=44,

SD=14 years). Thomas et al. (2013) employed ROI-based analysis on the pre-specified 36 brain areas and categorized them into five RS networks (DMN, dorsal attention, control, salience, and sensorimotor networks) based on previous reports by Zhang and Raichle (2010) and Shannon et al. (2011), to analyze intra- and inter-network RS-FC. Authors found that HIV-infected individuals had a loss of RS positive correlations between the right lateral parietal cortex and other nodes of the DMN such as the medial prefrontal cortex and the posterior cingulate cortex. Moreover, negative correlations were also lost in those individuals between the same area (i.e., right lateral parietal cortex) and anterior areas of the left parietal lobe (Thomas et al., 2013).

More recently, Guha et al. (2016) assessed RS data from individuals between 60 and 70 years of age, including 52 HIV seropositive subjects (age M=64, SD=3 years) infected on average for 20 years and almost 30% having detectable viral load; and 29 healthy controls (age M=65, SD=2 years). As in earlier study by Thomas et al. (2013), Guha et al. (2016) also employed ROI-based analysis on the same pre-specified brain regions. Looking for the effects of the HIV, Guha et al. (2016) found no significant alterations in the functional connectivity (FC) neither within nor between RS networks due to HIV serostatus. The only changes in salience network were revealed in terms of reductions in HIV infected individuals with detectable as compared to undetectable plasma HIV RNA.

Other researchers have studied particular functional connections chosen for analysis *a priori*. As such, Ipser et al. (2015) as well as Ortega et al. (2015) studied only the cortico-striatal FC. In the results of their examination, Ipser et al. (2015) described reductions in FC between the regions of dorsolateral prefrontal cortex, dorsal caudate, and thamalus in HIV seropositive individuals. Authors further stated, that there were no significant alterations in the FC between striatum and nodes of other RS networks such as control and sensory-motor

networks (Ortega et al., 2015).

Importantly, Ortega et al. (2015), have also analyzed the influence of cART using the seed-based analysis, where the seeds were placed in the striatal regions. Their participants comprised a total of 132 HIV+ individuals and 45 noninfected controls (age M=31.7, SD=10.9 years). HIV+ group included 82 subjects (age M=41.5, SD= 14.5 years) receiving cART for at least three months, with 77% of those subjects showing virological suppression (viral load<50 copies/ml); and 49 cART-naïve subjects (age M=34.9, SD=15.4 years) out of which 23% was showing virological suppression. Significant between-group differences were reported for age, sex, and in case of HIV+ subsamples – duration of infection. Ortega et al. (2015) observed that HIV seronegative and HIV seropositive individuals receiving cART had comparable FC between striatum and superior frontal cortex, one of the DMN regions. Control subject had the highest FC strength between the striatum and DMN and attention network as compared to the two HIV+ groups. However, HIV+ individuals on cART had higher FC between striatum and DMN, and attention network, as compared to HIV+ subjects not receiving treatment. Authors interpreted their results as revealing protective influence of cART use on the brain FC.

Ipser et al. (2015) have focused even more specifically on fronto-striatal FC. They have analyzed RS data from 15 HIV seropositive (age M=40.6, SD=14.46 years) infected for an average of seven years and most receiving cART; and 15 demographically matched controls (age M=39.73, SD=12.55 years). They have employed seed-based approach where the seed regions were dorsal caudate and mediodorsal thalamus. Authors reported reductions in FC between the dorsolateral prefrontal cortex and the dorsal caudate (Ipser et al., 2015). The authors noticed that the observed reductions were especially intensified in individuals below 50 years of age. Furthermore, Ipser et al. (2015) described reductions in FC between frontal and parietal regions

and dorsal caudate. The FC was not affected, however, between the mediodorsal thalamus and dorsolateral prefrontal cortex, nor between dorsal caudate and thalamus (Ipser et al., 2015).

In summary, findings support the notion that neuroinfectious actions of HIV infection commence early after seroconversion and are resistant to antiretroviral treatment implementation. Even though the exact mechanisms of the virus are not fully understood yet, its effects on the brain are evident. They take the form of structural changes of gray matter atrophy primarily found in basal ganglia and white matter reductions especially in corpus callosum, as well as widespread metabolic alterations. Multiple studies have documented functional activity of the brain to be altered during execution of various cognitive tasks, which was further related to the deficient cognitive performance. A few recent studies using resting state fMRI measures provided a new line of evidence showing that intra- as well as inter-network functional connectivity is compromised in HIV-infected individuals. This proves that brain metabolic changes are detectable regardless of cognitive demands conditions, which introduces RS-fMRI as a sensitive measure to the effects of HIV infection on the functioning of the brain.

2.2.2. Effects of HIV infection on the neurocognitive functioning

Initial reports of cognitive functioning in HIV infected individuals showed dramatic changes. Before the cART implementation in mid'90s, HIV infection led to acquired immunodeficiency syndrome (AIDS) dementia quickly, which within one year from infection could end in patient's death (Navia et al., 1986). Cognitive changes were progressing rapidly and manifested mainly in loss of attention and concentration as well as motor slowing (Navia et al., 1986). The use of antiretroviral treatment since 1995, has improved the expectancy of living near to uninfected population (van Sieghem et al., 2010), but also has visibly reduced the cognitive symptoms and

increased the quality of life of the HIV infected individuals (Maschke et al., 2000). Thus, the observed cognitive alterations are nowadays different from the initially reported. In the pre-cART era, the clinical presentation of HIV-neurocognitive disorder was mostly composed of motor impairments, cognitive speed and verbal fluency (Heaton et al., 2011). While in the cART era, the deficits are notable mostly in memory and learning, as well as executive functions (Heaton et al., 2011).

Currently, there is an ongoing debate on the subject of neurocognitive deficits caused by HIV infection (Nightingale et al., 2014). The Multicenter AIDS Cohort Study (Cole et al., 2007) has shown that asymptomatic patients with HIV infection undergoing successful treatment do not vary from age-matched HIV seronegative comparators on holistic neurocognitive assessment. Only some HIV infected individuals will experience neurocognitive deterioration even if the treatment outcome measures show to be successful (for review see Clifford et al., 2013). Importantly, the cognitive functioning is reported to fluctuate and depend on various illness- and treatment-related factors, making the cognitive assessment a methodologically complex task (Clifford et al., 2013). A handful of other factors may further influence the picture of cognitive functioning in the HIV infected population, for example, premorbid education and cognitive status, coexisting medical conditions (Heaton et al., 2011), illicit drugs use (Heaton et al., 2008), or physical activity (Fazeli et al., 2015). Studies on this complex issue still deliver inconsistent results. The potential reasons include the use of various cognitive assessment tools and differences in target population. However, based on a large cohort of the CNS HIV AntiRetroviral Therapy Effects Research – CHARTER (Heaton et al., 2010), most researchers agree on the notion that about a half of HIV-infected individuals have a chance of developing HIV-associated neurocognitive disorder – HAND. DSM-V defines neurocognitive disorder due

to HIV as meeting criteria for major or mild neurocognitive disorder and not being better explained by other non-HIV medical or mental conditions (APA, 2013). More precise discrimination between HAND categories is proposed in the Frascati conference-based revision of the American Academy of Neurology (AAN) criteria for HAND as follows: 1) asymptomatic neurocognitive impairment is defined by 1 SD below mean in two cognitive domains with no visible impairment in activities of daily living; 2) mild neurocognitive disorder – 1 SD below mean in two cognitive domains with impaired daily activities; 3) HIV-associated dementia – 2 SD below mean in two cognitive domains and notable impairment in activities of daily living (Antinori et al., 2007). HIV-infected individuals with asymptomatic neurocognitive impairment are at an elevated risk of progressing to milder and later more severe forms of HAND as compared to individuals with normal cognitive functioning (Heaton et al., 2004). However, the implementation of HAART has resulted in limiting such progression to severe forms and, thus, resulting in substantial increase in the prevalence of milder forms of HAND (McArthur et al., 2010).

Some recent studies describe cognitive alterations in the HIV infected population based on holistic cognitive evaluation, while most researchers decide on examining cognitive functions selectively. The CHARTER study has shown that the most prevalent cognitive deficits are found in attention, learning and memory, motor functioning, and verbal fluency (Heaton et al., 2010). In another large holistic study of cognitive functioning in HIV+ population, Łojek and Bornstein (2005) further distinguished dominant, stable neurocognitive patterns in HIV infected individuals as follows: psychomotor speed dysfunction; memory and learning dysfunction; and executive dysfunction (especially in information processing speed and categorical thinking). They described that HIV+ patients can show a particular pattern of cognitive deficits rather than global

impairment or impairment of all cognitive functions sensitive to HIV infection. Other researchers delivered further confirmation to the existence of cognitive impairment in this patient population particularly in the following functions: attention and concentration (Becker et al., 1997; Hardy et al., 1999; Heaton et al., 1995), verbal fluency and verbal skills (Becker et al., 2004), simple motor skills and sensory perception abilities (Rackstraw, 2011).

In sum, HIV infection is observed to lead to the cognitive decline despite the introduction of HAART. However, rapidly progressing deterioration in motor functions, psychomotor speed and verbal fluency is decelerated with the successful treatment and thus, not as evident as in the pre-HAART era. Nowadays, majority of HIV-infected individuals present asymptomatic forms of HAND. Nonetheless, HIV seropositive population still confronts cognitive decline, even though more subtle, mainly in attention, memory, psychomotor speed, executive functions, and verbal skills.

2.3. Age-HIV interaction effects on the resting state and neurocognitive functioning

Here, the author brings up the issue of aging with HIV infection in terms of the interaction effects of those factors on the resting state brain activity and neurocognitive functioning. Issues discussed in this chapter are of primary interest in the current dissertation and form the core of the Ph.D. study. Consequently, the author first concentrates on the effects of aging with HIV on the resting state of the brain. Two major hypothesis, i.e., accelerated aging and accentuated aging, are described and discussed in the light of up-to-date research with the scope of the RS. Then, a breviary is given on the interaction of aging and HIV infection on the neurocognitive functioning. Last, the author provides a discussion on the effects of aging with HIV on the relationship between resting state of the brain and neurocognitive functioning.

2.3.1. Age-HIV interaction effects on the resting state of the brain

In the current literature, HIV is often embraced by the hypothesis of the accelerated aging. This hypothesis suggests that the changes which occur due to aging in the general population are observed earlier in the course of life in HIV seropositive individuals. However, as noted by Volberding and Martin (2010), one should continue to critically approach the use of the term "accelerated aging" to describe this group of patients. It remains to be only a hypothesis that still requires the support from the empirical research. Karpiak and Havlik (in press) postulated that a more accurate term in HIV infection is the “accentuated aging”. What they mean is that changes due to HIV infection do not occur earlier in the life course, instead, a higher number of diseases co-occur at the same time and the symptoms of those diseases are more intensive in HIV-infected individuals than in the general population of the comparable age (Karpiak and Havlik, in press).

The question of whether aging and HIV infection cause additive or interaction effects on the RS of the brain remains unclear. Becker et al. (2012) found that there is a synergistic effect of aging and HIV serostatus on the alterations in the RS brain activity using the resting state magnetoencephalography. Other studies examining RS with RS functional magnetic resonance imaging did not confirm the findings of Becker et al. (2012). One of the possible explanations for the opposing results could be that Becker et al. (2012) compared whole-brain RS between infected and noninfected individuals, while other researchers mostly focused on regions or networks selected *a priori*. It could possibly put the light on the fact that interaction between aging and HIV infection could affect resting state connectivity between networks, while additive changes due to aging and HIV can be still noticed between particular brain regions and within specific networks.

Ances et al. (2010) showed that RS cerebral blood flow is decreased in elderly HIV infected individuals, but did not find interaction between age and HIV serostatus. The authors also observed a reduction in the activation of the RS of the brain due to aging in the uninfected individuals. Summing up the results of their research, the authors concluded that the pattern of RS brain activity in patients infected with HIV is alike to the brain activity of healthy individuals about 15 years older.

Thomas, Brier, Snyder, Vaida, and Ances (2013) also identified additive and no interaction effects of aging and HIV infection on decreased RS connectivity of intra- and internetwork correlations of the DMN and salience networks. They showed that the HIV virus causes weakness of the functional connections between the parietal cortex of the right hemisphere and the DMN; the medial prefrontal cortex and the posterior areas of the cingulate gyrus; the parietal cortex of the right hemisphere of the brain and the brain regions forming a salience network (Thomas et al., 2013). The observed changes were intensified with age in a comparable rate in both, HIV+ individuals and healthy controls. In addition, Thomas et al. (2013) reported no association between spontaneous activation of the brain and medical variables such as viral load, CD4 lymphocyte counts and types of medication as well as variables relating to the functioning of cognitive processes (psychomotor speed, verbal memory and executive functions). Results described by Thomas et al. (2013) testify the independent impact of HIV infection and age on the brain functioning. Both factors lead to a weakening of the strength of functional connections. Subsequent work of this research group using a more advanced analysis showed both the independent and interactive effects of aging and HIV on the resting brain activity. HIV infection was found to mainly cause a reduction in the integrity of particular resting state network with the other regions of the brain, and aging was found to cause the functional

reorganization in terms of decreased cohesiveness within the networks, especially sensorimotor networks. The researchers observed the interactive effect of HIV and age as a decrease in the strength of functional connections at the global level (Thomas et al., 2015).

In subsequent studies, researchers (Ipser et al., 2015; Ortega et al., 2015) showed that there is a weakening of the connections between the dorsal areas of the prefrontal cortex and the striatum in HIV-infected patients. In the same study (Ipser et al., 2015), aging had a similar effect as in HIV infection, but it was visible only at the level of a statistical trend. Such a low effect of age is surprising taking into account the results of previous research on this subject (e.g. Thomas et al., 2013). Ipser et al. (2015) speculated that the protective factor, which would explain the surprisingly small effect of age, could have been a higher level of education and a higher level of premorbid intelligence in older people infected with HIV as compared to younger comparators. However, further analysis denied this hypothesis (Ipser et al., 2015). Ortega et al. (2015) have further shown that HIV particularly results in deterioration of the strength of the functional connections between the striatum and the attention network and the DMN. They showed that cART implementation was a protective factor, since the strength of the functional connections between the above networks was higher in patients who were receiving antiretroviral medication as compared to treatment-naïve individuals (Ortega et al., 2015). Medical indicators such as the number of CD4+ T lymphocytes and viral levels as well as indicators related to the performance on cognitive tasks were not correlated with the strength of functional connections (Ortega et al., 2015). The researchers concluded that the measurement of the strength of the connections between the functional areas of striatum and prefrontal cortex may be a valuable indicator of the effectiveness of cART treatment.

The etiology of the neural-related changes observed in HIV is not well understood yet.

Until now, it is known that HIV virus attacks the CD8+ T cells which indirectly cause inflammation in the CNS by starting a sequence of structural changes in neurons (Anderson et al., 2015; Schrier et al., 2015). One of the hypothesis explains weakening of the functional connectivity as a result of the changes in the construction of neurons, especially in terms of neuronal synaptic pruning, which then leads to the delay of the glutamate cycle, which eventually translates into a reduction in brain metabolism that forms the grounds of the RS-fMRI measurement (Thomas et al., 2013). Microstructural changes also apply to the microglial cells and astrocytes (Lu et al., 2011). So far it is hypothesized that, following the reduction of these cells may cause disturbances in the synaptic and dendritic communication which could lead to disturbances in brain functional connections (Ortega et al., 2015). Another hypothesis of the etiology of atypical resting brain activation describes the dopaminergic disorders (Ipser et al., 2015). Reductions in the level of dopamine in the cerebral-spinal fluid have previously been documented in advanced stage of HIV infection (Larsson, Hagberg, Forsman and Norkrans, 1991).

In sum, the two hypothesis on aging with HIV infection, namely “accelerated” vs. “accentuated” still await scientific validation. Up-to-date literature provides evidence for the accuracy of rather accentuated than accelerated effects of aging on the health conditions in HIV-infected population. The growing research interest in studying resting state in this patient population can provide additional data on the additive vs. interactive effects of aging and HIV. So far, it is effects of aging on RS measures in HIV seropositive individuals do not show consistent results. Reported results point to the additive effects of age and HIV in the form of decreases in functional connectivity of the brain in HIV-infected adults.

2.3.2. Age-HIV interaction effects on the neurocognitive functioning

Age-HIV serostatus interaction effects on neurocognitive functioning became of interest over 30 years ago (Van Gorp, Hinkin, Evans, & Miller, 1989). Since then, age and HIV infection were found to independently generate cognitive declines in executive functions, memory and learning, and psychomotor speed (Kissel, Pukay-Martin, & Bornstein, 2005; Sacktor et al., 2007; Scott et al., 2011) and visuoconstruction deficits (Scott et al., 2011). Thomas et al. (2013) found additive effects of aging and HIV serostatus on cognitive functioning in terms of deficits in the information processing speed, psychomotor speed or verbal learning and memory. In contrast, a study by Becker et al. (1997) demonstrated interaction effect of advancing age causing accelerated cognitive processing speed decline in HIV seropositive individuals. Hardy et al. (1999) also showed that aging exacerbates neurocognitive decline in HIV-infected adults, with the largest effects exhibited in psychomotor speed and executive functions, and lesser in attention and concentration. Further research indicated the interaction between age and HIV serostatus in exacerbated cognitive deficits, especially in executive functions and verbal fluency (Becker, Lopez, Dew, & Aizenstein, 2004).

To sum up, literature provides descriptions of age and HIV infection as independently leading to cognitive deterioration especially in memory, executive, visual and psychomotor functions. However, other reports picture age and HIV as causing interaction effects in psychomotor and executive functions degradation as well as verbal fluency decline. Inconsistencies between the results can be accounted for multiple differences between studied cohorts in terms of the socio-demographic, health- and treatment-related variables, and used methodology. Noteworthy is the fact of changes across time in the administrated antiretroviral treatment, which becomes more and more successful and also determines a source of variability

in the cognitive outcomes in this patient population.

2.4. Age effects on the relationship between resting state of the brain and neurocognitive functioning

The issue of the effects of aging on the relationship between the RS and cognitive functioning has been undertaken by few researchers. Damoiseaux et al. (2008) found that the DMN connectivity is associated with cognitive performance in older (mean age of 71 years old) but not in younger adults (mean age of 23 years old). In older adults, decreased anterior DMN activity was related to deficits in executive functioning, but not with attention or concentration (Damoiseaux et al., 2008). In young adults no relationship was observed between the DMN connectivity patterns and attention, concentration, or executive functioning (Damoiseaux et al., 2008). Another study confirmed such characteristics of healthy aging (Wu et al., 2011). The authors showed that in healthy elderly there was decline of negative correlations between the BOLD signal in DMN network and the posterior cingulate cortex (PCC) involved in the attention processes and supplementary motor area (SMA) involved in planning, initiating and executing of motor acts (Damoiseaux et al., 2008). Functional changes of the brain, as described by Wu and colleagues (2011), may lead to decreased cognitive functioning in the working memory and executive functions.

In sum, research still provides limited explanation to the effects that advancing age has on the relationship between RS. Empirical evidence proves that the relationship between functional connectivity in particular RS networks, such as DMN, and neurocognitive functions, such as executive performance, is strengthened as a function of age.

2.5. HIV effects on the relationship between resting state of the brain and neurocognitive functioning

The literature focused particularly on the effects of HIV infection on the relationship between the RS and cognitive functioning is still very limited, which is expected considering the novelty of the RS-fMRI method, and its only recent applications in HIV infected population. The one study dedicated to this subject is published by Wang et al. (2011). Description of their sample is already described in Section 1.2.1.

Wang et al. (2011) examined moderating effects of HIV infection on the relationship between cognitive functions and major RS brain networks, i.e., auditory, default mode, executive-control, lateralized fronto-parietal, lateral occipital, primary visual, sensory motor, described by Damoiseaux and Greicius (2009). The outcomes of Wang's et al. (2011) research show the decrease in RS activity, especially in the occipital network, to be significantly related to decrease in psychomotor speed in young HIV seropositive but not in young HIV seronegative individuals. Strongly impaired connectivity indicated disturbance of this cognitive function. Importantly, there were no differences in the cognitive performance between HIV+ and HIV- individuals on the group level. Taking together the results, researchers proposed to interpret the RS-fMRI measures as a sensitive biomarker of changes in the brain that may preview the cognitive impairment later during the infection.

This study provides a clinical representation of the strengthening of the relationship between the RS-FC and neurocognitive functioning. An analogy can be made to healthy aging, where the brain mechanisms are triggered to compensate for cognitive deterioration, and can be successful when the FC is increased accordingly to the needs. In case of HIV infection, the two observations of Wang et al. (2011) have to be considered: first of the decreased FC and decreased

cognitive functioning; and second of the strengthened relationship in the HIV-infected individuals. Those can be interpreted as that the attempt to strain the neural resources in order to prevent cognitive functioning from further decline fails in HIV-infected individuals. This can be due to neuroinfectious actions of the virus which prevent successfully employment of the compensatory mechanisms, and as a result, the compensatory increases in the FC are not triggered. On the contrary, FC is decreasing potentially due to the neuroinflamation, and as a result causes further cognitive deterioration.

2.6. Age-HIV interaction effects on the relationship between resting state of the brain and neurocognitive functioning

Recently, the combined effects of aging and HIV infection on the relationship between the RS and cognitive functioning is increasingly addressed in the scientific debate. Some researchers (e.g., Thomas et al, 2013) suggest that changes in the functional connections of the brain can provide us with knowledge about the neural basis of cognitive impairment in people aging with the HIV infection. Yet, limited data is available on this issue. Up-to date scientific reports that examined this issue in aging HIV seropositive population, show lack of the relationship between the strength of functional connections of the brain and cognitive state. Hence, they could not follow with examining the age-HIV interaction effect on the relationship if the relationship was not found in the first place.

Thomas et al. (2013) observed no correlation between the strength of functional connectivity within the DMN, salience, executive or control networks and global cognitive score based on the measures of executive function, verbal memory and psychomotor speed (mean age 41 years old). Similar results were obtained by Ortega and colleagues (2015) in younger HIV+

sample (mean age 32 years old). Moreover, Ipser colleagues (2015) reported that changes in the strength of cortico-subcortical connections were most pronounced among HIV+ who did not show global neurocognitive disorder.

Importantly, those authors employed methodology for measuring global neurocognitive disorder after Carey et al. (2002). It is a method where cognitive performance across the measured cognitive functions is summarized as one score, in other words one value which is supposed to reflect the level of all of measured cognitive functions. Of note, a participant simultaneously showing very high and very low performance of separate functions will have a comparable score to the participant showing moderate performance across the cognitive functions. Therefore, this method may be not sensitive in case of selective cognitive decline in a clinical population such as HIV-infected individuals.

Given limited number of research reports on this topic, the above results should be interpreted with caution. One should keep in mind other factors that could significantly affect the clinical picture of HIV-infected individuals. In the latest study by Heaton et al. (2015) on the impact of HIV on the functioning of patients 40 years of age, it was demonstrated that the shape of cognitive function is dependent on receiving treatment. Moreover, in addition to the absence of treatment, variables that significantly contribute to a more rapid deterioration of cognitive functioning include higher multimorbidity, particularly significant depressive symptoms, and methamphetamine use throughout the life course (Heaton et al., 2015). In contrast, the protective variables that predicted even improvement in cognitive functions included, e.g., higher premorbid IQ level and lack of a diagnosis of depression in a life time (Heaton et al., 2015).

2.7. Summary

Resting state fMRI is a novel method of neuroimaging which assesses intrinsic brain activity, i.e., brain functioning during conditions of lack of overt cognitive processing. Previous literature describes cognitive involvement of resting state brain networks. This valid association between RS-fMRI measures and cognitive functioning fosters interdisciplinary studies on the neural bases of behavior. Currently, there is a growing body of research implying this technique in studies on health and disease, including aging and HIV infection. Recent research reports provide data on the sensitivity of RS-fMRI to the brain functional consequences of the neuroinfectious actions of the HIV virus in the CNS.

Multiple research reports have undertaken the subject of effects of aging as well as HIV infection on neurocognitive functions. Lesser amount of literature can be found on the effects of age and HIV infection on the resting state of the brain, which is expected due to the novelty of this neuroimaging technique.

Aging is related in healthy population to functional reorganization of the brain, which can be observed in terms of decline in short-range and increase in long-range FC. Also, compensatory mechanisms can be observed in healthy aging. Those may take form of functional dedifferentiation, unique recruitment or substitution. In terms of neurocognitive functioning, previous literature describes deterioration across cognitive domains, which starts early in the adulthood and is more pronounced later in the life time.

In turn, HIV infection is reported to lead to weakening of RS-FC as well as degradation of cognitive performance across cognitive functions. However, literature provides various and often times inconsistent results, which is understandable in the light of advancements of antiretroviral treatment. Increase in the success rate of the HAART translates into health

outcomes, which are also visible as deceleration of neurocognitive decline in this patient population.

The success of HAART has also led to prolonging life in HIV-infected individuals. This recent change in the portrait of HIV infection is mirrored in the current scientific studies which address the subject of aging in HIV infection. The number of reports on this issue is growing, however, within this literature, there is only few studies with the scope of examining resting state of the brain in relation to neurocognitive functioning. Therefore, the relationship between resting state of the brain and cognitive outcomes, as well as age and HIV effects on this relationship, remains unclear in this patient population.

EMPIRICAL PART

3. DESCRIPTION OF THE RESEARCH PROJECT

In this chapter, the author first gives the description of the Major Study, followed by the description of the current Ph.D. research.

3.1. Description of the Major Study "The Effects of Aging on Cognitive and Chemosensory Functions of the Brain in HIV Infection"

Here, the author provides the description of the Major Study, "The Effects of Aging on Cognitive and Chemosensory Functions of the Brain in HIV Infection" coordinated by prof. Łojek, Ph.D., in order to give an overview of the background, objective and methodology of this large research project. The description given below formulates the grounds and context for the development of current Ph.D. dissertation.

3.1.1. Background

The Major Study is a large collaborative research coordinated by prof. Łojek, Ph.D., and funded by the Narodowe Centrum Nauki through the program "Harmonia 3" (UMO-2012/06/M/H56/00316). The collaboration involved four Polish research facilities (Faculty of Psychology, University of Warsaw, Warsaw, Poland – leader of the project; Hospital for Infectious Diseases in Warsaw, Poland; Institute of Psychiatry and Neurology in Warsaw, Poland; at the Bioimaging Research Center – BRC, in Kajetany near Warsaw) and Faculty of Medicine at the Ohio State University (OSU), WI, USA. The project will be conducted in 2013 – 2016.

3.1.2. Rationale and Objective

It is already known that Human Immunodeficiency Virus (HIV) causes neurodegeneration and neurobehavioral dysfunction despite the introduction of highly active antiretroviral therapy – HAART (Brew, Crowe, Landay, Cysique, & Gullemin, 2009). However, the influence of age on the brain and its function in HIV infection remains unclear. Therefore, the purpose of this study is to examine the independent and interactive effects of age and HIV on measures of cognitive and chemosensory function, brain structures and metabolism.

3.1.3. Methodology

3.1.3.a. Participants and recruitment procedure

A total of 200 participants were recruited for the Major Study Stage I (i.e., medical, neuropsychological and chemosensory examination – for description see Section 3.1.3.c.). Out of those, 130 participants were retained for the Stage II of study (i.e., neuroimaging examination – for description see Section 3.1.3.d.).

Participants were recruited between December 2013 and January 2016. Recruitment took both, active and passive forms. The HIV+ participants (N=100) were recruited from the patients of the Hospital for Infectious Diseases in Warsaw, Poland, who were non-drug users, infected via sexual way (men who have sex with men), receiving antiretroviral treatment at the time of study and systematically following medical control. Control participants (N=100) were actively recruited from organizations for homosexual men localized in and around Warsaw, Poland. Furthermore, the study was advertised in posters and information leaflets placed in the Hospital for Infectious Diseases in Warsaw, Poland. There was also an informative Internet website (http://hiv-project.pl/) and a facebook page (https://www.facebook.com/HIVbadaniamozgu) created. Potential control participants followed initial over-the-phone or in-person interview, which determined their participation in the study according to the exclusion criteria.

The exclusion criteria were as follows: education level below high-school Matura Exam; deficits of learning; amnestic disorders; history of chronic or progressive neurological disorders; laryngological disorders; drug use within the last five years; alcohol consumption above the norm (3 units per day for men); current psychosis; current anxiety or depressive symptoms; diabetes; liver or renal dysfunction/failure; untreated hypertension; head trauma or brain injury; history of unconsciousness for at least 30 min.; cancer; other sexually-transmitted diseases; and in case of controls, HIV seropositive and HCV positive blood test result.

Subjects received financial recompensation for the participation in the study.

3.1.3.b. Standard protocol approvals and participant consents

The study was approved by Ethics Committee of the University of Warsaw. Subjects gave informed consent to participation in the study in two separate written forms, one for the medical,

neuropsychological and chemosensory examination and second form for the neuroimaging examination.

3.1.3.c. Medical, neuropsychological and chemosensory evaluation

There were two main, consecutive stages of the study. The first consisted of medical, neuropsychological and chemosensory examination. Evaluations were performed by an interdisciplinary research team including neuropsychologists, neurologist, psychiatrist, laryngologist, physician, and medical technician, from the Hospital for Infectious Diseases in Warsaw, Poland and Faculty of Psychology, University of Warsaw, Warsaw, Poland.

Medical assessment. Evaluation of: CD4 level; viral load (in blood); HCV infection; neurological and psychiatric disorders; and general mental ability.

Chemosensory assessment. Evaluation of laryngological, olfactory and taste functions.

Neuropsychological assessment. Neuropsychological assessment was conducted by trained neuropsychologists[3]. A comprehensive battery of neuropsychological tests comparable to those described in the book by Łojek (2000) "Neuropsychology of individuals living with HIV and AIDS" (*pl*. "Neuropsychologia osób zakażonych wirusem HIV i chorych na AIDS") was applied. Selection of standardized neuropsychological methods was based on their previously shown sensitivity to age- and HIV serostatus-related changes in cognitive functioning (Lezak, Howieson, & Loring, 2004; Łojek, 2000; Łojek & Bornstein, 2005). The tests assessed the following cognitive functions: psychomotor speed; learning and memory; executive functions; abstract thinking; nonverbal fluency; attentional functions; activity rate; verbal fluency;

[3]Anna Egbert, MA, Department of Neuropsychology, Faculty of Psychology, University of Warsaw, Poland;
Bogna Szymanska, MA, Hospital for Infectious Diseases in Warsaw, Poland;
Marta Sobanska, Ph.D., Department of Neuropsychology, Faculty of Psychology, University of Warsaw, Poland;
Natalia Gawron, Ph.D., Department of Neuropsychology, Faculty of Psychology, University of Warsaw, Poland;

expressive functions; as well as depression and anxiety.

The measures were administered in fixed interleaved order, determined based on whether they were assessing verbal or nonverbal cognitive functions, as follows:

1. The Brief Fatigue Questionnaire (BFI)
2. The Mini Mental State Examination (MMSE)
3. The Corsi blocks forward
4. The Corsi blocks backward
5. The California Verbal Learning Test (CVLT) – immediate and short delay recall

during the long delay gap in CVLT:

5.1. The Ruff Figural Fluency Test (RFFT)

5.2. The Color Trails Test – 1 (CTT-1, CTT-2)

5.3. The Grooved Pegboard Test

6. The California Verbal Learning Test (CVLT) – long delay recall and recognition
7. The WAIS-R(PL) – Digit Span forward
8. The WAIS-R(PL) – Digit Span backward

Break in the assessment (10-15min.)

9. The WAIS-R(PL) – Vocabulary
10. The Wisconsin Card Sorting Test (WCST)
11. The Verbal Fluency Test (VFT)
12. The Patient's Assessment of Own Functioning Inventory (PAOFI)
13. The State-Trait Anxiety Inventory (STAI)
14. The Center for Epidemiological Studies – Depression Scale (CES-D)
15. The Depression Questionnaire (KPD)

16. The Social Activity Questionnaire (SAQ)

17. The Social Support Questionnaire (SSQ)

18. The Personality Attributes Questionnaire (PAQ)

19. The Eating Habits Questionnaire (EHQ)

20. The Modified International Physical Activity Questionnaire (MIPAQ)

Testing session lasted approximately two hours including one break of 10 to 15 min. obligatory for all participants.

3.1.3.d. Neuroimaging examination

The second stage of the assessment consisted of neuroimaging examination. It was performed by an interdisciplinary team including engineers, neuropsychologists and technicians expertized in research using functional magnetic resonance imaging (fMRI), from the Bioimaging Research Center (BRC) in Kajetany near Warsaw, and Faculty of Psychology, University of Warsaw. The assessment using MRI, fMRI, and resting state-fMRI (RS-fMRI) was performed with the BRC research facilities.

Measures. Neuroimaging measurements included: volumetric MRI (Voxel Based Morphometry), diffusion MRI (Diffusion Tensor Imaging), fMRI with the administration of the numerical Stroop task and n-back task, and RS-fMRI. The whole MRI study lasted approx. 1.5 hours.

3.2. Ph.D. Study "The Effects of Aging and HIV Infection on the Relationship between the RS of the Brain and Neurocognitive Functioning"

This part consists in the description to the author's research (Ph.D. study). First, author gives the

background of the dissertation. Then, the research problem is described, followed by rationale and objective. Finally, the research questions and hypotheses are articulated.

3.2.1. Background

As stated earlier, the current Ph.D. research forms a partial fulfillment of a larger collaborative research project, here called the Major Study (see description in Section 3.1.) coordinated by prof. Łojek, Ph.D. This dissertation was conceptually elaborated at the Faculty of Psychology, University of Warsaw, Warsaw, Poland, and the Bioimaging Research Center (BRC) in Kajetany near Warsaw, Poland. The data was analyzed, investigated and interpreted at the Department of Biomedical Engineering (BMI), New Jersey Institute of Technology (NJIT), Newark, NJ, USA in collaboration with the two noted Polish institutions.

3.2.2. Rationale

In the era of accelerated development of medicine and technology, changes may be observed in, both, the clinical picture of individuals living and aging with HIV infection as well as the research approach to the health-related issues in this growing population. The results of recent studies on HIV indicate RS-fMRI to be a sensitive technique to changes in brain functioning resulting from HIV seroconversion even in the early asymptomatic phase of the infection. Although this is a relatively new area of exploration, scientists agree that HIV affects the pattern of spontaneous activity of the brain. The neural networks that show especially atypical pattern of decreased resting state activity are the DMN, attention network, executive network, salience network, as well as cortico-subcortical connections (particularly between areas of the prefrontal

cortex and striatum). However, considering the small number of reports which describe research in this area, those findings still require validation.

Furthermore, given the socio-demographic change in the image of HIV, which is observed as an increase in the average age of the HIV-positive population (UNAIDS, 2013), research has already started to shift toward studying HIV together with an additional factor of aging. Still, there is no agreement whether aging in people infected with HIV causes synergistic or independent changes in the pattern of spontaneous brain activity. Part of the research results support the hypothesis of accelerated aging of brain, since the pattern of spontaneous brain activity of people with HIV earlier similar activity pattern, which is visible in older people, but who are not HIV-positive (Ances et al., 2010). On the other hand, most research points to the hypothesis of accentuated aging of the brain in HIV infection. In that respect it is shown that as a result of HIV infection, changes in the resting state of the brain reflect the nature of the changes seen in aging, but these changes are much more profound (Ipser et al., 2013; Thomas et al., 2013). It is also important that the progress of these changes in HIV+ individuals is comparable to the rate in non-infected people (Thomas et al., 2013). On the basis of a limited number of studies on this subject we cannot, however, explicitly state the accuracy of either one, interactive or independent effects of aging with HIV.

3.2.3. Objective

This research had three objectives. The first goal was to examine the additive and interactive effects of aging and HIV infection on the resting state (RS) brain activity as well as neurocognitive functioning. The second aim was to describe the relationship between the RS brain activity showing age-HIV effects, and neurocognitive functioning. Finally, if those

relationships were distinguished, the third purpose was to investigate the moderating effects that age and HIV infection have independently as well as in interaction on the revealed relationships between the RS of the brain and neurocognitive functioning.

3.2.4. Research Questions

1. What is the relationship between advancing age and the resting state of the brain and neurocognitive functioning?
2. What is the relationship between HIV infection and the resting state of the brain and neurocognitive functioning?
3. What are the interaction effects of age and HIV infection on the resting state of the brain and neurocognitive functioning?
4. What is the relationship between the resting state of the brain showing effects of age – HIV interaction, and neurocognitive functioning?
5. How does age moderate the relationship between the resting state brain activity and neurocognitive functions?
6. How does HIV infection moderate the relationship between the resting state brain activity and neurocognitive functions?
7. Are the brain compensatory mechanisms evoked in aging of HIV-infected individuals exacerbated as compared to mechanisms in aging of HIV seronegative individuals?

3.2.5. Hypotheses

Hypothesis I. Advancing age is related to alterations in the resting state of the brain and neurocognitive functioning, especially in terms of inter-network RS-FC increases and

intra-network RS-FC decreases, and decline in attention, executive functions, memory, psychomotor, and semantic skills.

Hypothesis II. HIV infection is related to changes in the resting state of the brain and neurocognitive functioning, especially in terms of decreases in inter- and intra-network RS-FC and deficits in attention, memory, executive functions, psychomotor speed and verbal skills.

Hypothesis III. There are interaction effects of age and HIV infection on the resting state of the brain and neurocognitive functioning, observed especially in exacerbated increases in inter-network FC, as well as more profound deficits in executive, psychomotor functions and semantic skills.

Hypothesis IV. There are relationships between the resting state of the brain and neurocognitive functions which are sensitive to the interaction effects of aging and HIV infection, especially in terms of inter-network FC, and executive functions as well as semantic skills.

Hypothesis V. Advancing age reinforces the relationship between the decreasing RS brain activity and cognitive deficits, especially in intra-network FC of the DMN and executive functions.

Hypothesis VI. HIV infection reinforces the relationship between the decreasing RS brain activity and cognitive deficits, especially in intra-network FC of the Occipital Network and psychomotor speed.

Hypothesis VII. Brain compensatory mechanisms are exacerbated in aging HIV+ individuals and are visible in terms of strengthening of the inter-network FC which is related to the level of neurocognitive performance.

4. METHODOLOGY

4.1. Participants

The sample examined in this dissertation comprises 130 subjects who completed both stages of testing in the Major Study (i.e., Stage I – medical, neuropsychological and chemosensory examination; and Stage II – neuroimaging). The base cohort in the Major Study is composed of Caucasian White Polish males between 25 and 75 years old, half of who were HIV seropositive individuals selected from the patients of the Hospital for Infectious Diseases in Warsaw, Poland. The other half of the sample comprised HIV-noninfected sex-, ethnicity-, age-, and education-matched comparators. Detailed description of the recruitment of the participants and exclusion criteria is provided in Section 3.1.3.a.

A total of 108 participants (i.e., HIV=54; HIV-=54) was retained for final analysis following the application of quality assurance standards as described in Section 4.2.3. The sample comprised Caucasian White Polish males with the mean of 42 years of age, mean of 16 years of education, income above the national average level, and majority holding full- or part-time jobs. Descriptive statistics, shown in Table 1, determined no significant differences between HIV-seropositive and control subjects in the distribution of age, years of education, economic status, or depression.

HIV+ and HIV- groups were not matched in terms of sexual behaviors. 80% of the HIV+ individuals reported engaging exclusively in homosexual relations and 4% in only heterosexual relations, as opposed to 60% of controls reporting only homosexual relations and 30% only heterosexual relations. Furthermore, HIV seropositive individuals were engaged the current partner relationship for a significantly shorter time (M=4 years), as compared to noninfected control subjects (M=8.6 years).

Participants provided socio-demographic data on self-reported questionnaires.

Table 1. Socio-demographic characteristics of the study sample

Characteristics	HIV+	Controls	*p*-value
Demographics			
Male, N (%)	54 (100)	54 (100)	1.00b
Age, M (SD)	41.36 (12.27)	42.79 (12.0)	.495a
Age range (years)	25-75	25-69	
Race/Ethnicity – Caucasian White, N (%)	54 (100)	54 (100)	1.00b
Education years, M (SD)	15.91 (2.75)	16.74 (2.97)	.139a
Sexual behaviors, N (%)			.016*c
Only homosexual	43 (79.6)	32 (59.3)	
Mainly homosexual sometimes heterosexual	3 (5.6)	2 (3.7)	
Equally often homo- and hetero-sexual	3 (5.6)	2 (3.7)	
Mainly heterosexual	3 (5.6)	1 (1.9)	
Only heterosexual	2 (3.7)	16 (29.6)	
Data not provided	0	1	
Socio-economic status			
Current stable partner relationship in years, M (SD)	4.01 (7.49)	8.63 (11.98)	.023*a
Employment status, N (%)			.453c
Full- or part-time job	40 (74.1)	45 (83.3)	
Studying	2 (3.7)	3 (5.6)	
Retired or pension	6 (11.1)	2 (3.7)	
Unemployed	4 (7.4)	4 (7.4)	
Data not provided	2 (3.7)	0 (0.0)	
Income, N (%)			.825c
Above national average	24 (44.4)	32 (59.3)	
Below national average	11 (20.4)	11 (20.4)	
National minimum salary	3 (5.6)	3 (5.6)	
Data not provided	16 (29.6)	8 (14.8)	
MMSE, Mdn	29.00	30.00	.167b
Significant depressive symptoms, N (%)	14 (25.9)	13 (24.1)	.692b

Note: a-T-unpaired test; b-chi-square; c-likelihood ratio. MMSE- Mini Mental State Examination. Significant depressive symptoms- outcome score of Center for Epidemiological Studies – Depression Scale.

Clinical and treatment-related characteristics of HIV+ sample are presented in Table 2. The variability of health characteristics of the sample was predetermined by the study exclusion criteria, with no subjects reporting history of neurological illnesses. The mean age at seroconversion was 35 years of age, and ranged from 20 to 55 years of age. At the time of participation in the study, HIV+ participants were infected for at least ten months and were stable on antiretroviral treatment (CD4 count>200) for a minimum of six months. Viral load was

successfully suppressed to below the detectable level of 50 copies/ml in 95% of the HIV-infected sample. In case of 31 patients, treatment included multiple treatment schemes, while 23 patients were treated with only one HAART scheme. Clinical and treatment-related variables were obtained from participants' medical files from the Hospital for Infectious Diseases in Warsaw, Poland.

Table 2. Clinical and treatment-related characteristics of the HIV seropositive individuals.

Characteristics	HIV+
HIV-related clinical and treatment variables	
Age at seroconversion, M (SD)	35.02 (9.95)
Age at seroconversion range (years)	20-55
Duration of infection in years, M (SD)	6.34 (5.62)
Duration of infection range (years)	1-21
CD4 nadir, M (SD)	260.54 (134.767)
CD4 current, M (SD)	573.63 (192.74)
Viral load highest, M (SD)	181145.94 (464547.17)
Viral load current, N (%)	
<50	51 (94.44)
>50	3 (5.56)
Treatment scheme, N (multiple HAART schemes : HAART)	31:23

4.2. Assessment of resting state of the brain

4.2.1. Image acquisition

All neuroimaging was performed at the Bioimaging Research Center (BRC) in Kajetany near Warsaw, using a 3 Tesla Siemens TRIO research scanner which was equipped with a 32-channel head coil. The imaging protocol of interest in the current study included the structural and resting state sequences. A high-resolution, thee-dimensional T1-weighted MRI scans were acquired using a magnetization-prepared rapid gradient echo sequence (MPRAGE) (TR=1900ms, TE=2.21ms, voxel dimension=0.9x0.9x0.9mm isotropic, acquisition time=5 min). Resting state BOLD fMRI (REST) was performed directly following MPRAGE and used (TR=2000ms, TE=30ms, voxel dimension= 3x3x3mm isotropic, imaging matrix=64 x 64, slice

thickness=3mm, 41 slices with no gap, number of reference slice=1, acquisition time=8.08min, with a total of 250 frames). During the eight minute resting state session (no visual or auditory stimuli presented), participants were instructed to stay still, to relax with their eyes closed and not to think of anything in particular.

4.2.2. Structural and resting state data preprocessing

Preprocessing of the structural and RS data was established and performed at the BMI, NJIT, NJ, USA, in close collaboration with the BRC, Kajetany, Poland.

Preprocessing was carried out off-line on a Windows workstation by using customized image processing routines written in MATLAB8.5.1 environment (MathWorks; http://www.mathworks.com/) using SPM12 (Statistical Parametric Mapping; http://www.fil.ion.ucl.ac.uk/spm/), and partially on a Linux workstation using AFNI (https://afni.nimh.nih.gov/afni/).

Preprocessing steps followed standard pipeline as described earlier in Section 2.2.2. The standard order of implementing preprocessing steps was retained and the settings were implemented as follows: skull stripping; alignment; realignment; coregistration; deformations; normalization; smoothening was performed with FWHM=6; masks were cereated for WM and CSF; regressors were created for WM, CSF, and motion parameters; temporal regression was ran with and without temporal filtering of 0.01-0.1Hz consistent with previous studies (Biswal et al., 2010) giving result of two files, rponly_wrrest.nii and rpnofilt_wrrest.nii accordingly.

A binary mask was created to be used in second-level analysis in order to analyze only those brain regions that were present in the resting state fMRI scans of all subjects. The mask was created first for each participant from the rponly_wrrest.nii files. The binary mask was

created at the threshold of intensity equal to 100. The retained binary masks from the final sample were concatenated into one 4D file with the number of time points corresponding to the entered number of participants from the final sample. Then, one binary mask containing only those voxels that were present across all time points (i.e., participants) was created using fslmaths input.nii -Tmin output.nii command in FSL v5.0. The obtained mask that was applied in second-level analysis is presented in Figure 1.

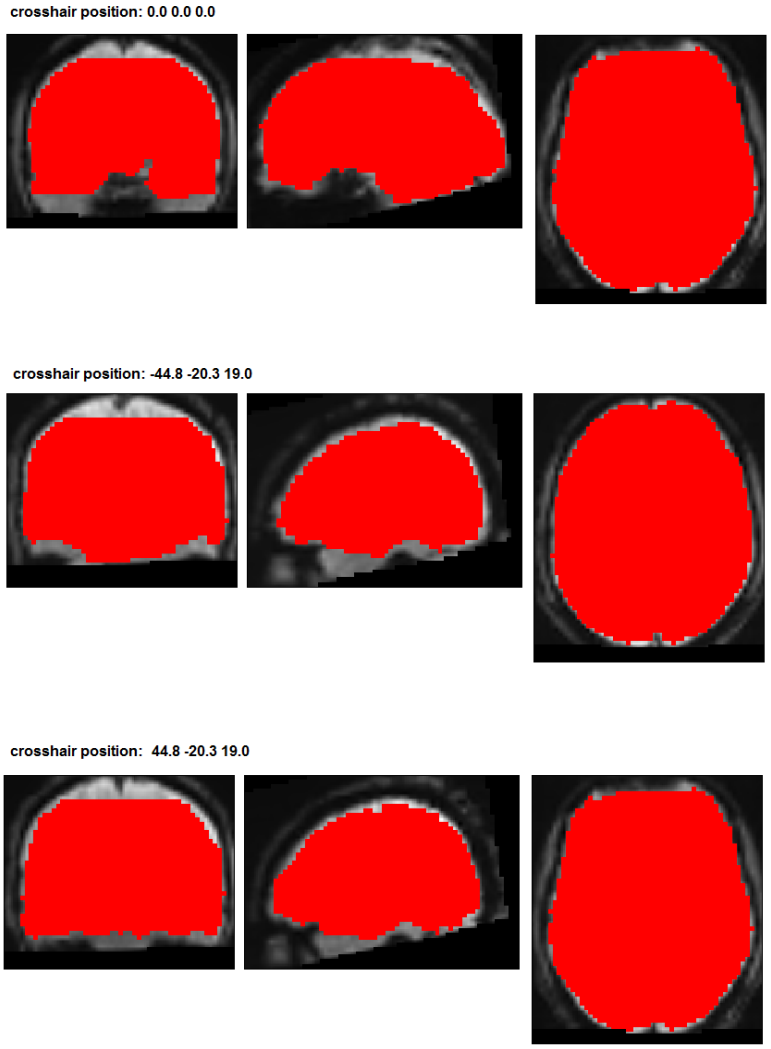

Fig. 1. Binary mask of voxels registered for all subjects from the final sample presented on a resting state scan of a sample control participant (subject #1023).

4.2.3. Quality assurance

Standards for the quality assurance in the resting state fMRI data for this dissertation were established at the BMI, NJIT, NJ, USA, and the BRC, Kajetany, Poland, following stringent recommendation of prof. Rao, Ph.D., Faculty of Medicine, OSU, WI, USA.

Measures of quality assurance (QA) included absolute and relative motion as well as framewise displacement (FD), as described earlier in Section 2.2.2. QA-based exclusion criteria were applied in three consecutive steps as follows: 1) absolute motion of above 2mm; 2) FD of mean translation/rotation above 0.2mm/0.2degrees and of maximum translation/rotation above 1.5mm/1.5degrees; 3) relative motion of above 0.5mm in at least 10% of time points.

In the first step of executing QA, four participants were excluded due to exceeding absolute motion threshold (two control and two HIV+ participants). The second step, i.e., FD, resulted in exclusion of four participants (three controls and one HIV+ subject). Following QA exclusion criteria in the third step, all four participants (two control and two HIV seropositive subjects) whose relative motion exceeded 0.5mm in 10% time points or more were excluded from further analysis. Therefore, out of 130 subjects, there was a total of twelve participants who were excluded from further analyses due to excessive head movement during resting state scanning.

4.2.4. Structural MRI postprocessing

Postprocessing of structural data included voxel-based morphometry (VBM) performed in SPM12. The smoothed and modulated data from the segmentation into GM and WM (i.e., step 7 of the preprocessing) was retained for VBM analysis. The group level comparisons of control vs. HIV+ participants was performed with a *T*-unpaired test with age of participants entered as

a covariant.

4.2.5. RS-fMRI postprocessing

Postprocessing of RS data was established and performed at the BMI, NJIT, NJ, USA, in close collaboration with the BRC, Kajetany, Poland. The analyses included three different approaches as follows: Regions of Interest (ROI) based analysis; Independent Component Analysis (ICA); and voxel-based analysis (for description of the techniques see Section 2.2.4.).

Regions of Interest based analysis

Based on the coordinates of 160 ROIs described in Dosenbach et al. (2010), ROIs for the current study were created as a sphere with a radius equal to 5mm in MarsBaR toolbox (http://marsbar.sourceforge.net/; Brett et al., 2002) in SPM12 software. The illustration of the 160 ROIs is presented in Figure 2 (reprint with permission from Dosenbach et al., 2010).

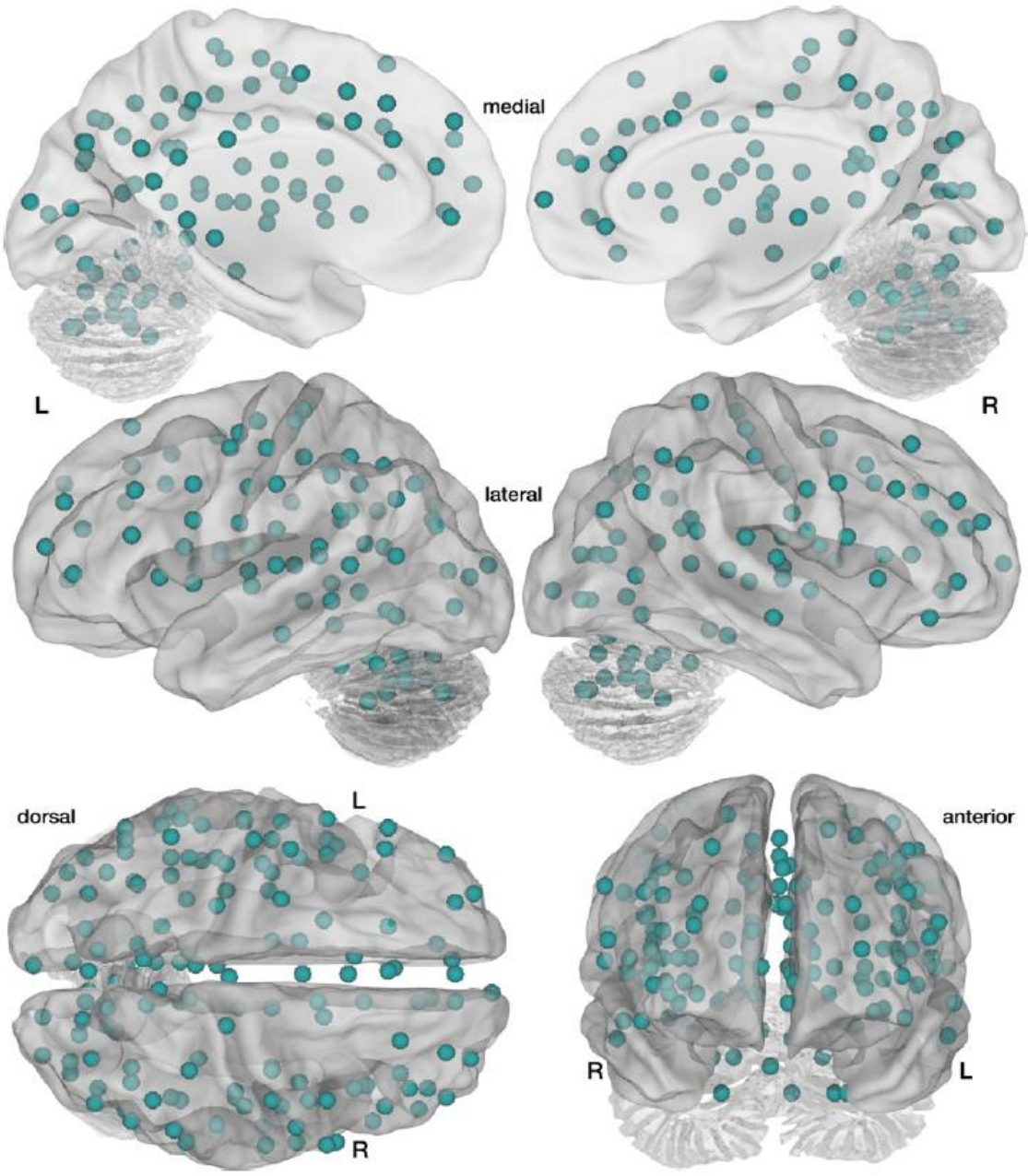

Fig. S1. *Regions of interest (ROIs). All 160 ROIs utilized in the analyses are displayed on a surface rendering of the brain (CARET 5.614).*

Fig. 2. 160 ROIs due to Dosenbach et al. (2010). Reprint with permission.

In order to check the registration of all ROIs time series across participants, the minmask was overlied. Twenty-seven ROIs were found to be not accessible in the data of at least one participant. Areas of the brain that were not registered across all participants included the following: fusiform gyrus; post insula; superior and dorsal frontal areas; anterior, ventral, and medial prefrontal areas; superior parietal areas; occipital areas; and cerebellum. Furthermore, signal was also not present for all participants in the regions of insula, caudate, and inferior frontal regions due to structural atrophy shown especially in HIV seropositive and older participants. Therefore, the second-level ROI-based analysis was restrained to the remaining 133 ROIs listed in Appendix 1. The second-level analysis was ran using customized routines written in MATLAB8.5.1 environment. In order to examine the main effect of HIV, age and interaction between HIV and age on functional connectivity (FC), it was calculated between the 133 ROIs using *T*-tests with the following variables: HIV serostatus (dichotomous variable); and age of participants (continuous variable).

Independent Component Analysis

ICA analysis was carried out on a Linux workstation using FSL v4.1 (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL) MELODIC software. Spatial ICA using 20 independent component (IC) maps was performed only on control participants in order to acquire near-to-normal maps of brain activation as described previously (Rytty et al., 2013). The 20 IC's explained 49.57% of total variance. Statistics of particular IC's are presented in Table 3.

Table 3. Statistics of 20 IC maps.

	% explained variance	% total variance	F-test on full model fit
IC 1	11.46	5.66	17.50
IC 2	11.31	5.59	45.56
IC 3	9.90	4.89	28.84
IC 4	8.97	4.44	21.19
IC 5	8.92	4.41	23.06
IC 6	7.32	3.62	15.36
IC 7	6.43	3.18	1.30
IC 8	5.91	2.92	7.93
IC 9	5.47	2.70	18.96
IC 10	4.31	2.13	3.66
IC 11	3.83	1.89	7.28
IC 12	3.47	1.72	5.23
IC 13	2.97	1.47	2.27
IC 14	2.66	1.31	0.00
IC 15	2.41	1.19	0.63
IC 16	1.70	0.84	0.55
IC 17	1.22	0.60	3.24
IC 18	1.18	0.58	2.61
IC 19	0.73	0.36	2.16
IC 20	0.15	0.07	0.97

The obtained IC maps thresholded at *p*-value=0.05 were analyzed by visual comparison of the 20 components with previous reports (Choi, Yeo, & Buckner, 2012; Damoiseaux & Greicius, 2009).

Next, voxel-wise comparisons for those 20 ICs were performed using the three stages of dual regression in FSL v5.0 (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL). Analysis of the effect of HIV infection (accounting for age and not accounting for age) and analysis of the interaction effect of HIV and age were performed for each group-IC component and resulted in corrected *p*-value images for each component. The output of the third stage was examined using AFNI software.

Voxel-based analysis

The following voxel-based analysis were performed: Regional Homogeneity (ReHo); Regional Homogeneity divided by the mean (mReHo); Amplitude of Low Frequency Flunctuations (ALFF); Amplitude of Low Frequency Flunctuations divided by the mean (mALFF).

ReHo, mReHo, ALFF, and mALFF maps were extracted using REST toolbox (http://restfmri.net/forum/index.php?q=rest). ReHo and mReHo were ran with the Kendall's Coefficient of Concordance (KCC-ReHo). Standard settings were applied (see Section 2.2.4.), band pass filter of 0.01-0.08 Hz with TR=2. Binary minmask was applied.

Second-level analysis was performed using FSL v.5.0. Analysis of the effect of HIV infection (accounting for age and not accounting for age) and analysis of the interaction effect of HIV and age were performed. The outputs were examined using AFNI software.

4.3. Assessment of neurocognitive functioning

4.3.1. Neuropsychological Testing

Neuropsychological assessment was conducted by the neuropsychologists from the Faculty of Psychology, University of Warsaw, Warsaw, Poland (see full list of testers in Section 3.1.3.c.). Participants completed a battery of neuropsychological tests on the same examination day as laryngological examination, but on a different day than neuroimaging testing (max. 2 weeks gap between examinations). Participants were asked not to drink coffee nor smoke directly before or during the examination. Neuropsychological testing was performed in a total of approximately two hours including one break of 10 to 15 min. obligatory for all participants.

For the purpose of the current dissertation, out of all tests and questionnaires that were used in the Major Study (see Section 2.2.2.), data of interest was retained for the following

measures: the Mini Mental State Examination (MMSE); the Corsi blocks forward and backward; the California Verbal Learning Test (CVLT) – immediate and short delay recall; the Ruff Figural Fluency Test (RFFT); the Color Trails Test (CTT-1, CTT-2); the Grooved Pegboard Test; the California Verbal Learning Test (CVLT) – long delay recall and recognition; the WAIS-R(PL) – Vocabulary, Digit Span forward and backward; the Wisconsin Card Sorting Test (WCST); the Verbal Fluency Test (VFT); the Center for Epidemiological Studies – Depression Scale (CES-D). Detailed description of measures is provided in Section 4.3.2.

4.3.2. Description of measures and evaluation procedures

The following paragraphs provide a description of each administered measurement, variables from each test that were analyzed in the current dissertation, as well as the scoring procedure.

Mini Mental State Examination

MMSE used in the current study was adapted and standardized by Stańczak (2010). The measure comprises eleven tests assessing major cognitive functions and may be used to discriminate advanced global cognitive disorders from intact functioning. The final score ranges from 0 to 30 points, with higher score describing higher global cognitive functioning. Measure was administered and evaluated due to the standard procedures. In the current dissertation, the outcome score from this measure was analyzed.

California Verbal Learning Test

CVLT used in the current study was adapted and standardized by Łojek and Stańczak (2010). The measure assesses verbal memory and learning, immediate recall, free recall and cued recall due to category after short and long (20 min.) delay, and recognition after long delay (Łojek & Stańczak, 2010). CVLT was administered and evaluated due to the standard procedures, due to

which nonverbal tasks were performed during the long delay gap (i.e., RFFT, CTT, and Grooved Pegboard Test). The results consist of 21 scores indicative of memory and learning functioning. In the current dissertation, index scores were used as follows: learning capacity (total hits for List A Trials 1-5), encoding (total hits in List A Trial 5), storage capacity (Free Recall after Long-Delay), and retrieval (Recognition hits) were retained for investigation. Cronbach's alpha in the current cohort was high (α=.855).

Center for Epidemiological Studies – Depression Scale

This screening depression scale (CES) was originally developed by Radloff (1977) and the current version (CES-D) was revised by Eaton, Muntaner, Smith, Tien, and Ybarra (2004) in English, with free access. For the exclusive use in the research project Harmonia-3, a Polish translation and adaptation of CES-D was prepared by Łojek, Ambroziak, Gawron, Pluta, and Sobańska, with linguistic corrections applied by Maras. This self-administered questionnaire consists of twenty statements assessing depressive symptoms of dysphoria, anhedonia, loss of appetite, problems with sleep, problems in thinking and concentration, feelings of worthlessness, fatigue, agitation, and suicidal ideation. The participant has to indicate how often each statement is valid for him/her on a scale: 'not at all'; '1-2 days/week'; '3-4 days/week'; '5-7 days/week'; 'almost every day during the past 2 weeks'. The maximum score is 80 and the score of above 16 indicates significant clinical implications of depressive symptoms. In the current dissertation, the outcome score from this scale was analyzed. Cronbach's alpha in the current cohort was very high (α =.920).

Color Trails Test

CTT used in the current study was adapted and standardized by Łojek and Stańczak (2012). CTT is composed of two parts (1 and 2), where the task is to connect numbers and letters in an

indicated order under the pressure of time. CTT-1 is indicative of psycho-motor speed, attention, visual search and scanning, while CTT-2 indicates the ability of cognitive flexibility, dividing and switching attention between stimuli (Łojek & Stańczak, 2012). Time of completion is the outcome score. CTT was administered and scored due to standardized procedures. In the current dissertation, the outcome scores of both parts (i.e., part 1 and part 2) were analyzed. Cronbach's alpha in the current cohort was acceptable (α=.707).

Corsi Blocks

Corsi blocks was originaly developed by Corsi (1972) as a Block-Tapping Task. For the exclusive use in the research project Harmonia-3, a Polish adaptation was prepared by Łojek, Ambroziak, Gawron, Pluta, and Sobańska. The measure assesses visual attention and visuo-spatial memory functioning with two tasks (forward and backward) (Corsi, 1972). The examiner points to several blocks on the board in a particular order and the examinee has to repeat it in the same order afterwards, while in the second task, examinee is asked to repeat it backwards. There are eight levels of increasing difficulty, from showing two to nine blocks. Task is discontinued after two consecutive errors in reponse within a level. Scoring involves summing up correct responses, with final score ranging between '0' and '16' for forward and backward tasks separately. In the current dissertation, both, forward and backward scores were included in the analysis. Cronbach's alpha in the current cohort was acceptable (α=.729).

Grooved Pegboard Test

Grooved Pegboard Test – GPT (Haaland, Cleeland, & Carr, 1977) was used in the current study to assess psychomotor speed and dexterity (Haaland, Cleeland, & Carr, 1977). In this test, participant is required to input pegs into the board first with dominant and then with nondominant hand, while the time of completion is measured and noted as the outcome score.

Grooved Pegboard Test was administered and scored due to standardized procedures. In the current dissertation, the outcome scores for both, dominant and nondominant hand input time, were analyzed. Cronbach's alpha in the current cohort was acceptable (α=.758).

Ruff Figural Fluency Test

RFFT used in the current study was adapted and standardized by Łojek and Stańczak (2004). It consists of five trials, where the participant creates unique graphical patters in a limited time (1 min.). The number of Unique Designs indicates nonverbal fluency and activity rate / initiation, while the Mistake Coefficient may be interpreted as indicating the ability to coordinate abilities of fluent / divergent thinking and flexibility in organization and planning strategy (Łojek & Stańczak, 2004). The evaluation involves counting the unique patterns and calculating the Mistake Coefficient from the ration of perseverations to the unique patters. RFFT was administered and scored due to standardized procedures. In the current dissertation, the score of Unique Designs was retained for analysis. Cronbach's alpha in the current cohort was low (α=.331).

WAIS-R(PL)

WAIS-R(PL) used in the current study was adapted and standardized by Brzeziński et al. (2004). Two subtests of WAIS-R(PL) battery were used: Digit Span; and Vocabulary. Digit Span consists of the presentation of acoustic verbal stimuli by the examiner and repetition in forward and backward order by the examinee, and thus, assesses verbal attention as well as verbal working memory functions (Brzeziński et al., 2004). Outcome scores are counted for the number of correct responses of the examinee. In Vocabulary subtest, examiner presents one word and asks examinee to give its definition using other words, and is interpreted as a measure of long-term verbal recall (Brzeziński et al., 2004). The outcome score here is derived based on the norms for

the answers described in the manual. Subtests were administered and scored due to standardized procedures. In the current dissertation, the two scores from Digit Span (i.e., Forward and Backward), and Vocabulary outcome score, were retained for analysis. Cronbach's alpha in the current cohort was high (α=.887).

Wisconsin Card Sorting Test

WCST used in the current study was adapted and standardized by Jaworowska (1999). It is a test of card sorting strategies that subject develops due to color, shape, or number presented in the cards, taking into consideration feedback obtained from the examiner. WCST indicates the level of executive functions and abstract thinking, flexibility of thinking and ability of adjusting responses according to changing conditions in the environment. Evaluation of correct, incorrect responses, and perseverations gives result of 16 outcome scores. WCST was administered and scored due to standardized procedures. In the current dissertation, the following outcome scores assessing executive functions were analyzed: score showing the number Completed Categories; score showing Breaks in correct responses; score showing Perseveration Errors in the responses. Cronbach's alpha in the current cohort was high (α=.854).

Verbal Fluency Test

VFT used in the current study is a Polish adaptation by Szepietowska and Gawda (2011). VFT is a measure of verbal fluency, where participants are asked to produce as many unique verbal reponses as possible within a limited time (1 min.) to a given word. There are six trials, out of which in three trials participant is asked to produce words starting with a particular letter (here: K, P, and M), and in the other three trials to produce words due to given category (here: animals, masculine names, plants). Outcome scores include Verbal Responses, which is a sum of correct responses and assesses the rate of production of verbal responses; Semantic Sum, which is a sum

of correct responses due to category and assesses semantic skills; and Phonemic Sum, which is a sum of correct responses due to particular letter and assesses phonemic skills. Responses were recorder with participant's permission and then correct unique responses, errors and perseverations were counted. In the current dissertation, the outcome score summarizing number of responses (Verbal Responses) as well as score summarizing semantically correct responses (Semantic Sum) were analyzed. Cronbach's alpha in the current cohort was high (α=.843).

4.3.3. Neurocognitive Factors

In order to reduce the number of cognitive variables for the analysis and limit the redundancy among them, as well as foster interpretability of the results, especially in relationship to the resting state data, five Neurocognitive Factors were computed. For the purpose of the current research, those Factors were conceptually derived based on previous literature describing sensitivity of the particular scores and indices of the administered measures to specific neurocognitive functions (see Section 4.3.2.). Outcome scores from administered measures (see Section 4.3.2.), were retained for the current analysis and used for the extraction of Neurocognitive Factors as follows.

Attention Factor was extracted based on the outcome scores of Digit Span Forward, Digit Span Backward, Block-Tapping Forward, Block-Tapping Backward, and CTT-1.

Executive Factor was extracted based on the outcome scores of RFFT Unique Designs, VFT Verbal Responses, WCST Completed Categories, WCST Breaks, WCST Perseverations, and CTT-2.

Memory Factor was extracted based on the outcome scores of CVLT Total Hits for List A, Trials1-5, Trial 5, Free Recall after Long-Delay, and Recognition Hits.

Psychomotor Factor was extracted based on the outcome scores of CTT-1, CTT-2, GPT dominant hand input time, GPT nondominant input time, and RFFT Unique Designs.

Semantic Skills Factor was extracted based on the outcome scores of WAIS-R Vocabulary and VFT Semantic Sum.

The statistical methods employed to derive the above five Factor scores is described in Section 4.3.4.

4.3.4. Statistical methods

Primary analyses of the neurocognitive data

Statistical analysis on the neurocognitive data as well as relationship between neurocognitive data and RS-FC measures were computed in IMS SPSS Version 22 (IBM, Somers, NY, USA).

Descriptive univariate analyses were computed by serostatus across sex, age, race/ethnicity, education, sexual behaviors, length of current stable partner relationship, employment status, income, and depressive symptoms. Normality of variance in descriptive variables was checked using the Shapiro-Wilks test at α=.05. Socio-demographic did not pass normality test. Accordingly, bivariate analysis of continuous variables was conducted with Mann-Whitney *U* test and analysis of categorical data with chi-square or likelihood ratio (in cases of the expected count assumption violation).

The reliability of selected neurocognitive scores and indexes in cognitive measures was assessed with Cronbach's alpha. The raw cognitive data was transformed into Z-scores based on the distribution of the entire sample of the Major Study (N=200). Then, T-scores were calculated for each variable based on the performance of the control group (N=100). T-scores were calculated in a way that a lower outcome scores signified worse performance for all measures.

Neurocognitive Factors were derived by averaging the sum of T-scores of included outcome scores and indexes as described earlier (see Section 4.3.3.). Shapiro-Wilks test at α=.05 revealed no normal distribution only for Executive and Psychomotor Factors in HIV+ sample.

Bivariate correlations between age variable on Neurocognitive Factor scores were assessed separately for HIV+ and HIV- groups, with the use of Pearson's Correlation Coefficient (*R*) for Attention, Memory, and Semantic Skills Factors, and Spearman's Correlation Coefficient (*Rho*).

Comparisons between HIV+ and HIV- groups on the Neurocognitive Factor scores were performed with *T*-unpaired test for Attention, Memory, and Semantic Skills Factors and with Mann-Whitney *U* test for Executive and Psychomotor Factors.

In order to check interaction effects between age and HIV serostatus on Neurocognitive Factors, first, a product term of age by HIV serostatus (i.e., age-HIV variable) was created. Multicollinearity diagnostics were computed and revealed high collinearity between age and age-HIV variable. To counteract this effect, centered variables for age, HIV serostatus, and age-HIV were created. Those variables were then entered into Hierarchical Multivariate Linear Regression models to estimate their effects on Neurocognitive Factors in the entire sample as follows: 1) Model 1 – main effects of age and HIV serostatus; 2) Model 2) interaction term (age – HIV product term).

Secondary analyses on the RS-FC measures and Neurocognitive Factors

To assess the relationship between RS-FC measures that showed interaction effects in the primary analysis and Neurocognitive Factors, the Pearson's Correlation Coefficient (*R*) was implied, analogously to previous studies in this clinical population (Ortega et al., 2015; Wang

et al., 2011). RS-FC measures that showed significant relationships with Neurocognitive Factors were retained for Multiple Linear Regression analysis.

The moderator effects of age and HIV infection on the established relationships were checked with the use of Multiple Linear Regression, according to the statistical method of examining moderation effects of the relationships described in Miles and Shevlin (2001). The moderator values for age and HIV serostatus with RS-FC measures were created based on the centered variables of age, HIV serostatus, and RS-FC meausures. The following centered outcome moderators were created: 1) moderator of age by RS-FC measures; 2) moderator of HIV serostatus in RS-FC measures.

To check effects of age on the relationship between RS-FC and Neurocognitive Factors, Multiple Linear Regresssion was conducted in control group. In the first block of regression, the predictive variable was entered as RS-FC measures and criterion variables as Neurocognitive Factors. In the second block, the predictive variable of the moderator of age by RS-FC measures was entered, and criterion variables as Neurocognitive Factors.

To check effects of HIV serostatus on the relationship between RS-FC and Neurocognitive Factors, Multiple Linear Regresssion was conducted for all participants. In the first block of regression, the predictive variable was entered as RS-FC measures and criterion variables as Neurocognitive Factors. In the second block, the predictive variable of the moderator of HIV serostatus by RS-FC measures was entered, and criterion variables as Neurocognitive Factors.

To check the effects of aging in HIV seropositive individuals on the relationship between RS-FC and Neurocognitive Factors, Multiple Linear Regresssion was conducted in HIV+ group. In the first block of regression, the predictive variable was entered as RS-FC measures and

criterion variables as Neurocognitive Factors. In the second block, the predictive variable of the moderator of age by RS-FC measures was entered, and criterion variables as Neurocognitive Factors.

The outcomes of those statistical analysis allow to read how the moderator influences the relationship between the predictive variable and the criterion variable as follows. The R2 change in the second block shows the percentage of variance in the criterion that is accounted for by the moderator in addition to the percentage of variance accounted for by the predictive variable. Beta coefficient and 95%CI of the moderator demonstrate the exact value of the effect as well as the direction of the effect (positive or negative).

5. RESULTS

5.1. Between group differences in brain structure

Comparisons between HIV+ and HIV- groups of the structural data using *T*-unpaired test with age entered as a covariate revealed decreased density in both, grey matter (GM) and white matter (WM) of the brain in HIV-infected participants as compared to controls.

Alterations in GM in the HIV+ participants appeared in Right Insula and Left Insula, at $p<0.001$ ($T=3.17$) after FDR correction for cluster size (k=387), as presented in Figure 3.

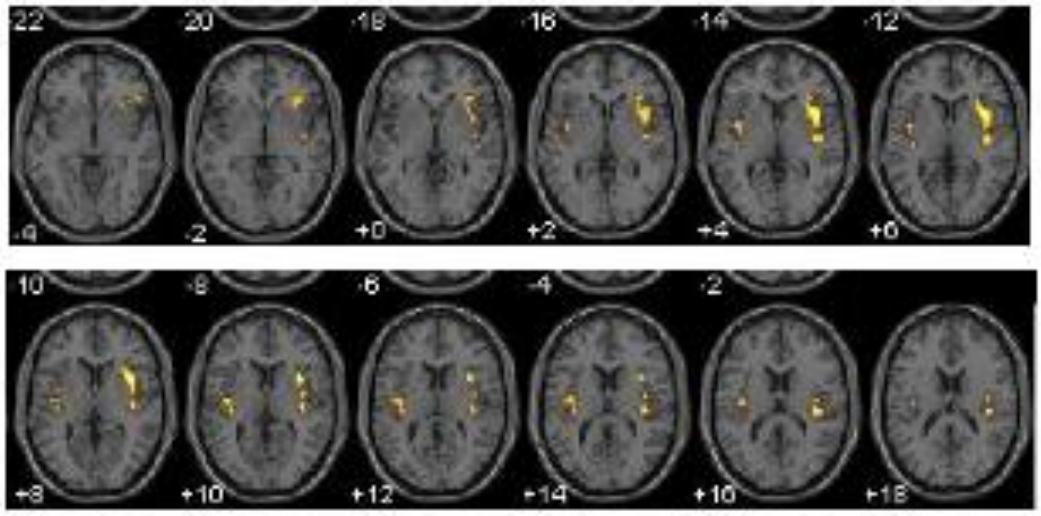

Figure 3. Alterations in grey matter in HIV-infected as compared to non-infected subjects.

Alterations in WM in the HIV+ group were shown in Left Claustrum, two regions of Right Caudate, Left Inferior Frontal Gyrus, Right Inferior Frontal Gyrus, and Right Lentiform Nucleus, at $p<0.001$ ($T=3.17$) after FDR correction (k=308), as presented in Figure 4.

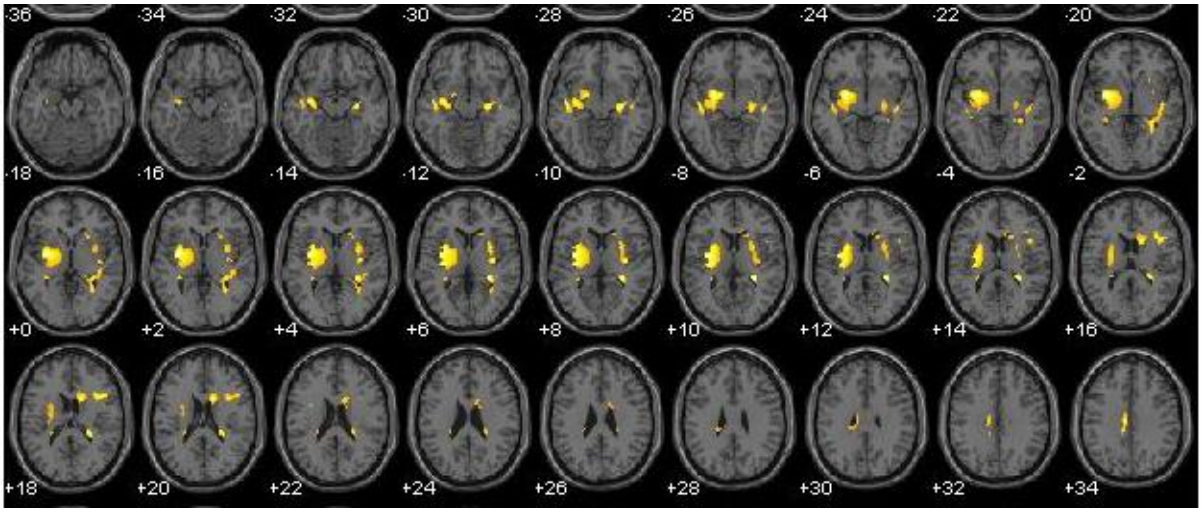

Figure 4. Alterations in white matter in HIV-infected as compared to non-infected individuals.

5.2. Age effects on RS-fMRI measures

5.2.1. ROI-based analysis

In healthy controls, age was found to be related to, both, increases and decreases in FC between regions within RS networks (as presented in Figure 5) as well as between separate RS networks (as shown in Figure 6). Table with detailed statistical outcomes can be found in Appendix 2.

As shown in Figure 5, intrinsic connectivity was noticed to increase with age between brain regions within FPN between prefrontal regions (R=.536, p<.001), and ON (R=.464, p<.001). Within DMN, CON and SMN, there were increases and decreases in advancing aging, depending of the brain regions as follows. Within DMN, there were increases with age in FC (R=.570, p<.001) between angular gyrus and posterior cingulate, precuneus, and between anterior prefrontal cortex and medial prefrontal cortex, while decreases with age in FC between areas of posterior cingulate (R=-.305, p=.025). Within CON, increases with age in FC (R=.419, p<.001) were observed between angular gyrus and basal ganglia, as well as between post insula and temporal regions, while decreases with age between medial frontal cortex and anterior insula (R=-.553, p<.001). Within SMN, increases in aging were shown between parietal regions (R=.409, p=.002), while decreases in FC (R=-.469, p<.000) between mid insula and precentral gyrus, as well as pre-SMA and ventral frontal cortex.

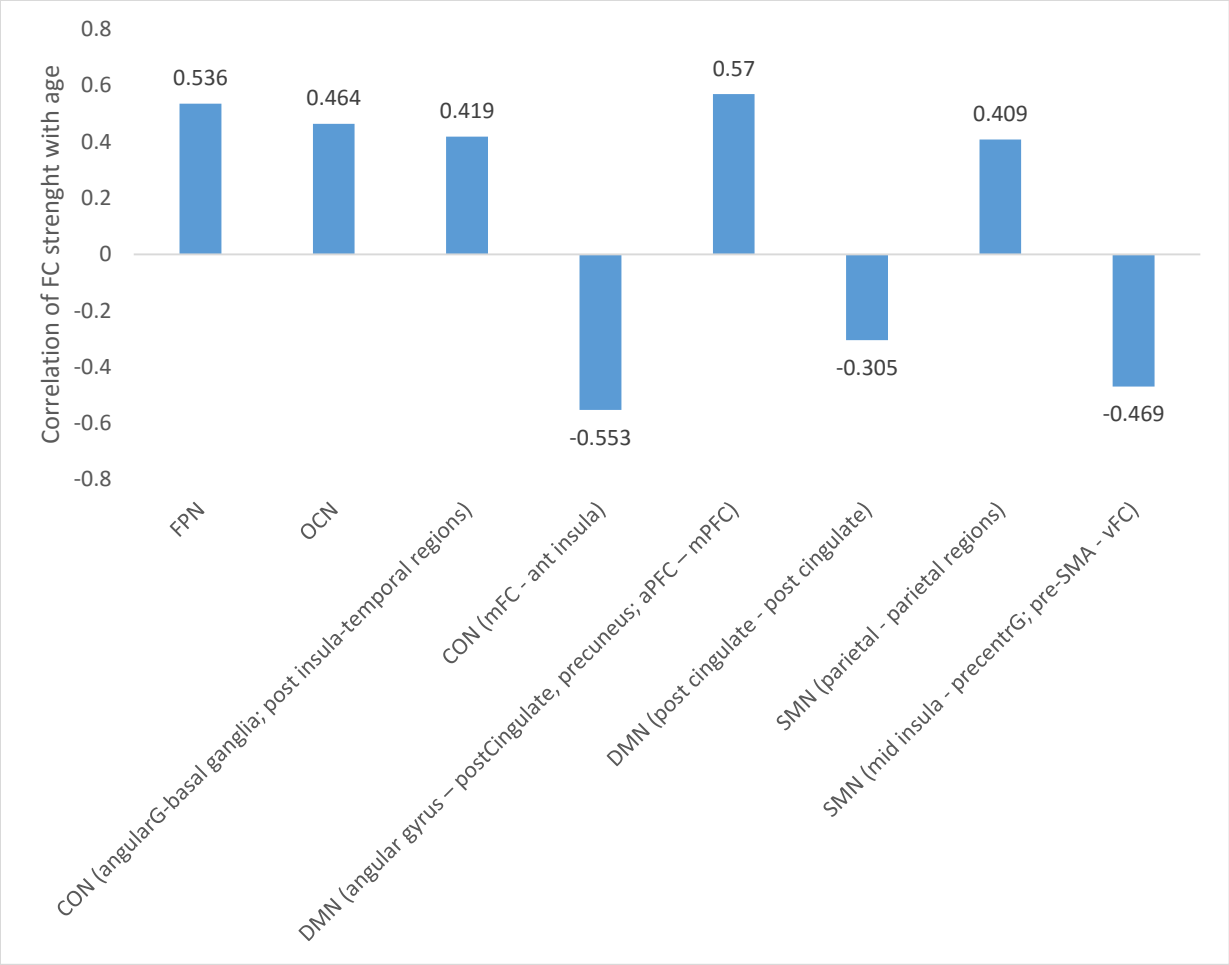

Figure 5. Correlation between age and intra-network FC strength.

As presented in Figure 6, majority of the functional connections between regions of separate RS networks were strengthened with advancing age. In particular, FC between regions of FPN, DMN, and CON were increasing with age (R<.656, *p*<.002). FC was found to be decreasing with age between regions of ON and SMN (R=-.532, *p*<.001), CON (R=-.420, *p*<.001), and FPN (R=-.313, *p*=.021).

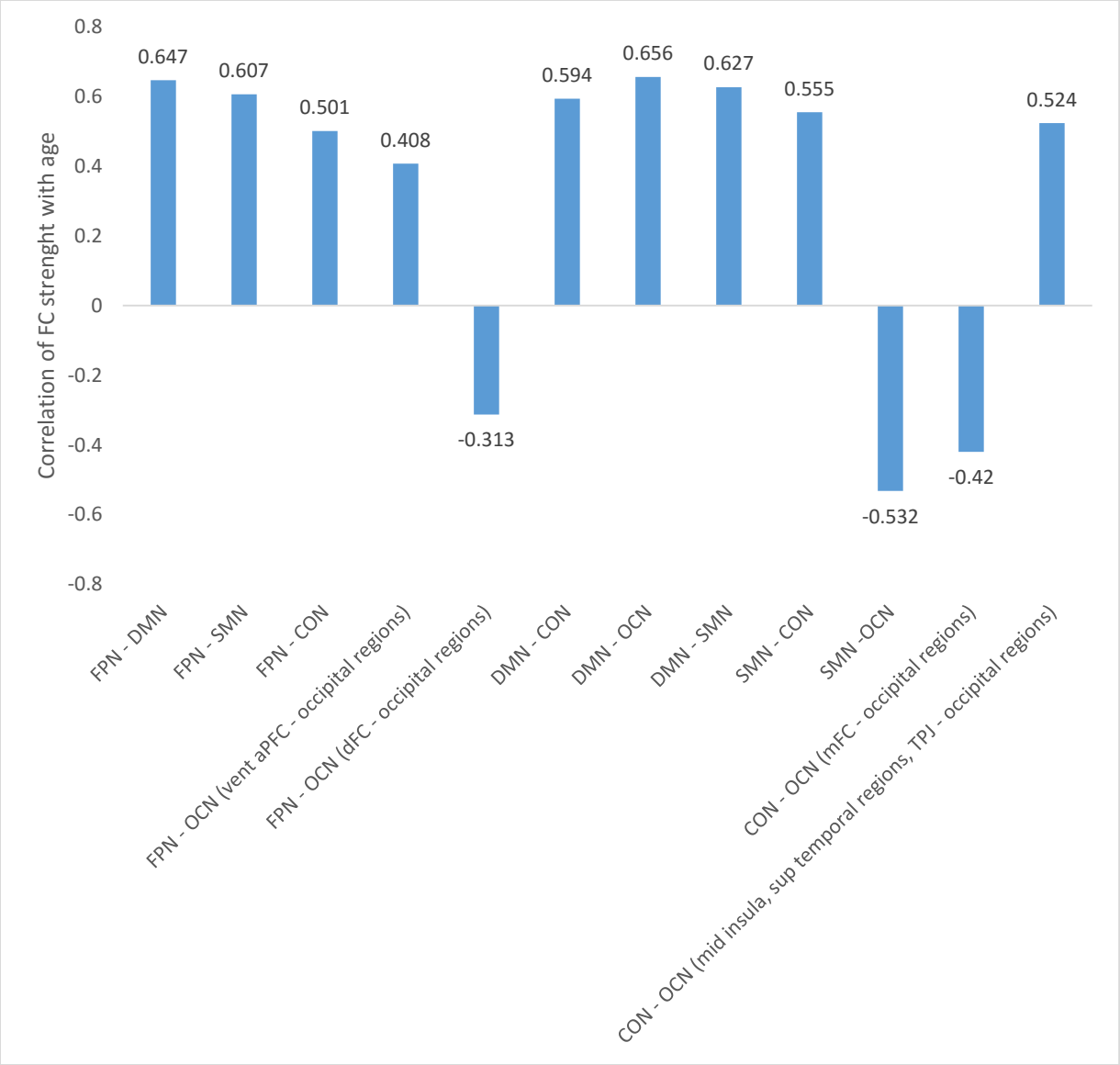

Figure 6. Correlation between age and inter-network FC strength.

5.2.2. Independent Component Analysis

Age effect in control group was shown for the posterior DMN (see Fig.7.). Aging was related to decreases in the R. Posterior Cingulate Gyrus, with T=(53)=3.254 and p<.001, Monte Carlo Cluster size of 24 voxels.

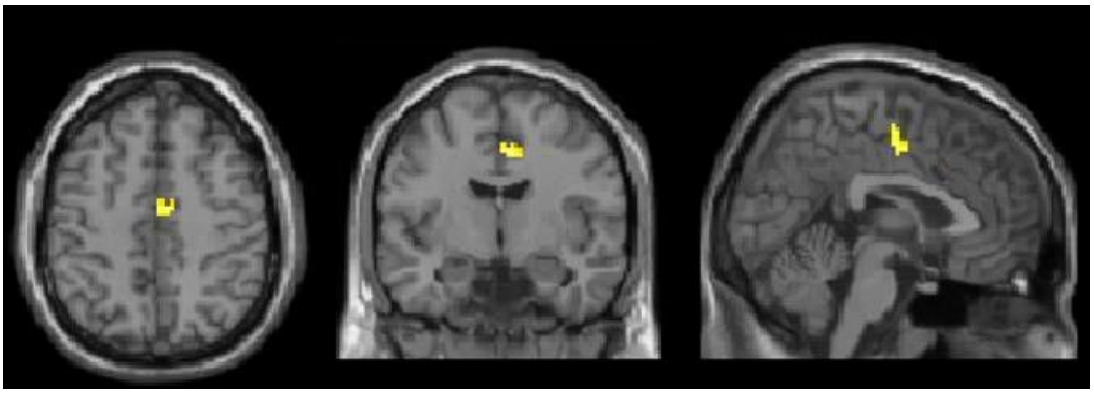

Figure 7. Effects of age on the functional connectivity within the posterior DMN in R. Posterior Cingulate Gyrus.

5.2.3. Voxel-based analysis

Aging was found to have significant effects on the measures of ReHo and mReHo in the control group.

In ReHo, as presented in Fig.8, advancing aging was related to decreases in control subjects in one cluster of 969 voxels with the peak activation in the R.Inferior Temporal Gyrus, at $p<.02$, after FDR correction for cluster size (k=427).

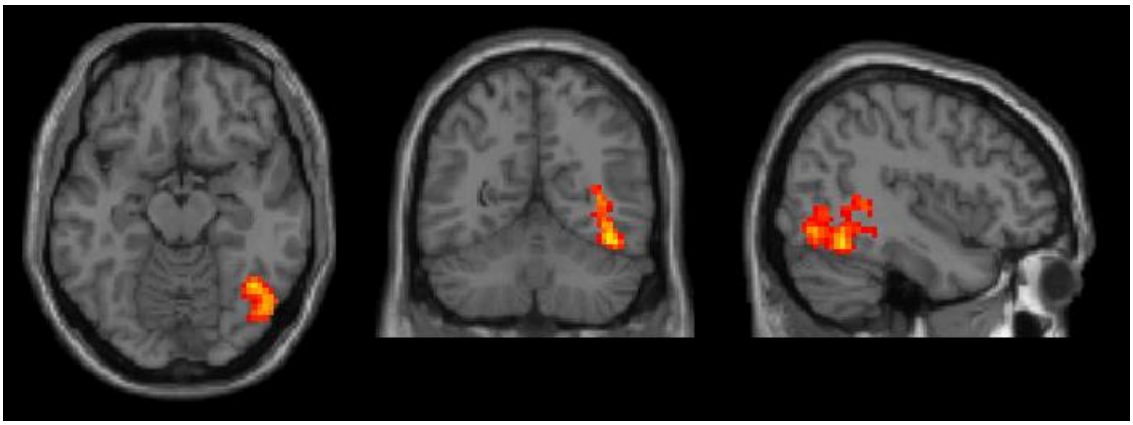

Figure 8. Age effects revealed with ReHo in control participants in R.Inferior Temporal Gyrus.

On the measure of mReHo, significant effects of age on were revealed in decreases of

five clusters (ranging in size from 131 to 386 voxels) as presented in Figure 9., in L.Cingulate Gyrus, Orbital Frontal Cortex, L.Amygdala, and Right and Left Medial Frontal Gyrus, at $p<.02$, after FDR correction for cluster size (k=427).

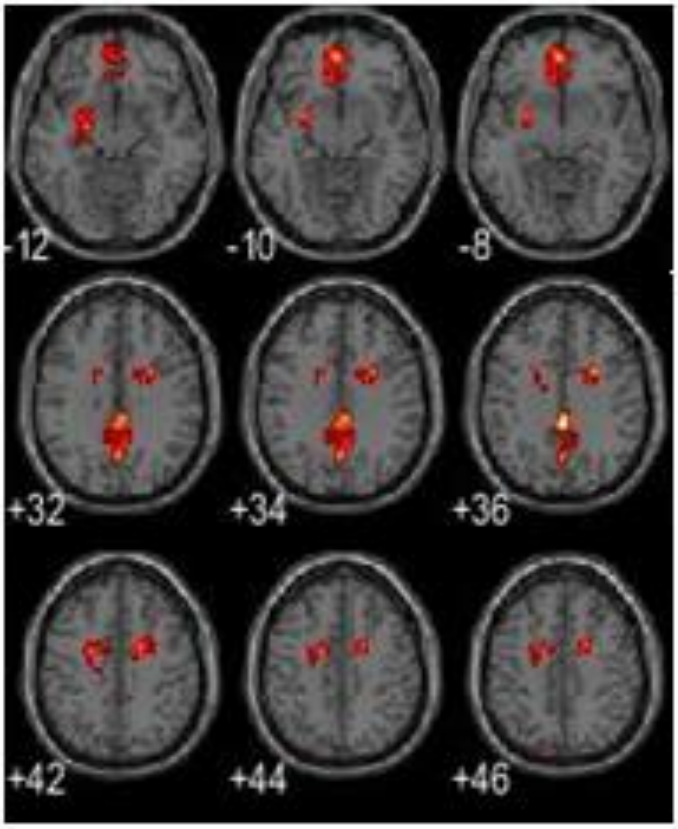

Figure 9. Age effects revealed with mReHo in control participants. Top row: L.Amygdala, Orbital Frontal Cortex; Middle row: L.Cingulate Gyrus; Bottom Row: Right and Left Medial Frontal Gyrus.

On the measure of ALFF and mALFF, no significant effects of age were revealed at $p<.02$, after FDR correction for cluster size (k=31).

5.3. Age effects on the neurocognitive measures

In control group, advancing aging was related to deterioration of neurocognitive. The observed changes were the most profound for Psychomotor (R=-.585, p<.001), then Executive (R=-.538, p<.001), and Attention (Rho=-.492, p<.000) factor scores. Less profound, but still significant, decline was revealed for Memory (R=-.279, p=.041). Semantic Skills Factor Scores were not significantly diminishing in increasing age (R=-.201, p=.144) in control participants. See Appendix 3 for details on the relationship of Neurocognitive Factors with other variable (health- and clinical- related).

5.4. HIV infection effects on the RS-fMRI measures

5.4.1. ROI-based analysis

Mean correlation matrixes for 133x133 ROIs across the networks for HIV+ and control groups are presented in Figure 10 below.

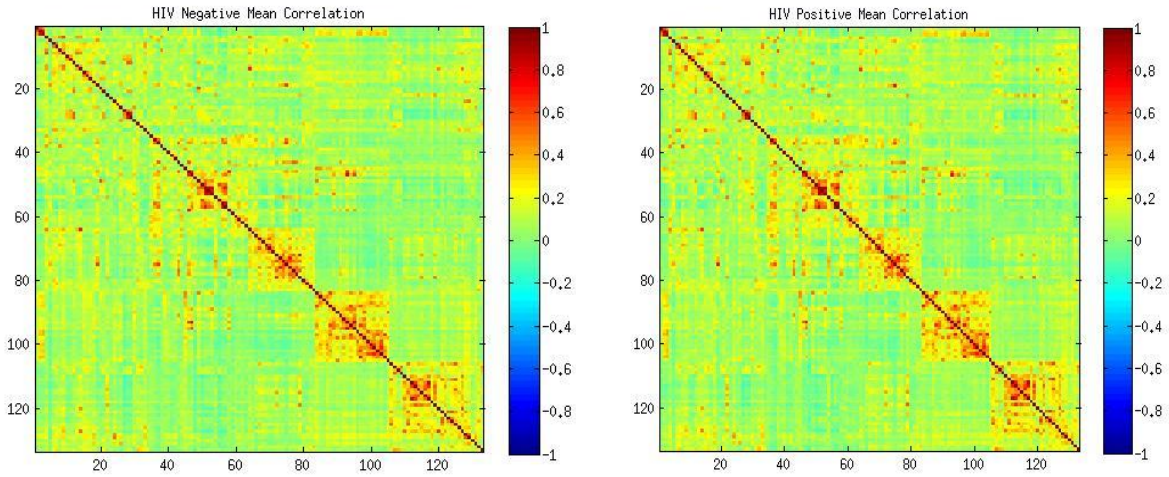

Figure 10. Correlation matrixes between 133x133 ROIs for the Control (left) and HIV-infected (right) groups.

Analysis of FC by serostatus, corrected for age across the entire sample, revealed significant decreases and increases at $p<.001$ in six ROI pairs (Table 4). HIV-infected subjects showed reductions in FC between L.IPL and L.MidTG (T=-3.380), as well as L.IPL and two regions of R.MidTG (T>-3.401) as compared to controls. At the same time, HIV+ individuals showed strengthened FC between the following: R.MidTG – L.SupTG (T=4.06); R.CingG – R.MidFG (T=3.710); and R.Culmen – L.PrecentG (T=3.750), in contrast to control subjects.

Table 4. FC of ROI pairs showing effects of HIV serostatus.

	Within networks		Between networks			
	FPN		DMN – SMN		DMN - FPN	Cerebellum - CON
	R. MidTG - L.IPL	R. MidTG - L.IPL	L.MidTG - L.IPL	R.MidTG - L.SupTG	R.CingG - R.MidFG	R.Culmen - L.PrecentG
Controls, M (SD)	.309 (.170)	.189 (.191)	.017 (.156)	.025 (.131)	-.034 (.177)	-.040 (.164)
HIV+, M (SD)	.197 (.172)	.057 (.187)	-.083 (.150)	.126 (.129)	.095 (.185)	.076 (.157)
HIV+ vs. controls, T (*p*)	-3.401 (.001)	-3.661 (.000)	-3.380 (.001)	4.06 (.000)	3.710 (.000)	3.750 (.000)

5.4.2. Independent Component Analysis

The effect of HIV infection, when accounting for participants' age, revealed Occipital Network (ON) as presented in Fig.11. HIV-infected individuals showed decreased Z-values in the left middle occipital gyrus (L.MOccG) within Occipital Network, with $T=(106)=3.703$ at $p<0.001$, Monte Carlo cluster size of 27 voxels.

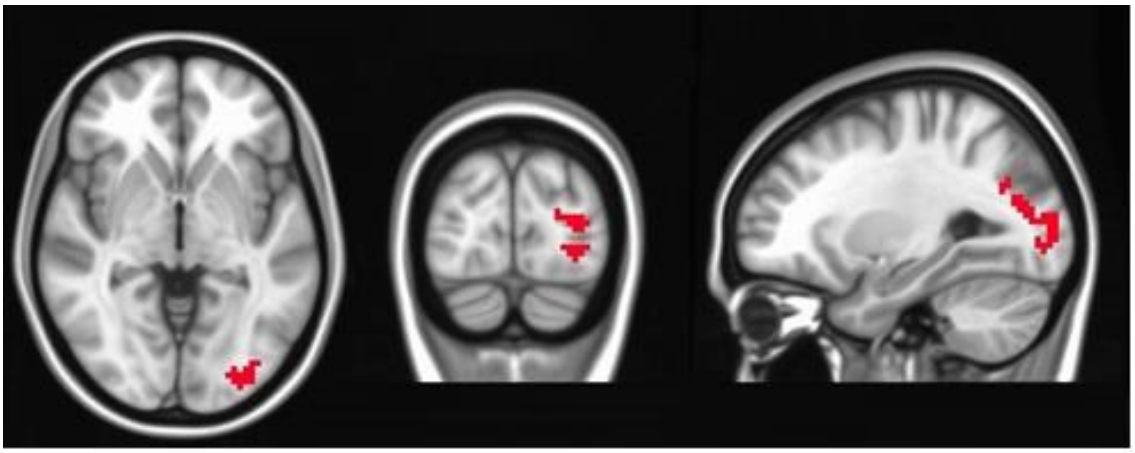

Figure 11. Effects of HIV infection on the functional connectivity within the Occipital Network.

5.4.3. Voxel-based analysis

Measures of ReHo and mReHo did not reveal significant effects of HIV infection.

Measures of ALFF and mALFF showed effect of HIV. In HIV-infected individuals, the connectivity was increased as compared to controls in one cluster of 452 voxels in the right Insula, at $p<.02$, Monte Carlo cluster size = 444.1 voxels (Fig. 12).

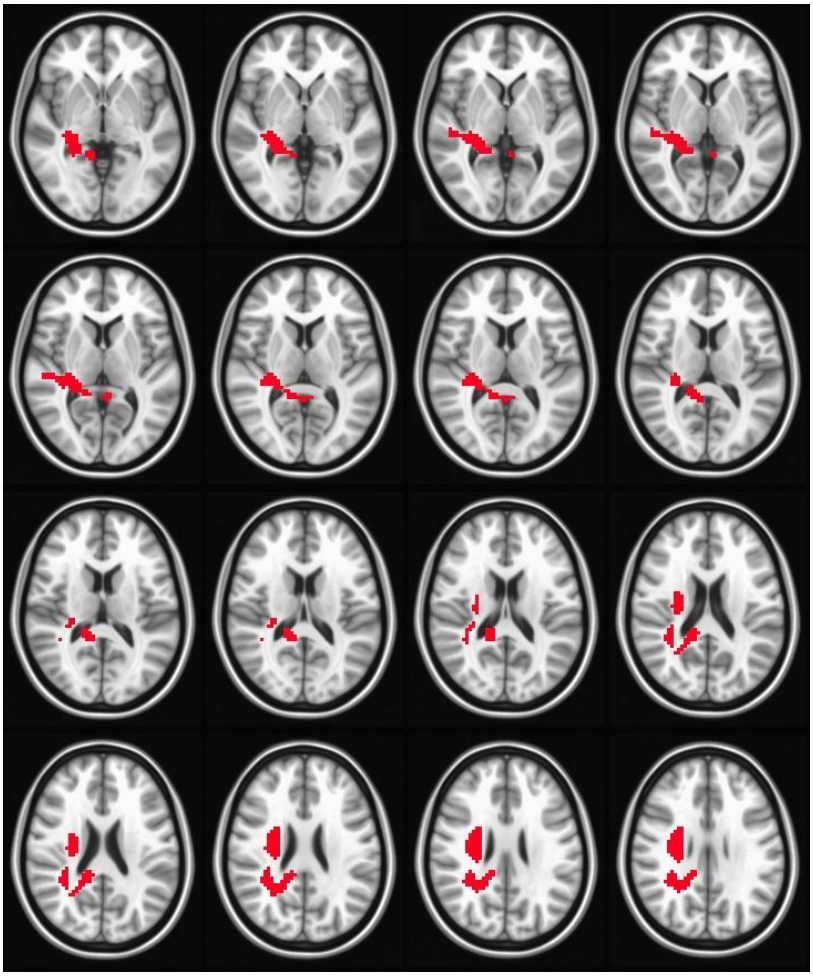

Figure 12. Increases in ALFF in HIV+ as compared to HIV- group.

5.5. HIV infection effects on the neurocognitive measures

HIV-seropositive individuals revealed significantly lower performance on factors of Attention (U=970.000, *p*=.003), and Semantic Skills (U=983.500, *p*=.008) than healthy controls (Appendix 3). Other cognitive factors did not show significant decline due to HIV infection as follows: Memory (T=-1.180, *p*=.241), Executive (T=1.227, *p*=.223), and Psychomotor (T=.051, *p*=.960).

5.6. Interaction effects of age and HIV on the RS-fMRI measures

5.6.1. ROI-based analysis

The primary whole-brain ROI analyses revealed a stable pattern of age–HIV serostatus interaction effect, where FC in HIV-infected individuals was decreasing, while in controls increasing as a function of age (Table 5).This effect was revealed for the following ten ROI pairs: 1) within FPN (R.IFG – L.IPL); 2) within CON (R.SupTG – L.SupTG); 3) between SMN and DMN (L.PostcentG – L.Prec, two regions of L.PostCing; R.PostcentG – L.Prec, L.AngG; and R.PrecentG – L.SupTG); 4) between CON and DMN (L.CingG – L.Prec); and 5) between CON and SMN (L.SupTG – R.PrecentG).

Table 5. Relationship between FC of ROI pairs showing interaction effect and demographic, health-related and clinical variables.

	Within networks		**Between networks**							
	FPN	**CON**	**CON - DMN**	**CON - SMN**	**SMN - DMN**					
	R.IFG - L.IPL	R.SupTG - L.SupTG	L.CingG - L.Prec	L.SupTG - R.PrecentG	L.PostcentG - L.PostCing	L.PostcentG - L.PostCing	L.PostcentG - L.Prec	R.PostcentG - L.Prec	R.PostcentG - L.AngG	R.PrecentG - L.SupTG
Controls, M (SD)	.254 (.215)	.168 (.205)	-.028 (.174)	.016 (178)	.025 (.171)	.030 (.187)	.040 (.152)	.027 (.180)	.015 (.137)	.058 (.154)
Age, R (*p*)	.301* .027	.430** .001	.187 .176	.277* .043	.385** .004	.306* .024	.167 .228	.267 .051	.228 .097	.075 .591
HIV+, M (SD)	.159 (.196)	.152 (.142)	-.016 (179)	.052 (.177)	-.011 (.220)	-.009 (.181)	-.003 (.186)	.017 (.191)	-.008 (.179)	.114 (.186)
Age, R (*p*)	-.335* .013	-.165 .232	.180 .193	-.401** .003	-.291* .033	-.433** .001	-.439** .001	-.377** .005	-.420** .002	-.546*** .000
Years post-infection, R (*p*)	-.389** .004	-.301* .027	.218 .114	-.314* .021	-.153 .270	-.258 .059	-.320* .018	-.404** .002	-.222 .107	-.441** .001
Nadir CD4, R (*p*)	.351 (.009)**	.114 (.412)	-.063 (.651)	.189 (.171)	.220 (.110)	.172 (.215)	.131 (.345)	.190 (.168)	.207 (.134)	.055 (.692)
CD4 current count, R (*p*)	.027 .845	-.057 .680	.032 .821	-.039 .781	.154 .268	-.013 .923	.004 .976	.078 .574	.125 .369	.013 .926
Viral load highest, R (*p*)	.134 .334	-.197 .153	-.157 .257	.025 .859	.022 .874	-.153 .268	-.053 .703	.060 .665	.112 .421	-.047 .736
CNS syphilis, R (*p*)	-.005 .971	.083 .551	.162 .241	-.160 .246	-.032 .818	-.105 .449	-.063 .651	-.060 .668	.018 .899	.040 .776

5.6.2. Independent Component Analysis

The interaction effect of age and HIV infection was shown for Motor Network – MN (Fig.13). Within MN, in HIV-infected individuals aging was related to the decreases of a medium slope (R=-.556, p<.001), while in controls to the increase of a flat slope (R=.294, p<.031) in the

Z-values for the left superior frontal gyrus (L.SupFG.), with T=(106)=4.058 at p<0.001, Monte Carlo cluster size of 22 voxels.

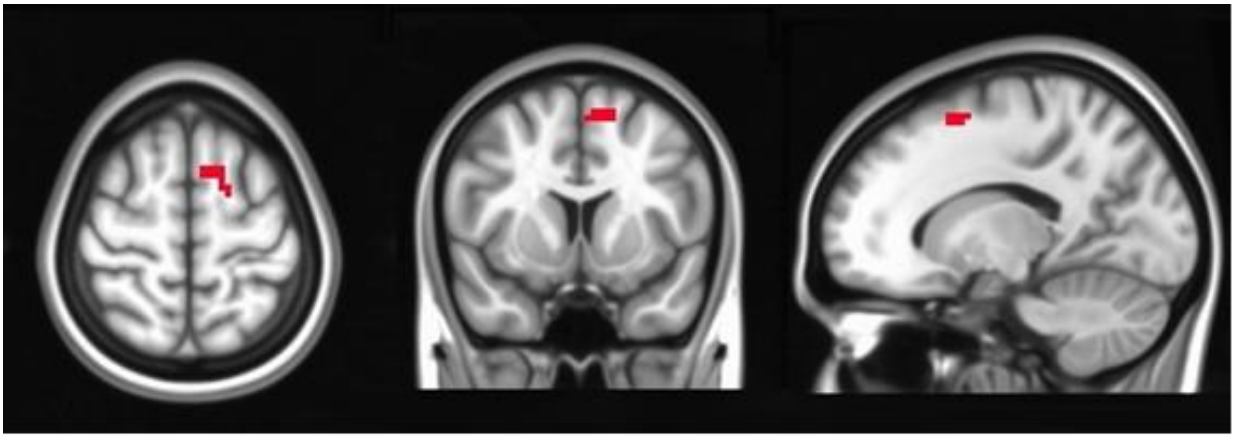

Figure 13. Interaction effects of age and HIV infection on the functional connectivity within the motor network in left superior frontal gyrus.

5.6.3. Voxel-based analysis

No significant of interaction effect between age and HIV-infection were observed on the measures of ReHo, mReHo, ALFF, and mALFF.

5.7. Interaction effects of age and HIV on the neurocognitive measures

No interaction effects of age and HIV were revealed in the studied sample for any of the Neurocognitive Factors (see Appendix 4 for statistical results).

5.8. Relationship between brain connectivity and neurocognitive measures in health

5.8.1. ROI-based analysis

In control group, functional connectivity between multiple pairs of brain regions showing

interaction effects of age and HIV infection, was found to be correlated with different cognitive factors. Increases in FC within CON were related to decline in Psychomotor (R=-.400, *p*=.003), Executive (R=-.360, *p*=.007), and Attention (R=-.360, *p*=.008) Factors. FC between regions of SMN and DMN was negatively related to Psychomotor (R=-.327, *p*=.016; R=-.314, *p*=.021), Memory (R=-.326, *p*=.016; R=-.282, *p*=.039), Executive (R=-.360, *p*=.008), and Semantic Skills (R=-.361, *p*=.007) Factor scores. FC within FPN as well as between regions of CON-DMN and CON-SMN did not reveal significant relationship to any of the cognitive factors. Further details on statistical results in Appendix 5.

5.8.2. Independent Component Analysis

Relationship was found between the intrinsic activity within Motor Network, which was found to be sensitive to the interaction effect of aging and HIV, and the cognitive factor scores. In healthy controls, activity in L.SupFG was negatively related to Executive Factor (R=-.272, *p*=.047), (see Appendix 8).

5.8.3. Voxel-based analysis

No interaction effects of voxel-based measures of RS, therefore, correlational analysis with Neurocognitive Factors were not performed.

5.9. Age effects on the relationship between brain connectivity and neurocognitive measures

5.9.1. ROI-based analysis

Moderating effect of age on the relationship between FC of the ROI pairs and neurocognitive functioning was shown in one out of 50 studied cases (ten functional connections by five cognitive domains) as presented in Appendix 6. Age as a moderator accounted for 2.4% of variance in the relationship between RS-FC of CON-SMN and Memory Factor. In detail, higher strength of FC between L.SupTG-R.PrecentG negatively affected Memory Factor scores, with age significantly determining (B=-.301; CI=-1.485, -.112; *p*=.024) how strength of this intrinsic brain connectivity affects cognitive functioning. For the relationship between the functional connectivity of other studied ROI pairs and neurocognitive functioning, aging was not a significant moderator.

5.9.2. Independent Component Analysis

There was no significant moderating effect of age observed for the relation between intrinsic brain activity in R.PoscG, L.SupFG, and Neurocognitive Factors (see Appendix 7).

5.10. HIV effects on the relationship between brain connectivity and neurocognitive measures

5.10.1. ROI-based analysis

In contrast to controls, HIV-infected individuals showed positive relationships between cognitive functioning and FC values (Appendix 5).

Initial descriptive statistics determined that in HIV+ individuals, Attention Factor T-scores were positively related to FC within FPN (R=.271, p=.048) and CON (R=.342, p=.011), while in controls negatively related to CON (R=-.360, p=.008) and SMN-DMN regions (R=-.282, p=.039). Memory in HIV+ group was positively related to CON-SMN (R=.285,

p=.037) and SMN-DMN regions FC (R=.273, p=.046), while in controls negatively related to SMN-DMN FC regions (R=--.326, p=.016). Executive factor T-scores in HIV-seropositive individuals were in positive relationship with FC in FPN (R=.300, p=.030), CON (R=.327, p=.018), and SMN-DMN (R=.386, p=.005), while in controls in negative relationship with FC in CON (R=-.360, p=.007) and SMN-DMN (R=-.360, p=.008). Psychomotor factor scores were positively correlated with FC in FPN (R=.287, p=.036), CON (R=.283, p=.038), CON-SMN (R=.323, p=.017), and SMN-DMN (R=.502, p=.000) in HIV+ participants, and negatively with FC in CON (R=-.400, p=.003), and SMN-DMN (R=-.327, p=.016) in controls. Semantic Skills T-scores in HIV+ group were positively related to FC values in SMN-DMN (R=.441, p=.001), while in controls were negatively related to FC in SMN-DMN (R=-.361, p=.007).

In detail, within FPN higher strength of FC between R.IFG-L.IPL positively affected Executive Factor scores, with HIV infection significantly determining (B=.210; CI=1.091, 23.199; *p*=.032), and Psychomotor Factor scores, with HIV infection significantly determining (B=.197; CI=.462, 28.363; *p*=.043), how strength of this intrinsic brain connectivity affects cognitive functioning.

Within CON, HIV infection significantly determined how much the higher strength of FC between R.Sup.TG-L.Sup.TG positively affected Attention Factor scores (B=.347; CI=12.969, 42.853; *p*=.000), Memory Factor scores (B=.231; CI=1.842, 27.265; *p*=.025), Executive Factor scores (B=.356; CI=10.769, 37.142; *p*=.000), and Psychomotor Factor scores (B=.348; CI=12.999, 46.379; *p*=.001).

Between CON and SMN, HIV infection significantly determined how much the higher strength of FC between L.SupTG-R.PrecentG positively affected Memory Factor scores (B=.248; CI=3.846, 27.258; *p*=.010), Executive Factor scores (B=.248; CI=4.022, 29.763;

p=.011), and Psychomotor Factor scores (B=.266; CI=6.670, 38.322; *p*=.006).

Between SMN and DMN, HIV infection significantly determined how much the higher strength of FC between L.PostcentG-L.PostCing positively affected Memory Factor scores (B=.214; CI=1.089, 23.045; *p*=.032), and Psychomotor Factor scores (B=.210; CI=1.058, 30.967; *p*=.036). HIV infection significantly determined how much the higher strength of FC between second pair of regions in L.PostcentG-L.PostCing positively affected Psychomotor Factor scores (B=.276; CI=7.279, 37.829; *p*=.004). HIV infection significantly determined how much the higher strength of FC between R.PostcentG-L.Prec positively affected Attention Factor scores (B=.237; CI=4.408, 31.933; *p*=.010), and Psychomotor Factor scores (B=.231; CI=3.409, 34.154; *p*=.017). HIV infection significantly determined how much the higher strength of FC between R.PostcentG-L.AngG positively affected Executive Factor scores (B=.224; CI=2.198, 31.420; *p*=.025). HIV infection significantly determined how much the higher strength of FC between R.PrecentG-L.SupTG positively affected Memory Factor scores (B=.205; CI=.918, 25.836; *p*=.036), Psychomotor Factor scores (B=.245; CI=5.445, 37.758; *p*=.009), and Semantic Skills Factor scores (B=.193; CI=.977, 38.834; *p*=.039).

5.10.2. Independent Component Analysis

Descriptive bivariate analysis revealed the pattern of relationships between brain connectivity and neurocognitive functioning is different in HIV+ vs. control group as presented in Appendix 8. The negative relationships of the intrinsic activity of L.SupFG with Executive Factor, which were found to be significant in case of controls, were lost in the HIV+ participants. At the same time, HIV+ group showed positive correlation between L.SupFG and Psychomotor Factor (R=.288, p=.035), which was not significant in control subjects.

Further regression analysis showed that HIV-positive serostatus moderates the causal relationship between intrinsic connectivity of L.SupFG and Psychomotor, Executive, and Memory Factor scores as presented in Table 6. RS activity in L.SupFG determines significantly less variance in Psychomotor (B=.291; CI=.572, 3.905; *p*=.009), Memory (B=.241; CI=.128, 2.607; *p*=.031), and Executive Factor scores (moderating effect: B=.235; CI=.094, 2.759; *p*=.036).

Table 6. Moderating effects of HIV on the relationship between intrinsic neural activity in L.SupFG. and neurocognitive factors.

	Attention	**Memory**	**Executive**	**Psychomotor**	**Semantic Skills**
Main effect of L.SupFG., B (95%CI), *p*-value	-.013 (-.824, .713), .886	-.014 (-.673, .582), .886	-.057 (-.872, .475), .561	.066 (-.563, 1.141), .502	-.012 (-.920, 1.039), .904
Moderating effect of HIV, B (95%CI), *p*-value	.195 (-.112, 2.945), .069	.241 (.128, 2.607), .031*	.235 (.094, 2.759), .036*	.291 (.572, 3.905), .009**	.119 (-.890, 3.048), .280
% of explained variance by moderating effect of age, R2 change (*p*-value)	.029 (.069)	.043 (.031*)	.042 (.036*)	.064 (.009**)	.011 (.280)
R2	.119	.057	.059	.068	.070

5.11. Effects of aging in HIV-seropositive individuals on the relationship between resting state brain functional connectivity and neurocognitive functioning

The moderating effects of aging on the relationship between RS-FC and neurocognitive functioning were comparable between HIV+ and HIV- groups. That is, in the HIV-infected group as in control group, there were no significant moderating effects of aging found on the relationship between RS-FC and Neurocognitive Factors. This was found in the results of ROI-based analysis (see Appendix 10) and ICA (see Appendix 11).

The graphs below illustrate the findings of similar effects of age in HIV+ and HIV-

groups on the example of the relationship between intrinsic brain activity and neurocognitive functioning on the example of RS-FC within CON (based of the ROI-based analysis) and Executive Factor scores.

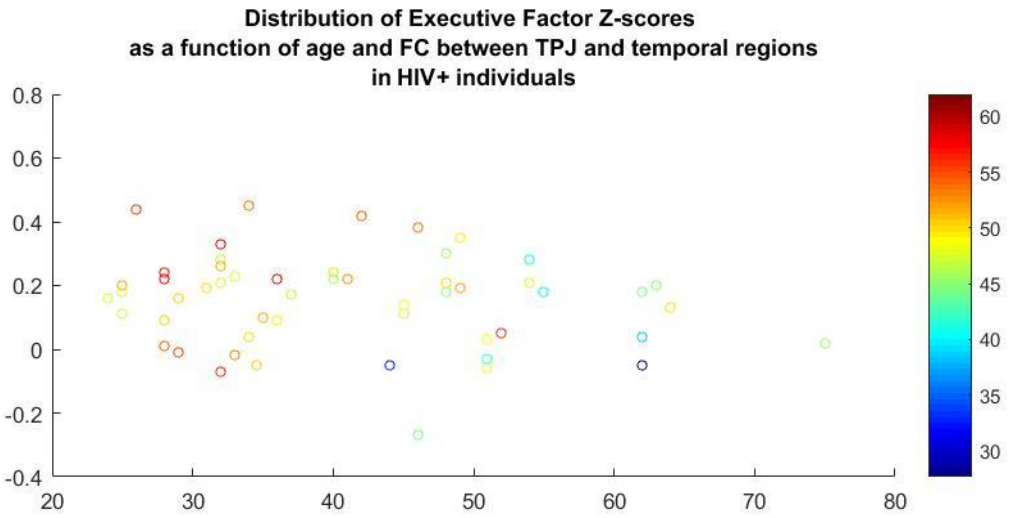

Figure 14. Distribution of Executive Factor Z-scores as a function of age and FC between TPJ and temporal regions in HIV seropositive group.

As shown in Figure 14, Executive Factor T-scores in HIV-infected individuals were increasing together with the strengthening of RS-FC within CON (R=.33, p=0.018), and decreasing with advancing age (R=-.522, p<.001). However, throughout the age range, the described relationship between the RS-FC and neurocognitive functioning did not deviate significantly. Therefore, age did not have a moderating effect on this relationship.

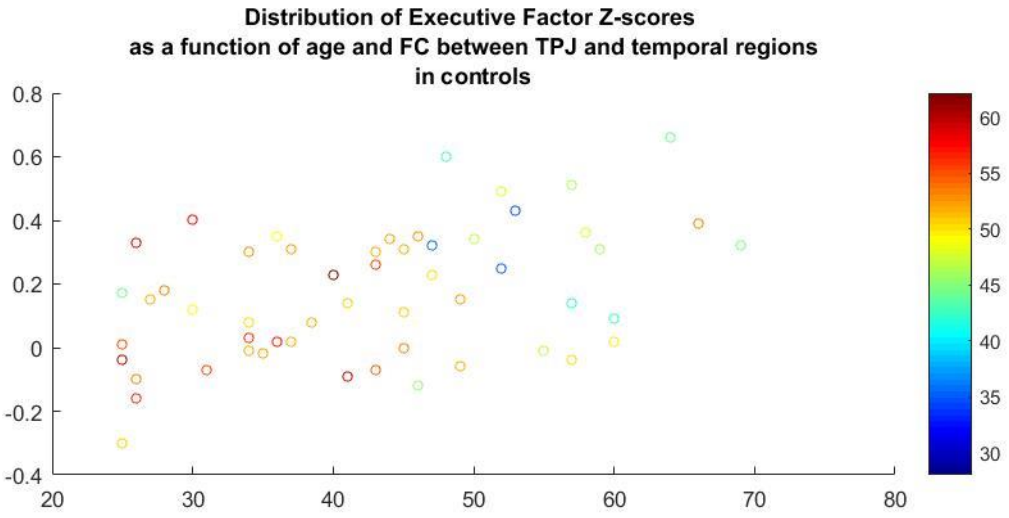

Figure 15. Distribution of Executive Factor Z-scores as a function of age and FC between TPJ and temporal regions in control group.

Figure 15 shows that in case of controls, Executive Factor T-scores were decreasing with the strengthening of RS-FC within CON (R=-.36, p=.007), and also decreasing in aging (R=-.380, p=.008). Age did not have a significant moderating effect on this relationship.

6. DISCUSSION

This study addresses the current health-related issues of aging HIV+ population. In particular, the dissertation focuses on alterations in the resting state functioning of the brain in relationship to neurocognitive status in aging HIV seropositive individuals. In this part of the dissertation, the author discusses key findings of the current research in light of the previous reports. The discussion is organized in accordance to the research questions addressed in this study.

First, RS-FC and neurocognitive alterations in aging of the HIV noninfected group are discussed in comparison to the findings of previous studies on general healthy population.

RS-FC and neurocognitive changes due to HIV infection are discussed in the light of previous literature. Then, author discusses the revealed interaction effects of age and HIV infection on the resting state of the brain measures and neurocognitive factors. Based on those findings, consequent analysis of the relationship between the RS-FC sensitive to the age-HIV interaction effects and neurocognitive factors are discussed. Next, independent moderating effects of age and HIV infection on the revealed relationships in healthy controls are presented in light of the previous studies. The moderating effects of age in the HIV seropositive individuals are discussed in the light of hypothesis of the accelerated and accentuated aging in this patient population. In the end, limitations and future directions are provided.

6.1. Effects of aging on the resting state of the brain

In accordance to the first research question, the relationship between age and the resting state of the brain was analyzed. Those analyses, performed on the control group, were valuable in the context of the current study as they led to the estimation of normality of the current control sample in terms of age-related alterations in the resting state of the brain. As hypothesized, aging in healthy adults was related to both, increases and decreases in intrinsic brain activity as assessed with the measures of remote and local RS-FC. The finding of controls showing age-related brain FC changes was comparable to described in previous studies on healthy population. This allowed for further comparisons and discussion of the effects of aging in the current HIV-infected sample to the effects of aging in the healthy controls – a representative sample of the general population.

This study revealed weakening in short-range FC within DMN between the areas of Posterior Cingulate in aging of the healthy subjects, which is in support to previous literature

(Andrew-Hanna et al., 2007; Damoiseaux et al., 2008; Mevel et al., 2011; Mowinckel, Espeseth, & Westlye, 2012; Song et al., 2014; Tomasi & Volkow, 2012; Wu et al., 2011). Those decreases in FC were found across the employed methods of RS data analysis (i.e., ROI-based, ICA, and voxel-based analysis). Further decreases in local connectivity in DMN regions (as assessed with ReHo and mReHo) were observed in Orbital Frontal Cortex, R. and L. medial Frontal Gyrus, and support previous findings of Tomasi and Volkow (2012).

However, there were also increases with age in long-range inter-hemispheric FC within DMN between left and right Prefrontal Cortices. Those DMN alterations in advancing age described for the current sample emulate the inter-hemispheric compensatory mechanisms of functional dedifferentiation between analogous brain regions in both hemispheres described in the HAROLD model. Moreover, increases were noticed between R.Angular Gyrus and R.Posterior Cingulate, and R.Precuneus, which is in opposition to the findings of Tomasi and Volkow (2012), who noted decreases in FC between those brain regions.

Revealed increases with age for within-network FC of ON between the regions of left and right hemisphere, as well as of the FPN between left and right prefrontal regions provide further empirical evidence for the HAROLD model of changes in aging in terms of inter-hemispheric dedifferentiation. Here, the compensatory mechanisms evoke contra-lateral intrinsic activation, which in result is shown as an increased inter-hemispheric FC between those regions. FPN alterations provides further support to the earlier descriptions of the anterior-posterior disconnections. As described here, increases FC within frontal regions of FPN show resemblance to report by Marstaller and co-workers (2015). Authors further stated that the increases in frontal regions also show lower consistency with posterior regions of FPN. This can consequently lead to the anterior – posterior shift, which is described in the PASA model of healthy aging of the

brain.

Intra-network FC of SMN and CON was found to show both, decreases and increases in advancing aging of the studied healthy participants, which is in line with the various results of previous reports. Here, decreases in advancing aging were noticed in intra-network FC of CON and SMN, which is in line with the findings of Mowinckel, Espeseth, and Westlye (2012). Meanwhile, increases of intra-network FC observed here for SMN between parietal regions are consistent with the findings by Song and co-workers (2014). Increases were also noticed within CON for inter-hemispheric connectivity, especially in FC of Angular Gyrus, Basal Ganglia, and Insula, which was also already described in literature (Tomasi and Volkow, 2012).

Decreases in local connectivity (as assessed with ReHo and mReHo) were further observed in L.Amygdala, which is a part of subcortical network that was, however, previously shown to increase in aging (Tomasi & Volkow, 2012).

The current observations of increases in FC between the regions of separate RS network (i.e., CON, FPN, and DMN), are in line with previous literature showing increased inter-network FC (Betzel et al., 2014; Geerlings et al., 2014). Those increases were observed in terms of both, inter-hemispheric and intra-hemispheric FC. The increases in those long-range functional connections can reflect recruitment of additional brain resources to counteract functional decline and brain atrophy, which is in accordance to the PASA model. In line with the PASA model, the increased FC with other regions in the same cerebral hemisphere, can be interpreted as the unique recruitment of additional brain resources, which commence to functionally compensate for the decline in another brain region. It can also take form of increased cooperation between those regions. At the same time, unique recruitment does not have to be limited to the same hemisphere, and, as shown in the current data, can take form of the recruitment of brain

resources from both cerebral hemispheres.

However, the revealed picture in the current research shows more complex changes that also include decreases in the long-range inter-network FC of the occipital regions of ON with the other regions that are a part of FPN, SMN and CON. This in turn, might be accounted for by the deterioration, lack or inefficiency of compensation. On the other hand, decline in those functional connections could also point to functional specification of the ON in healthy aging of the current sample.

To conclude, a near-to-normal patterns of RS-FC alterations in aging were revealed in the current sample of HIV noninfected subjects, as compared to previously described alterations in brain RS functioning. In specific, within DMN, weakening of the local functional connections were accompanied with the strengthening of the remote intra- and inter-hemispheric functional connections. Increases in the within-network FC of FPN and ON provide further evidence to the employment of the compensatory mechanisms of the interhemispheric dedifferentiation described in the HAROLD model of healthy aging. Moreover, higher engagement of the frontal regions points to another compensatory mechanism of the anterior – posterior shift as described in the PASA model. Observations of the increases and decreases in SMN and CON are also consistent with previous literature on this matter. Further increases in the FC between the RS networks were observed in the current sample, and show resemblance to the previous reports. Those findings can be interpreted in the light of the PASA model of aging, where additional brain resources are recruited to compensate for the functional decline.

Controvertial results were obtained in the local FC of the R.Amygdala, which is reported to show increases in healthy aging and not decreases as in the current sample. Also, FC decline was noticed for several between-network connections of ON, which may be interpreted as

inefficiency to compensate, or, alternatively, functional specification of this RS network in aging.

6.2. Effects of aging on the neurocognitive functioning

In line with the first research question, the issue of cognitive performance across the ages was addressed in the current dissertation. It was aimed to approximate whether age is related to deterioration in particular cognitive domains as previously described in healthy population. Consequently, the results described below were obtained from the analysis of the HIV noninfected participants. As hypothesized, advancing age in the healthy controls was found to be related to decline across the studied cognitive domains.

In particular, HIV noninfcted group in this study showed the most profound deterioration in psychomotor functions (comprising psychomotor speed, dexterity, and activity rate), executive functions (related to initiation, abstract thinking, flexibility of thinking, adjusting responding to the changing environmental conditions, and dividing and switching attention between stimuli), and attention (in terms of verbal and visuospatial attention). Degradation was less intense in memory functions (incorporating verbal memory, learning and storage capacity, encoding and retrieval), and semantic skills (comprising long-term verbal recall, and semantic fluency) in the current sample. These findings are in line with previous research showing that age-related decline across those cognitive domains starts in young adulthood (e.g., Falkenstein, Gajewski, & Getzmann, 2013; Glisky, 2007; Goh, An, & Resnik, 2012; Salthouse, 2004; Semenov et al., 2015).

Therefore, it can be said that the control sample revealed the decline across the studied neurocognitive domains, as it would be expected for the general population based on the previous studies on this matter. This observation leads to the conclusion that the age-related

cognitive decline in the control sample of the current study can reflect cognitive alterations due to age in the general population. It allows for further analysis in this dissertation to test and discuss age-related cognitive decline in HIV-infected individuals in comparison to this healthy comparator group.

6.3. Effects of HIV infection on the resting state of the brain

Analyses of the effects of HIV serostatus on the resting state of the brain addressed the second research question. The hypothesized reductions in inter- and intra-network RS-FC were partially supported by the current restults.

HIV positive serostatus, when accounted for age, was found to cause reduced RS-FC between the regions of DMN and SMN within left brain hemisphere as well as between the hemispheres. This supports previously described reductions in functional connections between the DMN and areas of parietal cortex in the study by Thomas et al. (2013). The current results further show decreases within ON and within FPN, which were not described yet. Even though Ortega et al. (2012) showed frontal-striatal disconnections, their research was focused only on those selected functional connections. Together with previous reports, current findings suggest that weakened connectivity of frontal regions may be more widespread and also include parietal regions.

The cortico-striatal disconnections between dorsolateral prefrontal cortex, dorsal caudate and thamalus, as reported by Ipser and co-workers (2015), were not observed in the current HIV-infected sample. However, decreased connectivity in the R.Insula was noticed here with the use of ALFF analysis. It can be expected accounting for the grey matter atrophy found in the R.Insula in HIV-infected as compared to noninfected individuals in the current sample.

Current results also show increased FC between R.MidFG and R.CingG, while Thomas et al. (2013) reported decreased FC between those brain regions. Furthermore, here, increases in FC were also found between the R.MidTG and L.SupTG as well as between R.Culmen and L.PrecentG. Up to date, literature does not describe increases in FC in HIV infection.

These findings call for attention, as they may point to the compensatory brain mechanisms, especially given that neurocognitive functioning in this HIV+ sample was also extraordinarily high. They can be interpreted as an employment of compensatory mechanisms in terms of additional brain resources, as is found in advancing age of healthy individuals. The observed recruitment of additional brain regions can be accounted for by the mechanism similar to the one described in the PASA model, where the additional brain regions commence to be activated in conjunction with the once in need of support. This can be seen as an increased FC between previously not related brain areas, as observed in HIV+ group after comparison to the noninfected individuals.

Explanations may be addressed by comparison of the current study sample in terms of the health- and clinical-related variables to the samples in the previous studies. In that sense, only about half of the HIV seropositive cohort studied by Thomas et al. (2013) was receiving HAART, while the current sample comprises only HIV-infected individuals stabilized on HAART treatment for at least one year. The success of treatment in the participants of the current study can determine one of the protective factors triggering brain compensatory mechanisms.

Moreover, participants of previous studies were excluded if they had history of neurological condition, stroke, major psychiatric disorder, or active illicit substance use (Ipser et al., 2015; Ortega et al., 2015, Thomas et al., 2013). Those studies, however, did not report the number of comorbid conditions. It is already described that individuals aging with HIV are at

elevated risk for developing multimorbidity (CDC report, 2013), which is defined as two or more chronic illnesses (Justice & Falutz, 2014). The most commonly found include cardiovascular disease, cancers, liver and kidney disorders, osteoporosis, neurocognitive impairment, and frailty (Havlik, Brennan, & Karpiak). The current study addressed that issue by broader exclusion criteria. Therefore, the examined sample was also free of the cancers, liver disfunction, untreated hypertension, diabetes, deficits of learning (for full list see Section 3.1.3.a.). Therefore, it can be speculated that the overall better health status, meaning, very low or lack of multimorbidity may also account for employing brain compensatory mechanisms in the current sample.

Another important factor underlying differential results of the current study from previous reports is that the noticed increases in FC were found between separate RS networks. Meanwhile, most of the previous studies have focused on analyzing within-network FC (Ipser et al., 2015; Ortega et al., 2015) or prespecified a limited number of brain regions (Thomas et al., 2013; Guha et al. 2016). In comparison to those reports, the current study assessed inter- and intranetwork FC between 133 ROIs using ROI-based analysis; within network connectivity using ICA; as well as voxel-based approaches for extracting local functional connectivity. Therefore, analysis in previous studies might have not revealed the effects of HIV on the inter-network FC.

In sum, the current study revealed that in HIV infection, there are both decreases as well as increases in RS-FC. In HIV-infected individuals weaker FC was observed between the temporal and parietal regions as compared to healthy controls, which is in line with previous literature. However, the current results also show decreases within ON and FPN, as well as strengthening of the inter-hemispheric inter-network FC between temporal regions, and between cingulate gyrus and frontal areas. Those findings may point to the employment of brain compensatory mechanisms similar to those found in healthy aging.

6.4. Effects of HIV infection on the neurocognitive functioning

The examination of the effects of HIV infection on the neurocognitive functioning also addressed the second research question. As hypothesized, HIV-infected individuals showed lower neurocognitive performance than HIV seronegative comparators in the attention and semantic skills. At the same time, they did not reveal hypothesized degradation in memory, executive and psychomotor functioning.

HIV+ and control groups did not differ significantly on the level of global cognition (MMSE). The assessed cognitive domains included attention, executive, memory, psychomotor, and semantic skills. At the group level, HIV-seropositive individuals revealed significantly lower functioning in terms of attention and semantic skills than healthy comparators. These findings are in line with previously described cognitive impairments found in HIV+ population (Becker et al., 2004; Becker et al., 1997; Hardy et al., 1999; Heaton et al., 1995).

The current sample did not reveal executive, memory or psychomotor deficits, which are also found in HIV-infected individuals (Lojek and Bornstein, 2005).

The above description, according to the criteria of DSM-V, suggests that the studied sample had an overall high cognitive functioning as for HIV-infected individuals and could be only categorized as showing asymptomatic or mild forms of HIV-associated cognitive disorder (HAND). This high level of neurocognitive functioning in the current sample is also in line with the findings of the CHARTER study, due to which about 50% HIV+ individuals have a chance of developing HAND. Other recent studies assessing RS and neurocognitive functioning also revealed asymptomatic and mild forms of complex cognitive HIV-related deficits in older HIV+ individuals (Guha et al., 2016).

There are multiple factors, which can potentially account for the observed high cognitive

functioning in the current HIV-infected sample. Above all, it must be noticed that HIV+ individuals participating the current research were highly functioning, independent in everyday activities with most individuals holding high job positions. This could be one of the protective factors from developing neurocognitive deficits in the current sample. Being employed is also closely related to the depressive symptoms in the HIV-infected population (Egbert et al., under review). Levels of depression and anxiety were not elevated in this sample as compared to control participants, suggesting the cognitive functioning to be accounted for by HIV serostatus rather than affective state. This also supports previously described lack of depression symptoms to be a protective factor from developing cognitive impairment in this patient population (Heaton et al., 2015). Also, other morbidities were comparable between the HIV+ and comparator groups. As shown by Heaton et al. (2015), higher multimorbidity is one of the most significant contributors to more rapid cognitive deterioration in HIV+ patients. Therefore, this sample may be considered as highly shielded from cognitive decline by their overall good medical and mental health.

Moreover, examined HIV+ individuals were on HAART treatment and were receiving constant medical care, which additionally provides a protective factor minimizing the neurocognitive decline. This provides support to the latest study by Heaton et al. (2015) on the impact of HIV infection on the functioning of patients 40 years of age, where it was demonstrated that the shape of cognitive function is dependent on receiving treatment. Another factor moderating the cognitive state in this sample could be the time when seroconversion occurred in the life-time. The later time of seroconversion together with less years post-infection can explain less intense cognitive impairment in the current sample.

In sum, HIV seropositive individuals exhibited deterioration in attention and semantic

skills, but not memory, executive and psychomotor functions, as compared to healthy controls. They could be further classified as showing asymptomatic or mild forms HAND. This could be expected due to high level of functioning, receiving HAART, and general good physical and mental health in the assessed HIV seropositive sample.

6.5. Interaction effects of aging and HIV infection on the resting state of the brain

In line with the third research question, the current study analyzed synergistic effects of aging and HIV infection on the resting state brain functioning. Analyzes were performed for intra- and inter-network FC with different measures of RS-fMRI (i.e., ICA, ROI-based and voxel-based analysis). As expected, whole brain ROI-based analyses exhibited the highest sensitivity to alterations in functional connectivity caused by aging with HIV, as it revealed both intra- and inter-network FC alterations. However, ICA also provided significant results.

This is the first study to reveal the interaction effects of aging and HIV infection on functional connectivity between particular regions of interest using RS-fMRI. Functional connectivity in HIV-infected individuals was observed to decrease, while in controls to increase with aging. This effect was revealed for functional connectivity between the frontal, parietal and temporal regions. Furthermore, using ICA, current results showed age-HIV interaction to affect FC within Motor Network. The effect had comparable directionality to ROI-based analysis, with FC within MN decreasing in HIV-infected individuals and increasing in control subjects.

Previous research has indicated additive and no interaction effects of aging and HIV on FC reductions of salience network (SAL) (Guha et al., 2016), and cortico-striatal connectivity (Ipser et al., 2015; Ortega et al., 2015). However, those reports were focused on regions selected *a priori*. Up to date, literature describing FC across the whole brain in HIV population is limited

to the study by Thomas et al. (2013), who showed additive and no synergistic effects of aging and HIV on decreased intranetwork FC of DMN, CON, and SAL, as well as internetwork FC for DMN–DAN and –SAL, and CON–SMN. However Thomas et al. (2013) used a smaller number of regions of interest than implied in the current research. Consequently, the relationships revealed in this study are shown for regions not directly tested in the previous reports.

Previously described interaction effects of aging and HIV on resting state of the brain were found only with the resting-state magnetoencephalography (MEG, Becker et al., 2012). MEG measures intraneuronal currents (George et al., 1995) at a wide range of frequency bands (from delta 0-4Hz to gamma 30-50Hz), while fMRI of hemodynamic response at a lower frequency (.01-.1Hz). Even though MEG can provide a more direct measure of intrinsic brain functioning, fMRI allows for more precise localization in the brain. In their report on whole-brain analyses, Becker et al. (2012) found the interaction of age and serostatus on the lowest frequency bands (0-4Hz). Authors reported the relationship between age and delta power to be large (r2 = .51) in the HIV+ subjects and small (r2 = .11) in HIV-negative individuals. Becker et al. (2012) further described that because of the small sample of HIV+ participants (N=10), they were unable to distinguish whether the observed effects of aging in HIV-infected individuals were accounted for by age of the participants, duration of the infection or impact of other comorbid conditions. In the current study, the sample of HIV+ subjects is significantly larger (N=54) and the analyzed illness-related data showed that the relationships of age and time post-infection with the strength of FC can be separated. In this study, both age and time since seroconverion was related to weakening of functional connections. Furthermore, the issue of multimorbidity noted by Becker and co-workers (2012) is accounted for here by strict exclusion criteria.

No interaction effects of age and HIV infection were observed on RS measures of local functional connectivity. Together with the observed changes on long-distance connections, this suggests that the alterations primarily affect remote and not local functional connectivity.

In sum, the current research provides further validation of the use of RS-fMRI technique in studying age-HIV interaction effects on the functioning of the brain. The employed ROI-based method of analysis covered 133 brain regions, and revealed interaction effects on both, intra- and inter-network FC. It was shown that FC is decreasing in advancing age of HIV+ individuals, while it is increasing in aging of noninfected individuals. Based on the current results of extracting particular functional connections that are vulnerable to the interaction effects of age and HIV infection, further analysis describing the relationship between the instrinsic connectivity and the cognitive functioning were implied.

6.6. Interaction effects of aging and HIV infection on the neurocognitive functioning

To address the third research question, analysis determining the interaction effects on the neurocognitive functioning were performed. It was hypothesized that interaction effects will be visible for semantic skills, executive and psychomotor functions.

The results showed no interaction effects of age and HIV infection across the studied cognitive domains (i.e., semantic skills, executive and psychomotor functions, as well as attention, and memory). Only independent effects of age and HIV infection were revealed in the current study, which confirms previous reports (Kissel, Pukay-Martin, & Bornstein, 2005; Sacktor et al., 2007; Scott et al., 2011; Thomas et al., 2013). Other researchers found interaction effects of aging in HIV-infected population to cause accelerated decline in processing speed

(Becker et al. (1997), executive functions (Hardy et al., 1999), and verbal fluency (Becker, Lopez, Dew, & Aizenstein, 2004).

One of the factors in the changing picture of aging with HIV infection is the constant improvement in antiretroviral medication effectiveness. As can be noticed, accelerated cognitive aging in HIV infected population was reported in earlier studies, where the participants could receive prior forms of treatment. More recent studies will have the access to patients receiving modernized HAART schemes. The overall increase rate of the success of treatment may translate into deceleration of cognitive changes. Moreover, analyzing the RS-fMRI outcomes in conjunction with these result of no interaction effects of age-HIV in the current study, it may provide further evidence to the employment of brain compensatory mechanisms. Those mechanisms, if successful enough, can diminish accelerated changes in cognitive functioning due to age. In other words, treatment could be a protective factor, which diminishes the high vulnerability of older adults living with HIV to developing brain functional connectivity decline, by allowing for the triggering of additional neural resources. Those compensatory mechanisms can then result in maintaining cognitive deterioration at the near-to-normal rate for their age as compared to noninfected individuals.

To sum up, in the current sample, there were no interaction effects of age and HIV infection visible on the neurocognitive functioning. It is in line with the recent studies, while in contrast to earlier research showing age-HIV interaction effects. This points to the changes in the clinical portrait of the older adults living with HIV infection, where the current state of medicine allows for decelerating cognitive implications of aging with the infection.

6.7. Relationship between brain connectivity and neurocognitive measures in health

This part of the research addressed the fourth research question. The analysis of the relationship between RS-FC and neurocognitive functioning were designated to give the base for further examination of the moderator effects of age and HIV infection on the relationship between RS-FC and neurocognitive functioning. In that light, the analysis of the relationship between RS-FC and neurocognitive factors was performed on the control group. Comparisons of the relationships between RS-FC and neurocognitive functioning in healthy controls to the previous reports allowed for the estimation of representativeness of the current sample. The hypothesized relationships between the RS inter-network FC and executive functions and semantic skills was supported by the current findings. Moreover, further significant relationship were distinguished.

Within CON FC was related to executive functioning. This relationship is in line with the literature describing cognitive involvement of the CON (Damoiseaux et al., 2006; Dosenbach et al., 2007; Zhang & Raichle, 2010). Furthermore, intra-network FC in Motor Network was related to cognitive performance in psychomotor functions, which supports previous descriptions of this network (Zhang and Raichle, 2010), but also memory and executive functions. Inter-network FC of DMN and SMN regions was related to Psychomotor, Memory, Executive, and Semantic Skills Factor scores.

The current results showed that, in control participants, higher intra- and inter-network FC was related to lower the cognitive functioning. This was revealed for all significant relationships of intra- as well as inter-network FC and across the studied cognitive domains. The directionality of those relationships can be interpreted as an inefficient attempt of brain resources to compensate for functional deterioration, which translates into cognitive decline. Considering that, in the current control sample, higher cognitive performance was related to younger age, the

results can also be interpreted in light of the Scaffolding Theory of Aging and Cognition (STAC) (Park and Reuter-Lorenz, 2009). It can be viewed as depiction of a fracture of a large-scale reorganization in the brain networks. However, for the research purpose of the current study, it was designed to analyze only those functional connections that are sensitive to the interaction effects of age and HIV infection.

In sum, significant relationship can be revealed between the studied intra- and inter-network FC and neurocognitive functioning. The direction of those relationships was consistent across the FC and cognitive domains, with higher FC being related to lower cognitive performance. Potential explanation can be found in the STAC, which described reorganization of the brain networks in response to aging. Within that view and keeping in mind cognitive deterioration observed in those participants, the observed relationships can be seen as an inefficient functional compensation in healthy controls. The obtained data allowed for further analysis on the moderating effects of age and HIV infection on the relationship between the FC and neurocognitive performance.

6.8. Effects of aging on the relationship between the resting state of the brain and neurocognitive functioning in health

In line with the fifth research question, the modulatory effects of age on the relationship between the brain resting state functioning and neurocognitive performance were assessed. In order to estimate how those relationships look in healthy aging, the analysis was performed on the control group. The hypothesized reinforcing effects of age on the relationship between decreasing RS brain activity and cognitive deficits was not supported by the current findings.

Age was found not to affect the majority of the studied relationships between intra- /

inter-network RS-FC and neurocognitive performance. Only one of the analyzed functional connection, in specific, between left superior temporal gyrus and right precentral gyrus determined 2.4% of the variance in the causal relation between strengthening of FC and decline in verbal memory functions. Therefore, previously described increase in the association between FC and cognitive performance in healthy aging (Damoiseaux et al., 2008; Wu et al., 2011) is not clearly evident in the current sample.

The current results can be interpreted as revealing lack of strengthening or weakening of the relationship between the studied ROI pairs FC and neurocognitive performance due to advancing age in the studied HIV noninfected sample. The only case where age determined how the strength of intrinsic brain connectivity affects cognitive functioning, was noted for RS-FC between left temporal gyrus and right precentral gyrus, and memory functioning. It must be considering that, in line with the focus of the current research, the studied relationships were performed only for the FC between ROI pairs that were sensitive to the interaction effects of age-HIV. This might be the reason for exhibiting the moderating effect of age on only one of the relationships between FC and neurocognitive functions.

In sum, current analysis showed that aging determines the strength of the relationship between RS-FC and neurocognitive performance selectively. For the purpose of the current research, this analysis provided an estimation of the effects of age on the relationships between FC and cognitive functions of interest. Those results are further considered a healthy comparator to the analysis on the moderating effects of HIV infection as well as moderating effects of aging in HIV-infected individuals.

6.9. Effects of HIV infection on the relationship between the resting state of the brain and neurocognitive functioning

This part of the research addresses the sixth research question on the moderating effects of HIV infection on the relationship between RS brain activity and neurocognitive functioning. It was hypothesized that HIV infection will reinforce the relationship between intra-network RS-FC in ON and psychomotor speed. Current analysis could not reveal effects on this particular relationship, as intra-ON functional connectivity was not distinguished in prior analytic steps to be sensitive to the age-HIV interaction effects and, thus, not retained for further analysis. Analyses were performed on the relationships of other RS functional connections and neurocognitive functions.

It was noticed that the direction of RS-FC – neurocognitive functioning is opposite between HIV-infected and control participants in the current study. In HIV+ individuals, the relationship between RS networks and cognitive factors was positive, while in controls it was negative.

The effects of HIV infection were revealed to be a significant moderator on the relationship of the intra-FPN FC and performance in executive and psychomotor domains, as well as on the relationship between the intra-CON FC and performance on tasks involving attention, memory, executive and psychomotor functions. HIV infection also significantly moderated relationship between intra-Motor Network RS-FC and memory, executive, and psychomotor functioning.

The moderating effects of HIV infection was revealed for functional connections between regions of CON and SMN in relation to memory, executive, and psychomotor functioning. It was also observed between FC of SMN-DMN regions and across the studied cognitive domains

(i.e., attention, executive, memory, psychomotor, and semantic skills).

It must be considering that the cognitive scores on the cognitive domains of memory, executive and psychomotor functions were not significantly different between the groups. In this context, the observation of the positive correlation between FC and neurocognitive functions in HIV+ sample and, importantly, the significant moderating effect of HIV infection on the relationship between intra-network connectivity and those cognitive domains, may be explained by the successful recruitment of additional brain reserves which maintain those complex neurocognitive processes. The visible deterioration of attention and semantic skills in HIV+ group as compared to healthy controls can be accounted for by not efficient employment of compensatory mechanisms in recruiting additional brain resources from within CON as well as separate brain networks (CON-SMN, DMN-SMN).

Previous studies have not found relationships between FC and cognitive performance in HIV-infected population, however, those reports were restricted only to the analysis of the global cognitive impairment (Ipser et al., 2015; Ortega et al., 2015; Thomas et al., 2013). Consequently, the analysis of the moderating effect of HIV on the relationships between FC and neurocognitive performance in this patient population were not previously described. In the current study, global cognitive impairment was also not observed in HIV+ individuals and global cognitive scores were not related to functional connectivity.

Together, the moderating effects of HIV seropositive status were observed in terms of the weakening across the negative relationships as well as changing into the positive relationships between RS-FC and Neurocognitive Factors as compared to healthy controls. Together with the effects of HIV infection on the neurocognitive performance, these findings point to the employment of compensatory mechanisms in HIV-infected individuals in terms of evoking

additional brain intrinsic activity, which is successful for maintaining cognitive functions of memory, executive and psychomotor skills at the optimum level, but which fails to efficiently compensate for declines in attention and semantic skills.

6.10. Effects of aging in HIV-infected individuals on the relationship between resting state of the brain and neurocognitive functioning

In line with the seventh research question, the analysis was performed to exhibit the changes in the relationship between the FC and neurocognitive functioning due to aging in HIV seropositive individuals. It was hypothesized that due to aging, brain compensatory mechanisms will be evoked in terms of exacerbation of the causal relation between inter-network FC and neurocognitive performance in HIV-seropositive individuals.

Results showed against the hypothesized moderating effects of age in HIV-infected individuals. On the contrary, age effects on the relationship between intra- / inter-network FC and neurocognitive functions were comparable between control and HIV-positive individuals. Each additional year of age did not significantly change the causal relationship between the RS-FC and neurocognitive functioning in HIV+ individuals, which is comparable to the effects of age on those relationships in HIV- individuals.

In sum, the current findings show evidence that the relationship between brain functional connectivity and neurocognitive functioning does not reveal acceleration or deceleration in aging of HIV seropositive sample as compared to a healthy sample. Keeping in mind the context of HIV-infected individuals showing efficient brain compensatory mechanisms in terms of selectively retaining neurocognitive functioning at the optimal level, it can be further interpreted that those compensatory mechanisms are rather stable across the ages in HIV-infected

population. This proves against the hypothesis of accelerated aging in HIV infection. In turn, the selectiveness in efficiency of those compensatory mechanisms points toward the hypothesis of accentuated aging in this patient population.

6.11. Limitations and future directions

HIV-infected participants in this study did not show more than one comorbid conditions, which was successfully treated either depression, diabetes or hypertension. That places the current sample in the top 5% "healthiest" HIV+ individuals in accordance to statistics provided by Guaraldi et al. (2011). This lack of comorbid conditions allowed to assess the effects of HIV infection without the contribution of those other illnesses. At the same time, the overall health outcomes of the analyzed individuals were better than in a random HIV+ older adult, which placed the current sample to be "healthy" above the chance.

Learning from the current results, future research should examine the potential factors that give the bases for triggering the observed neural compensatory mechanisms in HIV-infected individuals, such as clinical- and treatment-related variables. Another line of future research directions based on the current results, is to distinguish the factors underlying the interaction effects of age and HIV infection on the measures of RS-fMRI. Finally, future research should confirm current results on the cohort of HIV seropositive individuals exhibiting more normally distributed number of multimorbidities in order to generalize the current results to the majority of the HIV-infected population.

7. SUMMARY AND CONCLUSIONS

This dissertation addresses the health-related issues of the growing aging HIV seropositive population. The current work has a scope of examining the resting state of the brain in relationship to neurocognitive functioning in this patient population, with the use of the technique of RS-fMRI.

The first objective was to examine the independent and interaction effects of age and HIV infection on the functional connectivity of the brain and cognitive performance. In that respect, the first analysis assessed the relationships between age and RS-fMRI measures, as well as neurocognitive functioning in healthy controls. It was found that HIV noninfected participants reveal patterns of aging in terms of brain functional connectivity alterations, including brain compensatory mechanisms, comparable to the general population. Moreover, cognitive functions observed to deteriorate in relationship with advancing age in the current control group, were found to resemble cognitive decline found in the general healthy population.

In line with the above goal, consecutive analysis explored the relationships between HIV infection and RS-fMRI measures, as well as neurocognitive functioning. The results revealed that HIV infection leads to both, decreases and increases in RS-FC. The detected weakening of FC in HIV-infected individuals as compared to controls, was in line with the previous literature. The new finding of the current research was the depiction of the strengthening of RS-FC in HIV seropositive individuals in contrast to HIV seronegative individuals. This effect was found for inter-hemispheric inter-network functional connections and can be interpreted in terms of employment of brain compensatory mechanisms in this patient population. Furthermore, neurocognitive performance of the HIV-infected individuals, as compared to control participants, was degraded in attention and semantic skills, but not in memory, executive and psychomotor

functions. This finding, considering the high level of functioning in daily living of those subjects, places the current HIV+ sample as showing asymptomatic or mild forms of HAND. Moreover, this adds to the literature stating that neurocognitive performance should be addressed in research on HIV infection in terms of separate cognitive domains, rather than global cognitive functioning. Together, these results suggest that the current HIV-infected sample exhibits efficient brain compensatory mechanisms in terms of evoking additional neural resources, which can translate into retaining cognitive performance of memory, executive and psychomotor functions at the optimal level. Subsequent analyses were designated to further examine this statement and are summarized later in this chapter.

Within the same objective, interaction effects of age and HIV infection were then tested. Here, another key finding of the current dissertation consists in the exposition of the age-HIV interaction effects on the measures of RS-fMRI with the use of ROI-based analysis as well as ICA. The results of ROI-based analysis showed ten pairs of brain regions to be sensitive to the age-HIV interaction, two of which were intra-network (FPN and CON), and eight inter-network (DMN-SMN, CON-DMN, and CON-SMN) functional connections. The results of ICA revealed within-Motor Network FC to be susceptible to age-HIV interaction. In both cases (i.e., ROI-based analysis and ICA), FC was noted to be descending with age in HIV-seropositive individuals, and ascending with age in HIV-seronegative individuals. At the same time, regional homogeneity was not significantly affected by interaction of age and HIV infection. Together, these findings provide evidence that age-HIV interaction targets inter-network, remote functional connections to a larger extent than intra-network and local FC. It also should be noticed, that the observed change in the directionality of FC rather than exacerbation in the same direction, may reveal the accentuated rather than accelerated changes in FC due to aging in HIV-infected

individuals as compared to healthy population. The current findings contribute to the further validation of the use of RS-fMRI technique in examining age-HIV interaction effects on the functioning of the brain.

At the same time, the interaction effects of age and HIV infection on the neurocognitive functioning were not revealed to be significant in the current sample, which is in line with the recent reports on the HIV-infected population receiving HAART. Furthermore, this finding can be interpreted as showing that cognitive decline is not accelerated due to advancing age in HIV+ patients as compared to HIV- individuals.

The second purpose of the current dissertation was to describe the relationships between the RS brain activity showing effects of age-HIV interaction, and neurocognitive functioning. In order to address this aim, the relationships were examined between the functional connections distinguished to be sensitive to the age-HIV interaction effects and neurocognitive factor scores in the control group. It was found that in HIV noninfected individuals, there were negative relationships between intra- and inter-network functional connections and neurocognitive domains. This established the base of how the relationships between those RS functional connections and neurocognitive performance look like in health. The obtained results of significant relationships in healthy sample allowed to test the consecutive hypothesis of the modulatory effects of age and HIV infection on those relationships.

The third aim, as noted above, was to test the modulatory effects of age and HIV infection on the relationships between the brain resting state functioning and neurocognitive performance. First, the modulatory effects of age were examined in HIV noninfected individuals. Here, age was not a significant determinant for all but one studied relationship between intra- / inter-network RS-FC and neurocognitive performance. This presents that aging determines the

strength of the relationship between RS-FC and neurocognitive performance selectively. In the context of the current research, the analyses were performed for the relationships between functional connections showing interaction effects of age and HIV infection. Therefore, is it possible that age moderates other, not studied here relationships between FC and neurocognitive functions.

Then, moderation effects of HIV infection was tested. HIV infection was shown to change the directionality of the relationships between intra- / inter-network FC and neurocognitive functioning. Negative or nonsignificant relationships in controls were positive in HIV-infected individuals. This effect was especially exhibited for the relationship between intra- and inter-network functional connectivity and memory, executive, and psychomotor functioning. Together with the earlier observation of the current study of preserved cognitive functioning in those domains in HIV-infected participants, it can validate the statement of employment of brain compensatory mechanisms in this patient population. This interpretation includes the notion of the successful recruitment of additional brain reserves which maintain those complex neurocognitive processes at the optimal level in the current HIV-infected sample.

Addressing the aim above, modulatory effects of age on the relationships between RS-FC and neurocognitive performance in HIV-infected individuals were investigated. The analysis were performed on the RS functional connections showing age-HIV interaction effects and neurocognitive performance. Another key finding of the current research was revealed here as follows. Age was found not to significantly moderate the relationships between RS-FC and neurocognitive performance in HIV-seropositive individuals. As in case of healthy individuals, the relationships were neither ascending nor descending with age in individuals living with HIV. This finding is crucial in the context of the discussion of accelerated vs. accentuated aging in

HIV-infected population.

In sum, these result can be interpreted within the discussion of accelerated vs. accentuated aging in HIV-infected population. Keeping in mind the effects of HIV infection on the relationship between the FC and neurocognitive functioning, it can be said that the compensatory mechanisms revealed in HIV infected individuals, in terms of recruiting additional brain reserves and strengthening of the intrinsic FC between them, were not accelerating or decelerating due to age. Moreover, the finding of the specificity of employing brain compensatory mechanisms in HIV infection on particular FC and neurocognitive functions, may point to the rather accentuated aging in this aging HIV+ patient population. The exhibited cognitive decline in HIV seropositive individuals was shown for attention and semantic skills, and was related to strengthening of FC in HIV+ group, can be described as a inefficiency of brain compensatory mechanisms for those cognitive functions. Therefore, accentuation in neurocognitive functions in HIV infection will be revealed in terms of attention and semantic skills. However, there is no accelerating effect revealed on the employment of brain compensatory mechanisms in relation to cognitive functioning in this aging HIV seropositive sample.

To conclude, the current dissertation adds to the previous literature on HIV infection by providing at three key findings as follows.

First, this study informs that HIV infection leads not only to weakening, but also to strengthening in the resting state brain functional connectivity. It further finds that the increases are especially observed in inter-network and remote functional connections. Integration of this finding with the neurocognitive data provides evidence that the observed resting state FC

alterations can reflect the employment of brain compensatory mechanisms in terms of recruitment of additional brain resources in this patient population.

Furthermore, this dissertation adds to the current state of knowledge by revealing interaction effects of age and HIV infection on the RS-FC, which were not yet reported with the use of RS-fMRI. This provides further validation to the sensitivity of this neuroimaging technique in studying the functional consequences of the neuroinfectious actions of the virus in HIV-infected individuals.

The third key finding demonstrates the accuracy of rather accentuated than accelerated aging hypothesis in HIV-seropositive population. In that respect, the revealed brain compensatory mechanisms, in relation to neurocognitive functioning, show stability across the years of age together with specificity across the cognitive domains in HIV-infected individuals.

In the final statement, this dissertation adds to the current state of knowledge on the additive and synergistic effects of age and HIV infection on the functioning of the brain in relation to neurocognitive performance. It provides practitioners as well as researchers with a new resource to the discussion on the hypotheses of accelerated vs. accentuated aging with HIV infection. Finally, this study reinforces the need for the future research using RS-fMRI technique to examine the factors allowing for the employment of brain compensatory mechanisms in the individuals aging with the HIV infection.

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Appendix 1. 133 ROIs due to Dosenbach et al. (2010) retained for analysis.

Table I. Coordinates			ROI	RS network
-6	-60	-15	med cerebellum	cerebellum
-11	-72	-14	med cerebellum	cerebellum
5	-75	-11	med cerebellum	cerebellum
-2	30	27	ACC	cingulo-opercular
-41	-47	29	angular gyrus	cingulo-opercular
38	21	-1	ant insula	cingulo-opercular
-36	18	2	ant insula	cingulo-opercular
27	49	26	aPFC	cingulo-opercular
-6	17	34	basal ganglia	cingulo-opercular
-20	6	7	basal ganglia	cingulo-opercular
14	6	7	basal ganglia	cingulo-opercular
11	-24	2	basal ganglia	cingulo-opercular
9	20	34	dACC	cingulo-opercular
0	15	45	mFC	cingulo-opercular
37	-2	-3	mid insula	cingulo-opercular
32	-12	2	mid insula	cingulo-opercular
-30	-14	1	mid insula	cingulo-opercular
58	-41	20	parietal	cingulo-opercular
-55	-44	30	parietal	cingulo-opercular
-4	-31	-4	post cingulate	cingulo-opercular
-30	-28	9	post insula	cingulo-opercular
8	-40	50	precuneus	cingulo-opercular
42	-46	21	sup temporal	cingulo-opercular
51	-30	5	temporal	cingulo-opercular
43	-43	8	temporal	cingulo-opercular

(Table I continued on the next page)

Table I. 133 ROIs due to Dosenbach et al. (2010) retained for second-level analysis *(continued)*.

Coordinates			ROI	RS network
-59	-47	11	temporal	cingulo-opercular
-12	-3	13	thalamus	cingulo-opercular
-12	-12	6	thalamus	cingulo-opercular
11	-12	6	thalamus	cingulo-opercular
-52	-63	15	TPJ	cingulo-opercular
51	23	8	vFC	cingulo-opercular
-46	10	14	vFC	cingulo-opercular
-48	6	1	vFC	cingulo-opercular
34	32	7	vPFC	cingulo-opercular
9	39	20	ACC	default
51	-59	34	angular gyrus	default
-48	-63	35	angular gyrus	default
-25	51	27	aPFC	default
28	-37	-15	fusiform	default
52	-15	-13	inf temporal	default
-59	-25	-15	inf temporal	default
-61	-41	-2	inf temporal	default
-36	-69	40	IPS	default
0	51	32	mPFC	default
-28	-42	-11	occipital	default
-9	-72	41	occipital	default
-2	-75	32	occipital	default
1	-26	31	post cingulate	default
-8	-41	3	post cingulate	default
-5	-43	25	post cingulate	default

(Table I continued on the next page)

Table I. 133 ROIs due to Dosenbach et al. (2010) retained for second-level analysis *(continued)*.

Coordinates			ROI	RS network
-5	-52	17	post cingulate	default
10	-55	17	post cingulate	default
-11	-58	17	post cingulate	default
-3	-38	45	precuneus	default
9	-43	25	precuneus	default
5	-50	33	precuneus	default
-6	-56	29	precuneus	default
11	-68	42	precuneus	default
-16	29	54	sup frontal	default
9	51	16	vmPFC	default
-6	50	-1	vmPFC	default
-11	45	17	vmPFC	default
8	42	-5	vmPFC	default
-1	28	40	ACC	fronto-parietal
-29	57	10	aPFC	fronto-parietal
40	17	40	dFC	fronto-parietal
44	8	34	dFC	fronto-parietal
-42	7	36	dFC	fronto-parietal
40	36	29	dlPFC	fronto-parietal
46	28	31	dlPFC	fronto-parietal
-44	27	33	dlPFC	fronto-parietal
-41	-40	42	IPL	fronto-parietal
54	-44	43	IPL	fronto-parietal
-48	-47	49	IPL	fronto-parietal

(Table I continued on the next page)

Table I. 133 ROIs due to Dosenbach et al. (2010) retained for second-level analysis *(continued)*.

Coordinates			ROI	RS network
-53	-50	39	IPL	fronto-parietal
44	-52	47	IPL	fronto-parietal
-32	-58	46	IPS	fronto-parietal
32	-59	41	IPS	fronto-parietal
-35	-46	48	post parietal	fronto-parietal
42	48	-3	vent aPFC	fronto-parietal
-43	47	2	vent aPFC	fronto-parietal
39	42	16	vlPFC	fronto-parietal
-52	28	17	vPFC	fronto-parietal
-18	-50	1	occipital	occipital
-34	-60	-5	occipital	occipital
36	-60	-8	occipital	occipital
-44	-63	-7	occipital	occipital
19	-66	-1	occipital	occipital
17	-68	20	occipital	occipital
39	-71	13	occipital	occipital
29	-73	29	occipital	occipital
-29	-75	28	occipital	occipital
-16	-76	33	occipital	occipital
9	-76	14	occipital	occipital
15	-77	32	occipital	occipital
20	-78	-2	occipital	occipital
-5	-80	9	post occipital	occipital
29	-81	14	post occipital	occipital

(Table I continued on the next page)

Table I. 133 ROIs due to Dosenbach et al. (2010) retained for second-level analysis *(continued)*.

Coordinates			ROI	RS network
33	-81	-2	post occipital	occipital
-37	-83	-2	post occipital	occipital
-29	-88	8	post occipital	occipital
13	-91	2	post occipital	occipital
27	-91	2	post occipital	occipital
-4	-94	12	post occipital	occipital
46	-62	5	temporal	occipital
53	-3	32	frontal	sensorimotor
-42	-3	11	mid insula	sensorimotor
33	-12	16	mid insula	sensorimotor
-36	-12	15	mid insula	sensorimotor
-26	-8	54	parietal	sensorimotor
-47	-12	36	parietal	sensorimotor
-38	-15	59	parietal	sensorimotor
-47	-18	50	parietal	sensorimotor
46	-20	45	parietal	sensorimotor
-55	-22	38	parietal	sensorimotor
41	-23	55	parietal	sensorimotor
-38	-27	60	parietal	sensorimotor
42	-24	17	post insula	sensorimotor
-41	-31	48	post parietal	sensorimotor
10	5	51	pre-SMA	sensorimotor
58	-3	17	precentral gyrus	sensorimotor
-44	-6	49	precentral gyrus	sensorimotor

(Table I continued on the next page)

Table I. 133 ROIs due to Dosenbach et al. (2010) retained for second-level analysis *(continued)*.

Coordinates			ROI	RS network
46	-8	24	precentral gyrus	sensorimotor
-54	-9	23	precentral gyrus	sensorimotor
44	-11	38	precentral gyrus	sensorimotor
-54	-22	22	precentral gyrus	sensorimotor
0	-1	52	SMA	sensorimotor
59	-13	8	temporal	sensorimotor
-54	-22	9	temporal	sensorimotor
-41	-37	16	temporal	sensorimotor
-53	-37	13	temporal	sensorimotor
-55	7	23	vFC	sensorimotor
43	1	12	vFC	sensorimotor

Appendix 2.

Table II. Correlations between age and the RS-FC between ROIs in HIV+ and HIV- groups.

	Age R (*p*)	
RS-FC	**HIV+**	**HIV-**
Within RS networks		
FPN (L.aPFC – R.VLPFC; R.dFC – L.dFC; L.IPL-L.IPS)	.483 (.000***)	.536 (.000***)
ON (L.occipital cortex – R.occipital cortex)	.336 (.013*)	.464 (.000***)
CON (R.mFC – R.ant insula)	-.244 (.075)	-.553 (.000***)
(L.angularG-R.basal ganglia; L.post insula-R.temporal regions)	.409 (.002**)	.419 (.000***)
DMN (R.angular gyrus – R.postCingulate, R.precuneus; L.aPFC – R.mPFC)	.463 (.000***)	.570 (.000***)
(R.post cingulate – R.post cingulate)	-.345 (.011*)	-.305 (.025*)
SMN (L.parietal – L.parietal regions)	.283 (.038*)	.409 (.002**)
(R.mid insula – R.precentrG; R.pre-SMA – R.vFC)	-.516 (.000***)	-.469 (.000***)
Between RS networks		
FPN – DMN [b]	.589 (.000***)	.647 (.000***)
- SMN [a]	.302 (.026*)	.607 (.000***)
- CON [a]	.408 (.002**)	.501 (.000***)
FPN - ON (R.vent aPFC – R.occipital regions)	.408 (.002**)	.408 (.002**)
- ON (L.dFC – L. and R.occipital regions)	-313 (.021*)	-313 (.021*)
DMN - CON [a]	.459 (.000***)	.594 (.000***)
- ON [a]	.448 (001***)	.656 (000***)
- SMN [a]	.627 (.000***)	.627 (.000***)
SMN - CON [a]	.472 (.000***)	.555 (.000***)
- ON [a]	-.454 (.001***)	-.532 (.000***)
CON - ON (R.mFC – R.occipital regions)	-.420 (.000***)	-.420 (.000***)
- ON (R.mid insula, L.sup temporal regions, R.TPJ – L. and R.occipital regions)	.524 (.000***)	.524 (.000***)

Note. [a]- inter- and intra-hemispheric pairs of regions; [b]- inter-hemispheric pairs of regions.

Appendix 3.

Table III. Relationship between cognitive factor scores and demographic, health-related and clinical variables.

	Attention	Memory	Executive	Psychomotor	Semantic Skills
Controls					
M (SD)	50.79 (7.15)	50.77 (5.49)	50.36 (5.84)	49.50 (7.00)	50.84 (8.30)
Age, R (*p*)	-.492 (.000)**b	-.279 (.041)*a	-.538 (.000)***a	-.585 (.000)***a	-.201 (.144)b
Education years, R (*p*)	.359 (.008)**	.255 (.063)	.209 (.129)	.199 (.149)	.235 (.087)
HIV+					
M (SD)	46.58 (6.38)	52.03 (5.57)	48.95 (6.03)	49.43 (8.02)	46.55 (8.94)
Age, R (*p*)	-.474 (.000)***b	-.261 (.057)a	-.522 (.000)***a	-.658 (.000)***a	-.325 (.019)**b
Education years, R (*p*)	.147 (.289)	.225 (.102)	.333 (.016)*	.193 (.162)	.365 (.008)**
Years post-infection, R (*p*)	-.466 (.000)***	-.234 (.088)	-.567 (.000)***	-.568 (.000)***	-.480 (.000)***
Nadir CD4, R (*p*)	.227 (.098)	-.173 (.212)	.076 (.591)	.124 (.370)	-.043 (.760)
CD4 current count, R (*p*)	-.266 (.052)	.112 (.421)	-.053 (.708)	-.158 (.254)	-.076 (.590)
Viral load highest, R (*p*)	.222 (.106)	.088 (.526)	.038 (.790)	.138 (.319)	-.030(.832)
CNS syphilis, R (*p*)	.351 (.009)**	.189 (.171)	.220 (.110)	.172 (.215)	.131 (.345)
HIV+ - controls, T (*p*)	970.000 (.003)**	-1.180 (.241)	1.227 (.223)	.051 (.960)	983.500 (.008)*

Note. a- Pearson's R; b- Spearman's Rho; c- unpaired T-test; d- Mann-Whitney U Test. Only significant demographic and health-related variables are shown.

Appendix 4.

Table IV. Effects of age, HIV, and age-HIV interaction on neurocognitive factors.

	Attention	**Memory**	**Executive**	**Psychomo-tor**	**Semantic Skills**
Main effect of age, B (95%CI), *p*-value	-.440 (-.354, -.161), .000***	-.269 (-.208, -.038), .005**	-.527 (-.338, -.176), .000***	-.623 (-.480, -.292), .000***	-.270 (-.328, -.063), .004**
Main effect of HIV, B (95%CI), *p*-value	-.326 (-6.901, -2.260), .000***	.300 (-.975, 3.136), .300	-.153 (-3.769, .155), .071	-.042 (-2.886, 1.639), .586	-.261 (-.7.799, -1.380), .006**
Interaction effect of age – HIV, B (95%CI), *p*-value	.006 (-.186, .199), .946	.914 (-.161, .180), .914	.010 (-.152, .171), .904	-.071 (-.276, .099), .352	-.093 (-.399, .130), .314
R2	.283	.085	.291	.394	.141

Table 7. Relationship between FC and cognitive factors

		Within networks		Between networks							
		FPN	CON	CON - DMN	CON - SMN	SMN - DMN					
	Age R (*p*)	R.IFG - L.IPL	R.SupTG - L.SupTG	L.CingG - L.Prec	L.SupTG - R. PrecentG	L.PostcentG - L.PostCing	L.PostcentG - L.PostCing	L.PostcentG - L.Prec	R.PostcentG - L.Prec	R.PostcentG - L.AngG	R.PrecenG - L.SupTG
Controls											
Attention	-.437 (.001)**	-.160 (.247)	-.360 (.008)**	-.069 (.619)	-.204 (.138)	-.062 (.654)	-.071 (.609)	.041 (.770)	-.282 (.039)*	-.206 (.134)	.034 (.809)
Memory	-.279 (.041)*	-.163 (.238)	-.222 (.106)	-.052 (.707)	-.215 (.119)	-.308 (.023)*	-.183 (.185)	-.326 (.016)*	.094 (.499)	.097 (.486)	-.114 (.413)
Executive	-.538 (.000)***	-.109 (.432)	-.360 (.007)**	-.087 (.532)	-.267 (.051)	-.140 (.314)	-.036 (.798)	-.069 (.618)	-.192 (.164)	-.360 (.008)**	-.009 (.948)
Psychomotor	-.585 (.000)***	-.082 (.557)	-.400 (.003)**	-.088 (.525)	-.201 (.145)	-.327 (.016)*	-.314 (.021)*	-.162 (.241)	-.226 (.100)	-.123 (.377)	.001 (.993)
Semantic Skills	-.185 (.179)	-.057 (.682)	-.253 (.065)	.184 (.183)	-.163 (.239)	-.266 (.052)	-.062 (.656)	-.105 (.451)	-.179 (.196)	-.361 (.007)**	.017 (.903)
HIV+											
Attention	-.488 (.000)***	.271 (.048)*	.342 (.011)*	-.049 (.727)	.170 (.218)	-.001 (.994)	.105 (.448)	.031 (.824)	.208 (.130)	.088 (.525)	.176 (.202)
Memory	-.261 (.057)	.120 (.387)	.219 (.111)	.057 (.682)	.285 (.037)*	.085 (.540)	.128 (.358)	.114 (.411)	.126 (.364)	.273 (.046)*	.311 (.022)*
Executive	-.522 (.000)***	.300 (.030)*	.327 (.018)*	-.095 (.503)	.233 (.096)	.102 (.473)	.227 (.106)	.188 (.181)	.143 (.313)	.042 (.765)	.386 (.005)**
Psychomotor	-.658 (.000)***	.287 (.036)*	.283 (.038)*	-.137 (.325)	.323 (.017)*	.072 (.606)	.245 (.075)	.227 (.098)	.238 (.084)	.174 (.209)	.502 (.000)***
Semantic Skills	-.367 (.007)**	.203 (.149)	.131 (.356)	-.122 (.389)	.163 (.249)	.069 (.629)	.122 (.388)	.153 (.279)	.002 (.991)	-.084 (.553)	.441 (.001)**

Appendix 6.

Table VI. Moderating effect of age on the relationship between intrinsic activity of ROIs within networks and neurocognitive factors in control group.

	Attention	Memory	Executive	Psychomotor	Semantic Skills
Controls					
R.IFG-L.IPL, B (95%CI), *p*-value	-.031 (-9.846, 7.766), .814	-.087 (-9.435, 4.977), .537	-.556 (-5.150, 8.324), .638	.104 (-4.345, 11.121), .383	-.001 (-11.230, 11.126), .993
Moderating effect of age, B (95%CI), *p*-value	.057 (-.770, 1.098), .726	.055 (-.641, .888), .747	.144 (-.368, 1.049), .339	.090 (-.562, 1.074), .532	.180 (-.571, 1.778), .307
% of explained variance by moderating effect of age, R2 change (*p*-value)	.002 (.726)	.002 (.747)	.013 (.339)	.005 (.532)	.020 (.307)
R2	.194	.087	.306	.357	.055
R.Sup.TG-L.Sup.TG, B (95%CI), *p*-value	-.210 (-16.863, 2.207), .129	-.126 (-11.313, 4.591), .400	-.158 (-11.870, 2.864), .225	-.183 (-14.686, 2.206), .144	-.212 (-20.715, 3.562), .162
Moderating effect of age, B (95%CI), *p*-value	-.021 (-.751, .636), .869	-.234 (-1.053, .070), .085	-.071 (-.693, .376), .554	-.090 (-.851, .371), .434	-.242 (-1.624, .088), .078
% of explained variance by moderating effect of age, R2 change (*p*-value)	.000 (.869)	.053 (.085)	.005 (.554)	.008 (.434)	.057 (.078)
R2	.228	.143	.315	.377	.128
L.CingG-L.Prec, B (95%CI), *p*-value	.013 (-10.014, 11.073), .920	.000 (-8.665, 8.647), .998	.014 (-7.605, 8.552), .907	.021 (-8.457, 10.184), .853	.227 (-2.253, 23.805), .103
Moderating effect of age, B (95%CI), *p*-value	.037 (-.744, .987), .779	-.076 (-.901, .517), .589	.047 (-.536, .790), .703	-.031 (-.867, .664), .792	.079 (-.767, 1.367), .574
% of explained variance by moderating effect of age, R2 change (*p*-value)	.001 (.779)	.005 (.589)	.002 (.703)	.001 (.792)	.006 (.574)
R2	.193	.083	.292	.343	.090
L.SupTG-R.PrecentG, B (95%CI), *p*-value	-.090 (-14.102, 6.865), .492	-.149 (-13.131, 3.970), .287	-.128 (-12.177, 3.793), .297	-.042 (-10.964, 7.641), .721	-.121 (-18.891, 7.647), .399
Moderating effect of age, B (95%CI), *p*-value	-.020 (-.954, .819), .879	-.301 (-1.485, -.112), .024*	-.006 (-.694, .657), .957	-.012 (-.829, .745), .915	-.023 (-1.215, 1.029), .869
% of explained variance by moderating effect of age, R2 change (*p*-value)	.000 (.879)	.089 (.024*)	.000 (.957)	.000 (.915)	.001 (.869)
R2	.199	.187	.305	.344	.048
L.PostcentG-L.PostCing, B (95%CI), *p*-value	.124 (-6.160, 16.550), .363	-.236 (-16.737, 1.570), .102	.079 (-6.040, 11.440), .538	-.120 (-14.929, 5.130), .331	-.229 (-25.288, 3.082), .122
Moderating effect of age, B (95%CI), *p*-value	.191 (-.251, 1.516), .157	-.058 (-.873, .579), .686	.129 (-.337, 1.038), .310	.161 (-.258, 1.307), .185	.110 (-.698, 1.543), .452
% of explained variance by moderating effect of age, R2 change (*p*-value)	.032 (.157)	.003 (.686)	.015 (.310)	.023 (.185)	.010 (.452)
R2	.236	.128	.309	.377	.089

Table VI. Moderating effect of age on the relationship between intrinsic activity of ROIs within networks and neurocognitive factors in control group. (*continued*)

L.PostcentG-L.PostCing, B (95%CI), *p*-value	.069 (-7.463, 12.735), .603	-.108 (-11.423, 5.107), .447	.142 (-3.222, 12.095), .250	-.149 (-14.376, 3.258), .211	-.006 (-13.102, 12.591), .968
Moderating effect of age, B (95%CI), *p*-value	.148 (-.332, 1.207), .259	-.101 (-.864, .406), .473	.201 (-.088, 1.061), .098	.090 (-.416, .937), .443	.288 (.038, 1.940), .042
% of explained variance by moderating effect of age, R2 change (*p*-value)	.020 (.259)	.009 (.473)	.038 (.095)	.008 (.443)	.077 (.042)
R2	.216	.098	.346	.370	.112
L.PostcentG-L.Prec, B (95%CI), *p*-value	.117 (-6.440, 17.425), .360	-.288 (-19.816, -.944), .032*	.021 (-8.408, 10.025), .861	-.067 (-13.666, 7.544), .565	-.076 (-19.361, 11.078), .587
Moderating effect of age, B (95%CI), *p*-value	.025 (-.891, 1.072), .854	-.173 (-1.246, .283), .212	.042 (-.633, .883), .742	.054 (-.680, 1.062), .662	.118 (-.750, 1.739), .429
% of explained variance by moderating effect of age, R2 change (*p*-value)	.001 (.854)	.026 (.212)	.002 (.742)	.003 (.662)	.012 (.429)
R2	.205	.184	.292	.349	.052
R.PostcentG-L.Prec, B (95%CI), *p*-value	-.178 (-17.274, 3.129), .170	.181 (-2.873, 13.907), .193	-.052 (-9.647, 6.253), .670	-.076 (-12.095, 6.211), .522	-.139 (-19.467, 6.657), .330
Moderating effect of age, B (95%CI), *p*-value	.030 (-.887, 1.128), .811	.005 (-.813, .845), .970	-.024 (-.862, .708), .845	.006 (-.880, .929), .957	.093 (-.854, 1.715), .504
% of explained variance by moderating effect of age, R2 change (*p*-value)	.001 (.811)	.000 (.970)	.001 (.845)	.000 (.957)	.009 (.504)
R2	.222	.108	.293	.347	.061
R.PostcentG-L.AngG, B (95%CI), *p*-value	-.112 (-19.370, 7.601), .385	.169 (-4.177, 17.798), .219	-.250 (-20.663, .729), .036*	.011 (-11.431, 12.595), .923	-.336 (-36.674, -4.169), .015*
Moderating effect of age, B (95%CI), *p*-value	.045 (-1.081, 1.495), .748	-.034 (-1.172, .929), .817	-.117 (-1.390, .499), .348	-.003 (-1.161, 1.137), .983	.043 (-1.318, 1.787), .763
% of explained variance by moderating effect of age, R2 change (*p*-value)	.002 (.748)	.001 (.817)	.011 (.348)	.000 (.983)	.002 (.763)
R2	.205	.106	.360	.342	.143
R.PrecentG-L.SupTG, B (95%CI), *p*-value	.067 (-8.617, 14.812), .598	-.093 (-12.924, 6.271), .490	.031 (-7.804, 10.186), .791	.045 (-8.316, 12.426), .692	.031 (-13.223, 16.566), .823
Moderating effect of age, B (95%CI), *p*-value	.091 (-.614, 1.267), .489	.031 (-.689, .859), .827	.132 (-.327, 1.107), .280	-.059 (-1.042, .628), .620	.031 (-1.070, 1.333), .827
% of explained variance by moderating effect of age, R2 change (*p*-value)	.008 (.489)	.001 (.827)	.017 (.280)	.003 (.620)	.001 (.827)
R2	.204	.087	.307	.347	.036

Appendix 7.

Table VII. Moderating effect of age on the relationship between intrinsic activity of L.SupFG, and neurocognitive factors in control group.

	Attention	**Memory**	**Executive**	**Psychomotor**	**Semantic Skills**
Controls					
L.SupFG, B (95%CI), *p*-value	-.067 (-1.468, .874), .613	-.168 (-1.525, .376), .230	-.125 (-1.342, .439), .313	-.052 (-1.261, .812), .665	-.054 (-1.768, 1.207), .707
Moderating effect of age, B (95%CI), *p*-value	.231 (-.020, .142), .134	-.032 (-.074, .061), .845	.202 (-.018, .106), .159	.065 (-.004, .138), .065	.214 (-.038, .170), .206
% of explained variance by moderating effect of age, R2 change (*p*-value)	.036 (.134)	.001 (.845)	.027 (.159)	.044 (.065)	.031 (.206)
R2	.231	.104	.331	.388	.068

Appendix 8.

Table VIII. Correlation values between neurocognitive functions and the intrinsic signal from brain region showing interaction effects age and HIV infection.

	Attention R (*p*)	**Memory** R (*p*)	**Executive** R (*p*)	**Psychomotor** R (*p*)	**Semantic Skills** R (*p*)
Controls					
L.SupFG	-.190 (.170)	-.236 (.086)	-.272 (.047)*	-.219 (.112)	-.104 (.453)
HIV+					
L.SupFG	.162 (.242)	.182 (.188)	.133 (.347)	.288 (.035)*	.111 (.435)

Appendix 9.

Table IX. Moderating effect of HIV infection on the relationship between intrinsic activity between ROI pairs showing age-HIV interaction, and neurocognitive factors in HIV+ group.

	Attention	**Memory**	**Executive**	**Psychomotor**	**Semantic Skills**
HIV+					
R.IFG-L.IPL, B (95%CI), *p*-value	.032 (-5.292, 7.456), .737	-.028 (-5.939, 4.470), .780	.088 (-3.125, 8.064), .383	.108 (-3.185, 10.911), .280	.069 (-5.235, 11.033), .481
Moderating effect of HIV, B (95%CI), *p*-value	.205 (1.586, 26.727), .028*	.140 (-2.808, 17.999), .151	.210 (1.091, 23.199), .032*	.197 (.462, 28.363), .043*	.133 (-4.882, 27.692), .168
% of explained variance by moderating effect of HIV, R2 change (*p*-value)	.042 (.028*)	.019 (.151)	.044 (.032*)	.038 (.043*)	.017 (.168)
R2	.132	.033	.065	.050	.081
R.Sup.TG-L.Sup.TG, B (95%CI), *p*-value	-.087 (-10.893, 3.911), .352	-.039 (-7.303, 4.824), .686	-.076 (-9.069, 3.942), .436	-.095 (-12.285, 4.161), .330	-.087 (-13.763, 5.108), .365
Moderating effect of HIV, B (95%CI), *p*-value	.347 (12.969, 42.853), .000***	.231 (1.842, 27.265), .025*	.356 (10.769, 37.142), .000***	.348 (12.999, 46.379), .001***	.183 (-1.658, 38.313), .072
% of explained variance by moderating effect of HIV, R2 change (*p*-value)	.105 (.000***)	.047 (.025*)	.111 (.000***)	.106 (.001***)	.029 (.072)
R2	.202	.061	.131	.115	.096
L.CingG-L.Prec, B (95%CI), *p*-value	-.057 (-9.681, 5.135), .544	.003 (-5.951, 6.167), .972	-.090 (-9.726, 3.533), .356	-.114 (-13.065, 3.322), .241	.028 (-8.255, 11.069), .773
Moderating effect of HIV, B (95%CI), *p*-value	.014 (-13.792, 15.993), .884	.054 (-8.735, 15.597), .577	-.006 (-13.710, 12.947), .955	-.030 (-19.036, 13.895), .757	-.147 (-34.214, 4.186), .124
% of explained variance by moderating effect of HIV, R2 change (*p*-value)	.000 (.884)	.003 (.577)	.000 (.955)	.001 (.757)	.022 (.124)
R2	.093	.016	.022	.014	.082
L.SupTG-R.PrecentG, B (95%CI), *p*-value	-.027 (-8.448, 6.292), .772	.036 (-4.903, 7.128), .714	-.022 (-7.349, 5.857), .823	.078 (-4.890, 11.449), .428	.000 (-9.588, 9.591), 1.000
Moderating effect of HIV, B (95%CI), *p*-value	.179 (-.223, 28.874), .054	.248 (3.846, 27.258), .010*	.248 (4.022, 29.763), .011*	.266 (6.670, 38.322), .006**	.158 (-3.041, 35.050), .099
% of explained variance by moderating effect of HIV, R2 change (*p*-value)	.032 (.054)	.062 (.010*)	.061 (.011*)	.071 (.006**)	.025 (.099)
R2	.123	.076	.076	.077	.084
L.PostcentG-L.PostCing, B (95%CI), *p*-value	-.028 (-7.652, 5.648), .766	-.085 (-7.795, 3.029), .385	-.004 (-6.035, 5.773), .965	-.090 (-10.773, 3.956), .361	-.073 (-11.827, 5.271), .449
Moderating effect of HIV, B (95%CI), *p*-value	.036 (-11.207, 16.363), .712	.214 (1.089, 23.045), .032*	.124 (-4.532, 19.662), .218	.210 (1.058, 30.967), .036*	.174 (-1.667, 33.084), .076
% of explained variance by moderating effect of HIV, R2 change (*p*-value)	.001 (.712)	.043 (.032*)	.015 (.218)	.041 (.036*)	.029 (.076)
R2	.092	.063	.029	.049	.093

Table IX. Moderating effect of HIV infection on the relationship between intrinsic activity between ROI pairs showing age-HIV interaction, and neurocognitive factors in HIV+ group. (*continued*)

L.PostcentG-L.PostCing, B (95%CI), *p*-value	.010 (-6.723, 7.501), .914	-.029 (-6.683, 4.926), .765	.091 (-3.344, 9.289), .353	-.021 (-8.736, 7.070), .835	.029 (-7.821, 10.591), .766
Moderating effect of HIV, B (95%CI), *p*-value	.083 (-7.819, 20.676), .373	.154 (-2.246, 20.817), .113	.135 (-3.813, 21.408), .169	.276 (7.279, 37.829), .004**	.091 (-9.580, 27.358), .342
% of explained variance by moderating effect of HIV, R2 change (*p*-value)	.007 (.373)	.024 (.113)	.018 (.169)	.076 (.004**)	.008 (.342)
R2	.097	.037	.041	.077	.068
L.PostcentG-L.Prec, B (95%CI), *p*-value	.034 (-6.294, 9.096), .719	-.082 (-8.928, 3.602), .401	.071 (-4.395, 9.385), .474	.066 (-5.659, 11.419), .505	.037 (-8.072, 11.971), .700
Moderating effect of HIV, B (95%CI), *p*-value	-.010 (-16.638, 14.929), .915	.232 (2.670, 27.686), .018*	.125 (-5.050, 22.798), .209	.195 (.051, 34.434), .049*	.125 (-7.054, 33.438), .199
% of explained variance by moderating effect of HIV, R2 change (*p*-value)	.000 (.915)	.052 (.018*)	.015 (.209)	.036 (.049*)	.015 (.199)
R2	.091	.071	.034	.041	.076
R.PostcentG-L.Prec, B (95%CI), *p*-value	-.042 (-8.663, 5.455), .653	.110 (-2.439, 9.028), .257	-.020 (-6.865, 5.590), .839	.028 (-6.729, 8.970), .778	-.082 (-12.905, 5.119), .394
Moderating effect of HIV, B (95%CI), *p*-value	.237 (4.408, 31.933), .010**	.014 (-10.718, 12.362), .888	.167 (-1.649, 23.055), .089	.231 (3.409, 34.154), .017*	.087 (-9.759, 26.357), .364
% of explained variance by moderating effect of HIV, R2 change (*p*-value)	.056 (.010**)	.000 (.888)	.028 (.089)	.053 (.017*)	.008 (.364)
R2	.148	.025	.042	.054	.073
R.PostcentG-L.AngG, B (95%CI), *p*-value	-.044 (-10.183, 6.241), .635	.195 (.204, 13.368), .043*	-.130 (-12.079, 2.345), .184	.055 (-6.511, 11.733), .572	-.194 (-21.161, -.464), .041*
Moderating effect of HIV, B (95%CI), *p*-value	.157 (-2.967, 30.849), .105	.065 (-9.137, 18.256), .511	.224 (2.198, 31.420), .025*	.149 (-4.770, 32.879), .142	.159 (-3.454, 38.966), .100
% of explained variance by moderating effect of HIV, R2 change (*p*-value)	.023 (.105)	.004 (.511)	.047 (.025*)	.021 (.142)	.024 (.100)
R2	.114	.055	.078	.024	.121
R.PrecentG-L.SupTG, B (95%CI), *p*-value	.103 (-3.409, 11.862), .275	.120 (-2.359, 10.091), .221	.208 (.548, 13.718), .034*	.295 (4.675, 21.005), .002	.249 (3.239, 22.145), .009**
Moderating effect of HIV, B (95%CI), *p*-value	.054 (-11.086, 20.089), .568	.205 (.918, 25.836), .036*	.182 (-.600, 25.867), .061	.245 (5.445, 37.758), .009**	.193 (.977, 38.834), .039*
% of explained variance by moderating effect of HIV, R2 change (*p*-value)	.003 (.568)	.041 (.036*)	.032 (.061)	.058 (.009**)	.036 (.039*)
R2	.103	.068	.089	.143	.156

Appendix 10.

Table X. Moderating effect of age on the relationship between intrinsic activity of ROIs within networks and neurocognitive factors in HIV+ group.

	Attention	Memory	Executive	Psychomotor	Semantic Skills
HIV+					
R.IFG-L.IPL, B (95%CI), *p*-value	.121 (-4.482, 12.359), .814	-037 (-7.138, 9.248), .797	.134 (-3.812, 11.997), .303	.075 (-6.103, 12.233), .505	.085 (-9.027, 16.714), .551
Moderating effect of age, B (95%CI), *p*-value	-.080 (-.710, .384), .726	.251 (-.072, .966), .090	.039 (-.434, .584), .769	.060 (-.442, .750), .606	.017 (-.781, .879), .907
% of explained variance by moderating effect of age, R2 change (*p*-value)	.005 (.553)	.053 (.090)	.001 (.769)	.003 (.606)	.000 (.907)
R2	.257	.122	.289	.441	.141
R.Sup.TG-L.Sup.TG, B (95%CI), *p*-value	-269 (1.431, 22.744), .027*	.181 (-3.504, 17.717), .185	.245 (.300, 20.270), .044*	.180 (-1.636, 21.937), .090	.070 (-12.411, 21.157), .603
Moderating effect of age, B (95%CI), *p*-value	-.055 (-1.298, .823), .654	-.124 (-1.517, .582), .375	.126 (-.476, 1.488), .306	.006 (-1.142, 1.209), .954	.175 (-.599, 2.865), .208
% of explained variance by moderating effect of age, R2 change (*p*-value)	.003 (.654)	.014 (.375)	.015 (.306)	.000 (.954)	.028 (.208)
R2	.312	.114	.345	.464	.168
L.CingG-L.Prec, B (95%CI), *p*-value	.121 (-4.482, 12.359), .352	.037 (-7.138, 9.248), .797	.134 (-3.812, 11.997), .303	.075 (-6.103, 12.233), .505	.085 (-9.027, 16.714), .551
Moderating effect of age, B (95%CI), *p*-value	-.080 (-.710, .384), .553	.251 (-.072, .966), .090	.039 (-.434, .584), .769	.060 (-.442, .750), .606	.017 (-.781, .879), .907
% of explained variance by moderating effect of age, R2 change (*p*-value)	.005 (.553)	.053 (.090)	.001 (.769)	.003 (.606)	.000 (.907)
R2	.257	.122	.289	.441	.141
L.SupTG-R.PrecentG, B (95%CI), *p*-value	.040 (-7.446, 10.332), .746	.108 (-5.190, 11.885), .435	-.001 (-8.663, 8.588), .993	-.019 (-10.491, 8.797), .861	-.058 (-16.881, 10.955), .671
Moderating effect of age, B (95%CI), *p*-value	-.170 (-1.227, .228), .174	-.198 (-1.207, .187), .148	-.063 (-.859, .515), .618	-.159 (-1.374, .199), .140	.033 (-.977, 1.244), .810
% of explained variance by moderating effect of age, R2 change (*p*-value)	.028 (.174)	.038 (.148)	.004 (.618)	.024 (.140)	.001 (.810)
R2	.268	.117	.276	.458	.139
L.PostcentG-L.PostCing, B (95%CI), *p*-value	-.030 (-10.738, 8.550), .821	.215 (-2.375, 15.864), .144	.028 (-8.367, 10.317), .835	.070 (-7.251, 13.596), .544	.018 (-14.171, 16.039), .902
Moderating effect of age, B (95%CI), *p*-value	.400 (-1.457, .150), .109	.326 (.203, 1.669), .013*	.029 (-.675, .851), .818	.020 (-.808, .974), .853	.074 (-.897, 1.564), .589
% of explained variance by moderating effect of age, R2 change (*p*-value)	.039 (.109)	.104 (.013*)	.001 (.818)	.000 (.853)	.005 (.589)
R2	.278	.210	.274	.438	.140

Table X. Moderating effect of age on the relationship between intrinsic activity of ROIs within networks and neurocognitive factors in HIV+ group (continued).

	Attention	Memory	Executive	Psychomotor	Semantic Skills
HIV+					
L.PostcentG-L.PostCing, B (95%CI), *p*-value	-.156 (-11.861, 2.790), .220	.010 (-6.917, 7.439), .942	-.054 (-8.473, 5.536), .675	-.131 (-12.711, 3.189), .235	-.041 (-12.998, 9.668), .769
Moderating effect of age, B (95%CI), *p*-value	-.196 (-1.206, .189), .149	.418 (.300, 1.589), .005**	.044 (-.564, .774), .754	.174 (-.191, 1.321), .140	.071 (-.830, 1.332), .642
% of explained variance by moderating effect of age, R2 change (*p*-value)	.030 (.149)	.138 (.005**)	.002 (.754)	.024 (.140)	.004 (.642)
R2	.291	.206	.276	.472	.086
L.PostcentG-L.Prec, B (95%CI), *p*-value	-.131 (-14.103, 4.897), .335	-018 (-8.701, -9.806), .905	.001 (-9.176, 9.235), .995	.050 (-12.583, 8.170), .671	-.045 (-17.134, 12.599), .761
Moderating effect of age, B (95%CI), *p*-value	-.190 (-1.125, .225), .186	.304 (-.016, 1.274), .056	.050 (-.531, .752), .730	.208 (-.110, 1.349), .094	.111 (-.667, 1.395), .481
% of explained variance by moderating effect of age, R2 change (*p*-value)	.026 (.186)	.066 (.056)	.002 (.730)	.031 (.094)	.009 (.481)
R2	.278	.135	.274	.466	.145
R.PostcentG-L.Prec, B (95%CI), *p*-value	-.1227 (-16.853, 1.313), .092	.000 (-9.029, 9.007), .998	-.050 (-10.631, 7.325), .713	-.076 (-13.356, 6.818), .518	-.010 (-15.020, 14.044), .946
Moderating effect of age, B (95%CI), *p*-value	-.105 (-.977, .444), .455	.346 (.094, 1.443), .026(	.006 (-.665, .692), .968	.184 (-.186, 1.365), .133	.056 (-.890, 1.304), .706
% of explained variance by moderating effect of age, R2 change (*p*-value)	.008 (.455)	.088 (.026*)	.000 (.968)	.025 (.133)	.003 (.706)
R2	.288	.156	.274	.463	.083
R.PostcentG-L.AngG, B (95%CI), *p*-value	.029 (-7.904, 9.823), .829	.032 (-7.608, 9.504), .825	-.059 (-10.100, 6.418), .656	-.012 (-10.116, 9.110), .917	-.156 (-20.462, 5.967), .276
Moderating effect of age, B (95%CI), *p*-value	.018 (-.666, .761), .895	.192 (-.238, 1.117), .199	.036 (-.572, .749), .789	.166 (-.211, 1.306), .153	.113 (-.644, 1.459), .440
% of explained variance by moderating effect of age, R2 change (*p*-value)	.000 (.895)	.031 (.199)	.001 (.789)	.023 (.153)	.011 (.440)
R2	.239	.099	.276	.456	.166
R.PrecentG-L.SupTG, B (95%CI), *p*-value	-.142 (-14.538, 4.474), .293	.198 (-2.972, 15.259), .182	-.210 (-15.793, 1.759), .115	-.124 (-15.857, 4.747), .284	-.285 (-28.117, -.161), .048*
Moderating effect of age, B (95%CI), *p*-value	-.160 (-.950, .237), .233	.228 (-.120, 1.007), .120	-.055 (-.662, .434), .678	.045 (-.526, .777), .700	.075 (-.642, 1.103), .598
% of explained variance by moderating effect of age, R2 change (*p*-value)	.021 (.233)	.043 (.120)	.003 (.678)	.002 (.700)	.005 (.598)
R2	.276	.092	.268	.447	.207

Appendix 11.

Table XI. Moderating effect of age on the relationship between intrinsic activity within networks revealed with ICA and neurocognitive factors in HIV+ group.

	Attention	Memory	Executive	Psychomotor	Semantic Skills
HIV+					
L.SupFG, B (95%CI), *p*-value	-.159 (-1.600, .472), .280	-.053 (-.846, 1.175), .161	-.228 (-1.703, .196), .117	-.113 (-1.631, .624), .374	-.136 (-2.228, .898), .397
Moderating effect of age, B (95%CI), *p*-value	.044 (-.054, .076), .726	.110 (-.038, .088), .427	.063 (-.044, .075), .608	.129 (-.028, .112), .229	.015 (-.093, .104), .910
% of explained variance by moderating effect of age, R2 change (*p*-value)	.002 (.726)	.012 (.427)	.004 (.608)	.016 (.229)	.000 (.910)
R2	.258	.082	.312	.458	.148