NEUROCOGNITIVE NETWORKS:

ALTERED BY DEMENTIA BUT NOT WORKING MEMORY TRAINING

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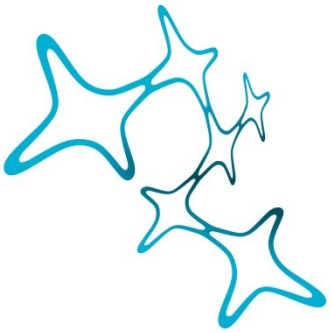

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The thesis is dedicated to my grandfather, a former judge who loved to sing, wave his hat and walking stick when being out for walks,

and to my grandmother, a former teacher with a strong will for education and independence.

I learned with both to laugh about strange behaviour occurring when suffering from dementia – especially when no cure is in sight.

Bescheidenheit schickt sich für den Gelehrten, aber nicht für die Ideen, die in ihm wohnen und die er verteidigen soll.

Marie Curie

Abstract

Functional magnetic resonance imaging (fMRI) studies have reported a link between cognitive performance and large-scale neurocognitive networks (NCN). In dementing disorders altered integrity of these NCN have been reported. As of today, no pharmacological treatments exist to slow down, stop or reverse neuronal cell death causing these altered integrities of NCN and cognitive decline. As a consequence, cognitive training programs have become a popular tool to improve cognitive skills in dementia but also in healthy subjects. Especially, working memory (WM) training was observed to lead to a performance improvement in the trained task but also to generalized improvements in non-trained tasks. Hence, these so-called transfer effects developed into an index of the putative effectiveness of WM training. Despite growing interest in cognitive interventions from academia and industry, the literature reports heterogeneous results on transfer effects. Likewise, there is very little evidence of neural correlates underlying transfer. Accordingly, the effects of WM training on NCN remain understudied.

Within this cumulative thesis, project one investigated impairments of NCN in Alzheimer's disease (AD) and behavioural variant frontotemporal dementia (bvFTD), the two most common causes of dementia among patients less than 65 years of age. To this end, simultaneous fMRI and positron emission tomography in combination with Fluordesoxyglucose (FDG-PET) data was acquired enabling the comparison of NCN integrity measures between patient groups, as well as between neuroimaging modalities. In project two, we assessed the effectiveness of WM training in regards to transfer effects in healthy middle-aged participants – an age group directly preceding or equivalent to that seen in early-stage dementia. Hypothesized transfer effect-related neural plasticity was evaluated in terms of change in NCN integrity between pre- and post-training. Equivalent to project one, both fMRI and FDG-PET was used to measure two linked but distinct marker of neural plasticity. The additional assessment of an extensive cognitive test battery captured changes in nearest, near and far transfer tasks. To this end, all training induced changes were contrasted to an active control group. Overall, the thesis aims to assess the applicability of WM training to decrease AD and bvFTD specific NCN integrity impairments.

Based on the results achieved within project one, we report significant differences in NCN integrity impairments between AD and bvFTD. We could also show that the pattern of network alterations differed between the neuroimaging modalities, with the fMRI-based NCN showing a generally lower disease specificity. The integrity of the anterior default mode network as measured with FDG-PET alone accurately differentiated between patients with AD and bvFTD. Based on the results obtained in project two, we report the lack of WM training induced neural plasticity in NCN in healthy middle-aged participants. Equivalently, on the behavioural level no near or far transfer effects were observed. Thus, WM training-related gains appear not to generalize to other cognitive domains and only to an extremely limited degree to other WM tasks.

Overall, these results discourage the potential applicability of WM training in dementia to decrease NCN integrity impairments. However, looking beyond the concept of transfer as revealed by comparing WM training-induced changes in the active control and experimental group, we see positive effects in form of cognitive improvements in some tasks. Thus, I propose to test WM training along with multiple other cognitive training paradigms to maximize the range of cognitive improvements in patients with a mild cognitive impairment.

Abbreviations

AD	Alzheimer's Disease
BOLD	blood oxygen level dependent
bvFTD	behavioural variant frontotemporal dementia
CAA	cerebral amyloid angiopathy
CEN	central executive network
CSF	cerebral spinal fluid
CT	Cognitive training
DMN	default mode network
FC	functional connectivity
FDG-6P	Fluordesoxyglucose -6-Phosphate
FDG-PET	positron emission tomography in combination with Fluordesoxyglucose
fMRI	functional magnetic resonance imaging
FTD	frontotemporal dementia
G6P	glucose-6-phosphat
HR	haemodynamic response
HS	healthy subjects
ICA	independent component analysis
LOR	line of response
LSNN	large scale neural networks
LTM	long-term memory
MC	metabolic connectivity
MCI	mild cognitive impairment
MMSE	Mini Mental State Examination
MRI	Magnetic resonance imaging
NCN	neurocognitive networks
NMR	nuclear magnetic resonance
p.i.	post injection
PCA	principal component analysis
PCC	posterior cingulate cortex
PPA	primary progressive aphasia
RF	radio frequency
ROI	region of interest
rsfMRI	resting state functional magnetic resonance imaging
RSN	detectable resting state networks
SN	salience network
STM	short-term memory
WM	working memory

Content

1. Introduction

"*If you find ways to repair the memory damaged by Alzheimer's disease or dementia and so forth, it is very likely that the same methods could be used to upgrade the memory of completely healthy people*"

- Yuval Noah Harari

The fear of losing your mind is possibly one of the greatest fears humans have. There is nothing more frightful than the idea of not cognitively functioning anymore. Throughout our life we collect numerous amounts of memories and knowledge. Nevertheless, no one is immune to losing all that. Researchers around the whole world are in search of a cure or treatment for dementia, but as of today no breakthrough has been achieved.

Following Yuval Noah Harari's line of thought, wouldn't it be promising to be able to work against dementia before its actual onset? To reach that goal, cognitive training has been promoted as a powerful tool to sustain cognitive capabilities. Proven it to be effective, this would mean a cognitive upgrade in healthy and a cognitive repair mechanism or protective measure in dementia. This dissertation tries to discover the underlying principles of the aforementioned approach.

1.1. Dementia

The life expectancy in Germany was 64.6 years for men and 68.5 years for women in 1950 and rose up to 78.9 years and 83.6 years for men and women respectively in 2020. These numbers are estimated to rise up to 84.4 for years for men and 88.8 years for women in 2060 (Statistisches Bundesamt 2020a). While in 2000, around 16.65% of the German population were 65 years or older, this proportion increased to 20.63% in 2011. The estimated proportion of people over 65 in Germany is estimated to increase even further to 34% in 2060 (Statistisches Bundesamt 2013). Thus, the percentage proportion of people above 65 years is expected to grow over the next decades drastically in Germany but also worldwide (Eurostat 2020). These numbers are alerting in regards to age-related healthcare costs: in 2015 healthcare costs of 168,40€ billion for over 65-year-olds accumulated which equalled to 49.79% of the total healthcare costs in 2015 of 338.2€ billion (Statistisches Bundesamt 2017). This proportion will rise above 50% over the next

decades according to the rising estimated proportion of above 65-year-olds. Here we see that the costs exceeded the proportion of this age group by 2.4 times.

If the medical costs in Germany are ranked by the main diagnostic groups according to ICD-10, we observe that in 2015 (Statistisches Bundesamt 2020b) the second largest share was covered by psychological and behavioural disorders (F00-F99) (44.4 billion euros; 13.1% of all medical costs). Within that group dementia (F00-F03) is the second biggest cost factor with (15.1 billion euros; 4.5% of all medical costs). Aggregated health care costs for Dementia and Alzheimer's Disease (AD; G30) sum up to 16 billion euros (4.73% of all medical costs) of which 98.3% are spent on people above 65 years. Thus, dementia and AD represent a huge proportion of the medical costs spent on people above 65 years.

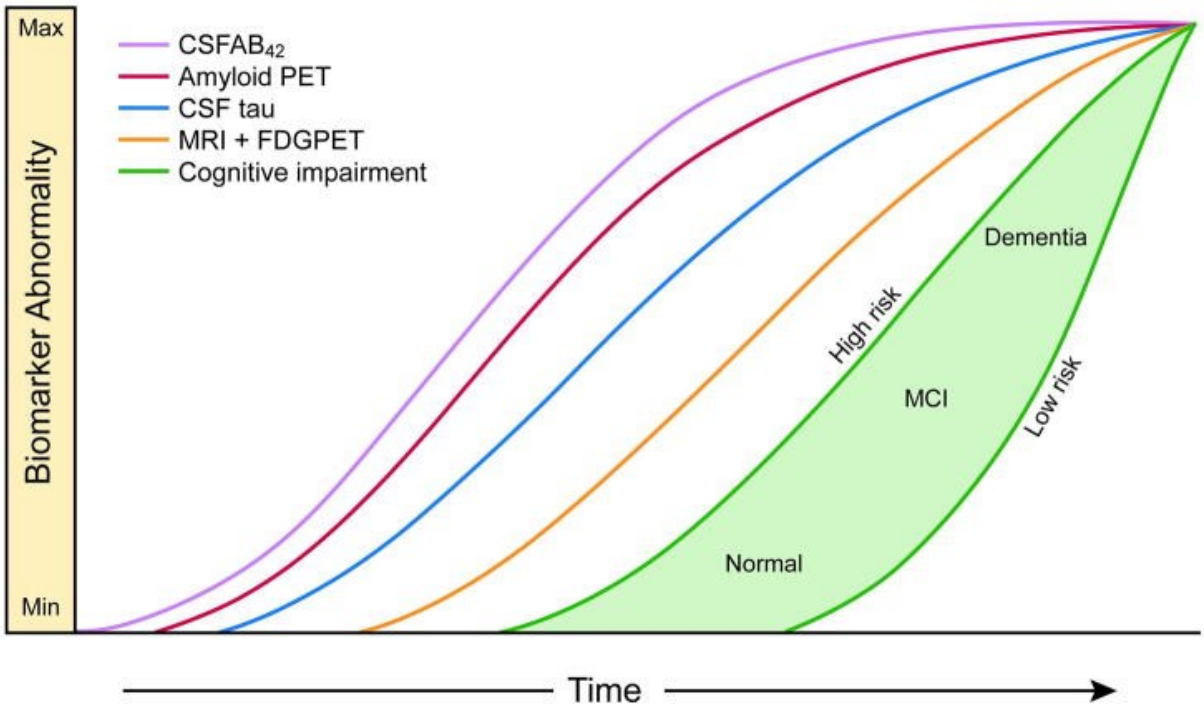
Against the background of a rising average age in the course of demographic development in Germany the number of people suffering from dementia could rise to around 3 million by 2050. In 2016, 1.63 million dementia patients were counted nationwide - around two thirds of them suffered from AD (Deutsches Zentrum für Altersfragen; Alzheimer Europe 2018).

Dementia is characterized by progressive memory loss and the reduction of cognitive abilities. ICD-10 describes clinical information for the diagnose group F03 (Unspecified dementia) as "A condition in which a person loses the ability to think, remember, learn, make decisions, and solve problems. Symptoms may also include personality changes and emotional problems. There are many causes of dementia, including alzheimer disease, brain cancer, and brain injury. Dementia usually gets worse over time." But also the normal aging process is accompanied by a change in cognitive performance (Harada, Natelson Love, and Triebel 2013). Despite the fact that AD represents the biggest proportion of dementia worldwide (Alzheimer's Association 2020), a differential diagnosis has to be made between different forms of dementia. However, as of today differential diagnostics underlie clinical evaluation and therefore clinical judgment (Thies et al. 1999). With this background, biomarkers have been a hot topic in dementia research to objectify and ease the diagnostic procedure (Humpel 2011).

Biomarkers could be of especial importance for diagnosis in early stages of dementia when clinical symptoms are very mild and therefore even more difficult to differentiate

from other psychological diseases. In AD, this presymptomatic stage lasts around 2-3 years and is characterized by first amyloid-beta plaques and neurofibrillary tau tangles accumulation in the brain. These first neuropathological alterations cause synaptic dysfunction in terms of disturbed signal transfer and neuronal loss. Thus, the symptoms in terms of episodic memory impairments due to neurodegeneration increase over time and start with the clinical syndrome of amnestic mild cognitive impairment (MCI). The time period of MCI preceded AD and can last up to several years. Within that time AD pathology can increase leading to AD dementia (Dubois et al. 2016). Figure 1 represents a hypothetical model of different biomarkers preceding MCI and dementia by Jack et al. (2013). In that respect, the identification of biomarkers has a multiple potential. It is crucial for differential diagnostics between different types of dementia, tracking disease progression and clinical trials.

Figure 1: Hypothetical model of dynamic biomarkers of the AD pathological cascade (Jack et al. 2013)



Amyloid-beta plaques measured in cerebral spinal fluid (CSFAβ42; purple) or by positron emission tomography (Amyloid PET; red). Increased neurofibrillary tau tangles measured in cerebral spinal fluid (CSF tau; blue). Neurodegeneration estimated by Fluordesoxyglucose Positron Emission Tomography (FDG-PET) and/or structural magnetic resonance imaging (MRI; orange). Cognitive impairment indicated as filled area (green). Cognitive impairment due to pathophysiology of AD is shifted to the left side (i.e. high risk) and cognitive impairment with low risk for AD pathophysiology is shifted to the right side (i.e. low risk). Y-axis represents minimum (bottom) to maximum (top) biomarker abnormality; X-Axis represents time. With permission from Jack et al. (2013).

1.1.1. Alzheimer's Disease & Frontotemporal Dementia

Especially for frontotemporal dementia (FTD) and AD, the two most common causes of dementia among patients less than 65 years of age (Ratnavalli et al. 2002; Zhou et al. 2010), the (differential) diagnosis is challenging due to their atypical manifestations (Musa et al. 2020). FTD is a neurodegenerative disorder which is characterized by cell death in the frontal and temporal lobes (Olney, Spina, and Miller 2017). It can be divided into a behavioural variant (bvFTD) and a language variant called primary progressive aphasia (PPA) which further can be subdivided into semantic variant and nonfluent/agrammatic variant PPA (Elahi and Miller 2017; Musa et al. 2020). But, bvFTD is approximately four times as common as PPA (Hogan et al. 2016).

Clinical symptoms of AD include primarily an impaired episodic memory, executive functioning, language and visuospatial skills. However, personality changes, behavioural changes and executive dysfunctions can also occur (McKhann et al. 2011; Mendez 2017; Ossenkoppele et al. 2015). On the other hand, bvFTD is characterized by significant personality changes including lack of empathy, apathy, disinhibition, obsessions, and even the development or change of eating habits. Other cognitive areas such as memory or executive functioning can be relatively preserved but this is inconsistent across the patient group (Piguet et al. 2011; Rosness, Engedal, and Chemali 2016). Thus, the symptoms between bvFTD and AD can overlap especially within early phases with only mild symptoms present (Musa et al. 2020) leading to misdiagnoses. In fact, "neuropathological diagnosis of AD, which is defined by the presence at autopsy of both amyloid-ß plaques and tau neurofibrillary tangles, has been found in up to 30% of clinically diagnosed FTD cases" (Casoli et al. 2019).

Despite no cure has been found yet for AD or bvFTD, early diagnoses are of importance. The main goal of treatment is to improve the quality of life of the patients and their relatives. Disease specific treatment plans aiming to slow down cognitive decline, provide psychological and social help have a positive impact on the patient and the patient's relatives' wellbeing (Bradford et al. 2009). Thus, it is an urgent need to identify biomarkers facilitating an adequate diagnosis for and between bvFTD and AD[1].

[1] Please see Isaacs and Boenink (2020) for a critical comment on the usefulness of biomarker in dementia.

1.2. Neuroimaging

So called large scale neural networks (LSNN) (i.e. brain connectivity) have been discussed to serve as a potential biomarker within the field of neurodegenerative diseases (Hohenfeld, Werner, and Reetz 2018; Sala and Perani 2019) and also specifically to detect and distinguish AD and bvFTD (Agosta et al. 2012; Binnewijzend et al. 2012; Greicius et al. 2004; Zhou et al. 2010).

LSNN are neuroimaging-based estimates of macro-scale neural connectivity (i.e. between different brain regions). LSNN can be captured with neuroimaging application such as functional magnetic resonance imaging (fMRI) representing functional connectivity (FC), or with positron emission tomography in combination with Fluordesoxyglucose (FDG-PET) representing metabolic connectivity (MC). Neuroimaging based biomarker have the advantage that they represent a relatively ease of use and cost-effectiveness (Hohenfeld et al. 2018). Also, both fMRI and FDG-PET are non- or only minimal-invasive, respectively. These are important attributes for tracking biomarkers in slow proceeding diseases including presymptomatic stages (Young et al. 2020)as observed in both types of diseases.

In the following, I will explain the underlying principles of fMRI and FDG-PET to obtain FC and MC, respectively.

1.2.1. Functional Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) which makes use of the nuclear magnetic resonance (NMR) phenomenon. NMR describes the physical property of nuclei within a strong magnetic field (B0) excited by a second oscillating magnetic field (B1) which is perpendicular to B0. B1 is applied via radio frequency (RF) transmitter coils. The excited nuclei produce an own electromagnetic signal (i.e. magnetic resonance) near resonance, that is dependent on the applied magnetic field. The underlying principle comes down to the so-called nuclear spins of atomic or subatomic particles, which are always [2] precessing. The abruptly applied oscillating B1 field changes the orientation of the spins (i.e. magnetic moments) from one energy state to another. Thus, B1 changes the orientation of the spins aligned along B0. After some time, the spins return back to their initial alignment along B0. The time needed for realignment to magnetic field B0 is called relaxation time. RF receiver coils detect the energy level difference between the two

[2] As long there is a magnetic field present; for example, the earth's magnetic field. (Mohorič et al. 2004)

populations of spins during relaxation. This signal is amplified and serves as the basis for the resulting image. Within one sample the net magnetization M represents the sum of many spins (Rigden 1986). A subsequent Fourier transform is applied to the measured signals to convert the signal from the time domain to the frequency domain. A temporary image space called k-space stores the frequency information. The k-space image is then mathematically reconstructed producing a phase encoded final image. The final image yields signals per voxel which represent tissue specific contrast values, as each tissue class within the sample has different magnetic properties. A clinical anatomical MRI captures the signal from hydrogen (^{1}H) nuclei. Thus, a voxel value corresponds to the number of hydrogen nuclei in the tissue. The measured contrast (by means of a grayscale value) reflects the difference in signal intensity between adjacent but distinct types of brain tissues, such as grey matter, white matter, cerebral spinal fluid (CSF), etc. (Gerber and Peterson 2008).

Functional MRI reflects local ratios of oxygenated to deoxygenated blood flow. This is achieved by measuring different relaxation times as the ones used for structural MRI as described above. This yields the so-called blood oxygen level dependent (BOLD) contrast. Local magnetic field distortions (susceptibility gradients) are being caused by the paramagnetic deoxyhemoglobin within red blood cells. Thus, the BOLD effect stands in direct relationship with the concentration of deoxyhemoglobin.

Biologically, neural activity is measured indirectly through amount of oxygen in blood supplying a given brain region (Chen 2018). This so-called neurovascular coupling is based on a complex interplay between local cerebral blood flow, volume, and cerebral metabolic rate of oxygen (Kim and Ogawa 2012). The rapid delivery of blood to active neuronal tissues is called haemodynamic response (HR).

For fMRI, multiple images (i.e. a time-series) are acquired over a time period reflecting dynamic neural activity. Typically, the subject is measured either during resting state (i.e. the participant is resting and instructed to think of nothing in particular), during sensory stimulation or cognitive engagement (i.e. performing a cognitive task). Coherently, the terms ‘resting state fMRI’ (rsfMRI) and ‘task fMRI’ are being used. This allows time, and if applied, stimulus dependent measures of local neural activity by means of BOLD.

The typical fMRI achieves a spatial resolution of 3–4 mm (pixel size) (Glover 2011). The basic[3] temporal resolution of fMRI depends on the chosen sampling rate (TR). TR defines the repetition of the pulses (i.e. the time between two sequential scans of the same point in the brain).

1.2.2. Positron Emission Tomography

PET requires, different than MRI, a radiopharmaceutical (or tracer) binding to a biological target of interest. The tracer is injected into the subject prior to imaging. The underlying principle comprises of the detection of photons emitted by an annihilation reaction due to radioactive decay. Different radiopharmaceuticals with different radioisotopes exist. Depending on the clinical research question a tracer of interest is chosen. However, the underlying mechanisms of signal detection are equivalent.

During radioactive decay an unstable atomic nucleus loses energy by emitting radiation. The type of radioactive decay in PET is beta plus decay (β+ decay) or in other words positron emission. A proton inside the radionuclide nucleus is converted into a neutron while emitting a positron (e^+) and an electron neutrino (ν_e). The emitted electron neutrino is a chargeless and almost massless particle which does not interact with matter. However, the emitted positron (e^+) is a positively charged antiparticle of the electron, which unites with a nearby electron (e^-) in an annihilation reaction. This reaction releases two anticolinear (180° apart) high-energy photons (i.e. gamma-rays) of 511keV. Thus, the emitted energy in form of gamma-rays is able to travel unperturbed through most tissues and is detectable outside the body via a PET detector ring. If two gamma-rays hit two detectors which are 180° apart approximately at the same time a coinciding event is recorded. Thus, the positron annihilation is assumed to have happened somewhere along the line of response (LOR) connecting[4] the two detectors. The coincidence-resolving time window between detectors is typically 4–5 nanoseconds but this is a topic of ongoing research and development aiming to improve temporal resolution even further (Spanoudaki and Levin 2010). The PET detector consists mostly of an inorganic crystal (scintillator material) making use of the excitation effect of incident radiation (i.e. the

[3] For task fMRI, the temporal resolution is limited by the hemodynamic response time. Preprocessing of task fMRI data includes convolution of the BOLD signal with the haemodynamic response function (Glover 2011).

[4] No physical line of response exists between the 180° apart PET detectors.

gamma-rays) on scintillator material. Hereby, the crystals absorb the gamma-rays and produce visible light photons which are converted into an electrical signal after signal amplification. Scattering effects, actual location of annihilation event (at radioisotope location or in close proximity of it), the spatial-temporal relationship of recorded coincidence events and especially the size of the gamma-ray detectors are limiting factors for spatial resolution. "Modern PET scanners are typically able to achieve a spatial resolution of about 4–6 mm, of which physical effects (positron range and photon noncolinearity) contribute about 2 mm (Townsend 2004)" (Lameka, Farwell, and Ichise 2016). The temporal resolution of the PET is in the range of minutes due to a limited availability of radio decay count rates (Glover 2011). Commonly, only one PET image per scanning session is acquired (for further details, see below).

Taken together, based on the sum of coincidences recorded, the location of radiotracer accumulation in the body can be deducted giving rise to conclusions on metabolic or neurotransmitter processes depending on the used tracer (Bailey, Karp, and Surti 2005). In this dissertation I will focus on the use of PET in combination with FDG. FDG is a glucose analogue attached with a fluorine-18 radioisotope. Thus, FDG-PET allows quantification and visualization of cerebral glucose metabolism. Equivalent to glucose, FDG is taken up into the cells by a glucose transporter where it enters the metabolic pathway of glycolysis. The first step in glycolysis is phosphorylation by hexokinase. Thus, FDG is phosphorylated to FDG-6-Phosphate (FDG-6P). FDG is missing a hydroxyl group at C-2 position because that is where the radioisotope F-18 is attached (Bessell and Thomas 1973). Unlike the phosphorylated glucose (i.e. glucose-6-phosphat; G6P), FDG-6P is not further metabolized due to its missing hydroxyl group. This prohibits that FDG-6P is isomerized to fructose-6-phosphat. Therefore, it is assumed that FDG-6P is not further metabolized and becomes irreversibly trapped in the cell (Reivich et al. 1979). Another factor for trapping is the negative charge of the attached phosphate group of FDG-6P (Korn, Coates, and Milstine 2009). However, in a rat study it has also been shown that FDG-6P is further metabolized, meaning that FDG-6P is in fact not the 'terminal metabolite' serving as a substrate for signal detection during image acquisition (Southworth et al. 2003). But, the majority of these further metabolites have been observed to retain within each tissue (except in the liver and kidney), and "thus still indicate gross tissue FDG uptake" (Southworth et al. 2003). Also, hexokinase acts as a "gatekeeper" in glycolysis affecting the rate of all subsequent metabolic steps. Consequently, intracellular concentrations of FDG

metabolites reflect hexokinase activity. And most importantly, cerebral activity of glucose-6-phosphatase is very low (Gallagher et al. 1978) preventing dephosphorylation of FDG-6P back to FDG theoretically allowing FDG to leave the cell back to the blood pool. Therefore, FDG-6P plus any other subsequent 'terminal metabolites' of FDG are assumed to be a proxy for the entire glycolytic process. Hence, FDG-PET is supposed to capture neural/synaptic activity by estimating glucose consumption in terms of neurometabolic coupling. Consequently, hypometabolism (i.e. reduced FDG-uptake) indicates neuronal death and synaptic dysfunction with relatively disease-specific reduction patterns (Magistretti 2000). FDG-PET shows a high sensitivity in detecting metabolic abnormalities at a single subject level even for early clinical stages of cognitive decline (Iaccarino et al. 2017). That is why FDG–PET is an established clinical tool for early and differential diagnosis (Bohnen et al. 2012; Whitwell et al. 2017).

European Association of Nuclear Medicine procedure guidelines for PET brain imaging using FDG recommend to start imaging 30-60min post injection (p.i.) of FDG (Varrone et al. 2009). The subject is asked to fast 4-6h prior injection to ensure a sufficiently low enough blood-sugar level for efficient FDG-uptake. During the first 15-30min after tracer injection, the subject is asked to sit in a quiet, dimly lit room with closed eyes. The subject is further told not to speak during that time. These instructions are being given to ensure that resting state cerebral glucose metabolism is measured. After the uptake period, FDG-uptake is assumed to be in a steady-state, meaning plasma FDG concentration is considered to be constant, and an equilibrium between free and plasma compartments is reached (Patlak and Blasberg 1985). It is assumed that this steady state lasts up to 120min p.i. and that the distribution of FDG remains "frozen" thereafter (Chiaravalloti et al. 2019; Haier et al. 1988). Using clinical routine PET protocols (e.g. for diagnostic purposes) only one image is reconstructed based on a timeframe of certain length acquired within this 120min p.i. This image represents primarily[5] FDG-uptake during the initial FDG-uptake period (i.e. resting state associated cerebral glucose metabolism).

The above mentioned minimal invasive procedures for clinical routine neuroimaging protocols using FDG-PET include intravenous injection of FDG and indirectly, a radiation

[5] The highest proportion of FDG-uptake occurs during the first 15-30min p.i. (Sasaki et al. 1986). It is a matter of ongoing research to quantify the amount of FDG-uptake following the initial 15-30min p.i. (Ishii et al. 2002, 2006; Kumar et al. 1992). Nevertheless, the reconstructed final FDG-PET image represents an integral of trapped FDG detected between the start and end of the timeframe chosen for reconstruction.

exposure which depends on the amount of injected FDG and whether a PET/computed tomography or a PET/MRI is used.

1.3. Brain Connectivity

The underlying concept of brain connectivity (i.e. LSNN) is that the brain functions as a network itself. This means, that different regions continuously exchange information forming a complex integrative network over the entire brain (van den Heuvel and Hulshoff Pol 2010). This stands in contrast to the historical view on how the brain works: in the early days of neuroscience, two contradicting views existed. First, the brain has a strictly dedicated structure-function relationship with functions localized in specialized brain regions (localism). Second, the brain relies on integration of the whole brain (holism) (Nazarova and Blagovechtchenski 2015). Nowadays, neuroscientists believe the truth is found in between both concepts with specialized cell types processing and contributing to very specialized tasks while being integrated in a complex, brain wide network exchanging information (Northoff 2014).

Friston, who pioneered in the field of brain connectivity, defined FC as the temporal dependence of neuronal activity patterns of anatomically separated brain regions (Friston et al. 1993). Thus, FC is based on temporally co-varying BOLD signals between brain regions. Low frequency oscillations of rsfMRI time-series (~0.01–0.1 Hz) are assumed to originate from neural activity and represent therefore the frequencies of interest for subsequent FC computation. However, the true nature of these frequencies is still a subject of research (Yuen, Osachoff, and Chen 2019).

1.4. Estimating Brain Connectivity

There are several options to estimate FC which fall within two main categories: model-driven methods and data-driven methods. Model driven methods include seed-based analyses. This method requires a selection of a region of interest (ROI; i.e. the seed). The seed averaged time-series is subsequently correlated (e.g. Pearson correlation) against time-series from other ROIs or the whole brain (e.g. every voxel). However, the latter option requires much more computational power. Data-driven methods include independent component analysis (ICA) and classification techniques. These methods do not require *a priori* selection of ROIs, so all time-series are considered when estimating FC. ICA, the by far most frequently applied data-driven technique attempts to decompose

the linearly mixed signals from the temporal dimension into independent spatial sources which are maximally independent non-Gaussian signals. First, the fMRI dataset from each subject is reduced in dimension by a principal component analysis (PCA). The resulting data are concatenated for a group ICA (Calhoun et al. 2001) which extracts group derived spatial network maps (i.e. independent components). Running a group ICA has the benefit of extracting one group derived set of components, instead of multiple different sets of components (i.e. when running individual ICAs). Subsequently, subject-specific spatial maps and time courses for each extracted component are estimated with a back-reconstruction method. The subjects' component specific time-series can subsequently be used for group comparisons or inter- or intra-network connectivity correlations. Classification techniques include, amongst others, clustering algorithms and multivariate pattern classification. Clustering algorithms group brain regions based on a set of relevant characteristics (e.g. a time-series of interest). Multivariate pattern classification groups brain regions based on feature extraction trained on a training data set. For a review on FC estimation methods please see van den Heuvel and Hulshoff Pol (2010) and Lee et al. (2013). Independent from the chosen method, conceptually the resulting FC maps represent networks whose BOLD signals (time-series) co-vary to a certain degree, and thus are thought to be connected.

MC can be estimated equivalently to FC. For a review see Yakushev et al. (2017). However, different to FC, MC is so far only estimated on a group level instead of on a single subject level. Reason for this lays in the fact that MC lacks the temporal component. Meaning, only one FDG-PET image per subject is acquired using clinical routine PET protocols (see Positron Emission Tomography) (Varrone et al. 2009). Only recently, a new imaging protocol was developed called functional FDG-PET (fFDG-PET) which is characterized by continuous FDG injection throughout the scanning session (Villien et al. 2014). Hence, equivalent to fMRI-based FC, dynamic MC estimation is possible due to a constant supply of available FDG within the blood pool while acquiring data. However, in this dissertation I will focus on non-dynamic MC acquired with the standard FDG-PET protocol (Varrone et al. 2009). Independent of the chosen methods for estimating connectivity, the extracted MC maps represent networks whose regional glucose metabolism (i.e. magnitude in FDG-uptake) coherently vary across individual subjects (Savio et al. 2017).

1.4.1. Resting State Networks

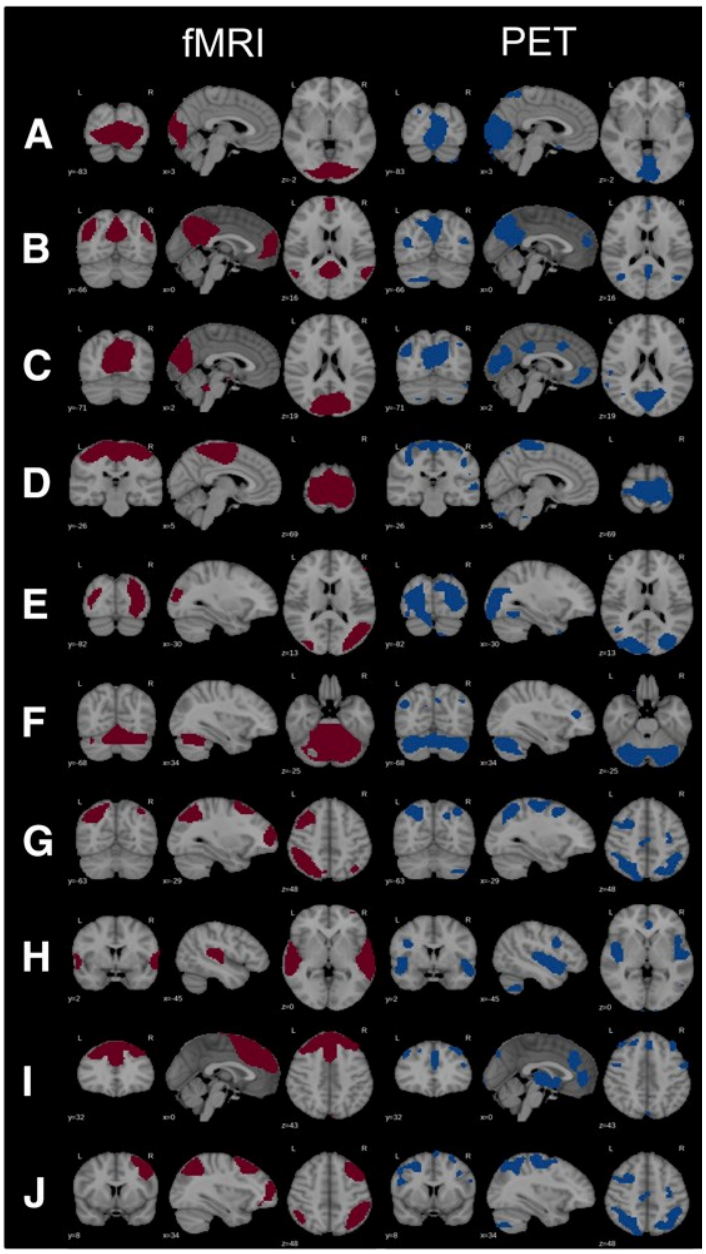
In Biswal's seminar paper from 1995 (1995) resting state associated intrinsically correlated voxel activity based on fMRI was firstly described. The authors observed correlated activity within sensorimotor regions. Importantly, due to technical limitations back then the authors only acquired a single axial slice across the motor cortex from each volunteer. Over a decade later, the first templates of other detectable resting state networks (RSN) spanning over the entire brain were published (Allen et al. 2011; Yeo et al. 2011).

Most of the correlated activity seems to occur between regions which share common characteristics in function as well as in neuroanatomy. Examples are the sensory-motor, auditory and visual network (Damoiseaux et al. 2006; De Luca et al. 2005). Thus, it seems that brain areas which simultaneously process information, even when anatomically separated, stay connected during rest by an intrinsic (correlated) neural activity (van den Heuvel and Hulshoff Pol 2010). One set of RSN have been identified to process cognitive functions and are called neurocognitive networks (NCN) (Bressler and Tognoli 2006; Mesulam 1990). Among these NCN, the central executive network (CEN) is known to be related to attention and goal-directed selection of stimuli (Bressler and Menon 2010; Corbetta and Shulman 2002; Fox et al. 2005). The CEN shows activation during cognitive task performance (task fMRI) and it comprises the dorsolateral prefrontal cortex and posterior parietal cortex (Binder et al. 1999; Shulman et al. 1997). The default mode network (DMN) shows deactivation during cognitive processing and is hypothesized to drive self-referential and integrative processes. The DMN involves the posterior cingulate cortex (PCC), precuneus, medial prefrontal cortex and lateral parietal cortex (Raichle et al. 2001). The salience network (SN) has been discussed to act as a modulator between the task-positive and task-negative brain states (Menon and Uddin 2010). Furthermore, the SN processes information relating to maintaining vigilance and arousal as well as responding to salient stimuli (Seeley et al. 2007; Seitzman et al. 2019). It comprises the dorsal anterior cingulate cortex, bilateral insula and pre-supplementary motor area (Smitha et al. 2017).

While functional RSN have been investigated extensively, metabolic RSN could be identified in FDG-PET data only recently (Di and Biswal 2012; Savio et al. 2017; Trotta et al. 2018; Yakushev et al. 2013). Consequently, FDG-PET and rsfMRI are based on linked

but distinct physiological mechanisms of neuronal activity pointing towards a common neural substrate of RSN. See Figure 2 for a visualisation of matching RSN based on rsfMRI and FDG-PET adapted from Savio et al. (2017).

Figure 2: Matched RSN in rsfMRI and FDG-PET data (Savio et al. 2017)



A) Primary visual posterior network; B) default mode network; C) primary visual (posterior); D) sensori-motor network; E) secondary visual network; F) cerebellar network; G) right central executive network; H) auditor network; I) executive control network; J) left central executive network. Because right and left central executive networks were captured as one independent component in PET data, G and J for FDG-PET are the same. Adapted with permission from Savio et al. (2017).

1.4.2. Resting State Network Impairments in Dementia

Based on FDG-PET, AD typically demonstrates bilateral hypometabolism within the PCC and anterior and mesial temporal lobes. However, asymmetry in hypometabolism is often present (Lameka et al. 2016). Due to the reduced activity within the PCC, a core region within the DMN, Greicius et al. (2004) hypothesized an impaired DMN connectivity in AD compared to healthy subjects (HS) measured with rsfMRI. In fact, the authors and many following studies observed that the connectivity of the DMN is impaired in AD. For other NCN, heterogeneous results have been reported (for a review see Hohenfeld et al. (2018)).

Based on FDG-PET, bvFTD typically demonstrates hypometabolism in the frontal and anterior temporal lobes. Equivalent to AD, asymmetry in hypometabolism are often present (Lameka et al. 2016). Studies on functional RSN connectivity alteration in bvFTD are less common than in AD. However, a common finding is an impaired SN (Caminiti et al. 2015; Farb et al. 2013; Filippi et al. 2013; Trojsi et al. 2015; Zhou et al. 2010). Inconsistent results have been reported for the DMN. Here, observations of an increased (Farb et al. 2013; Rytty et al. 2013; Trojsi et al. 2015; Zhou et al. 2010) and decreased DMN connectivity in bvFTD (Farb et al. 2013; Filippi et al. 2013) have been reported. Whitwell et al. (2011) reported an increased connectivity within parietal DMN regions and decreased DMN connectivity in lateral temporal and medial prefrontal areas.

A direct comparison of RSN connectivity alterations between AD and bvFTD with the aim to identify biomarkers for differential diagnoses has been performed less often. Filippi et al. (2013) and Zhou et al. (2010) both report a decreased SN in bvFTD compared to AD. While Filippi et al. (2013) do not report impaired DMN connectivity between both patient groups, Zhou et al. (2010) report an increased parietal FC of the DMN in bvFTD compared with AD.

No study so far investigated metabolic RSN connectivity alterations between AD and bvFTD.

1.5. Non-Pharmacological Interventions

As mentioned above, no cure has been found yet to treat either AD or bvFTD. Both diseases are characterized by a progressive increase of neuronal death and cognitive

decline. For AD, the most applied pharmacological intervention tackling cognitive symptoms are Cholinesterase inhibitors. However, the effectiveness of this drug is under debate as it does not stop cognitive decline and shows adverse side effects (Sharma 2019). For bvFTD no U.S. Food and Drug Administration approved pharmacological treatment exists (Hu et al. 2010; Manoochehri and Huey 2012). Still, psychiatric medications are given to decrease the behavioural symptoms of bvFTD (Manoochehri and Huey 2012).

Due to the limited availability of pharmacological treatments in dementia, a range of non-pharmacological interventions aiming to improve the patient's quality of life and/or slow down the rate of cognitive decline have been suggested (Berg-Weger and Stewart 2017). Cognitive training (CT) is hereby a widely used application which exercises one or multiple cognitive domains to improve cognitive functioning. CT ban be computer or non-computer based and is often adaptive, allowing an increase in task difficulty as performance increases (Huntley et al. 2015). CT can lead to a performance improvement in the trained task but also generalised improvements in non-trained tasks. While the former is called practice effect, the latter are called transfer effects (Vianin 2016; Zelinski 2009). Transfer is categorized through its "distance" from the trained tasks; the more similar the transfer task to the training task, the "nearer" the transfer. Hereafter, I refer to cognitive improvements in the trained task as practice effects (Chen, Kuo, and Wang 2019; Jolles et al. 2010), whereas improvements in contextually very similar tasks are nearest (also known as direct) transfer effects, followed by near, and far transfer effects, where the training improves performance in another cognitive domain. Especially far transfer effects are a desirable outcome following CT as they could manifest in improved skills for daily functioning (Jobe et al. 2001). Specifically, working memory (WM) training became increasingly popular and a core feature in many CT programs (Hill et al. 2017). Reason for the popularity lays in the fact that WM is linked to attention and executive functioning skills (Holdnack et al. 2019) which are commonly impaired in dementia (Silveri et al. 2007), including bvFTD (Moreira et al. 2017) and AD (Guarino et al. 2019). Thus, the aim of WM training in dementia is to increase, prevent deterioration or slow down the decline of cognitive performances. However, it is to mention that only subjects with a beginning cognitive decline, as subjects with a MCI, are eligible for CT. In case of a full blown dementia such as AD, CT represents a too difficult task for the patients as the cognitive impairments is too sever at this stage.

In the following, I will first describe WM as a cognitive system followed by a brief discussion why WM training became a popular tool to train cognitive functioning in both healthy subjects and patients with dementia.

1.5.1. Working Memory

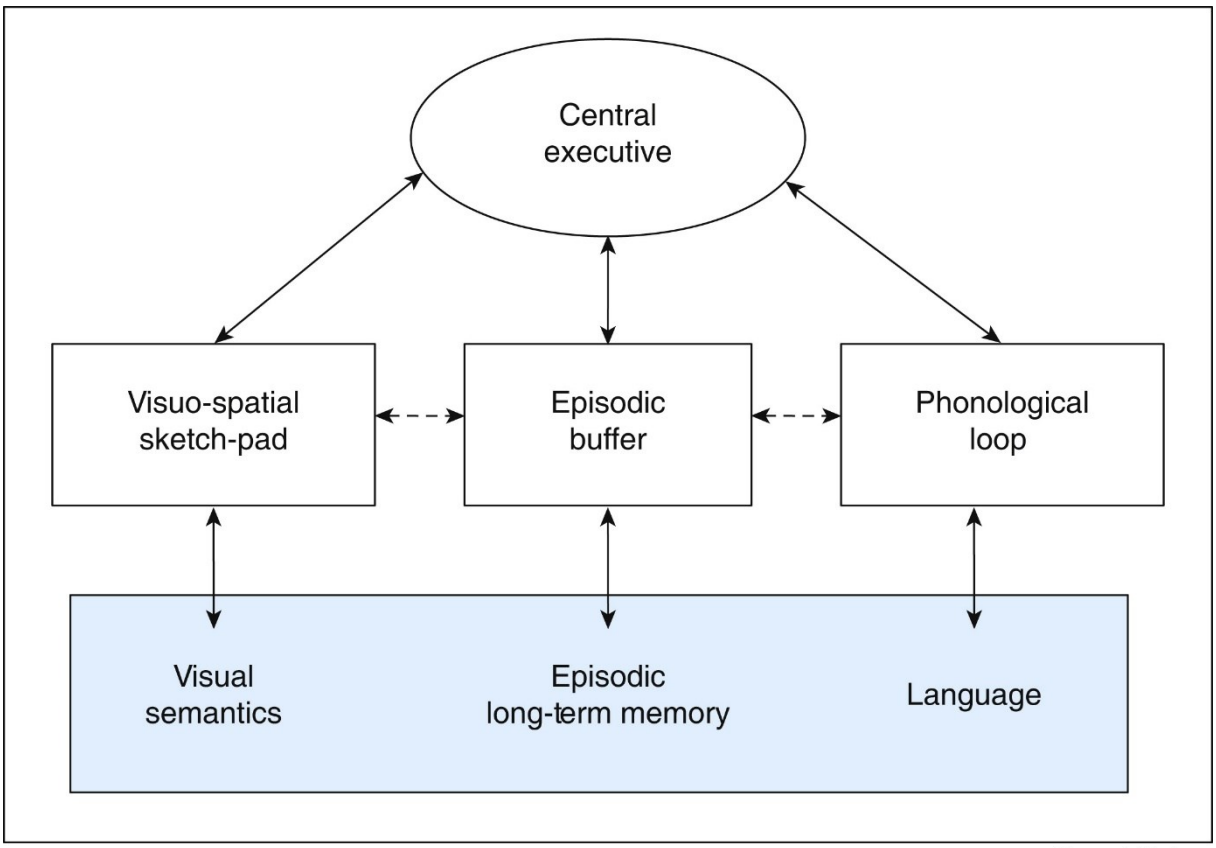
Working memory is a theoretical construct aiming to explain how we process incoming information, identify the nature of them and work with them to drive executive control of goal-directed behaviour (Baddeley 1986) (i.e. solving a cognitive task or correspond in an everyday situation appropriately). However, different theoretical WM models exist (Adams, Nguyen, and Cowan 2018; Chein and Fiez 2010). I will focus on the most prominent model of WM (Chai, Abd Hamid, and Abdullah 2018), the *multicomponent working memory model*. It was originally formulated by Baddeley and Hitch (1974) and over the years underwent further developments (for a review on the development of the current WM model based on the originally formulated model by Baddeley and Hitch, please see Baddeley (2012)).

The *multicomponent working memory model* consists of three components: the *central executive* which involves the attentional control system and two domain-specific "slave systems", namely the *phonological loop* and the *visuospatial sketchpad* for information maintenance. *The phonological loop* represents a temporary storage for spoken and written material (i.e. language) limited in capacity. The *visuospatial sketchpad* represents a temporary storage for visual and spatial material (i.e. visual semantics) limited in capacity. Both slave systems refer to short-term memory (STM). Thus, WM is not completely distinct from STM (Cowan 2008). Baddeley defines STM as the simple temporary storage of information, and WM as a combination of storage and manipulation (Baddeley 2012).

The *visuospatial sketchpad* and the *phonological loop* relate to long-term memory (LTM). Here, LTM delivers knowledge about the nature of information the two systems hold. The retrieved information serves as a base for controlling and regulating the goal directed behaviour forming the *central executive.* The theoretical workspace in which the whole information processing for the *central executive* occurs is called *episodic buffer*. *Episodic buffer* can therefore be seen as a space allowing cross-domain associations in working memory, "such as the retention of links between names and faces" (Cowan 2008). Please

see Figure 3 for a schematic representation of the *multicomponent working memory model* by Baddeley (2010).

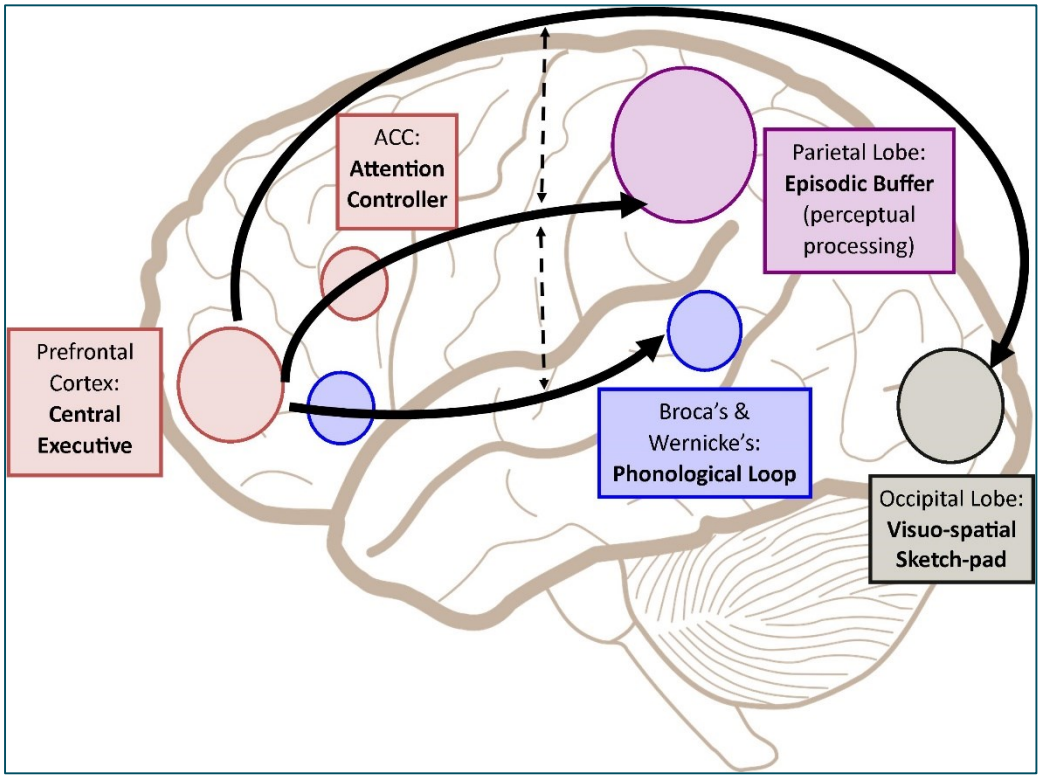
Figure 3: Schematic representation of the multicomponent working memory model (Baddeley 2010)



With permission from Baddeley (2010).

Numerous studies have aimed to decode the WM model to its neuroanatomical location. From a neuroscientific point of view, it became clear that WM cannot be assigned to one single brain region, instead, as other cognitive systems, it relies on functional integration of different brain areas (for a review see Chai et al. (2018)). Figure 4 represents a sketch of Baddeley's *multicomponent working memory model* to specific regions in the human brain (Chai et al. 2018).

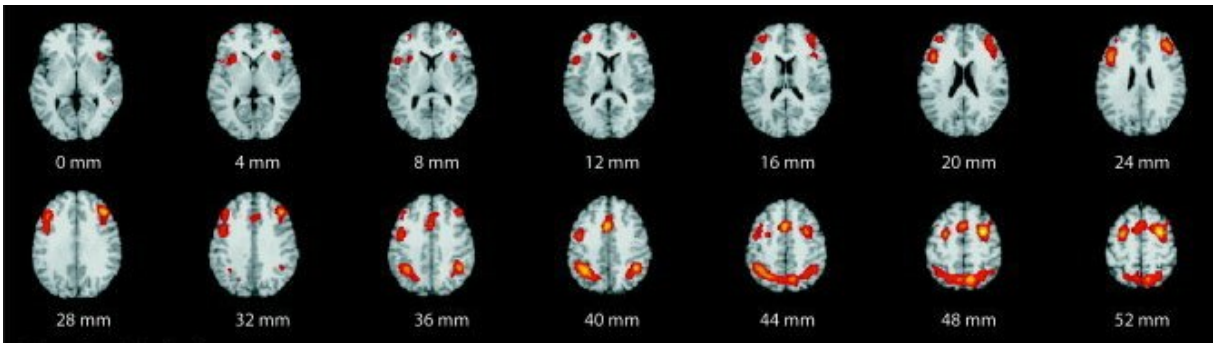
Figure 4: Neuroanatomical representation of working memory (Chai et al. 2018)



ACC, Anterior cingulate cortex. With permission from Chai et al. (2018).

Meta-analysis of task fMRI activations underlying WM revealed consistent activation of frontal and parietal cortical regions representing a great overlap with regions belonging to the CEN (Emch, von Bastian, and Koch 2019; Nee et al. 2013; Rottschy et al. 2012; Wager and Smith 2003). Activated brain regions underlying WM in form of a n-back task (see 4) is shown in Figure 5 from a meta-analysis by Owen et al. (2005).

Figure 5: Meta-analytic activation map for n-back studies (Owen et al. 2005)



"Regions consistently activated across studies are color-coded according to the probability of false discovery (voxelwise P < 0.01; FDR corrected). The right side of each section represents the right side of the brain; the z-coordinate in Talairach space is indicated below each section" (Owen et al. 2005). With permission from Owen et al. (2005).

1.5.2. Working Memory Training

WM, the storage and manipulation of information for goal-directed behaviour, is limited in capacity. However, it is not clear which of the participating components of the *multicomponent working memory model* represents the limiting factor, or if it is a combination of each components' limited capacity forming an overall limited WM capacity (Miller and Buschman 2015). The majority of studies aiming to quantify WM capacity take a descriptive approach, "referring to the fact that people can hold only a limited amount of mental content available for processing" (Constantinidis and Klingberg 2016; Oberauer et al. 2016). It has been shown that the amount of accessible information (i.e. WM capacity) varies considerably between individuals (Wilhelm, Hildebrandt, and Oberauer 2013). And, WM capacity is closely correlated with other high order cognitive functions such as fluid intelligence, abstract reasoning, and reading comprehension (Chooi 2012; Daneman and Carpenter 1980; Fukuda et al. 2010). This association motivated the development of WM training paradigms targeting to increase WM capacity (von Bastian and Oberauer 2014; Chai et al. 2018; Redick 2019; Sala, Aksayli, Tatlidil, Tatsumi, et al. 2019; Soveri et al. 2017; Teixeira-Santos et al. 2019). In this context, performance improvements following WM training were not only seen for the trained task but also in other cognitive tasks. Thus, WM training has been linked to transfer effects which are an index of the putative effectiveness of WM training (Klingberg, Forssberg, and Westerberg 2002). However, the magnitude of nearest, near and far transfer is unclear and heterogeneous results have been reported. Recent meta-analyses reported significantly greater effect sizes for nearest compared to near transfer effects, suggesting that WM training mainly yields task-specific transfer rather than a general cognitive improvement (Sala, Aksayli, Tatlidil, Gondo, et al. 2019; Soveri et al. 2017). However, the main goal of most WM training studies is to produce far transfer effects, which could manifest in improved skills for daily functioning (Jobe et al. 2001), especially for individuals undergoing cognitive decline. Remarkably, even meta-analyses of this topic have yielded contradictory conclusions. Hence, the meta-analysis of Au et al. (2015) reported a small, but significant positive transfer effect on fluid intelligence in healthy young adults. But, subsequent meta-analyses did not find any significant far transfer effects (Melby-Lervåg, Redick, and Hulme 2016; Soveri et al. 2017) when effects of WM training were compared to an active control group, i.e., a group practicing alternative tasks with little WM demands. Along with differences in the classification of cognitive

tasks, training intensity, and type of training task, the presence or absence of an active control group has been proposed as a key factor contributing to the discrepant findings (Teixeira-Santos et al. 2019). Taken together, there is no consensus on the efficiency of WM regarding transfer effects. Understanding the neural correlates underlying these changes could provide additional information on brain plasticity relating to (improved) cognitive functions (Constantinidis and Klingberg 2016). Neural plasticity is a blanket term for acquired or learned changes in neural oscillations, myelin reformation, and synaptogenesis (Chang, Redmond, and Chan 2016; Fuchs and Flugge 2014; Guerra et al. 2019). In the field of learning research, these processes are indirectly measured using neuroimaging methods.

So far, most imaging studies investigating the neural substrates of cognitive gains induced by WM training have used task fMRI. Here, longitudinal study designs analyse brain activation differences between pre- and post-training underlying the WM training task. Thus, many studies focused on neural correlates of practice rather than transfer effects, as reviewed by Constantinidis & Klingberg (2016). However, if transfer exists/occurs, the respective neural correlates should be detectable (i.e. serving as a biological substrate for the change in cognitive performance). On the behavioural level, transfer is categorized through its "distance" between the trained task and the transfer task. But, no definition exists of *neural correlates of transfer* making it difficult to explicitly study those brain activation patterns. In the following, I will present an attempt of categorizing neural correlates of transfer, however, this is a suggestion which has not been empirically validated yet:

Following the same concept as when categorizing transfer tasks, the more similar the brain activation pattern of the transfer task relative to the training task, the "nearer" the transfer. And vice versa, the more different the brain activation pattern of the transfer task relative to the training task, the "further" the transfer. Thus, neural correlates of a transfer task should represent changes in neural activity underlying the same transfer task (due to the WM training; e.g. computed by a pre-/post-training comparison). Neural correlates of transfer could represent changes in spatial extent and/or changes in intensity of neural activation patterns. However, neural activation patterns underlying a variety of transfer tasks are unknown. Thus, determining in a pilot study brain activation patterns for each specific cognitive task would enable to draw ROIs and/or time-series of

interest for each category of transfer. Despite the benefits of this hypothetical approach, the execution of this pilot study would be linked to a huge body of work prior to the actual study. Having said that, another analytical approach investigating brain wide neural activation patterns to identify potential neural correlates of transfer could be a more feasible and attractive option: Due to the link between RSN (i.e. brain wide neural activation pattern) and cognitive performances (Cole et al. 2016), RSN seem to be the ideal substrate to examine neural correlates of transfer. In fact, Ito et al. (2017) showed that RSN topologies predict the information flow for task processing and that task-specific information transfer is coordinated by global hub regions within NCN. These findings strongly argue for the possibility that transfer effects should be reflected by RSN changes. In this regard, ICA represents the means of choice to reliably extract RSN from both rsfMRI and FDG-PET data by a data-driven approach (Calhoun et al. 2001; Savio et al. 2017). Overall, WM training effects on RSN integrity could serve as a potential marker of the efficiency of WM training in regards to transfer effects.

However, only a few studies investigated effects of WM training on the magnitude of intrinsic neural activity at rest (Takeuchi et al. 2017). The authors found increased activity in the right dorsolateral prefrontal cortex, frontopolar area, and medial prefrontal cortex. Only two fMRI studies have investigated functional RSN connectivity changes in relation to WM training (Jolles et al. 2013; Takeuchi et al. 2013). Using *a priori* defined ROIs or networks of interest, these two studies reported connectivity changes, both increases and decreases, within and between regions of the frontal parietal and DMN. Neither of these studies used an active control group nor did their analyses cover the whole brain. Although some FDG-PET studies investigated neural correlates of mental exercise (Förster et al. 2011; Shah et al. 2014; Small et al. 2006), there has so far been no such FDG-PET study in conjunction with WM training. This seems surprising, given that the entire concept of neurometabolic coupling that underlies FDG-PET (Sokoloff 1977) is supposed to be mediated by changes in neuro-glial energy pathways in support of synaptogenesis or synaptic plasticity (for a review see Magistretti (2006)). Taken together, the effects of WM training on RSN are understudied.

In the context of dementia and their known RSN impairments (see above), it is desirable to understand if WM training has the potential to repair or slow down these RSN impairments. However, older people (Park and Bischof 2013) and people suffering from

a neurodegenerative disease (Mesulam 1999) show a reduced and/or altered neuroplasticity. Thus, the efficiency of WM training in terms of magnitude of WM training-induced neural plasticity in NCN should be analysed first in a healthy cohort and ideally in an age group similar to that seen in early-stage dementia. Healthy middle-aged subjects represent the ideal target group to measure WM training effects on NCN to get an estimate whether this CT could serve as a potential non-pharmacological intervention in AD and bvFTD to repair or slow down respective NCN impairments.

2. Aims of the Thesis

The goal of this thesis was twofold. Project one aimed to investigate AD and bvFTD specific NCN integrity alterations. Knowing that rsfMRI and FDG-PET are based on linked but distinct physiological mechanisms of neuronal activity, we analysed NCN integrity alterations based on both neuroimaging methods. Thus, differences in NCN integrity alterations between rsfMRI and FDG-PET were highlighted and their respective use as biomarker for differential diagnosis was evaluated.

Project two aimed to assess the effectiveness of WM training in regards to transfer effects in healthy middle-aged participants – an age group directly preceding or equivalent to that seen in early-stage dementia. Hypothesized transfer effect-related neural plasticity was evaluated in terms of change in NCN integrity between pre- and post-training. Given the multifactorial nature of neural plasticity, NCN integrity values were measured with both rsfMRI and FDG-PET. The additional assessment of an extensive cognitive test battery captured changes in nearest, near and far transfer tasks. An increased WM capacity is known to be correlated with performance in transfer tasks. Thus, the isolation of WM capacity-related transfer effects both on the behavioural and neuroimaging level was achieved by controlling for overall cognitive intervention effects by means of an active control group. Of note, in this thesis I will focus on the analysis and interpretation of the behavioural, rsfMRI and FDG-PET network analysis data conducted in project two. Additional analyses on white matter integrity based on diffusion tensor imaging and voxel-wise FDG-uptake and amplitude of low frequency fluctuations based on rsfMRI data was conducted.

Overall, based on the results achieved by project one and two the thesis discusses if WM training may be a potential non-pharmacological intervention for subjects showing

cognitive decline. The thesis evaluates whether the observations made in project two using healthy middle-aged participants are transferable to early stage dementia patients to discuss the overall question if WM training has the ability to decrease NCN integrity impairments as observed in project one by means of neural plasticity.

3. Project 1: Neurocognitive Network Impairments in Dementia

The current chapter includes the research article “Integrity of Neurocognitive Networks in Dementing Disorders as Measured with Simultaneous PET/Functional MRI”. This article reports NCN integrity impairments in AD and bvFTD. The article was published in *The Journal of Nuclear Medicine* in 2020.

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Contributions:

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The author of this thesis is the first author of this manuscript. TS, VC and IY designed research. OG, JC, DH, JDS, TG and IY collected the data. IR, TS and AS analysed the data. IR, IY and TS wrote the manuscript. All co-authors critically revised the manuscript.

Integrity of Neurocognitive Networks in Dementing Disorders as Measured with Simultaneous PET/Functional MRI

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Functional MRI (fMRI) studies have reported altered integrity of large-scale neurocognitive networks (NCNs) in dementing disorders. However, findings on the specificity of these alterations in patients with Alzheimer disease (AD) and behavioral-variant frontotemporal dementia (bvFTD) are still limited. Recently, NCNs have been successfully captured using PET with ^{18}F-FDG. **Methods:** Network integrity was measured in 72 individuals (38 male) with mild AD or bvFTD, and in healthy controls, using a simultaneous resting-state fMRI and ^{18}F-FDG PET. Indices of network integrity were calculated for each subject, network, and imaging modality. **Results:** In either modality, independent-component analysis revealed 4 major NCNs: anterior default-mode network (DMN), posterior DMN, salience network, and right central executive network (CEN). In fMRI data, the integrity of the posterior DMN was found to be significantly reduced in both patient groups relative to controls. In the AD group the anterior DMN and CEN appeared to be additionally affected. In PET data, only the integrity of the posterior DMN in patients with AD was reduced, whereas 3 remaining networks appeared to be affected only in patients with bvFTD. In a logistic regression analysis, the integrity of the anterior DMN as measured with PET alone accurately differentiated between the patient groups. A correlation between indices of 2 imaging modalities was low overall. **Conclusion:** FMRI and ^{18}F-FDG PET capture partly different aspects of network integrity. A higher disease specificity for NCNs as derived from PET data supports metabolic connectivity imaging as a promising diagnostic tool.

Key Words: Alzheimer disease; frontotemporal dementia; PET; multimodal neuroimaging; resting-state networks

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In the last few decades, resting-state networks (RSNs) have been a hot topic of cognitive and clinical neuroscience. Using resting-state functional MRI (fMRI), abnormalities in so-called neurocognitive networks (NCNs) have been found in numerous neuropsychiatric disorders (*1*). Neurodegenerative diseases, including dementia, are not an exception (*2,3*). In their seminal paper, Greicius et al. (*4*) reported decreased functional connectivity of the default-mode network (DMN) in patients with Alzheimer disease (AD) as compared with healthy subjects. A further study suggested even a differential disruption of network connectivity in dementing disorders. Thus, DMN was reported to be affected in AD, and the salience network (SN) was reported to be affected in behavioral-variant frontotemporal disease (bvFTD) (*5*). However, observations on this topic have been rather inconsistent. For instance, reduced in-phase connectivity with the DMN was found in patients with bvFTD (*6*). Others reported an increased functional connectivity within the frontal networks in AD subjects (*7*). In agreement with these heterogeneous results, the clinical applicability of resting-state fMRI remains limited. Among putative reasons are a low signal-to-noise ratio and a low reproducibility of the findings at a single-subject level (*8*). PET with ^{18}F-FDG is an established clinical tool for early and differential diagnosis of dementing and movement disorders (*9,10*). Although multivariate decomposition of PET data has been successfully applied in both neurodegenerative dementia (*11*) and Parkinsonian syndromes (*12*), RSNs could be identified in ^{18}F-FDG PET data only recently (*13–16*). In particular, our group has found spatially similar RSNs in fMRI and ^{18}F-FDG PET data in the same group of healthy subjects (*15*). The present study addressed the value of ^{18}F-FDG PET in assessing the integrity of NCNs in dementing disorders, in comparison with fMRI. To this end, resting-state fMRI and ^{18}F-FDG PET data were acquired simultaneously in the same group of patients with AD or bvFTD, as well as in healthy controls (HCs). A simultaneous data acquisition allows minimization of variability in RSNs due to different brain states, excitement levels, or moods of the person (*17,18*).

MATERIALS AND METHODS

Subjects

We retrospectively analyzed data from patients who were referred to our center for a PET/MRI examination as part of a diagnostic workup for a suspected neurodegenerative disorder. Only subjects with an expert diagnosis of AD or bvFTD were considered. The expert diagnosis was made by a consensus of at least 2 experienced psychiatrists under consideration of a clinical examination, the results of neuropsychologic and lab testing, imaging results, and cerebrospinal fluid biomarkers. The imaging biomarkers included structural MRI, ^{18}F-FDG PET, and in some cases amyloid PET. The diagnosis of AD was made according to the

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NINCDS-ADRDA (*19*) or NIA-AA (*20*) criteria. In the latter case, the clinical diagnosis of MCI due to AD was supported by AD-typical biomarker findings. BvFTD was diagnosed according to published diagnostic criteria (*21*). Only patients with a Mini Mental State Examination score of at least 18 were included. The group of HCs consisted of individuals without psychiatric and neurologic symptoms and no complaints about cognitive impairment. They were recruited mainly via advertisements in local newspapers.

The study was performed in accordance with the latest version of the Declaration of Helsinki after the consent procedures had been approved by the local ethics committee of the medical faculty at the Technische Universität München. Written informed consent was obtained from all subjects.

Image Data Acquisition

Imaging was performed on a 3-T Siemens Biograph mMR scanner (Siemens Healthineers AG) under standard resting conditions. Structural T1-weighted (magnetization-prepared rapid gradient-echo) images were acquired using a 3-dimensional normal gradient-recalled sequence (repeat time, 2,300.0 ms; echo time, 2.98 ms; 9.0° flip angle) measuring 160 sagittal slices (field of view, 240 × 256 mm; pixel spacing, 1 mm; 256 × 240 scan matrix; slice thickness, 1.0 mm). Resting-state fMRI was performed with the following parameters: repeat time, 2,000.0 ms; echo time, 30 ms; flip angle, 90°; 35 slices (gap, 0.6 mm); alignment to the anterior–posterior commissure covering the whole brain; field of view, 192 mm; matrix size, 64 × 64; and voxel size, 3.0 × 3.0 × 3.0 mm. The PET acquisition ran in parallel for 15 min, starting 30 min after intravenous injection of, on average, 198 MBq (range, 154–237 MBq). The subjects had fasted for at least 6 h before undergoing scanning. Raw ^{18}F-FDG PET data were reconstructed using filtered backprojection and an isotropic Hamming filter (5 mm in full width at half maximum). Attenuation correction was performed using a default Dixon MRI sequence.

Image Preprocessing

The image data were preprocessed mainly using SPM12 (Wellcome Trust Center for Neuroimaging). After segmentation, T1-weighted images were spatially normalized into the Montreal Neurologic Institute space. Echo-planar images were slice-time–corrected, realigned, coregistered to the subject's specific T1-weighted images in Montreal Neurologic Institute space, and band-pass–filtered (0.01 and 0.08 Hz). The first 3 images (6 s) of each subject's fMRI data were discarded to allow for equilibration of the magnetic field. In addition, a component-based noise correction (aCompCor) (*22,23*) based on cerebrospinal fluid signal was applied. The applied preprocessing pipeline is available as an open-source software tool (https://github.com/neurita/pypes/tree/v0.2.1) (*24*). ^{18}F-FDG PET images were spatially normalized to the Montreal Neurologic Institute space using a study-specific ^{18}F-FDG PET template and smoothed with a gaussian kernel of 8 mm in full width at half maximum, in analogy with fMRI data. No correction for partial-volume effects was applied. First, a uniform method for fMRI and ^{18}F-FDG PET data does not exist; different methods may have biased the results in favor of one imaging modality (*25*). Second, our analyses focused on larger cortical structures (networks), and patients with only mild disease, in whom relevant atrophy is unlikely, were included.

Analyses of Motion Artifacts

To minimize a negative methodologic bias toward fMRI data, particular attention was paid to potential motion artifacts. A Rapidart ArtifactDetect algorithm from NiPype (*26*) was used for signal nuisance correction by regressing out motion and intensity artifacts, if present (*27*). The tool computes the movement of the center of each face of a cuboid centered around the head and returns the maximal movement across the center. It is also implemented in Artifact Detection Tools (http://web.mit.edu/swg/software.htm). The following measures were recorded: total number of volumes that are affected by movement (motion outliers), maximum norm of the movement vector (maximum norm), and the SD of the movement norms of the subjects. Four patients with AD, 5 patients with bvFTD, and no HCs were discarded from further analyses because of significant movement. This was defined as more than 30 motion outliers, a maximum norm larger than 4 mm, or an SD larger than 1 mm.

Independent-Component Analysis (ICA)

To extract RSNs, a spatial ICA was applied independently to fMRI and PET data. Individual-subject fMRI time-series images were concatenated for the group ICA (*28*). A concatenation of 1 mean PET image per subject was used for the group ICA (*13–15,29*). We applied a 30-component ICA model for both imaging modalities. This intermediate model order ($n = 30$) was chosen to extract robust spatial maps, preventing coherent RSNs from being split into several subnetworks (*30–32*). In view of the known perturbations in NCNs in dementing disorders, we a priori focused analyses on the following networks of interest: DMN, SN, and central executive network (CEN). Following previous studies, the primary visual and auditory networks were chosen as reference networks, as they are supposed to be unaffected in AD and bvFTD, at least at a clinically mild disease stage (*33,34*). In both imaging modalities, relevant spatial maps were selected using a spatial correlation with established functional templates (*32*).

We used the GIFT toolbox (version 3.0a; Medical Imaging Analysis Lab, The Mind Research Network; http://mialab.mrn.org/software/gift). Basically, ICA attempts to decompose the linearly mixed signals from the temporal dimension into independent spatial sources, which are maximally independent non-Gaussian signals. As a first step of subject-specific data whitening and reduction, a principal-component analysis is performed. After this, we applied a group data reduction step retaining the number of principal components defined using the expectation-maximization algorithm to avoid prohibitive memory requirements (*35*). Aggregate spatial correlation maps are estimated as the centrotypes of component clusters to reduce sensitivity to initial algorithm parameters.

Indices of Network Integrity

In both imaging modalities, subject-specific spatial maps and time courses were estimated with a group-ICA3 back-reconstruction method, consisting of a 2-step multiple regression (*36*). This method is based on a principal-component analysis compression and projection (*28,37*). To derive individual indices of network integrity for fMRI data, a spatiotemporal regression—also called dual regression—was computed against group-based maps (*38,39*). For PET data, we computed so-called loading coefficients, a degree of component (RSN) expression in individual subjects (*28,29*). A conceptually equivalent representation underlies network integrity measures of both imaging modalities. Finally, indices of network integrity were available for each subject, network, and imaging modality.

Calculation of Loading Coefficients

ICA is a data-driven method that extracts a set of components from a set of a mixed signal observations. The independent components are orthogonal to each other. Therefore, the different n component signals $s = [s1, s2, \ldots sn]$ are assumed to be independent but linearly mixed in m observations. The generative model $x = As$, where A is the mixing matrix, separates the different signals. Hereby, the elements of A represent the loading coefficients measuring a subject's spatial deviation from an average group-derived component, that is, RSN. Because the extracted components are expressed in individual subjects to a different degree, the mixing matrix entries (elements of A), that is, the loading coefficients or integrity values, represent the spatial overlap between every subject's specific RSN and the equivalent group-based

RSN (*28,29*). Loading coefficients around 0 represent a strong coherence between the subject-specific and group-based RSNs. For fMRI-derived RSNs, the network integrity is quantified as the multiple (spatiotemporal) regression coefficient between a given group-derived RSN and the equivalent subject-specific RSN. Regression values around 1 represent a strong coherence between the subject-specific and group-based RSNs.

White Matter Hyperintensities (WMH) and Hemorrhages

The results of network analyses prompted us to perform additional post hoc analyses. First, we quantified a volume of WMH on T2-weighted fluid-attenuated inversion recovery images (*40*). Second, we assessed the presence of eventual hemorrhages as an index of sporadic cerebral amyloid angiopathy (CAA). To this end, an experienced neuroradiologist read T2*-weighted images for CAA according to established criteria (*41*).

Statistics

Integrity indices were compared between the groups independently for each modality using ANOVA with a post hoc 2-sample *t* test. A *P* value of less than 0.05 Bonferroni-corrected for multiple tests, that is, RSNs of interest, was accepted as the significance level. For explorative reasons, we also present results with an uncorrected *P* value of less than 0.05. A binary logistic regression (stepwise) with resubstitution and cross-validation (leave-one-out classification) was performed to predict the diagnostic status (AD vs. bvFTD) using indices of network integrity (SPSS Statistics, version 22; IBM). An association between the integrity indices of 2 modalities for the same network was tested using a nonparametric Spearman correlation. A nonparametric Mann–Whitney *U* test was applied to test for differences in WMH volume between the groups. A χ^2 test was applied to test for differences in a proportion of subjects with CAA (possible and probable were pooled) among 3 groups. Results were considered significant at a *P* level of less than 0.05.

RESULTS

Subjects

Following the inclusion criteria, 72 subjects were selected for the study. Their demographic characteristics are summarized in Table 1. There was no significant difference in age, sex, or Mini Mental State Examination score between the groups. Thus, no correction for these variables was applied (*42*). The AD group included patients with MCI due to AD ($n = 19$) and dementia due to AD ($n = 10$).

ICA

Figure 1 depicts the RSNs of interest for each imaging modality. In both modalities, the DMN was split into the anterior and posterior networks. Only the right CEN could be identified in PET data. Thus, further analyses focused on the following 6 networks: posterior DMN, anterior DMN, SN, right CEN, primary visual, and auditory.

RSNs of Interest

Figure 2 shows a distribution of the network integrity among the groups for each imaging modality. Each RSN (Fig. 1) was common for all subjects under the study, and network integrity measures were available for every subject. In the ^{18}F-FDG PET data, we observed a significantly lower integrity of the anterior DMN and SN in bvFTD subjects than in AD subjects. The integrity of the posterior DMN was significantly higher in bvFTD subjects than in AD subjects. In comparison to HCs, the integrity of the posterior DMN was significantly lower in AD subjects, and the integrity of the anterior DMN, SN, and right CEN was significantly lower in bvFTD subjects. For fMRI-derived RSNs, we observed a significantly lower integrity of the posterior DMN, anterior DMN, and right CEN in AD subjects than in HCs. In bvFTD subjects, a significantly lower integrity of the posterior DMN than in HCs was found. At a *P* value of less than 0.05, uncorrected, the integrity of each RSN of interest was lower in AD subjects than in HCs.

TABLE 1
Demographics

Demographic	AD	bvFTD	HC	*P*
Total patients (*n*)	29	21	22	—
Sex (*n*)				0.055*
Male	11	15	12	
Female	18	6	10	
Mean age ± SD (y)	64.3 ± 5.8	61.8 ± 9.4	60.4 ± 9.2	0.227†
Mean MMSE ± SD	24.3 ± 3.0	25.5 ± 3.3	Not available	0.660‡

*χ^2 test.
†1-way ANOVA.
‡*t* test.
MMSE = Mini Mental State Examination.

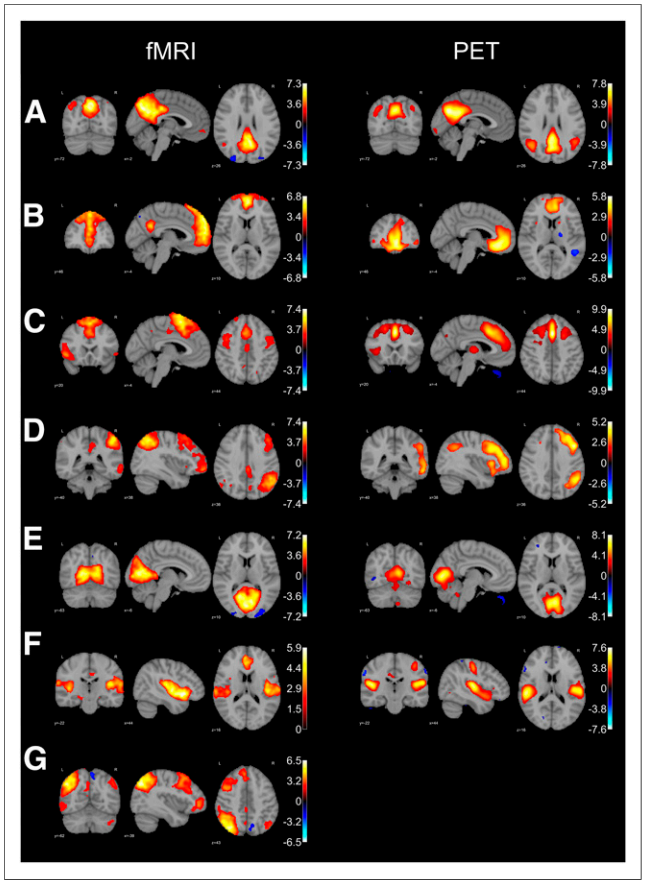

FIGURE 1. RSNs of interest. Overlay is shown of IC maps at threshold of $z > 2.0$ on T1 template in Montreal Neurologic Institute space. Color bar represents z values. (A) Posterior DMN. (B) Anterior DMN. (C) SN. (D) Right CEN. (E) Primary visual. (F) Auditory. (G) Left CEN.

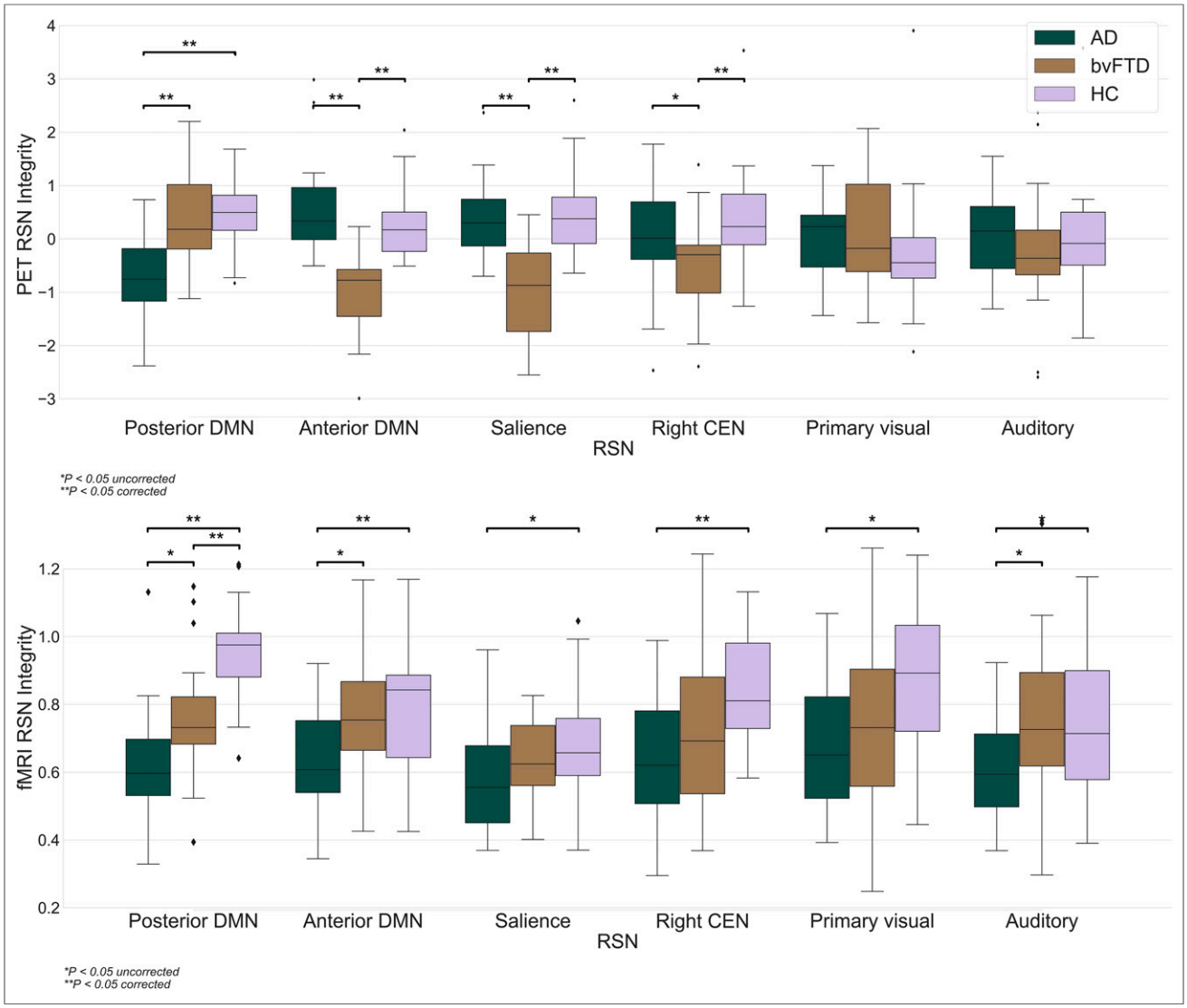

FIGURE 2. Distribution of network integrity indices. Boxes show quartiles of dataset, and whiskers extend to show rest of distribution, except for points that are determined to be outliers using method that is function of interquartile range. *y*-axis indicates spatiotemporal regression for fMRI and loading coefficients for ^{18}F-FDG PET. Both indicate individual degree of network integrity.

Regression and Correlation Analyses

In fMRI data, the integrity indices of the posterior DMN appeared as a single significant predictor of the diagnostic status, providing an accuracy of 64% ($P = 0.017$; sensitivity of 79%, specificity of 43%). In PET data, the anterior DMN was the strongest predictor, with an accuracy of 94% ($P = 0.002$; sensitivity of 97%, specificity of 91%), whereas addition of the SN slightly but significantly increased the accuracy up to 96% ($P = 0.016$; sensitivity of 97%, specificity of 95%). The correlation analyses revealed at best a low within-network–between-modalities correlation, with the highest R (0.33, $P = 0.005$) being for the anterior DMN.

WMH and Hemorrhages

The volume of WMH was 4.8 ± 9.3, 2.6 ± 2.9, and 2.7 ± 3.9 cm^3 in the AD, bvFTD, and HC groups, respectively. There was no statistically significant difference among the groups ($P > 0.05$). T2*-weighted images were available for 25 subjects with AD, all subjects with bvFTD, and 21 HCs. In the AD group, there were 4 subjects with possible and 1 subject with probable CAA. None of subjects with bvFTD appeared to have CAA. In the HC group, possible CAA was diagnosed in 1 subject. The proportion of subjects with CAA was significantly larger in the AD group than in the bvFTD group ($P = 0.03$) but not the HC group ($P = 0.13$). There was no difference between the bvFTD and HC groups ($P = 0.31$).

DISCUSSION

In the present study, we examined the integrity of NCNs in AD and bvFTD subjects using simultaneous resting-state fMRI and ^{18}F-FDG PET. As in our previous work on healthy subjects (*15*), spatially similar RSNs were found in both imaging modalities. In PET data, the integrity of NCNs was differentially affected in the 2 dementing disorders. In fMRI data, all networks of interest showed the lowest integrity in AD subjects and a lower integrity in bvFTD subjects than in HCs. The integrity of the anterior DMN—as measured with ^{18}F-FDG PET—accurately discriminated between the 2 patient groups.

Such a distinction was not possible using the same NCNs from fMRI data.

Whereas ^{18}F-FDG PET is supposed to capture neural or synaptic activity by estimating glucose consumption in terms of neurometabolic coupling (*43*), fMRI measures neural activity less directly, through the amount of oxygen in blood supplying a given brain region (*44*). This so-called neurovascular coupling is based on a complex interplay between local cerebral blood flow, volume, and the cerebral metabolic rate of oxygen (*45*). Thus, the partly different findings in our fMRI and ^{18}F-FDG PET data, as well as a low correlation between integrity measurements of fMRI- and PET-based networks, are not surprising. In particular, we observed a lower integrity across all fMRI-based NCNs plus the primary visual network in both patient groups relative to HCs, with the AD group being consistently more impaired than the bvFTD group. This observation may have both a biologic and a methodologic background. Different neurodegenerative disorders are known to share common pathophysiologic phenomena such as production of toxic oligomers that cause intercellular miscommunication (*46,47*). The toxic effects lead to a dyssynchrony of network activity that may manifest as impaired RSN integrity (*48*). As compared with blood oxygenation level–dependent (BOLD) fMRI, ^{18}F-FDG PET possesses a much lower temporal resolution. A snapshot of ^{18}F-FDG delivery over minutes may be more robust to nonspecific whole brain (e.g., toxic) effects. In addition, ICA on PET data as in the present study identifies brain regions sharing similar ^{18}F-FDG uptake, rather than synchronicity of the BOLD signal fluctuations. Hence, relative to fMRI data, alterations in RSNs in ^{18}F-FDG PET data seem to be driven more by a disease-specific neurodegeneration. In the same vein, and unlike fMRI data, the integrity of reference (non-NCN) RSNs in PET data appeared to be preserved.

As a further finding, the integrity of RSNs in fMRI data was consistently more impaired in the AD group than in the bvFTD one. This finding can be explained by, for instance, a more profound cerebrovascular disease in AD patients, as well by sporadic CAA, which is often associated with AD (*49*). Thus, neurovascular decoupling as measured with fMRI was shown to be associated with the severity of CAA. Hereby, patients with CAA had a lower amplitude of fMRI response within the visual cortex during a visual task than did HCs (*50*). That study also reported a correlation between the impaired fMRI amplitude and a higher WMH volume in CAA patients. A recent study reported a limited reproducibility of functional connectivity networks, particularly in patients with cerebral small-vessel disease (*51*). On one hand, because of vascular lesions, routine pathways of functional connectivity may be at least in part replaced by other, less consistent, routes (*51*). On the other hand, vascular pathology may affect the BOLD hemodynamic response, reducing interregional correlations (*52,53*). Further, altered DMN connectivity was shown to be significantly correlated with WMH burden (*54*), and other studies confirmed the central role of the white matter lesions in disrupting functional connectivity (*55–57*). Our post hoc analyses support this hypothesis. Specifically, patients with AD showed nearly double the WMH of patients with bvFTD and HCs. Yet, apparently because of a high variability in the AD group, the difference was not statistically significant. Furthermore, the proportion of subjects with CAA was higher in patients with AD than in the 2 other groups.

Overall, the pattern of NCN alterations in ^{18}F-FDG PET rather than in fMRI data agrees with the known pathologic changes in AD and bvFTD patients. Thus, a posterior NCN such as the posterior DMN appeared to be affected in AD subjects, whereas anterior NCNs such as the anterior DMN and SN were disturbed in bvFTD subjects. The right CEN, covering both the anterior and the posterior parts of the brain, was affected in bvFTD subjects, in line with the known executive dysfunction in these patients (*58*). The posterior DMN was consistently affected in both modalities; that is, its integrity was significantly lower in AD subjects than in bvFTD subjects or HCs. This observation agrees well with the fMRI literature (*4,59*). However, a significant difference in a test measure does not necessarily mean that this measure is accurate with respect to class prediction or, in clinical terms, with respect to differential diagnosis. To address this issue, we performed a stepwise logistic regression analysis. Among fMRI-based NCNs, the integrity of the posterior DMN appeared to be the only significant predictor of the diagnosis (AD vs. bvFTD), with an accuracy of only 64%. This result is well below the accuracy values of 100% reported by Zhou et al. (*5*). Apart from methodologic differences, the discrepancy can be explained by smaller patient groups (n = 12 each) and by more advanced disease in patients with AD (average Mini Mental State Examination score of 21.2, vs. 24.3 in our study) in the study of Zhou et al. (*5*). As for NCNs extracted from PET data, the integrity of the anterior DMN appeared to be the strongest predictor of the diagnostic status, providing an accuracy of 94%. All other NCNs on their own were significant predictors, too, but with a lower accuracy. In a stepwise logistic regression with all PET-based NCNs, the integrity of the SN slightly improved the discrimination (96% accuracy).

An advantage of our study was the well-characterized and well-matched groups of patients and HCs. Furthermore, the PET and fMRI data were acquired simultaneously, preprocessed, and analyzed in an analogous manner. To minimize a negative bias toward fMRI, we applied a state-of-the-art image analysis, with special attention to the quality control of the fMRI data (e.g., analyses of motion artifacts). As a limitation, our study focused on the established NCNs. However, other networks, such as the limbic network, may also be of relevance in neurodegenerative dementia in general and in bvFTD in particular (*60*). Future studies should address this issue. As a further limitation, the results of the logistic regression were cross-validated using a leave-one-out approach. Thus, they may be too optimistic; a prospective validation in another cohort is essential.

CONCLUSION

Our study provides novel insights into alterations of the established RSNs in AD and bvFTD, supporting metabolic connectivity imaging as a valuable tool in the field of brain connectivity. We propose to establish an atlas of ^{18}F-FDG PET–based RSNs similar to that of Allen et al. for fMRI (*32*). This would allow us to characterize disease-specific connectivity patterns at the metabolic network level (*12*).

DISCLOSURE

Timo Grimmer has received consulting fees from Actelion, Biogen, Eli Lilly, Iqvia/Quintiles, MSD, Novartis, Quintiles, and Roche Pharma; lecture fees from Biogen, Lilly, Parexel, Roche, and Pharma; and grants to his institution from Actelion, Novartis, and PreDemTech. Igor Yakushev has received consultant or lecture fees from Blue Earth Diagnostics, ABC-CRO, and Piramal. No other potential conflict of interest relevant to this article was reported.

KEY POINTS

QUESTION: What is the value of altered network integrity—as measured with ^{18}F-FDG PET and fMRI—in dementing disorders?

PERTINENT FINDINGS: The pattern of network alterations differed between the modalities, with the fMRI-based NCNs showing a generally lower disease specificity. The integrity of the anterior DMN as measured with PET alone accurately differentiated between patients with mild AD and bvFTD dementia.

IMPLICATIONS FOR PATIENT CARE: A higher disease specificity of NCNs as derived from PET data supports metabolic connectivity imaging as a promising diagnostic tool.

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4. Project 2: Effects of Working Memory Training on Neurocognitive Networks

The current chapter includes the research article “A comprehensive cognitive and neuroimaging study of transfer effects due to working memory training”. This article reports working memory training effects in middle aged healthy participants on the behavioural and neuroimaging level.

Contributions:

Isabelle Ripp, Monica Emch, Qiong Wu, Aldana Lizarraga, Claudia C. von Bastian, Kathrin Koch, Igor Yakushev

The author of this thesis is the shared first author of this manuscript together with ME. IY, CCvB, KK and ME designed research. IR and ME collected the data. IR analysed fMRI, and FDG-PET data. ME analysed behavioural data, together with AL DTI data, and preprocessed fMRI data. QW analysed voxel-level fMRI and behavioural data. IR and ME wrote the manuscript. All co-authors critically revised the manuscript.

A comprehensive cognitive and neuroimaging study of transfer effects due to working memory training

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Abstract

Despite growing interest in cognitive interventions from academia and industry, it remains unclear if working memory (WM) training, the most established cognitive intervention, produces transfer effects. We administered an 8-week adaptive *n*-back training to 55 healthy middle-aged participants, followed by an extensive test battery. State-of-the-art multimodal neuroimaging was used to search for potential anatomic and functional changes. This prospective, randomized, controlled, and single blind study offers the most thorough assessment of WM training effects hitherto reported. Compared to active controls, no near or far transfer effects were detected. Equivalently, no training-related changes in diffusion tensor imaging, resting state functional magnetic resonance imaging, and positron emission tomography data were observed. Posthoc tests revealed that practice effects on untargeted cognitive domains conditioned apparent transfer effects sometimes reported in the literature. While improving WM capacity, WM training produces no transfer effects at the behavioral level or in terms of neural structure and function.

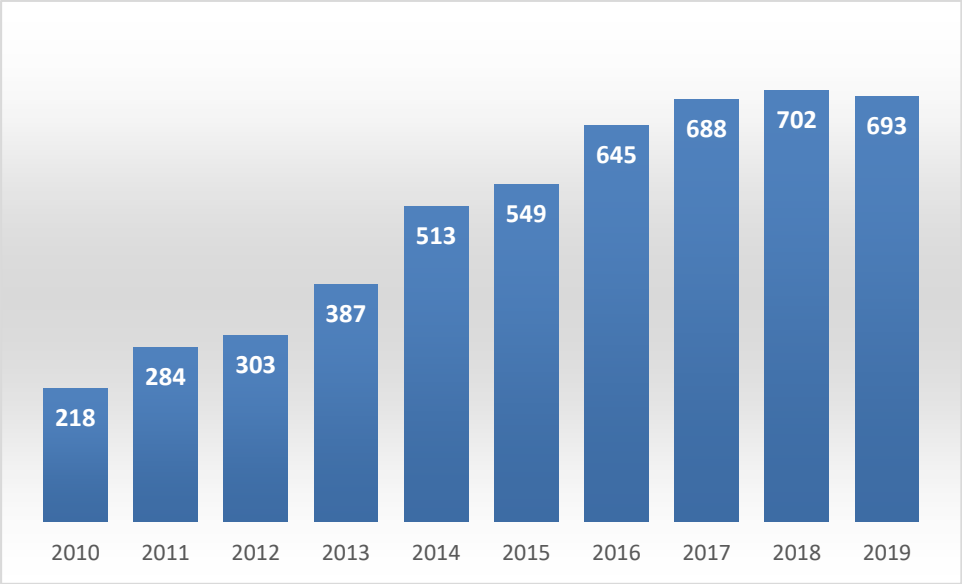
Keywords: Working Memory Training, Neural Plasticity, Transfer Effects, Resting State Networks, FDG-PET, Multimodal Neuroimaging

Introduction

Working memory (WM) is the ability to retain temporary access to a limited amount of information in the service of ongoing cognitive processing [1]. The amount of accessible information is determined by WM capacity, which varies considerably between individuals [2]. As such, WM capacity is closely correlated with other high order cognitive functions such as fluid intelligence, abstract reasoning, and reading comprehension [3,4]. This association motivated the development of cognitive tasks targeting WM capacity [5–10]. In the context of WM training, the concept of cognitive transfer effects is of key importance. Transfer effects are phenomena whereby training a particular task (e.g., WM task) leads to improved performance in other cognitive tasks (e.g., increased WM capacity). Thus, the transfer effects are an index of the putative effectiveness of WM training [11]. Transfer is categorized through its "distance" from the trained tasks; the more similar the transfer task to the training task, the "nearer" the transfer. Hereafter, we refer to cognitive improvements in the trained task as practice effects [12,13], whereas improvements in contextually very similar tasks are nearest (also known as direct) transfer effects, followed by near, and far transfer effects, where the training improves performance in another cognitive domain. Recent meta-analyses reported significantly greater effect sizes for nearest compared to near transfer effects, suggesting that WM training mainly yields task-specific transfer rather than a general improvement in WM [8,14]. However, the main goal of most WM training studies is to produce far transfer effects, which could manifest in improved skills for daily functioning [15], especially for individuals undergoing cognitive decline. Remarkably, even meta-analyses of this topic have yielded contradictory conclusions. Hence, the meta-analysis of Au et al. [16] reported a small, but significant positive transfer effect on fluid intelligence in healthy young adults. However, subsequent meta-analyses did not find any significant far transfer effects [8,17] when effects of WM training were compared to an active control group, i.e., a group practicing alternative tasks with little WM demands. Along with

differences in the classification of cognitive tasks, training intensity, and type of training task, the presence or absence of an active control group has been proposed as a key factor contributing to the discrepant findings [9]. Despite the lack of clear evidence for far transfer effects even in healthy young populations, the number of WM training studies is increasing from year to year, see figure 1. The indication now extends to the elderly healthy and as remediation for cognitive impairment [18–22]. Moreover, WM training is a common component of cognitive training programs that attract an increasing attention of major industry [23].

Figure 1: Number of studies published annually in the past decade as retrieved from PubMed using key words « "working memory", training ».



Given the inconsistent literature, it seems worthwhile to capture the process of WM learning not only through cognitive performance, but also in terms of neural plasticity. Indeed, neuroimaging might depict evidence of neural plasticity that precedes measurable changes in cognition [24]. Furthermore, recording neuroimaging and cognitive changes induced by the same activity (i.e., WM training) allows testing for associations between different indices, which can improve the robustness of findings. Neural plasticity is a blanket term for acquired or learned changes in neural oscillations, myelin reformation, and synaptogenesis [25–27]. In the field of learning research, these processes are indirectly measured using functional magnetic resonance

(fMRI), diffusion tensor imaging (DTI), and positron emission tomography with F18-fluordesoxyglucose (FDG-PET), respectively. Needless to say, the different forms of neural plasticity occur simultaneously, and the neuroimaging methods give only rough proxies of these changes at the macroscopic level [28]. Because it is still unknown which neuroimaging modality is most sensitive to learning-induced neural plasticity, we followed an exploratory multi-modal approach in this study.

So far, most imaging studies of the neural substrates of cognitive gains induced by WM training have used task fMRI. However, many such studies focused on neural correlates of practice rather than transfer effects, as reviewed by Constantinidis & Klingberg [29]. Moreover, to the best of our knowledge, only one study has investigated effects of WM training on the magnitude of intrinsic neural activity at rest [30]. The authors found increased activity in the right dorsolateral prefrontal cortex, frontopolar area, and medial prefrontal cortex. Recently, the focus of neuroimaging studies has moved from voxel-wise analyses of signal amplitude to network-wise analyses. In particular, so called resting state networks (RSN) are drawing considerable attention in neuroscience research [31]. However, only two fMRI studies have investigated resting state functional connectivity changes in relation to WM training [32,33]. Using *a priori* defined ROIs or networks of interest, these two studies reported connectivity changes, both increases and decreases, within and between regions of the frontal parietal and the default mode network (DMN). Neither of these studies used an active control group nor did their analyses cover the whole brain. Similarly, only a few studies have investigated changes in structural connectivity, i.e., neural tracts, following WM training [34–36]. Results indicated training-associated changes in frontal and parietal white matter tracts [35] or the corpus callosum [34]. Takeuchi et al. [36] reported that WM training increased the mean diffusivity in regions of the dopaminergic system. Although some FDG-PET studies investigated neural correlates of mental exercise [37–39], there has so far been no such PET study in conjunction with WM training. This seems surprising, given that the entire concept of neurometabolic coupling that underlies

FDG-PET [40] is supposed to be mediated by changes in neuro-glial energy pathways in support of synaptogenesis or synaptic plasticity (for a review see Magistretti [41]).

Thus, the goal of this study was to investigate effects of an 8-week adaptive *n*-back training in healthy middle-aged subjects. We chose the n-back training because it is regarded as one of the most applied forms of WM training [8]. More importantly, a meta-analysis reported a trend for n-back being the most efficient WM training [17]. We chose this age group due to its potential clinical relevance. Specifically, middle age directly precedes aging that is associated with a number of neurodegenerative disorders such as Alzheimer's disease. Thus, should the current WM training program prove effective, it might serve as an intervention in older subjects to delay subsequent age- or disease-associated cognitive decline. Furthermore, healthy middle-aged subjects typically have no significant atrophy or vascular pathology that might otherwise interfere with WM-related neural plasticity [42]. We applied state of the art hybrid PET/MRI equipment for simultaneous acquisition of MRI and PET data at baseline and after WM training. All neuroimaging data were analysed at the whole brain level using both voxel- and network-wise approaches.

Methods and Materials

Subjects

The study was approved by the Federal Office for Radiation Protection and the local ethics review board. Participants were recruited via advertisements in the internet and on hospital bulletin boards. The subjects were right-handed, in the age range 50 – 64 years, free of cognitive deficits, neurological or psychiatric diseases. Further inclusion criteria were absence of contraindications for MRI and no brain anomalies on structural MRI images. All participants provided written, informed consent. They were randomly assigned single-blinded to an experimental or an active control group. Among initially recruited subjects 7 were excluded: two due image artefacts from large falx ossifications on MRI, one due to an excessive head

motion, one due to a failure to follow the training program; imaging data of two subjects were saved incompletely; one participant dropped out for private reasons after the first neuroimaging session. Finally, data of fifty-five participants (30 males) with a mean age of 55.9 years (SD: 4.2 years) were available for further analyses: 28 in the experimental and 27 in the active control group.

Working memory training

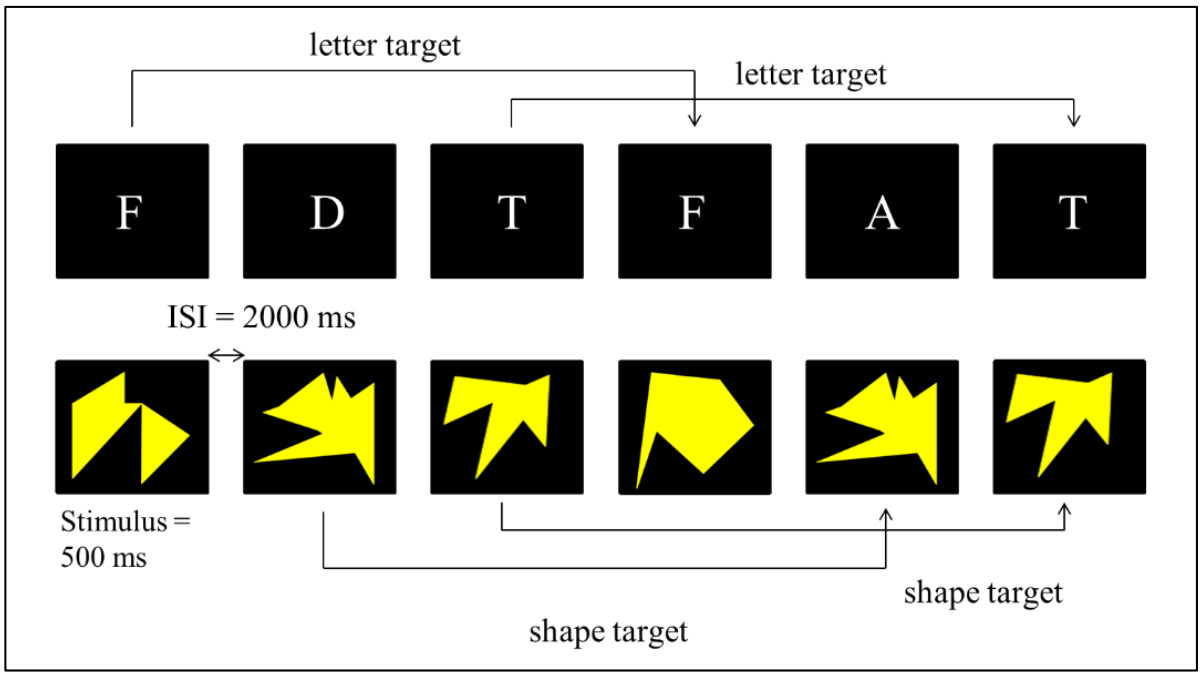
All participants underwent supervised training on a personal computer at home using a visual and verbal *n*-back task. Hereby, the participant had to identify a target stimulus out of a sequence of shown ones. The target stimulus corresponds to a stimulus shown *n* positions back (figure 4). Each stimulus was presented for 500 ms followed by a 2000 ms long interstimulus interval. The participants were instructed to use the key "A" as a response button to identify target stimuli. Pressing the key counted as a "hit" and a "false alarm" during target and non-target trials, respectively. Not pressing it counted as a "miss" and a "correct rejection" during target and non-target trials, respectively.

The experimental group performed an adaptive *n*-back paradigm for visual and verbal tasks adapted from Jaeggi et al. [43]. The training consisted of 9 blocks per task type, resulting in a total of 18 training blocks per session. Each block was designed to include a randomised sequence of 6 targets and 14 non-target trials. The *n*-back level was adapted to the participant's performance based on a summed score of misses (i.e. undetected target) and false alarms (i.e. incorrectly detected target). Herewith, the *n*-back level increased for a subsequent block if more than 90 % of correct responses were given, and it decreased if less than 80% of correct responses were given. If correct responses were in between, the *n*-back level remained the same. The adaptive level of *n* ranged from 1-back to a maximum difficulty level of 9-back. Only one subject reached the 9-back level, indicating the absence of ceiling effect at the group level.

The active control group performed non-adaptive low level visual and verbal *n*-back training (i.e., 1-back verbal task and X-back visual task), using equivalent stimuli. The X-back task is a purely attentional task, in which participants must press the "A" key whenever the target shape is presented. The same target shape for visual X-back was shown at the beginning of every X-back block throughout the entire training. Per training session, the active control group completed 9 blocks of 20 trials of the visual X-back task and 21 trials of the verbal 1-back task each. The structure of the blocks was the same as for the experimental group, i.e., 6 target and 14 non-target trials.

The order of tasks trained (visual or verbal *n*-back) was counterbalanced between subjects in each group. A training session took approximately 20 minutes. The participants were instructed to complete four training sessions per week and one training session per day. After each training session, logfiles were automatically uploaded to the Millisecond Software website (https://www.millisecond.com/). Based on information saved in the logfiles, a weekly training progress report was sent via email to all participants.

Figure 2: Example of a verbal 3-back level (top) and a visual 3-back level (bottom).



ISI, interstimulus interval

Cognitive test battery

A test battery was administered one week before the start and one week after the end of the WM training intervention. Before the first cognitive assessment, each task was explained by an experimenter, and the participants practiced a short version of the task in the presence of the experimenter. Cognitive testing lasted approximately 80 minutes. To assess nearest transfer effects, the following three tests were used: Digit Span test for verbal WM (forward and backward version; subtest from HAWIE-R) [44], Simple Visual Reaction Time (SVRT) task for motor response velocity and attention [45], and the Corsi-Block Tapping test for visual WM [46]. Performance assessment was based on scores for each subtest for the Digit Span test, the mean latency value for the SVRT task, and the achieved block span for the Corsi-Block Tapping test [47]. The near transfer effects were investigated using a VST [48] and the Color Word Stroop task (CWST) [49]. For both interference tasks, we calculated correct responses for incongruent and congruent trials separately. In addition, a short-term memory task Verbaler Lern- und Merkfähigkeitstest – VLMT [50] and a Rapid Visual Information Processing (RVIP) task to investigate sustained attention [51] were employed. For the VLMT, we analysed three dependent variables: the difference in the number of correct answers between the recall before and after presentation of the interference list (Dg5-Dg6), the difference in the number of correct answers between the recall before and 20-30 minutes after presentation of the interference list (Dg5-Dg7), and the scores from the Word Recognition List (WR). For the RVIP, we analysed the proportion of correct target detections. To assess far transfer effects, we used a short version of the Raven's Advanced Progressive Matrices Test (short-APM) [52], and the Iowa Gambling Task [53], which assess fluid-intelligence and decision-making, respectively. Performance in the short-APM was scored by the number of correct responses, whereas the Iowa Gambling Task was ranked by the net score (good play – bad play). The Digit Span task and VLMT were orally presented, whereas the other tests were administered by PC with an in-house adaptation of the Millisecond website test library (Inquisit 5; retrieved from: https://www.millisecond.com). The

short-APM was coded in the Inquisit programming language. Digit Span forward requires the subject to repeat numbers in the same order as presented by the examiner. A minimum length of three and a maximum length of nine digits is presented. Digit Span backward requires the subject to repeat the digits in the reverse order as presented by the examiner. Here, a minimum of two and a maximum of eight digits is presented. The number of digits increases when the participant correctly repeats at least one out of two trials.

Imaging data acquisition

Imaging data were acquired on a 3T hybrid PET/MR Siemens Biograph mMR scanner with a vendor-supplied 16-channel head coil. The subjects were instructed to fast for six hours prior to each of two PET/MR sessions. Around 100 MBq FDG were injected intravenously to participants sitting in a quiet, dimly lit room, after confirming normal blood glucose levels. The following MR sequences were acquired over the first 30 min of imaging (i.e., 30– 60 min p.i.): localizer, μ-map, structural T1-weighted, FLAIR, echo-planar imaging (EPI) 2D diffusion for diffusion tensor imaging (DTI) and EPI- Prospective Acquisition Correction sequence for resting state functional MRI (rsfMRI). For rsfMRI participants were instructed to close their eyes and think of nothing in particular. Task-fMRI was acquired 60 to 90 min p.i. For each subject we reconstructed a single frame FDG-PET summation image for 30-60 min p.i. Detailed parameters of PET acquisition and MR sequences are described in Supplementary Material. The same imaging protocol was used in both sessions. The presence of significant microangiopathic lesions and incidental findings were excluded upon visual assessment of structural MRI images.

Experimental design and statistical analyses

Imaging data analysis

All DICOM neuroimaging data was converted to 3D-NIFTI volumes using the dcm2niix tool (https://github.com/neurolabusc/dcm2niix), expect for fMRI data, for which we used dm2nii. FMRI and FDG-PET data were pre-processed using SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) and MATLAB v2017b (The MathWorks Inc., Natick, Massachusetts, USA). DTI data was pre-processed using the University of Oxford's Centre for Functional Magnetic Resonance Imaging of the Brain Software Library (FSL) version 6 (http://www.fmrib.ox.ac.uk/fsl/index.html). PET images were spatially normalized into the MNI space using a study-specific FDG-PET template, followed by smoothing with an 8 mm isotropic Gaussian filter. The first three images of the fMRI data were discarded. FMRI data preprocessing included motion correction, coregistration of the subjects' T1-weighted image to the functional images, spatial normalization to MNI space using DARTEL [54] and smoothing with an 8 mm isotropic Gaussian filter. Excessive head motion was defined as translation > 3 mm or rotation > 3° [55,56].

The Amplitude of Low Frequency Fluctuations (ALFF) analysis was carried out using Data Processing Assistant for Resting-state fMRI (http://rfmri.org/dpabi) [57] and SPM12. The pre-processed and smoothed rsfMRI data (see above) were further processed using linear de-trending, nuisance regression (i.e., white matter signal, cerebrospinal fluid signal, 6 motion parameters and their first derivatives) and band-pass filtering (0.01 – 0.08 Hz) to remove low-frequency drifts and other high-frequency physiological noises. Then, ALFF maps were calculated as described in previous studies [58,59]. In brief, the filtered time series were transformed into the frequency domain with fast fourier transform. Then, the square root of the power spectrum was computed and averaged at each voxel.

Following a visual inspection, passed DTI images were corrected for susceptibility induced distortions, eddy currents, subject movement and signal dropout using the tool Eddy [60]. Brain

tissue was derived using the brain extraction tool [61]. Images of four subjects, three experimental and one control, had to be excluded from further DTI analyses due to an incorrect phase encoding direction. To obtain eigenvalues L1 (axial diffusivity, AD), L2, and L3 with corresponding eigenvectors, as well as maps of fractional anisotropy (FA) and mean diffusivity (MD), a diffusion tensor model was fitted at each voxel using FSL's DTIFIT https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT. Additionally, radial diffusivity (RD) maps were created by averaging the L2 and L3 maps. Individual FA maps were spatially normalized to the MNI152 standard space. A mean FA map was used to compute an average white matter tract skeleton using a threshold of FA > 0.2. Finally, Tract-Based Spatial Statistics as implemented in FSL was conducted for FA, MD, AD and RD maps [62].

Independent component analysis

We applied a spatial independent component analysis (ICA) [63] to the rsfMRI data and a spatially constrained ICA to the FDG-PET data using GIFT toolbox v3.0b (Medical Imaging Analysis Lab, The Mind Research Network; http://mialab.mrn.org/software/gift). Individual subject fMRI time-series images were thus concatenated for the group ICA using the Infomax algorithm [64]. We chose a 30 component ICA model, as previous studies have shown that this intermediate model order delivers robust and coherent RSNs [65–67]. We applied the resulting spatial maps as reference templates for the spatially constrained ICA applied to the FDG-PET data. Hereby, a concatenation of one PET image per subject was used for the group ICA [68–71], while employing the same brain mask as for fMRI ICA. For further details on the spatially constrained ICA for FDG-PET data see Supplementary Materials. We focused our analyses on the following (neurocognitive) networks of interest *a priori*: anterior and posterior DMN, salience network (SN), and left and right central executive network (CEN). The auditory network was chosen as a reference network, as this was assumed to be unaffected by visual and verbal *n*-back training.

Indices of network integrity

Network integrity indices were calculated both for rsfMRI- and FDG-PET-based RSNs. For rsfMRI data, we calculated a multiple regression against the group-derived component maps using the function "icatb_multipleRegression" provided by GIFT toolbox. This analysis returned the beta-coefficient (β) value for each component of interest in each subject, reflecting the degree to which the spatial pattern of each subjects' particular network explained the spatial pattern of the equivalent group derived network. For this computational step, a z-threshold of 1 for the reconstructed subject specific component maps was applied. This procedure has been conducted before [72] and in a similar way [73]. For FDG-PET data, we extracted the so-called loading coefficients [71,72]. These are the mixing matrix entries of A from the generative model x = As, which separates the different signals [74,75]. The values were read out from the estimated "timecourse" file with each timepoint representing one subject (see above). Herewith, loading coefficients close to zero represent a high spatial overlap between every subject's RSN and the equivalent group-derived RSN. Finally, indices of network integrity were available for each subject, network, and imaging modality [72]. Potential WM training effects on network integrity indices were analysed with a two-way mixed-effects analysis of variance (ANOVA) for repeated measures using the between-subjects factor *group* (CON, EXP) and the within-subjects factor *time* (T1, T2) using SPSS 19.0 (IBM Corporation, Somers, NY). We considered results as statistically significant at $p < 0.05$ after Bonferroni correction, i.e., 0.05/6 = 0.008 for six networks of interest.

Statistical analyses of the training data

We used in-house written Python 3 scripts to analyse the training data. In the experimental group, we studied the mean *n*-back level achieved in each session and the *d* prime for both types of training. Based on signal detection theory, *d* prime is calculated from the hit rate and false

alarm rate [76,77]. For the control group, we only analysed *d* prime since those subjects performed at a stable low *n*-back level in both training procedures (i.e., 1-back level for verbal stimuli and X-back level for visual stimuli). Because the last three sessions of one subject in the experimental group and two last sessions of one subject in the control group were lost, we interpolated the missing data with their own previous training data using a forward linear method. Assumptions of normality were rejected for the *n*-back training data (all *p*-values < 0.05 in Kolmogorov–Smirnov test). To assess practice effects, we performed a two-sided Wilcoxon signed-rank test between the mean of the first four and the mean of the last four training sessions for *d* prime, separately for each group and WM training modality (i.e., visual and verbal). Additionally, we computed a two-sided Wilcoxon signed-rank test between the mean of the first four and the mean of the last four sessions for *n*-back level values for the experimental group separately for each training modality (i.e., visual and verbal).

Statistical analyses of the cognitive test battery

Assumptions of normality were tested using a one-sample Kolmogorov–Smirnov test. As primary analysis, we conducted a *group* (CON, EXP) by *time* (T1, T2) multivariate ANOVA for each transfer category (i.e., nearest, near, far). In case of a significant *group x time* interaction per category, we performed a *post-hoc* ANOVA for this category. Results were considered as statistically significant at $p < 0.05$ with Bonferroni correction, i.e., 0.05/4 = 0.0125; 0.05/15 = 0.003; 0.05/2 = 0.025 for 4, 15, and 2 tests for nearest, near and far-transfer category, respectively. ANOVA is known to be robust for not normally distributed data with an equal sample size [78]. In addition, we computed two-sided paired *t*-tests or Wilcoxon signed-rank tests (depending on the distribution) for all cognitive tests within the experimental and control group (table 3). Results were considered as statistically significant at $p < 0.05$ with Bonferroni correction, i.e., 0.05/21 = $p < 0.002$ (for 21 tests). All statistical analyses were performed using SPSS 19.0 (IBM Corporation, Somers, NY).

Statistical analyses of the imaging data

For ALFF and FDG-PET data, we conducted ANOVA with the between-subjects factor *group* (CON, EXP) and the within-subjects factor *time* (T1, T2) using the full factorial model in SPM12. For FDG-PET data grand mean scaling and global calculation using SPM's global mean were applied. A $p < 0.05$ familywise error - corrected for multiple comparisons at a voxel-level was set as the significance threshold. To analyse DTI data voxel-wise, we applied permutation-based statistics using the *randomise* function in FSL [79]. The random permutation number was set at 5000, and we considered results as statistically significant at $p < 0.05$ threshold-free cluster enhancement - corrected for multiple comparisons at a voxel-level. A two-way mixed-effect ANOVA for repeated measures was conducted with the between-subjects factor *group* (CON, EXP) and the within-subjects factor *time* (T1, T2) for FA, MD, AD, and RD maps.

Results

Demographics

Demographic characteristics of the participants are summarized in table 1. There was no significant difference for age ($p = 0.92$), sex ($p = 0.70$), BMI ($p = 0.19$) or years of education ($p = 0.38$) between the experimental and the active control groups. Thus, no correction for these variables was applied [80].

Table 1: Demographics

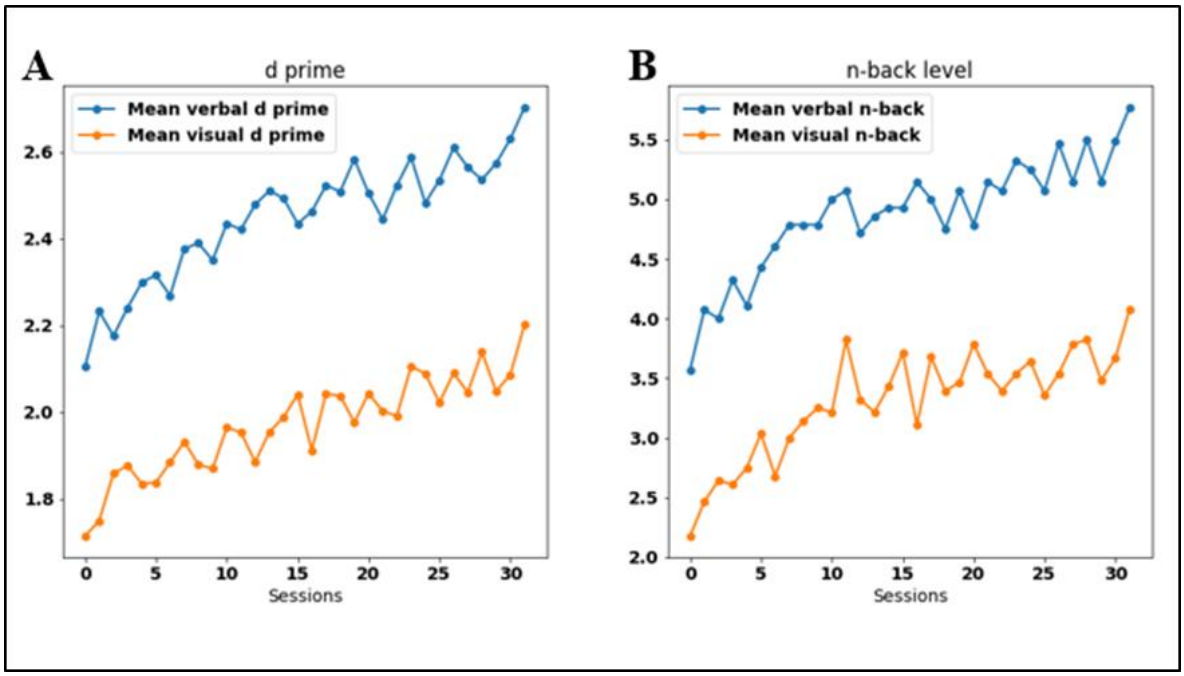
	N	M/F	Age	BMI	YoE
Experimental	28	16/12	56.00 ± 4.23	25.83 ± 4.15	16.79 ± 3.14
Active control	27	14/13	55.88 ± 4.23	24.49 ± 3.33	16.01 ± 3.21

M, male; F, female; BMI, body mass index; YoE, years of education; data presented as mean ± standard deviation; two-sided two sample t-tests was applied for age, body-mass index and years of education; chi-squared test was applied for sex.

Working Memory Training

The experimental group showed significant practice effects both in verbal *n*-back training (Z = 7, *p* = 8.07e-6) and visual *n*-back training (Z = 13, *p* = 1.51e-05), figure 2A. They also showed a significant improvement in the *n*-back level achieved in verbal *n*-back training (Z = 21, *p* = 3.34e-05) and in visual *n*-back training (Z = 18.5, *p* = 6.51e-05), figure 2B. In the active control group, *d* prime did not significantly differ between the beginning and the end of verbal *n*-back training or visual *n*-back training.

Figure 3: Training results for the experimental group



A) d prime mean values per session, B) n-back level mean values per session; blue line: verbal WM training, orange line: visual WM training

In the multivariate analysis of variance (ANOVA), a significant *group* × *time* interaction was found only for the nearest transfer effect category ($F_{(4,50)} = 5.3$, $p < 0.013$). Follow-up univariate analysis of variance revealed a significant *group* × *time* interaction for the Digit Span forward test, table 2.

Table 2: ANOVA for the nearest transfer category

Tests	EXP	CON	Interaction

					group × time	
	T1 M (SD)	T2 M (SD)	T1 M (SD)	T2 M (SD)	*F*	*p*
Digit Span						
Forward	7.8 (2.2)	8.8 (1.7)	7.5 (2.2)	7.0 (1.8)	16.97	0.0001
Backward	6.8 (1.3)	7.5 (2.1)	7.1 (2.4)	7.6 (2.5)	0.11	0.75
Corsi	46.1 (16.5)	47.7 (16.5)	44.1 (19.1)	44.7 (16.4)	0.04	0.85
SVRT						
Mean latency	287 (34)	299 (42)	285 (33)	283 (35)	3.12	0.08

M (SD), mean (standard deviation); Corsi, Corsi-Block Tapping test; SVRT, simple visual reaction time task

The experimental group showed a significant improvement in the Digit Span forward test at T2 compared to T1, table 3. Subjects in both groups showed quicker reaction times in the Visual Simon task (VST) at T2 compared to T1. Here, the experimental group improved in the incongruent trials (RT-incong), whereas the control group improved both in congruent and incongruent trials.

***Table 3**: Comparisons within each group for all cognitive tests*

	Tests	EXP (T1 vs. T2)		CON (T1 vs. T2)	
			p		***p***
Nearest transfer	**Digit Span**				
	Forward	T = -3.48	0.002**	T = 2.27	0.03*
	Backward	T = -1.54	0.14	T = -1.37	0.18
	Corsi-Block Tapping	Z = -0.16	0.25	Z = -0.30	0.76
	SVRT				
	Mean latency	T = -2.39	0.02*	T = 0.40	0.69
Near transfer	**VLMT**				
	Dg5-6	Z = -0.16	0.13	Z = -0.21	0.83
	Dg5-7	T = 0.31	0.76	T = -0.85	0.40
	w-f	T = -0.72	0.48	T = -1.35	0.19
	RVIP				
	Accuracy	T = -2.93	0.007*	T = -2.03	0.05
	RT	T = -0.54	0.59	T = 1.14	0.26
	CWST				
	RT-cong	T = 1.80	0.08	T = 0.70	0.49
	RT-incong	T = 1.43	0.17	T = -0.16	0.87
	RT-neutral	T = 1.67	0.11	T = -0.18	0.86
	%-cong	Z = -1.52	0.13	Z = -0.67	0.50
	%-incong	Z = -0.26	0.80	Z = -0.061	0.95
	%-neutral	Z = -0.76	0.45	Z = -0.56	0.56
	VST				
	RT-cong	T = 2.66	0.01*	T = 4.47	0.0001**
	RT-incong	T = 3.47	0.002**	T = 4.68	0.0001**
	%-cong	Z = -1.13	0.26	Z = -1.24	0.24
	%-incong	Z = -0.07	0.94	Z = -1.77	0.08
Far transfer	**Short-APM**	T = -2.95	0.006*	T = -1.17	0.25
	IGT	T = -2.00	0.056	T = -1.15	0.26

*Corsi, Corsi-Block Tapping test; SVRT, simple visual reaction time task; RVIP, the rapid visual information processing task; Accuracy = number of correct hits – FA; RT (ms), mean reaction time of correct target, in millisecond; CWST, the color-word Stroop task; RT-cong; mean reaction time for congruent condition; RT-incong, mean reaction time for incongruent condition; RT-neutral, mean reaction in neutral condition; %-cong, proportion correct for congruent condition; %-incong, proportion correct for incongruent condition; %-neutral, proportion correct for neutral condition; VST, visual Simon task; Short-APM, the short version of Raven's Advanced Progressive Matrices Test; IGT, Iowa Gambling Task, independent variable here is net score. For all measures except RT negative T-values represent improvements in performance from T1 to T2. T-values for two-sided paired t-tests, Z-value for two sided Wilcoxon signed-rank test * Significant at $p < 0.05$ uncorrected; ** significant at $p < 0.05$ Bonferroni corrected ($p < 0.002$ uncorrected)*

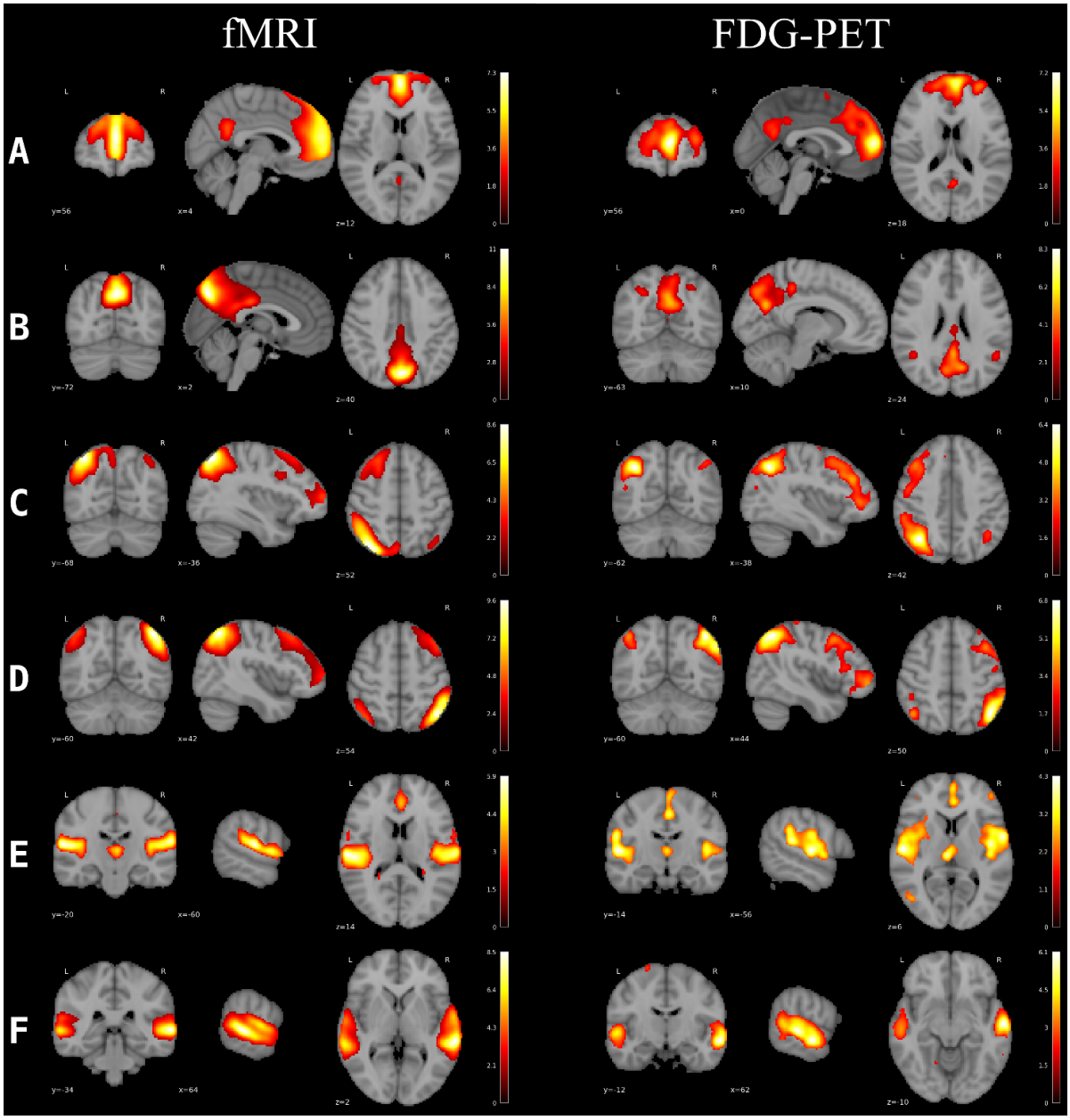
Voxel-wise analyses of amplitude of low frequency fluctuations and PET data

The *group* x *time* interaction was not significant.

Network analyses of resting state fMRI and PET data

Figure 3 shows the RSNs of interest as extracted from fMRI and PET data. ANOVAs revealed no significant *group x time* interaction for any network neither in fMRI nor FDG-PET data.

Figure 4: Resting state networks of interest



A) anterior default mode network, B) posterior default mode network, C) left central executive network, D) right central executive network, E) salience network, F) auditory network

Tract-based spatial statistics

The two-way mixed-effect ANOVA for repeated measures showed no significant *group x time* interaction in any DTI map.

Discussion

Following 8-week *n*-back training, no near or far transfer effects were detected in middle-aged adults, despite the presence of significant practice effects. Consistently, there were no significant changes in a comprehensive analysis of the multimodal neuroimaging data. Given the discrepant findings reported so far with respect to transfer effects, we designed our study to address a common limitation of WM training studies, specifically the lack of an active control group. Moreover, we tested a larger-than average sample [81] of a typically neglected age group using an intensive, adaptive home-based intervention, for which we ensured close supervision. As a further hallmark of our study, we utilized a state-of-the-art hybrid PET/MRI system that enables simultaneous acquisition of MRI and PET data. Neural correlates of WM training were comprehensively searched for in the fMRI, DTI, and FDG-PET data at voxel and network levels. Thus, the present study offers the most thorough assessment of WM training effects hitherto reported.

In line with results of multiple studies [12,13] we found significant practice effects in the experimental group. Significant transfer effects were present only in one subtest of the nearest transfer category, namely the Digit Span forward. There was no corresponding improvement even in Digit Span backward, a closely related subtest with the same stimuli. Neither near nor far transfer effects were detected. Of note, by transfer effects we explicitly mean test improvements in an experimental group relative to an active control group. This definition allows isolation of any cognitive gains *specifically due to* adaptive *n*-back training. Thus, WM training-related gains appear to generalize to performance in other WM tasks only to an extremely limited degree. Moreover, the gains are generalizable neither within the same domain nor to other cognitive domains.

As outlined above, the literature regarding near and far transfer effects is rather discrepant, although recent meta-analyses argues for lack of transfer effects from WM training [7,8,82]. Undoubtedly, the inconsistent findings in the field are related to methodological differences

between the studies, notably different training tasks (e.g., *n*-back vs. complex span tasks), training conditions (duration and frequency), and age of participants. However, in our opinion, the key factor contributing to the discrepant findings in previous cognition and neuroimaging studies is the presence and type of control intervention (passive or active). Remarkably, the above meta-analyses explicitly distinguished between types of control group. Whereas a passive (or no-contact) control group accounts for test-retest effects, only an active control group accounts for non-specific training effects such as engaging regularly in a computerized task, expectancy, and placebo effects [10]. Moreover, practicing WM tasks also triggers cognition in domains that are unrelated to WM capacity, such as attention and visual integration [83,84], or the development of task- or material-specific expertise [82]. Therefore, it is essential to discriminate between transfer that is specifically related or unrelated to the trained domain, such as WM capacity in the present case. This differentiation is possible only by including an active control group. In the present study, the active control group practiced with identical materials as the experimental group but on a low and non-adaptive difficulty level. This design allows for isolating gains specific to taxing the limits of WM capacity from performance improvements due to material- or task-specific expertise. Our results indicate that including an active control group is essential: within the experimental group, we observed significant changes in all three transfer categories, including far transfer, although they did not survive correction for multiple tests. We also observed some significant near transfer effects in the control group. Importantly, however, the experimental group did not improve over and above the changes observed in the control group. Therefore, we can conclude that these improvements do not reflect increased WM capacity. In this context we propose the term *pseudo-transfer effects* to describe such gains that are unrelated to increases in WM capacity. We attribute these pseudo-transfer effects to the adaptive character and consequently greater difficulty of training in the experimental group. For example, increasing the task difficulty may have encouraged participants to develop effective strategies to memorize long lists of stimuli such as chunking or visualization [85].

However, this phenomenon is unrelated to increased WM capacity *per se*. This explanation is in line with the only nearest transfer effect that we observed in the experimental group contrasted against the active control group. As there was no transfer to any other task, it is highly unlikely that the effect was driven by increased WM capacity. Instead, we argue that the observed improvement in the forward Digit Span, a measure of verbal short-term memory, more likely is a pseudo-transfer effect imparted by co-engagement of short-term memory and acquisition of effective strategies during adaptive *n*-back training. Finally, transfer effects within and between cognitive domains have been shown to be of equivalent magnitude when comparing different WM training paradigms (e.g. n-back training and complex span training) [86]. Therefore, we argue that our results are transferable to other types of WM trainings.

There are relatively few investigations of the neural substrates of WM training. While this is the first such FDG-PET study, others have investigated the effects of WM training on intrinsic neural activity as measured with fractional ALFF [30]. The authors reported increased brain activity in the dorsal prefrontal cortex following WM training. Nonetheless, we detected no changes in ALFF or glucose metabolism following WM training. This may reflect the lack of an active control group in Takeuchi et al. [30]. So far, only two studies have explored an impact of WM training on RSN connectivity, with findings of increased and decreased connectivity within DMN as well as between DMN and central executive network (CEN) [32,33]. Here, we did not find any training induced changes in the DMN, CEN or other established neurocognitive RSNs, even in exploratory analysis without correction for multiple tests (data not shown). Again, the absence of significant effects in our study may be explained by our inclusion of an active control group. While there has been no previous DTI study with TBSS on the effects of WM training, a few reports have explored effects of this kind of training on white matter integrity using voxel-based morphometry or an ROI analysis [34–36]. These studies reported training associated-changes in frontal and parietal white matter tracts [35], corpus callosum [34], and in regions of the dopaminergic system [36]. However, in line with our other neuroimaging

results, we found no significant effects of WM training on white matter integrity. Again, the above studies either had no control group [35] or a passive control group [34,36].

In summary, in this prospective, randomized, controlled, single blind study, we found neither near nor far transfer effects following 8-week adaptive WM training in healthy middle-aged subjects. Repeated multimodal imaging revealed no changes in resting state fMRI, DTI, and FDG-PET data in association with WM training, despite a pronounced improvement in *n*-bask task performance. Our results highlight the critical impact of an active control intervention on the interpretation of WM training and transfer effects. We propose the term "pseudo-transfer effects" to characterize gains in a trained task resulting from co-engagement of non-targeted cognitive domains. Although the idea of transfer is fascinating and has engendered a major industry, the present study strongly argues for absence of transfer, either cognitive or in terms of neural structure and function. Further research is necessary to study efficacy of cognitive interventions that trigger (multiple) pseudo-transfer effects due to engagement of multiple cognitive domains.

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Competing interests:

The authors declare that they have no conflict of interest.

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Supplementary Material

Details on image data acquisition

Positron emission tomography

PET data were acquired for 60 min in list mode with a craniocaudal scan direction and a z-axis distance of 26 cm. PET image reconstruction was performed offline using Siemens e7 Tools (Siemens Molecular Imaging, Knoxville, USA). Ordered subsets expectation maximisation (OSEM) algorithm with 3 iterations of 24 subsets with a 5 mm Gaussian filter, to eliminate the high frequency noise, was used. The resulting PET images had a matrix dimensions of 344 × 344 with 127 sagittal slices with a reconstructed voxel size of 1.04 × 1.04 × 2.03 mm3. Tissue segmentation based magnetic resonance attenuation correction (MRAC) was performed using an ultra-short time of echo (UTE) μ-map which was acquired with the following parameters: 300 sagittal slices; voxel size = 1.6 × 1.6 × 1.6 mm3; matrix size = 300 × 300 mm.

Structural T1-weighted MRI

Structural T1-weighted (MPRAGE) images were acquired using a three-dimensional (3D) normal gradient recalled sequence with the following parameters: 160 sagittal slices; time of repetition (TR) = 2300.0 ms; echo time (TE) = 2.98 ms; flip angle = 9.0º; field of view (FOV)

= 256mm; bandwith = 240 Hz/Pz; matrix size = 256 × 240 mm; slice thickness = 1.0 mm (no gap) and voxel size = 1.0 × 1.0 × 1.0 mm3 voxel size.

Resting state fMRI

FMRI data were acquired using an echo planar imaging pulse (EPI) sequence with the following parameters: 40 slices; 212 volumes; TR = 2230 ms; TE = 30 ms; flip angle = 90 º; FOV= 192 mm; bandwith= 2232 Hz/Px; matrix size 192 x 144 mm; slice thickness = 3.0 mm (0.6 mm gap); 3.0 x 3.0 x 3.0 mm3 voxel size and interleaved acquisition.

Diffusion tensor imaging (DTI)

DTI data were acquired using an EPI sequence with the following parameters: 60 slices; 30 volumes; TR = 10800 ms; TE = 82 ms; flip angle = 90°; FOV = 260 mm; bandwidth = 1672 Hz/Px; matrix size = 130 ×130; slice thickness = 2 mm (no gap) and 2.0 × 2.0 × 2.0 mm3 voxel size. Diffusion weighting was performed in multi-directional diffusion weighting (MDDW) mode along 30 diffusion gradient directions with b = 800 s/mm2 complemented by one image without diffusion weighting (b = 0 s/mm2). We used bipolar diffusion gradients to reduce motion artifacts.

Spatially constrained ICA

A spatially constrained ICA is a semi-blind ICA algorithm which uses prior information about sources as reference signals (i.e. computed spatial maps from the fMRI data), enabling to extract only the desired sources [1]. The resulting independent components have higher SNR ratio than traditional ICA algorithms [1]. Applying a spatially constrained ICA to FDG-PET data ensured a high cross modality network similarity leading to an accurate comparison of training effects on equivalent but modality specific derived networks. We chose to apply components extracted from fMRI data as reference spatial maps because well-established RSN templates from fMRI data exist, which were used for RSN identification [2,3].

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Discussion

The main findings of the thesis are that i) AD and bvFTD are characterized by differently impaired NCN integrities which furthermore differ between neuroimaging modalities with FDG-PET showing a higher disease specificity than rsfMRI and ii) WM training in healthy middle-aged participants does not elicit near or far transfer effects. The comparison of change in NCN integrity measures derived from rsfMRI and FDG-PET as well as change in cognitive performances in transfer tasks between the experimental and the active control group revealed only in one subtest of the nearest transfer category a significant improvement in the experimental group. Thus, WM training-related gains appear not to generalize to other cognitive domains and only to an extremely limited degree to other WM tasks. Overall, these results discourage the potential applicability of WM training in early stage dementia to decrease NCN integrity impairments.

4.1. On the nature of Resting State Network Integrity Measures

Considerable methodological differences in estimating functional RSN connectivity exist, even if derived with ICA. Here, I will briefly review the RSN integrity estimates chosen in our study (for project one and two) and compare it to other estimates of RSN connectivity for subsequent discrimination analysis between AD and bvFTD.

In our study whole sample-derived (i.e. AD, bvFTD and HC) independent components were back-projected to the subject-specific fMRI data resulting in subject-specific time-courses and spatial maps for each component. A subsequent multiple regression was computed to obtain RSN integrity values per subject. The multiple regression returned a beta-value (β) for each component of interest in each subject, reflecting the degree to which the spatial pattern of each subject's network of interest explained the spatial pattern of the equivalent group derived network. This procedure has been conducted before in a similar way (Gordon, Stollstorff, and Vaidya 2011). Importantly, the multiple regression estimates each voxel's contribution per subject to each network of interest while controlling for the influence of all other networks (including artefact associated components, such as head motion and physiological noise). Here, differences between subjects (and ultimately between groups) are due to subject variability in regards to voxels being assigned to components. During back-projection first the temporal regression is performed and then the spatial regression for assigning each subject's voxel

to a component while ensuring temporal coherence between the voxels assigned to each detected source signal (i.e. component). “Thus, individual differences in connectivity with a given network may manifest in any brain region – irrespective of whether that brain region falls within the set of regions typically associated with that network” (Smith et al. 2014). Together, the analysis approach chosen in our study measures how much one voxel contributed to each network of interest while controlling for the influence of all other networks.

Based on the posterior DMN network integrity measures, we calculated a 64% diagnostic status accuracy. However, Zhou et al. (2010) calculated a 100% diagnostic status accuracy based on connectivity strength values for the SN and DMN. But, the methodological approach obtaining the numbers underlying the linear discriminant analysis between Zhou et al. (2010) and our study is different. The authors extracted averaged z-values per subject from regions within the SN and within the DMN. The z-value of each network obtained via an ICA reflects the strength or participation of the voxel in the specific network. Thus, the z-value is also called connectivity strength, although it does not reflect connectivity *per se*. The within network regions were identified by a conjunction analysis of bvFTD < controls and AD > controls for the SN and in AD < controls and bvFTD > controls for the DMN. Thus, the directionality of dementia specific impairments was predefined as revealed by a prior analysis by the authors. In contrast, our approach was based on a *non a priori* assumption of impairment directionality of connectivity alterations. The difference in discriminant analysis between our study and Zhou et al.’s (2010) points towards the possibility that a discrimination analysis using fMRI derived connectivity estimates of RSN is more successful (i.e. higher accuracy) when connectivity values are used from regions known to be affected on a sub-network level. Hence, it seems, the finer the scale, the more successful the discriminant analysis. Conceptually, this could be explained by a focal regional neurodegeneration in AD and bvFTD whose severity is averaged out to a certain extend when including non-affected regions (i.e. on a network level) in the analysis, as in our study. However, another or additional possibility underlying differential results in linear discrimination analysis could be due to smaller patient groups (n = 12 each) and more advanced disease in patients with AD (average Mini Mental State Examination (MMSE) score of 21.2, vs. 24.3 in our study) in the study of Zhou et al (2010). MMSE is the most widely applied test to assess cognition (Folstein, Folstein, and McHugh 1975). Disease severity reflected by a lower MMSE due to a more

advanced neurodegeneration could lead to significantly higher diagnostic discrimination results based on more severely impaired measures of neural activity (Liu et al. 2014). As for NCNs extracted from FDG-PET data in our study, the integrity of the anterior DMN appeared to be the strongest predictor of the diagnostic status, providing an accuracy of 94%. All other NCNs on their own were significant predictors, too, but with a lower accuracy. In a stepwise logistic regression with all PET-based NCNs, the integrity of the SN slightly improved the discrimination (96% accuracy). We were the first study reporting metabolic RSN connectivity in AD or bvFTD. FGD-PET based integrity measures do not inform about directionality of impairments, meaning regionally decreased or increased FDG-uptake are not reflected by these values. The integrity measures are the so-called loading coefficients (Shaffer et al. 2013) stored as mixing matrix entries of A from the generative model x = As, which separates the different source signals (Calhoun and Adalı 2012; Kakeda et al. 2020). These values represent to which degree the subjects' specific components had to be modulated to fit to the group-based component (i.e. solving the equation x = As).

Overall, the method used for discriminating AD and bvFTD in our study and by Zhou et al. (2010) shows higher accuracy values than discrimination analyses using voxel-wise FDG-uptake. Here, a study by Nestor et al. (2018) evaluating the clinical utility of FDG-PET for differential diagnosis among the main forms of dementia reported only a fair empirical study evidence for discriminating FTD from AD. The reported accuracy values from included literature reports showed a range of 87% to 89.2%. Thus, the network approach for disease classification based on both rsfMRI and FDG-PET seems to be superior. Specifically, the network approach using fMRI might rely on only including regions showing significantly altered neural activity for reaching a high accuracy, whereas the network approach using FDG-PET delivers a high classification accuracy using a purely data-driven approach (i.e. whole brain). Further research is needed to study the effects of atypical AD and bvFTD and early and late disease stages on network-based discrimination approaches.

4.2. Network Integrity Differences between Functional Magnetic Resonance Imaging and Fluordesoxyglucose Positron Emission Tomography

We showed a higher disease specificity using FDG-PET than fMRI derived integrity measures. Overall, the results obtained in the study support the use of metabolic connectivity imaging as a valuable tool in the field of brain connectivity. Biologically, the higher disease specificity could be due to different aspects being measured with each modality. FDG-PET is supposed to capture neural or synaptic activity by estimating glucose consumption in terms of neurometabolic coupling (Magistretti and Allaman 2015) and fMRI measures neural activity less directly, through the amount of oxygen in blood supplying a given brain region (Chen 2018). This so-called neurovascular coupling is based on a complex interplay between local cerebral blood flow, volume, and the cerebral metabolic rate of oxygen (Kim and Ogawa 2012). Methodologically, the shortcoming of FDG-PET, namely the lack of information on the temporal domain, might actually be co-responsible for the high accuracy in disease discrimination observed in our study: Due to fMRI's strong dependence on the bloodflow, age- and dementia-related cerebral vascular impairments, such as cerebral amyloid angiopathy (CAA) heavily affect fMRI measures (Dumas et al. 2012; Montagne, Pa, and Zlokovic 2015). On the other hand, FDG-PET reflects FDG-uptake which occurred over a certain time frame (in the range of several minutes). Thus, cerebral vascular impairments, despite present, might affect the FDG-PET signal to a smaller extent than the fMRI signal. However, further research is needed to understand the impact of cerebral vascular activity and architecture on fMRI and FDG-PET signal. All in all, the partly different findings in our fMRI and FDG-PET data, as well as a low correlation between integrity measurements of fMRI- and PET-based networks, are not surprising.

4.3. Impaired Neurocognitive Network Integrity in Alzheimer's Disease and behavioural-variant Frontotemporal Dementia

Overall, in the first project we showed that both AD and bvFTD are characterized by NCN integrity impairments based on two different neuroimaging methods. And we showed, that these NCN impairments successfully differentiated between AD and bvFTD with a 96% accuracy. As outlined in the introduction, RSN alterations have been linked in both types of dementia to clinical symptoms, such as cognitive decline (Lin et al. 2018; Zhou and Seeley 2014). Thus, potential repair mechanisms for these impaired NCN could lead

to increase, prevent deterioration or slow down the decline of cognitive performances. However, as of today no pharmacological treatment has been found to repair RSN impairments due to neurodegeneration. On the behavioural level, non-pharmacological interventions have shown positive effects. Specifically, far transfer effects following WM training could manifest in improved skills for daily functioning (Jobe et al. 2001), especially for individuals undergoing cognitive decline. However, heterogeneous results have been obtained for transfer effects, while practice effects following WM training have been consistently reported (Sala, Aksayli, Tatlidil, Gondo, et al. 2019; Soveri et al. 2017). Equivalently, neural correlates of transfer come with no definition and have been studied very rarely. Here, a meta-analysis on neural correlates of transfer by Salmi et al. (2018) "provisionally" linked the fronto-striatal system to near transfer. However, the authors also stated that "the existing brain imaging studies are not well-suited in addressing the important question whether WM training yields transfer beyond the WM domain".

4.4. Transfer Effects Following Working Memory Training in Healthy Middle-Aged Participants

In project 2 we investigated the effects of an eight weeks WM training (n-back) in healthy middle-aged participants. Based on a pre-/post-training comparison while controlling for overall program interventional effects by including an active control group we evaluated transfer effects on the behavioural and neuroimaging level. Thus, by transfer effects we explicitly mean test improvements in an experimental group relative to an active control group. Only one significant change was observed in the study (next to significant practice effects), namely a significant nearest transfer effect which was only present in one subtest of all included nearest transfer tasks. Hence, we conclude that WM training-related gains appear not to generalize to other cognitive domains and only to an extremely limited degree to other WM tasks.

The literature reports heterogeneous results regarding the effectiveness of WM training. A recent meta-analysis by Sala et al. (2019) reported large practice effects, only modest near transfer and near zero far transfer effects following WM training in healthy older subjects. Furthermore, far transfer effects were null when an active control group was included. Different to the meta-analysis, our results do not show near-transfer effects. However, most importantly, in this meta-analysis out of 43 included studies, there were only three studies in which the control group performed the equivalent task as the

experimental group but on a steady low level (i.e. non-adaptive vs adaptive) (Brehmer et al. 2011; Brehmer, Westerberg, and Bäckman 2012; Chan et al. 2015). Here, Brehmer et al. (2011) observed significant nearest transfer effects as revealed by improvements in "very similar" tasks compared to the training task using a group x time interaction analysis. Brehmer et al. (2012) reported nearest, near and far transfer effects based on a group x time interaction analysis. However, the near-transfer effects are based on tasks which we categorized in our study as nearest transfer tasks (e.g. Digit Span) and the far transfer-effect was reported for a sustained attention task (PASAT) which we did not assess. Further, the authors did not observe significant far-transfer effects in a task which we also assessed, namely Raven's Advanced Progressive Matrices. Chan et al. (2015) only investigated and observed practice and nearest transfer effects. Thus, our results are in line with the results obtained by Brehmer et al. (2011, 2012). The existing meta-analyses separated WM training studies so far only by 'active control group' and 'non active control group' (Karbach and Verhaeghen 2014; Melby-Lervåg and Hulme 2013; Melby-Lervåg et al. 2016; Sala, Aksayli, Tatlidil, Gondo, et al. 2019; Sala, Aksayli, Tatlidil, Tatsumi, et al. 2019; Schwaighofer, Fischer, and Bühner 2015; Teixeira-Santos et al. 2019). But there is a huge variance in type of active control training which, I argue, heavily affects the statistical outcome in a group x time interaction comparison. Hence, I argue that this classification is not sufficient enough. In the following, I will briefly outline the effects of type of control group.

The lack of a control group leads to a capturing of overall training program effects. This means, the pre-/post comparison leads to the detection of behavioural and neural activity changes driven by the overall program. This includes all related effects of the chosen training including regularity to perform a task, computer-interaction (in case the training was computer based), attentional requirements to concentrate on the given task, developing a task strategy (like chunking) (Laine et al. 2018), motivational aspects like having to do a repeating certain task over and over, etc. The inclusion of a passive control group just controls for potential longitudinal changes occurred in between the two points in time (i.e. pre- and post-training assessment). These measurements can also be used to correct for test-retest variance (Goghari and Lawlor-Savage 2017). The inclusion of an active control group allows to isolate training paradigm specific effects (von Bastian and Oberauer 2014) However, the degree of isolating training paradigm specific effects depends on the control group task. The more similar the control group training is to the

experimental group training, the higher the training paradigm specific effects when contrasting both groups over time. In our study, the control group performed a steady low-level n-back task for both visual and verbal WM training. Our experimental group conducted exactly the same training but with an increasing difficulty level depending on the subject's performance (i.e. adaptive). Only this specific design allows to isolate WM training effects which are due to and solely due to an increased WM capacity. And WM capacity has been hypothesized to mediate transfer (von Bastian and Oberauer 2014; Harrison et al. 2013; Lange and Süß 2015; Tidwell et al. 2014). Thus, the main goal of project 2 was to isolate effects due to an increased WM capacity (i.e. higher level of n due to adaptive n-back). However, we show that an increased WM capacity – as present in the contrast analysis – does not trigger transfer effects, neither on the behavioural level, nor on the neuroimaging level. To understand where the long-standing assumption of transfer effects comes from, we conducted a post-hoc analysis in which we showed training effects revealed by within-group contrasts. Here, we observed transfer effects even present in the control group. This implicates that both training types, no matter how specific they have been designed, trigger performance improvements which are not due to an increased WM capacity, but most likely due to overall training effects, such as trained attention (Brehmer et al. 2012; Lilienthal et al. 2013). Here, it is important to note that no matter how specific a cognitive task was designed in terms of maximizing the sole recruitment of one specific cognitive domain, it can never be 100% specific. Minear et al. (2016) state that "[p]erformance on a working-memory task may improve with training due to any mixture of reasons such as (1) increased capacity of short-term store/primary memory, (2) improved executive function which may involve better attentional focus or the suppression of irrelevant information or both, or (3) other task-specific processes such as updating or shifting." In fact, it has even been argued that WM itself "may reflect a conglomerate of basic psychological constructs like attention, updating, and executive functions" (Gajewski et al. 2018). Hence it is obvious that WM training such as n-back "co-trains" several cognitive domains. Throughout the rest of the discussion I will call these *pseudo training effects*.

However, it needs to be discussed what caused the observed nearest transfer effect if not an increased WM capacity? We argue that the observed improvement in the forward Digit Span test, a measure of verbal short-term memory, is due to a large recruitment of cognitive skills which were also needed for performing the n-back task (Redick and

Lindsey 2013). Thus, Digit Span benefits greatly from the training due to the great similarity to n-back task. Hence, the amount of transfer is minimal. Furthermore, I assume that the *pseudo training effects* increase depending on task difficulty which would explain why the experimental group shows more performance improvements in transfer tasks than the control group as revealed by the within-group comparison. However, more research is needed to clarify the magnitude and extent of these *pseudo transfer effects.*

Overall, we refute that an increased WM capacity triggers transfer effects on the behavioural and neuroimaging level. While these results might be discouraging in regards to the fascinating idea of obtaining general cognitive improvements in a rather "easy" way by just training one type of cognitive task, the results are also encouraging as we do see cognitive training-induced performance improvements as shown by the within-group comparisons. These observations point towards the need to study the effects of CT which not only targets one single but multiple cognitive domains. A training program which is characterized by a variety of tasks leads to the recruitment of more than just one cognitive domain. Thus, I argue, that a variety of practice effects as well as each task's *pseudo-transfer effects* would potentially lead to cognitive skill improvements in a much wider range than just due to a WM training.

4.5.Applicability of Working Memory Training in Dementia

The aim of the thesis was to evaluate the potential applicability of WM training in dementia. Based on the results obtained in project 2, WM training does not have the power to repair NCN integrity impairments as seen in AD and bvFTD as there is no evidence for these neuroplastic effects or for the underlying concept on the behavioural level in healthy middle-aged subjects. The age range in project 2 was chosen as it is similar to that observed in subjects with MCI, which would represent a potential target group for WM training so slow down cognitive decline. Even though studies show the maintenance of brain plasticity throughout aging as well as in the presence of AD pathology (Hill, Kolanowski, and Gill 2011) reports also state that neural plasticity in dementia occurs mainly in form of compensatory activation changes to outbalance neuronal loss (Hill et al. 2011). Despite a remaining neural plasticity in subjects with MCI has been shown, the extend is significantly smaller to the neuroplasticity in healthy subjects (Calero and Navarro 2004). Thus, it is unlikely that MCI subjects show greater neural plasticity in RSN due to WM training than similar-aged healthy controls. However, in this thesis I did not

directly study WM training effects in AD, bvFTD or subjects with MCI. In the following, I will justify my reasoning for transferring the observations made in a healthy cohort to dementia.

Studies investigating the efficiency of WM training in early stage dementia reported heterogeneous results. Here, Weng et al. (2019) reported significant practice and far transfer effects in subjects with MCI relative to an active control group which was subjected to a mental leisure activity program. Flak et al. (2019) reported the lack of transfer effects due to WM training in subjects with MCI compared to an active control group (non-adaptive WM training). Huntley at al. (2017) showed significant practice and transfer effects in patients with mild AD compared to an active control group. The same study even reported neural correlates of practice effects in form of bilateral reduction in lateral prefrontal and parietal cortex activation based on fMRI in the training group compared with controls. All in all, the results obtained in dementia are equivalently heterogeneous as in healthy older subjects. However, none of these studies investigated neural correlates of transfer which represents the main aim in WM training.

On a cognitive level, changing performance strategies underlying n-back task across the life-span have been reported. Here Gajewski et al. (2018) showed that in older age "mainly attentional, verbal memory, and updating and to a lesser extent executive processes seem to play a crucial role in the n-back task". In younger subjects, on the other hand, performance was most related to executive functions. Thus, it seems that older subjects process cognitive tasks more decentralized. The effects of dementia on cognitive task processing should be investigated to understand if the overall concept of WM training-induced transfer (i.e. based on an increased WM capacity) is even applicable in these patient cohorts and to which extent. Also on a neuronal level, significant changes due to ageing have been reported. Here, age-related associations to lower modularity and local efficiency (Iordan et al. 2018), weaker within-network connectivity, lower system segregation and reduced within-network connectivity (Varangis et al. 2019) have been drawn. The concept of *neural dedifferentiation describes* global reorganization of functional networks with sensory modules kept intact while NCN undergo age-related change (Song et al. 2014) (for a review see Koen et al. (2020)). In dementia, functional network disruptions have been shown consistently (for a review Pievani (2011) and Sala and Perani (2019)). The effects of these network disruptions might have a direct impact

on the functionality of transfer. However, this is only speculative as the underlying principles of transfer *per se* are not understood. It has been shown however, that the architecture of RSN serves as an underlying skeleton for cognitive task evoked information flow (Cole et al. 2016). Thus, if between- and within-network communication play a role in transfer, the magnitude of transfer should be heavily impaired in old age and especially in dementia. All in all, it is clear that older subjects and assumingly subjects with dementia process cognitive tasks on a behavioural level differently, which is driven by network disruptions and topological network changes due to age and dementia. Therefore, the underlying concept and apparent driving factor of transfer has to be defined for all age ranges and in dementia before being indulged by the fascinating idea of it.

4.6. Limitations

The present thesis comprises several limitations. First, we included dementia patients in early stages of AD and bvFTD representing a rather mild disease. Thus, we cannot guarantee that the results obtained based on this patient cohort is transferable to more severe stages of AD and bvFTD. Second, a methodological limitation regards the ICA. In both projects we computed the ICA over the whole sample size. Thus, the extracted components represent a mixture of AD, bvFTD and healthy subjects and pre- and post-training data from the experimental and control group in the first and second study, respectively. However, we decided for this approach as no other method so far exists to extract networks with a pure data driven method and guarantee that the components are equal across the different groups. Thus, we investigated signal differences within components which were equivalent for all subjects. However, this approach rather leads to an under-, than overestimation of group specific differences (Rytty et al. 2013). Third, in project two we conclude that no transfer effects exist due to an adaptive n-back training in contrast to training gains of an active control group. We cannot rule out that other WM training paradigms could elicit transfer effects. However, n-back is one of the most frequently applied WM training paradigms (Soveri et al. 2017) and more importantly, a meta-analysis reported a trend for n-back being the most efficient WM training (Melby-Lervåg et al. 2016). Fourth, in project two the participants performed an adaptive online n-back training without controlling for lure items. A lure item is a non-target item that matches an item earlier in the sequence but not at the current position (Oberauer 2005).

This means that the participants could potentially have pressed the button when the lure item was presented because of familiarity and not because of the specific location. Strong reliance on familiarity can potentially lead to interference. Fifth, in project two we did not cover the whole cerebellum as measured with fMRI due to the trade-off between brain coverage and repetition time. Hence, we could not study the effects of WM training on the inferior part of the cerebellum.

5. Conclusion & Outlook

The outcome of my PhD project is twofold. First, neurocognitive network integrities as measured with FDG-PET serve as a potential differential diagnostic tool in dementia, successfully differentiating between bvFTD and AD based on the anterior DMN. Second, WM training-related gains do not elicit changes in neurocognitive network integrities in healthy middle-aged participants. Therefore, I suggest that working memory training does not serve as a treatment to repair neurocognitive network impairments in dementia.

Along with our results, recent research reports and meta-analyses conclude that especially far-transfer effects following WM is a fragile concept. The choice of a non-active or active control group significantly influences the outcome and interpretation of transfer (Sala, Aksayli, Tatlidil, Gondo, et al. 2019). However, effect of type of control group training has been neglected. The more similar the control and experimental group training paradigm, the narrower the causal inferences of training outcome in the experimental group can be drawn. Our study design allowed to isolate training gains specifically due to the adaptive character of an n-back training paradigm. Interpreting this as a measure of increased WM-capacity we draw the conclusion that no transfer effects due to an increased WM capacity exist, neither on the behavioural, nor on the neural level.

Looking beyond the concept of transfer, we see overall positive effects in form of cognitive improvements on the behavioural level in both, the control and experimental group. Alongside with a general agreement on the benefits of CT in early-stage dementia (Simon et al. 2020), I argue that WM training is beneficial in dementia or subjects with MCI. However, due to the lack of transfer underlying WM training as detected in our study, I propose to test WM training along with multiple other cognitive training paradigms to maximize the range of cognitive improvements. As a future outlook, I propose to investigate which training paradigm or composition of multiple training paradigms elicit the most and widest cross-cognitive domain practice effects on the behavioural and neural level.

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